Arronax and Nuclear Medicine
Innovations in molecular imaging and targeted radionuclide therapy

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Radioactivity?
A Nuclear Medicine Pioneer

William H. Beierwaltes (1917 – 2005), Nuclear Medicine pioneer with the use of iodine-131 invented meta-iodo-benzyl-guanidine (MIBG) and was the first to administer antibodies (polyclonal) labeled with iodine-131 to a melanoma patient in 1951.

Nuclear Medicine

Use of radioactive drugs (radiopharmaceuticals) to:

• Visualize lesions or measure physiological functions
  – by single photon imaging with gamma emitting radionuclides
    • scintigraphy
    • whole bod scans
    • Single Photon Emission Tomography (SPET or SPECT)
  – by Positron Emission Tomography (PET) with positron emitting radionuclides

• Kill cancer cells with electron or alpha-particle emitting radionuclides
  – by brachytherapy
  – by targeted radionuclide therapy

Nuclear Medicine deals with all medical domains, particularly oncology, neurology and cardiology. This presentation will be limited to Nuclear Oncology.
Single photon imaging

Gamma imaging: planar imaging, whole body imaging and single photon emission tomography (SPECT)

Radionuclides: iodine-131, iodine-123, technetium-99m, indium-111…
Specific delivery of radionuclides to tumors

Lung metastases from thyroid carcinoma

Images: courtesy of Dr Glenn Flux, The Royal Marsden, London, UK
Bone scintigraphy

![Bone scintigraphy diagram]

- Normal scintigraphy
- Metastatic prostate cancer

$\text{HO}_2\text{PO}_4\text{HO}^{\text{99m Tc}}_x$
Immunoscintigraphy with an iodine-131-labeled anti-CEA antibody

Immunoscintigraphy with an iodine-123-labeled anti-CEA F(ab')$_2$ fragment

Melanoma imaging with an anti-p97 Fab labeled with iodine-131

Antibody internalization and catabolism of labeled antibodies

Melanoma imaging with an indium-111-labeled internalizing antibody

POSITRON EMISSION TOMOGRAPHY (PET)
Principle of PET-Scan

Radionuclides:

- carbon-11
- fluorine-18
- gallium-68
- copper-64
- iodine-124
- zirconium-89
FDG: imaging of GLUT's

- Glucose → Glut → Glucose \( \rightarrow \text{hexokinase} \) → G-6-P

- Glucose → Glut → *FDG

Metabolically active cells:
- brain cells
- heart muscle cells (decreased at rest)
- tumor cells
- inflammation cells
PET imaging with $^{18}$F-FDG


PET-Scan: image fusion

PET-CT
FDG-PET imaging of tumors

FDG-PET is highly effective at detecting a variety of tumors:
- lung cancer
- Hodgkin's lymphoma
- non-Hodgkin's lymphoma
- colorectal cancer
- breast cancer
- ...

Not so good in:
- brain tumors
- prostate cancer

Inflammation as possible false positive

Response to chemotherapy in breast cancer

### Table 3. Relative Changes of FDG Uptake (SUV<sub>max</sub>) During Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>%</th>
<th>Mean (%)</th>
<th>SD (%)</th>
<th>Mean (%)</th>
<th>SD (%)</th>
<th>Mean (%)</th>
<th>SD (%)</th>
<th>Mean (%)</th>
<th>SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>10</td>
<td>100</td>
<td>-59.6</td>
<td>12.6</td>
<td>-78.7</td>
<td>11.4</td>
<td>-86.3</td>
<td>15.8</td>
<td>-90.2</td>
<td>21.7</td>
</tr>
<tr>
<td>Group B</td>
<td>25</td>
<td>100</td>
<td>-35.6</td>
<td>16.2</td>
<td>-47.9</td>
<td>18.7</td>
<td>-61.3</td>
<td>26.0</td>
<td>-74.8</td>
<td>30.7</td>
</tr>
<tr>
<td>Groups C + D</td>
<td>28</td>
<td>100</td>
<td>-16.3</td>
<td>20.9</td>
<td>-22.6</td>
<td>21.8</td>
<td>-35.6</td>
<td>21.4</td>
<td>-53.2</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, [¹⁸F]fluorodeoxyglucose; SUV<sub>max</sub>, maximum standard uptake value; SD, standard deviation.

Bone scintigraphy with $^{18}$F-fluoride

Imaging bone metastases of lung, prostate, breast cancers

Not tumor specific: marker of osteoblast metabolism

Imaging tumor proliferation with $^{18}$F-FLT

PET imaging of tumor angiogenesis

Normal scintigraphy with F-18-Fluoromisonidazole (FMISO)

FDG-FMISO comparison

Non-small cell lung cancer

Tumor hypoxia assessment using Cu-ATSM in cervical cancer

Target volume in external beam radiotherapy

GTV: gross tumor volume

CTV: clinical target volume

PTV: planned target volume
Somatostatin analogues

Targeting neuroendocrine tumors that over-express somatostatin receptors

Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp
Cys-Ser-Thr-Phe-Thr-Lys
Somatostatin 14

DPhe-Cys-Phe-DTrp
Thr(ol)-Cys-Thr-Lys
Octreotide

DOTA-DPhe-Cys-Phe-DTrp
Thr(ol)-Cys-Thr-Lys
[DOTA\(^0\)]octreotide (DOTAOC)

\[^{111}\text{In-DTPA-Octreotide (OctreoScan\textsuperscript{\textregistered})}\]

[Tyr\(^3\)]octreotide
D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr(ol)

[Tyr\(^3\)]octreotate
D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr
$^{68}$Ga-PET (DOTA-octreotate)
PET imaging of neuroendocrine tumors

Tumor lesions negative for $^{68}$Ga-DOTA-TATE: contraindication for treatment with $^{177}$Lu-DOTA-TATE

Non-specific uptake of FDG

Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, Dickson J, Caplin M, Ell PJ. Functional imaging of neuroendocrine tumors with combined PET/CT using $^{68}$Ga-DOTATATE (DOTA-DPhe$^1$, Tyr$^3$-octreotate) and $^{18}$F-FDG. Cancer. 2008;112:2447-55.
Long half-life positron emitters: zirconium-89

TARGETED RADIONUCLIDE THERAPY
Magic bullets have nothing magic

Biodistribution of indium-111-labeled epratuzumab (anti-CD22, Immunomedics)

Patient specific Monte-Carlo dosimetry

- Corrections:
  - dead time
  - attenuation
  - scatter
- Registration
- Calculation of $\tilde{\mathbf{A}}$ map at the voxel level

**OEDIPE software**
- Specific voxel-based geometry
- Automatic segmentation (lungs, bone, soft tissue and air)
- Manual segmentation

**MCNPX**

$d_0, d_1, d_3, ...$

Dosimetry

Radionuclide therapy is the only treatment modality that allows the agent delivering treatment to be directly imaged.
Targeted radionuclide therapy: coping with disseminated diseases
Radiotherapy of metastatic thyroid cancer with $^{131}$I-iodide

<table>
<thead>
<tr>
<th>Lung metastases</th>
<th>Response rate</th>
<th>10-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic (normal CT)</td>
<td>83 %</td>
<td>91 %</td>
</tr>
<tr>
<td>Microscopic (abnormal CT)</td>
<td>53 %</td>
<td>63 %</td>
</tr>
<tr>
<td>Macroscopic</td>
<td>14 %</td>
<td>11 %</td>
</tr>
</tbody>
</table>

Radioimmunotherapy

- Radioimmunotherapy (RIT) has been developed for more than 20 years
- With important improvements: new stable chelates, humanized antibodies and pretargeting methods
- Effects of RIT result from both radiobiological and immunological mechanisms (ADCC, CDC, Apoptosis)
- RIT may destroy tumour cells that do not bind by the drug through a cross-fire effect
Expression of the CD20 antigen

Rituximab (Rituxan®), chimeric
Tositumomab (Bexxar®), $^{131}$I-Murine
Ibritumomab (Zevalin®), $^{90}$Y-Murine

Zevalin® vs Rituximab in non-Hodgkin's malignant lymphoma

Zevalin: yttrium-90-labeled anti-CD20 antibody
Rituximab: unlabeled anti-CD20 antibody

$^{18}$F-FDG imaging in Zevalin therapy (90Y-labeled anti-CD20 antibody)

Pre-RIT

After 1 injection of Zevalin

Courtesy of Françoise Kraeber-Bodéré, Médecine Nucléaire, CHU de Nantes

Consolidation radioimmunotherapy of follicular lymphoma

Targeting of other antigens than CD20: $^{90}\text{Y}$-labeled epratuzumab (hLL2)

Repeated injections of $^{90}\text{Y}$-labeled epratuzumab

Solid tumors

• Example:

• However: 5 disease stabilizations for 29 treated patients

Physiological constraints: antibody extravasation

Radiolabeled antibody Bound to a tumor cell

Blood vessel

Tumor cells
Small size tumor lesions

Radioimmunotherapy of residual disease in colon cancer


Examples of pretargeting methods

AES Pretargeting

Immunoscintigraphy versus TEP

AES radioimmunotherapy of Medullary Thyroid Carcinoma

80 mCi of $^{131}$I-hapten

Toxicity: grade 0 (WBC, PLT)

AES radioimmunotherapy of Medullary Thyroid Carcinoma


Disease stabilization

Beneficial to cancer patients?
AES radioimmunotherapy of Medullary Thyroid Carcinoma

The "Dock and Lock" system

Anchoring domains (AD) of A kinase anchor proteins (AKAPs)

Dimerization and docking domain (DDD) of the regulatory subunit of PKA

TF2: 157 kDa divalent x monovalent anti-CEA x anti-HSG

# Electrons and alpha particles

<table>
<thead>
<tr>
<th></th>
<th>Positron, Electron</th>
<th>Helium nucleus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean range</td>
<td>360 µm</td>
<td>60 µm</td>
</tr>
<tr>
<td>Energy</td>
<td>0.182 MeV</td>
<td>5.9 MeV</td>
</tr>
<tr>
<td>LET</td>
<td>0.5 keV/µm</td>
<td>100 keV/µm</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 days</td>
<td>46 min</td>
</tr>
<tr>
<td>iodine-131</td>
<td></td>
<td>bismuth-213</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Alpha-immunotherapy

$^{131}$I, $^{90}$Y, $^{177}$Lu, $^{67}$Cu, $^{47}$Sc

$^{213}$Bi, $^{212}$Bi, $^{212}$Pb, $^{211}$At

Phase 1 $^{211}$At-labeled chimeric 81C6 in recurrent brain tumor patients

Alpha-immunotherapy of multiple myeloma

Bismuth-213-labelled anti-CD138 injected i.v. C57 Bl/KaLwRij mice

Courtesy of Michel Chérel and François Davodeau
<table>
<thead>
<tr>
<th>Use</th>
<th>Radionuclide</th>
<th>T1/2 (hr)</th>
<th>Emission</th>
<th>Emax (keV)</th>
<th>Production</th>
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<tbody>
<tr>
<td>Gamma Imaging</td>
<td>Iodine-131</td>
<td>193</td>
<td>β⁺, γ</td>
<td>610, 362</td>
<td>Reactor</td>
</tr>
<tr>
<td></td>
<td>Iodine-123</td>
<td>13.3</td>
<td>γ</td>
<td>159</td>
<td>Cyclotron</td>
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<tr>
<td></td>
<td>Technetium-99m</td>
<td>6.0</td>
<td>γ</td>
<td>141</td>
<td>Reactor (Generator)</td>
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<tr>
<td></td>
<td>Indium-111</td>
<td>67</td>
<td>γ</td>
<td>171, 245</td>
<td>Cyclotron</td>
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<td></td>
<td>Gallium-67</td>
<td>78</td>
<td>β⁺, γ</td>
<td>607-907, 93</td>
<td>Cyclotron</td>
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<td>PET</td>
<td>Carbon-11</td>
<td>0.34</td>
<td>β⁺</td>
<td>961</td>
<td>Cyclotron</td>
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<tr>
<td></td>
<td>Fluorine-18</td>
<td>1.8</td>
<td>β⁺</td>
<td>633</td>
<td>Cyclotron</td>
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<tr>
<td></td>
<td>Scandium-44/44m</td>
<td>3.9/59</td>
<td>β⁺</td>
<td>1474</td>
<td>Cyclotron (Generator)</td>
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<tr>
<td></td>
<td>Gallium-68</td>
<td>1.1</td>
<td>β⁺</td>
<td>1899</td>
<td>Cyclotron (Generator)</td>
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<td></td>
<td>Copper-64</td>
<td>12.7</td>
<td>β⁺, β⁻</td>
<td>653, 1675</td>
<td>Cyclotron</td>
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<tr>
<td></td>
<td>Iodine-124</td>
<td>100.2</td>
<td>β⁺</td>
<td>1535 and 2138</td>
<td>Cyclotron</td>
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<tr>
<td></td>
<td>Zirconium-89</td>
<td>78.4</td>
<td>β⁺, γ</td>
<td>897, 909</td>
<td>Cyclotron</td>
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<tr>
<td>Therapy</td>
<td>Iodine-131</td>
<td>193</td>
<td>β⁺, γ</td>
<td>610, 362</td>
<td>Reactor</td>
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<td></td>
<td>Yttrium-90</td>
<td>64</td>
<td>β⁻</td>
<td>2250</td>
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<td></td>
<td>Rhenium-188</td>
<td>17</td>
<td>β⁺, γ</td>
<td>2120, 155</td>
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<tr>
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<td>Lutetium-177</td>
<td>161</td>
<td>β⁺, γ</td>
<td>498, 208</td>
<td>Reactor</td>
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<tr>
<td></td>
<td>Copper-67</td>
<td>61.8</td>
<td>β⁺, γ</td>
<td>392-577, 185</td>
<td>Cyclotron</td>
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<td>Scandium-47</td>
<td>80</td>
<td>β⁺, γ</td>
<td>441, 159</td>
<td>Cyclotron</td>
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<tr>
<td></td>
<td>Bismuth-213</td>
<td>0.76</td>
<td>α, γ</td>
<td>5869 and 8376</td>
<td>Nuclear waste (Generator)</td>
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<tr>
<td></td>
<td>Astatine-211</td>
<td>7.2</td>
<td>α, X</td>
<td>5869 and 7450</td>
<td>Cyclotron</td>
</tr>
</tbody>
</table>
The Arronax building
 Vaults and beam lines
The cyclotron (Vault CC)
Vault doors

Motorized door on rails (35 t)
Beam switches
AX Vault: radiolysis and radiobiology
Radionuclide production beam line

Targetry system
Shielded hoods
Main characteristics:
High energy - High intensity

<table>
<thead>
<tr>
<th>Beam</th>
<th>Accelerated particles</th>
<th>Energy range (MeV)</th>
<th>Intensity (µA)</th>
<th>Dual beam</th>
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</thead>
<tbody>
<tr>
<td>Proton</td>
<td>H⁻</td>
<td>30-70</td>
<td>&lt;375</td>
<td>Yes</td>
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<tr>
<td></td>
<td>HH⁺</td>
<td>17</td>
<td>&lt;50</td>
<td>No</td>
</tr>
<tr>
<td>Deuteron</td>
<td>D⁻</td>
<td>15-35</td>
<td>&lt;50</td>
<td>Yes</td>
</tr>
<tr>
<td>Alpha</td>
<td>He⁺⁺</td>
<td>68</td>
<td>&lt;70</td>
<td>No</td>
</tr>
</tbody>
</table>

Specifications have been achieved and the cyclotron is fully operational since January 2011
375 µA on each target

Neutrals: less than 10 %.

24 hours
Arronax missions

• To produce radionuclides for research purposes (Nuclear Medicine)
  – Not suitable to produce fluorine-18 or carbon-11. A priority list of radionuclides has been set.
• To serve as an irradiation facility for radiolysis and radiobiology research projects
  – Alpha particle pulsed beam, protons, gammas (cesium-137 source), even neutrons (Adiabatic Resonance Crossing system with AAA).
• To produce radionuclide for commercial purposes and help regional economy development
• To participate in student (University and Ecole des Mines) and professional training

Major projects

• Alpha-immunotherapy (cooperation with the Oncology Research team of the Nantes-Angers Cancer Research Center, Chelatec and Atlab Pharma)
  – Production of astatine-211
  – Treatment of multiple myeloma and prostrate cancer (AlphaRIT consortium)

• Brachytherapy (cooperation with AAA)
  – Neutron activation for the production of holmium-166
  – Treatment of liver cancer (Theranean consortium)

• Pairs of electron/positron emitters for targeted radionuclide therapy
  – Copper-67/copper-64
  – Scandium-47/scandium-44

• Studies of water radiolysis with the pulsed alpha-beam in the context of nuclear waste storage

• Pulsed alpha-beam for radiobiology studies

• Industrial projects
  – Strontium-82 for strontium-82/rubidium-82 generators (TEP in cardiology)
  – Germanium-68 for germanium-68/gallium-68 generators (TEP in oncology)
Strontium-82 production: target

\[ ^{85}\text{Rb} + p \rightarrow ^{82}\text{Sr} + 4n \]

- **Pressed** pellet of RbCl
  
Purity > 99.8%
  
  mass = 4.0 g

- **Encapsulated** in laser welded stainless steel

- **Dual target**
Specifications of the final product

- **Total Radioactivity** at Calibration Time

- **Specific Activity*** ≥ 925MBq/mg (≥ 25mCi/mg)

- **Activity concentration*** ≥ 1850MBq/mL (≥ 50mCi/ml)

- **Radionuclide identity**
  Energy of major photoelectric peak having energy of 776.5keV via the Rb-82 daughter at the equilibrium

- **Radionuclide purity***

  \[
  ^{85}\text{Sr} \leq 5 \text{ GBq/GBq}^{82}\text{Sr} \ (\leq 5\text{mCi} \ ^{85}\text{Sr}/\text{mCi} \ ^{82}\text{Sr})
  \]

  \[
  ^{83}\text{Rb} \leq 0.0015 \text{ GBq/GBq}^{82}\text{Sr} \ (\leq 0.0015 \text{mCi} \ ^{83}\text{Rb}/\text{mCi} \ ^{82}\text{Sr})
  \]

  \[
  ^{84}\text{Rb} \leq 0.0015 \text{ GBq/GBq}^{82}\text{Sr} \ (\leq 0.0015 \text{mCi} \ ^{84}\text{Rb}/\text{mCi} \ ^{82}\text{Sr})
  \]

  \[
  ^{83}\text{Sr} \leq 0.0015 \text{ GBq/GBq}^{82}\text{Sr} \ (\leq 0.0015 \text{mCi} \ ^{83}\text{Sr}/\text{mCi} \ ^{82}\text{Sr})
  \]

  All other radiocontaminants ≤ 0.01 GBq/GBq \(^{82}\text{Sr}\) (≤ 0.01 mCi/mCi \(^{82}\text{Sr}\))

- **Appearance**: Clear, colorless solution

*specifications are given at the calibration time (7 days after ship date)

This radiochemical is not tested for sterility or pyrogenicity.
Copper-64 production

\[ ^{64}\text{Ni} + p \rightarrow n + ^{64}\text{Cu} \]

Target: electroplated nickel-64 on a gold support

Extraction yield: >90%
Radionuclide purity > 99.9%
Ni recovery >90%

Production started at Arronax in September 2011
Astatine-211 production

\[ ^{209}\text{Bi} + \text{alpha} \rightarrow ^{211}\text{At} + 2\text{n} \]

Bismuth deposited under vacuum on AlN

Extraction by distillation

Production: 200-300MBq /week at CEMHTI/CNRS (Orléans, France)

Yield: around 80%

Production is expected to start at Arronax 1\textsuperscript{er} semester of 2012
Optimisation of radionuclide production

- To calculate expected activities
  - development of an analytical calculation code
  - use of Monte-Carlo codes

\[ A_{ct} = \phi \frac{N_A \cdot \rho}{A} \left(1 - e^{-\lambda t}\right) \int_{E_{min}}^{E_{max}} \frac{\sigma(E)}{dE/dx} dE \]

- Measurement of production cross section
  - Development of an experimental device on ARRONAX (stacked foils)

Results

\[ ^{nat}Ti(p,X)^{44}Sc \]
Proton Induced X-ray Emission at ARRONAX

- High energy PIXE at ARRONAX (up to 70MeV)
  - information deeper than the surface
  - multi layer analysis (RX and gamma information)
  - various type of incident particles (p, d, alpha)
- Feasibility studies in progress
Conclusion

• Nuclear Medicine is making progress in imaging (PET) and therapy (Targeted Radionuclide Therapy)
• Radionuclides other than the traditional ones are needed
• Arronax will supply some of these as it is a now running with the original specifications met
• Production of radionuclides and radiochemistry experiments have started
• We still need a few months to deliver radionuclides to research teams and industry
• One challenge will be for us to be capable of producing radionuclides such as strontium-82 or copper-67 at the very high intensities that the cyclotron can deliver
• Another challenge will be to meet GMP standards
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  - V. Métivier
  - A. Guertin
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  - J.M. Buhour