RADIOISOTOPES in MEDICINE:
Requirements - Production - Application and future prospectives

4
Isotopes for future Nuclear Medicine

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THIRD INTERNATIONAL SUMMER STUDENT SCHOOL
NUCLEAR PHYSICS METHODS AND ACCELERATORS IN BIOLOGY AND MEDICINE
Dubna, July 01-11, 2005
NUCLEAR MEDICINE 2005

**DIAGNOSIS**

**SPECT** (SINGLE PHOTON EMISSION TOMOGRAPHY)
- increase of diagnostic value
- new radiopharmaceuticals
- dedicated instrumentation & quantification

**PET AS RESEARCH TOOL**
- Molecular in vivo biochemistry
- Gene expression
- Clinical research

**PET AS CLINICAL TOOL**
- Oncology
  - Reimbursement of FDG-studies
- Neurology
- Cardiology

**Multi-modality Imaging**
- combined SPECT-PET
  - (image of the year at the 46.SNM)
- Function and morphology
  - \( PET - CT \)

**THERAPIE**

**NEW APPROACHES IN RADIONUCLIDE THERAPY**
- bio-selective antibodies
  - (mab = monoclonal antibodies)
- bio-specific peptides
  - (Octreotides, others)
- gene therapy
- free chelators like EDTMP
- Lyposomes
- Nanoparticles

**NEW RADIONUCLIDES for THERAPY**
- \( \beta \)-emitters
- \( \alpha \)-emitters

\( \alpha \)-THERAPY & AUGER THERAPY

**PET FOR IN VIVO DOSIMETRY**
- metallic positron emitters
- labelled drugs
- dose localization

G.BEYER (HUG, Geneva, 2005)
Future Demand for Isotopes in Medicine

Status 1998, USA only:

Health care totally: \( \text{ca. } 10^{12} \text{ US$} \)
Surgery: \((50-100) \times 10^9 \text{ US$}\)
Radiation: \((1-5) \times 10^9 \text{ US$}\)

Roy Brown: \(10^7\) nucl. med. examinations per year

Richard Reba: Isotope demand for therapy only
1996: \(48 \times 10^6 \text{ US$}\)
2001: \(62 \times 10^6 \text{ US$}\)
2020: \(6000 \times 10^6 \text{ US$}\)

Résumé from the Medical Isotope Workshop, Dallas, May 2-3, 1998
CANCER

About 1 000 000 new cancer cases per year in EU (15)
58 % local disease, 42 % generalized

45 % cured (5 year survival)

22 % surgery alone
12 % radiation therapy
6 % combination surgery + radiation
5 % chemo-therapy

just beginning of systemic radionuclide therapy

HOW: expose cancer cells or cancer tissue with sufficient radiation doses?
**ISOTOPES in Therapy = surgery with radiation**

<table>
<thead>
<tr>
<th>ISOTOPE</th>
<th>Tissue surgery</th>
<th>Cell surgery</th>
<th>Molecular surgery</th>
</tr>
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<td>ISOTOPE</td>
<td>131I, 90Y, 153Sm, 166Ho, 177Lu Others Eβ 1 – 3 MeV</td>
<td>212, 213 Bi, 211At, 149Tb, 223, 224Ra Eα 4–8 MeV</td>
<td>125I 165Er Ee few eV</td>
</tr>
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<td>Range</td>
<td>about 1 cm</td>
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<td>1 µm</td>
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<tr>
<td>β-Knife</td>
<td></td>
<td>α-Knife</td>
<td>Auger Knife</td>
</tr>
</tbody>
</table>
Brachytherapy

Local Eradication of a Tumor by Radioactive Implants

Theragenics

IBt
RIT = RADIOISOTOPE THERAPY
or RADIOIMMUNO THERAPY
or systemic radionuclide therapy

1936 $^{32}$P against leukemia, J.H.Lawrence
1939 $^{89}$Sr uptake in bone metastases, C.Pecher
1946 $^{131}$I treatment of thyroid cancer, S.M.Seilin et al.
1963 Radioactive colloides, B.Ansell et al
1976 $^{89}$Sr against pain from bone metastases, N.Firusian
1978 Radiolabelled mab, D.Goldenberg
1982 Treatment with $^{131}$I labelled mab, S.Larson et al.
1990 Somatostatine receptor binding tracers, E.Krenning
1993 $^{89}$Sr, FDA approval
2000 FDA approval of $^{131}$I-CD20 against Lymphoma?

Development of therapeutics delayed
X-ray Structure of Y-DOTA-D-PheNH₂ a Model DOTA-Peptide Conjugate

distorted square antiprismatic geometry

m₂-type

Δ(δδδδ) configuration

O₄-N₄ 2.51 Å
O₄-Y 1.22 Å
N₄-Y 1.29 Å

H.Mäcke, Basel
Rats with SSR-positive tumours in liver model mimics disseminated disease ⇒ PRRT
(PRRT = Peptide Receptor Radionuclide Therapy)
Questions to be answered:

- Relationship between radiation dose delivered to a lesion and the therapeutic response
  * In vivo dosimetry by quantitative PET imaging
  * Need for $\beta^+$-emitting metallic radionuclides

- Relationship between beta-energy and therapeutic response
  * Variation of radionuclides with different $\beta$-energy
  * Need for metallic $\beta^-$-emitters with very different energy
\(\beta^-\) emitter for therapy
RIT = RADIOISOTOPE THERAPY
or
RADIOIMMUNO THERAPY

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>$E_{\beta_{\text{max}}} \text{[MeV]}$</th>
<th>Range [mm]</th>
<th>$T_{1/2}$ [h]</th>
<th>photons [keV]</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{90}\text{Y}$</td>
<td>2.3</td>
<td>4.2</td>
<td>64.1</td>
<td>no</td>
<td>Easy available</td>
</tr>
<tr>
<td>$^{188}\text{Re}$</td>
<td>2.1</td>
<td>17</td>
<td>155</td>
<td>(81 keV)</td>
<td>Difficult, generator</td>
</tr>
<tr>
<td>$^{166}\text{Ho}$</td>
<td>1.9</td>
<td>0.7</td>
<td>26.8</td>
<td>(81 keV)</td>
<td>difficult</td>
</tr>
<tr>
<td>$^{89}\text{Sr}$</td>
<td>1.5</td>
<td>50.5</td>
<td>no</td>
<td></td>
<td>Palliation only</td>
</tr>
<tr>
<td>$^{186}\text{Re}$</td>
<td>1.1</td>
<td>90.6</td>
<td>137</td>
<td></td>
<td>Carrier</td>
</tr>
<tr>
<td>$^{153}\text{Sm}$</td>
<td>0.8</td>
<td>0.269</td>
<td>46.8</td>
<td>103</td>
<td>Easy, carrier</td>
</tr>
<tr>
<td>$^{131}\text{I}$</td>
<td>0.8</td>
<td>8.04</td>
<td>(364keV)</td>
<td></td>
<td>Most common</td>
</tr>
<tr>
<td>$^{177}\text{Lu}$</td>
<td>0.5</td>
<td>0.147</td>
<td>6.7</td>
<td>113/208</td>
<td>Not easy</td>
</tr>
<tr>
<td>$^{67}\text{Cu}$</td>
<td>0.4/0.6</td>
<td>61.9</td>
<td>185</td>
<td></td>
<td>Interesting</td>
</tr>
<tr>
<td>$^{47}\text{Sc}$</td>
<td>0.4/0.6</td>
<td>80.4</td>
<td>159</td>
<td></td>
<td>interesting</td>
</tr>
<tr>
<td>$^{169}\text{Er}$</td>
<td>0.3</td>
<td>0.1</td>
<td>9.4</td>
<td>no</td>
<td>soft</td>
</tr>
</tbody>
</table>
Beta spectra

Intensity as % betas per 1 keV channel

- $^{144}$Ce: 319 keV
- $^{144}$Pr: 2998 keV
- $^{169}$Er: 351 keV
- $^{177}$Lu: 498 keV
- $^{47}$Sc: 600 keV
- $^{153}$Sm: 808 keV
- $^{143}$Pr: 934 keV
- $^{166}$Ho: 1855 keV
- $^{90}$Y: 2300 keV
Why metallic radionuclides?

• $^{131}$I cannot fulfill all requirements (weak in vivo stability)
• We learnt to make bio-conjugates, that contain chelating groups
• Universality: the chelated bio-conjugates can be labelled practically with any metallic radionuclide of group III and group IV elements
• The radiolabeled bio-conjugates are stable in vivo
• The bio-selective ligands are mainly monoclonal antibodies or peptides
$\beta^+$ emitters
for
in vivo dosimetry
Scintigraphic abdominal images 5 & 24 h p.i. affected by carcinoid with extensive hepatic and paraaortal metastases.

Patients:
- 3 patients with metastases of carcinoid tumor (histologically confirmed)
- No therapy with unlabeled somatostatin > 4 weeks
- Age: 46 – 67 years, male
- All were candidates for a possible $^{90}$Y-DOTATOC therapy
Radiation doses for $[^{90}\text{Y}]\text{DOTATOC}$ therapy
(based on $[^{86}\text{Y}]\text{DOTATOC-PET}$)

Patient #1
Patient #2
Patient #3

$D_{\text{tumor}}$ (mGy/MBq)

25
20
15
10
5
0

$[^{86}\text{Y}]\text{-DOTATOC}$
$[^{111}\text{In}]\text{-DTPA-octreotide}$

Large discrepancies in tumor masses

H. Wagner Jr: A diagnostic dosimetric imaging procedure will be unavoidable a part of the protocol for the radioimmuno therapy (individual in vivo dosimetry).

F. Rösch et al.
<table>
<thead>
<tr>
<th>Nuclide</th>
<th>T½</th>
<th>% β⁺</th>
<th>MeV</th>
<th>MeV γ / %</th>
<th>Production Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>⁴³Sc</td>
<td>3.9 h</td>
<td>88</td>
<td>1.2</td>
<td></td>
<td>⁴³Ca (p,n) ⁴³Sc, ⁴⁴Ca (p,2n) ⁴³Sc</td>
</tr>
<tr>
<td>⁴⁴Sc</td>
<td>3.9 h</td>
<td>94</td>
<td>1.5</td>
<td></td>
<td>⁴⁴Ti decay (generator), ⁴⁵Sc (p,2n) ⁴⁴Ti V, Ti (p,spall)</td>
</tr>
<tr>
<td>⁸⁵ᵐY</td>
<td>4.9 h</td>
<td>67</td>
<td>2.3</td>
<td>238 34</td>
<td>⁸⁶Sr (p,2n) ⁸⁵ᵐY, ISOLDE</td>
</tr>
<tr>
<td>⁸⁶Y</td>
<td>14.7 h</td>
<td>32</td>
<td>1.2</td>
<td>637 33 1077 83</td>
<td>⁸⁶Sr (p,n) ⁸⁶Y ISOLDE</td>
</tr>
<tr>
<td>¹³⁴Ce</td>
<td>75.9 h</td>
<td>EC</td>
<td>2.7</td>
<td>No 605</td>
<td>Ta, Er, Gd (p,spall) ¹³²Ba (α,2n) ¹³⁴Ce</td>
</tr>
<tr>
<td>¹³⁴Pr</td>
<td>6.7 m</td>
<td>64</td>
<td>2.7</td>
<td></td>
<td>Ta, Er, Gd (p,spall) ¹³⁶Ce (α,2n) ¹³⁸Nd, ISOLDE</td>
</tr>
<tr>
<td>¹³⁸Nd</td>
<td>5.2 h</td>
<td>EC</td>
<td>3.4</td>
<td>No 789 4</td>
<td>Ta, Er, Gd (p,spall) ¹³⁶Ce (α,2n) ¹³⁸Nd, ISOLDE</td>
</tr>
<tr>
<td>¹³⁸Pr</td>
<td>1.5 m</td>
<td>76</td>
<td>3.4</td>
<td></td>
<td>Ta, Er, Gd (p,spall), ISOLDE ¹⁴¹Pr (p,2n) ¹⁴⁰Nd,</td>
</tr>
<tr>
<td>¹⁴⁰Nd</td>
<td>3.4 d</td>
<td>EC</td>
<td>2.4</td>
<td>No  No</td>
<td>Ta, Er, Gd (p,spall), ISOLDE ¹⁴¹Pr (p,2n) ¹⁴⁰Nd,</td>
</tr>
<tr>
<td>¹⁴²Sm</td>
<td>72.4 m</td>
<td>6</td>
<td>1.5</td>
<td>No  No</td>
<td>Ta, Er, Gd (p,spall), ISOLDE ¹⁴²Nd (α,4n) ¹⁴²Sm</td>
</tr>
<tr>
<td>¹⁴²Pm</td>
<td>40.5 s</td>
<td>78</td>
<td>3.9</td>
<td></td>
<td>Ta, Er, Gd (p,spall), ISOLDE ¹⁴²Nd (α,4n) ¹⁴²Sm</td>
</tr>
<tr>
<td>¹⁵²Tb</td>
<td>17.5 h</td>
<td>20</td>
<td>2.8</td>
<td>Div</td>
<td>Ta (p,spall) ISOLDE ¹⁵²Gd (p,4n) ¹⁴⁹Tb, ¹⁴²Nd(¹²C,5n)¹⁴⁹Dy</td>
</tr>
</tbody>
</table>
Positron emitting radiolanthanides

PET phantom studies

$^{134}$Ce/La
$^{140}$Nd/Pr
$^{149}$Tb

$^{138}$Nd/Pr
$^{142}$Sm/EDTMP in vivo study
$^{142}$Sm/Pm
$^{152}$Tb
### ISOTOPES in Therapy = surgery with radiation

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<td>α-Knife</td>
<td>Auger Knife</td>
<td></td>
</tr>
</tbody>
</table>

#### Range
- **β-Knife**: about 1 cm
- **α-Knife**: 30 – 80 µm
- **Auger Knife**: 1 µm
$\alpha$-emitters for therapy
### Alpha Emitters for Therapy

<table>
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<tr>
<th>Element</th>
<th>Half-Life</th>
<th>Process Description</th>
<th>Decay Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{225}$Ac</td>
<td>10 d</td>
<td>$^{233}$U decay chain</td>
<td>$^{226}$Ra (p,2n) $^{225}$Ac</td>
</tr>
<tr>
<td>$^{224}$Ra</td>
<td>3.66 d</td>
<td>$^{228}$Th ($\alpha$-decay)</td>
<td>$^{226}$Ra ($n,\gamma$) $^{227}$Ac</td>
</tr>
<tr>
<td>$^{223}$Ra</td>
<td>11.4 d</td>
<td>$^{227}$Ac decay chain</td>
<td>$^{226}$Ra ($n,\gamma$) $^{227}$Ac</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>45.6 m</td>
<td>$^{225}$Ac decay chain</td>
<td>Ac–Bi generator</td>
</tr>
<tr>
<td>$^{212}$Bi</td>
<td>60 m</td>
<td>$^{224}$Ra decay chain</td>
<td>Ra–Bi/Pb generator</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>7.2 h</td>
<td></td>
<td>$^{209}$Bi ($\alpha$,$2n$) $^{211}$At</td>
</tr>
<tr>
<td>$^{149}$Tb</td>
<td>4.1 h</td>
<td></td>
<td>Ta (p,spall) $^{152}$Gd (p,4n) $^{149}$Tb</td>
</tr>
<tr>
<td>$^{255}$Fm</td>
<td>20.1 h</td>
<td>$^{255}$Ei (39.8 d)-decay</td>
<td>$^{255}$Ei - $^{255}$Fm generator</td>
</tr>
</tbody>
</table>
2 days later the mice have been divided into 4 groups:

1. NO treatment
2. 10^5 lymphoma cells injected to all mice (Daudi cells of Burkitt lymphoma)
3. 5 µg MoAb (Rituximab, specific to CD20 antigens of B cells)
4. 300 µg MoAb

First in vivo experiment to demonstrate the efficiency of alpha targeted therapy using ^{149}Tb produced at ISOLDE, Summer 2001
Survival of SCID mice

- 5 MBq $^{149}$Tb, 5 µg MoAb
- 300 µg MoAb, cold
- 5 µg MoAb, cold

G.J.Beyer, M.Miederer, J.Comor et al. EJNM 2004, 31 (4), 547-554
103 d p.i. 300 µg mab cold

108 d p.i. 5 MBq $^{149}$Tb-mab (5 µg)
AUGER electron emitters for therapy
- Only very few radionuclides exist that decay exclusively by EC-mode without any accompanying radiation.
- $^{165}$Er is one of them.
- All labeling techniques used for the three-valent radionuclides can be adapted without modifications.
- Generated in the EC-decay of the mother isotope $^{165}$Tm.
- Production routes suitable for the TESLA accelerator:
  
  **Yield:**
  
  $^{165}$Ho ($p,n$) $^{165}$Er
  
  $^{165}$Ho ($p,n$) $^{165}$Er
  
  15 MeV $p$
  
  50 $\mu$A
  
  5 h
  
  10 GBq

G. J. Beyer, S. K. Zeisler and D. W. Becker

Radiochimica Acta 92 (4-6), 219, 2004
Isotope Production with Cyclotrons

The classical SPECT isotopes are produced via the (p,2n) process, the related p-energy is ~25 MeV.

Because of the continuous high demand of $^{201}$Tl, the (p,3n) is usually considered as a main product. The upper p-energy for producing $^{201}$Tl is 30 MeV.

The short-lived PET isotopes are based mainly on the (p,n) process, ~15 MeV is the preferable proton energy. Normally dedicated small cyclotrons are used for PET. However, due to the high standard of targetry and production technology a large scale FDG-production can be integrated economically today into the program of a larger cyclotron, because of the low beam time demand.

New trends in radioimmuno therapy require alpha emitting nuclides. The $^{211}$At needs to be produced via the ($\alpha$,2n) Process. The related $\alpha$-energy is 28 MeV.

A cyclotron, that can accelerate alpha particles to 28-30 MeV can principally accelerate p to energies higher than 30 MeV. Consequently, higher reaction processes such as (p,4n) or generally (p,xn) or even (p,xn,yp) processes are possible.

Such a multipurpose cyclotron with the option of high particle beam intensity and well developed tools for beam diagnosis and a certain variation of particle beam energy is an excellent universal instrument supporting commercial isotope production and R&D in the field of medical isotope application for diagnosis and therapy.
Commercial Isotope Production with cyclotrons
\(~30 \text{ MeV proton beam}\)

- \( {}^{201}\text{Tl} \): \( {}^{203}\text{Tl} (\text{p,3n}) {}^{201}\text{Pb} \rightarrow {}^{201}\text{Tl} \)
  
  most important SPECT isotope, commercialized by all radiopharmaceutical Co. The worldwide installed production capacity exceeds the demand.

- \( {}^{123}\text{I} \): \( {}^{124}\text{Xe} (\text{p,2n}) {}^{123}\text{Cs} \rightarrow {}^{123}\text{I} \)
  
  very important SPECT isotope, corresponding target design from Karlsruhe is installed worldwide. Batch size up to 10 Ci possible.

- \( {}^{111}\text{In} \): \( {}^{112}\text{Cd} (\text{p,2n}) {}^{111}\text{In} \)
  
  important for certain SPECT techniques, expensive because of low demand.

- \( {}^{67}\text{Ga} \): \( {}^{68}\text{Zn} (\text{p,2n}) {}^{67}\text{Ga} \)
  
  easy to make, low and decreasing demand.
Target station for the production of $^{201}$TI with beam diagnosis elements and Automatic active target transport chain
Isotope Production with Cyclotrons

(p,n) process with ~15 MeV protons

- **18F**: $^{18}O (p, n) ^{18}F$
  most important PET isotope, commercialized by many centers using dedicated small cyclotrons, however also done at 30 MeV or even at 65 MeV cyclotrons as well (Nice)

- **124I**: $^{124}Te (p, n) ^{124}I$
  very important PET isotope with commercial interest (in-vivo dosimetry), large scale production technology not yet available, same technology could be used for medium scale $^{123}I$ production based on $^{123}Te$ target material

- **86Y**: $^{86}Sr (p, n) ^{86}Y$
  very important PET isotope with commercial interest (in-vivo dosimetry)

- **64Cu**: $^{64}Ni (p, n) ^{64}Ga$
  easy to make, therapeutic isotope for RIT, PET allows the measurement of the biodistribution in situ.

- **186Re**: $^{186}W(p,n) ^{186}Re$
  $^{186}Re$ (3.7 d) is one of the two important therapeutic isotopes of Re. The advantage over $^{188}Re$ (16 h) is the longer half-life, the advantage over the reactor based $^{185}Re(n,\gamma) ^{186}Re$ process is the carrier free quality.

- **Remark**: The (p,n) process requires ~15 MeV only, and is performed normally at dedicated small PET cyclotrons. However, due to the high productivity of dedicated targets combined with a modern system for beam diagnosis allows to run these reaction under economical conditions at larger cyclotrons as well using only a small fraction of the available beam time.
COSTIS : Test Installation in Belgrade

COSTIS and its constructors at the low energy beam line of the mVINIS ECR ion source at the TESLA Accelerator Installation in Belgrade, Yugoslavia
Production of other useful isotopes with < 20 MeV proton induced reactions

<table>
<thead>
<tr>
<th>Isotope</th>
<th>T 1/2</th>
<th>Reaction</th>
<th>Batch size</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>45Ti</td>
<td>3.08 h</td>
<td>nat-Sc (p,n) 45Ti</td>
<td>100 GBq</td>
<td>PET: bioconjugates</td>
</tr>
<tr>
<td>55Co</td>
<td>17.54 h</td>
<td>nat-Fe (p,2n) 55Co</td>
<td>50 GBq</td>
<td>PET, enzymes, vitamins</td>
</tr>
<tr>
<td>64Cu</td>
<td>12.7 h</td>
<td>64Ni (p,n) 64Cu</td>
<td>100 GBq</td>
<td>PET &amp; therapy,</td>
</tr>
<tr>
<td>67Cu</td>
<td>61.9 h</td>
<td>70Zn (p,α) 67Cu</td>
<td>50 GBq</td>
<td>therapy, bioconjugates</td>
</tr>
<tr>
<td>66Ga</td>
<td>9.4 h</td>
<td>66Zn (p,n) 66Ga</td>
<td>50 GBq</td>
<td>PET</td>
</tr>
<tr>
<td>76Br</td>
<td>16 h</td>
<td>76Se (p,n) 76Br</td>
<td>10 GBq</td>
<td>PET</td>
</tr>
<tr>
<td>81Rb</td>
<td>4.58 h</td>
<td>82Kr (p,2n) 81Rb</td>
<td>20 GBq</td>
<td>Generator, SPECT</td>
</tr>
<tr>
<td>86Y</td>
<td>14.7 h</td>
<td>86Sr (p,n) 86Y</td>
<td>50 GBq</td>
<td>PET, bioconjugates</td>
</tr>
<tr>
<td>89Zr</td>
<td>78.4 h</td>
<td>89Y (p,n) 89Zr</td>
<td>20 GBq</td>
<td>PET, bioconjugates</td>
</tr>
<tr>
<td>90Nb</td>
<td>14.6 h</td>
<td>90Zr (p,n) 90Nb</td>
<td>20 GBq</td>
<td>PET, bioconjugates</td>
</tr>
<tr>
<td>94Tc</td>
<td>4.9 h</td>
<td>94Mo (p,n) 94Tc</td>
<td>20 GBq</td>
<td>PET</td>
</tr>
<tr>
<td>110In</td>
<td>69.1 m</td>
<td>110Cd (p,n) 110In</td>
<td>20 GBq</td>
<td>PET</td>
</tr>
<tr>
<td>120I</td>
<td>1.35 h</td>
<td>120Te (p,n) 120I</td>
<td>10 GBq</td>
<td>PET</td>
</tr>
<tr>
<td>123I</td>
<td>13.2 h</td>
<td>123Te (p,n) 123I</td>
<td>20 GBq</td>
<td>SPECT</td>
</tr>
<tr>
<td>124I</td>
<td>4.15 d</td>
<td>124Te (p,n) 124I</td>
<td>2 GBq</td>
<td>PET</td>
</tr>
<tr>
<td>165Er</td>
<td>10.3 h</td>
<td>nat-Ho (p,n) 165Er</td>
<td>40 GBq</td>
<td>Auger Therapy</td>
</tr>
<tr>
<td>186Re</td>
<td>90.6 h</td>
<td>186W (p,n) 186Re</td>
<td>20 GBq</td>
<td>Therapy</td>
</tr>
</tbody>
</table>

The irradiation of solid materials requires much better beam quality parameters than gas targets. Consequently, beam homogenisation and beam manipulation is needed, usually not possible at the PET cyclotrons.

External beam lines, known from classical isotope production at cyclotrons, will take this function over.

The new generation of multi-purpose cyclotrons will be equipped with high-tech diagnostic tools and provide higher beam current than in the past.
PET-isotope production at the IBA 30 MeV cyclotron:

Target station at the end of one beam line equipped with 5 target ports

- $^{18}$F: $H_2^{18}O$ target
- $^{11}$C: $N_2$-target
- $^{15}$O: $N_2$-target

2 positions free
123-IODINE PRODUCTION ROUTES

\[ ^{123}\text{Cs} \xrightarrow{5.9 \text{ min}} ^{123}\text{Xe} \xrightarrow{2.08 \text{ h}} ^{123}\text{I} \]

123Cs \( \rightarrow \) 123Xe \( \rightarrow \) 123I

- 123Cs \rightarrow 123Xe
- 123Xe \rightarrow 123I

ALTERNATIVES:

- local 123 I production using PET cyclotrons
- \(^{123}\text{Te} (p,n) ^{123}\text{I}\)
- 15 MeV p, 150 MBq/µAh
- Fast, easy, reliable, clean product, suitable for direct labeling.
$^{124}\text{I}$: $^{124}\text{TeO}_2$ (p,n) $^{124}\text{I}$

$^{124}\text{I}$

- $T_{1/2} = 4.17$ d
- $\beta^+ = 22.8\%$
- $E_{\beta_{\text{max}}} = 2.1$ MeV

$\sim 13$ MeV, 0.45 mCi/µAh $^{124}\text{I}$

$^{123}\text{I} = 0.1\%$ EOB + 2 d

R.J. Ylimaki, M.Y. Kiselev, J.J. Čomor, G.-J. Beyer

- DEVELOPMENT OF TARGET DELIVERY AND RECOVERY SYSTEM FOR COMMERCIAL PRODUCTION OF HIGH PURITY IODINE-124

WTTC 10, Madison (USA), 2004

<table>
<thead>
<tr>
<th>Irradiation Energy (MeV)</th>
<th>$^{124}\text{I}$: (p,n)</th>
<th>$^{123}\text{I}$: (p,2n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>250</td>
<td>680</td>
</tr>
<tr>
<td>13</td>
<td>150 MBq</td>
<td>75 MBq</td>
</tr>
</tbody>
</table>

After 2 d: 178 / 51 MBq

---

![Graph showing 511 keV peak for $^{124}\text{I}$](image_url)
$^{86}\text{Sr} \ (p,n) \ ^{86}\text{Y}$
enriched $^{86}\text{SrO}$ target, Pt-backing,
$\sim 15$ MeV p
electrochemical separation technology
Yield: 3.2 mCi/µAh with 13 MeV,
[Rösch, 1990 ZfK-728]
10 – 50 GBq possible

511 keV
**Isotope Production with Cyclotrons**

**The (p,4n) process**

- **$^{82}\text{Sr}$**: $^{85}\text{Rb} (p,4n) ^{82}\text{Sr}$
  
  $^{82}\text{Sr}$ generates the short-lived $^{82}\text{Rb}$ (80 sec), which is an positron emitter. This generator nuclide is used for PET in nuclear cardiology. The low availability and the still relatively high price hampered a larger distribution so far. Produced at TRIUMF(Ca), Protvino (Ru), South Africa and LosAlamos. Liquid Rb-metal sealed in silver bodies is used as target. High beam intensity is used.

- **$^{52}\text{Fe}$**: $^{55}\text{Mn} (p,4n) ^{52}\text{Fe}$
  
  $^{52}\text{Fe}$ is an interesting radionuclide for PET, it generates the 20 min $^{52}\text{Mn}$ daughter nuclide that can be used in PET.

- **$^{149}\text{Tb}$**: $^{152}\text{Gd} (p,4n) ^{149}\text{Tb}$
  
  $^{149}\text{Tb}$ has shown its potential in TAT (targeted alpha therapy) as it is a partial alpha emitting nuclide and any bio-conjugate (monoclonal antibodies or peptides) can be easily labeled with this interesting nuclide.

---

**Graphical Representation**

- $^{52}\text{Fe} \xrightarrow{\beta^+, EC} ^{52}\text{Mn} \xrightarrow{\beta^+, EC} ^{52}\text{Cr}$

  - $\beta^+$ from $^{52}\text{Fe} - ^{52}\text{Mn}$
    - 55.0% 29.6%

---

**% betas per 1 keV channel**

- $^{52}\text{Fe}$
- $^{52}\text{Mn}$
Isotope Production with Cyclotrons
The ($\alpha$,2n) process

- $^{211}\text{At}$: $^{209}\text{Bi}(\alpha,2n)\; ^{211}\text{At}$

Among the very few suitable alpha emitting radionuclides for the $^{211}\text{At}$ turns out to be the most suitable candidate for the medical application (targeted alpha therapy) presently a subject of intense international research activity. The $^{211}\text{At}$ can be produced by irradiating of natural Bi targets with 28 MeV alpha particles. Newly developed targets allow a production on large scale: Production yield is $\sim 40\; \text{MBq/Ah}$, production batches of 10 GBq are technically possible. A typical patient dose for therapy will range between 0.4 and 2 GBq.
$^{211}$At (7.2h)

$^{207}$Bi ($\alpha,2n$) $^{211}$At

28 MeV, ~20 MBq/µAh
Segment of the decay chain $A = 149$

**Indirect production routes**
- $^{145}_{63}Eu$
  - $^{145}_{62}Sm$
  - $^{149}_{64}Gd$
- $^{149}_{63}Eu$

**Direct production routes**
- $^{149}_{66}Dy$
  - $^{149}_{65}Tb$
  - $^{145}_{63}Eu$

Decay modes and probabilities:
- $\beta^+ \sim 7\%$
- $EC + \beta^+ = 83\%$
- $EC (27/2^-) 2661.1$ ms
- $EC (7/2^-) 0$ ms
- $\alpha 0.022\%$
- $\alpha 16.7\%$
- $\alpha 0.00043\%$
- $1/2^+ 0$ ms

Stability times:
- $4.118$ h
- $5.93$ d
- $9.28$ d
- $340$ d
Indirect production routes

- $^{138}\text{Ce}(^{16}\text{O},5\text{n})^{149}\text{Dy}$
- $^{143}\text{Nd}(^{12}\text{C},6\text{n})^{149}\text{Dy}$
- $^{136}\text{Ce}(^{16}\text{O},3\text{n})^{149}\text{Dy}$
- $^{142}\text{Nd}(^{12}\text{C},5\text{n})^{149}\text{Dy}$
- $^{144}\text{Sm}(^{9}\text{Be},4\text{n})^{149}\text{Dy}$
- $^{152}\text{Gd} (\alpha,7\text{n})^{149}\text{Dy}$
- $^{152}\text{Gd} (\text{p}, 4\text{n})^{149}\text{Tb}$
Higher Quality is required
Why is high specific activity that important?

- The receptor density is low for peptide ligands
- The infusion speed is limited for certain therapeutical approaches
- We do not want to dilute our biospecific ligands with inactive atoms
Influence of production mode for $^{177}$Lu $^{176}$Lu-route versus $^{176}$Yb-route

Wouter A.P. Breeman
Erasmus MC Rotterdam
The Netherlands

$^{200}$ MBq $^{177}$Lu of NRG vs Nordion

Factor of 4

Low carrier - shorter infusion time

200 MBq $^{177}$Lu
incubation:
- pH = 4.5
- T = 80 oC
- T = 20 min
Peptide variation
• R&D needed for development of alternative technologies producing carrierfree radioisotope preparations for therapy.

• Reactor versus cyclotron production routes:
  \[ ^{185}\text{Re} \text{(n,}\gamma\text{)}^{186}\text{Re} \quad // \quad ^{186}\text{W} \text{(p,n)}^{186}\text{Re} \]
  \[ \text{67Cu} \]
  others

• Other alternatives:
  spallation reaction (CERN)
  isotope separation (of radioactive preparations)
Radiolanthanides at ISOLDE

spallation or fission
1 or 1.4 GeV protons
pulsed beam, $3 \times 10^{13}$ p/pulse (~1µA)
Ta-foil- or U-carbide target
Surface ionization ion source
122 g/cm$^2$ Ta (rolls of 25 µm foils)
  at 2400 °C
W-tube as ionizer at 2800°C
Radioactive Ion Beams of
40 elements possible today

<table>
<thead>
<tr>
<th>mass number</th>
<th>148</th>
<th>149</th>
<th>150</th>
<th>151</th>
<th>152</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Alternative Production Route:

high energy proton induced Spallation Reaction
1 MW target for $10^{15}$ fissions per s
Hg-jet p-converter target
The SNS neutron source target station under construction

- Operating pressure: 100 Bar
- Flow rate: 2 t/m
- Jet speed: 30 m/s
- Jet diameter: 10 mm
- Temperature:
  - Inlet to target: 30°C
  - Exit from target: 100°C
- Power absorbed in Hg-jet: 1 MW
- Total Hg inventory: 10 t
- Pump power: 50 kW
The MEGAPIE 1MW molten PbBi target under construction at PSI

Operation scheduled for 2006
What can nuclear centers do?

- Own specific medical isotope programs
- Keep existing classical facilities running ($^{211}$At)
- Alternative ways for isotope production
- High-tech radiochemistry
- Integrate physical methods into the isotope programs (mass separation for example)
- Collaboration with bio-chemistry and medicine (oncology, radiology, nuclear med.)
- International collaboration and integration into existing research network

G.Beyer, PLSRNC-1, Varna (Bulgaria) 21-27 Sept. 2003