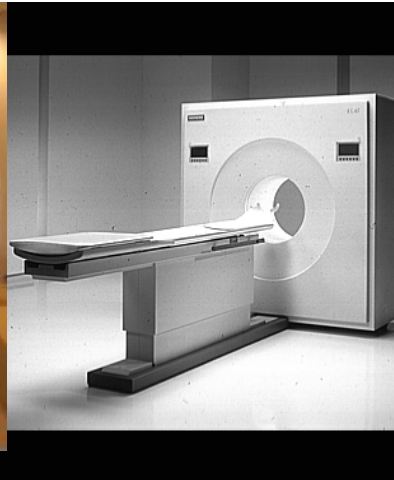


Isotopes for Nuclear Medicine

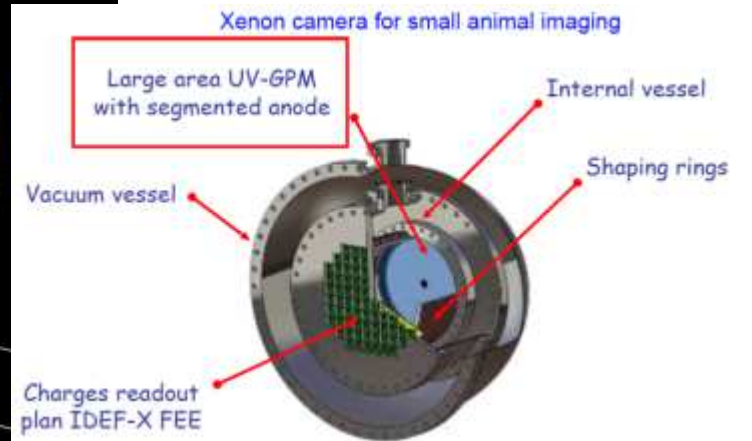
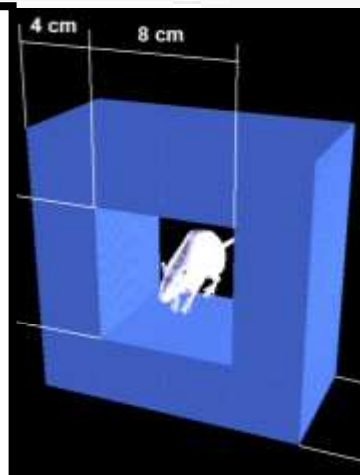
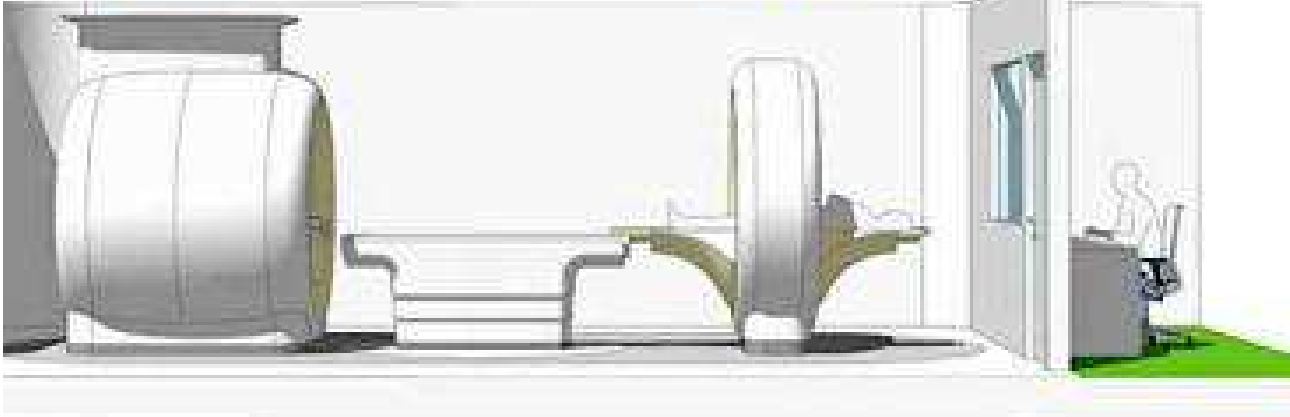
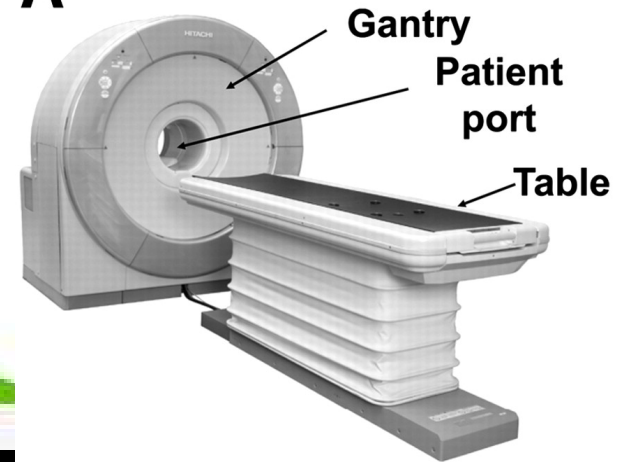
Ulli Köster

Institut Laue Langevin, Grenoble



PET

A

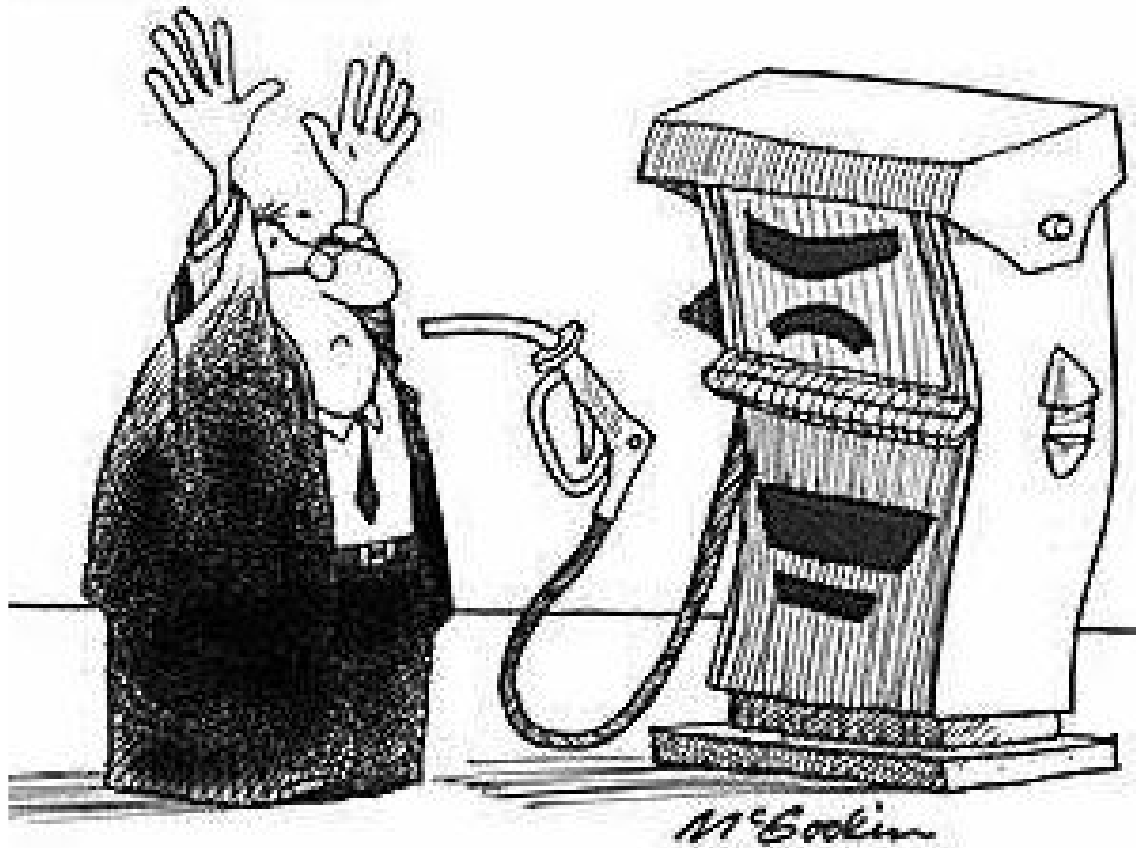




GENEVA 8-18 MARCH 2012 **82ND INTERNATIONAL MOTOR SHOW AND ACCESSORIES**



Don't forget the fuel!



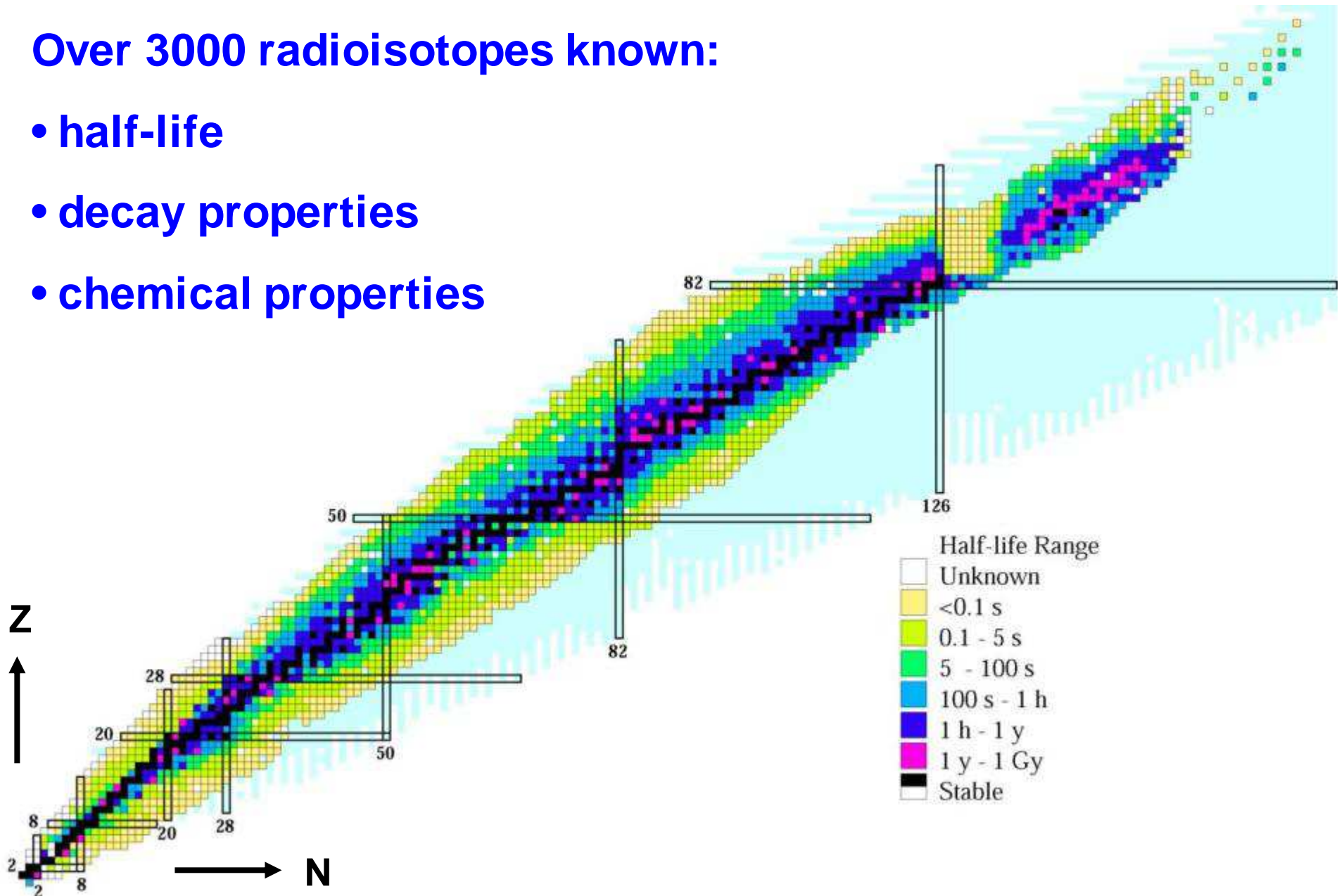
Radioisotopes: the “fuel” for nuclear medicine

- 1. What is the optimum fuel for an application ?**
- 2. Are we using today the optimum fuel ?**
- 3. Is there sufficient supply of fuel
at reasonable cost?**
- 4. How reliable is the fuel supply ?**

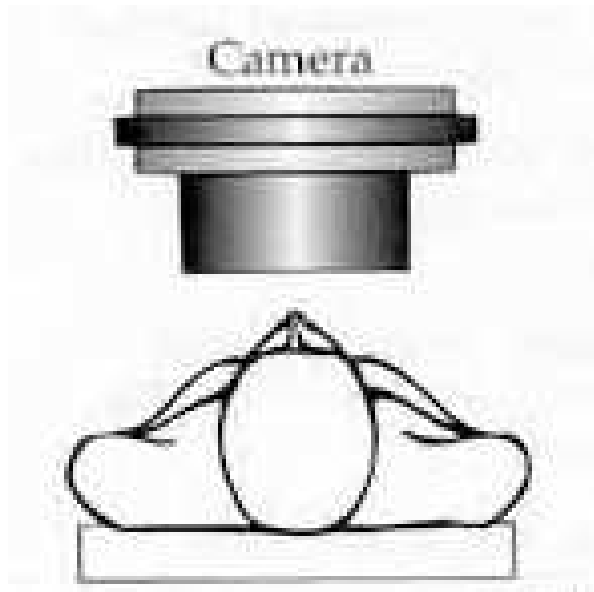
The quest for the optimum isotope

Over 3000 radioisotopes known:

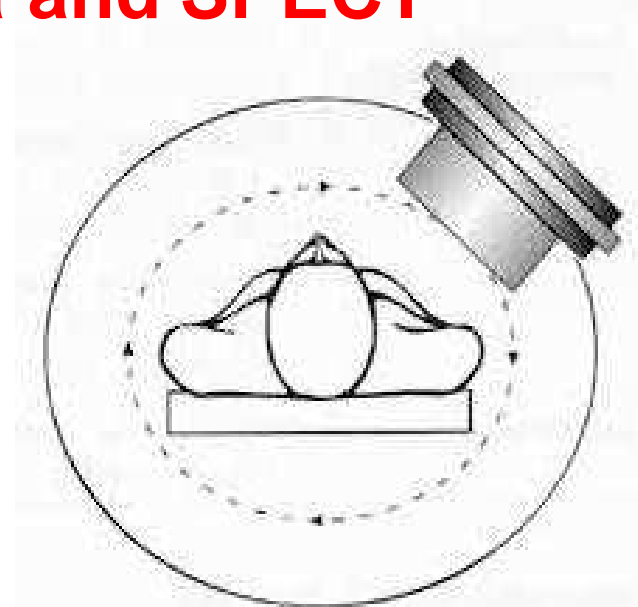
- half-life
- decay properties
- chemical properties



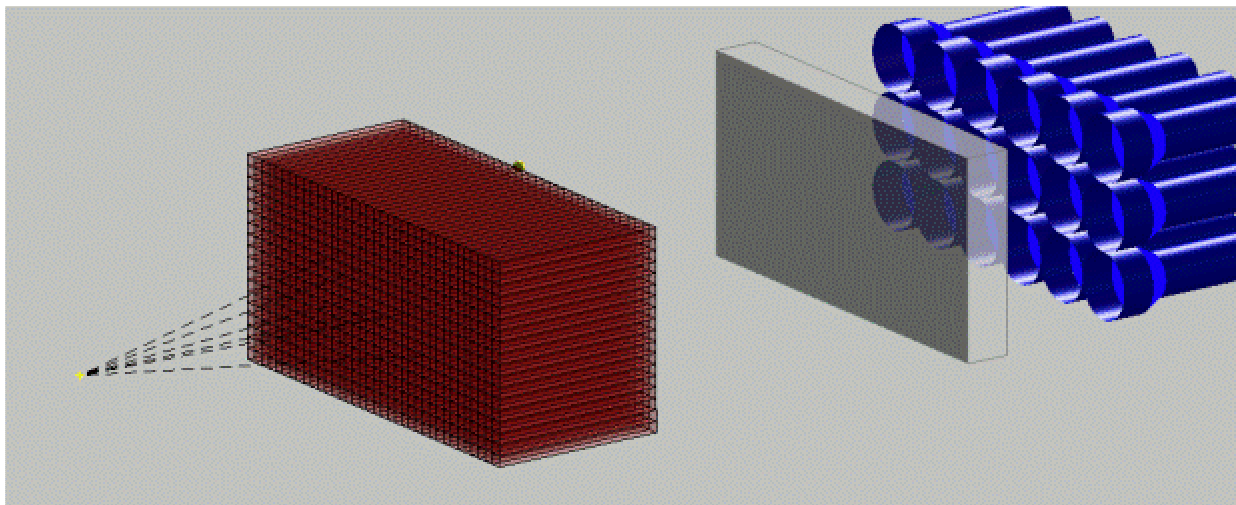
Gamma camera and SPECT



2D: planar scan



**3D: SPECT: Single Photon Emission
Computer Tomography**



$E_{\gamma} > 70 \text{ keV}$
absorption in body
 $E_{\gamma} < 300 \text{ keV}$
*efficient collimation
and detection*

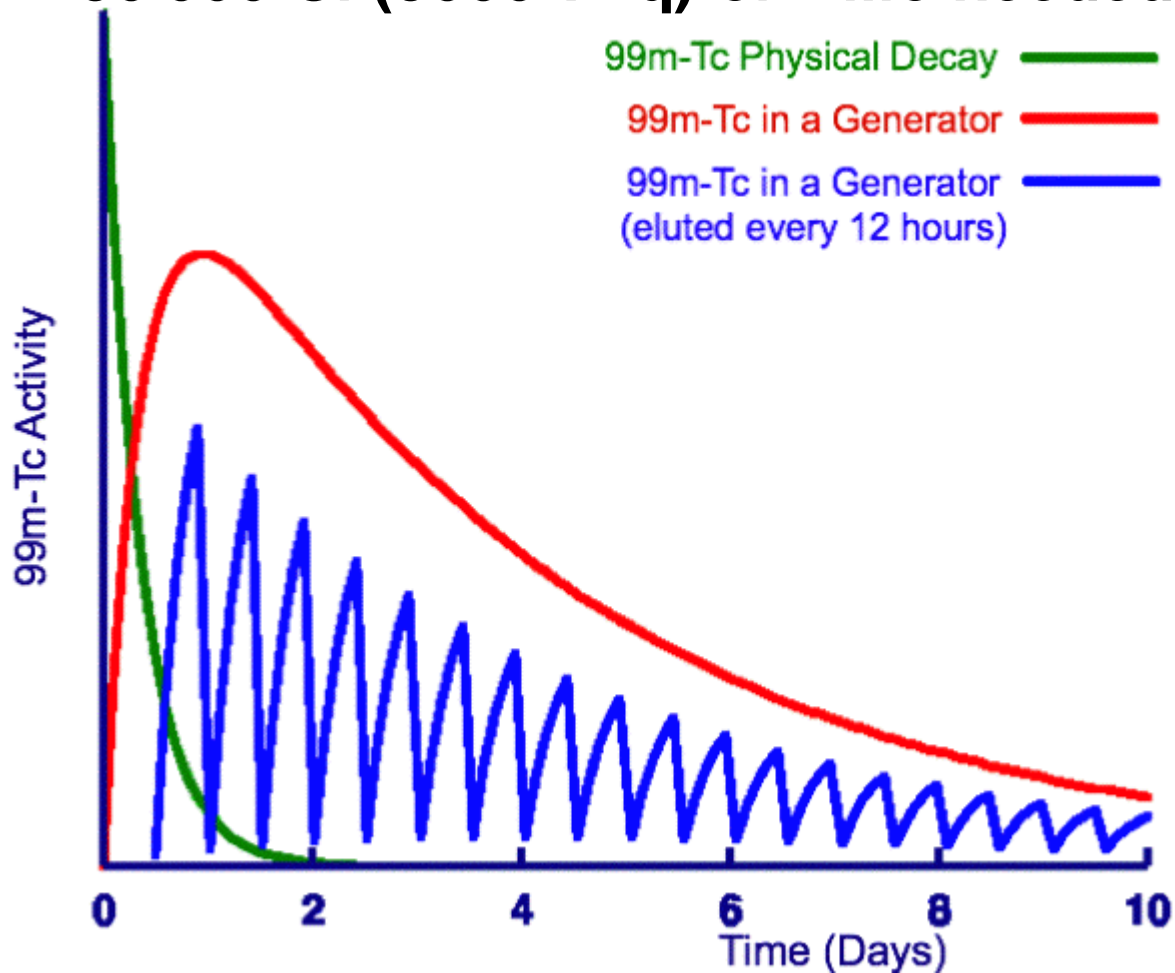
^{99m}Tc: ideal for SPECT and gamma cameras

Ru 98 1.87 <small>$\sigma < 8$</small>	Ru 99 12.76 <small>$\sigma < 4$</small>	Ru 100 12.60 <small>$\sigma < 5.8$</small>	Ru 101 17.06 <small>$\sigma < 5$</small>	Ru 102 31.55 <small>$\sigma < 1.2$</small>
Tc 97 92.2 d <small>4.0 · 10⁶ a</small> <small>h_γ (97) e⁻</small>	Tc 98 4.2 · 10 ⁶ a <small>β⁻ 0.4 γ 745; 652 σ 0.9 + ?</small>	Tc 99 6.0 h <small>h_γ 141... e⁻ β⁻... γ (322...)</small>	Tc 100 15.8 s <small>β⁻ 3.4... ε γ 540; 591...</small>	Tc 101 14.2 m <small>β⁻ 1.3... γ 307; 545...</small>
Mo 96 16.68 <small>$\sigma < 0.5$</small>	Mo 97 9.56 <small>$\sigma < 2.5$ $\sigma_{n, \alpha} < 4E-7$</small>	Mo 98 24.19 <small>$\sigma < 0.14$</small>	Mo 99 66.0 h <small>β⁻ 1.2... γ 740; 182; 778... m; g</small>	Mo 100 9.67 <small>1.15 · 10¹⁹ a 2 β⁻ σ 0.19</small>

- IT with 89% 140.5 keV gamma ray, $T_{1/2} = 6$ h
- decays to quasi-stable daughter
- ^{99m}Tc fed in 88% of β⁻ decays of ⁹⁹Mo, $T_{1/2} = 66$ h
- produces nearly carrier-free product

The “technetium cow” ($^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator)

- $^{99\text{m}}\text{Tc}$ is the most important radionuclide in nuclear medicine (80% of all nuclear medicine applications)
- 30 million applications per year
- 80 000 Ci (3000 TBq) of ^{99}Mo needed per week




BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head 
BNL Patent Office

SUBJECT: P-701 and P-702 - PREPARATION OF
CARRIER-FREE MOLYBDENUM AND OF
TECHNETIUM FROM FISSION PRODUCTS

The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not at present desire to prepare a patent application on this item for the following reason:

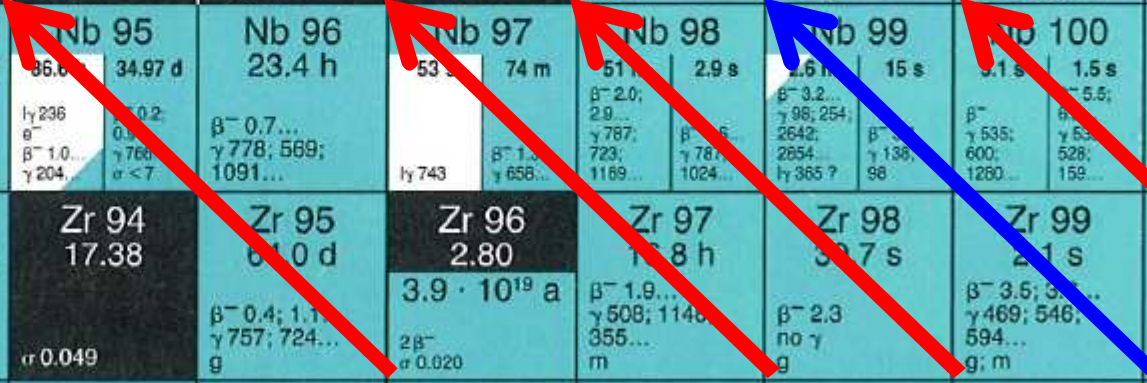
"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (GNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with .1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."

believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

Fission production

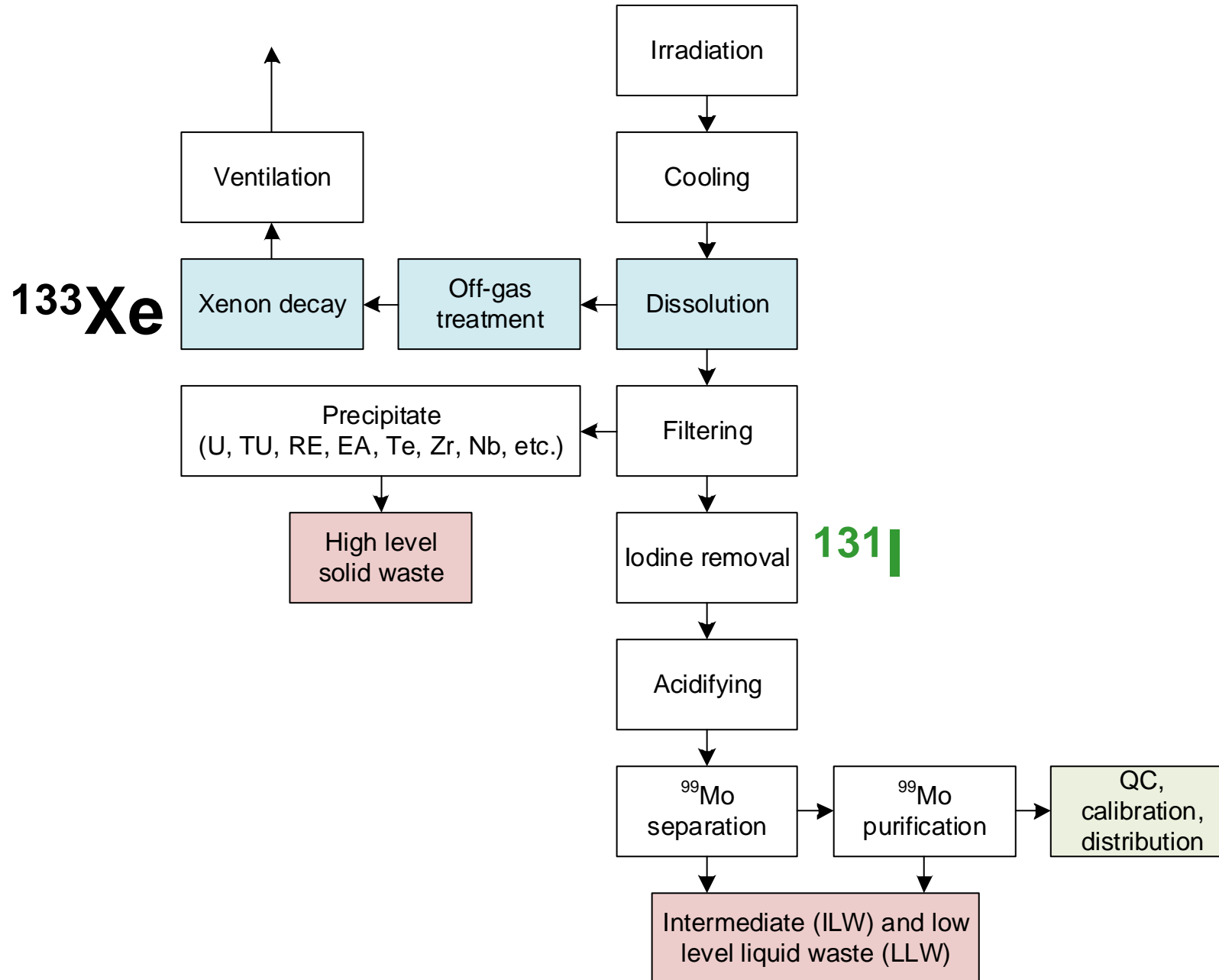
Ru 94 51.8 m ε γ 367; 891... m	Ru 95 1.65 h ε; β ⁺ 1.2... γ 336; 1097; 627... g	Ru 96 5.54 α 0.23	Ru 97 2.9 d ε γ 216; 324... g	Ru 98 1.87 α < 8	Ru 99 12.76 α 4	Ru 100 12.60 α 5.8	Ru 101 17.06 α 5	Ru 102 31.55 α 1.2	Ru 103 39.35 d β ⁻ 0.2; 0.7... γ 497; 610... m σ < 20
Tc 93 43.5 m β ⁺ 0.8... γ 1363; 2645... g	Tc 94 2.7 h 53 m 4.9 h β ⁺ 0.8 γ 871; 703; 850... β ⁺ 2.5... γ 871... g	Tc 95 60 d 20 h ε; β ⁺ ... γ 204; 582; 835... β ⁺ 39) γ 766; 1074... g	Tc 96 52 m 4.3 d β ⁻ 1.4... γ 778; 1200... e ⁻	Tc 97 92.2 d 4.0 · 10 ⁶ a β ⁻ 0.4 γ 745; 652 σ 0.9 + ? e ⁻ no γ	Tc 98 4.2 · 10 ⁶ a β ⁻ 0.4 γ 745; 652 σ 0.9 + ?	Tc 99 6.0 h 2.1 · 10 ⁵ a β ⁻ 0.3 γ (90) σ 23 β ⁻ 141... e ⁻ γ (322...)	Tc 100 15.8 s β ⁻ 3.4... ε γ 540; 591... g	Tc 101 14.2 m β ⁻ 1.3... γ 307; 545... g	Tc 102 4.3 m 5.3 s β ⁻ 1.6; 3.2... γ 475; 631; 628... β ⁻ 4.2... γ 475... g
Mo 92 14.77 α 2E-7 + 0.06	Mo 93 6.9 h 3.5 · 10 ³ a β ⁻ 1477; 685; 263...; ε γ (950...) g	Mo 94 9.23 α 0.02	Mo 95 15.90 α 0.5	Mo 96 16.68 α 0.5	Mo 97 9.56 α 0.5	Mo 98 24.19 α 0.5	Mo 99 66.0 h β ⁻ 1.2... γ 740; 182... g	Mo 100 9.67 1.15 · 10 ¹⁹ a α 1.8	Mo 101 14.6 m β ⁻ 0.8; 2.6... γ 192; 591; 1013; 506... g
Nb 91 50.9 d 680 a β ⁻ (105) e ⁻ ε; β ⁺ ... γ 1205	Nb 92 10.15 d 3.6 · 10 ⁷ a ε β ⁺ ... γ 934... g	Nb 93 16.13 a 100 β ⁻ (31) e ⁻ α 0.86 + 0.29	Nb 94 6.26 m 2 · 10 ⁴ a β ⁻ 0.5 γ 871; 703 β ⁻ ... σ 0.6 + 14.4 γ (871...)	Nb 95 36.6 d 34.97 d β ⁻ 0.2; 0... e ⁻ β ⁻ 1.0... γ 760 γ 204... σ < 7	Nb 96 23.4 h β ⁻ 0.7... γ 778; 569; 1091... g	Nb 97 53 s 74 m β ⁻ 1.0... γ 656... β ⁻ 743	Nb 98 51 s 2.9 s β ⁻ 2.0; 2.9... γ 787; 723; 1169... β ⁻ 5 γ 78; 1024... g	Nb 99 2.6 h 15 s β ⁻ 3.2... γ 98; 254; 2642... β ⁻ ... 2654... γ 136; 98... g	Nb 100 0.1 s 1.5 s β ⁻ ... γ 535; 600; 1260... β ⁻ 5.5; γ 63... 528; 159... g
Zr 90 51.45 α -0.014	Zr 91 11.22 α 1.2	Zr 92 17.15 α 0.2	Zr 93 1.5 · 10 ⁶ a β ⁻ 0.06... m σ < 4	Zr 94 17.38 α 0.049	Zr 95 61.0 d β ⁻ 0.4; 1.1... γ 757; 724... g	Zr 96 2.80 3.9 · 10 ¹⁹ a 2β ⁻ α 0.020	Zr 97 1.8 h β ⁻ 1.9... γ 508; 1140... 355... m	Zr 98 30.7 s β ⁻ 2.3 no γ g	Zr 99 21 s β ⁻ 3.5; 3... γ 469; 546; 594... g; m
Y 89 16.0 s 100 β ⁻ 909	Y 90 3.19 h 64.1 h β ⁻ 203; 480...; β ⁻ ... γ (2319...) α < 6.5	Y 91 49.7 m 59.5 d β ⁻ 1.5... γ (1205) σ 1.4	Y 92 3.54 h β ⁻ 3.6... γ 934; 1405; 561; 449... g	Y 93 10.1 h β ⁻ 2.9... γ 267; 947; 1918... g	Y 94 18.7 m β ⁻ 4.9... γ 919; 1139; 551... g	Y 95 10.3 m β ⁻ 4.4... γ 954; 2176; 3577; 1324; 2633... g	Y 96 9.6 s 5.34 s β ⁻ 2.6... γ 1751; 915; 617; 1107... β ⁻ 7.1... γ 1750... g	Y 97 1.2 s 3.75 s β ⁻ 5.1; 6.0... γ 3286; 1103; 3401; 161; 970; 1997... β ⁻ 6.7... γ 3286; 3401; 161; 970; 1997... β ⁻ 6.7... γ 3286; 3401; 161; 970; 1997... g	Y 98 2.0 s 0.55 s β ⁻ 4.9; 7.4... γ 1223; 2941; 1591... β ⁻ 8.8... γ 1223; 2941; 1591... g

6.5% 6.0% 5.8% 6.1% 6.3%

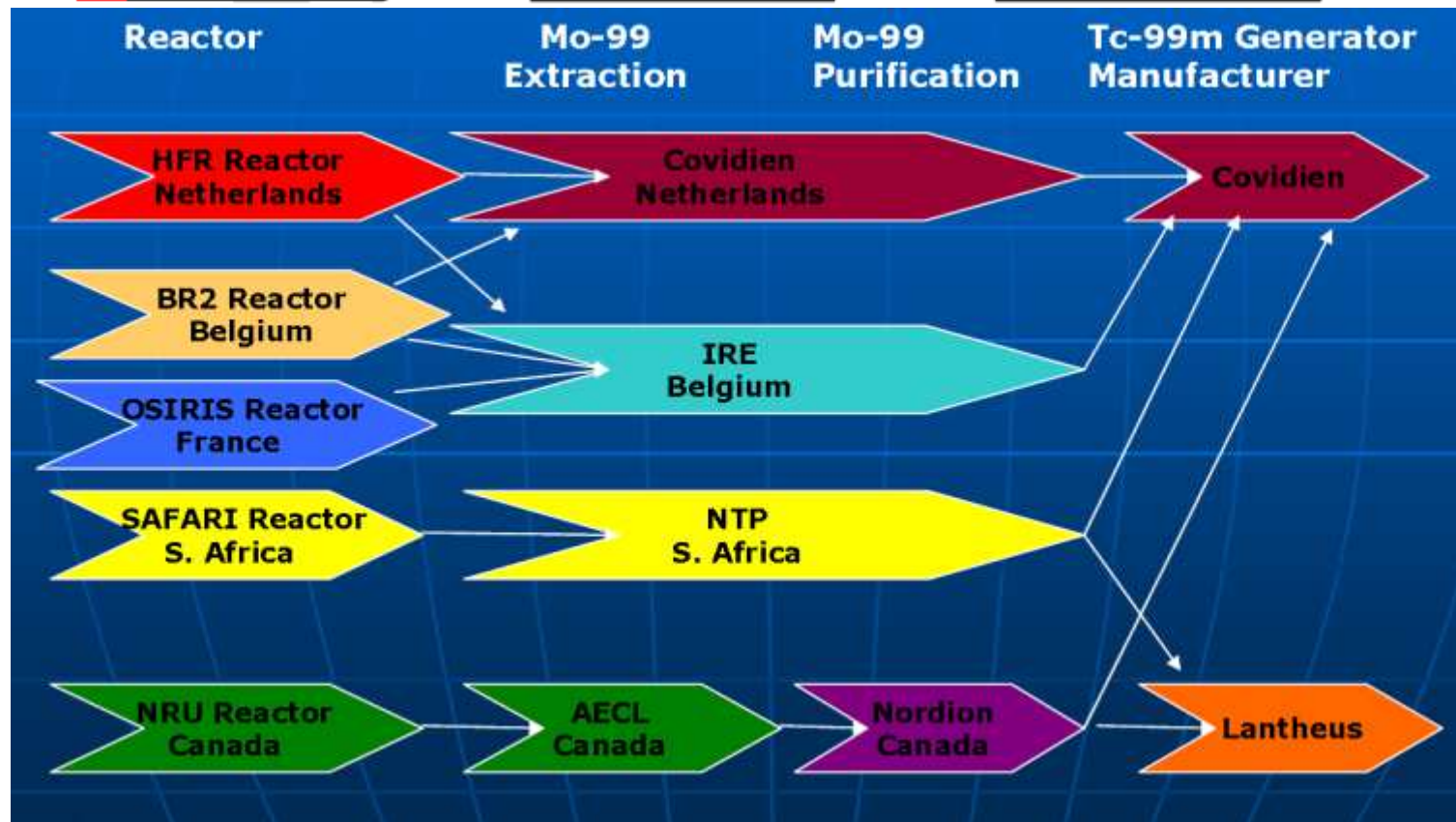
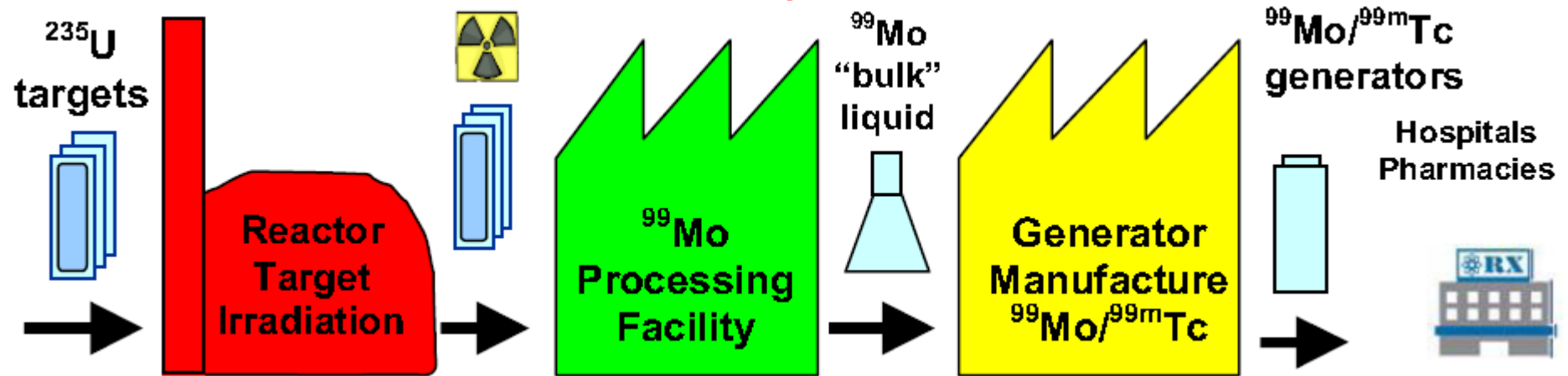


After irradiation, decay and chemical processing:
⁹⁹Mo/^{all}Mo ≈ 10%, i.e. **10% of theoretical specific activity 480 kCi/g**

Extraction of fission-moly



The traditional supply chain of $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$



Reactors presently used for ^{99}Mo production with HEU targets

Reactor	Location	Country	Power (MW)	Fuel	Operation (days per year)	Operation since	Typical ^{99}Mo world market share
NRU	Chalk River	Canada	135	LEU	315	1957	40%
HFR	Petten	Netherlands	45	LEU	290	1961	30%
BR2	Mol	Belgium	100	HEU	115	1961	10%
OSIRIS	Saclay	France	70	LEU	220	1966	3%
SAFARI	Pelindaba	South Africa	20	HEU	315	1965	10%

European hospitals cope with Mo-99 supply crisis

Petten reactor shutdown disrupts nuclear medicine in 20 European countries and U.S. until mid-January

01 December 2008

EUROPE

MOLYBDENUM SUPPLY REVIEW

L'inquiétante pénurie d'isotopes pour l'imagerie

Le 02 septembre 2010 à 00h 00 par A. P.

Engpässe in der Tumormedizin

SPIEGEL

Krebsärzten gehen die Diagnosemittel aus

Isotopes médicaux - Crise mondiale à l'horizon

Aucune solution n'existe pour résoudre le problème d'approvisionnement

Pauline Gravel 23 mai 2009 Santé

We Need to Expand
Medical Isotope Production!

Isotope shortage means a healthcare crisis

Los Angeles Times

The radioisotope is needed to scan for heart disease and cancer. Two nuclear reactors that produce it have been shut down, severely limiting the supply, and alternatives are scant.

L'OCDE s'inquiète des risques de pénurie d'isotopes médicaux

Isotope shortage to get worse with closing of more reactors

Mangel an medizinisch verwendbaren Isotopen

Frankfurter Allgemeine

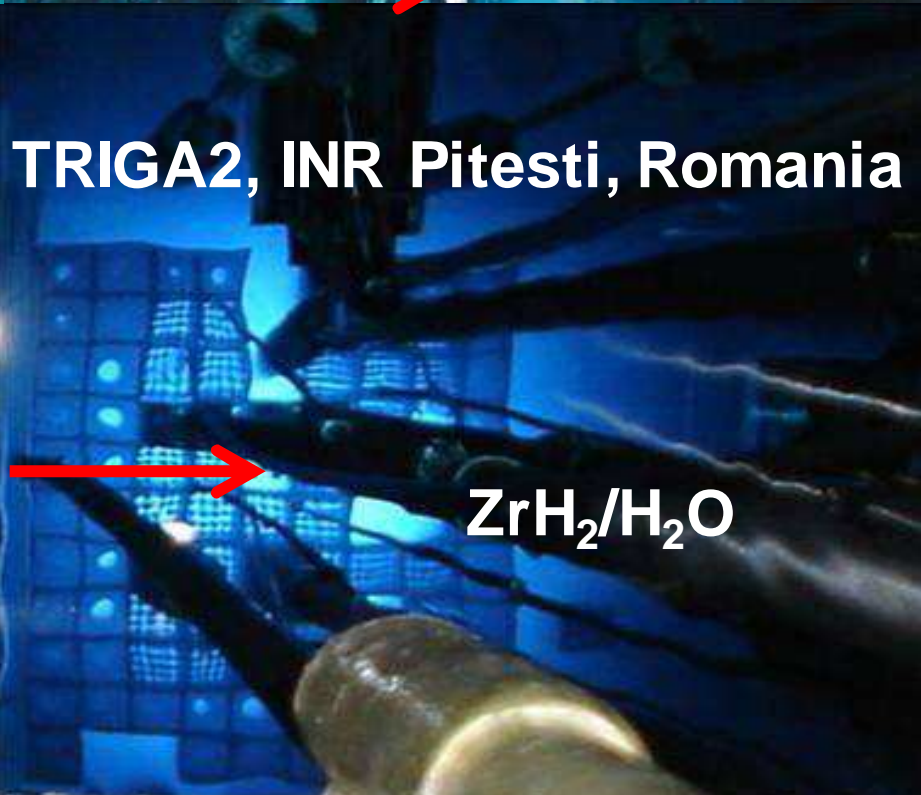
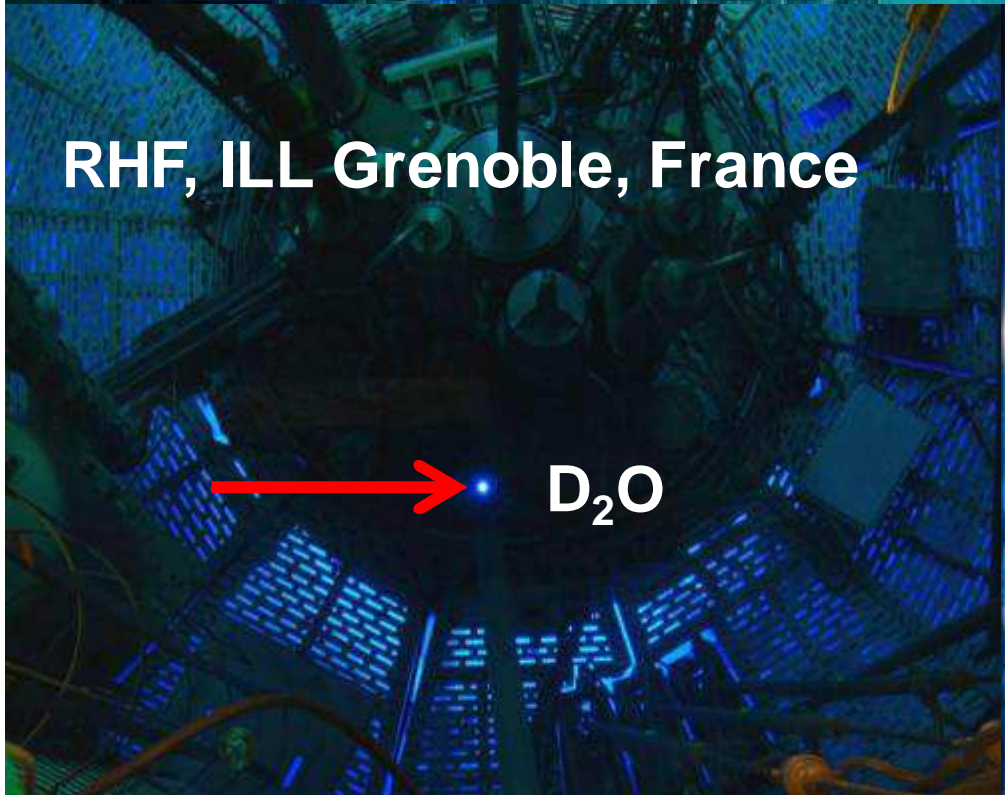
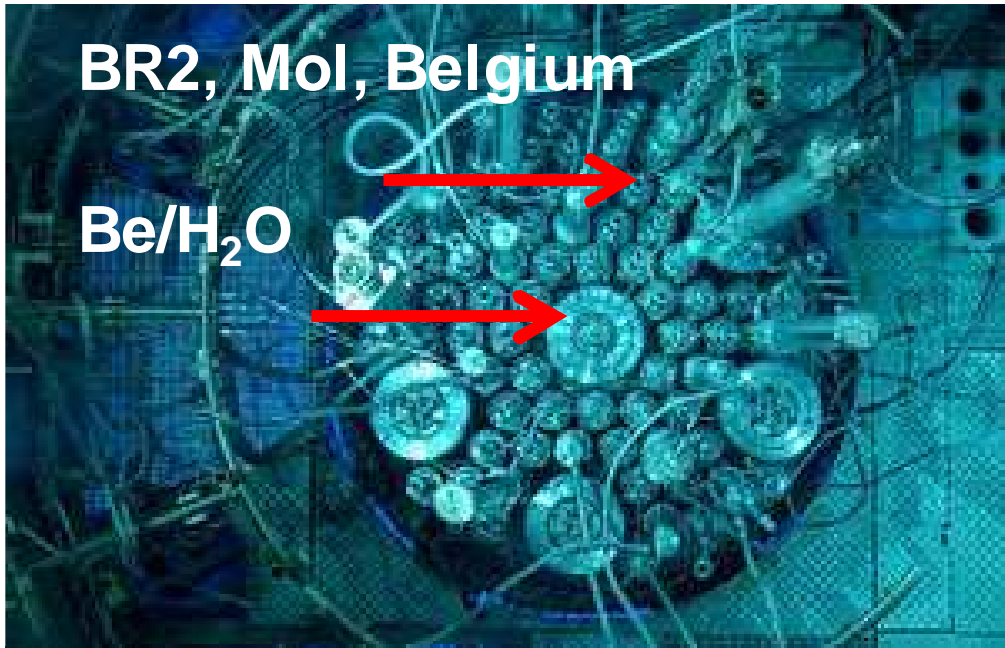
Mo-99 crisis

Szintigraphien fallen aus, für Februar droht der Notstand

⁹⁹Mo production by neutron capture

Ru 96 5.54 σ 0.23	Ru 97 2.9 d ϵ γ 216; 324... g	Ru 98 1.87 σ < 8	Ru 99 12.76 σ 4	Ru 100 12.60 σ 5.8	Ru 101 17.06 σ 5	Ru 102 31.55 σ 1.2	Ru 103 39.35 d β^- 0.2; 0.7... γ 497; 610... m σ < 20
Tc 95 60 d 20 h ϵ ; β^+ ... γ 204; 582; 835... I γ (39)	Tc 96 52 m 4.3 d I γ (34) ϵ β^- γ 778; 1200...	Tc 97 92.2 d 4.0 · 10 ⁵ a ϵ I γ (97) β^-	Tc 98 4.2 · 10 ⁶ a β^- 0.4 γ 745; 652 σ 0.9 + ?	Tc 99 6.0 h 2.1 · 10 ⁵ a I γ 141... β^- ... γ (322...)	Tc 100 15.8 s β^- 3.4... ϵ γ 540; 591...	Tc 101 14.2 m β^- 1.3... γ 307; 545...	Tc 102 4.3 m 5.3 s β^- 1.6; 3.2... γ 475; 631; 628... I γ β^- 4.2... γ 475...
Mo 94 9.23 σ 0.02	Mo 95 15.90 σ 13.4 $\sigma_{n,\alpha}$ 0.000030	Mo 96 16.68 σ 0.5	Mo 97 9.56 σ 2.5 $\sigma_{n,\alpha}$ 4E-7	Mo 98 24.19 σ 0.14	Mo 99 66.0 h β^- 0.4; 182; 778... m; g	Mo 100 9.67 1.15 · 10 ¹⁹ a 2 β^- σ 0.19	Mo 101 14.6 m β^- 0.8; 2.6... γ 192; 591; 1013; 506...
Nb 93 16.13 a 100 I γ (31) β^- σ 0.86 + 0.29	Nb 94 6.26 m 2 · 10 ⁴ a I γ (41) β^- ... σ 0.6 + 14.4	Nb 95 86.6 h 34.97 d I γ 236 β^- 0.2; 0.9 σ < 7	Nb 96 23.4 h β^- 0.7... γ 778; 569; 1091...	Nb 97 53 s 74 m β^- 1.3 γ 658...	Nb 98 51 m 2.9 s β^- 2.0; 2.9... γ 787; 723; 1169... β^- 4.6... γ 787; 1024...	Nb 99 2.6 m 15 s β^- 3.2... γ 98; 254; 2642; 2654... I γ 365 ? β^- 3.1 γ 138; 98	Nb 100 3.1 s 1.5 s β^- ... γ 535; 600; 1260... β^- 5.5; 6.2... γ 535; 528; 159...

Due to very low ($n_{th,\gamma}$) cross-section of 0.13 b a very high neutron flux is needed to reach the required specific activity!
2.2 Ci/g saturation activity in 1E14 n/cm²/s flux



Results of test irradiations

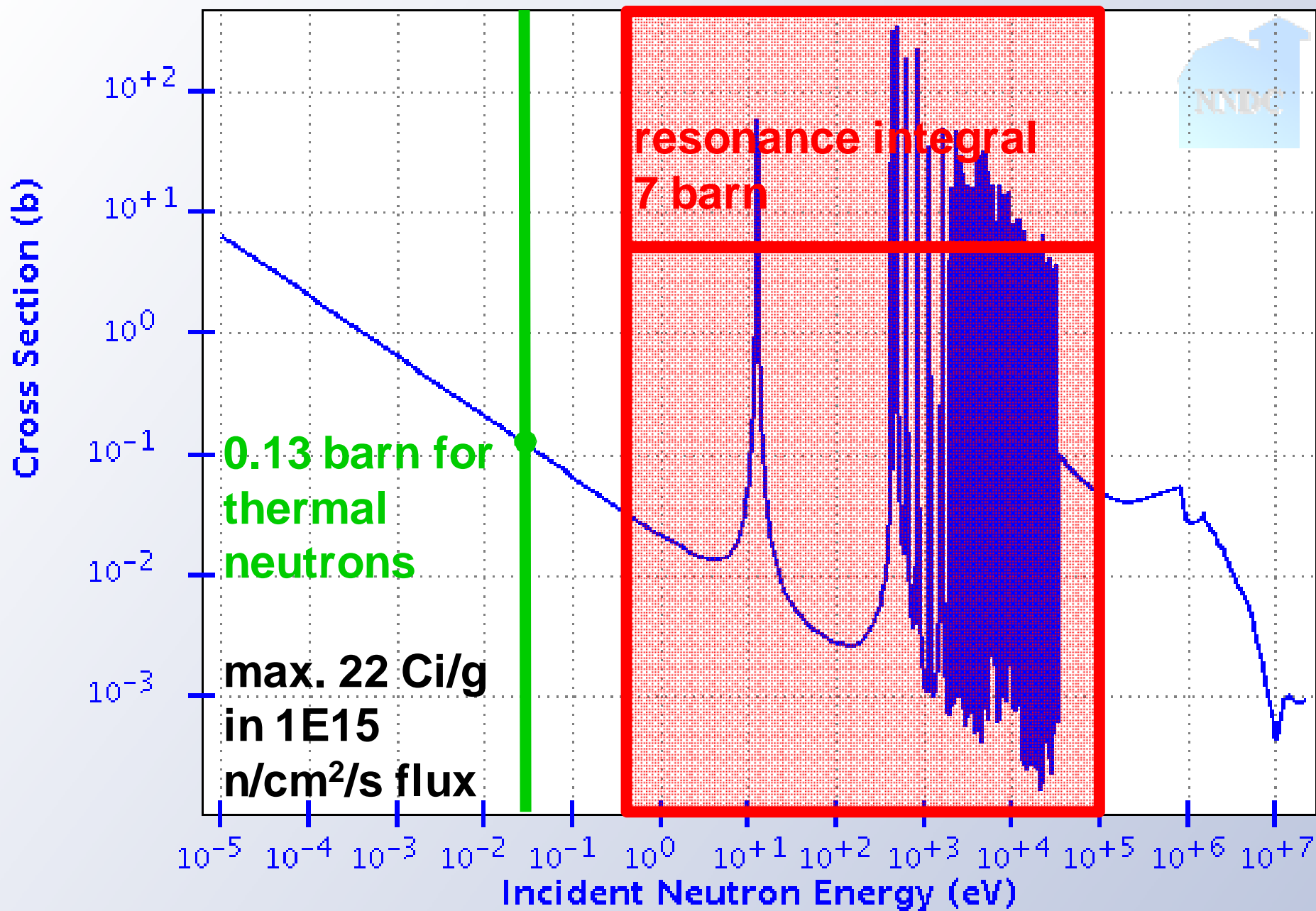
Reactor	Power	Position	Thermal flux	Irrad. time	Specific activity at EOI		Epi-thermal gain
	(MW)		(cm ⁻² /s)		(GBq/g)	(Ci/g)	
ILL	54	V4 (3)	1.2E+15	6.8	951	26	22%
ILL	54	V4 (4)	1.1E+15	8	838	23	8%
BR2	68	H1 (300°)	1.0E+15	20.4	(2800)	(76)	(254%)
BR2	68	F46	3.6E+14	7	369	10	55%
TRIGA II	14	XC-1	2.6E+14	8.1	350	9.4	91%
FRM2	20	KBA1	1.3E+14	7	86	2.3	9%

How to produce 1000 “6-d-Ci” [50% of European weekly need]

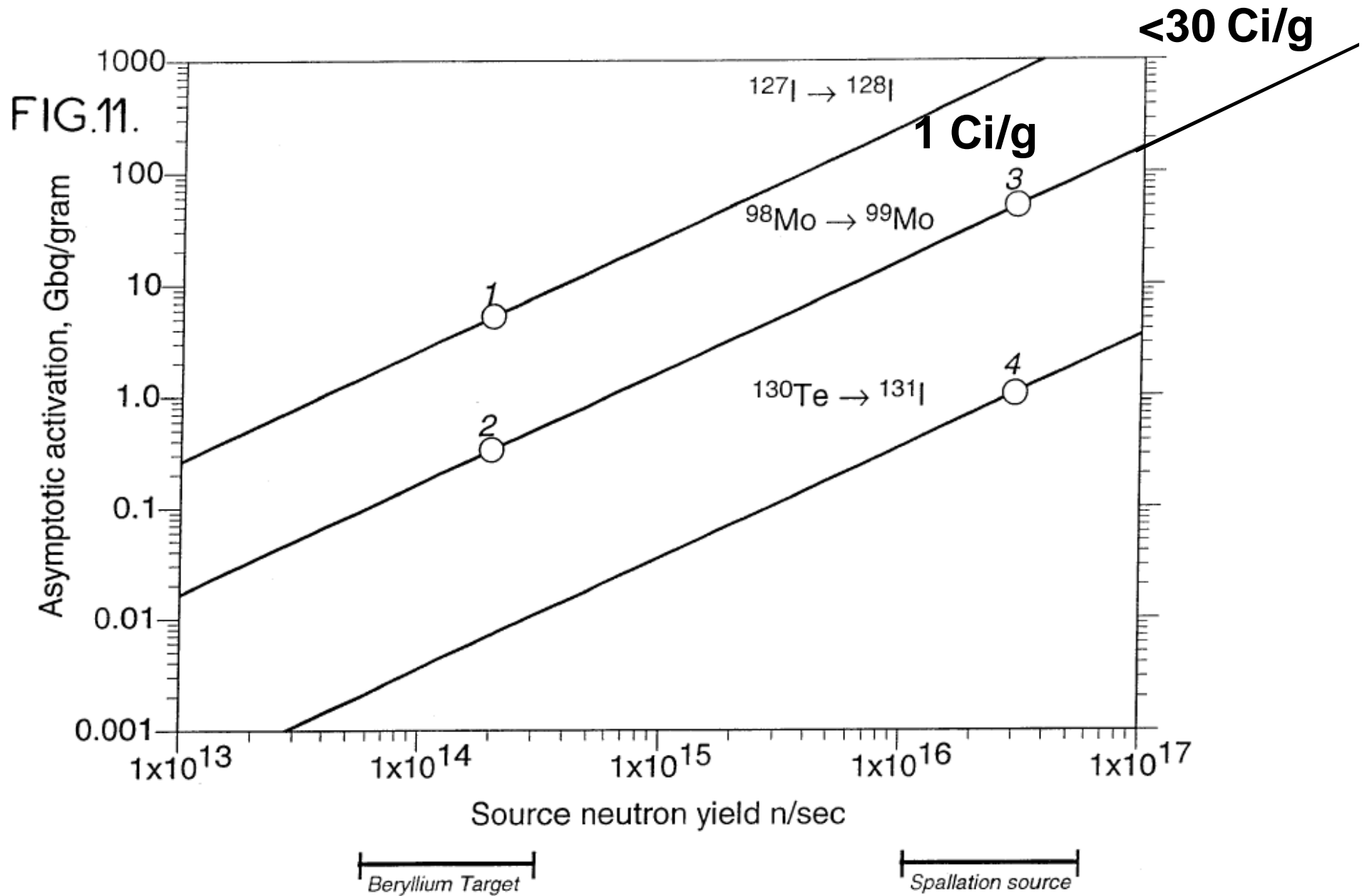
7 d irradiation, 2 d processing+shipping, 6 d use

- 360 g ⁹⁸Mo at ILL: **2 capsules metallic Mo** or 8 caps. MoO₃
- <400 g ⁹⁸Mo at BR2 (H1): **2 caps. metallic Mo** or 8 caps. MoO₃
- 1200 g ⁹⁸Mo at BR2 (F46): **7 caps. met. Mo** or 26 caps. MoO₃
- 1600 g ⁹⁸Mo at TRIGA2: >9 caps. met. Mo or **36 caps. MoO₃**

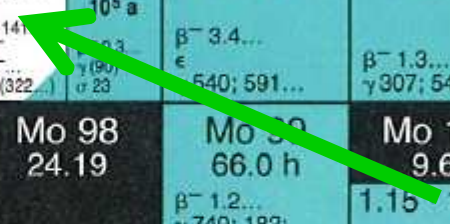
42-Mo-98(n,gamma) JEFF-3.1

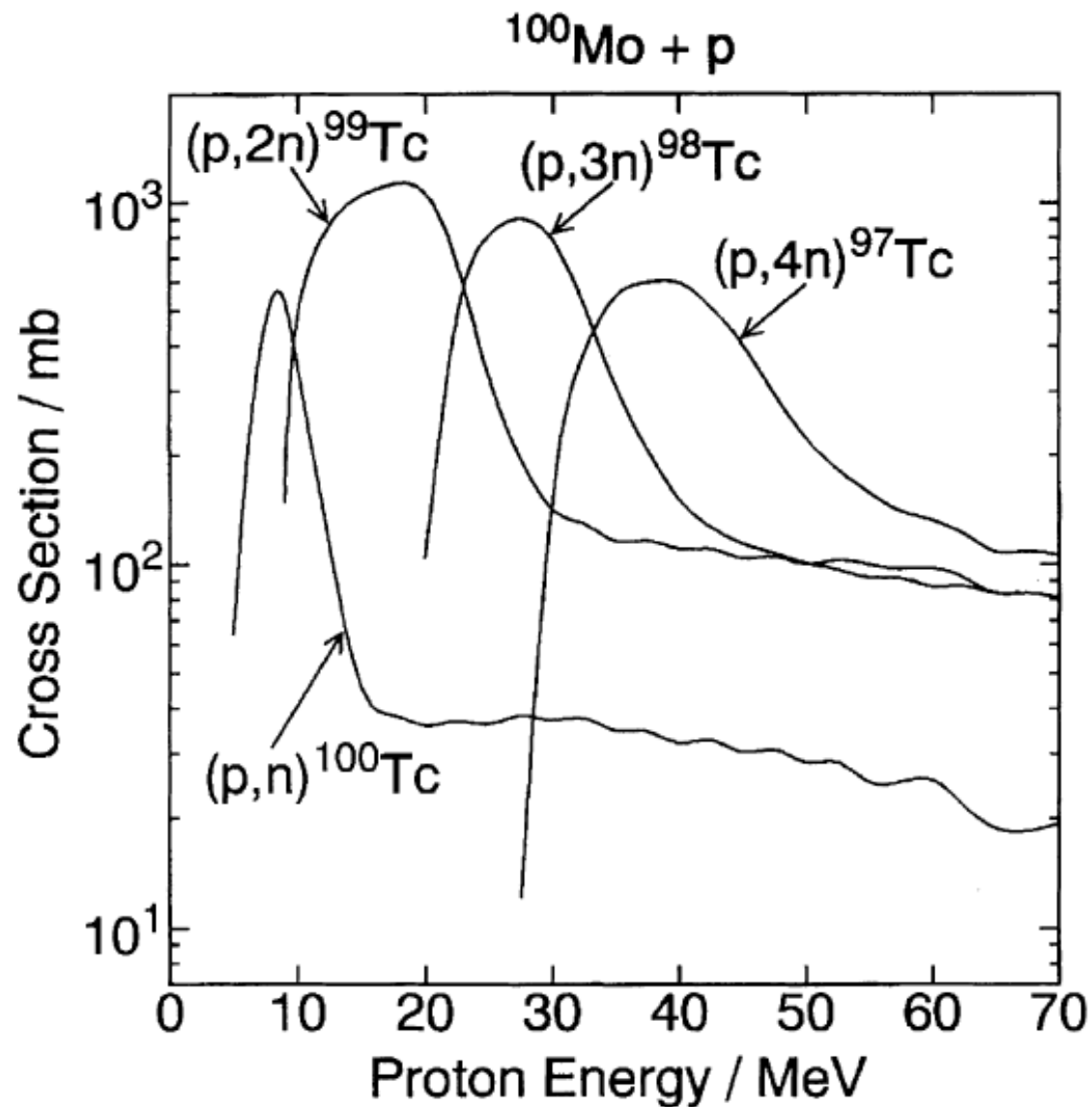


Adiabatic Resonance Crossing



<p>Ru 94 51.8 m</p> <p>ϵ γ 367; 891... m</p>	<p>Ru 95 1.65 h</p> <p>ϵ; β^+ 1.2... γ 336; 1097; 627... g</p>	<p>Ru 96 5.54</p> <p>α 0.23</p>	<p>Ru 97 2.9 d</p> <p>ϵ γ 216; 324... g</p>	<p>Ru 98 1.87</p> <p>α < 8</p>	<p>Ru 99 12.76</p> <p>α 4</p>	<p>Ru 100 12.60</p> <p>α 5.8</p>	<p>Ru 101 17.06</p> <p>α 5</p>	<p>Ru 102 31.55</p> <p>α 1.2</p>	<p>Ru 103 39.35 d</p> <p>β^- 0.2; 0.7... γ 497; 610... m σ < 20</p>
<p>Tc 93 43.5 m 2.7 h</p> <p>$t_{1/2}$ 392 ϵ γ 2645... g</p> <p>β^+ 0.8... γ 1363; 1520; 1477...; g</p>	<p>Tc 94 53 m 4.9 h</p> <p>β^+ 0.8 γ 871; 703; 850... β^+ 2.5... γ 871... g</p>	<p>Tc 95 60 d 20 h</p> <p>ϵ; β^+... γ 204; 582; 835... $t_{1/2}$ (39)</p> <p>ϵ no β^+ γ 766; 1074... g</p>	<p>Tc 96 52 m 4.3 d</p> <p>$t_{1/2}$ (34) ϵ γ 778; 1200... g</p> <p>ϵ no β^+ γ 778; 850; 813... g</p>	<p>Tc 97 92.2 d 4.0 · 10⁵ a</p> <p>$t_{1/2}$ (97) ϵ no γ</p>	<p>Tc 98 4.2 · 10⁶ a</p> <p>β^- 0.4 γ 746; 652 σ 0.9 + ?</p>	<p>Tc 99 6.0 h 21 · 10⁵ a</p> <p>$t_{1/2}$ (14) ϵ β^-... γ (322...) σ 23</p>	<p>Tc 100 15.8 s</p> <p>β^- 3.4... ϵ 540; 591... m; g</p>	<p>Tc 101 14.2 m</p> <p>β^- 1.3... γ 307; 545... m</p>	<p>Tc 102 4.3 m 5.3 s</p> <p>β^- 1.6; 3.2... γ 475; 631; 628...; $t_{1/2}$ β^- 4.2... γ 475... m</p>
<p>Mo 92 14.77</p> <p>α 2E-7 + 0.06</p>	<p>Mo 93 6.9 h 3.5 · 10³ a</p> <p>$t_{1/2}$ 1477; 685; 263...; ϵ γ (950...) g</p> <p>ϵ m</p>	<p>Mo 94 9.23</p> <p>α 0.02</p>	<p>Mo 95 15.90</p> <p>α 13.4 α 0.000030</p>	<p>Mo 96 16.68</p> <p>α 0.5</p>	<p>Mo 97 9.56</p> <p>α 2.5 α 0, α 4E-7</p>	<p>Mo 98 24.19</p> <p>α 0.14</p>	<p>Mo 99 66.0 h</p> <p>β^- 1.2... γ 740; 182; 778... m; g</p>	<p>Mo 100 9.67</p> <p>1.15 · 10¹⁹ a 2 β^- α 0.19</p>	<p>Mo 101 14.6 m</p> <p>β^- 0.8; 2.6... γ 192; 591; 1013; 506... m</p>
<p>Nb 91 60.9 d 680 a</p> <p>$t_{1/2}$ (105) ϵ γ 1205</p> <p>ϵ β^+...</p>	<p>Nb 92 10.15 d 3.6 · 10⁷ a</p> <p>ϵ γ 934... g</p> <p>ϵ β^+...</p>	<p>Nb 93 16.13 a 100</p> <p>$t_{1/2}$ (31) ϵ α 0.86 + 0.23</p>	<p>Nb 94 6.26 m 2 · 10⁴ a</p> <p>$t_{1/2}$ (41) ϵ β^-... γ (871...)</p> <p>β^- 0.5 γ 871; 703 α 0.6 + 14.4</p>	<p>Nb 95 86.6 h 34.97 d</p> <p>$t_{1/2}$ 236 ϵ β^- 1.0... γ 204...</p> <p>β^- 0.2; 0.9 σ < 7</p>	<p>Nb 96 23.4 h</p> <p>β^- 0.7... γ 778; 569; 1091...</p>	<p>Nb 97 53 s 74 m</p> <p>$t_{1/2}$ 743</p> <p>β^- 1.3... γ 658...</p>	<p>Nb 98 51 m 2.9 s</p> <p>β^- 2.0; 2.9... γ 787; 723; γ 787; 1169... β^- 4.6... γ 787; 1024...</p>	<p>Nb 99 2.6 m 15 s</p> <p>β^- 3.2... γ 98; 254; 2642; 2654... $t_{1/2}$ 365 ?</p> <p>β^- 3.1 γ 138; 98</p>	<p>Nb 100 3.1 s 1.5 s</p> <p>β^- γ 535; 600; 1260... β^- 5.5; 8.2... γ 535; 528; 159... m</p>
<p>Zr 90 51.45</p> <p>α -0.014</p>	<p>Zr 91 11.22</p> <p>α 1.2</p>	<p>Zr 92 17.15</p> <p>α 0.2</p>	<p>Zr 93 1.5 · 10⁶ a</p> <p>β^- 0.06... m σ < 4</p>	<p>Zr 94 17.38</p> <p>α 0.049</p>	<p>Zr 95 64.0 d</p> <p>β^- 0.4; 1.1... γ 757; 724... g</p>	<p>Zr 96 2.80</p> <p>3.9 · 10¹⁹ a 2 β^- α 0.020</p>	<p>Zr 97 16.8 h</p> <p>β^- 1.9... γ 508; 1148; 355... m</p>	<p>Zr 98 30.7 s</p> <p>β^- 2.3 no γ g</p>	<p>Zr 99 2.1 s</p> <p>β^- 3.5; 3.6... γ 469; 546; 594... g; m</p>
<p>Y 89 16.0 s 100</p> <p>$t_{1/2}$ 909 α 0.001 + 1.25</p>	<p>Y 90 3.19 h 64.1 h</p> <p>$t_{1/2}$ 203; 490...; β^-... γ (2319...)</p> <p>β^- 2.3... γ (2186...) α < 6.5</p>	<p>Y 91 49.7 m 59.5 d</p> <p>β^- 1.5... γ (1205) α 1.4</p>	<p>Y 92 3.54 h</p> <p>β^- 3.6... γ 934; 1405; 561; 449... m</p>	<p>Y 93 10.1 h</p> <p>β^- 2.9... γ 267; 947; 1918... m</p>	<p>Y 94 18.7 m</p> <p>β^- 4.9... γ 919; 1139; 551... m</p>	<p>Y 95 10.3 m</p> <p>β^- 4.4... γ 954; 2176; 3577; 1324; 2633... m</p>	<p>Y 96 9.6 s 5.34 s</p> <p>β^- 2.6... γ 1751; 915; 617; 1107... β^- 7.1... γ 1750... m</p>	<p>Y 97 1.2 s 3.75 s</p> <p>β^- 5.1; 6.0... γ 1103; 161; 970; $t_{1/2}$ (668)</p> <p>β^- 6.7... γ 3288; 3401; 1997... β n</p>	<p>Y 98 2.0 s 0.55 s</p> <p>β^- 4.9; 7.4... γ 1223; 621... β n</p> <p>β^- 8.8... γ 1223; 2941; 1591... β n</p>

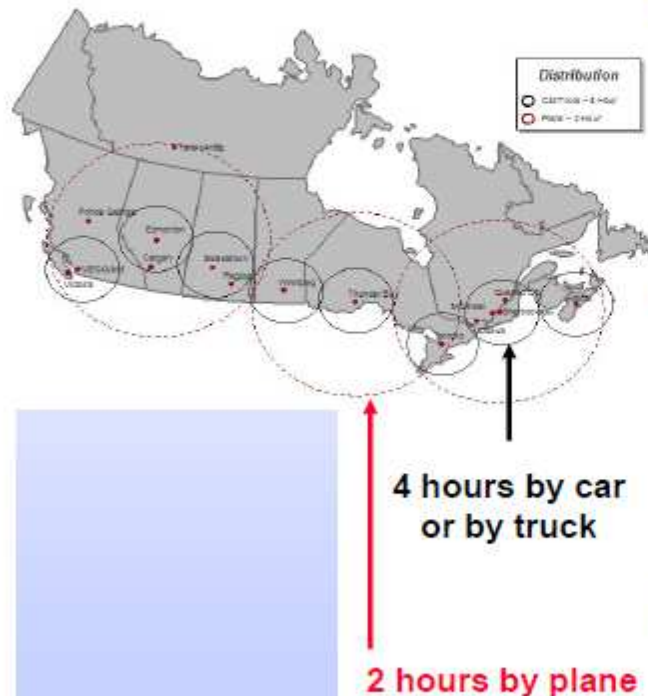




**Direct, decentralized production of $^{99\text{m}}\text{Tc}$ requires enriched targets and <30 MeV protons.
22 MeV p, 0.1 mA: 10 Ci $^{99\text{m}}\text{Tc}$ at saturation.**

4. New projects for Mo-99 and Tc-99m production

CANADA >>> Direct ^{99m}Tc production by cyclotron : $^{100}\text{Mo}(p,2n)^{99m}\text{Tc}$



PONSARD B.
Copyright © 2012
SCK•CEN

- In July 2009, Advanced Cyclotron Systems Inc. (ACSI), together with several Canadian universities and research centres, proposed to develop commercial scale production of **Tc-99m in Canada** using cyclotrons as an alternative to the reactor produced $^{99}\text{Mo}/^{99m}\text{Tc}$ (NRU will stop producing Mo-99 in 2016).
- The research and development activities are focused on the development of commercial, cost efficient production of Tc-99m using high-current cyclotrons (18MeV/300µA) manufactured in Canada by ACSI.
 - Low cross sections
 - Mo-100 not yet commercially available, recycling mandatory
- The **network of cyclotron centres** would not only supply Tc-99m by direct route, but would also have the capacity to provide a full spectrum of PET and SPECT radioisotopes such as F-18, Cu-64, I-123, I-124, Ge-68.

Back to the roots ?

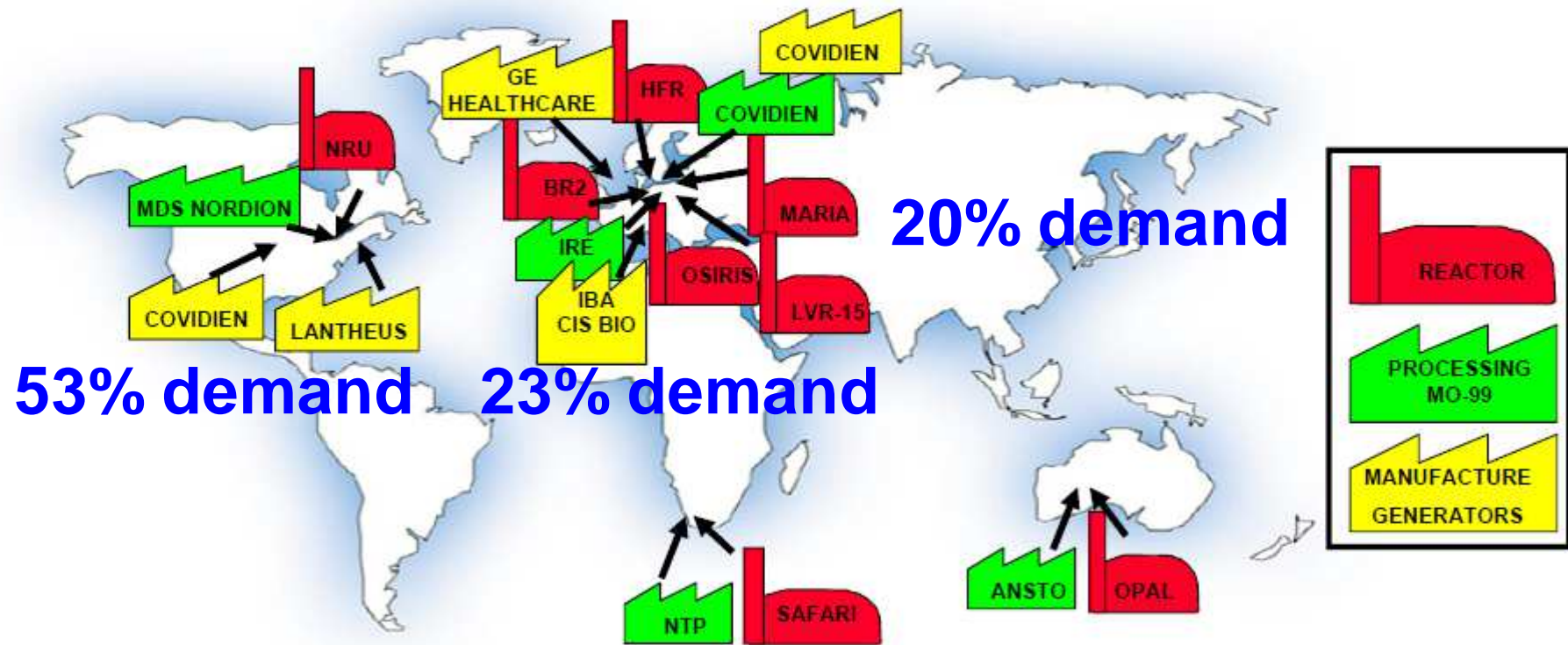
Original discovery of Tc in cyclotron-irradiated Mo !

C. Perrier, E. Segrè, J. Chem. Phys. 5 (1937) 712.

Alternative methods of producing ^{99}Mo

1. Neutron irradiation $^{98}\text{Mo}(n,\gamma)$
2. Liquid core reactor $^{235}\text{U}(n,f)$
3. Cyclotron bombardment $^{100}\text{Mo}(p,pn)$
4. Photo-nuclear reaction $^{100}\text{Mo}(\gamma,n)$
5. Photo-fission $^{238}\text{U}(\gamma,f)$
6. Fast neutrons $^{100}\text{Mo}(n,2n)$
7. Spallation source: $^{98}\text{Mo}(n,\gamma)$ with adiabatic resonance crossing
8. Accelerator driven subcritical assembly $^{235}\text{U}(n,f)$
9. Direct $^{99\text{m}}\text{Tc}$ production by $^{100}\text{Mo}(p,2n)$

2. The current Mo-99/Tc-99m supply situation



⁹⁹Mo Global Supply Chain

JUNE 2011

Nuclear Energy in Perspective



The Path to a Reliable Supply of Medical Radioisotopes

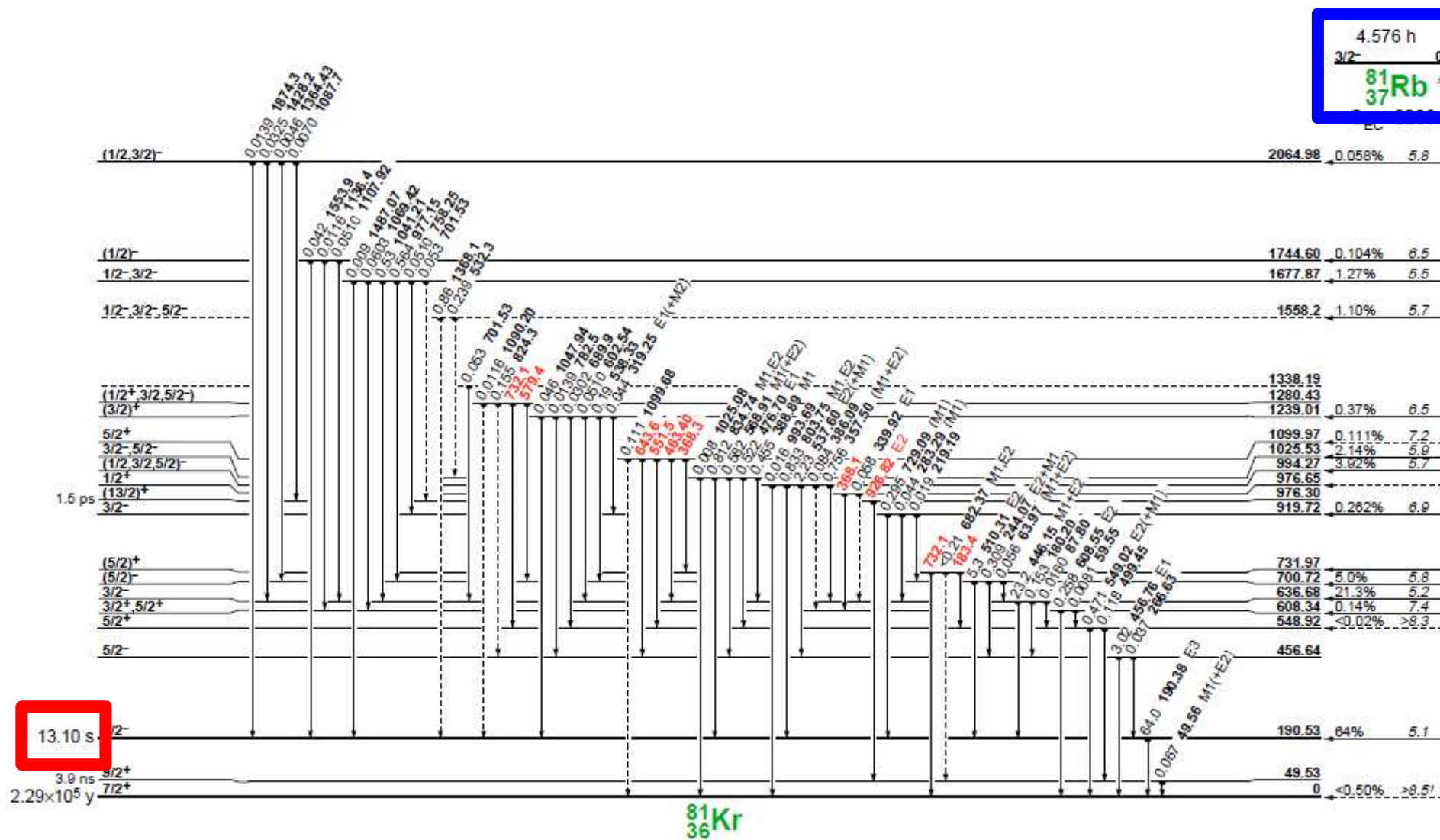
The producing reactor gets only 0.26 EUR per ^{99m}Tc patient dose, similar to the price of a single cheap pill.

	Irradiation value within final radiopharmaceutical price (EUR)	Irradiation value as % of final procedure costs
Pre-shortage situation	0.26	0.11
Required for economic sustainability	0.33-2.39	0.14-0.97

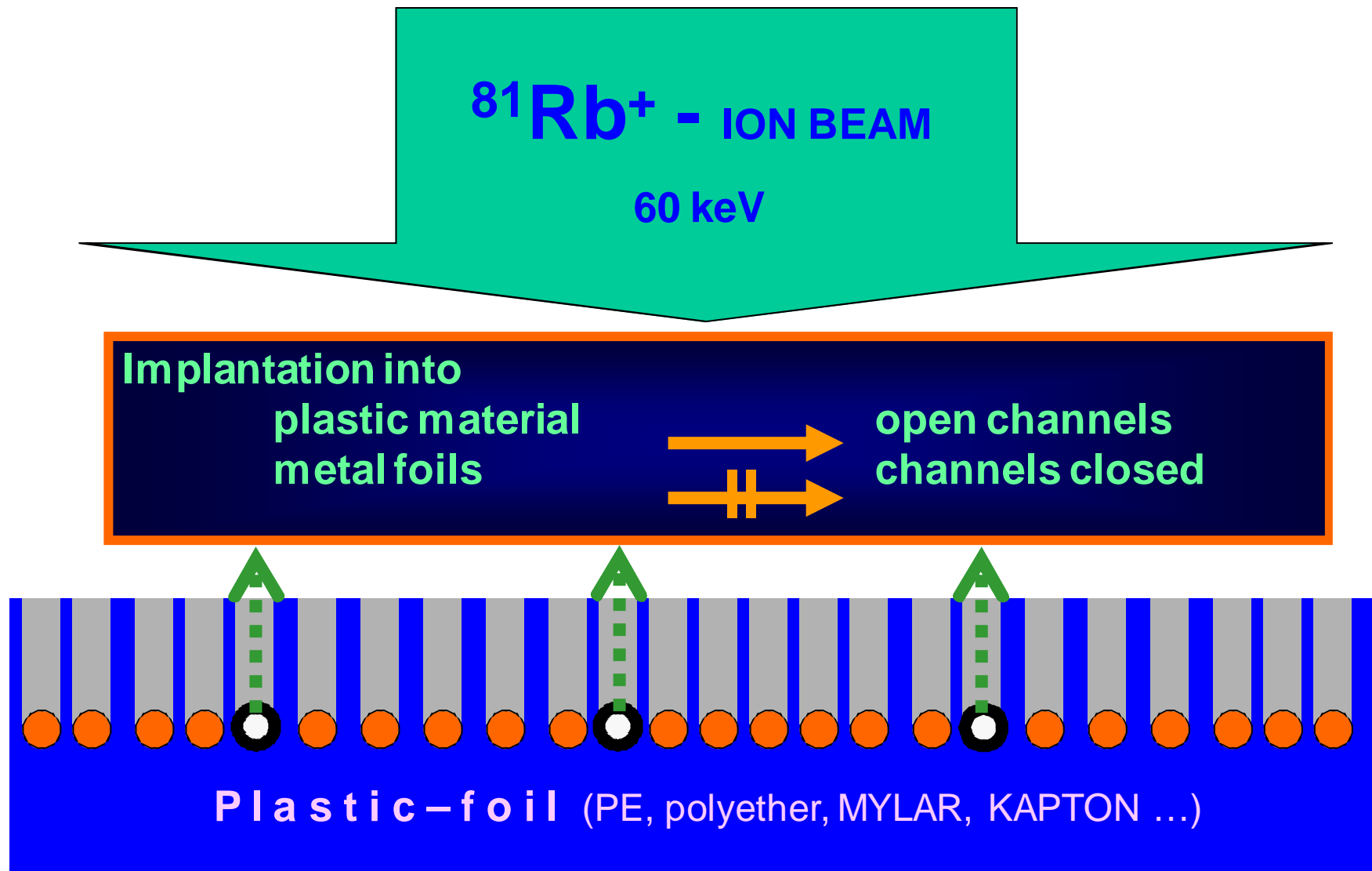
SPECT Tracer

Radio-nuclide	Half-life (h)	E_{γ} (keV)	Branching ratio γ (%)	Decay type
Ga-67	78	93	42	EC
Kr-81m	0.004	190	64	IT
Tc-99m	6	141	89	IT
In-111	67	245	94	EC
I-123	13	159	83	EC
Xe-133	126	81	38	β^-
Tl-201	73	167	10	EC
I-131	192	364	82	β^-
Lu-177	161	208	10.4	β^-

$^{81}\text{Rb}/^{81\text{m}}\text{Kr}$ generator

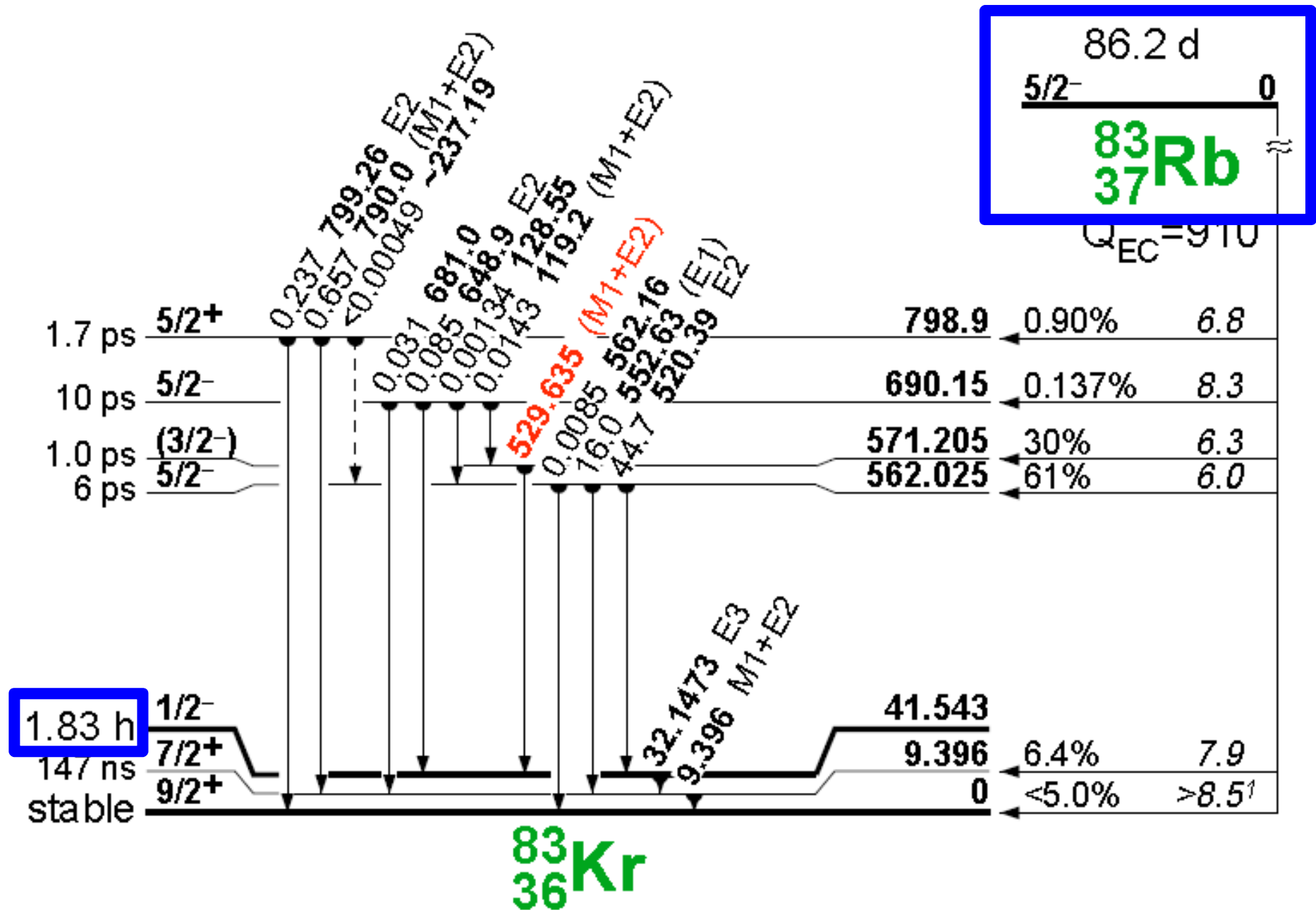


Implantation type $^{81}\text{Rb} / ^{81\text{m}}\text{Kr}$ generator



G.J. Beyer, H.L. Ravn, Y. Huang, *Int. J. Appl. Radiat. Isot.* 35 (1984) 1075.
G.J. Beyer, H.L. Ravn, *Appl. Rad. Isot.* 42 (1991) 141.

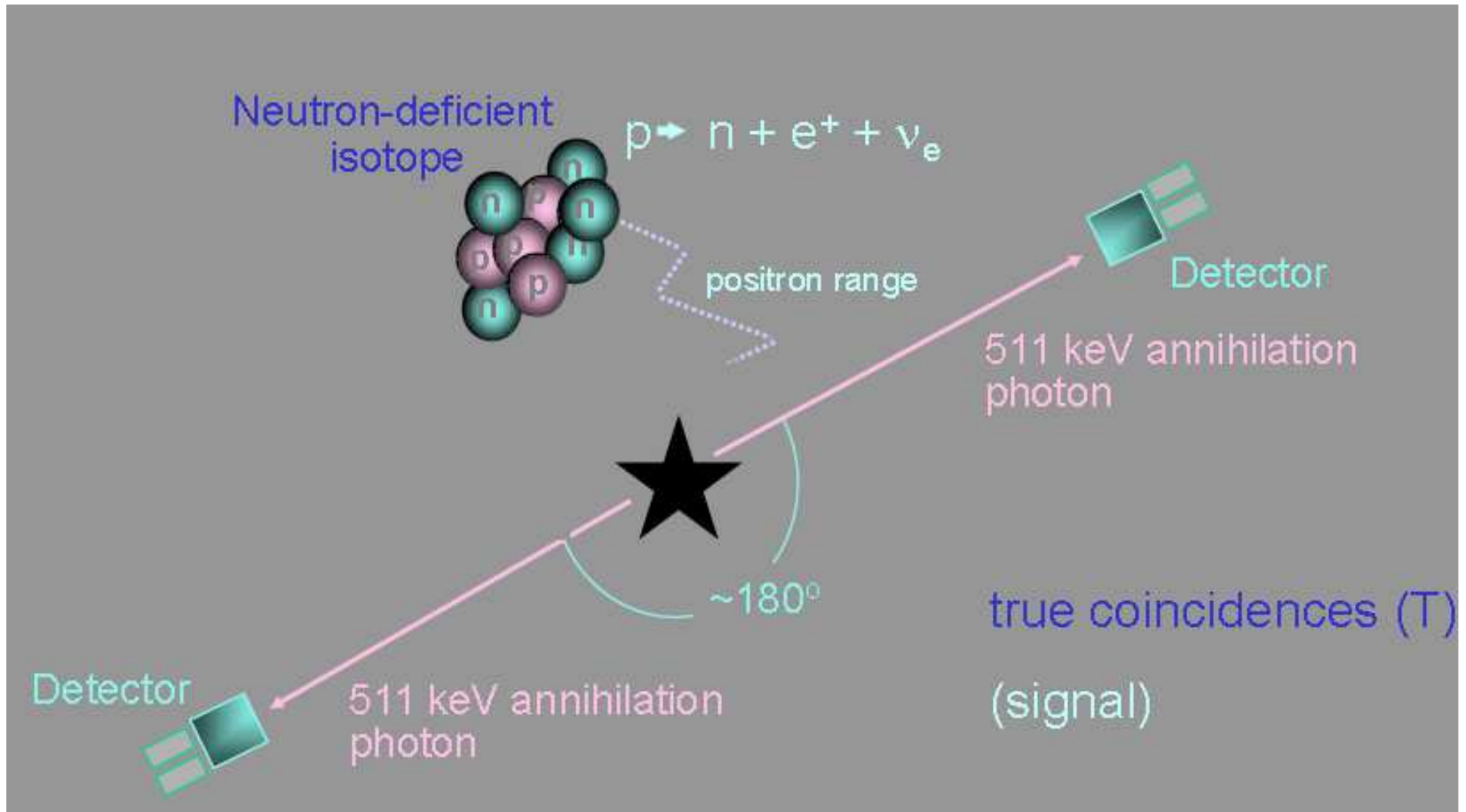
Implantation type $^{83}\text{Rb}/^{83\text{m}}\text{Kr}$ generator



^{83}mKr for on-line calibration of large gas detectors



PET: Positron Emission Tomography

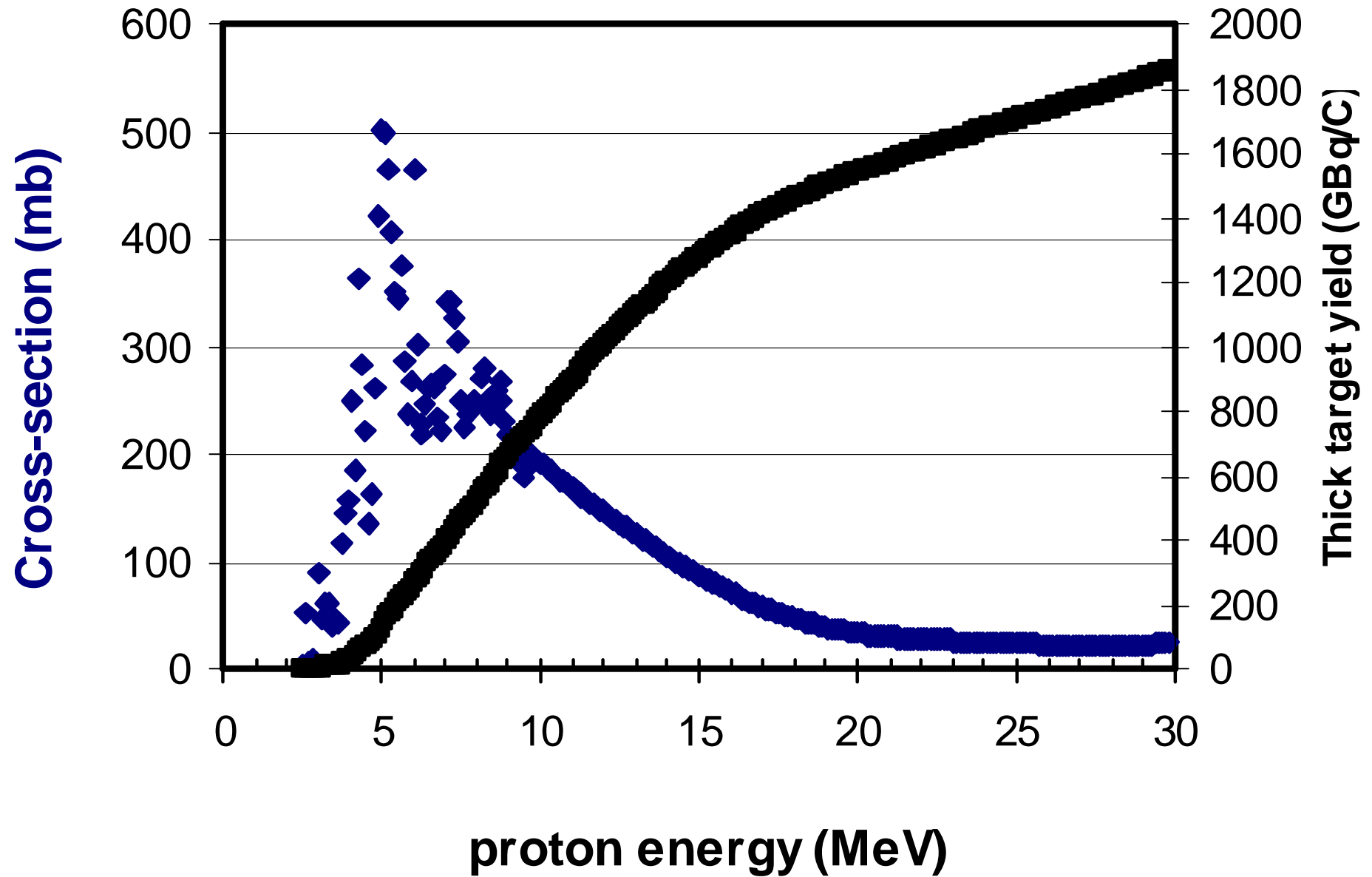


Low β^+ energy to minimize range > better spatial resolution.

PET isotopes

Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	E mean (MeV)	Range (mm)
F-18	1.83	96.7	0.25	0.7
C-11	0.34	99.8	0.39	1.3
N-13	0.17	99.8	0.49	1.8
O-15	0.03	99.9	0.74	3.2

$^{18}\text{O}(p,n)^{18}\text{F}$ cross-section



FLUORINE-18 PRODUCTION AT A 590 MeV SYNCHROCYCLOTRON:
RADIOPHARMACEUTICAL SYNTHESIS AND BIODISTRIBUTION.

H. J. TOCHON-DANGUY, D. TOWNSEND, M. WENSVEEN, P. FREY, A. CHRISTIN,
A. GEISSBUHLER, A. DONATH

Division of Nuclear Medicine, University Hospital, 1211 Geneva, (Switzerland).

H. RAVN

ISOLDE Group, CERN, Geneva (Switzerland)

R. DELTENRE

SC Group, CERN, Geneva (Switzerland)

J. Fluorine Chemistry 41 (1988) 33.

HIDAC camera

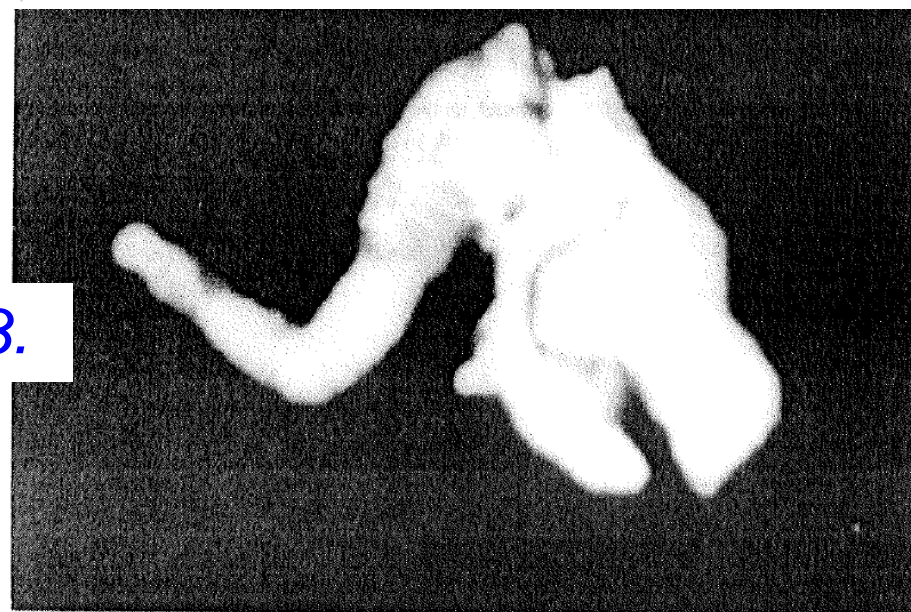
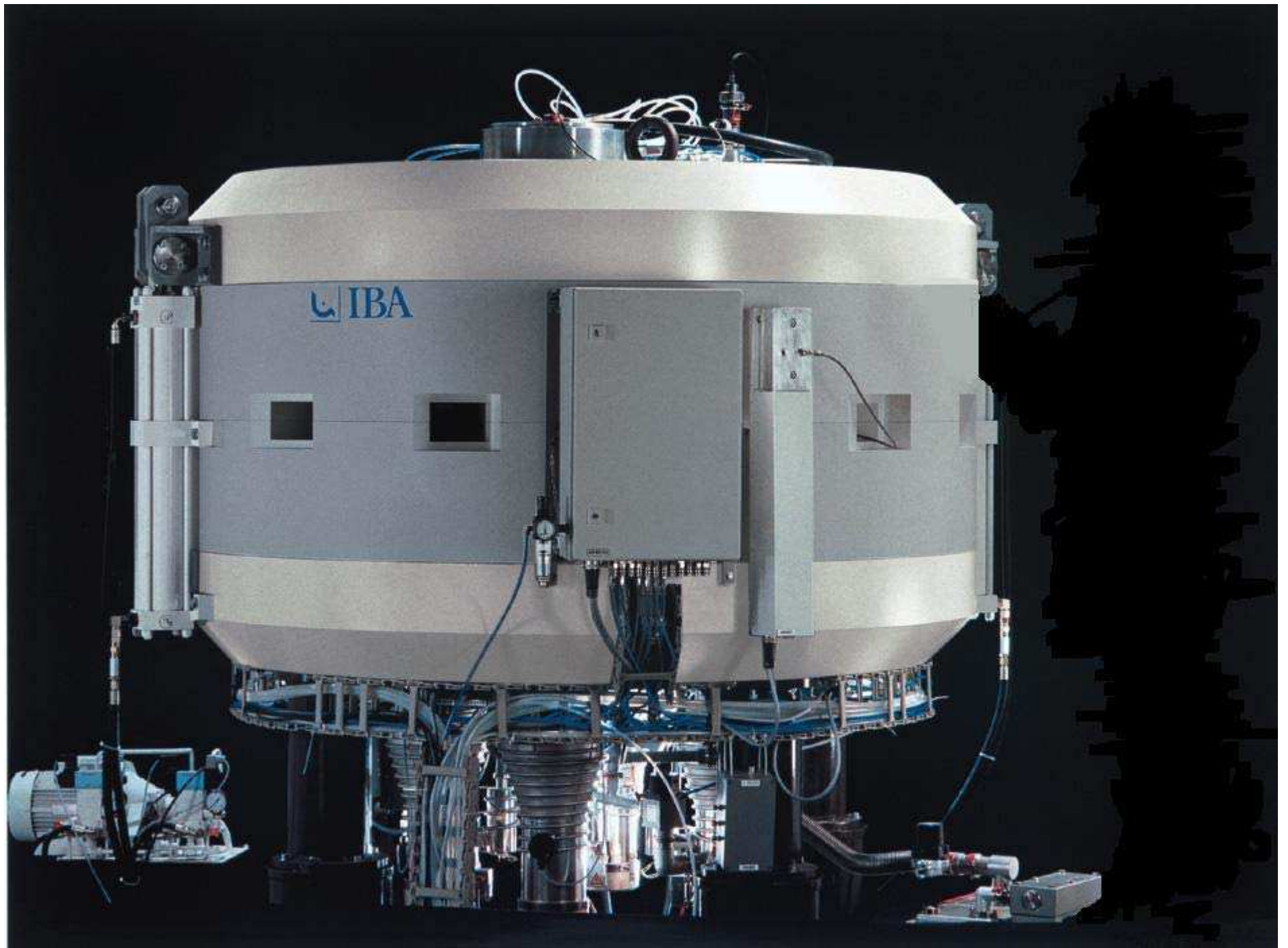
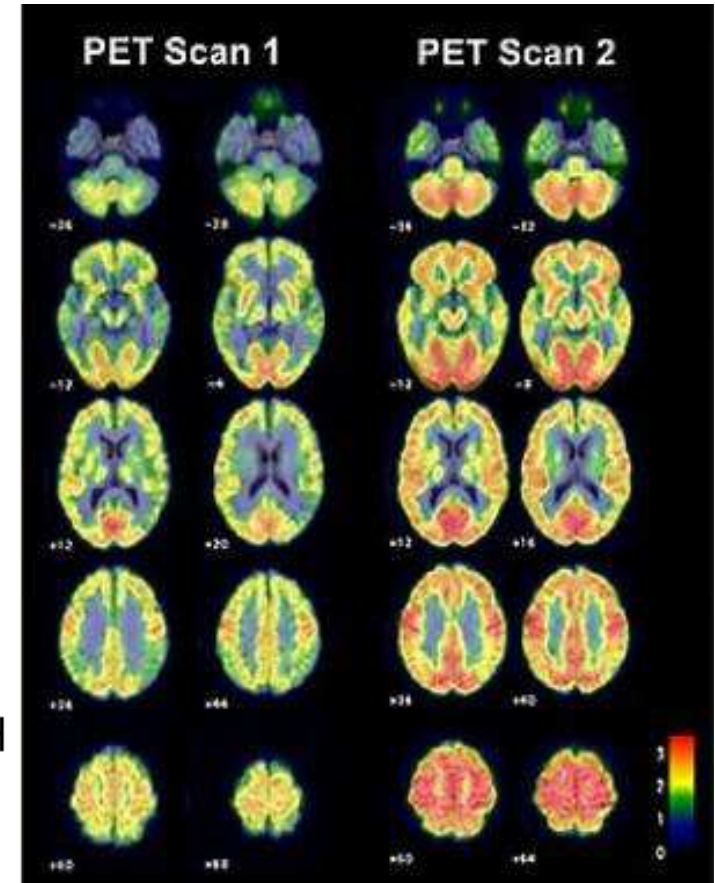
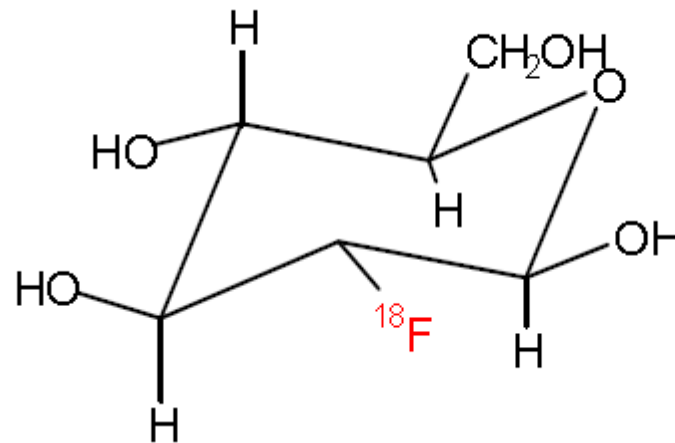


Fig. 3. Shaded-graphics display of the skull of a rabbit imaged 45 min after injection of a solution of Na^{18}F .



FDG



2-Deoxy-2-[¹⁸F]fluoro-D-β-glucose (2-FDG)

*“Building a robust European
PET infrastructure”*

Advanced Accelerator Applications

- 12 production and R&D facilities
- more than 210 employees
in 9 countries
- 2011 revenues €36.4 million

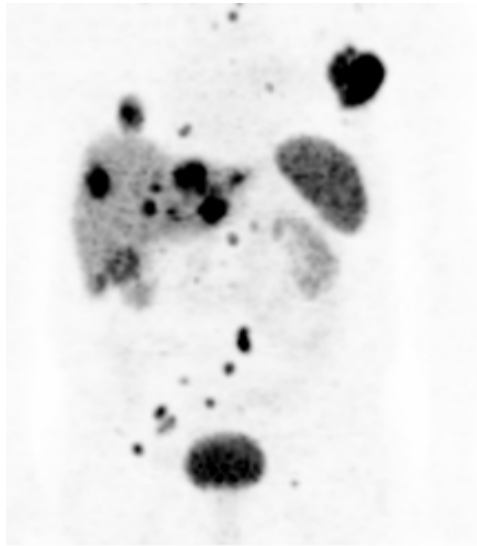


PET isotopes

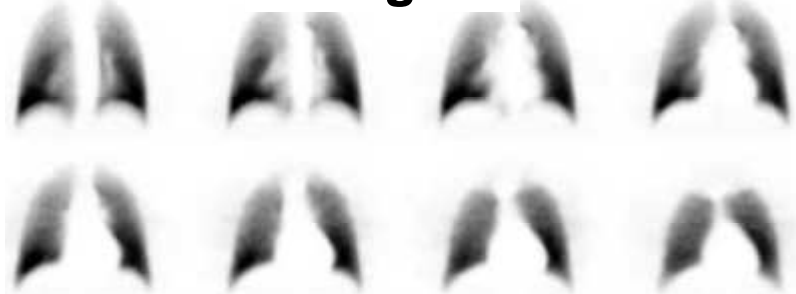
Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	E mean (MeV)	Range (mm)
F-18	1.83	96.7	0.25	0.7
C-11	0.34	99.8	0.39	1.3
N-13	0.17	99.8	0.49	1.8
O-15	0.03	99.9	0.74	3.2
Ga-68	1.13	89.1	0.83	3.8
Rb-82	0.02	95.4	3.38	20
Sc-44	3.97	94.3	0.63	2.5

Use of ^{68}Ga as PET nuclide

Somatostatin analogues

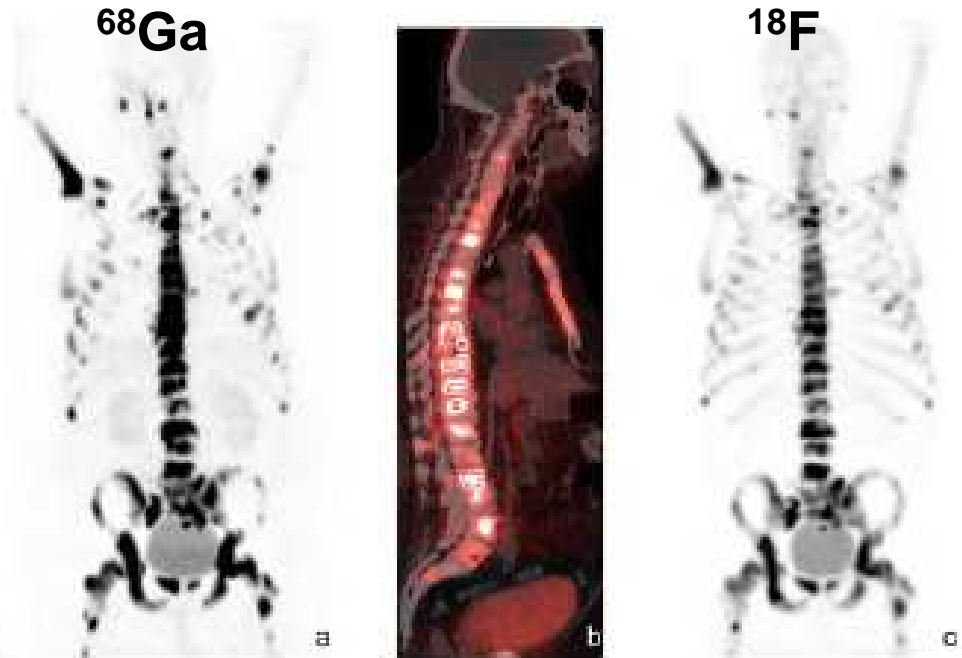


Galligas™



(Kotzerke et al.; Eur J Nucl Med Mol Imaging 2010)

Bisphosphonates (^{68}Ga vs. ^{18}F)

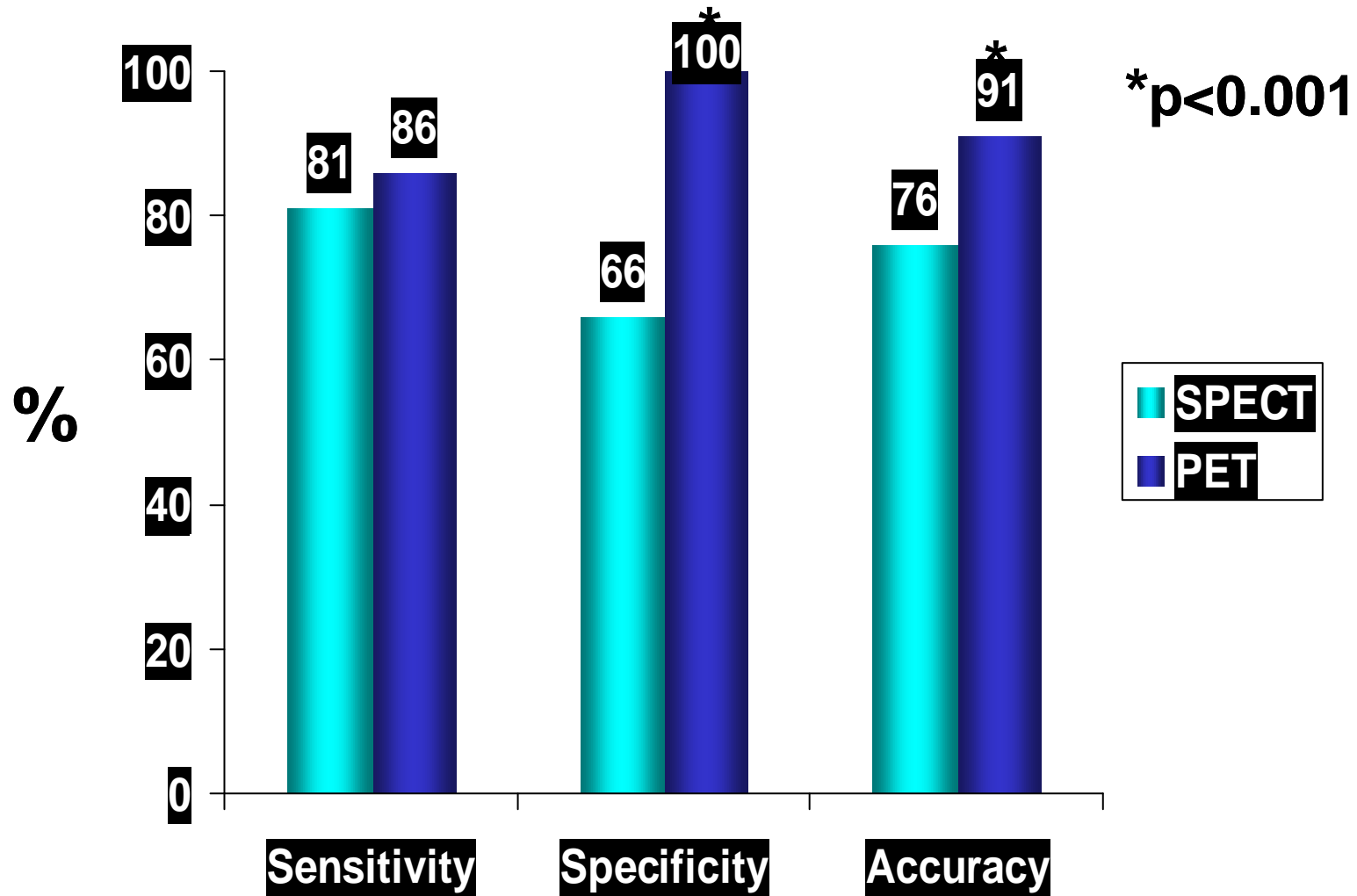


(Fellner et al.; Eur J Nucl Med Mol Imaging 2010)

Bombesin

Ga-microspheres

Diagnostic Accuracy: PET vs SPECT



PET isotopes

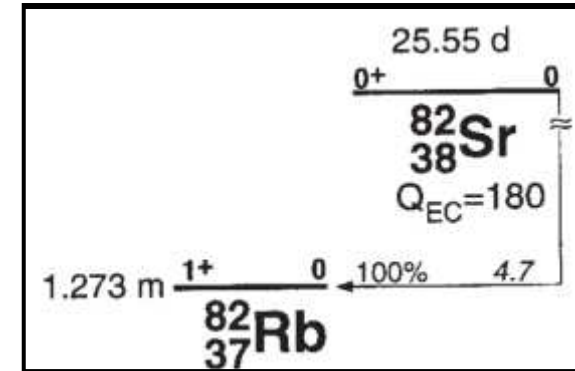
Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	E mean (MeV)	Range (mm)
F-18	1.83	96.7	0.25	0.7
C-11	0.34	99.8	0.39	1.3
N-13	0.17	99.8	0.49	1.8
O-15	0.03	99.9	0.74	2.2
Ga-68	1.13	89.1	0.83	
Rb-82	0.02	95.4	3.38	
Sc-44	3.97	94.3	0.63	

Mother isotope:
271 d
25 d
60 y

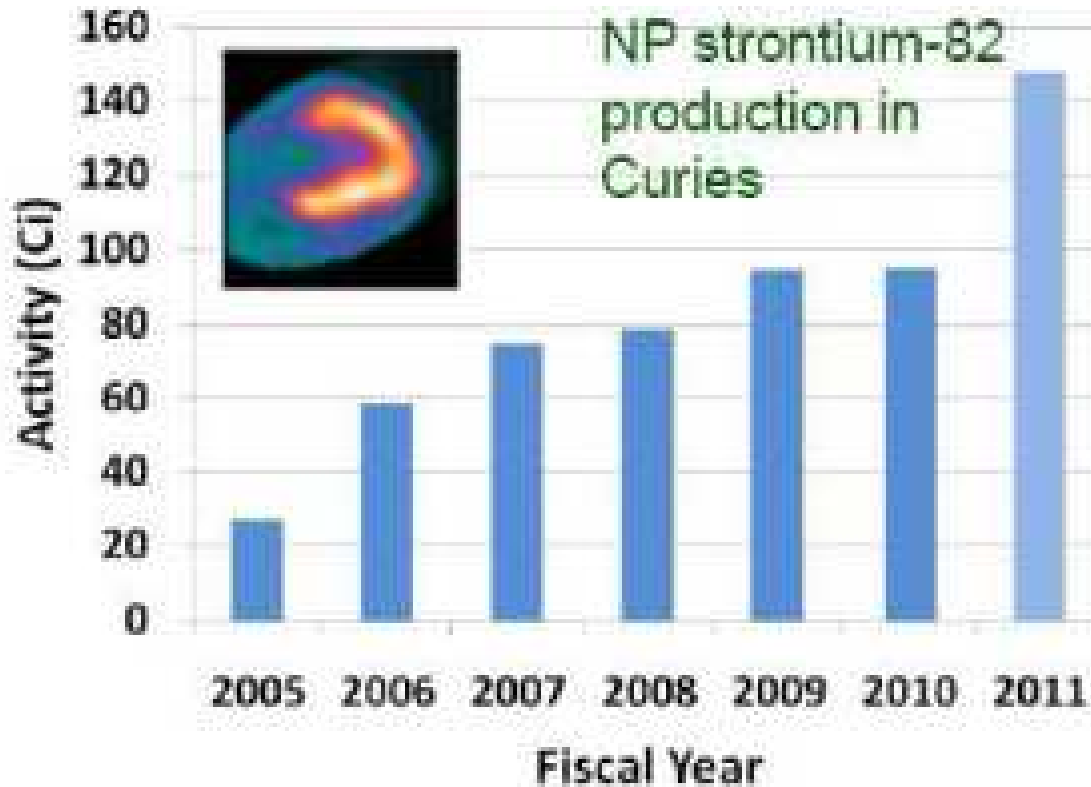
Transport of short-lived radioisotopes



^{82}Rb is used for PET in cardiology
 → $^{82}\text{Sr}/^{82}\text{Rb}$ generator



Evolution of ^{82}Sr demand in the USA



(source : Department of Energy, USA)

Facilities producing Sr-82 in the world

- LANL, USA –100 MeV, 200 μ A

- BNL, USA –200 MeV, 100 μ A

- INR, Russia –160 MeV, 120 μ A



BLIP

- iThemba, South Africa –66 MeV, 250 μ A

- TRIUMF, Canada –110 MeV, 70 μ A



5 accelerators – 2 generator manufacturers – 1 generator

Mar - Jul 2011: outage of 2 accelerators > ⁸²Sr shortage

Jul '11 - Feb '12: generator recalled

Problem: Concentration on few players





New players



Upcoming:

70 MeV cyclotrons in Legnaro, Texas,...

Two new $^{82}\text{Sr}/^{82}\text{Rb}$ generators (Draximage, Quanticardi)

Longer-lived PET isotopes

Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	E mean (MeV)	Range (mm)
Sc-44	3.97	94.3	0.63	2.5
Cu-64	12.7	17.6	0.28	0.8
Y-86	14.7	31.9	0.66	2.6
Zr-89	78.4	22.7	0.40	1.4
I-124	100.2	22.8	0.82	3.8
Tb-152	17.5	17	1.08	5

From diagnostics

The death and the radiologist.

*Bad news:
you are going
to die soon.*

*Oh my God!
Where did you find
all these nude
photos of me?*



to therapy

Cancer and efficiency of treatments

At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	58%	42%	100%
Cured by:			
Surgery	22%		
Radiation therapy	12%		
Surgery+radiation therapy	6%		
All other treatments and combinations incl. chemotherapy		5%	
Total cured	40%	5%	45%
Fraction cured	69%	12%	45%

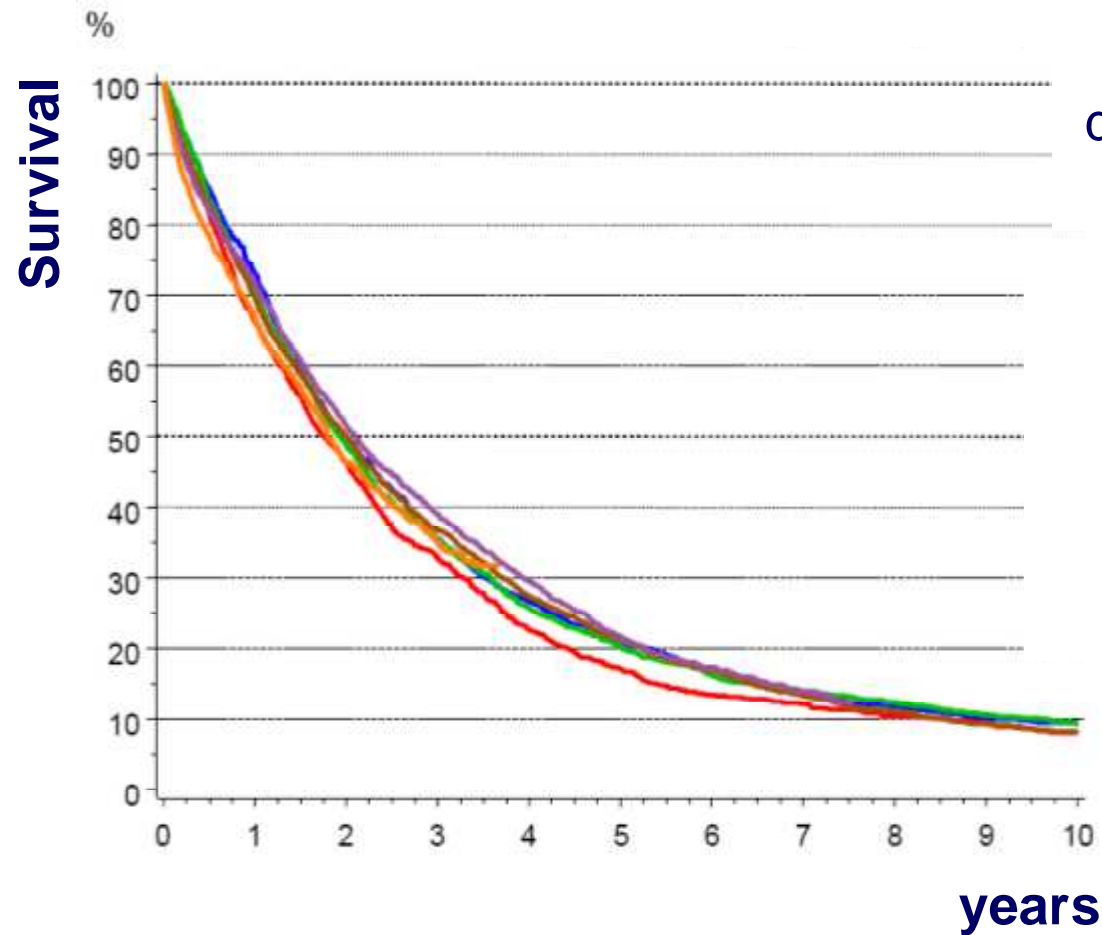
Per year over **one million cancer deaths** in the EU.

⇒ improve early diagnosis

⇒ improve **systemic treatments**

Mammary Carcinoma

Survival time since diagnosis of metastases



Results for 6 time periods
data from tumor centre Munich
n = 9228

1980-1984

1985-1989

1990-1994

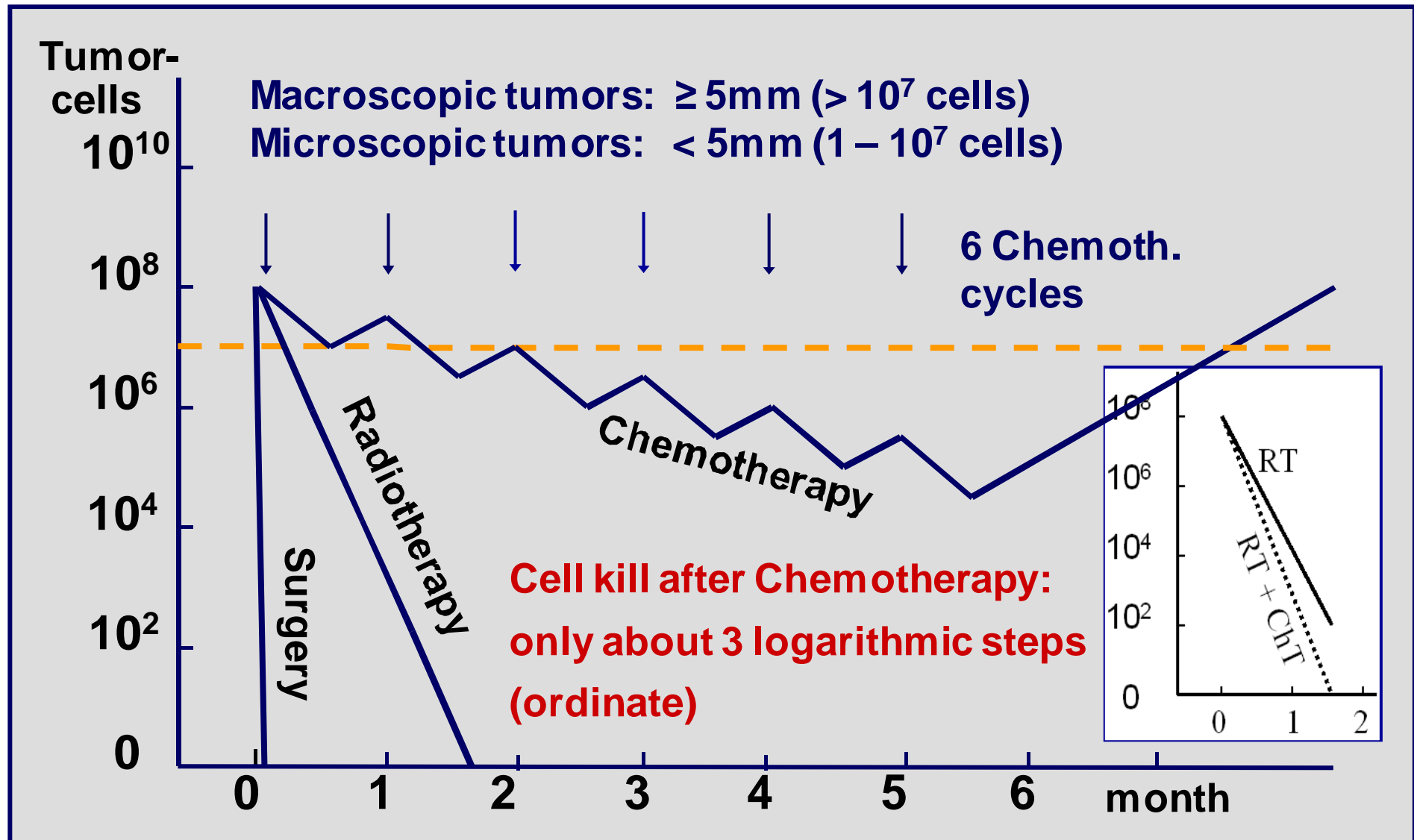
1995-1999

2000-2003

since 2004

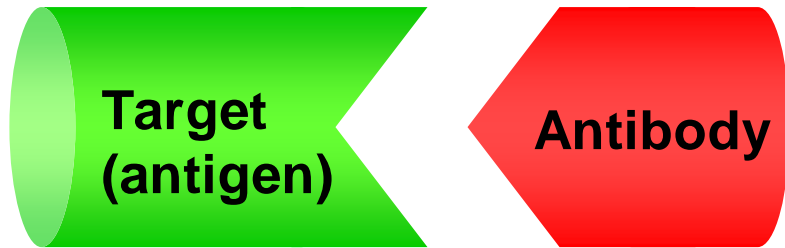
**Little/no improvement
with (modern)
chemotherapies!**

Comparison of Therapies

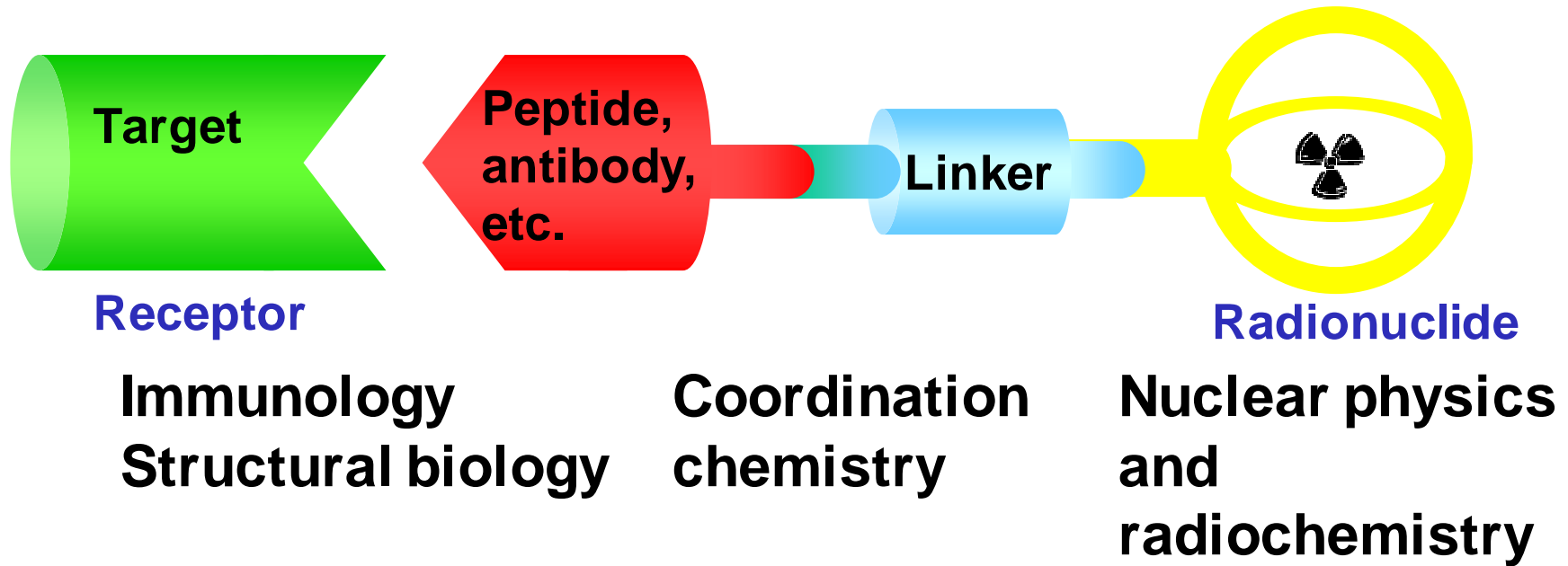


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

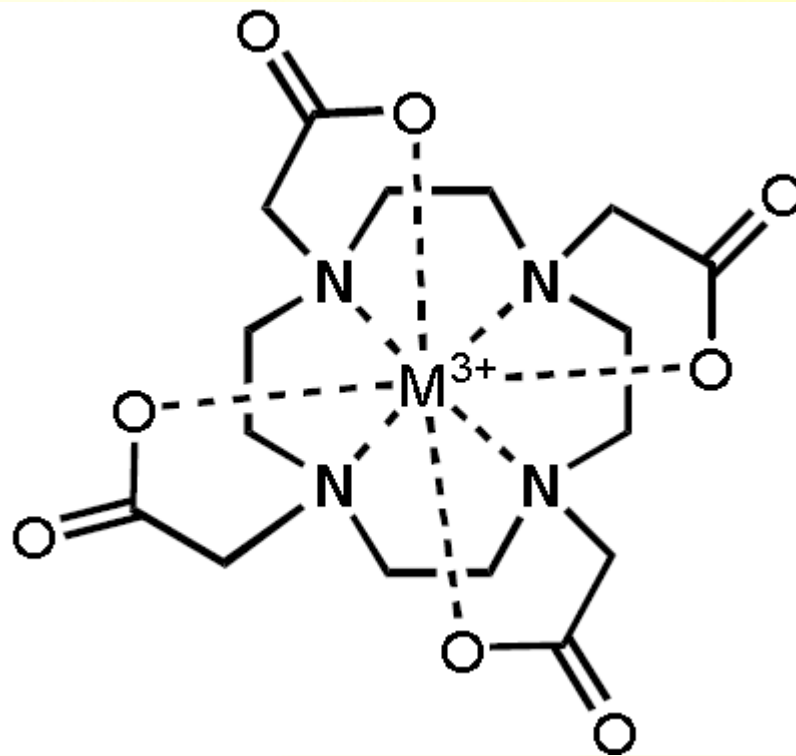
Immunology approach



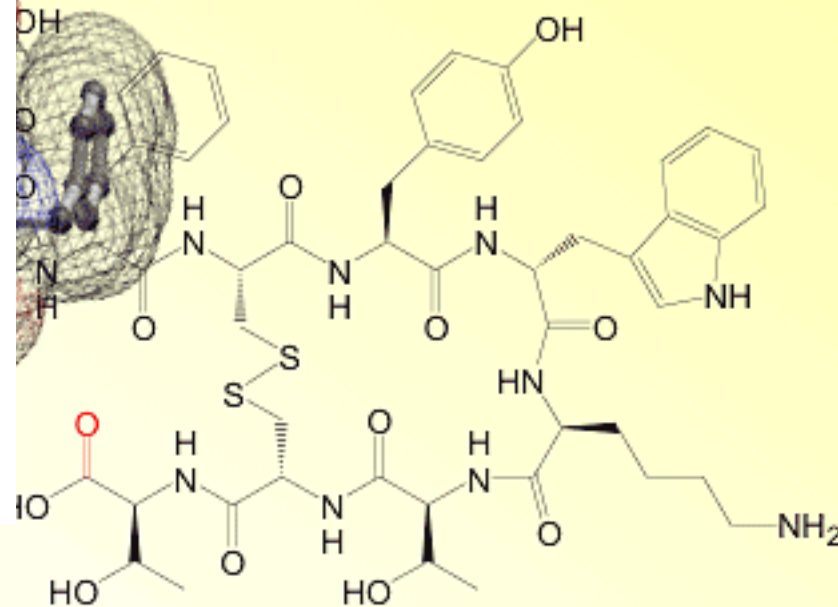
Multidisciplinary collaboration to fight cancer



Structural Formula of DOTA-TOC/TATE



DOTA-TATE

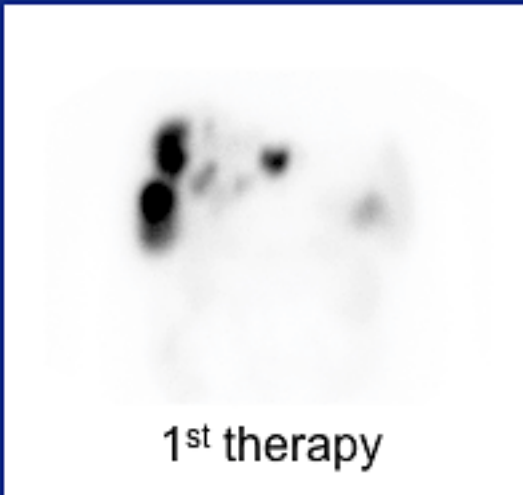
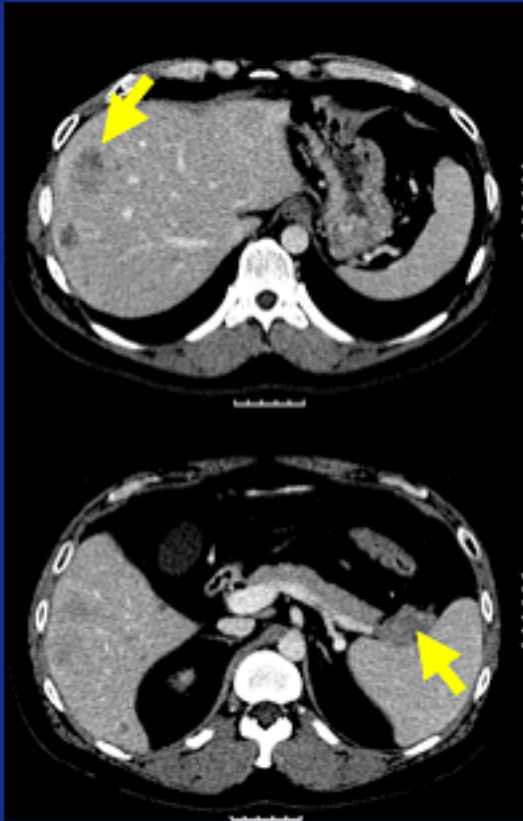


1,4,7,10-tetraazacyclododecantetraacetate

- ^{111}In ^{90}Y
- ^{67}Ga ^{177}Lu
- ^{68}Ga ^{213}Bi

$\text{IC}_{50} (\text{Y}^{\text{III}}) = 1.6 \pm 0.4 \text{ nM}$

Helmut Maecke, EANM-2007.



Male

36 years of age

Small cell pancreatic
neuroendocrine
tumour

Liver metastases

Ki-67 index 10-15%
(liver biopsy)

4 cycles with ^{177}Lu -
octreotate and
capecitabine

Partial remission

1st therapy

4th therapy

Roelf Valkema, EANM-2008.

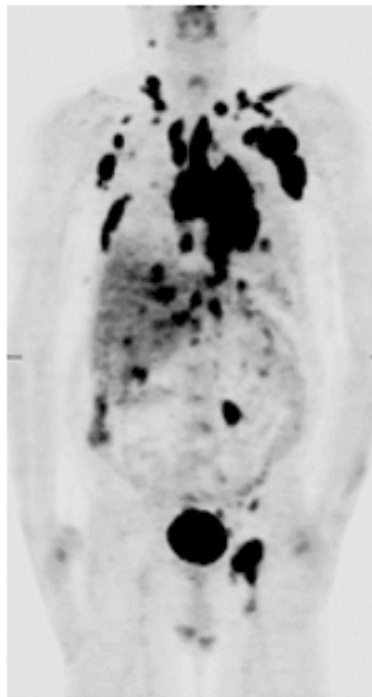
What success does PRRT offer?

- ✓ CR+ PR + MR in about 50% of patients: YES
- ✓ Reduce symptoms and improve quality of life: YES
- ✓ Increase survival time: YES
- ✓ Safety and tolerability: YES

Lymphoma therapy: RITUXIMAB+¹⁷⁷Lu

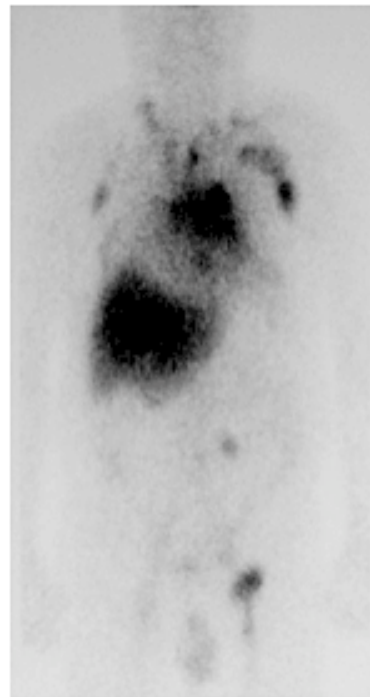
E.B., 1941 (m): UPN 6

¹⁸FDG PET



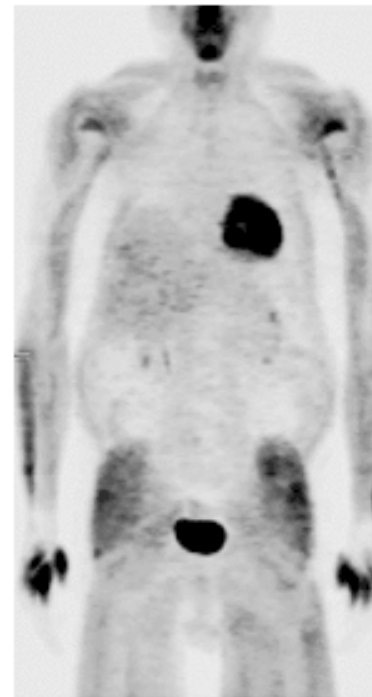
1.9.2002

¹⁷⁷Lu-Scan



13.9.2002

¹⁸FDG PET

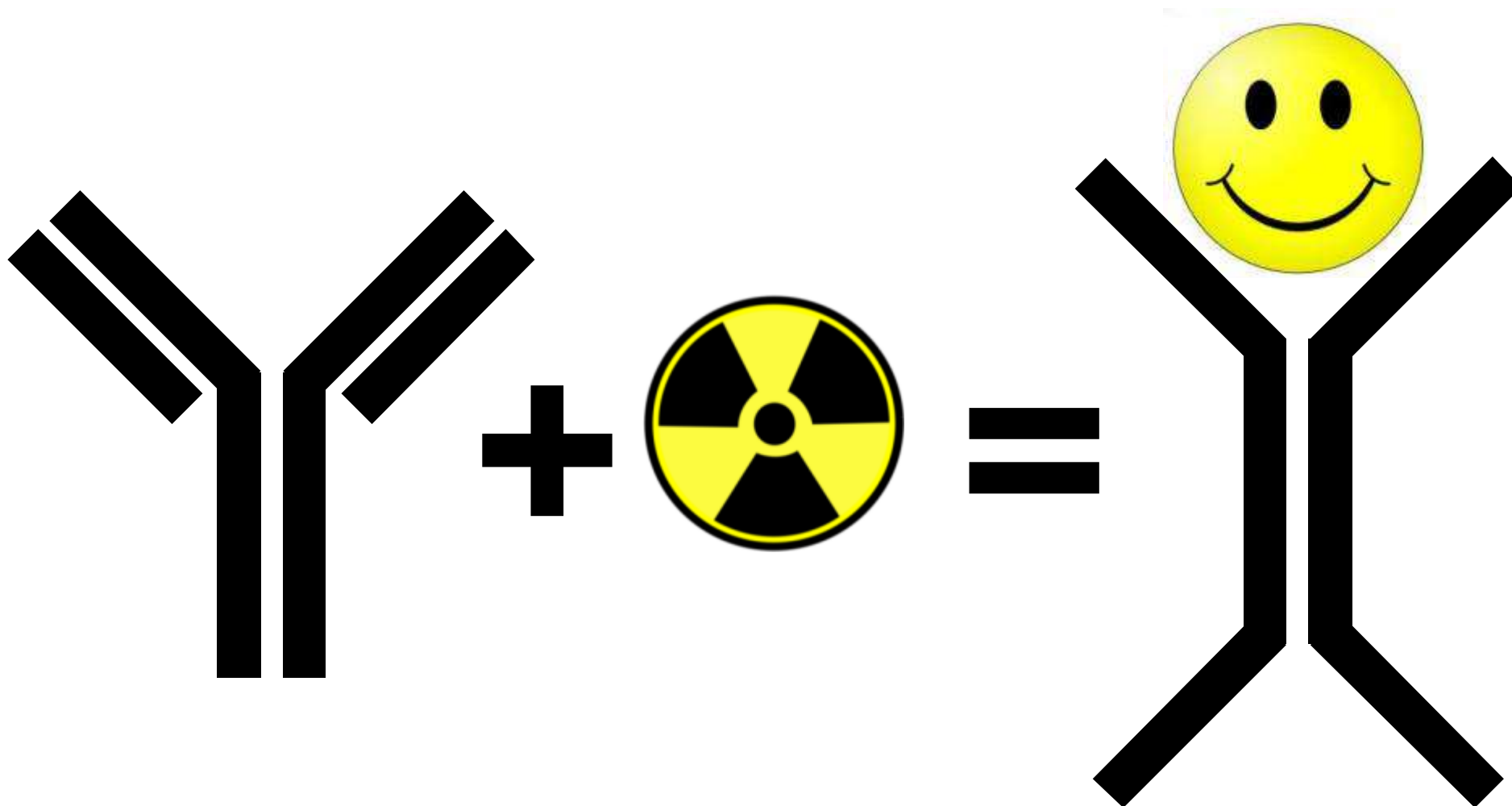


15.11.2002

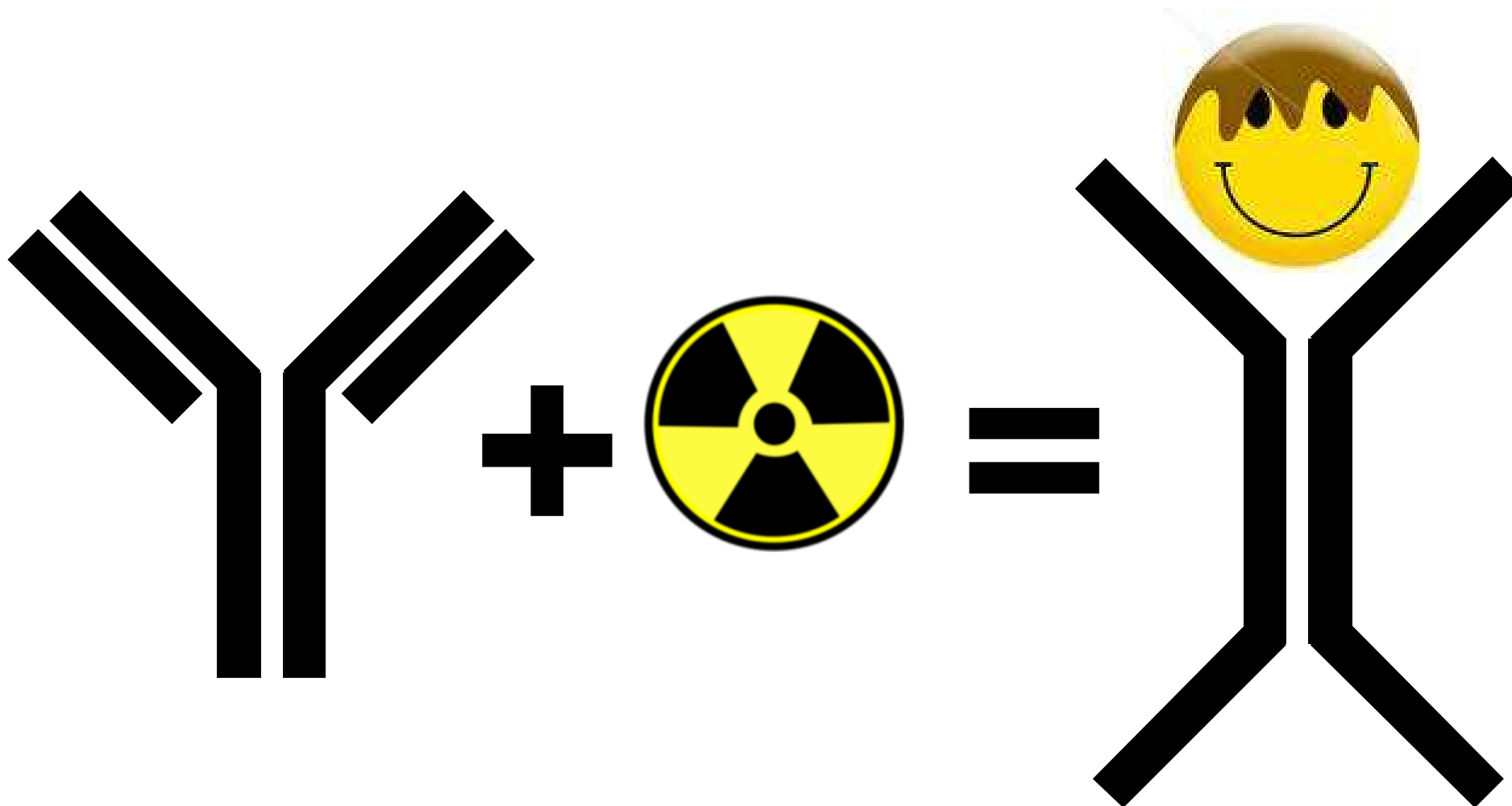
**Still
in
CR**

15.9.2009

Radioimmunotherapy

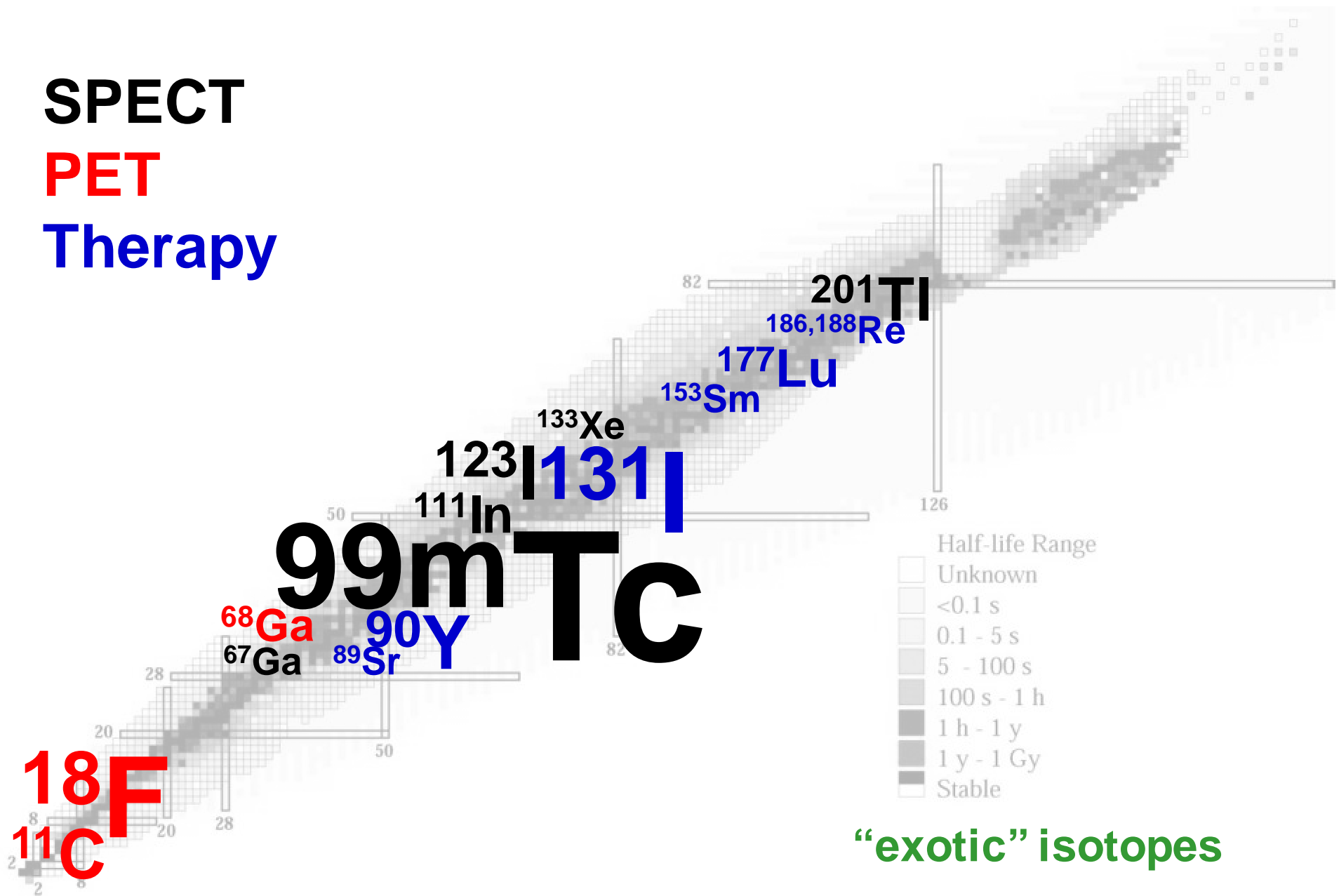


Radioimmunotherapy



The chart of nuclides – nuclear medicine perspective

SPECT
PET
Therapy

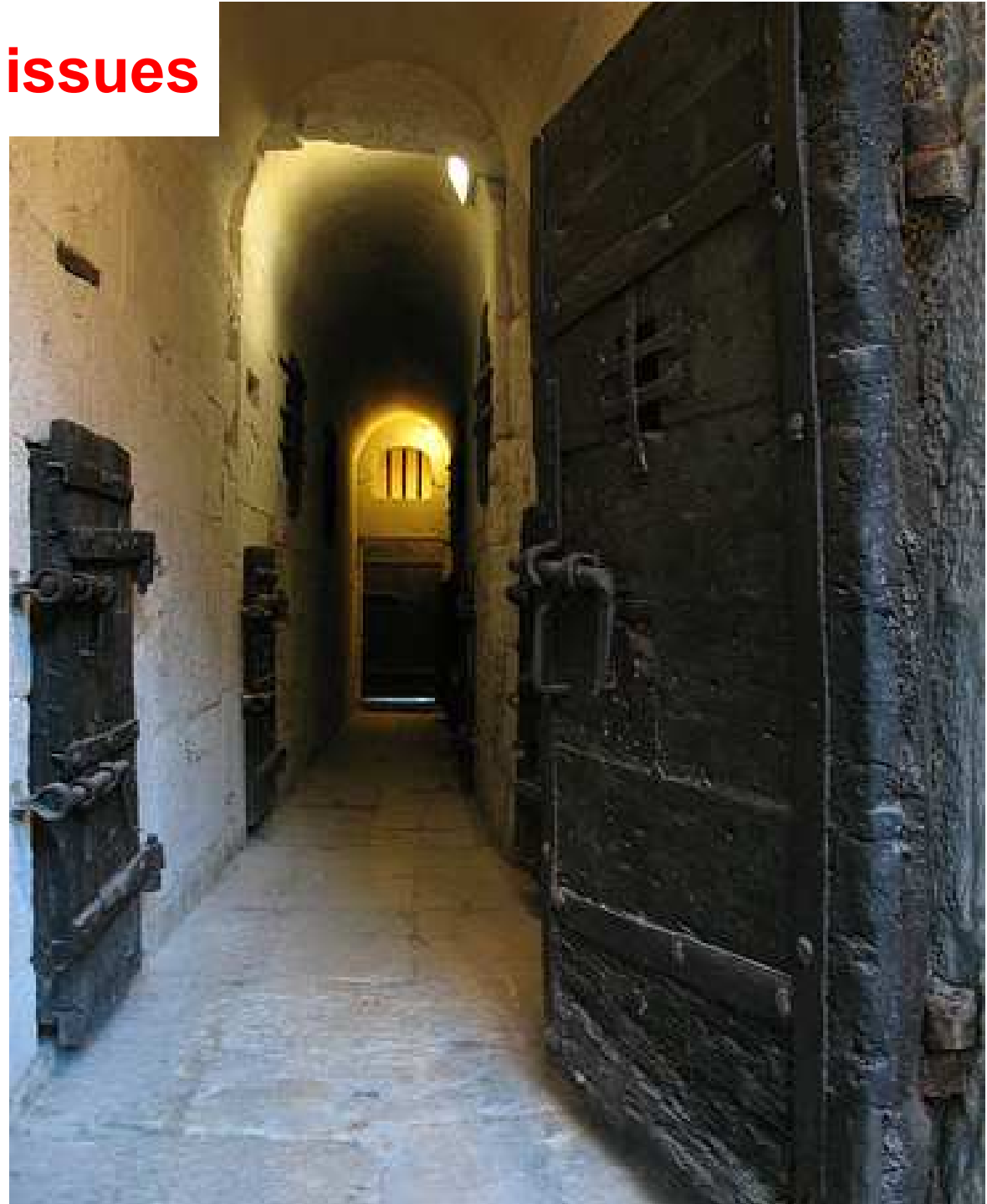


¹³¹I: radioprotection issues

**364 keV gamma ray
emitted with 82% B.R.**

**3.7 GBq patient dose
⇒ 0.2 mSv/h at 1 m**

**requires dedicated
shielded treatment
rooms**



^{90}Y : collateral damage from long range betas ?

$Q_{\beta^-} = 2.28 \text{ MeV}$
up to 12 mm range



Radionuclides for RIT and PRRT

Radio-nuclide	Half-life (d)	E mean (keV)	E γ (B.R.) (keV)	Range
Y-90	2.7	934 β	-	12 mm
I-131	8.0	182 β	364 (82%)	3 mm
Lu-177	6.7	134 β	208 (10%) 113 (6%)	2 mm

Established isotopes

Emerging isotope

Production of ^{177}Lu

Ta 175 10.5 h ϵ γ 207; 349; 267; 82; 126; 1793...	Ta 176 8.1 h ϵ β^+ ... γ 1159; 88; 1225...	Ta 177 56.6 h ϵ β^+ γ 113; 208... g	Ta 178 $\xleftrightarrow{9.25\text{ m}}$ $\xleftrightarrow{2.45\text{ h}}$ ϵ β^+ 0.9 γ 93; 135; 1341... g ϵ γ 332... m_i	Ta 179 665 d ϵ $n\alpha$ γ g σ 930	Ta 180 0.012 $> 10^{15}\text{ a}$	Ta 181 99.988 σ 0.012 + 20 $\sigma_n, \alpha < 10^{-6}$
Hf 174 0.16 $2.0 \cdot 10^{15}\text{ a}$ α 2.50 σ 600	Hf 175 70.0 d ϵ γ 343...	Hf 176 5.26 σ 23	Hf 177 51 m 1.1 s 18.60 γ 277; 295; 327... γ 208; 229; 379... σ 10 ⁻⁷ σ 1 σ 375	Hf 178 31 a 4.0 s 27.28 γ 574; 495; 217... γ 426; 326; 213; σ 45 89... σ ? σ 54 σ 32	Hf 179 25 d 18.7 s 13.62 γ 454; 363; 123; γ 214 σ 0.43 σ 46	Hf 180 5.5 h 35.08 γ 332; 443; 215; β^- ... σ 13 $\sigma_n, \alpha < 1.3 \cdot 10^{-6}$
Lu 173 1.37 a ϵ γ 272; 79; 101... e^-	Lu 174 142 d 3.31 a γ 45; 67... $e^-; \epsilon$ γ (992; 273...) ϵ β^+ ... γ 1242; 78...	Lu 175 97.41 σ 16 + 8	Lu 176 2.59 3.68 h 3.8 · 10 ¹⁰ a β^- 1.2; 1.3...; ϵ γ 88... e^- σ 2 + 2100	Lu 177 160.1 d 6.71 d β^- 0.2 0.5... γ 419; 208; 310; 122... m_i σ 3.2 σ 1000	Lu 178 22.7 m 28.4 m β^- 2.0... γ 93; 1341; 1310; 1269...; g	Lu 179 4.6 h β^- 1.4... γ 214... g
Yb 172 21.83 $\sigma \sim 1.3$ $\sigma_n, \alpha < 1E-6$	Yb 173 16.13 σ 16 $\sigma_n, \alpha < 1E-6$	Yb 174 31.83 σ 63 $\sigma_n, \alpha < 0.00002$	Yb 175 4.2 d β^- 0.5... γ 396; 283; 114...	Yb 176 12 s 12.76 γ 293 390; 190; 96... σ 3.1 $\sigma_n, \alpha < 1E-6$	Yb 177 6.5 s 1.9 h β^- 1.4... γ 150; 1080; 122; 1241... g	Yb 178 74 m β^- 0.6... γ 391; 348;... g
Tm 171 1.92 a	Tm 172 63.6 h	Tm 173 8.2 h	Tm 174 2.29 e 1.54 m	Tm 175 15.2 m	Tm 176 1.9 m	Tm 177 85 s

Waste problem for hospitals!

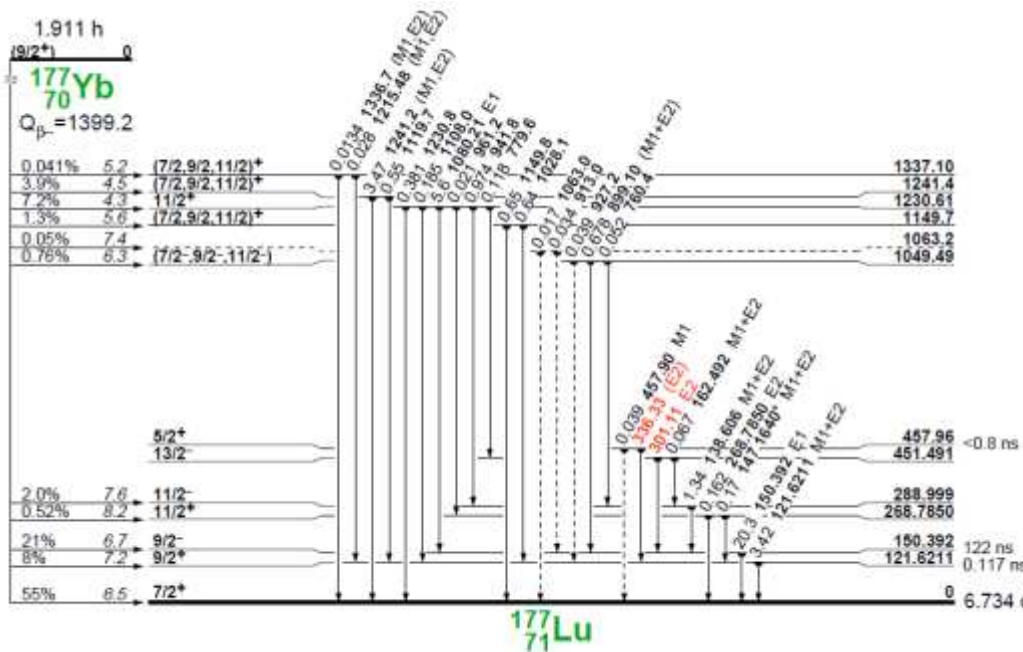
R. Henkelmann et al., Eur. J. Nucl. Med. Mol. Imag. 36 (2009) S260.

The curse of the *K*-isomer !



"So it'll pollute the lake. It will also make the fish glow in the dark when we go night-fishing !"

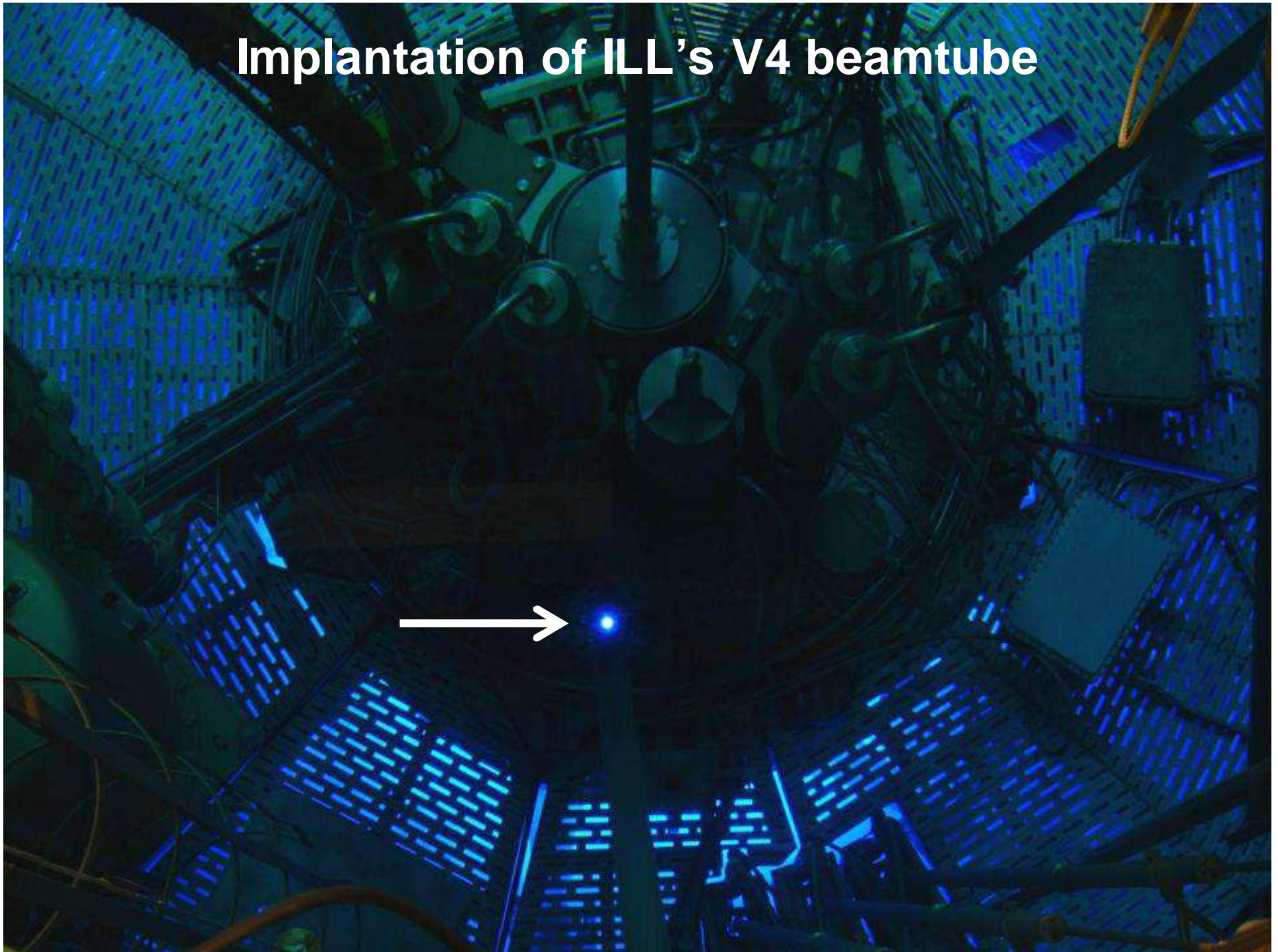
Alternative production route to ^{177}Lu



Ta 179 665 d ε n0 γ g σ 930	Ta 180 0.012 > 10 ¹⁵ a σ ~560 ε β ⁻ 0.7... γ 93; 104 g	Ta 181 99.988 σ 0.012 + 20 σ _n , α < 10 ⁻⁵				
Hf 178 31 a ly 574; 495; 217... σ 45	Hf 179 27.28 25 d ly 454; 363; 123; 146... σ 45 +54 +32	Hf 180 13.62 18.7 s ly 214 σ 0.43 +46 5.5 h ly 332; 443; 215; 57... β ⁻ ... σ 13 σ _n , α < 13 · 10 ⁻⁵				
Lu 177 160.1 d β ⁻ 0.2 ly 414; 319; 122... σ 3.2	Lu 178 6.71 d β ⁻ 0.5... γ 208; 113... g σ 1000	Lu 179 22.7 m β ⁻ 1.2... γ 332... g 28.4 m β ⁻ 2.0... γ 93; 1341; 1310; 1269...; g				
Yb 172 21.83 σ ~1.3 σ _n , α < 1E-6	Yb 173 16.13 σ 16 σ _n , α < 1E-6	Yb 174 31.83 σ 63 σ _n , α < 0.00002	Yb 175 4.2 d β ⁻ 0.5... γ 396; 283; 114...	Yb 176 12 s ly 293; 390; 190; 96... σ 3.1 σ _n , α < 1E-6	Yb 177 6.5 s ly 104; 228 e ⁻ g 1.9 h β ⁻ 1.4... γ 150; 1080; 122; 1241	Yb 178 74 m β ⁻ 0.6... γ 391; 348;... g
Tm 171 1.92 a β ⁻ 0.1... γ (67); e ⁻ σ ~160	Tm 172 63.6 h β ⁻ 1.8; 1.9... γ 79; 1094; 1387; 1530; 1466; 1609...					Tm 177 85 s β ⁻ γ 105; 518... g; m

- Free of long-lived isomer
- Non-carrier-added quality
- “Needs” high-flux reactor

Implantation of ILL's V4 beamtube



The rising star for therapy



The history of lutetium separation

**1878 Separation of Yb in Geneva
by Jean-Charles Galissard de Marignac**

**1907 Separation of Lu from Yb
Georges Urbain
Carl Auer von Welsbach
Charles James**

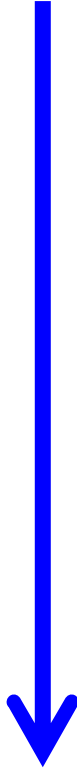
**1995- Large-scale separation of Lu
for production of LSO crystals
by Mark Andreaco (CTI) and
George Schweitzer (Univ. Tennessee)**

**2007 Rapid large-scale separation
of n.c.a. ^{177}Lu from irradiated Yb
by ITG Garching**




Radionuclides for RIT and PRRT

Radio-nuclide	Half-life	E mean (keV)	E γ (B.R.) (keV)	Range
Y-90	64 h	934 β	-	12 mm
I-131	8 days	182 β	364 (82%)	3 mm
Lu-177	7 days	134 β	208 (10%) 113 (6%)	2 mm
Tb-161	7 days	154 β 5, 17, 40 e $^-$	75 (10%)	2 mm 1-30 μm
Tb-149	4.1 h	3967 α	165,..	25 μm
Ge-71	11 days	8 e $^-$	-	1.7 μm
Er-165	10.3 h	5.3 e $^-$	-	0.6 μm



localized

cross-fire



Established isotopes

Emerging isotopes

R&D isotopes: supply-limited!

Modern, better targeted bioconjugates require shorter-range radiation \Rightarrow need for **adequate (R&D) radioisotope supply.**

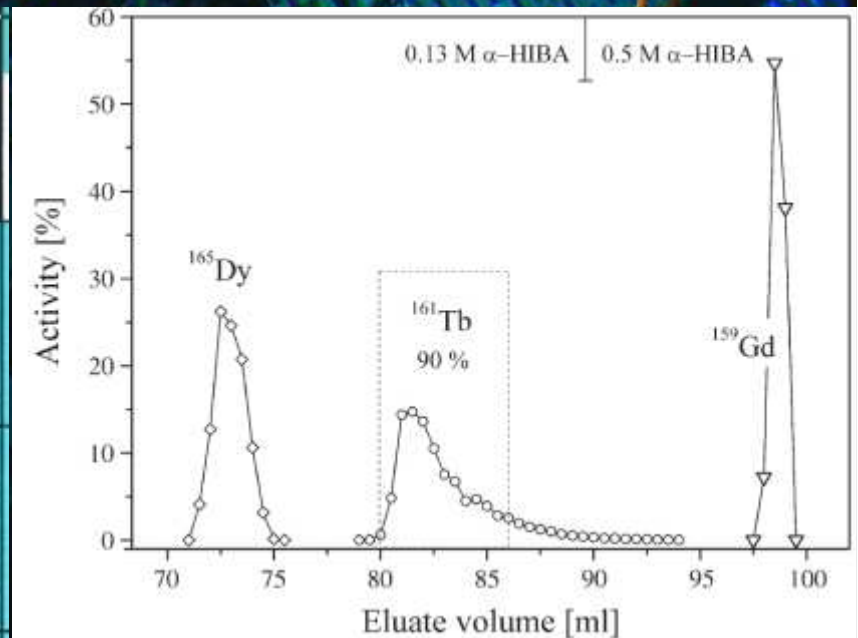
Terbium: a unique element for nuclear medicine



Dy 150 7.2 m	Dy 151 17 m	Dy 152 2.4 h	Dy 153 6.29 h	Dy 154 3.0 · 10 ⁵ a	Dy 155 10.0 h	Dy 156 0.056	Dy 157 8.1 h	Dy 158 0.095	Dy 159 144.4 d	Dy 160 2.329	Dy 161 18.889	Dy 162 25.475
Tb 149 4.2 m	Tb 150 5.8 m	Tb 151 25 s	Tb 152 4.2 m	Tb 153 2.34 d	Tb 154 22 h	Tb 155 5.32 d	Tb 156 4 h 57 m	Tb 157 99 a	Tb 158 10.5 s	Tb 159 100	Tb 160 72.3 d	Tb 161 6.90 d
Gd 148 74.6 a	Gd 149 9.28 d	Gd 150 1.8 · 10 ⁵ a	Gd 151 120 d	Gd 152 0.20	Gd 153 239.47 d	Gd 154 2.18	Gd 155 14.80	Gd 156 20.47	Gd 157 15.65	Gd 158 24.84	Gd 159 18.48 h	Gd 160 21.86

Production of non-carrier-added ^{161}Tb

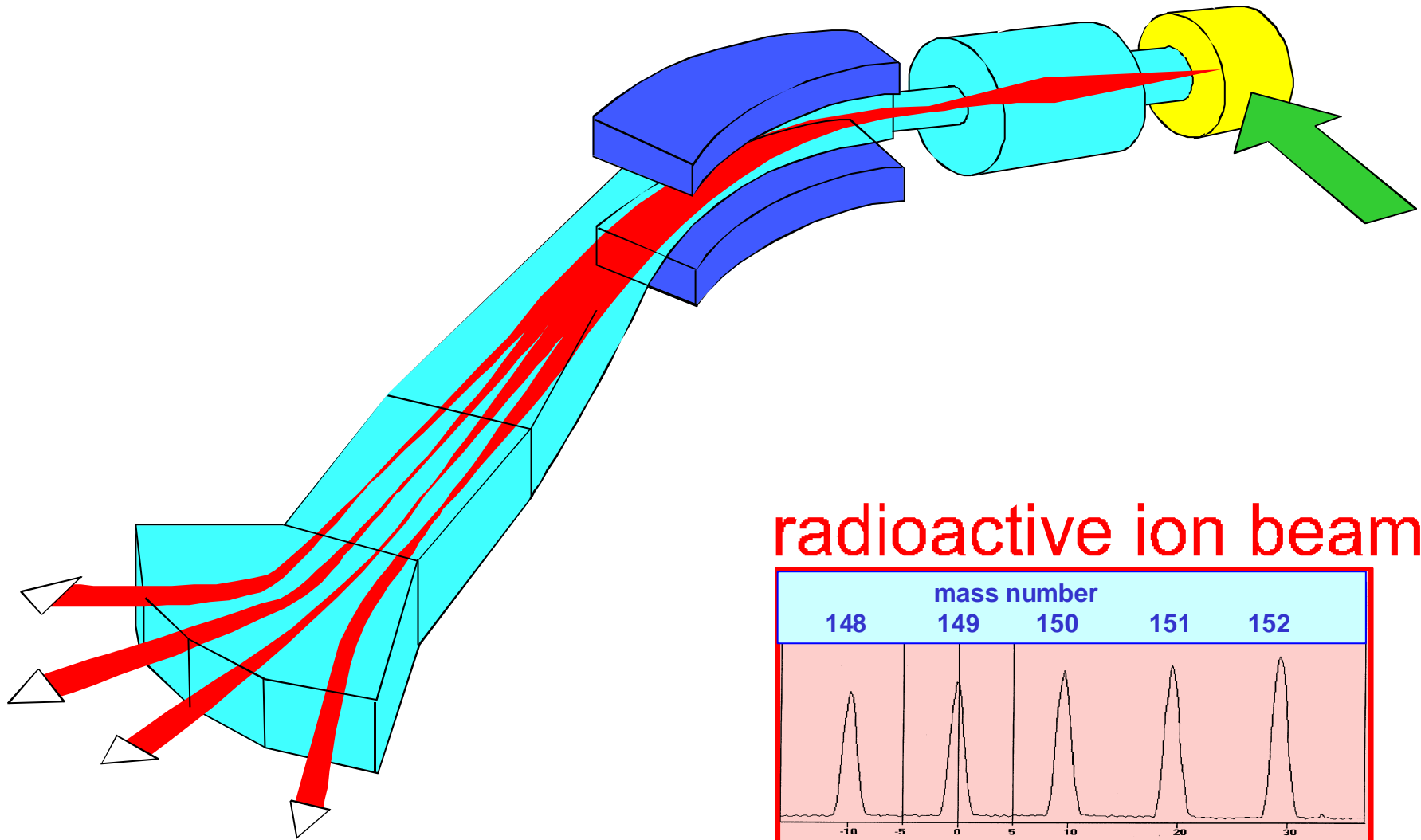
Dy 160 2.329 σ 60 $\sigma_{n, \alpha} < 0.0003$	Dy 161 18.889 σ 600 $\sigma_{n, \alpha} < 1\text{E-}6$	Dy 162 25.475 σ 170	Dy 163 24.896 σ 120 $\sigma_{n, \alpha} < 2\text{E-}5$	Dy 164 28.260 σ 1610 + 1040
Tb 159 100 σ 23.2	Tb 160 72.3 d β^- 0.6; 1.7... γ 879; 299; 966... σ 570	Tb 161 6.90 d β^- 0.5; 0... γ 26; 49; 5... e^-	Tb 162 7.76 m β^- 1.4; 2.4... γ 260; 808; 888...	Tb 163 19.5 m β^- 0.8; 1.3... γ 351; 390; 494...
Gd 158 24.84 σ 2.3	Gd 159 18.48 h β^- 1.0... γ 364; 58...	Gd 160 21.86 σ 1.5	Gd 161 3.66 m β^- 1.6; 1.7... γ 361; 315; 102... σ 20000	Gd 162 8.2 m β^- 1.0... γ 442; 403...



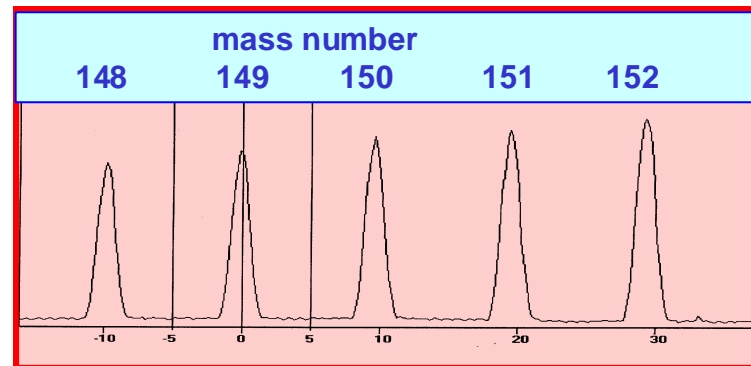
Irradiation in high flux reactor, then chemical separation

S. Lehenberger et al., Nucl. Med. Biol. 38 (2011) 917.

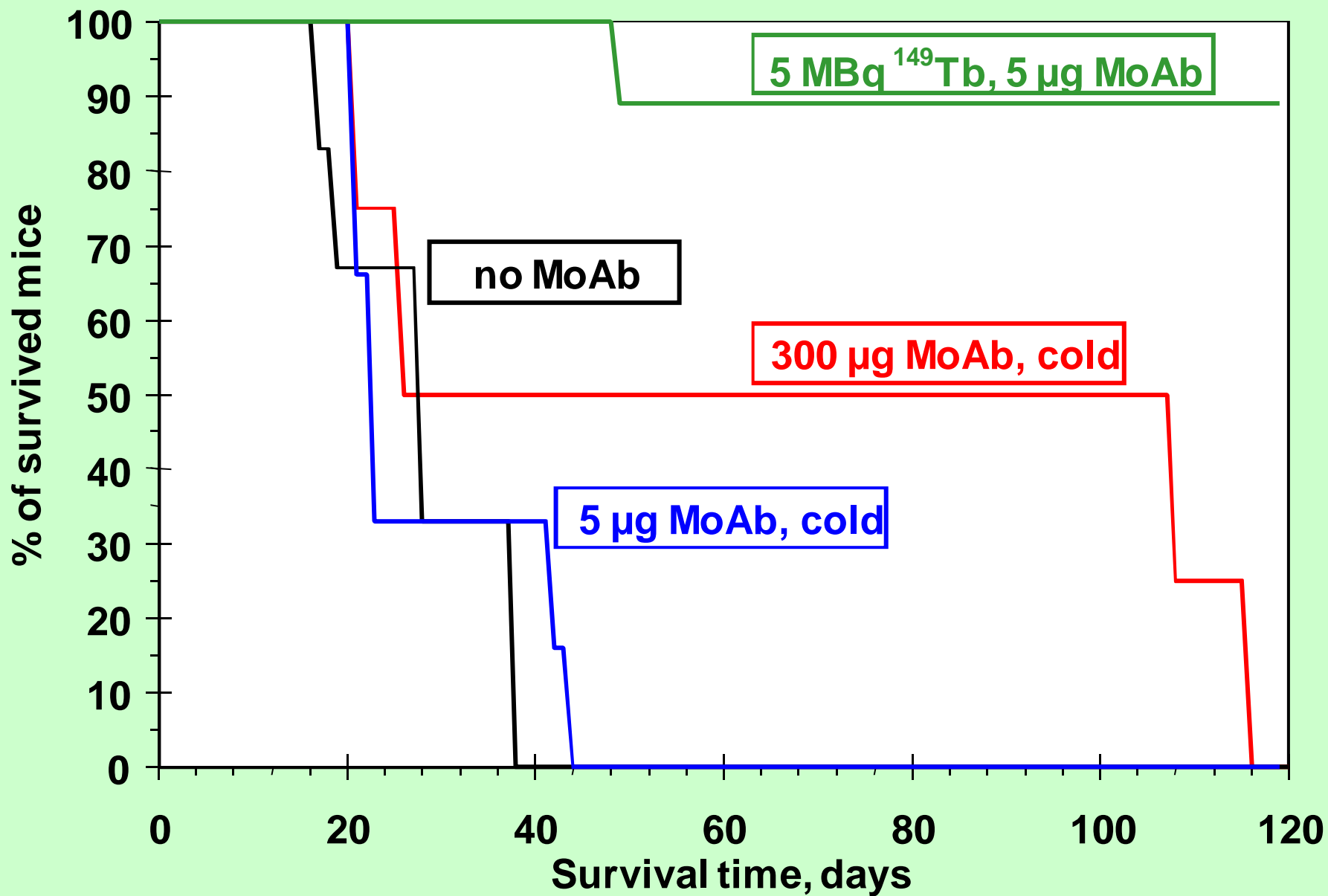
Production of ^{149}Tb , ^{152}Tb and ^{155}Tb at ISOLDE



radioactive ion beams

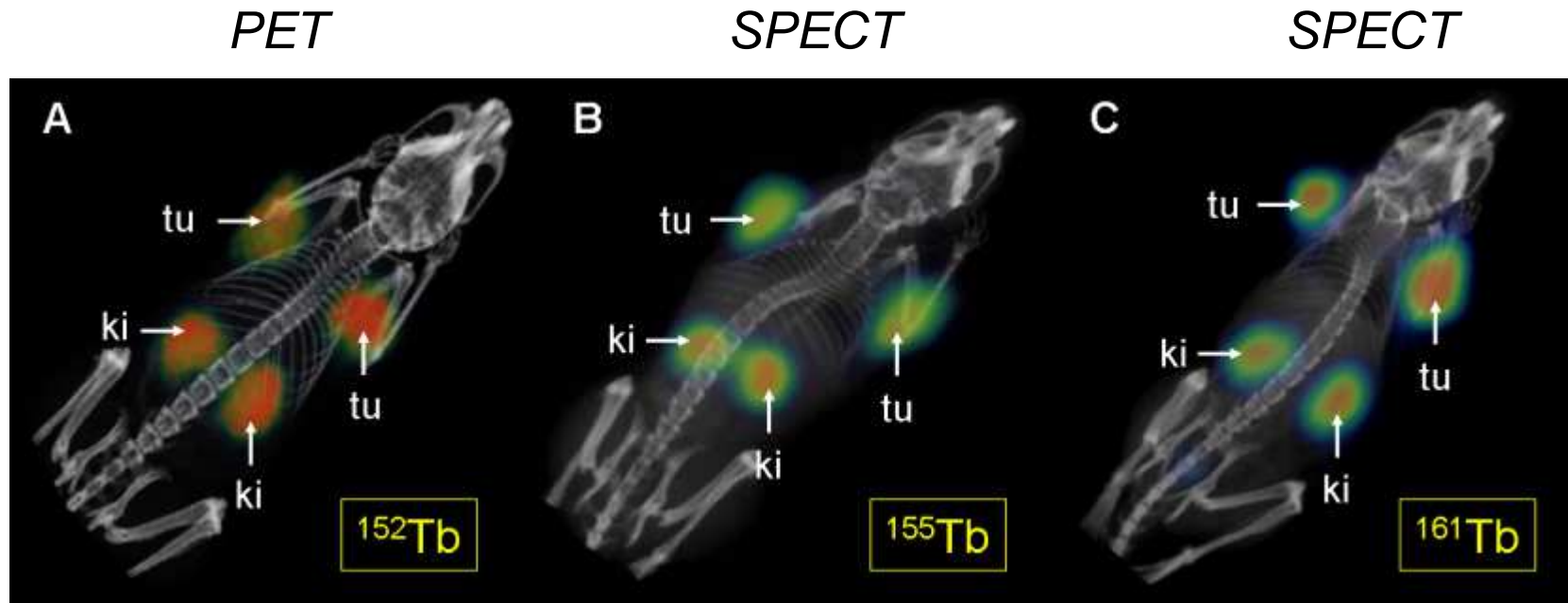


Targeted alpha therapy with ^{149}Tb from ISOLDE



G.J. Beyer et al., *Eur. J. Nucl. Med. Molec. Imaging* **31** (2004) 547.

Theranostics with terbium isotopes



^{152}Tb -folate: 9 MBq
Scan Start: 24 h p.i.
Scan Time: 4 h

^{155}Tb -folate: 4 MBq
Scan Start: 24 h p.i.
Scan Time: 1 h

^{161}Tb -folate: 30 MBq
Scan Start: 24 h p.i.
Scan Time: 20 min



ISOLDE



ISOLDE

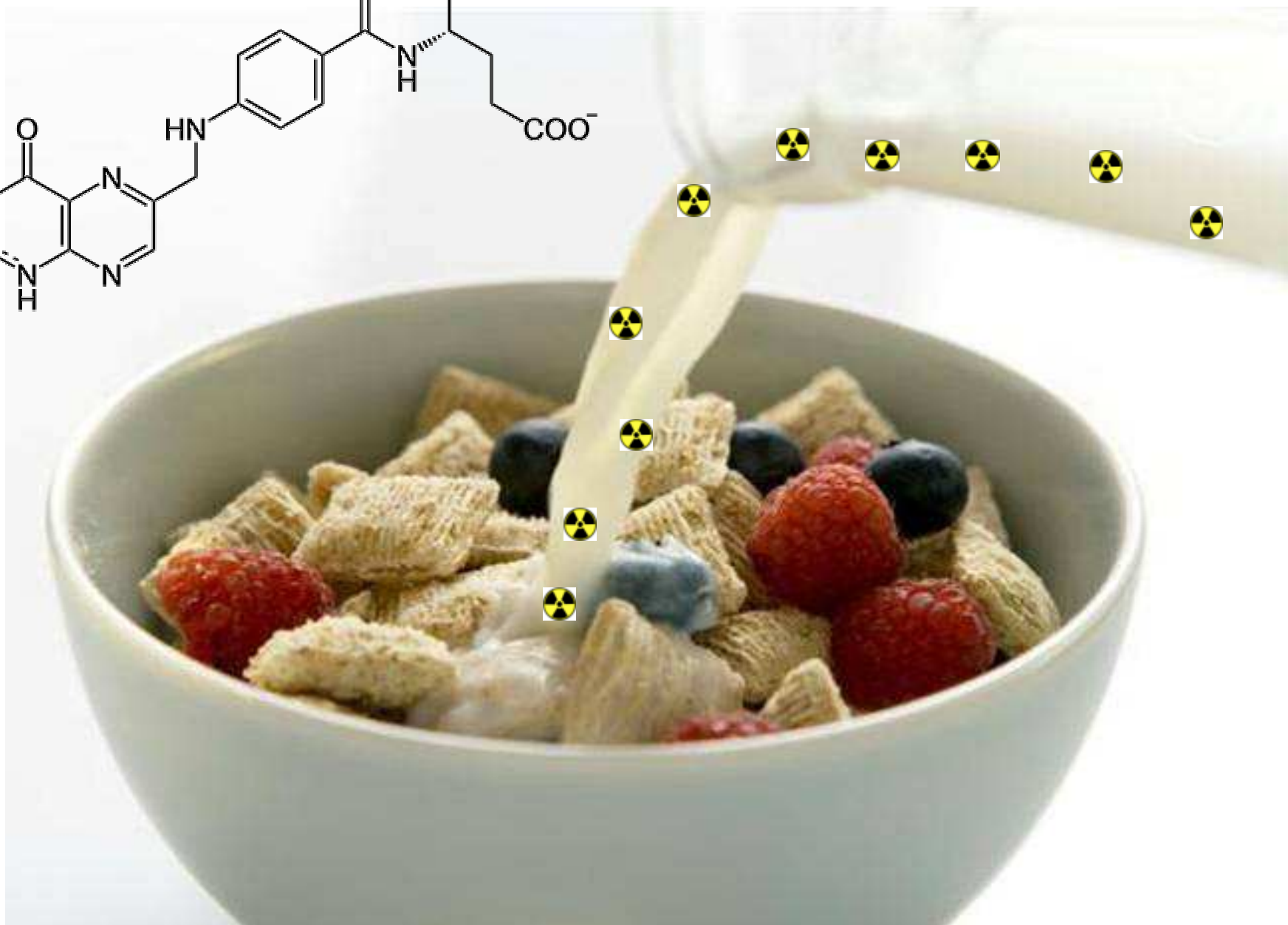
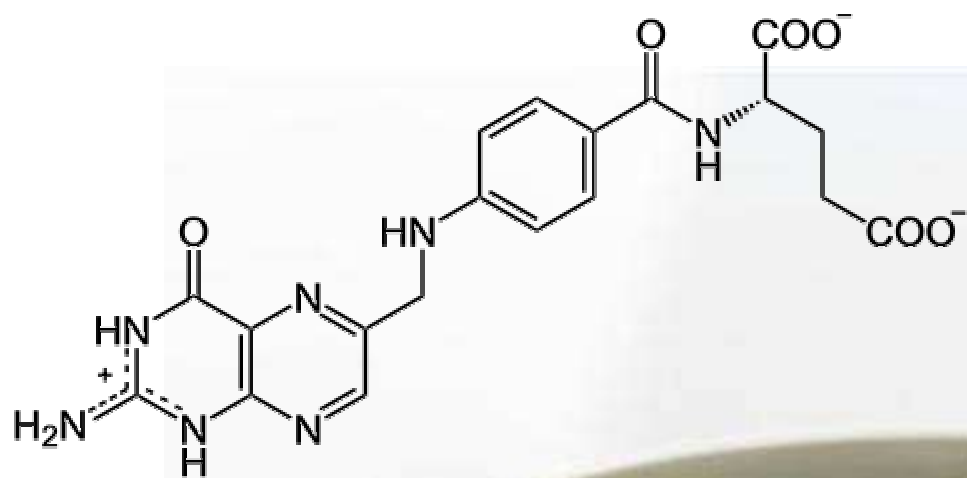
PAUL SCHERRER INSTITUT

PSI

ILL
NEUTRONS
FOR SCIENCE

IS528 Collaboration: C. Müller et al., J. Nucl. Med. (2012), in press.

Folic acid



Radioisotopes available at ISOLDE-CERN

Isotopes on-line separated at ISOLDE																					
Long-lived isotopes available at ISOLDE																					
Decay daughters of ISOLDE beams																					
1																	2				
H																	He				
3	4															5	6	7	8	9	10
Li	Be															B	C	N	O	F	Ne
11	12															13	14	15	16	17	18
Na	Mg															Al	Si	P	S	Cl	Ar
19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36				
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr				
37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54				
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe				
55	56	57	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86				
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn				
87	88	89	104	105	106	107	108	109	110	111	112	113	114	115	116		118				
Fr	Ra	Ac	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg											

58	59	60	61	62	63	64	65	66	67	68	69	70	71
Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
90	91	92	93	94	95	96	97	98	99	100	101	102	103
Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

Currently available: more than 1000 different radioisotopes/-isomers
 Saturation activities of longer-lived radioisotopes: GBq and more
 Unique radiochemical techniques (e.g. P. Hoff et al., NIM 221 (1984) 313.)

Bone metastases



BM are a frequent complication of advanced prostate, breast, kidney, lung,... cancers

1.5 million patients worldwide suffer from BM:

- **severe pain**
- **weakened bones causing fracture**
- **damaged nerves**
- **red bone marrow produces less red/white blood cells**

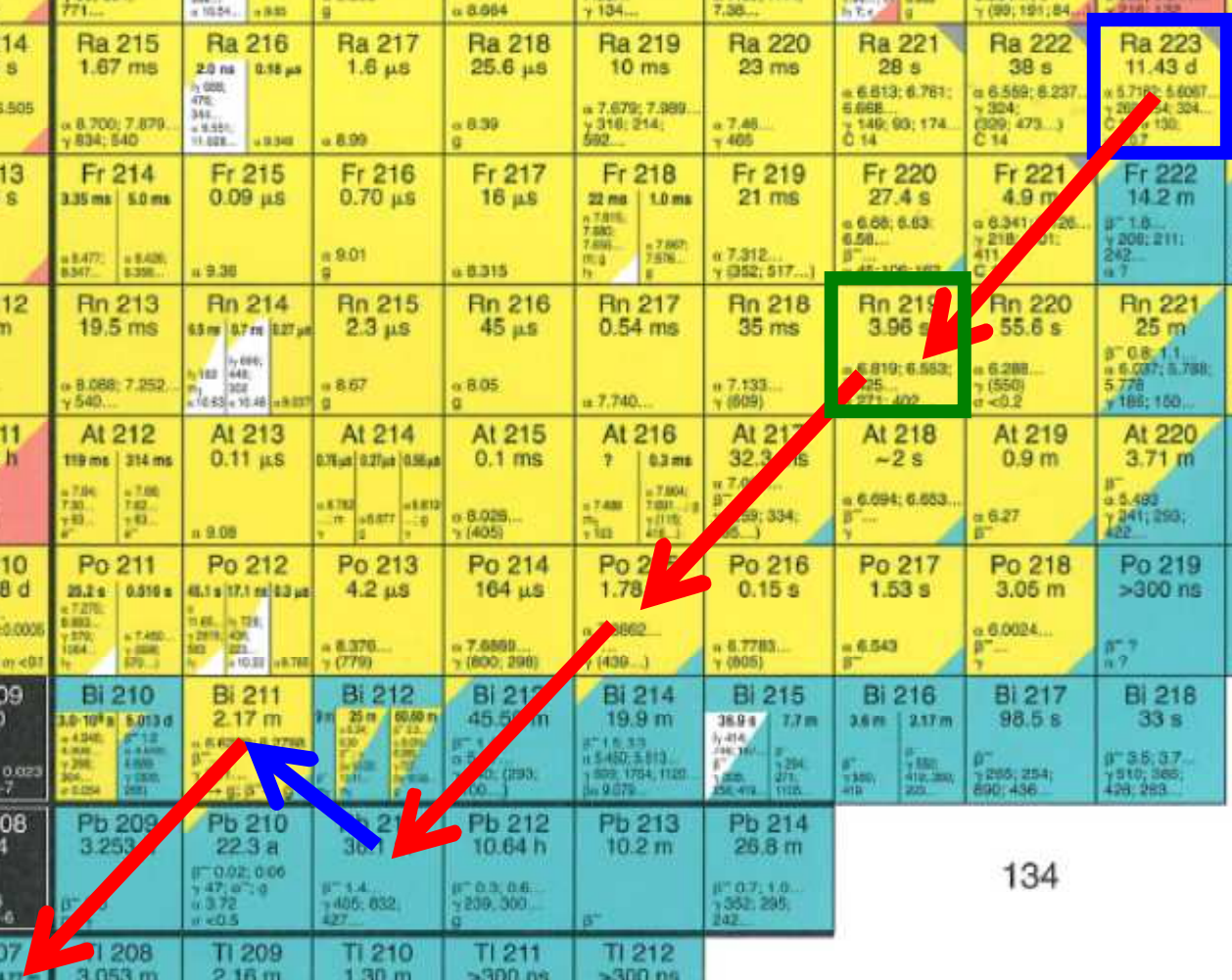
Isotopes for targeted alpha therapy

12	Ac 213 0.80 s	Ac 214 8.2 s	Ac 215 0.17 s	Ac 216 0.44 ms	Ac 217 0.74 μ s 69 ns	Ac 218 1.1 μ s	Ac 219 11.8 μ s	Ac 220 26 ms	Ac 221 52 ms	Ac 222 55 s 5.0 s	Ac 223 2.10 m	Ac 224 2.9 h	Ac 225 10.0 d	Ac 226 29 h
11	Ra 212 13.0 s	Ra 213 2.1 ms 2.74 m	Ra 214 2.46 s	Ra 215 1.67 ms	Ra 216 2.0 ns 0.16 μ s	Ra 217 1.6 μ s	Ra 218 25.6 μ s	Ra 219 10 ms	Ra 220 23 ms	Ra 221 28 s	Ra 222 38 s	Ra 223 11.43 d	Ra 224 3.66 d	Ra 225 14.8 d
10	Fr 211 3.10 m	Fr 212 20.0 m	Fr 213 34.6 s	Fr 214 3.35 ms 5.0 ms	Fr 215 0.09 μ s	Fr 216 0.70 μ s	Fr 217 16 μ s	Fr 218 22 ms 1.0 ms	Fr 219 21 ms	Fr 220 27.4 s	Fr 221 4.9 m	Fr 222 14.2 m	Fr 223 21.8 m	Fr 224 3.3 m
09	Rn 210 2.4 h	Rn 211 14.6 h	Rn 212 24 m	Rn 213 19.5 ms	Rn 214 63 ns 0.7 m 0.27 μ s	Rn 215 2.3 μ s	Rn 216 45 μ s	Rn 217 0.54 ms	Rn 218 35 ms	Rn 219 3.96 s	Rn 220 55.6 s	Rn 221 25 m	Rn 222 3.825 d	Rn 223 23.2 m
08	At 209 5.4 h	At 210 8.3 h	At 211 7.22 h	At 212 119 ms 214 ms	At 213 0.11 μ s	At 214 0.71 μ s 0.27 μ s 0.96 μ s	At 215 0.1 ms	At 216 ? 0.3 ms	At 217 32.3 ms	At 218 -2 s	At 219 0.9 m	At 220 3.71 m	At 221 2.3 m	At 222 54 s
07	Po 208 2.898 a	Po 209 102 a	Po 210 138.38 d	Po 211 26.2 s 0.316 a	Po 212 46.1 s 17.1 ms 0.3 μ s	Po 213 4.2 μ s	Po 214 164 μ s	Po 215 1.78 ms	Po 216 0.15 s	Po 217 1.53 s	Po 218 3.05 m	Po 219 >300 ns	Po 220 >300 ns	
06	Bi 207 31.55 a	Bi 208 3.68 $\cdot 10^3$ a	Bi 209 100	Bi 210 3.8 $\cdot 10^4$ a 5.013 d	Bi 211 2.17 m	Bi 212 20 ns 66.6 ns	Bi 213 45.59 m	Bi 214 19.9 m	Bi 215 38.9 s 7.7 m	Bi 216 3.6 m 217 m	Bi 217 98.5 s	Bi 218 33 s		136
05	Pb 206 24.1	Pb 207 22.1	Pb 208 52.4	Pb 209 3.253 h	Pb 210 22.3 a	Pb 211 36.1 m	Pb 212 10.64 h	Pb 213 10.2 m	Pb 214 26.8 m					134
04	Tl 205 70.48	Tl 206 3.7 m 4.29 m	Tl 207 1.33 s 4.77 m	Tl 208 3.053 m	Tl 209 2.16 m	Tl 210 1.30 m	Tl 211 >300 ns	Tl 212 >300 ns						132



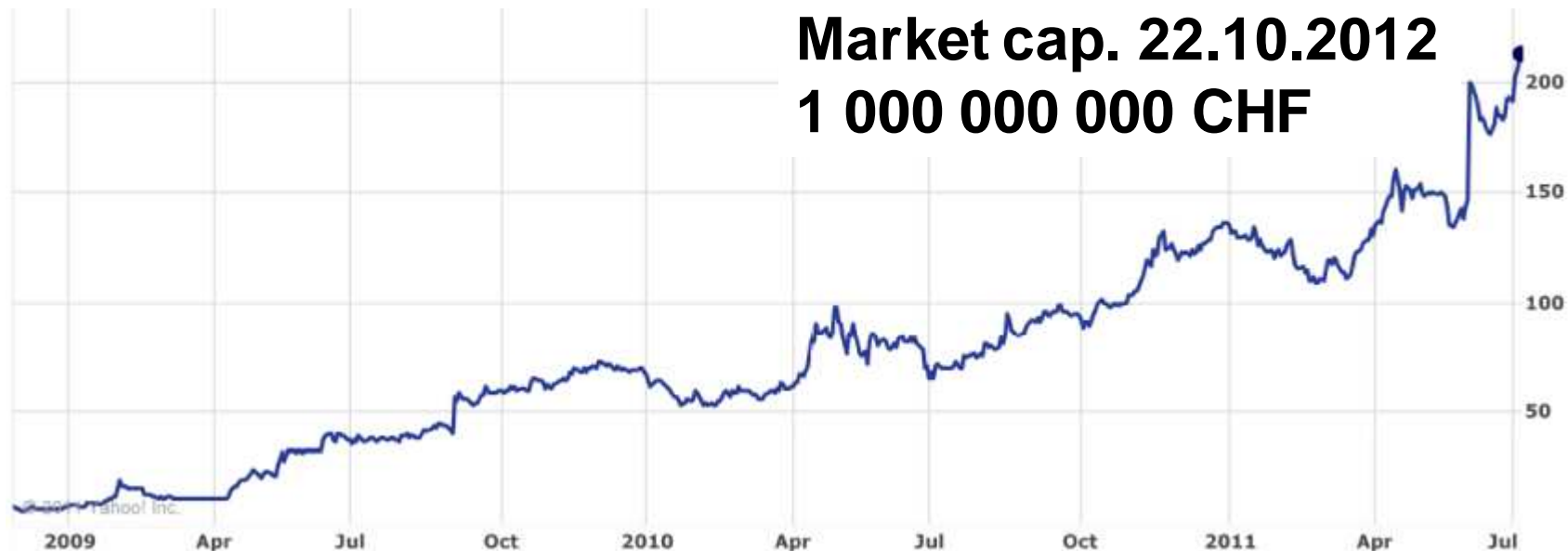
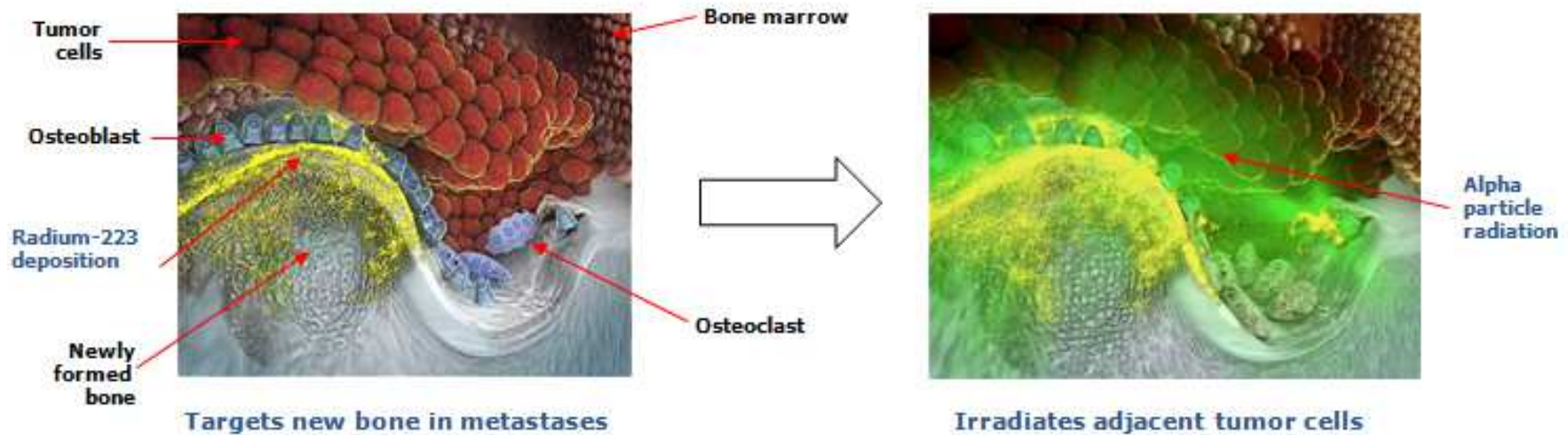
Isotopes for targeted alpha therapy

12	Ac 213 0.80 s	Ac 214 8.2 s	Ac 215 0.17 s	Ac 216 0.44 ms	Ac 217 0.74 μ s 69 ns	Ac 218 1.1 μ s	Ac 219 11.8 μ s	Ac 220 26 ms	Ac 221 52 ms	Ac 222 63 s 5.0 s	Ac 223 2.10 m	Ac 224 2.9 h	Ac 225 10.0 d	Ac 226 29 h	
11	Ra 212 13.0 s	Ra 213 2.1 ms 2.74 m	Ra 214 2.46 s	Ra 215 1.67 ms	Ra 216 2.0 ns 0.18 μ s	Ra 217 1.6 μ s	Ra 218 25.6 μ s	Ra 219 10 ms	Ra 220 23 ms	Ra 221 28 s	Ra 222 38 s	Ra 223 11.43 d	Ra 224 3.66 d	Ra 225 14.8 d	
10	Fr 211 3.10 m	Fr 212 20.0 m	Fr 213 34.6 s	Fr 214 3.35 ms 5.0 ms	Fr 215 0.09 μ s	Fr 216 0.70 μ s	Fr 217 16 μ s	Fr 218 22 ms 1.0 ms	Fr 219 21 ms	Fr 220 27.4 s	Fr 221 4.9 m	Fr 222 14.2 m	Fr 223 21.8 m	Fr 224 3.3 m	
09	Rn 210 2.4 h	Rn 211 14.6 h	Rn 212 24 m	Rn 213 19.5 ms	Rn 214 63 ns 0.7 m 0.27 μ s	Rn 215 2.3 μ s	Rn 216 45 μ s	Rn 217 0.54 ms	Rn 218 35 ms	Rn 219 3.96 s	Rn 220 55.6 s	Rn 221 25 m	Rn 222 3.825 d	Rn 223 23.2 m	
08	At 209 5.4 h	At 210 8.3 h	At 211 7.22 h	At 212 119 ms 214 ms	At 213 0.11 μ s	At 214 0.71 μ s 0.27 μ s 0.96 μ s	At 215 0.1 ms	At 216 ? 0.3 ms	At 217 32.3 ms	At 218 -2 s	At 219 0.9 m	At 220 3.71 m	At 221 2.3 m	At 222 54 s	
07	Po 208 2.898 a	Po 209 102 a	Po 210 138.38 d	Po 211 28.2 s 0.316 a	Po 212 45.1 s 17.1 ms 0.3 μ s	Po 213 4.2 μ s	Po 214 164 μ s	Po 215 1.78 s	Po 216 0.15 s	Po 217 1.53 s	Po 218 3.05 m	Po 219 >300 ns	Po 220 >300 ns		
06	Bi 207 31.55 a	Bi 208 3.68 $\cdot 10^3$ a	Bi 209 100	Bi 210 3.8 $\cdot 10^4$ a 5.013 d	Bi 211 2.17 m	Bi 212 20 m 66.6 ns	Bi 213 45.5 m	Bi 214 19.9 m	Bi 215 38.9 s 7.7 m	Bi 216 3.6 m 2.17 m	Bi 217 98.5 s	Bi 218 33 s		136	
05	Pb 206	Pb 207 22.1	Pb 208 52.4	Pb 209 3.253 h	Pb 210 22.3 a	Pb 211 36.1 m	Pb 212 10.64 h	Pb 213 10.2 m	Pb 214 26.8 m						134
04	Tl 205	Tl 206 3.7 m 4.23 m	Tl 207 4.77 m	Tl 208 3.053 m	Tl 209 2.16 m	Tl 210 1.30 m	Tl 211 >300 ns	Tl 212 >300 ns							132



ALGETA: ^{223}Ra against bone metastases

Start-up company from Oslo University & Rikshospitalet
R&D on cancer therapies with alpha emitters



Radionuclides for RIT and PRRT

Radio-nuclide	Half-life	E mean (keV)	E γ (B.R.) (keV)	Range
Y-90	64 h	934 β	-	12 mm
I-131	8 days	182 β	364 (82%)	3 mm
Lu-177	7 days	134 β	208 (10%) 113 (6%)	2 mm
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Ge-71	11 days	8 e $^-$	-	1.7 μm
Er-165	10.3 h	5.3 e $^-$	-	0.6 μm

localized

cross-fire

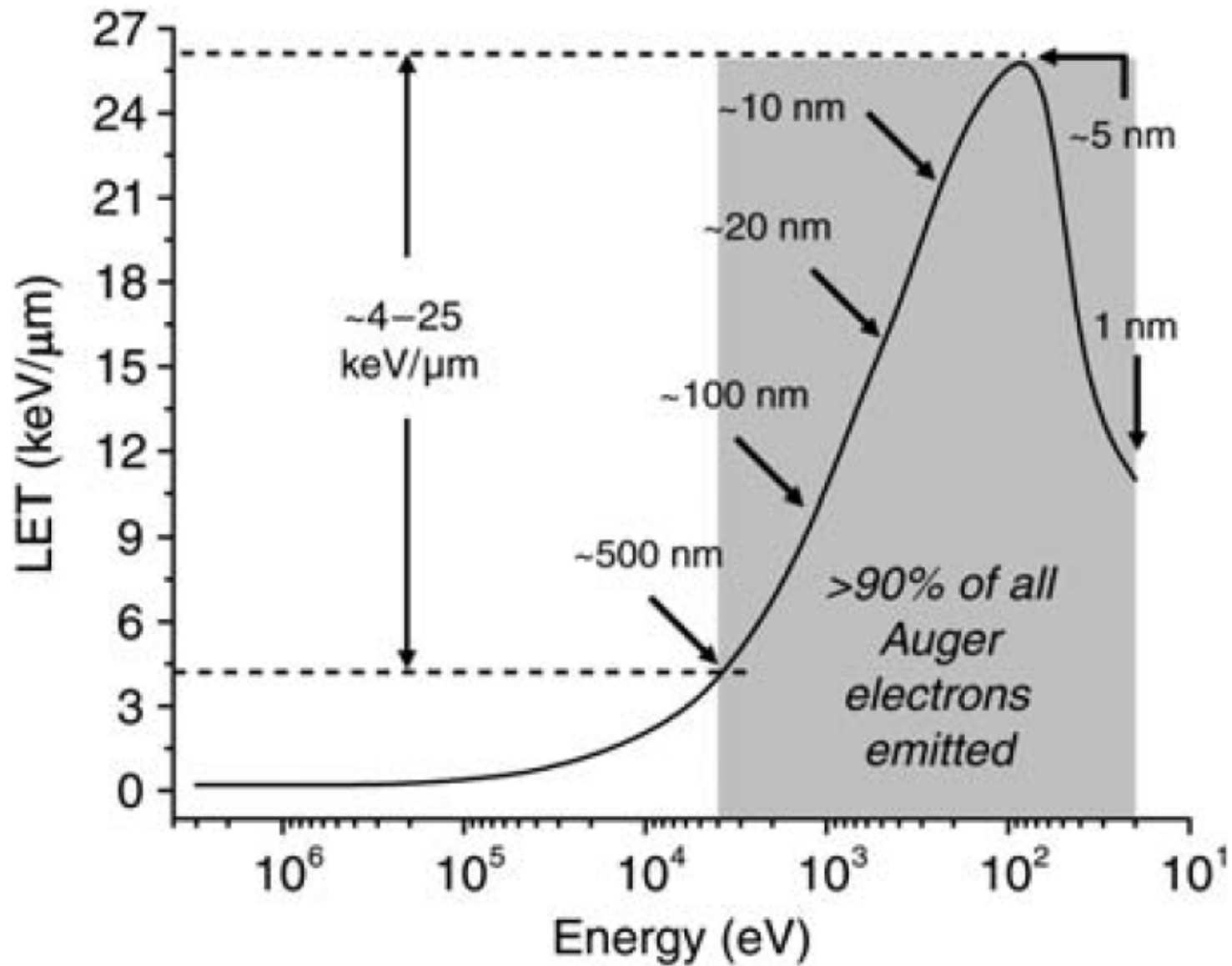
Established isotopes

Emerging isotopes

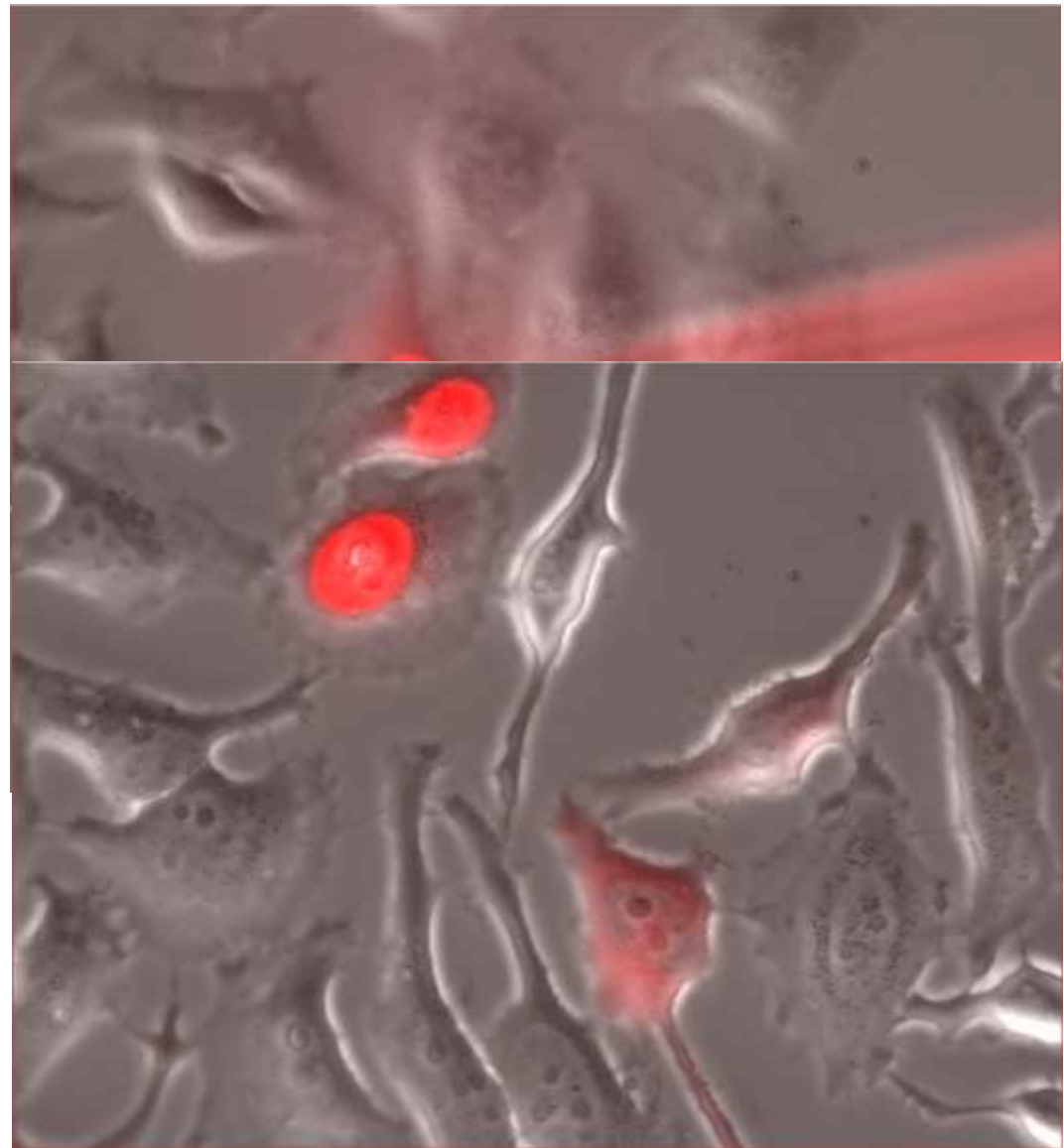
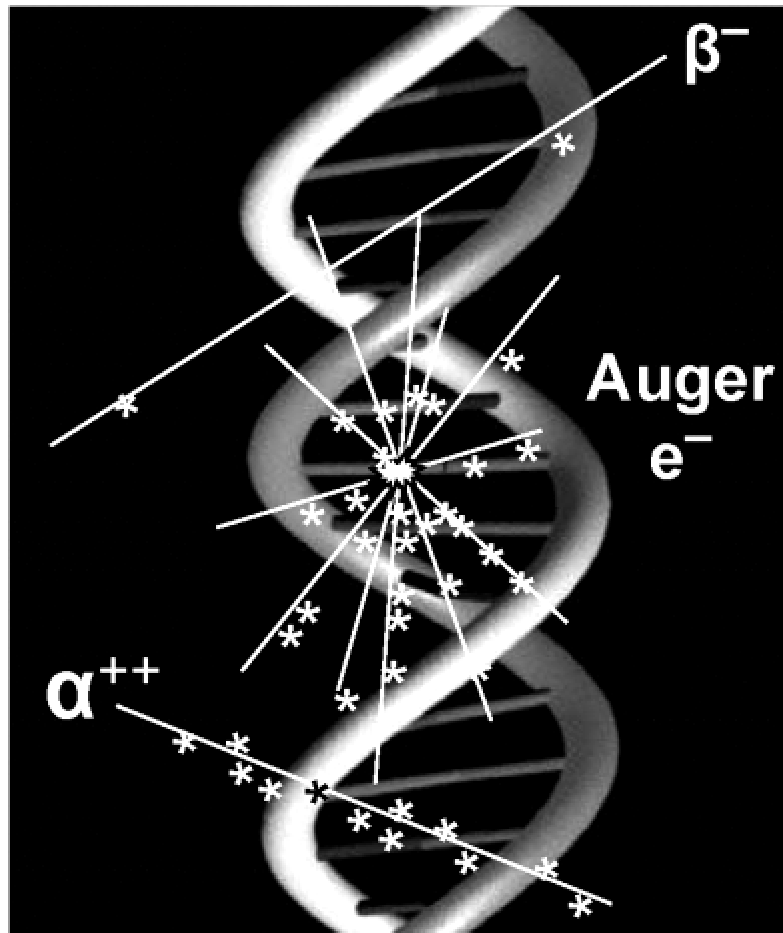
R&D isotopes: supply-limited!

Modern, better targeted bioconjugates require shorter-range radiation \Rightarrow need for **adequate (R&D) radioisotope supply.**

LET of Auger electrons



Radiobiology of Auger electron emitters ?



M. Jensen et al., DTU Risø

Outlook

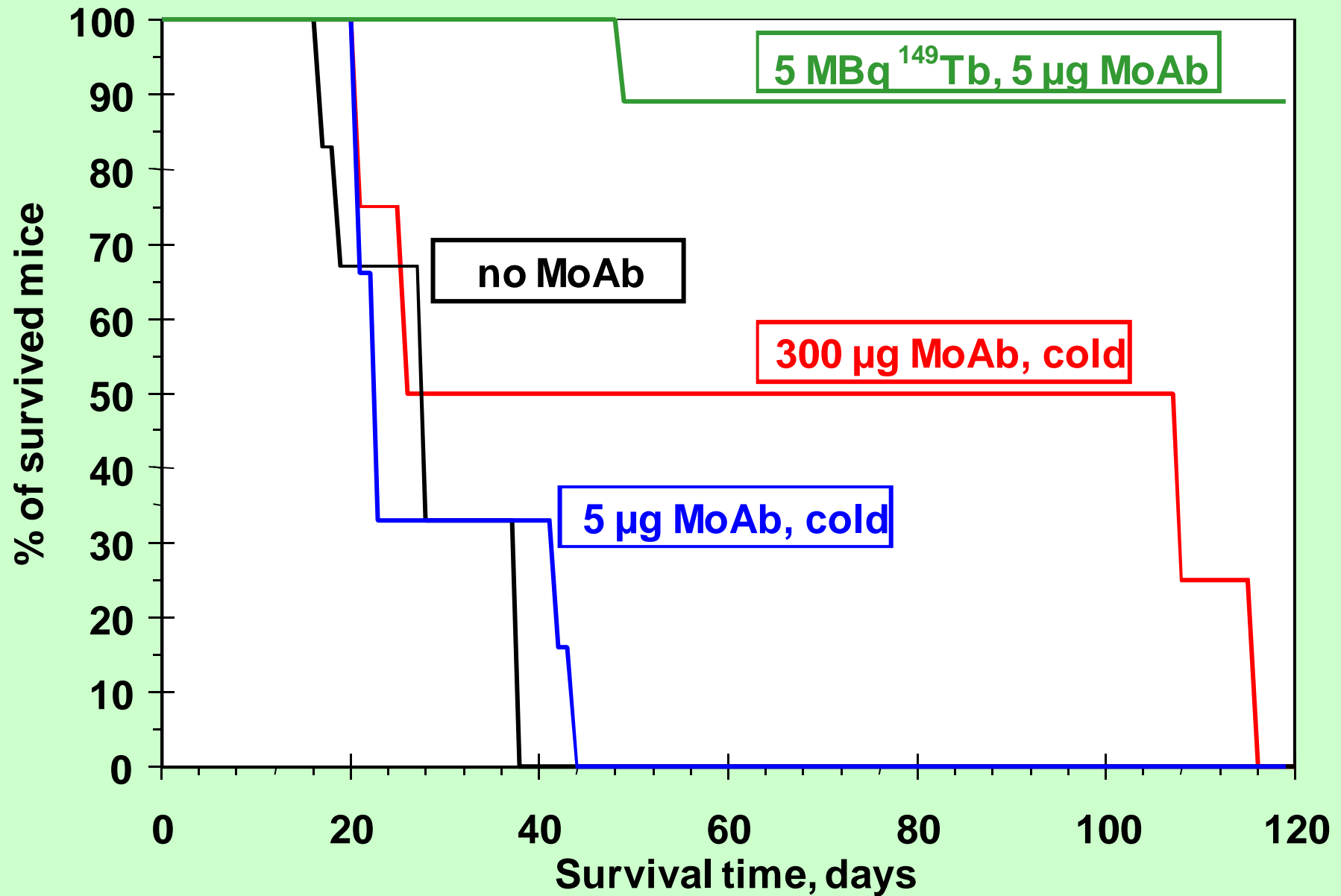
The **ideal agent for cancer therapy** would consist of heavy **elements capable of emitting radiations of molecular dimensions**, which could be administered to the organism and selectively fixed in the protoplasm of cells one seeks to destroy. While this is perhaps not impossible to achieve, the attempts so far have been unsuccessful.

*C. Regaud, A. Lacassagne, Radiophysiologie et Radiotherapie 1 (1927) 95.
Translation : A.I. Kassis, Int. J. Radiat. Biol. 80 (2004) 789.*

Today we are closer than ever to reach this goal !

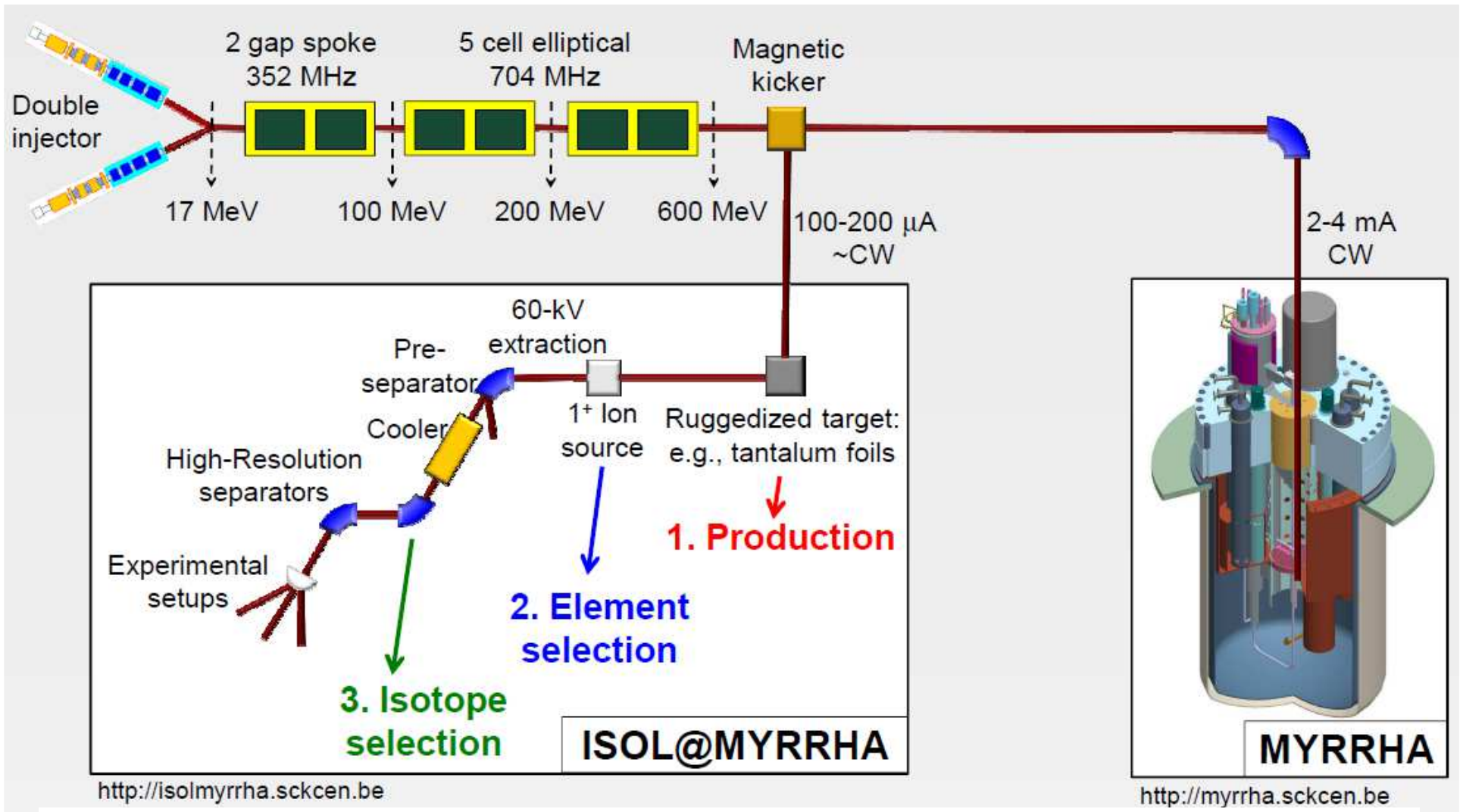
From lab to patient

Idea: Targeted alpha therapy with ^{149}Tb



G.J. Beyer et al., Eur. J. Nucl. Med. Molec. Imaging **31** (2004) 547.

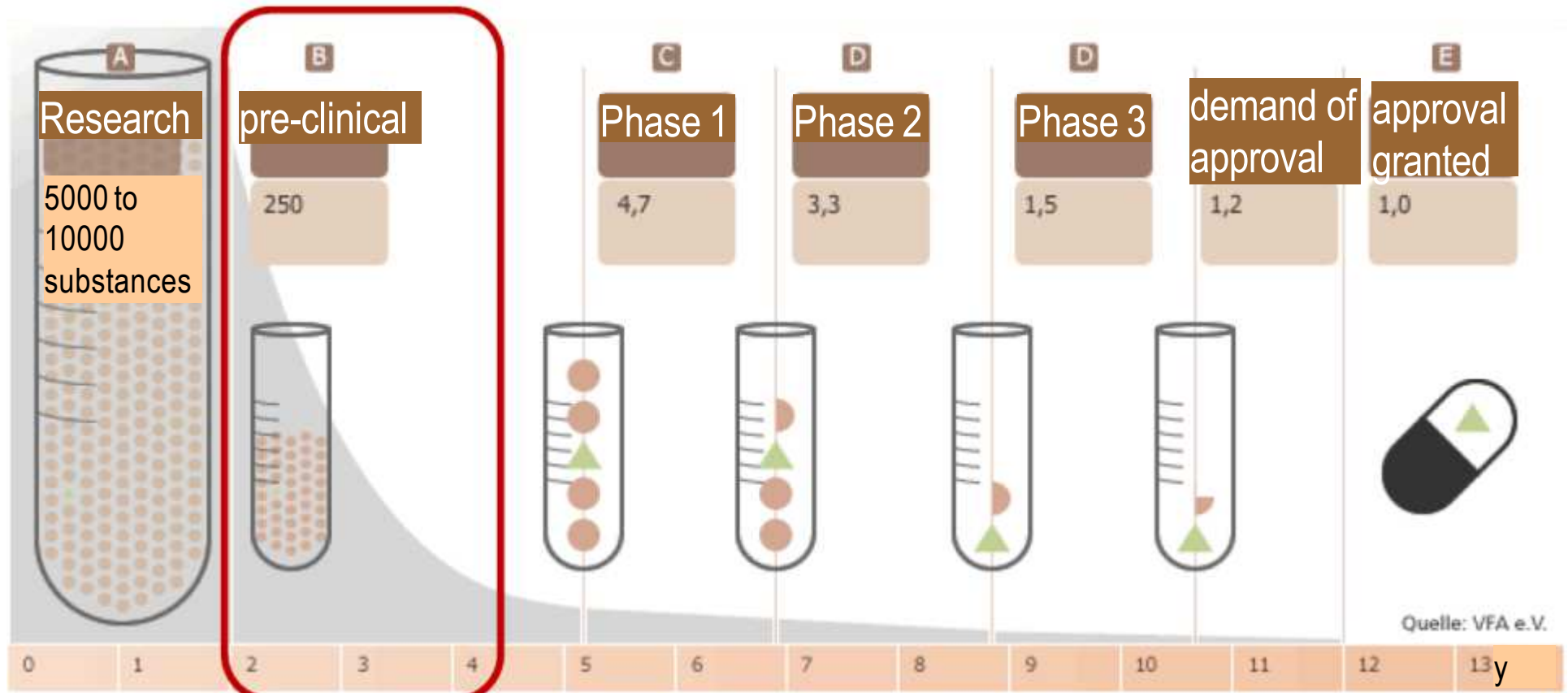
Vision: large-scale production possible



Also possible at:

PSI, ISIS, SNS, LANL, J-PARC, ESS, SPL, EURISOL,...

Endurance: Development of pharmaceuticals



**Screening in vitro tests
animal exp.**

tests with humans

toxicity
side effects

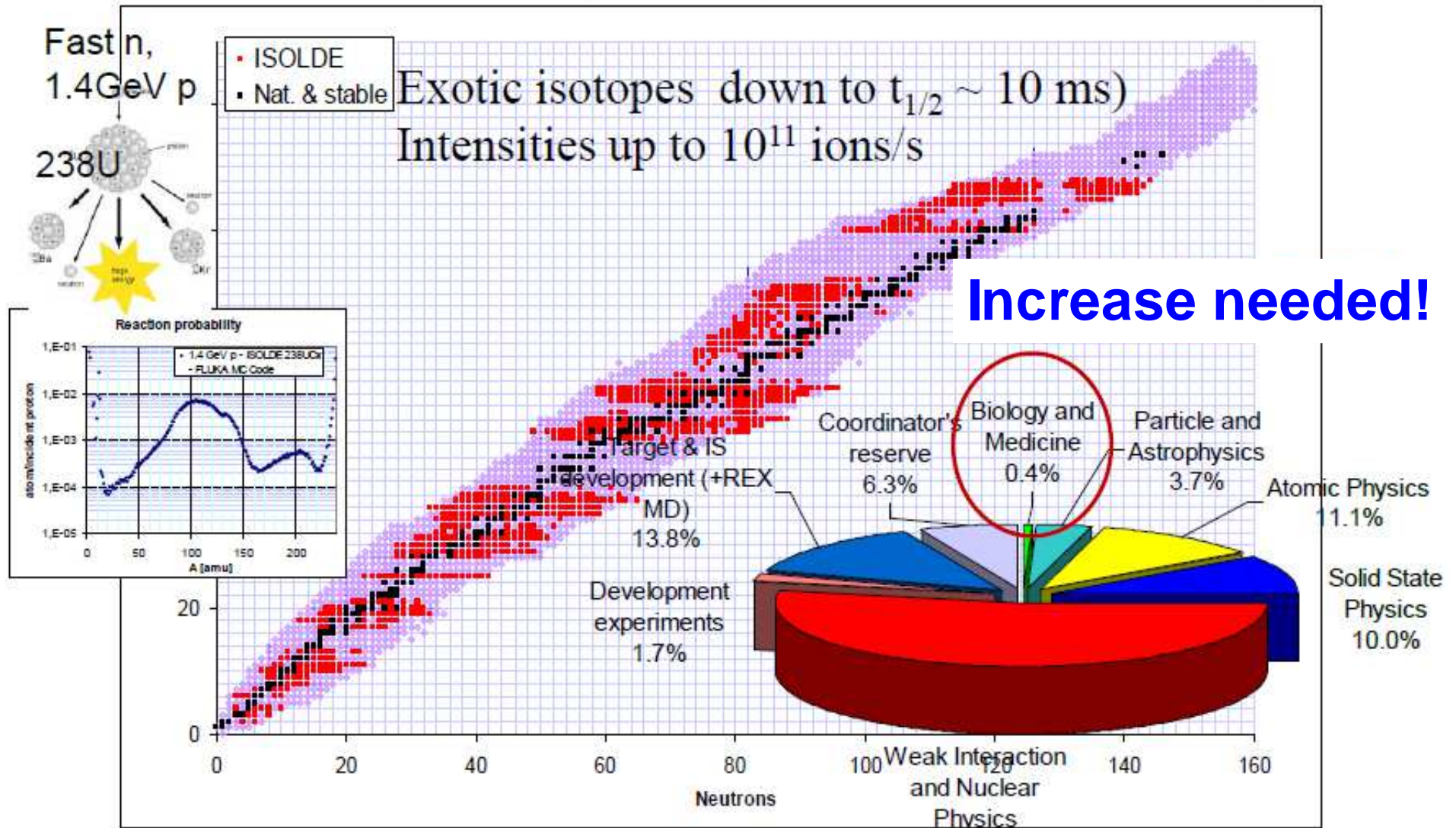
wanted effect

comparison
with standard

20-80 healthy volunteers
100-300 patients
x00-x000 patients

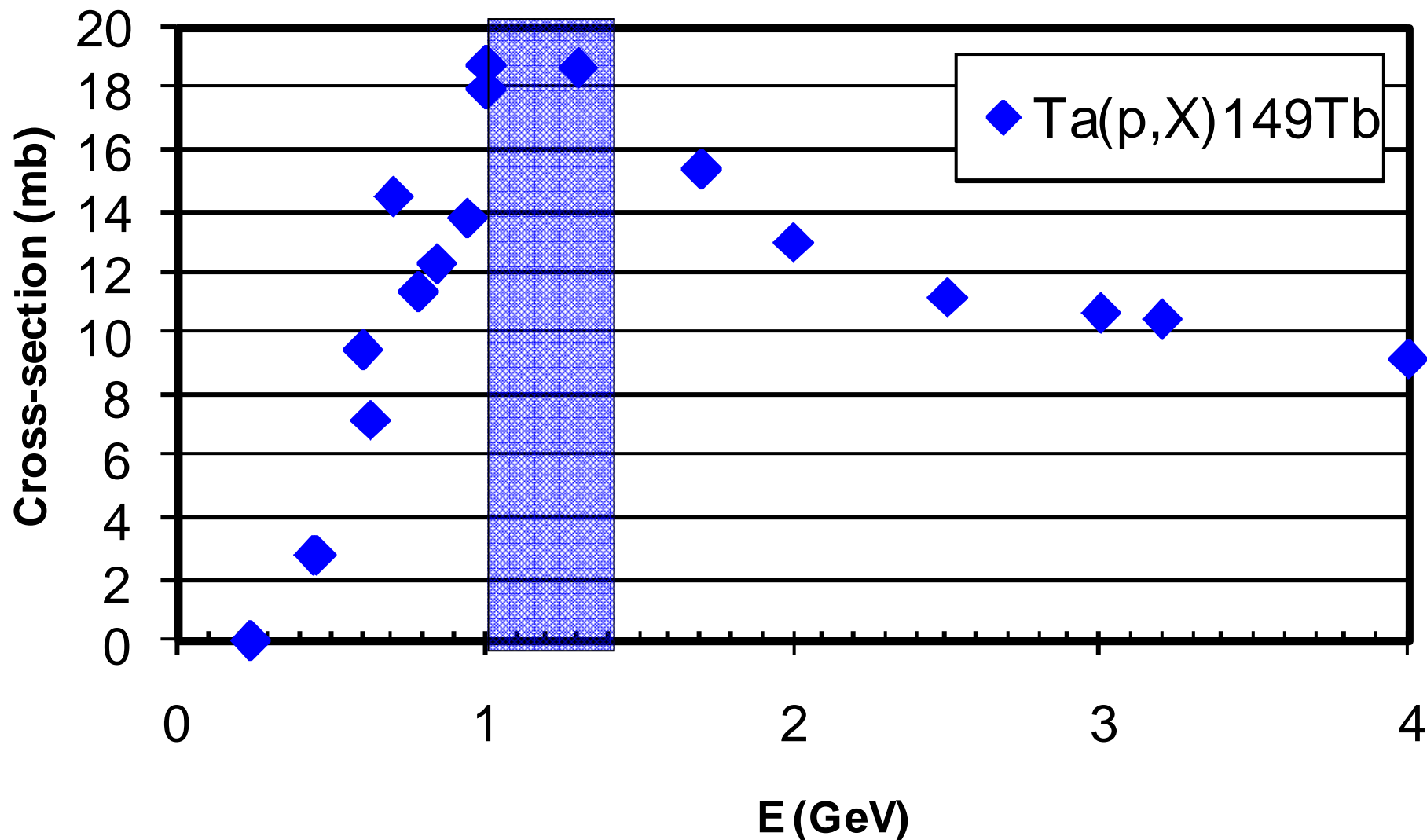
Isolde: a multi-use facility

1000+ isotopes (70+ elements)



Accelerator Wishlist

GeV protons for spallation production

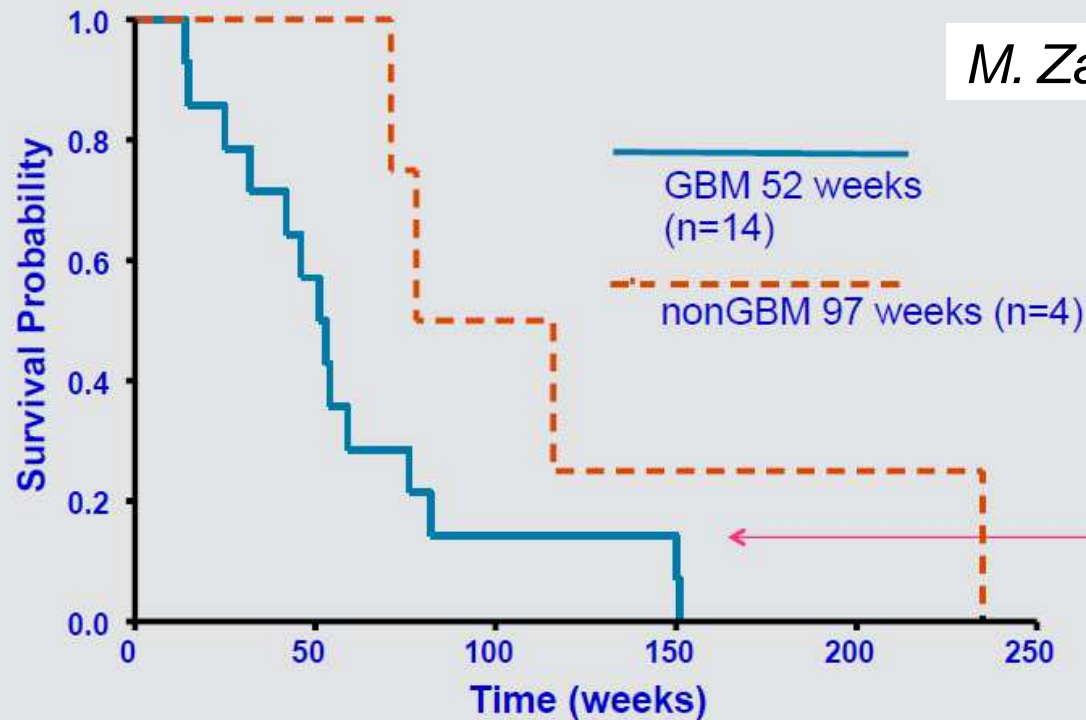


> 1 GeV, $\approx 100 \mu\text{A}$, "parasitic use"
also > 100 MeV in beam dumps (${}^{44}\text{Ti}$)

^4He beams with tens of MeV

Phase 1 ^{211}At -Labeled Chimeric 81C6 in Recurrent Brain Tumor Patients: Outcome

M. Zalutsky

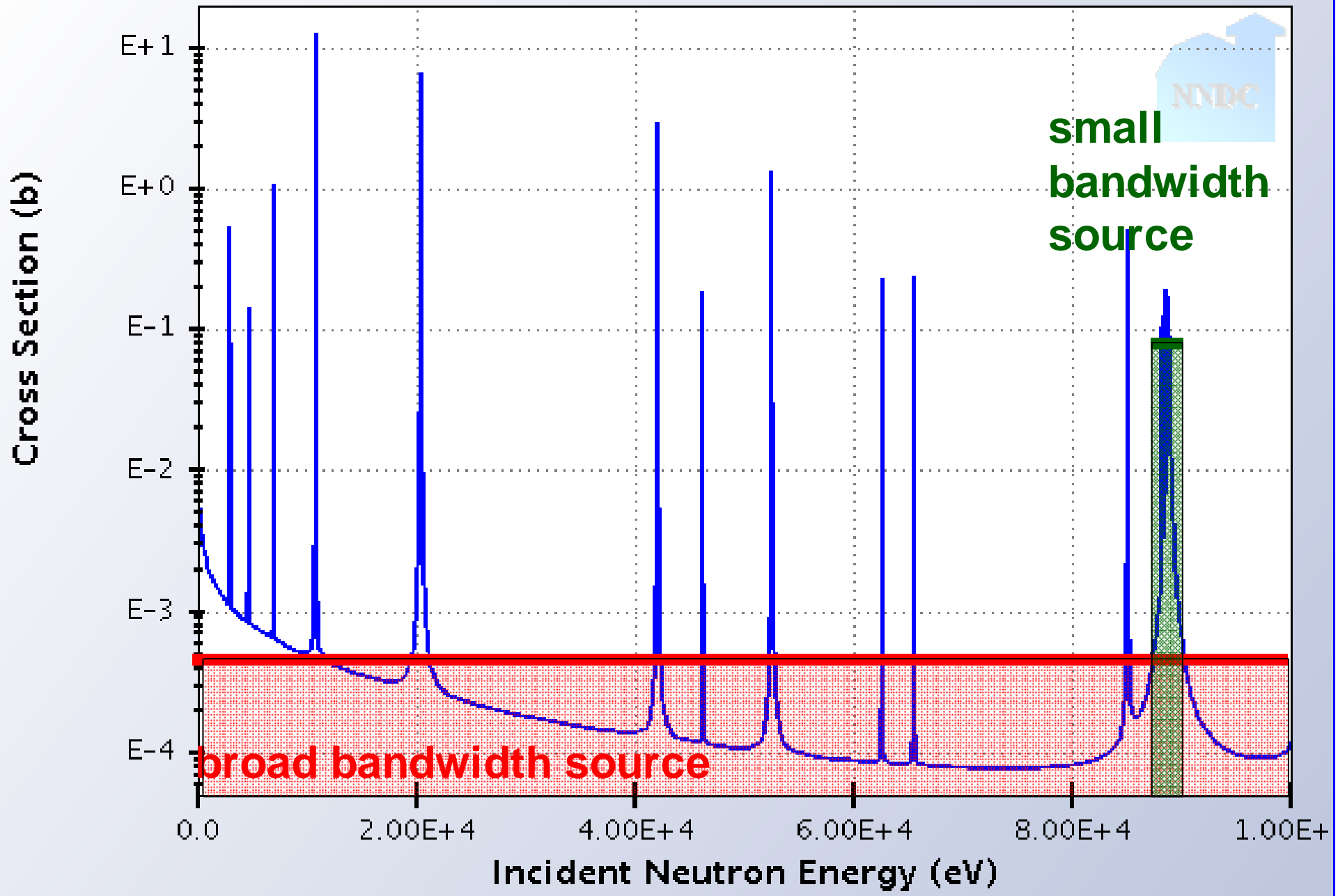


Historical Control: GBM 31 weeks
Brem et al. 1995

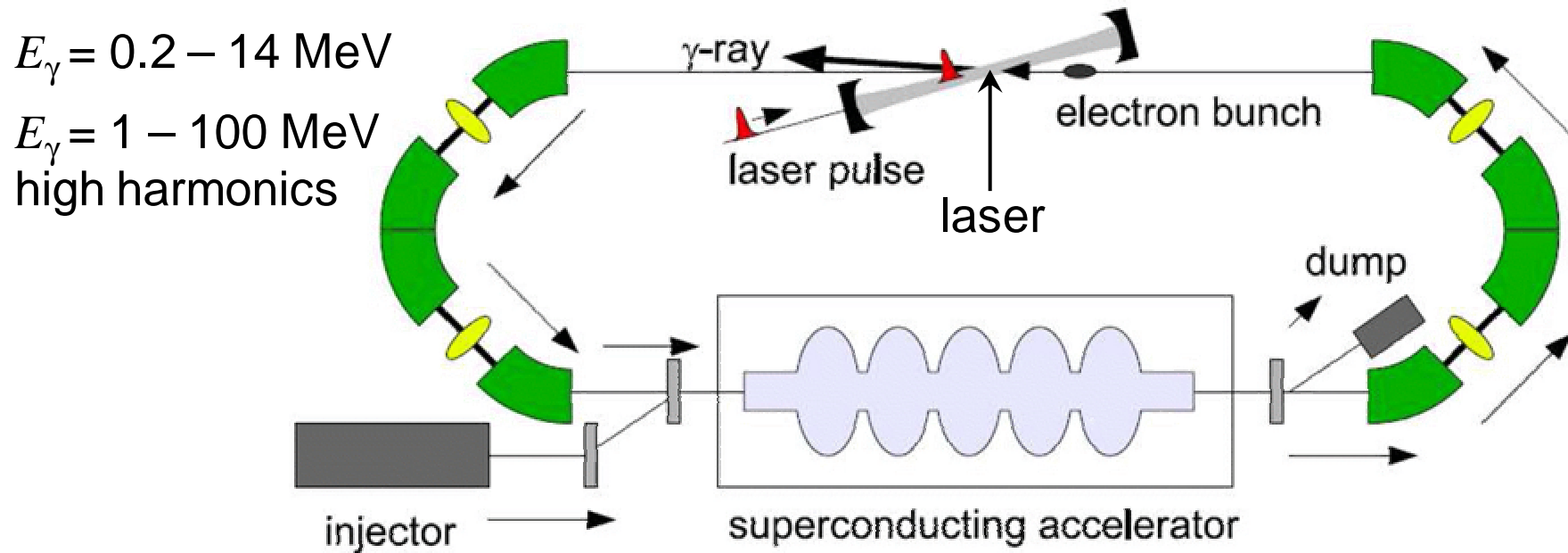


$\approx 100 \mu\text{A}$, 29 MeV $^4\text{He}^{2+}$ for $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$
tens of MeV for other (α, xn) reactions

20-Ca-40(n,gamma) ENDF/B-VII.0



Energy recovery linac (ERL)



100's MeV e^- , 1 – 100 mA ERL, 10's μm interaction area

$^{226}\text{Ra}(\gamma, n)^{225}\text{Ra}$ 1 Ci/day using few mCi ^{226}Ra targets

$^{195}\text{Pt}(\gamma, \gamma')^{195\text{m}}\text{Pt}$ 2 Ci/mg

$^{170}\text{Er}(\gamma, n)^{169}\text{Er}$ 20 Ci/mg

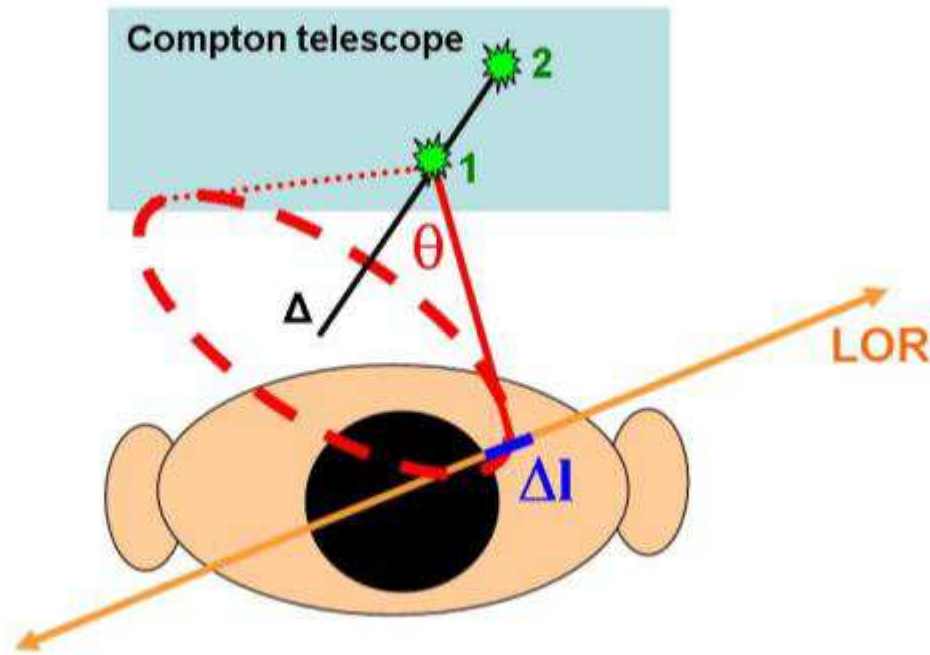
etc.

Detector Wishlist

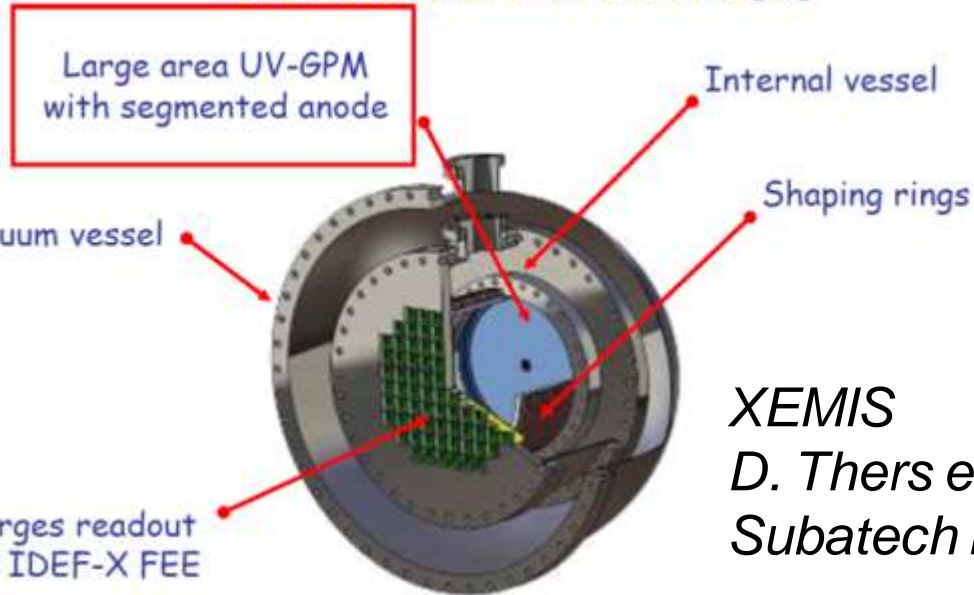
Longer-lived PET isotopes

Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	Branching ratio γ (%)	h_{10} (mSv/h/GBq)
Sc-44	3.97	94.3	101	0.324
Cu-64	12.7	17.6	0.5	0.03
Y-86	14.7	31.9	320	0.515
Zr-89	78.4	22.7	100	0.182
I-124	100.2	22.8	99	0.17
Tb-152	17.5	17	142	

3-photon-cameras

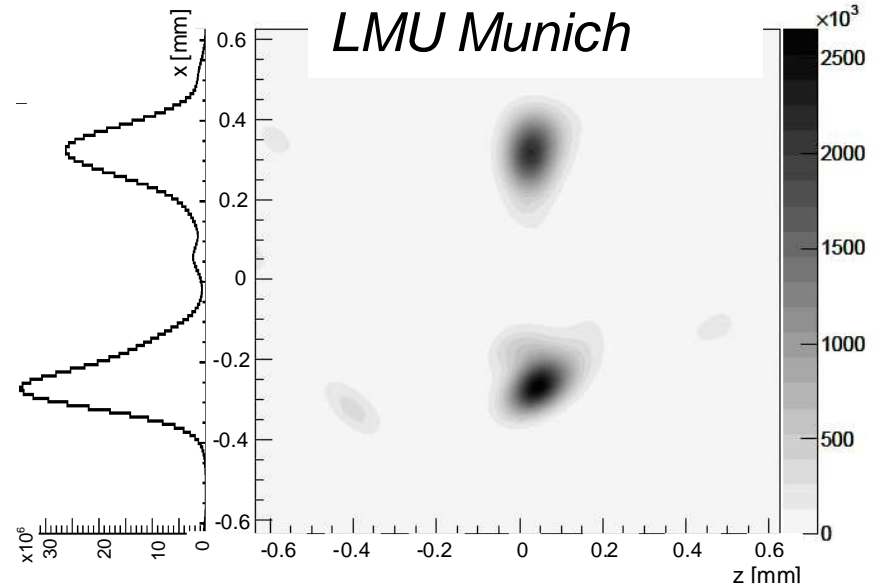


Xenon camera for small animal imaging



XEMIS
D. Thers et al.,
Subatech Nantes

Compton camera
C. Lang et al.
LMU Munich



Applications:

^{34m}Cl

^{44}Sc

^{52m}Mn

^{86}Y

$^{94(m)}\text{Tc}$

^{124}I

^{152}Tb

Summary: Radioisotopes for Medicine

1. Trends

- alternative ^{99m}Tc production (economic question, not technical)
- more PET isotopes, more generators, more “big” accelerators
- molecular therapy of cancer \Rightarrow better isotopes ($^{177}\text{Lu}, \dots$)
- Theranostics (personalized medicine) \Rightarrow need of radiometals
- earlier treatment \Rightarrow shorter range \Rightarrow new isotopes (alpha, Auger)

2. Highly interdisciplinary

- physics (accelerator, target) + radiochemistry (target, separation, labeling) + biochemistry (vectors) + pharmacy (QC, QA) + medicine (preclinical and clinical trials)
- need for interdisciplinary education and training, in particular metal (radio-)chemistry

3. Very long leadtimes

- shortage of R&D isotopes \Rightarrow eventually affects many patients
- unusual technologies must be nurtured by research facilities
- facilitate facility access for physicians (“mail-out-users”)

Production of innovative radioisotopes in 2016

high flux reactor
ISOLDE-CERN
70 MeV cyclotron
 $^{224}\text{Ra}/^{212}\text{Pb}$ (Areva)

