Medical radioisotopes

Ulli Köster (koester@ill.fr)

Institut Laue-Langevin & UGA

ESIPAP

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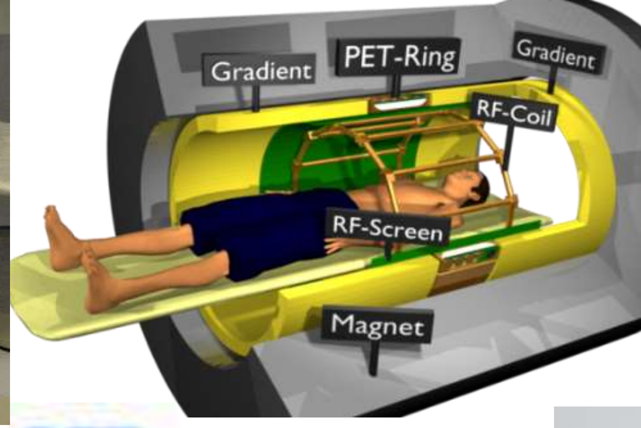
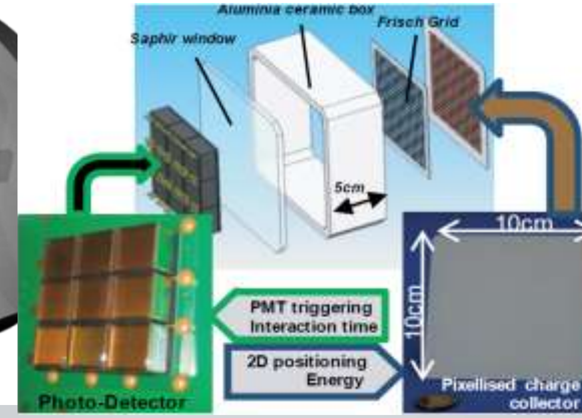
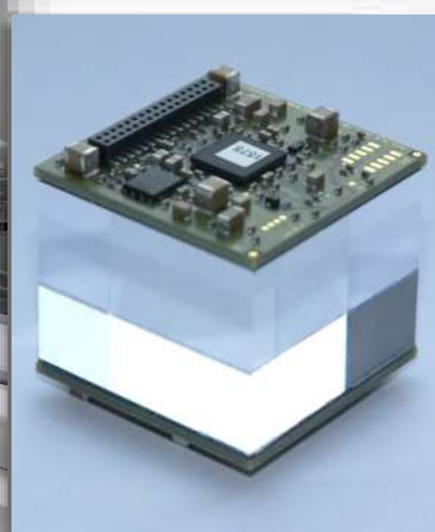
Grands Instruments Européens

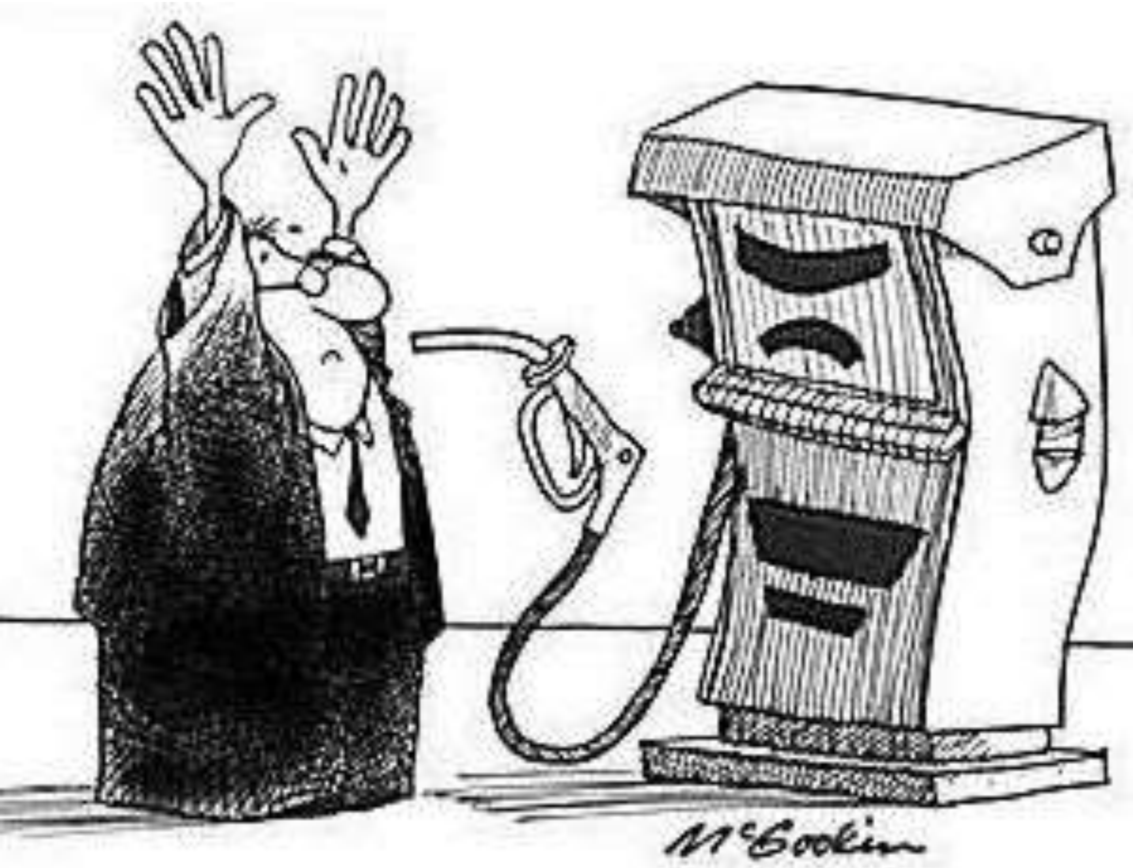

Gradient
PET-Ring
Gradient
RF-Coil
RF-Screen
Magnet


Aluminia ceramic box
Saphir window
Frisch Grid
5cm
10cm
10cm
PMT triggering
Interaction time
2D positioning
Energy
Pixellised charge
collector
Photo-Detector


IRM
PET



Don’t forget the fuel!



Radioisotopes: the “fuel” for nuclear medicine

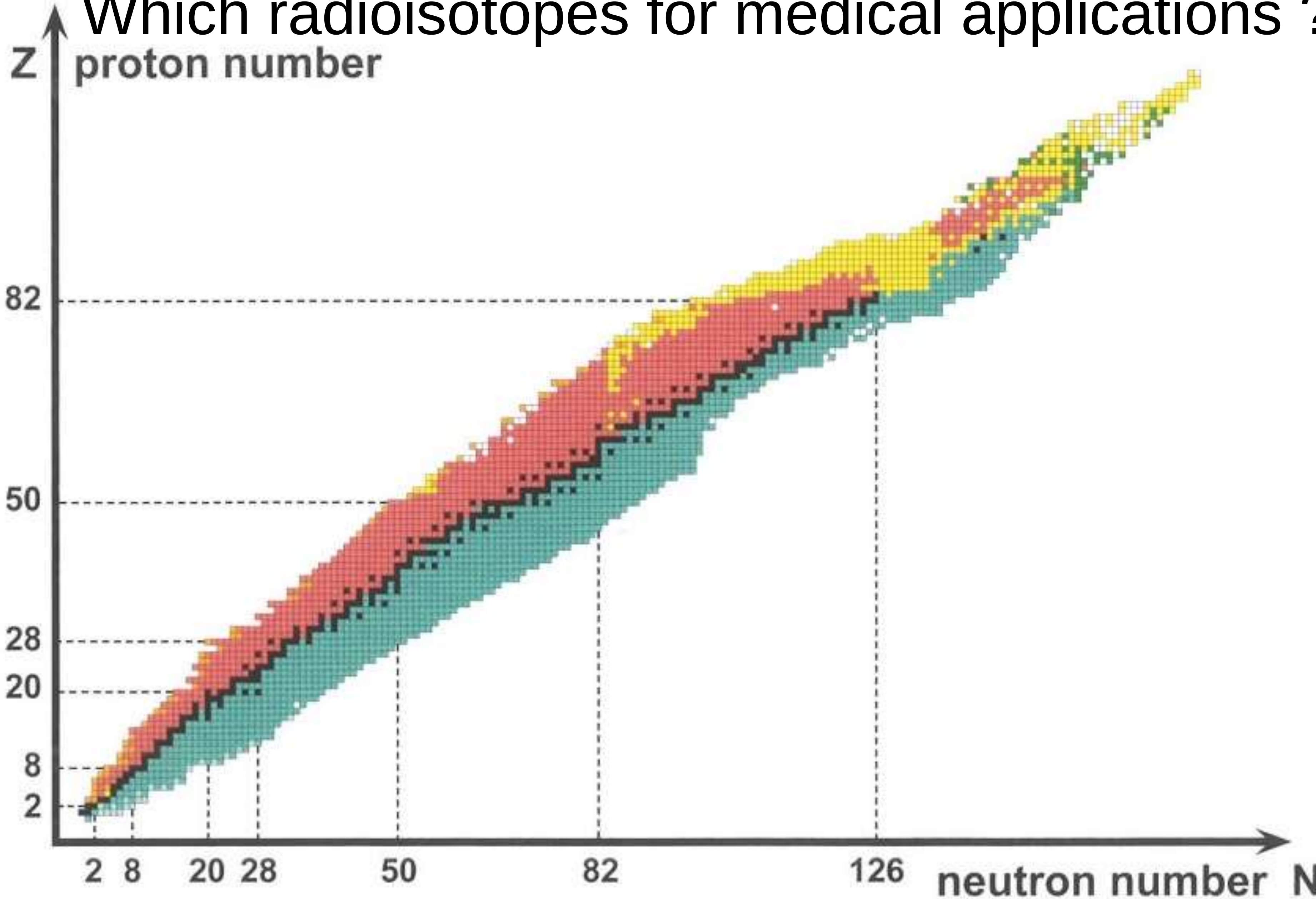
1. What is the optimum fuel for an application ?

2. Are we using the optimum fuel today ?

3. Where does this fuel come from ?

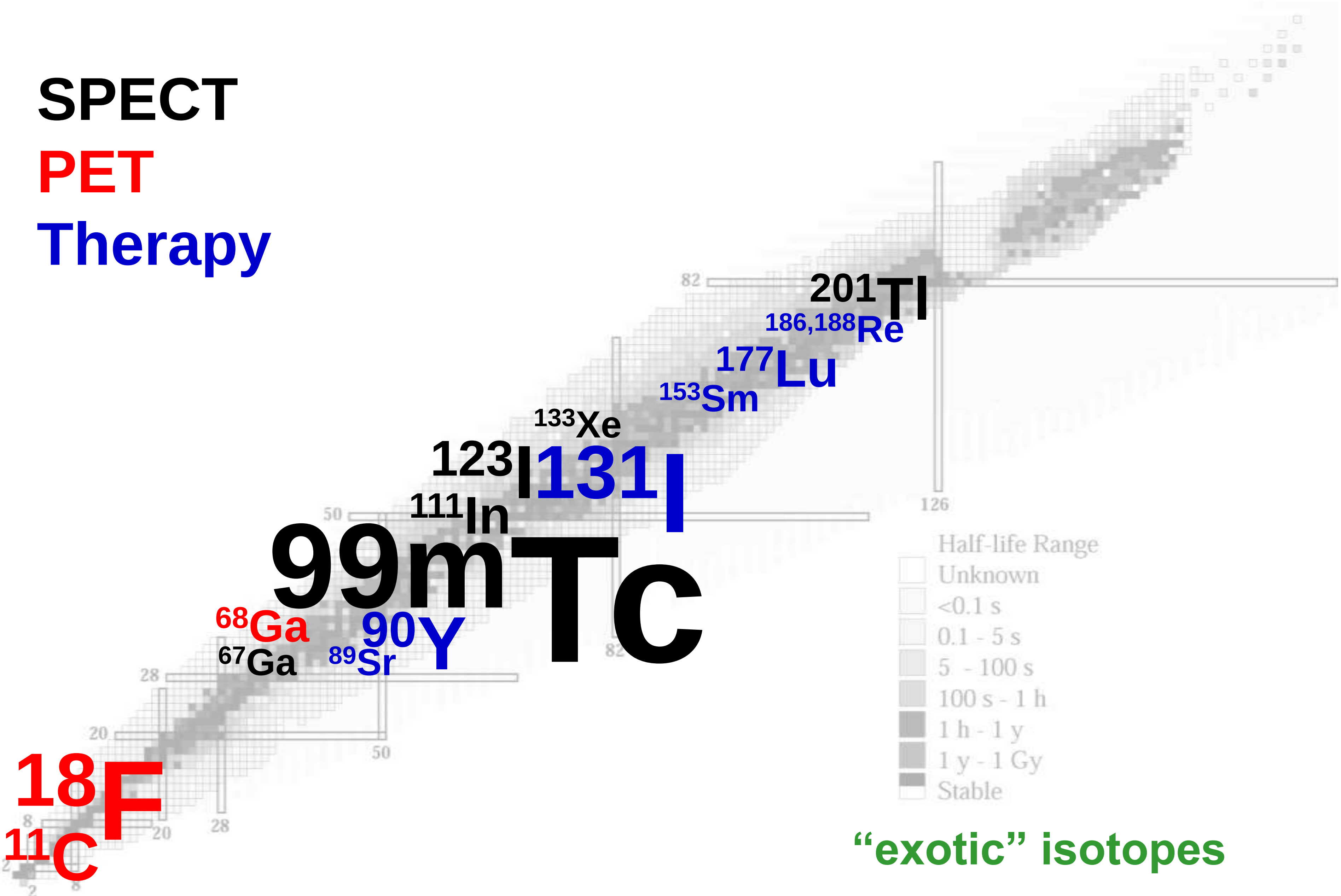
Question

Which radioisotopes for medical applications ?

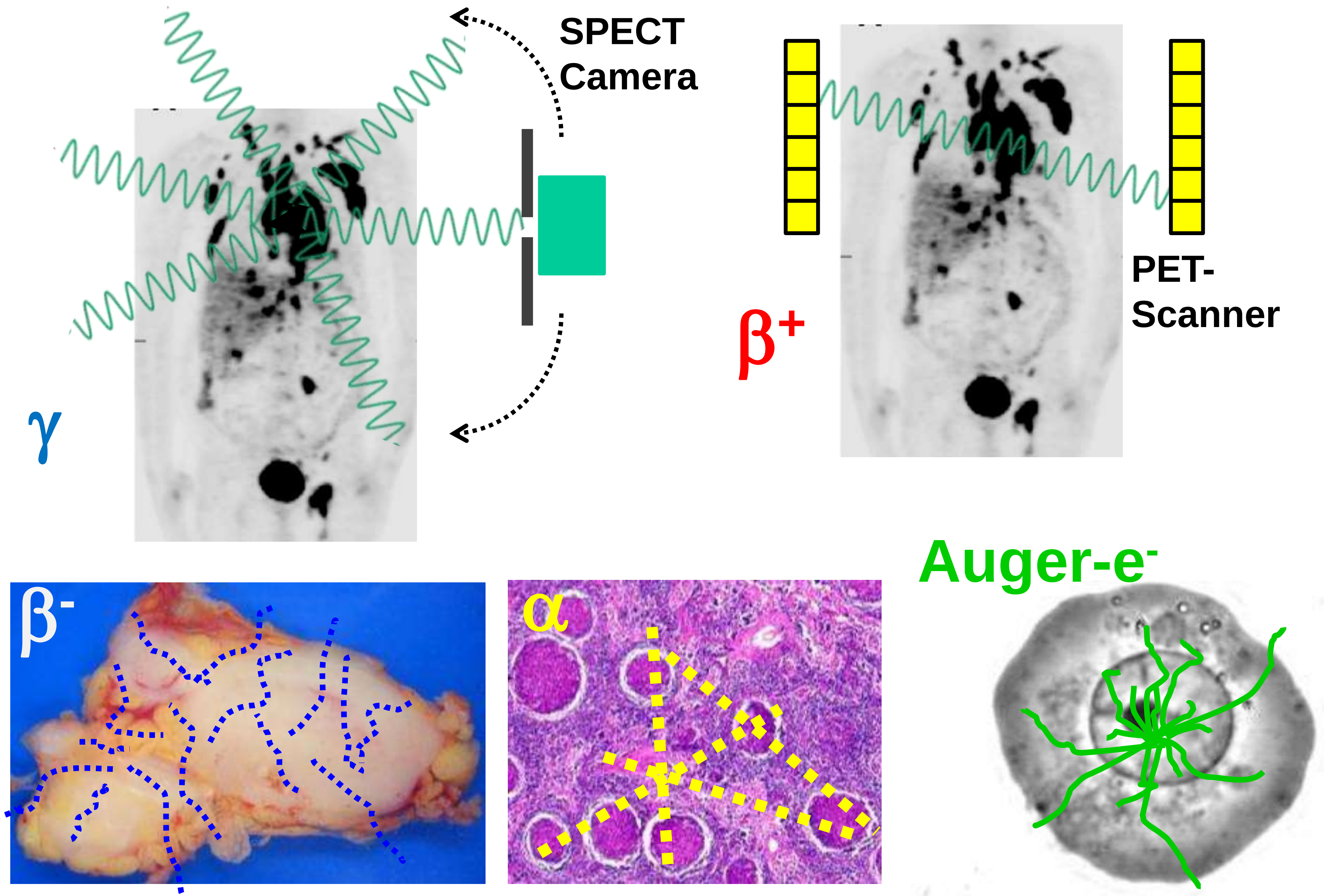


The chart of nuclides – nuclear medicine perspective

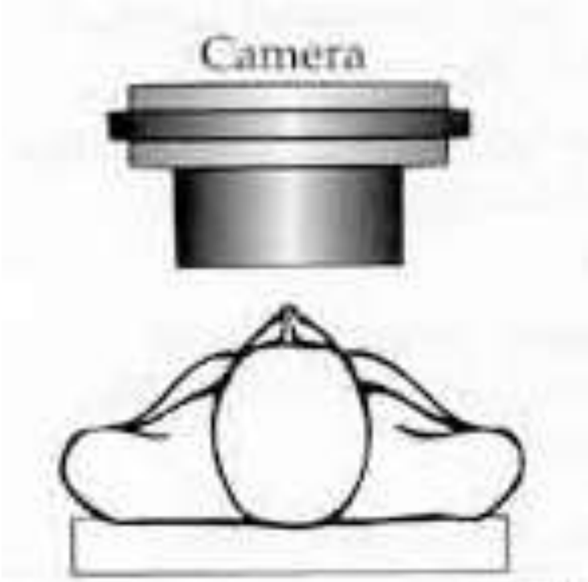
SPECT
PET
Therapy

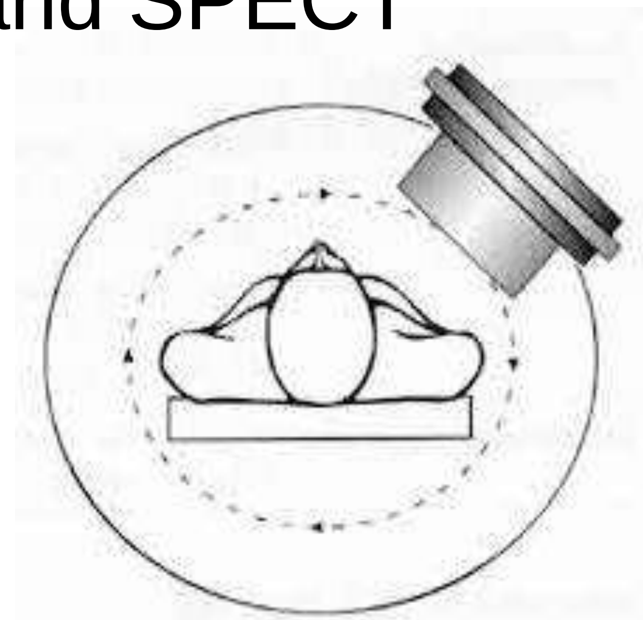


The Nuclear Medicine Alphabet



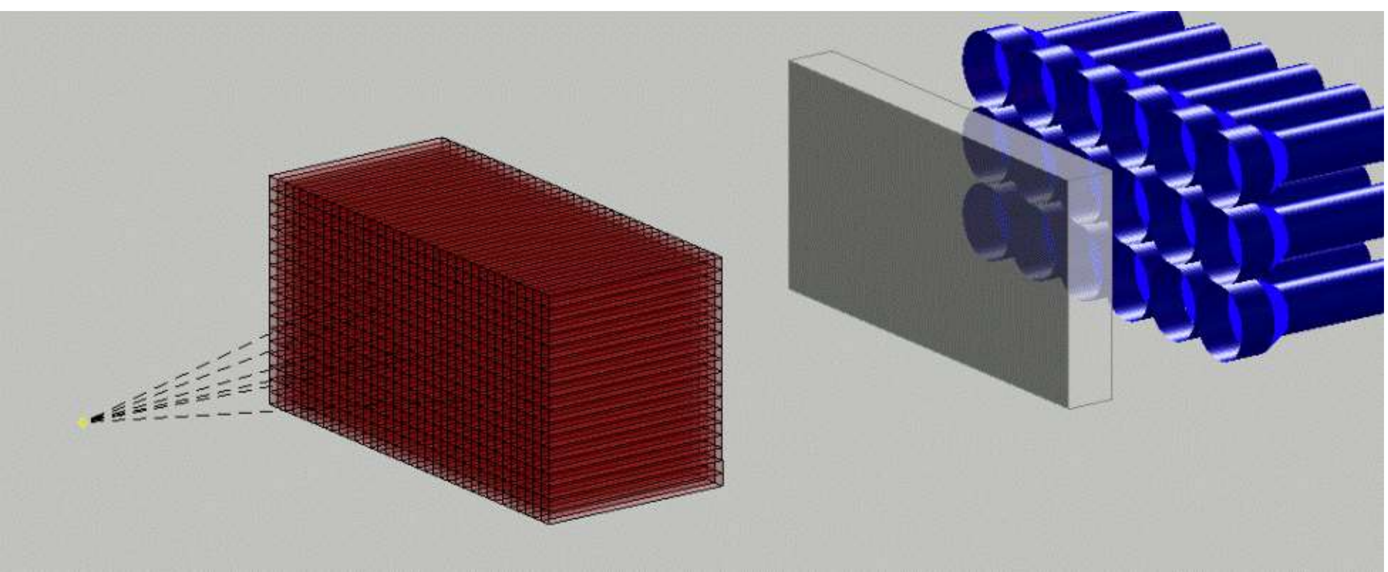
Scintigraphy and SPECT



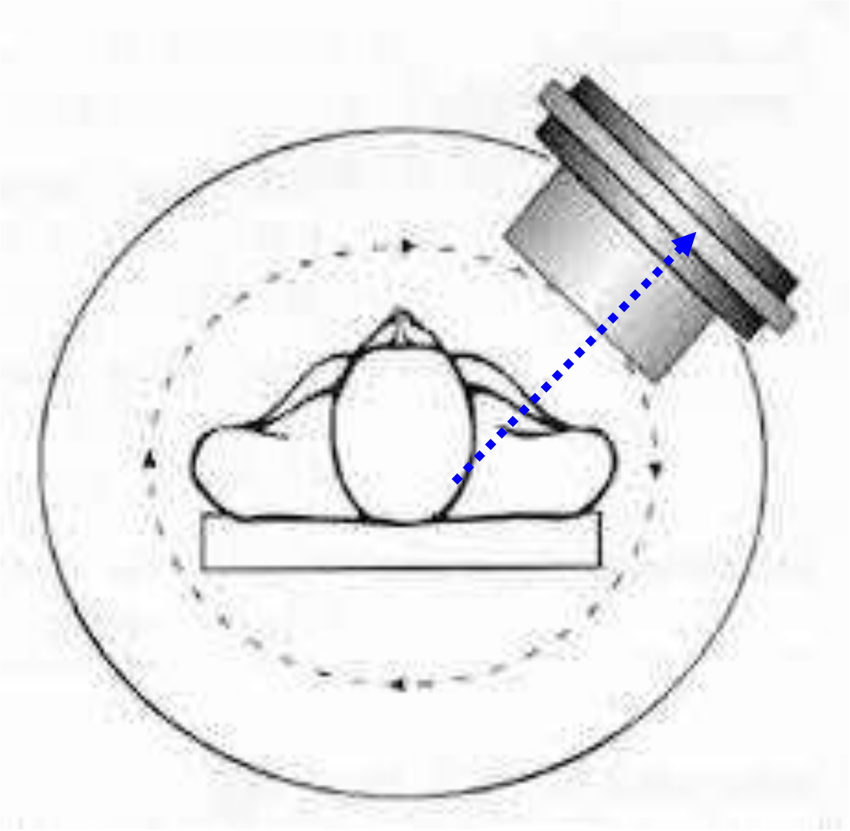


2D: planar scan (Gamma camera)

3D: SPECT: Single Photon Emission Computed Tomography



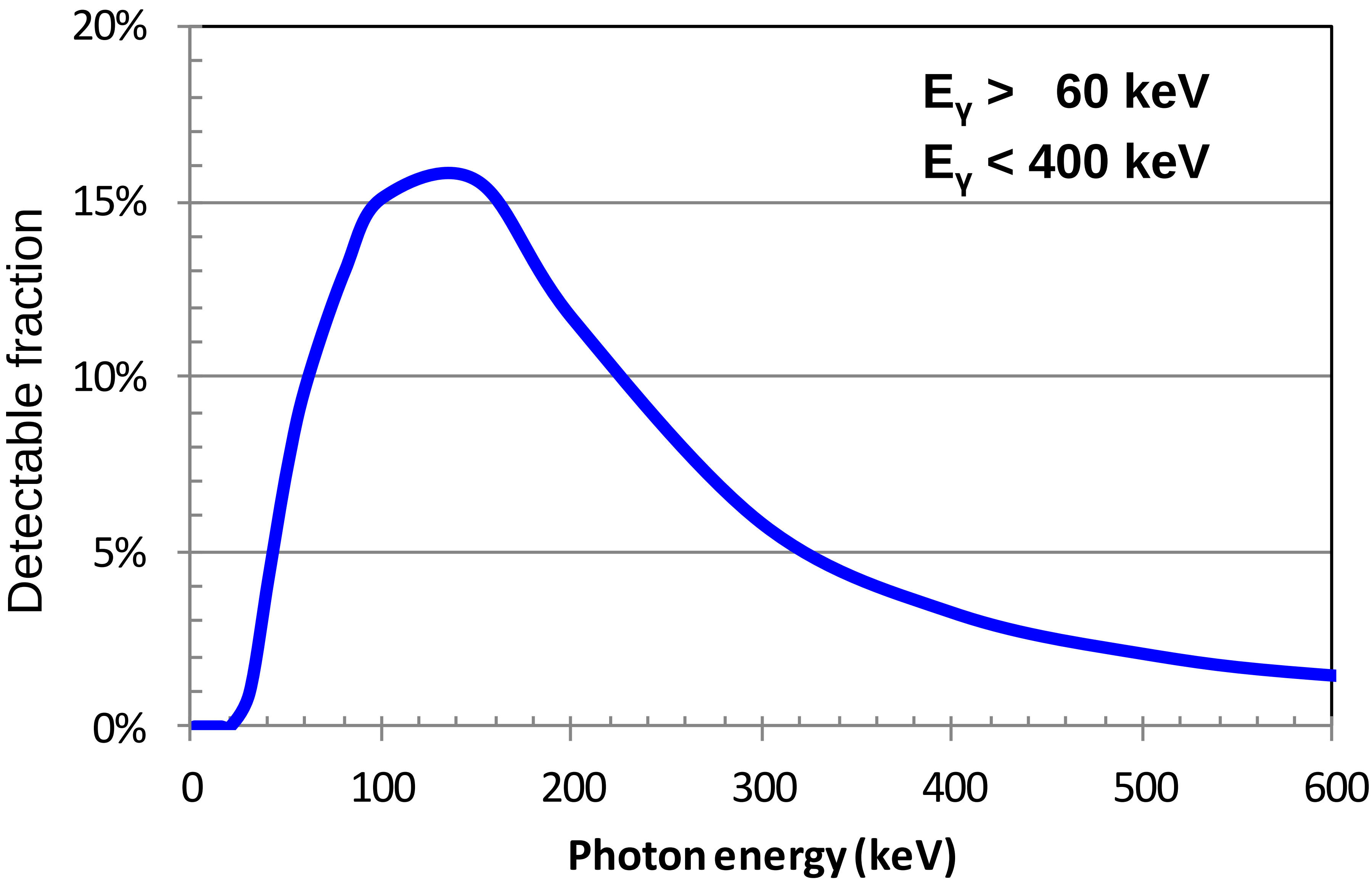
Question: Ideal gamma ray energy for scintigraphy/SPECT?



$$N = N_0\, e^{-\int_0^d \mu(x)dx}$$

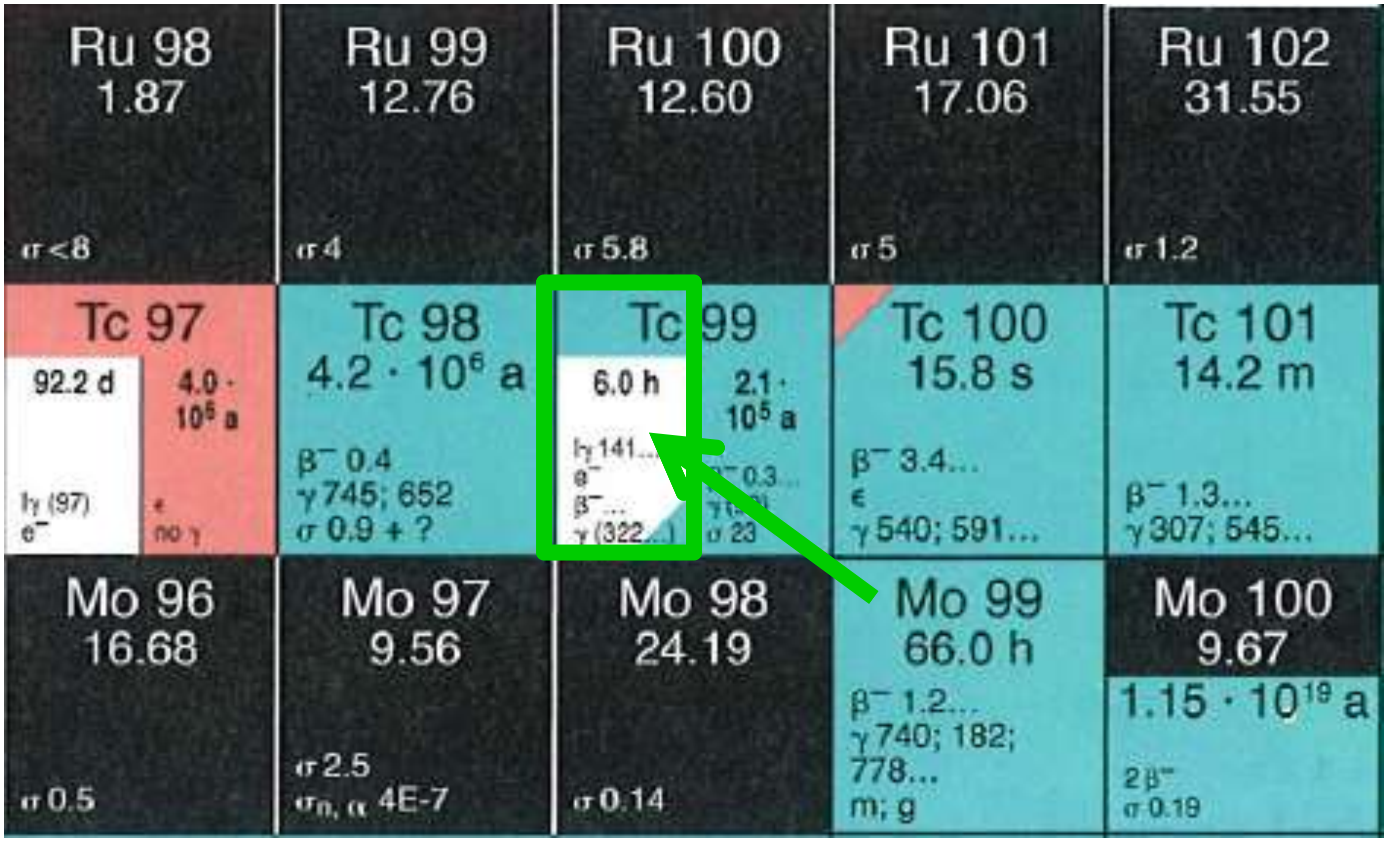
10 cm soft tissue
0.2 cm aluminium (detector encapsulation)
1 cm NaI

Ideal gamma ray energy for scintigraphy/SPECT



10 cm soft tissue, 0.2 cm aluminium (detector encapsulation), 1 cm NaI

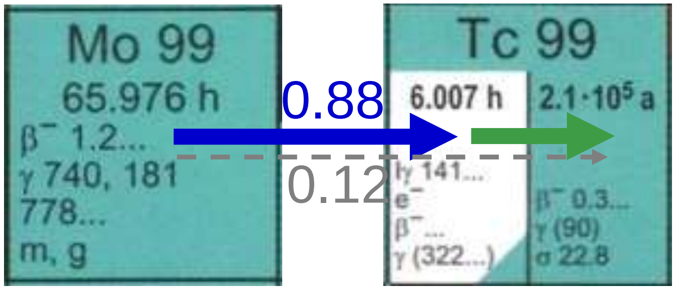
^{99m}Tc: ideal for SPECT and gamma cameras



- 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 ^{99}Mo, $T_{1/2}$ = 66 h
- produces nearly carrier-free product

The Bateman equations

$^{99}\mathbf{Mo} \rightarrow {}^{99m}\mathrm{Tc}$



$^{99}\mathrm{Mo} \rightarrow {}^{99m}\mathbf{Tc} \rightarrow {}^{99g}\mathrm{Tc}$

$$dN_1/dt = -\lambda_1 N_1$$

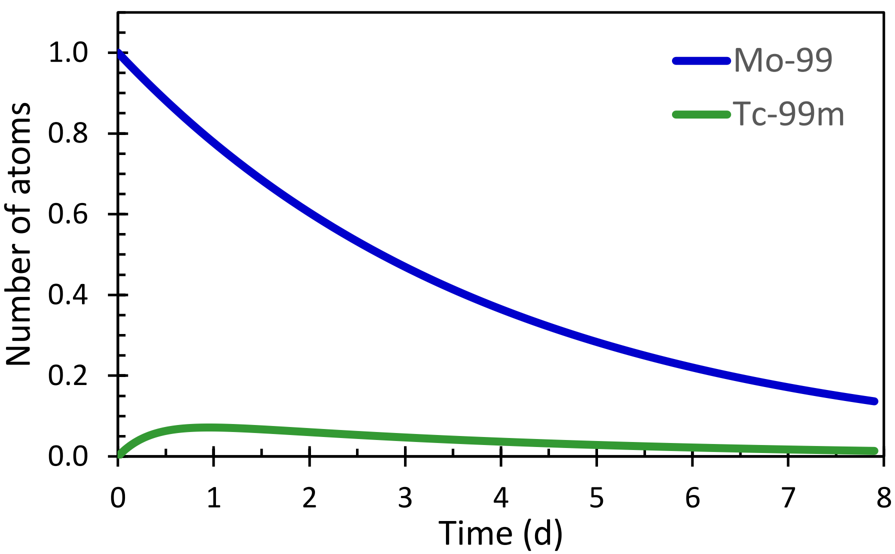
$$N_1(t) = N_1(0)\exp(-\lambda_1 t)$$

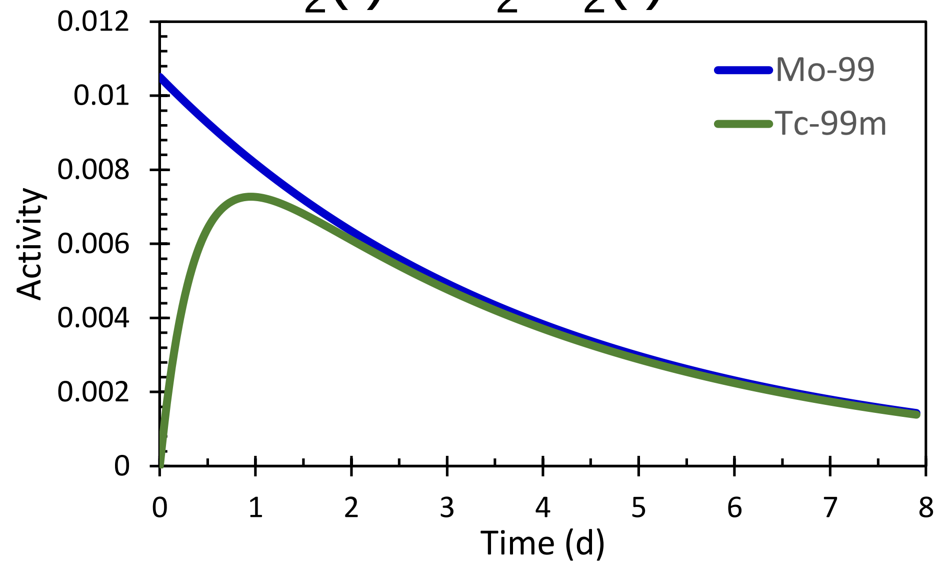
$$A_1 = \lambda_1 N_1 = \lambda_1 N_1(0)\exp(-\lambda_1 t)$$

$$dN_2/dt = \lambda_1 N_1 - \lambda_2 N_2$$

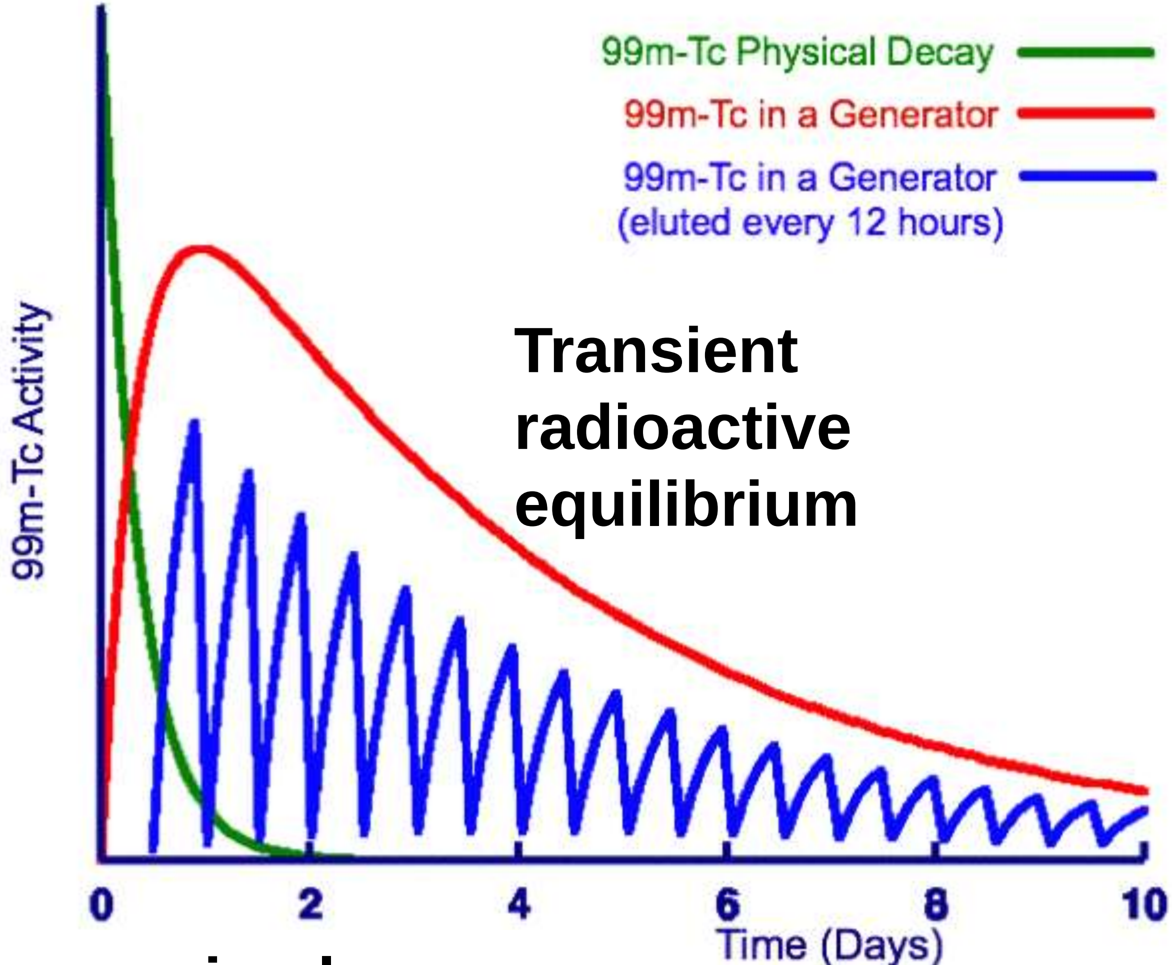
$$N_2(t) = N_2(0)\exp(-\lambda_2 t) + \frac{\lambda_1}{\lambda_2 - \lambda_1} N_1(0)\left[\exp(-\lambda_1 t) - \exp(-\lambda_2 t)\right] * 0.88$$

$$A_2(t) = \lambda_2 N_2(t)$$





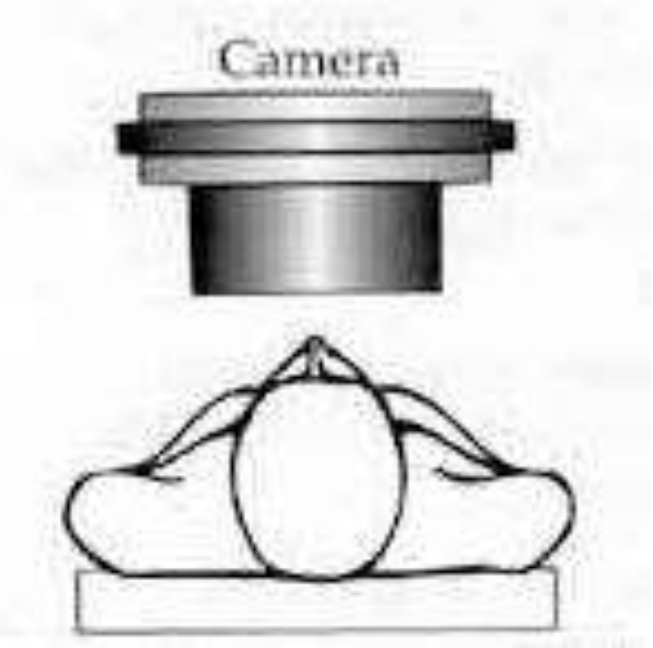
$^{99}Mo/^{99m}Tc$ generator

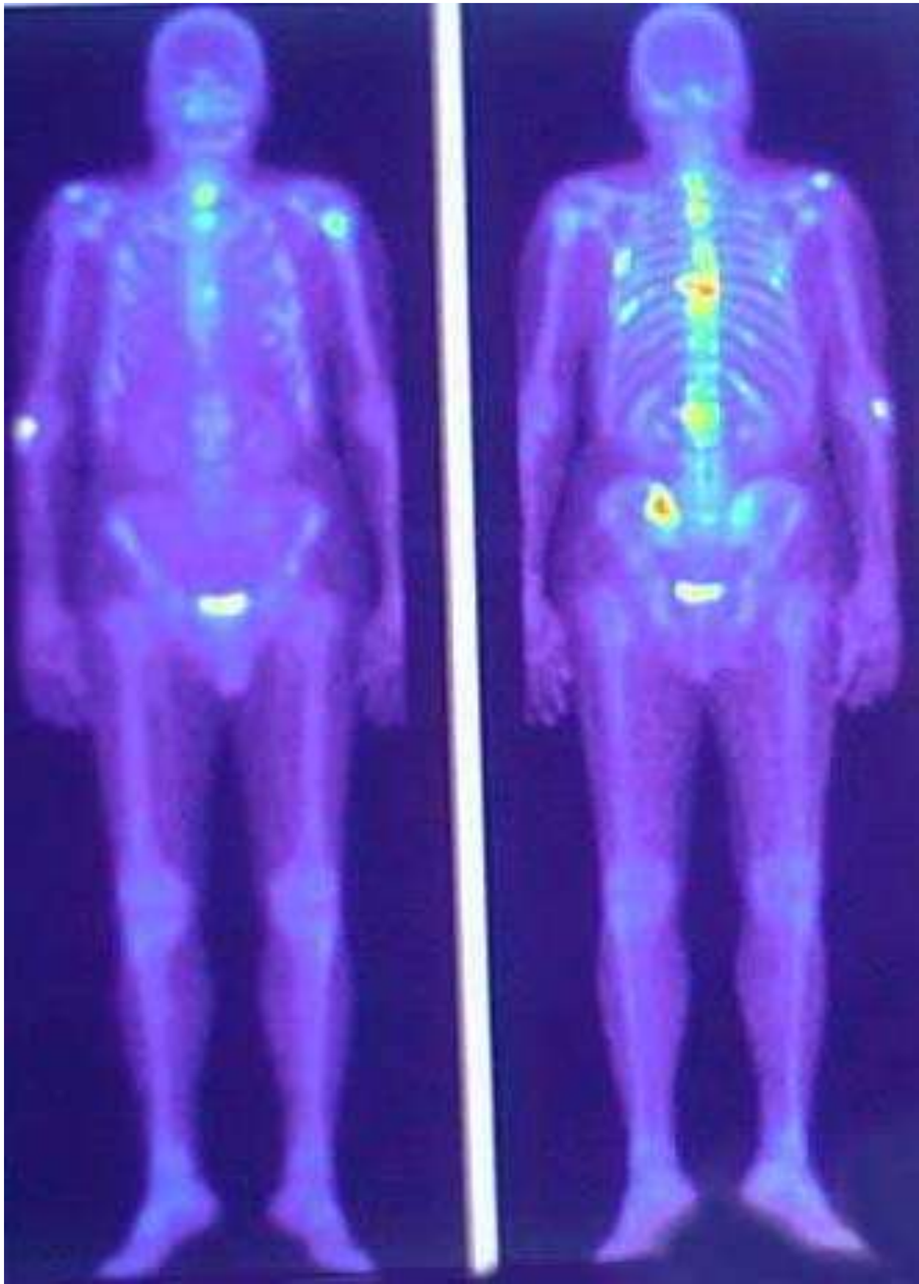


Transient radioactive equilibrium

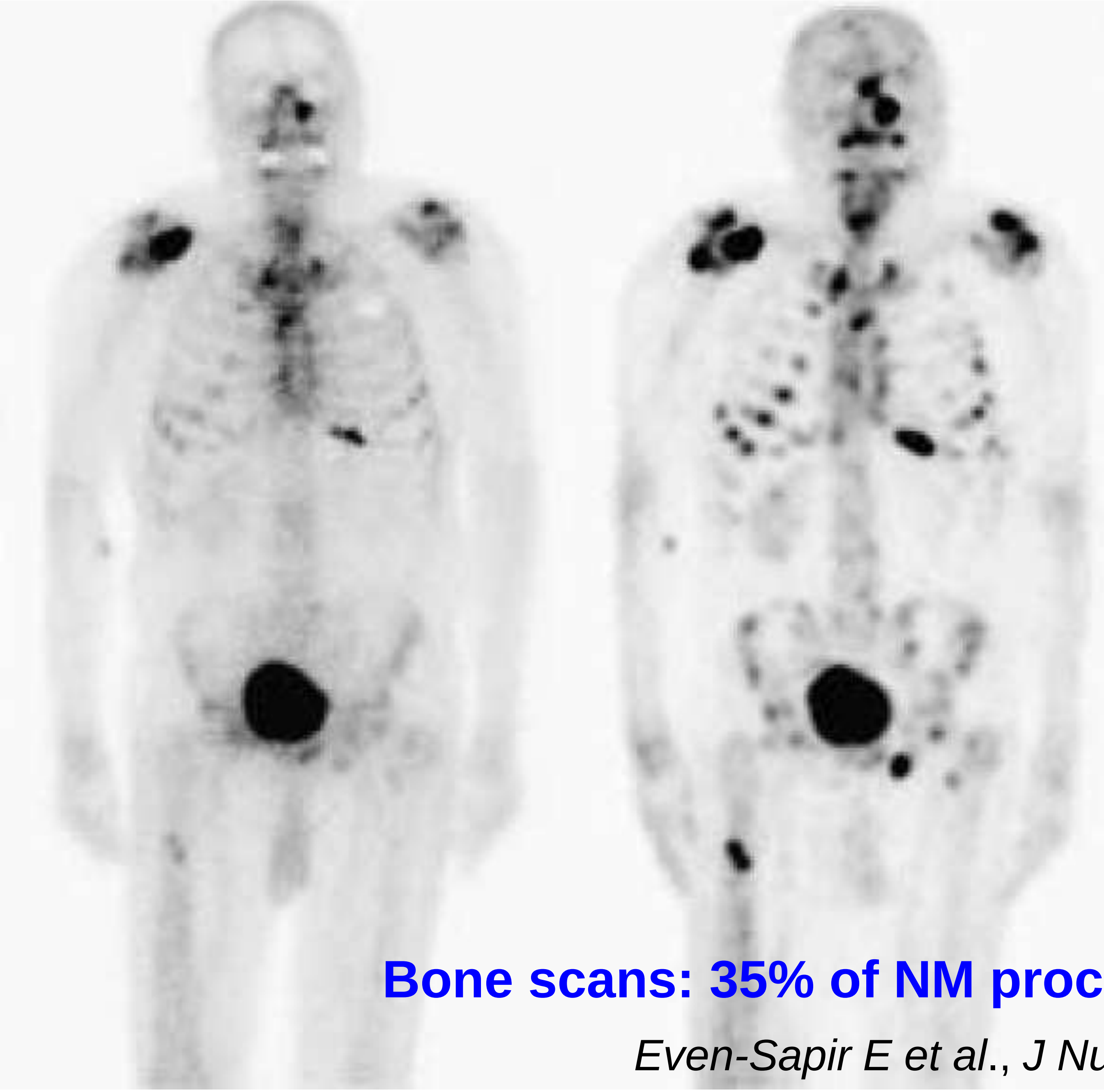
- **simple**
- **reliable**
- **portable**
- **self-shielded**

Bone metastases





- planar or SPECT scan for bone metastases
- differentiate between local and generalized disease
- decide on treatment options: surgery or radiation therapy versus systemic therapy

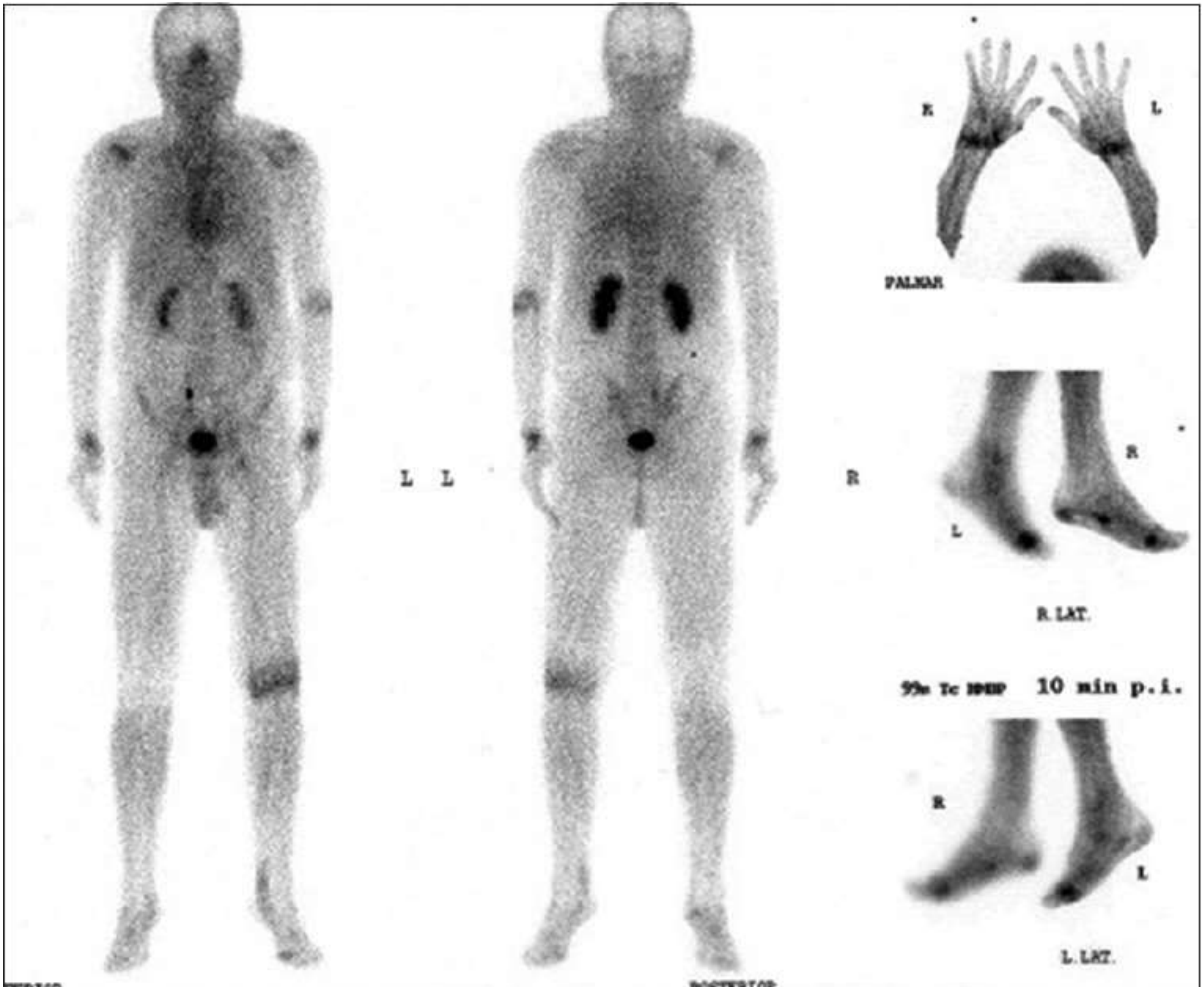


Bone scans: 35% of NM procedures in Europe

Even-Sapir E et al., *J Nucl Med* 2006; 47: 287.

^{99m}Tc-MDP planar **^{99m}Tc-MDP SPECT**

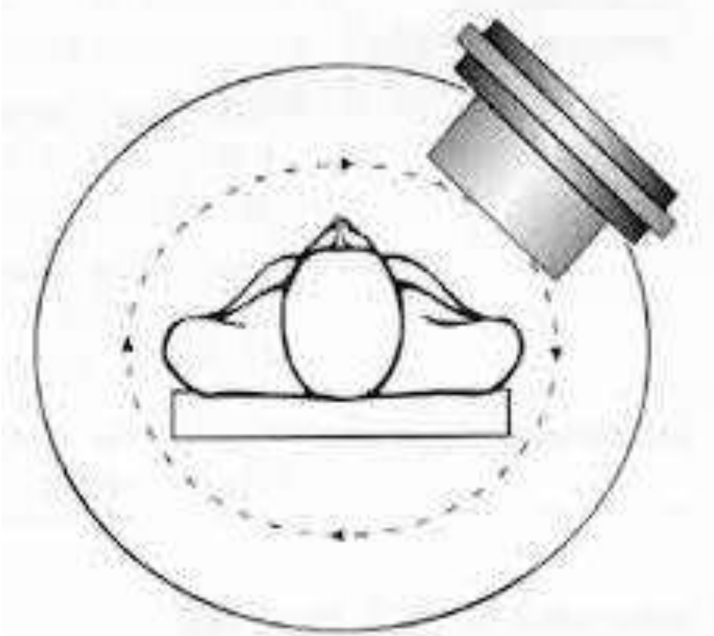
Rheumathoid arthritis

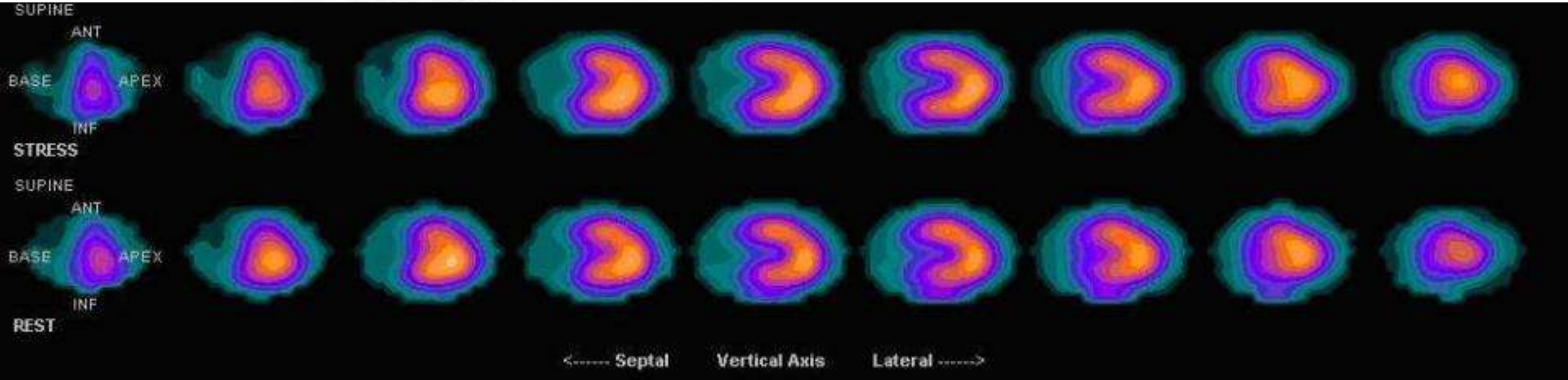


L. Knut, World J Nucl Med. 2015; 14:10.

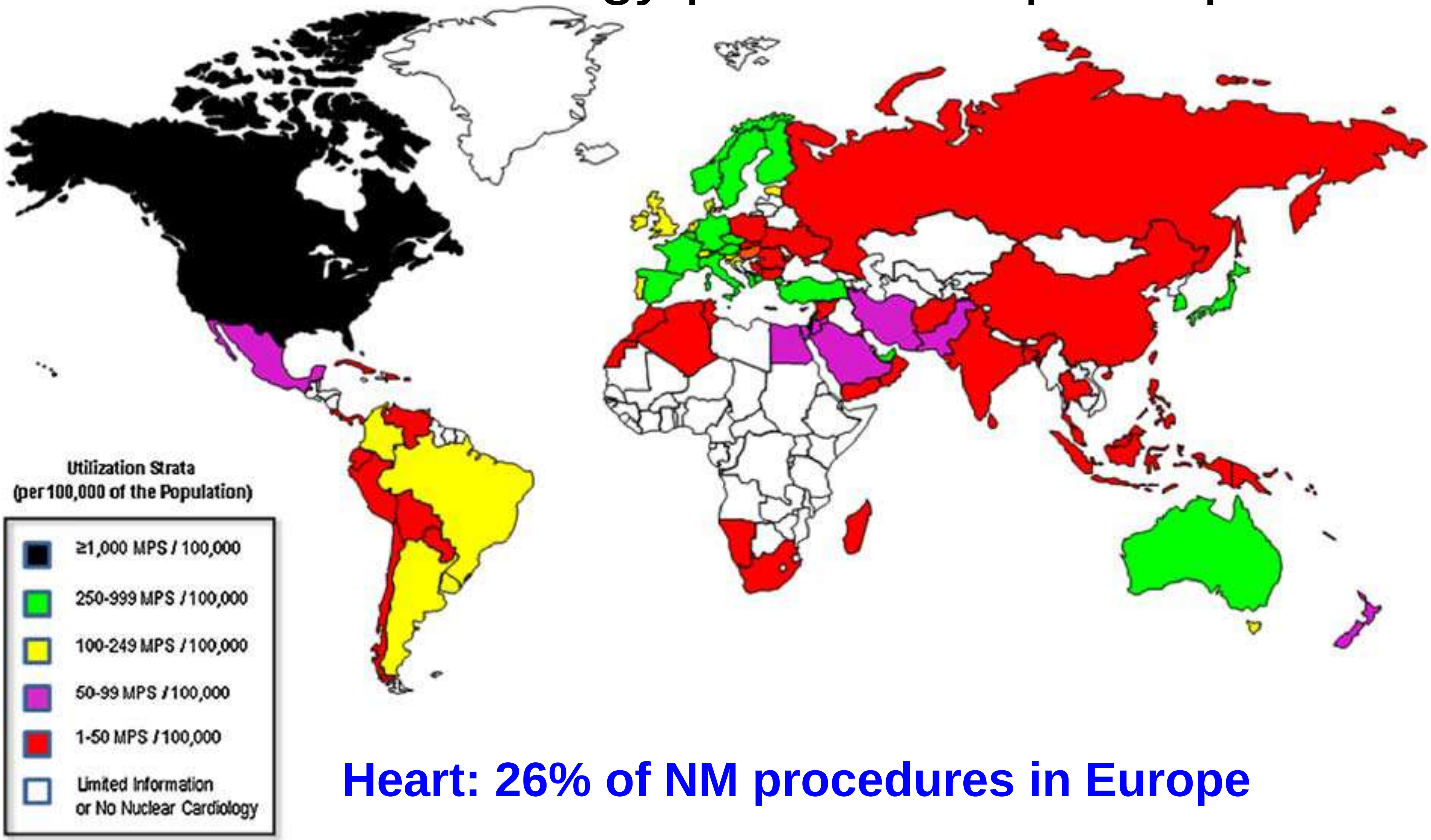
Ischemic heart disease

- diagnose by ECG and cardiac stress test with SPECT
- treatment by medication, angioplasty or bypass surgery





Nuclear cardiology procedures per capita

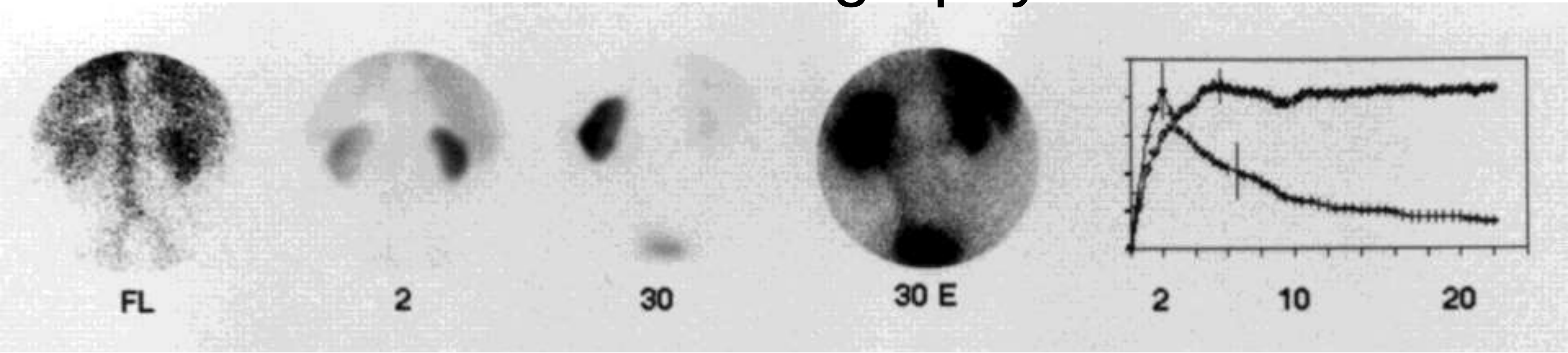


Heart: 26% of NM procedures in Europe

2007: 8.54M myocardial perfusion SPECT procedures reimbursed in the USA

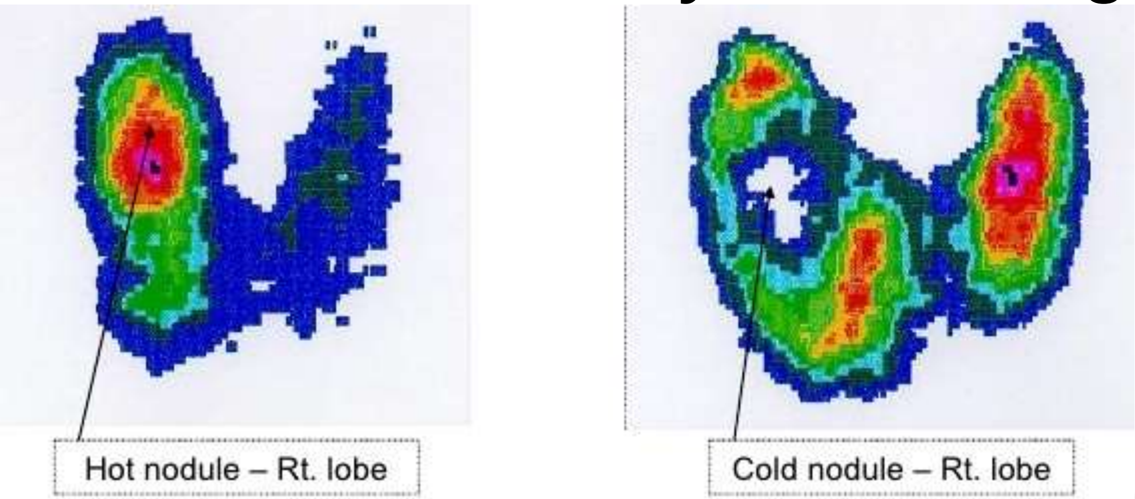
J.V. Vitola et al., J Nucl Cardiol 2009;16:956.

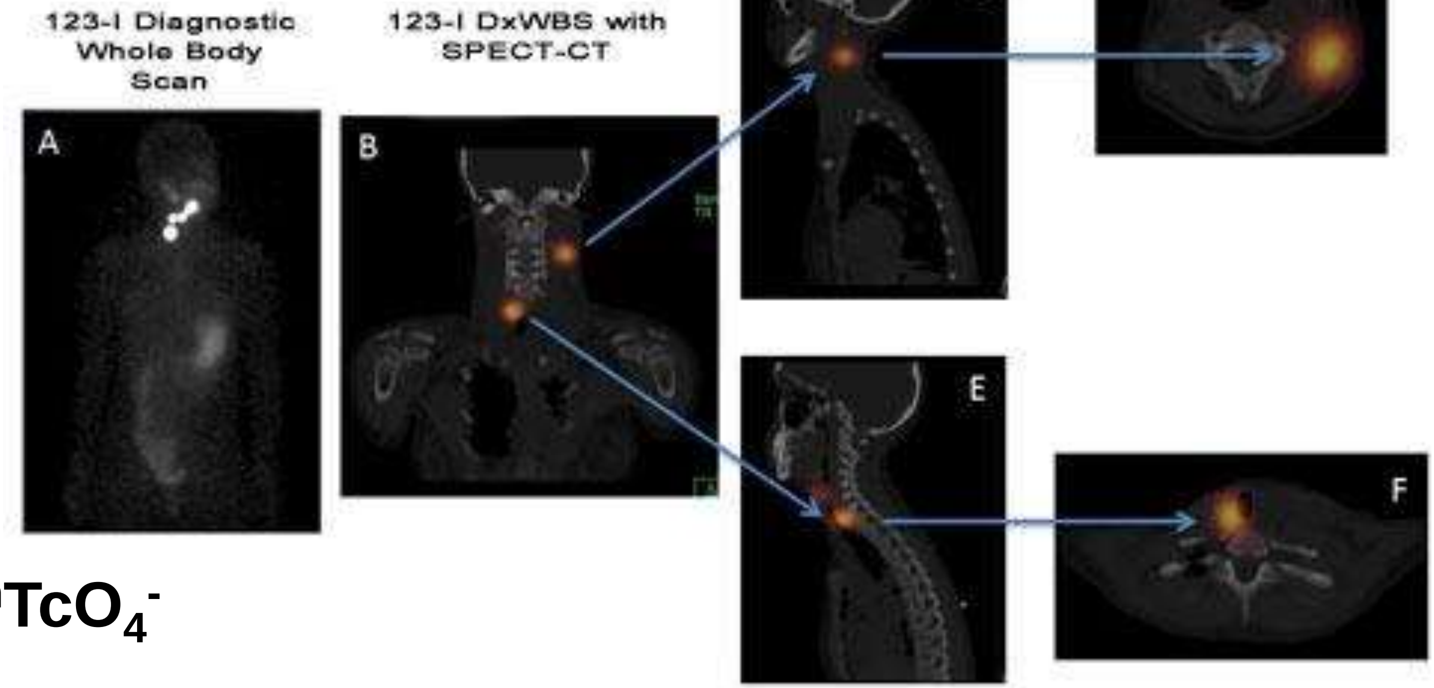
Scintirenography



Kidney: 13% of NM procedures in Europe

Thyroid scintigraphy



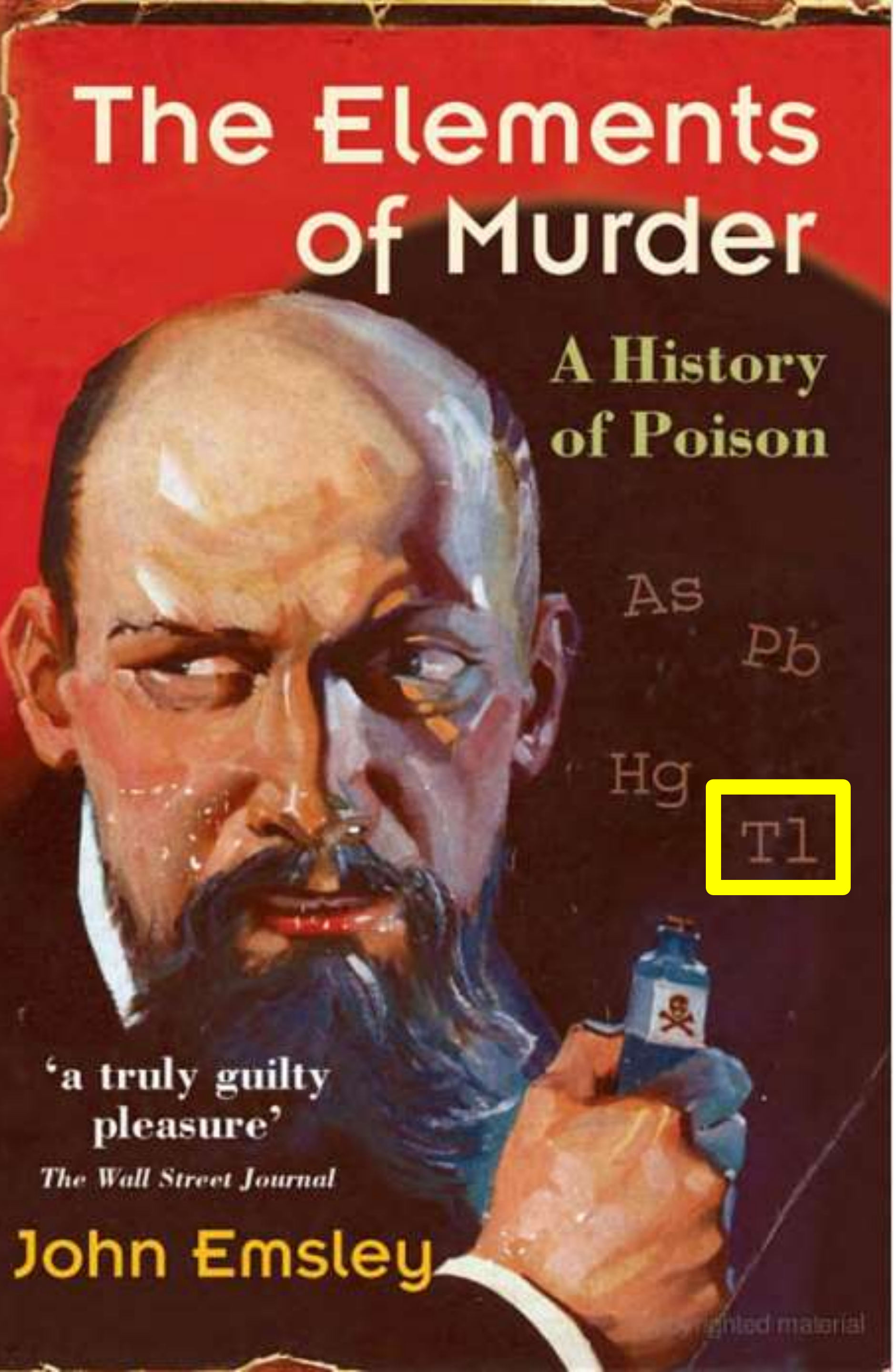


$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$

Thyroid: 12% of NM procedures in Europe

SPECT isotopes

Radio-nuclide	Half-life (h)	Eγ (keV)	Iγ (%)	Decay type
Ga-67	78	93 185	42 21	EC
Kr-81m	0.004	190	64	IT
Tc-99m	6	141	89	IT
In-111	67	171 245	91 94	EC
I-123	13	159	83	EC
Xe-133	126	81	38	β^-
Tl-201	73	70 167	59 10	EC
I-131	192	364	82	β^-
Lu-177	161	113 208	6 10	β^-



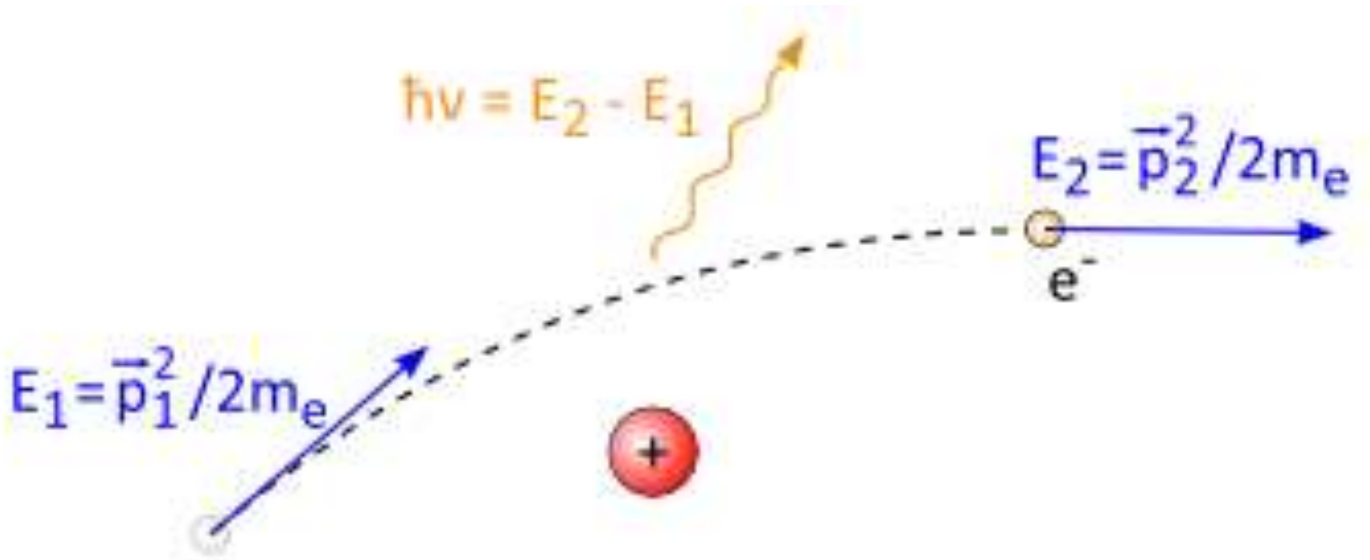
Thallium for patients ?

- MBq to GBq activities correspond to ng to μg
- no chemical toxicity at this level
- provided stable isotopes are absent ("carrier-free") or relatively low abundant ("non-carrier-added")
- high specific activity is frequently a decisive quality criterion for nuclear medicine applications!

$$A/m = \lambda N_A/M = N_A \ln(2)/(M \cdot T_{1/2})$$

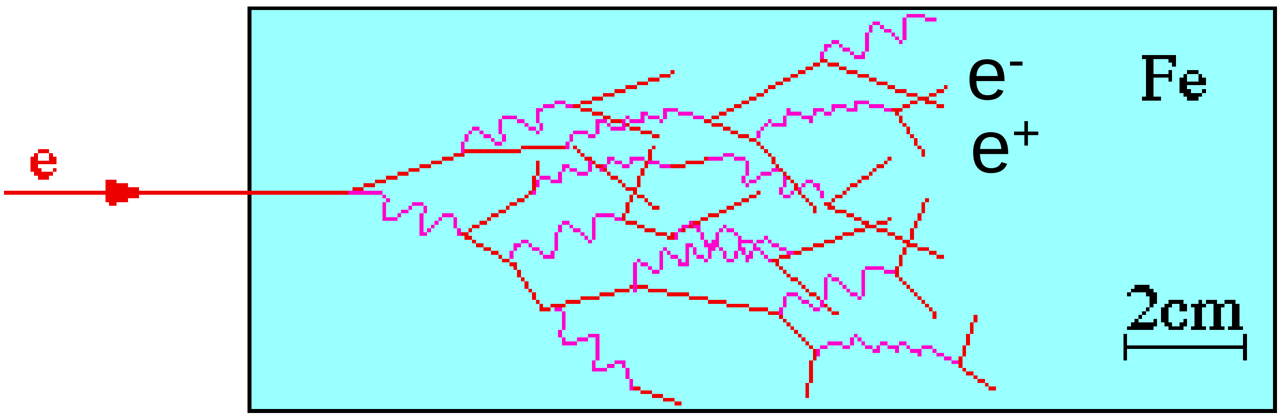
specific activity (Bq/g)

Bremsstrahlung

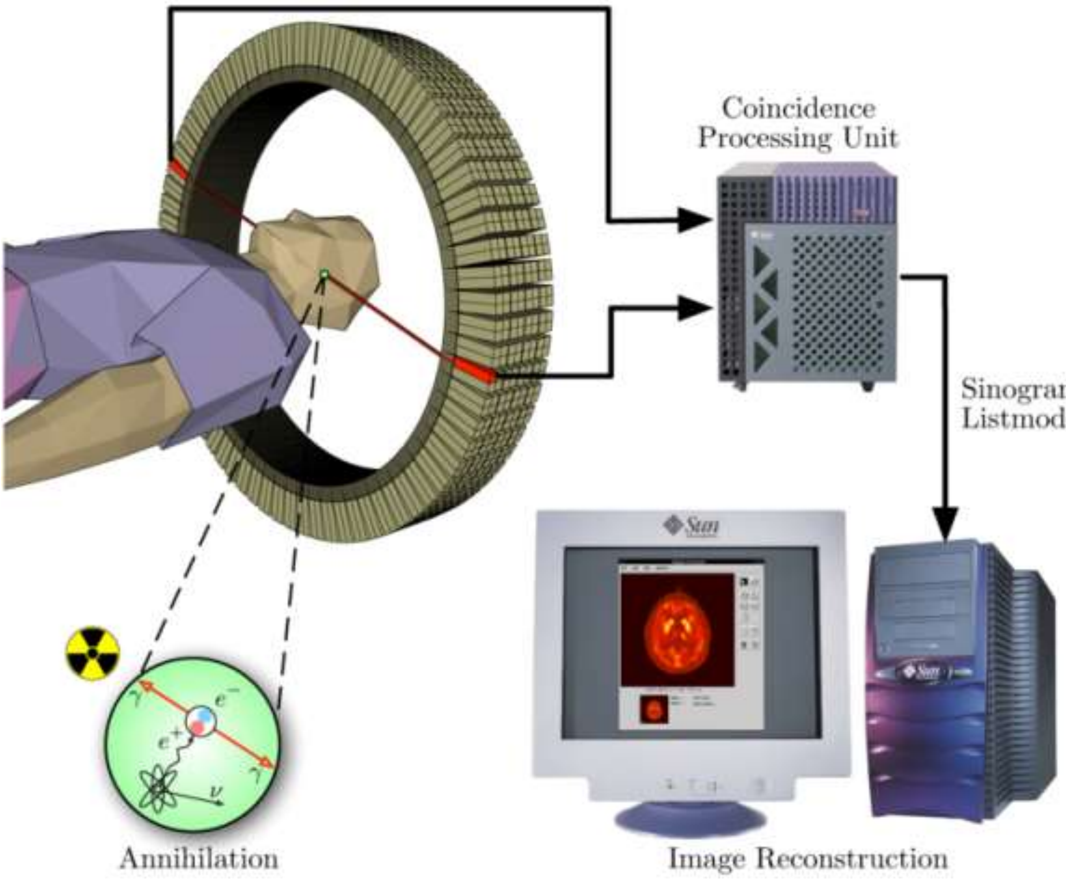


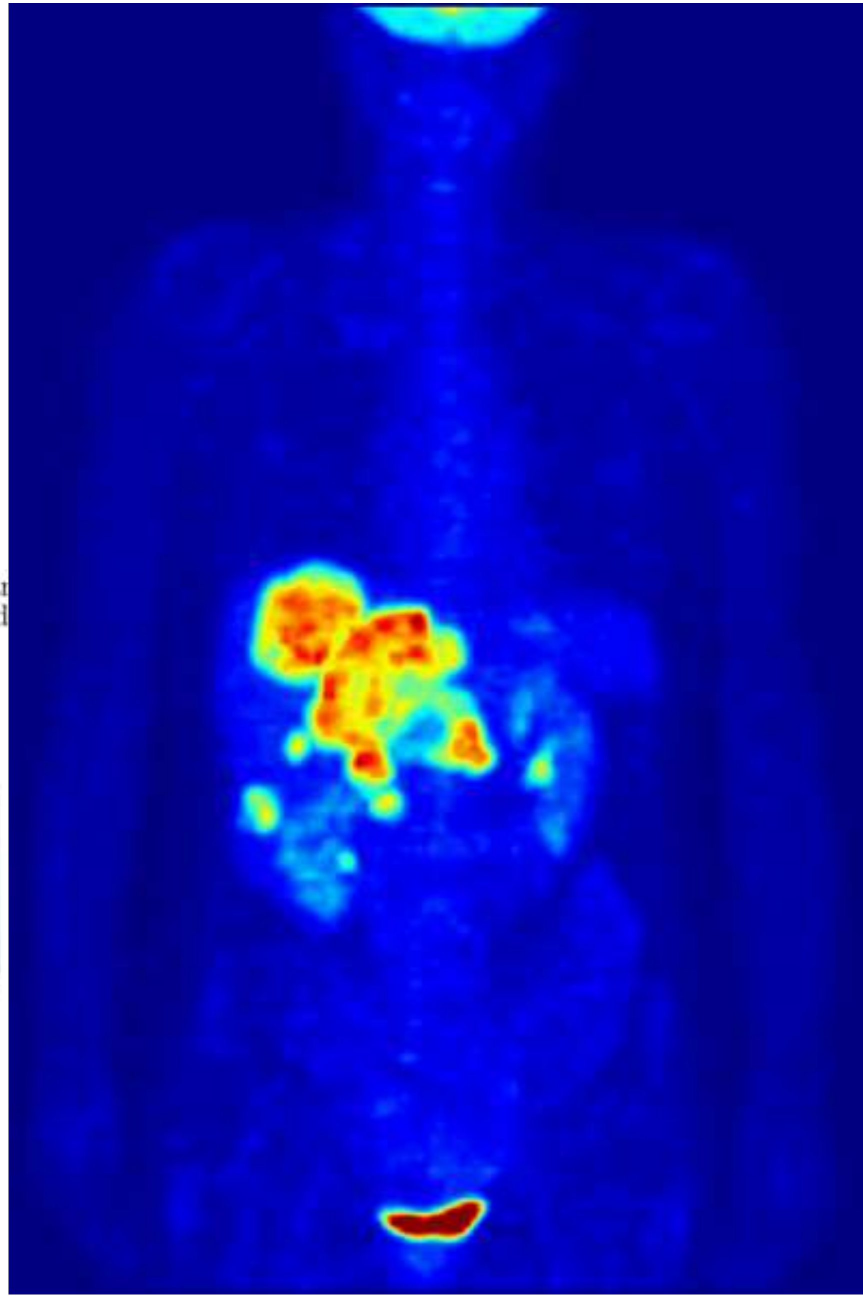
$$\left.\frac{dE}{dx}\right|_{BS} = -\frac{E}{X_0} \qquad X_0 \propto \frac{A}{Z^2} \quad \text{radiation length}$$

air 300 m, water 36 cm, Fe 1.8 cm, Pb 0.56 cm

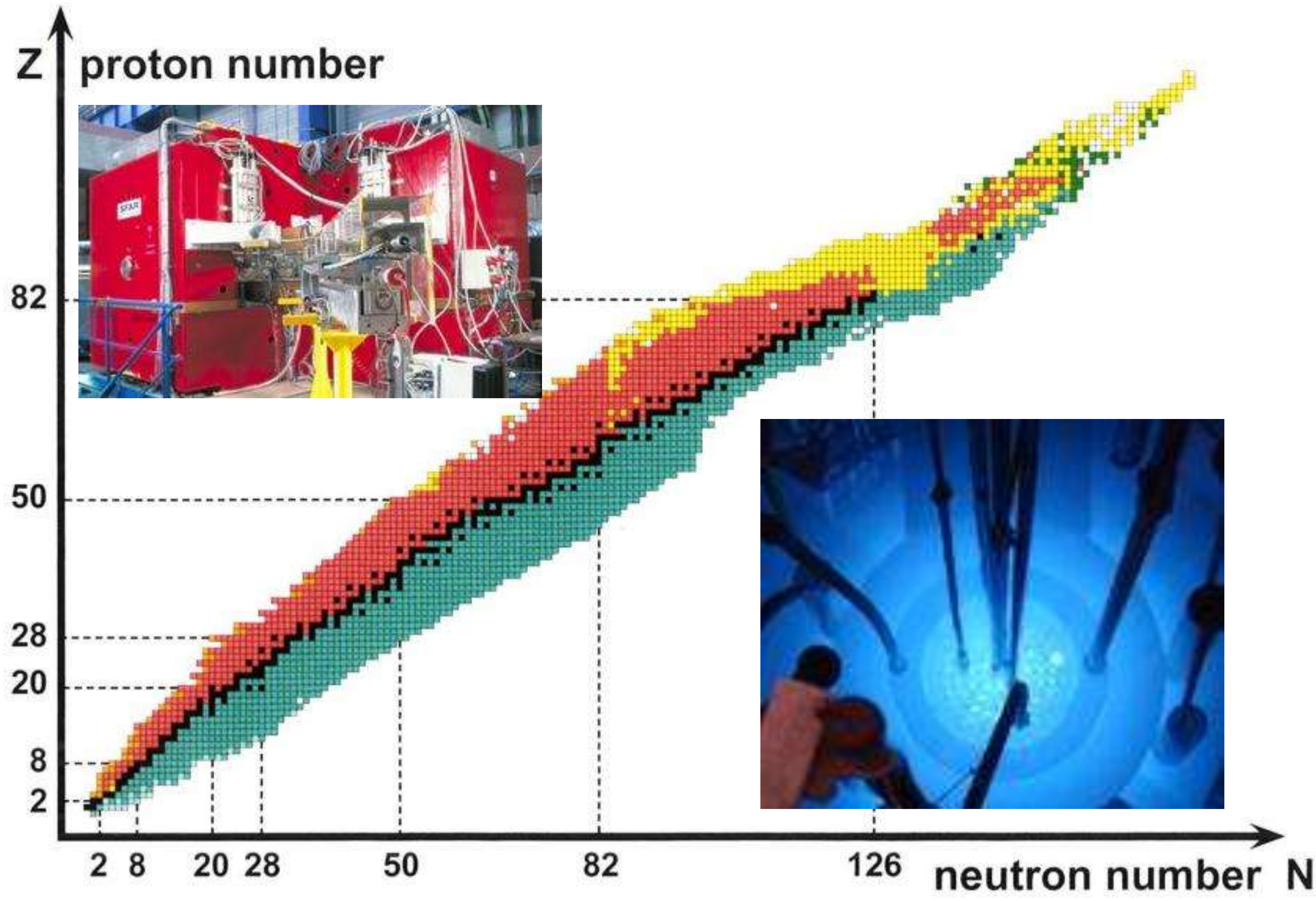


Positron Emission Tomography

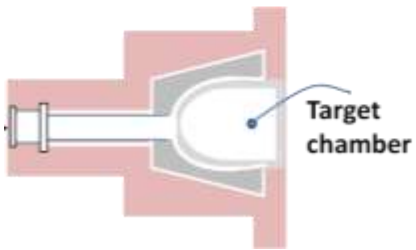




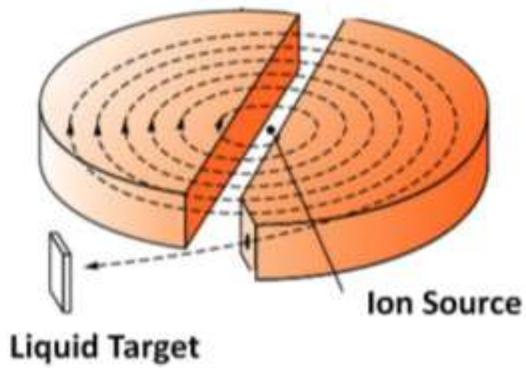
The Tordesillas meridian of radioisotope production



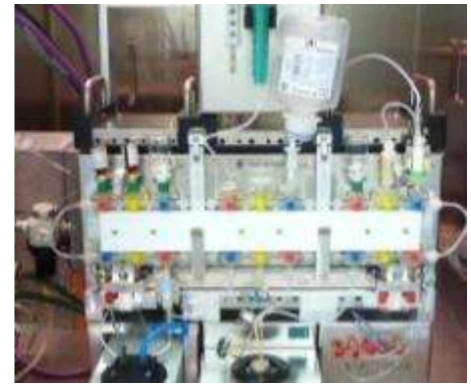
^{18}F production via $^{18}O(p,n)$



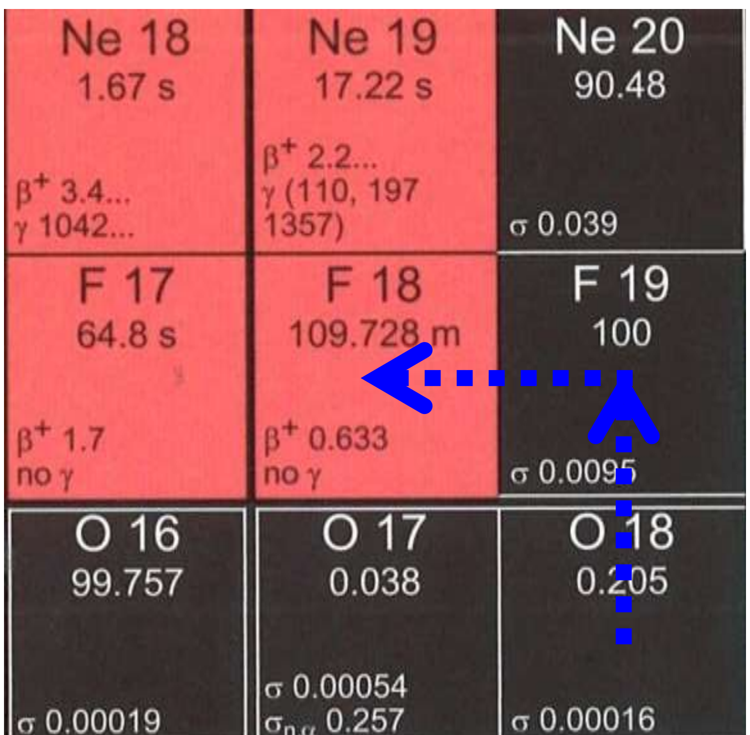
$H_2{}^{18}O$ (water)

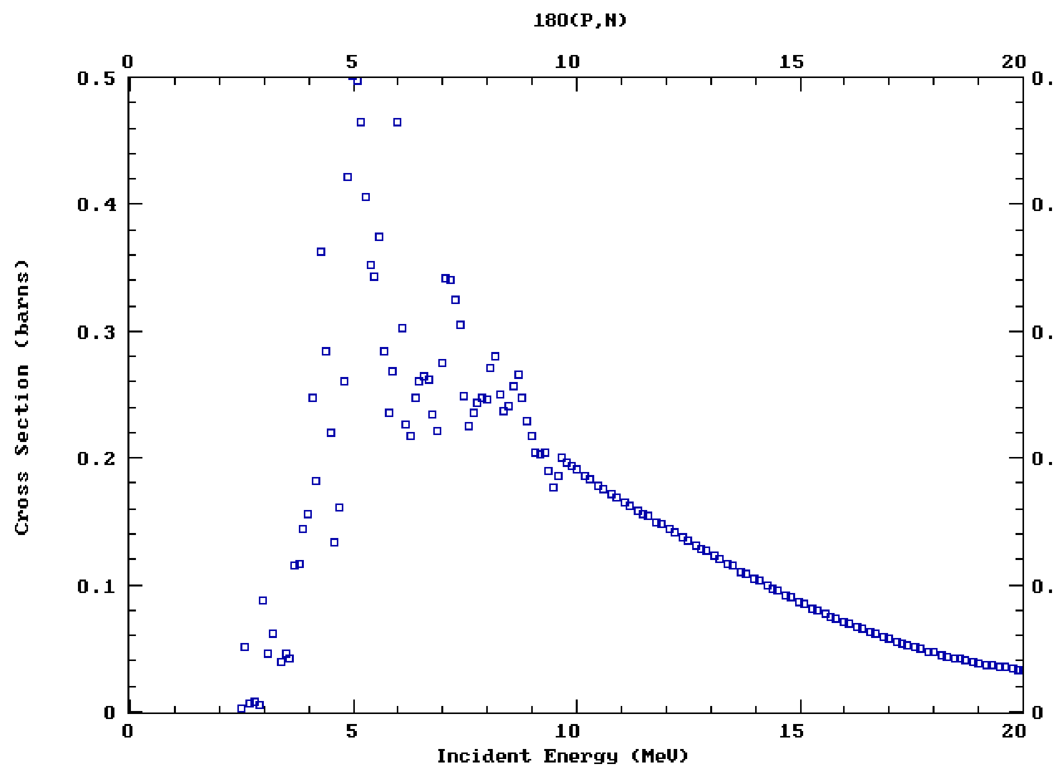


Cyclotron irradiation



Transformation into FDG



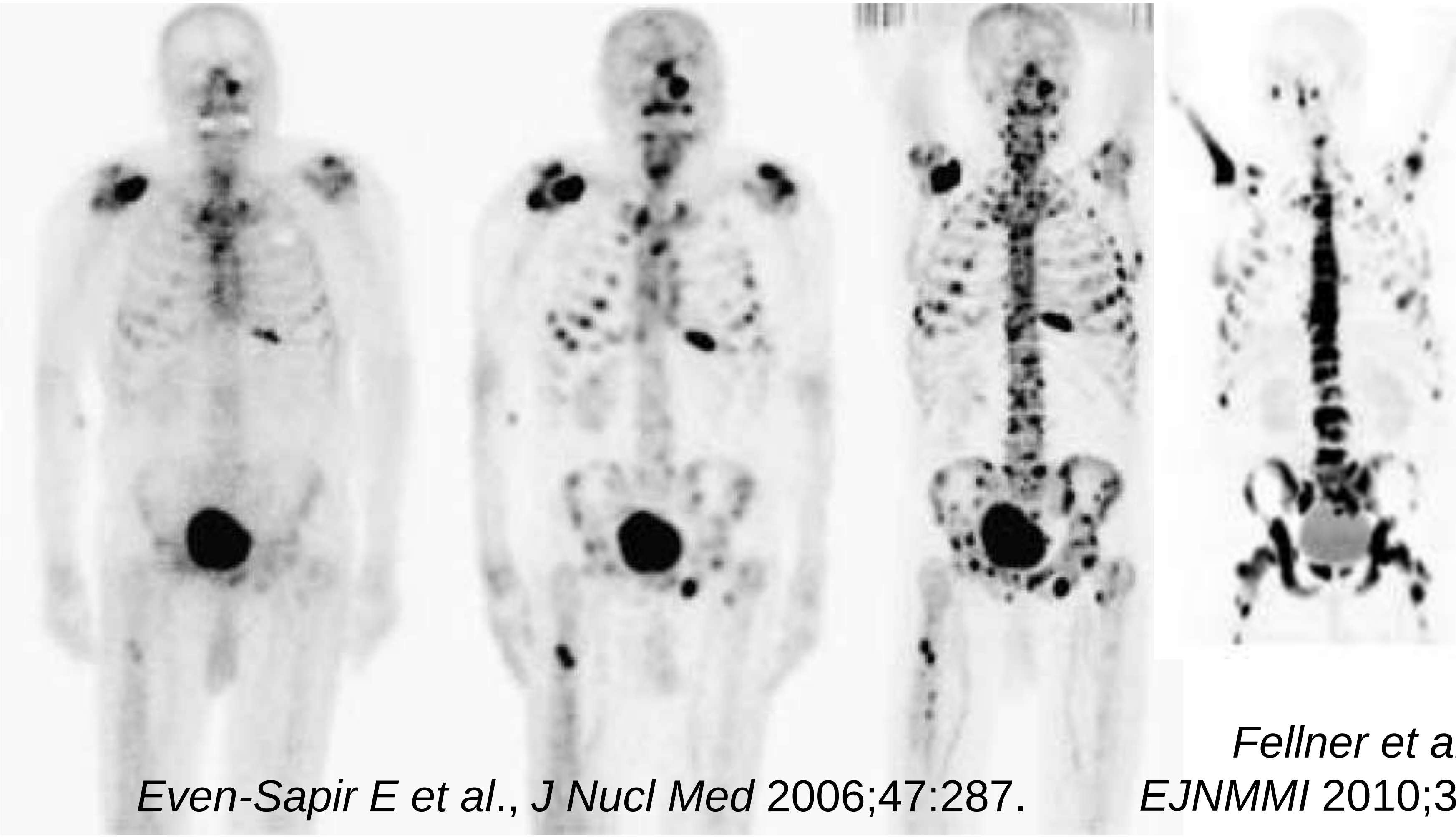


PET isotopes

Radio-nuclide	Half-life (h)	Intensity β^+ (%)	E mean (MeV)	Range (mm)
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
F-18	1.83	96.7	0.25	0.7
Ga-68	1.13	89.1	0.83	3.8
Rb-82	0.02	95.4	3.38	20

^{18}F-Fluorodeoxyglucose (FDG)

Bone scans for bone metastasis screening



Even-Sapir E et al., *J Nucl Med* 2006;47:287.

Fellner et al., *EJNMMI* 2010;37:834.

^{99m}Tc-MDP planar **^{99m}Tc-MDP SPECT** **$^{18}F^{-}$ PET** **^{68}Ga-BPAMD PET**

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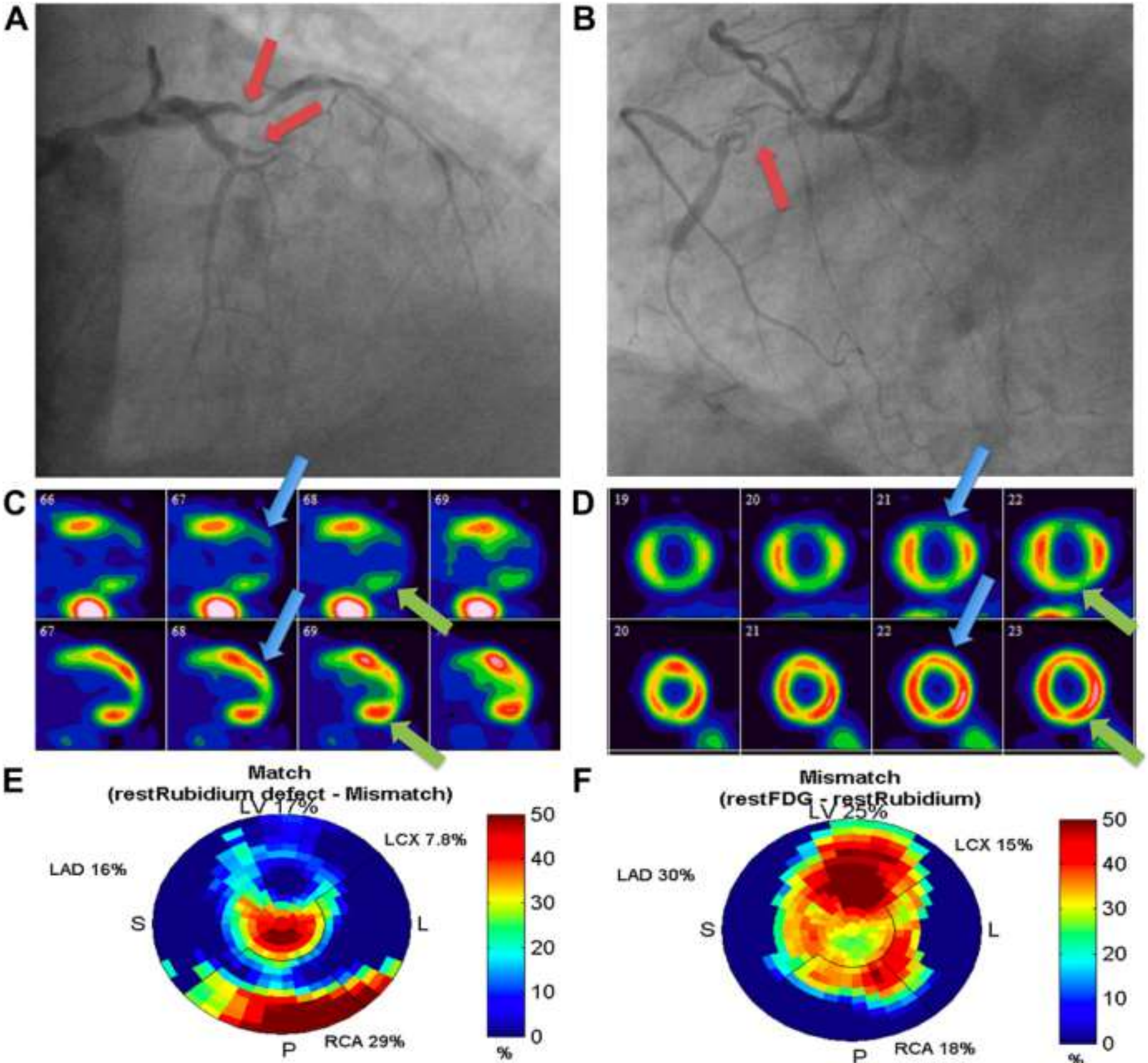
Rb-82	0.02		3.38	20

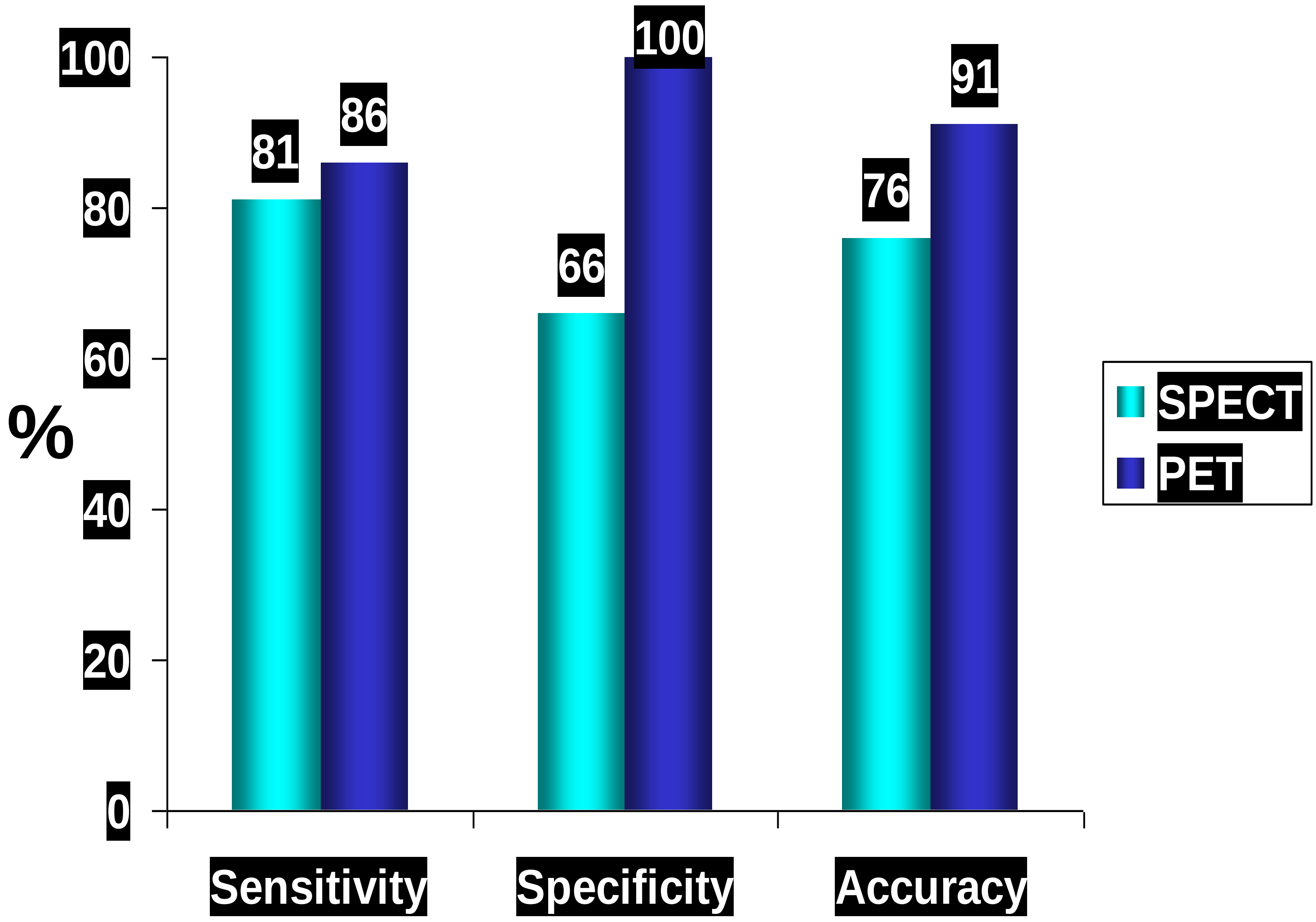
Mother isotope:
271 d
25 d

Cardiology applications



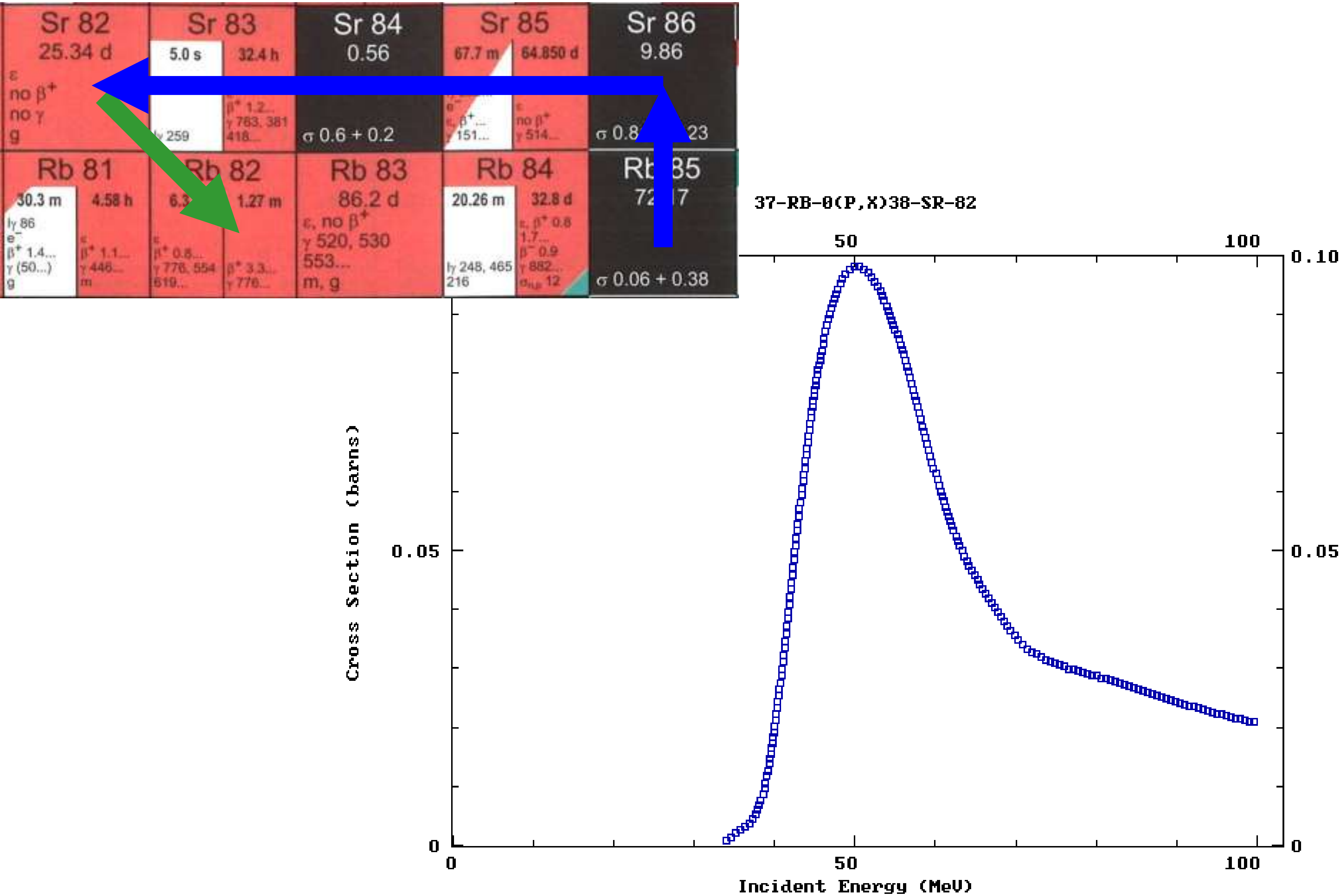
B.A. Mc Ardle, Can. J. Cardiology 29 (2013) 399.

Diagnostic Accuracy: ^{82}Rb PET vs ^{99m}Tc SPECT

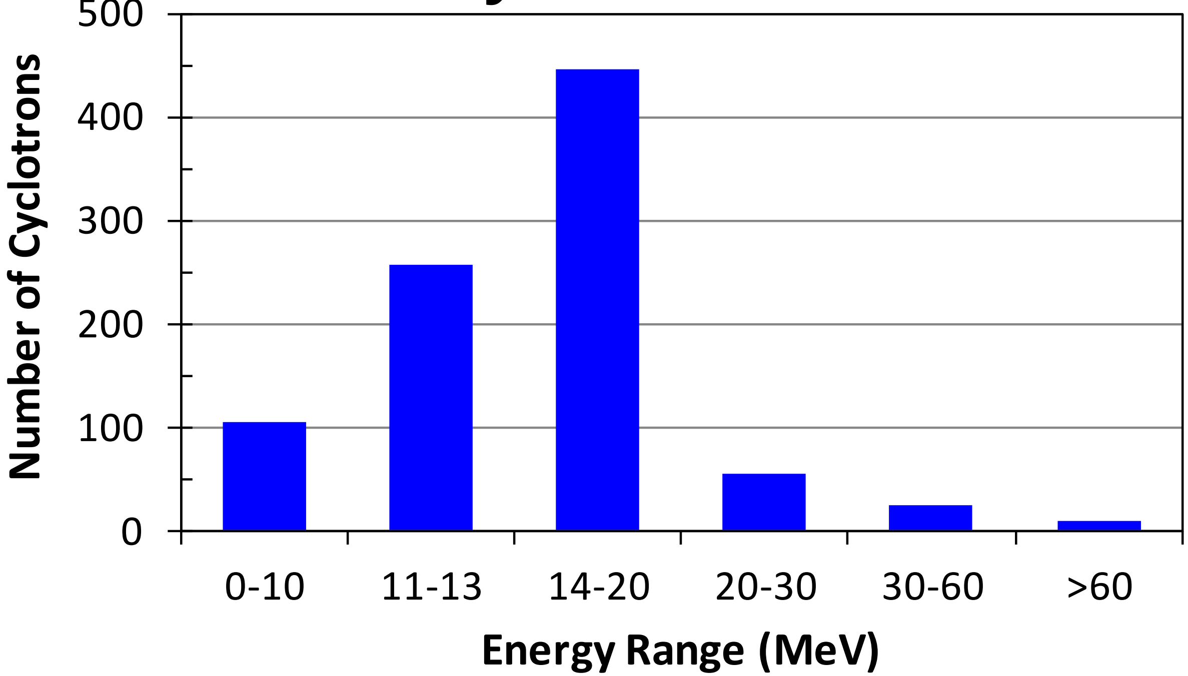


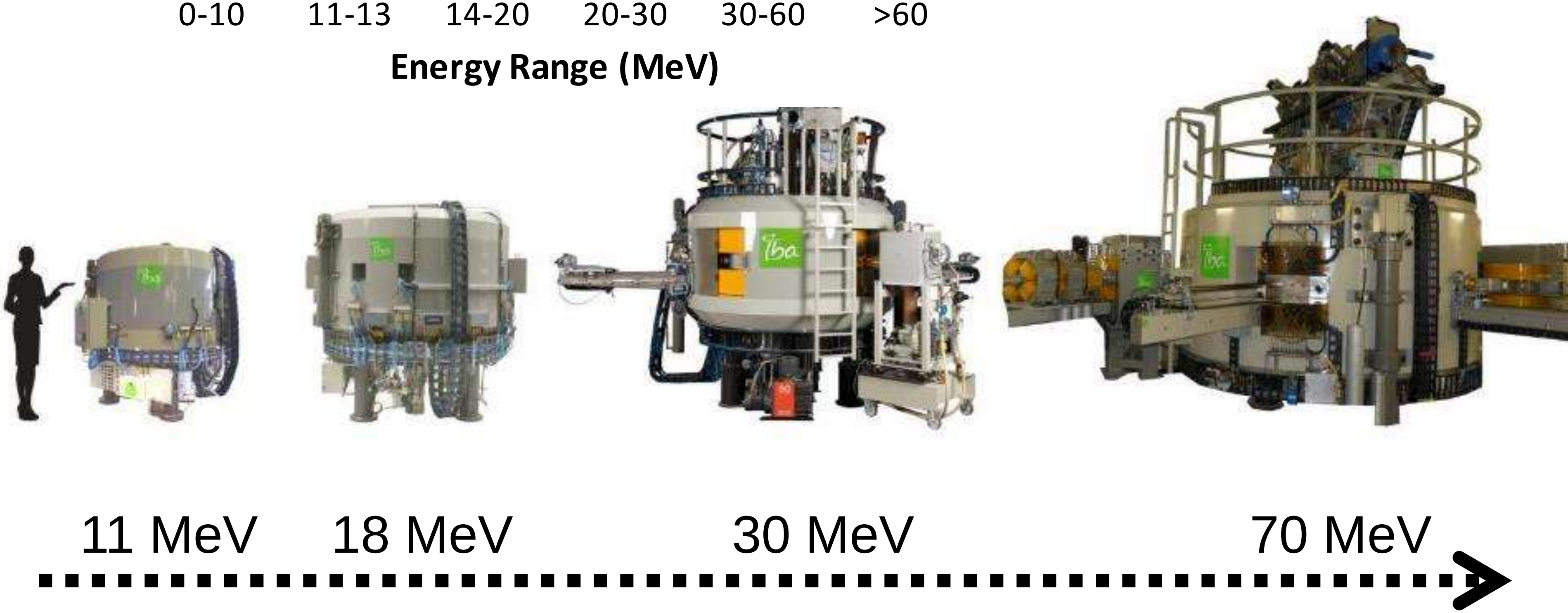
Bateman et al, J Nucl Cardiol 2006;13:24.

^{82}Sr production



Cyclotrons: the work horses





Facilities producing ^{82}Sr

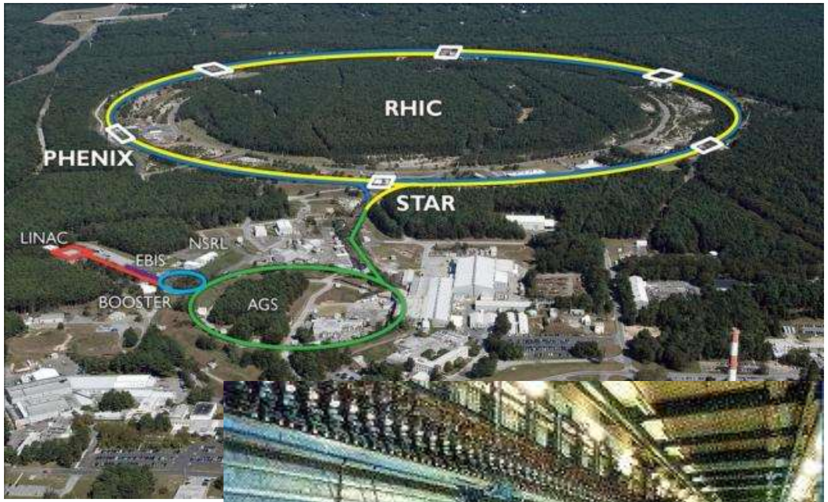
BNL, USA – 200 MeV, 100 μA

LANL, USA – 100 MeV, 200 μA

INR, Russia – 160 MeV, 120 μA

TRIUMF, Canada – 110 MeV, 70 μA

iThemba, South Africa – 66 MeV, 250 μA



Facilities producing ^{82}Sr

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LANL, USA – 100 MeV, 200 µA

INR, Russia – 160 MeV, 120 µA

TRIUMF, Canada – 110 MeV, 70 µA

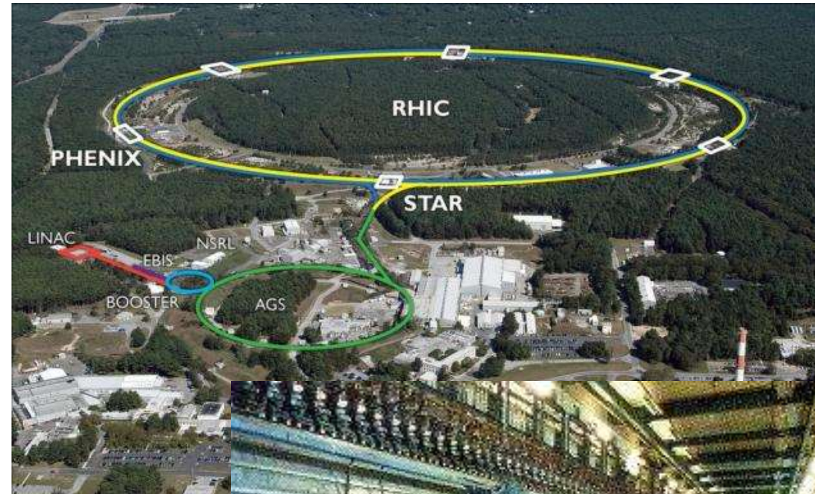
iThemba, South Africa – 66 MeV, 250 µA

ARRONAX, France – 70 MeV, < 750 µA

SPES, Italy – 70 MeV, < 1000 µA

Zevacor, USA – 70 MeV, < 750 µA

ZDNM, Russia – 70 MeV, < 750 µA

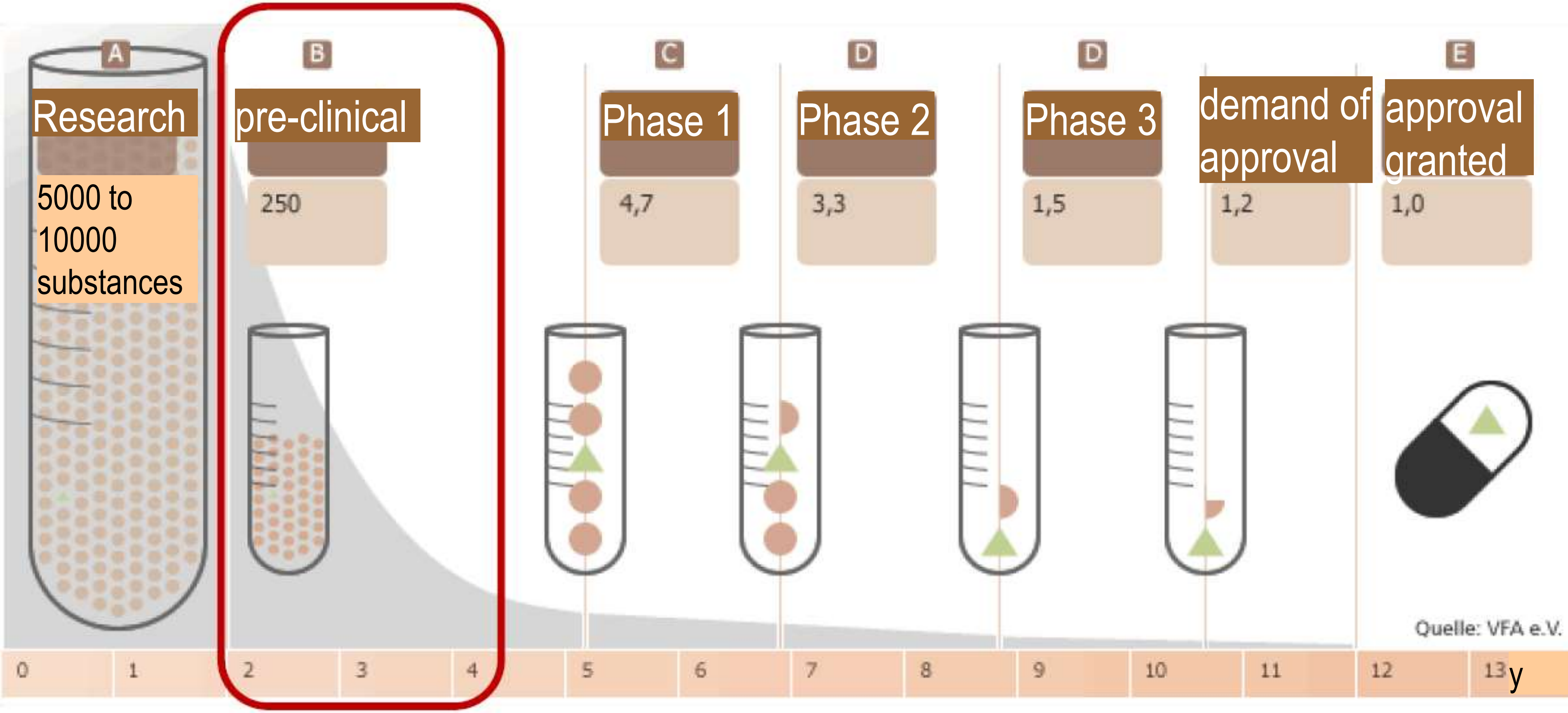


Longer-lived PET isotopes

Radio-nuclide	Half-life (h)	Intensity 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
Br-76	16.2	55	1.18	6
Y-86	14.7	31.9	0.66	2.6
Zr-89	78.4	22.7	0.40	1.4
I-124	100	22.8	0.82	3.8

Molecular imaging without patients?

Development of pharmaceuticals



Screening

in vitro tests
animal exp.

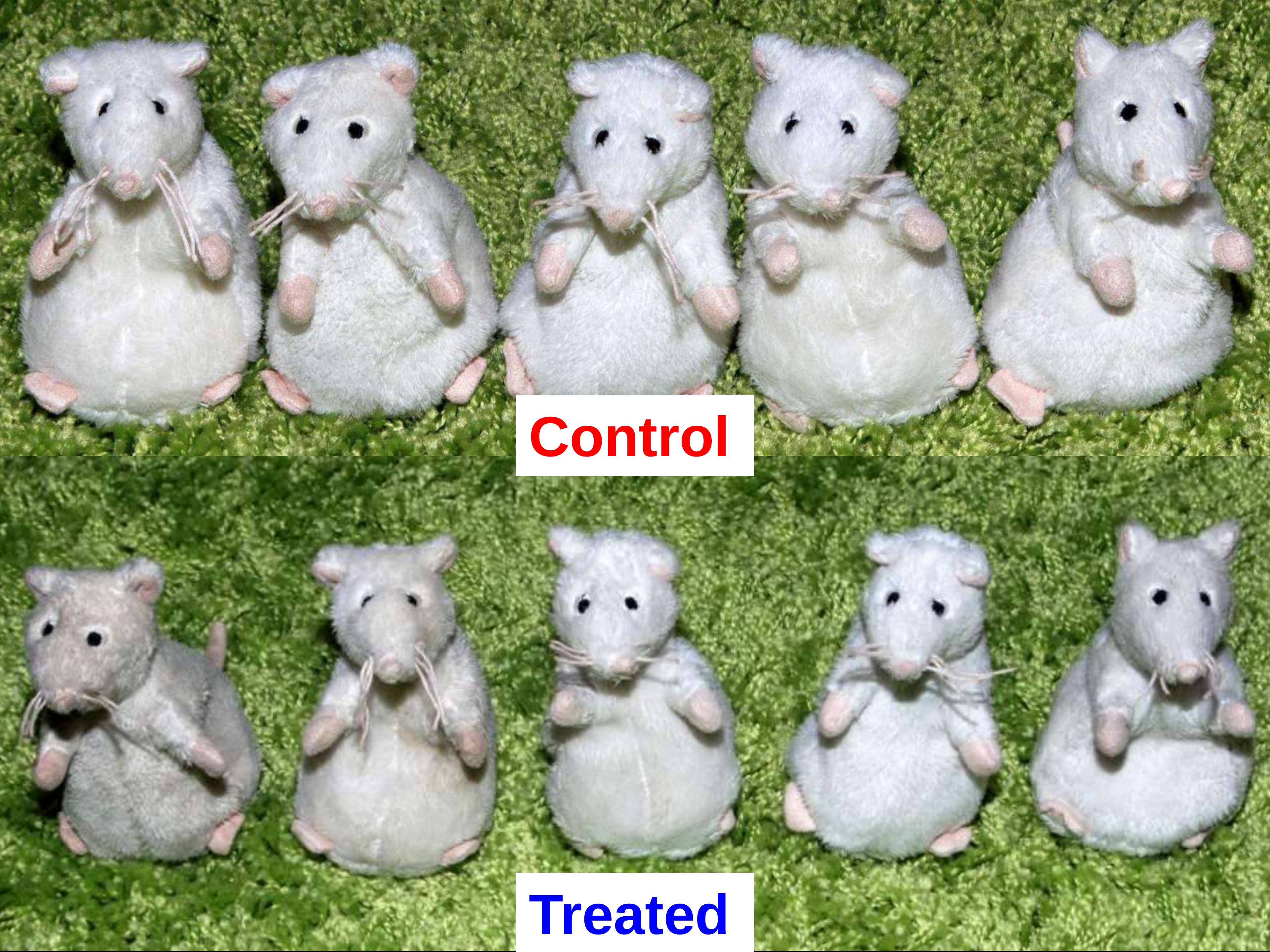
tests with humans

toxicity side effects	wanted effect	comparison with standard
20-80 healthy volunteers	100-300 patients	x00-x000 patients

Pre-clinical studies (1)

Pre-clinical studies (2)

Pre-clinical studies (3)


Control
Treated


Control


Treated


Control


Treated

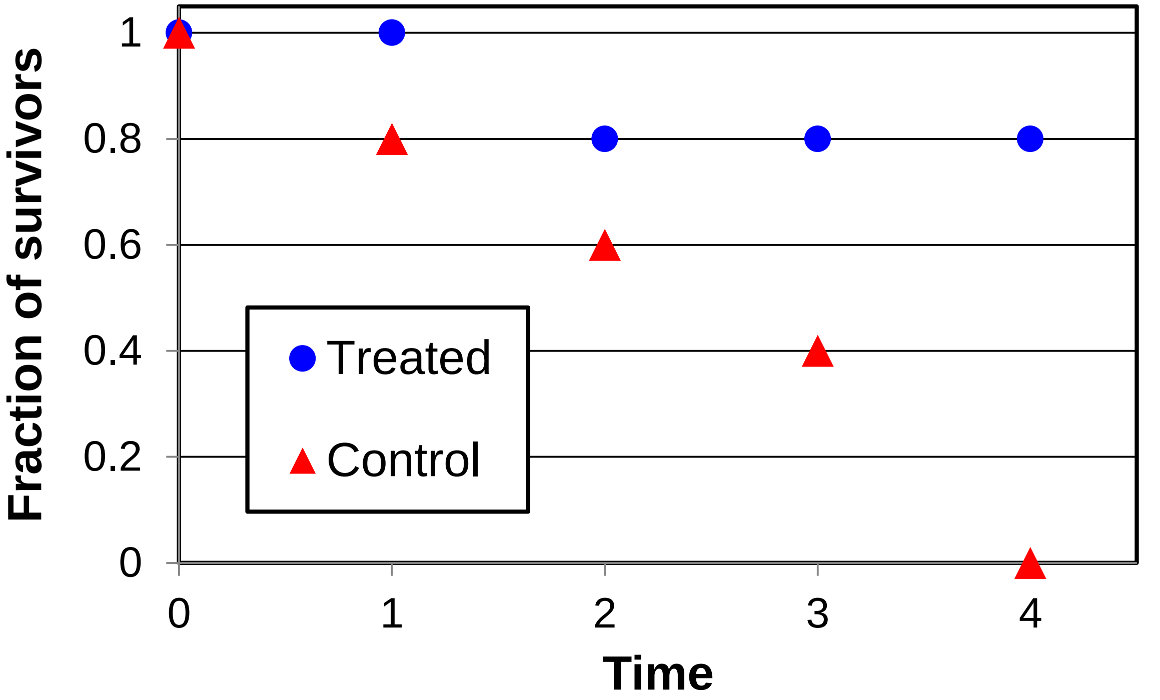

Control


Treated


Control


Treated

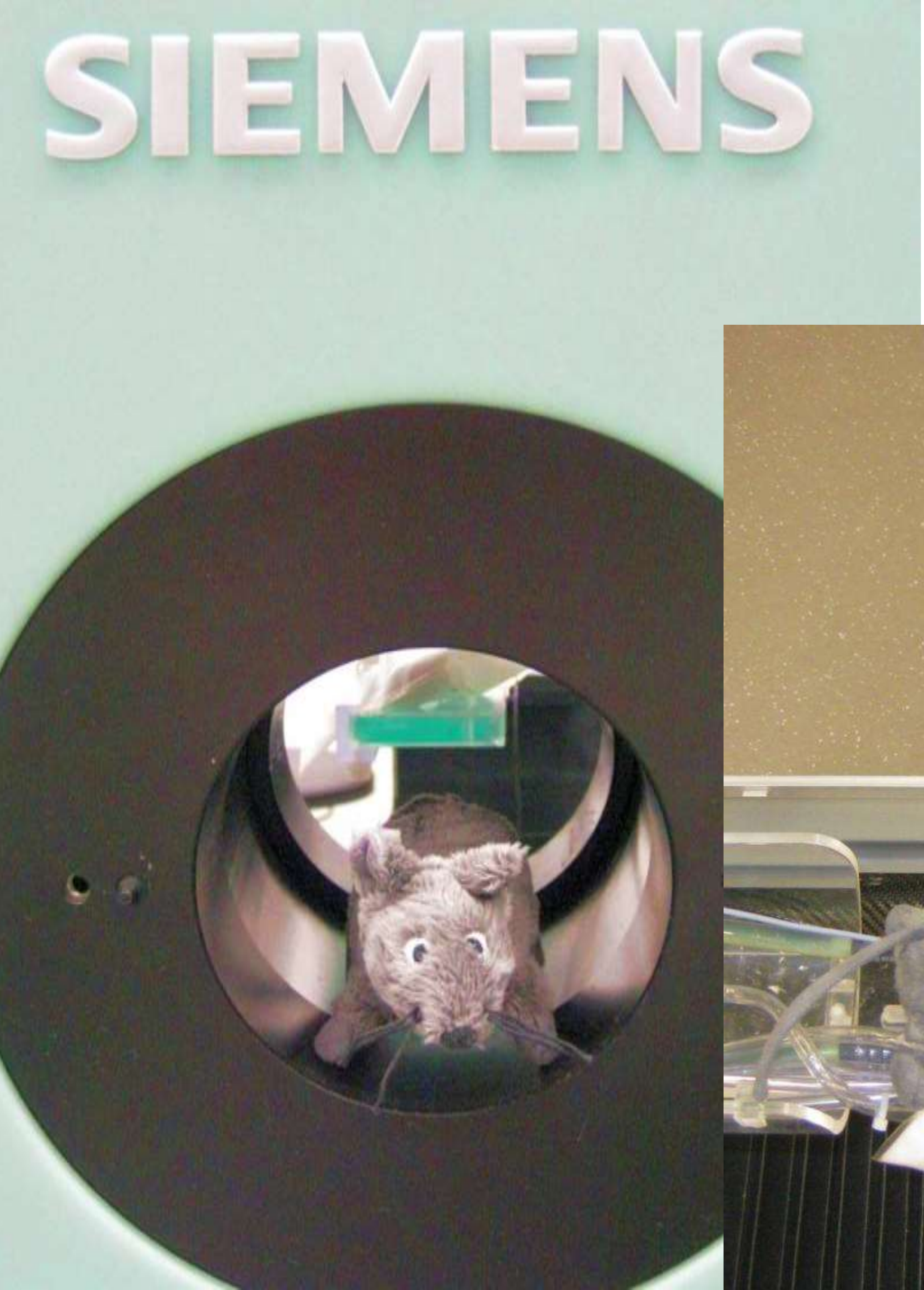
Survival curve



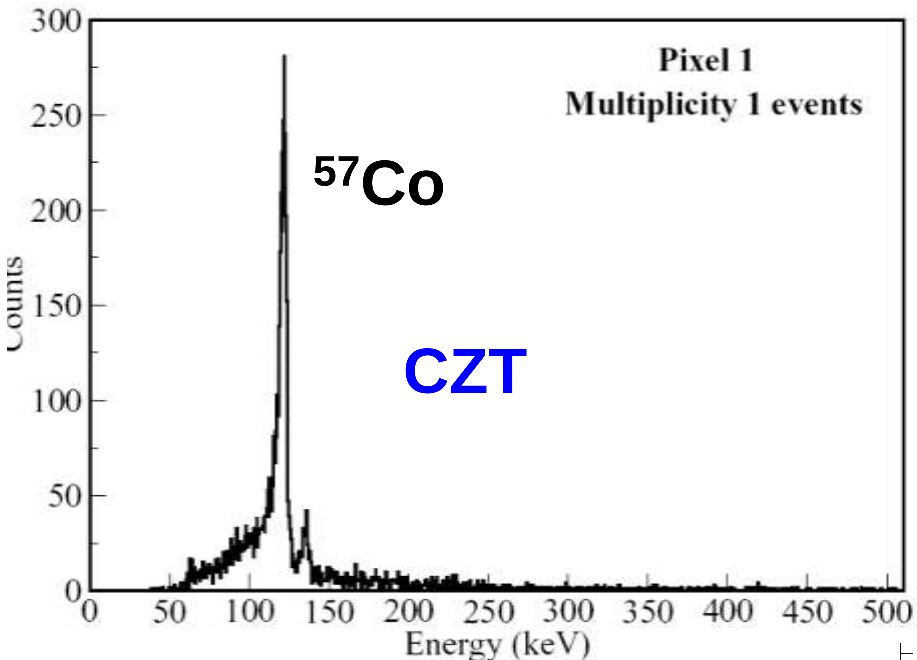
- **medium survival time, median survival time, survival benefit**
- **shows final benefit but not detailed mechanism**

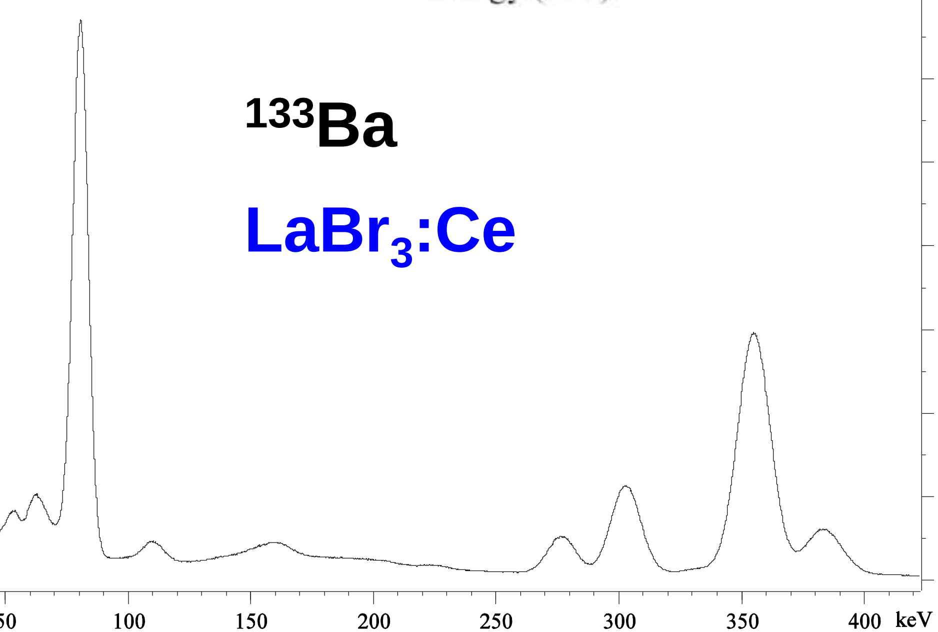
- **more information from bio-distribution studies**
- **preferentially on-line with suitable radiotracers and small animal SPECT or PET**

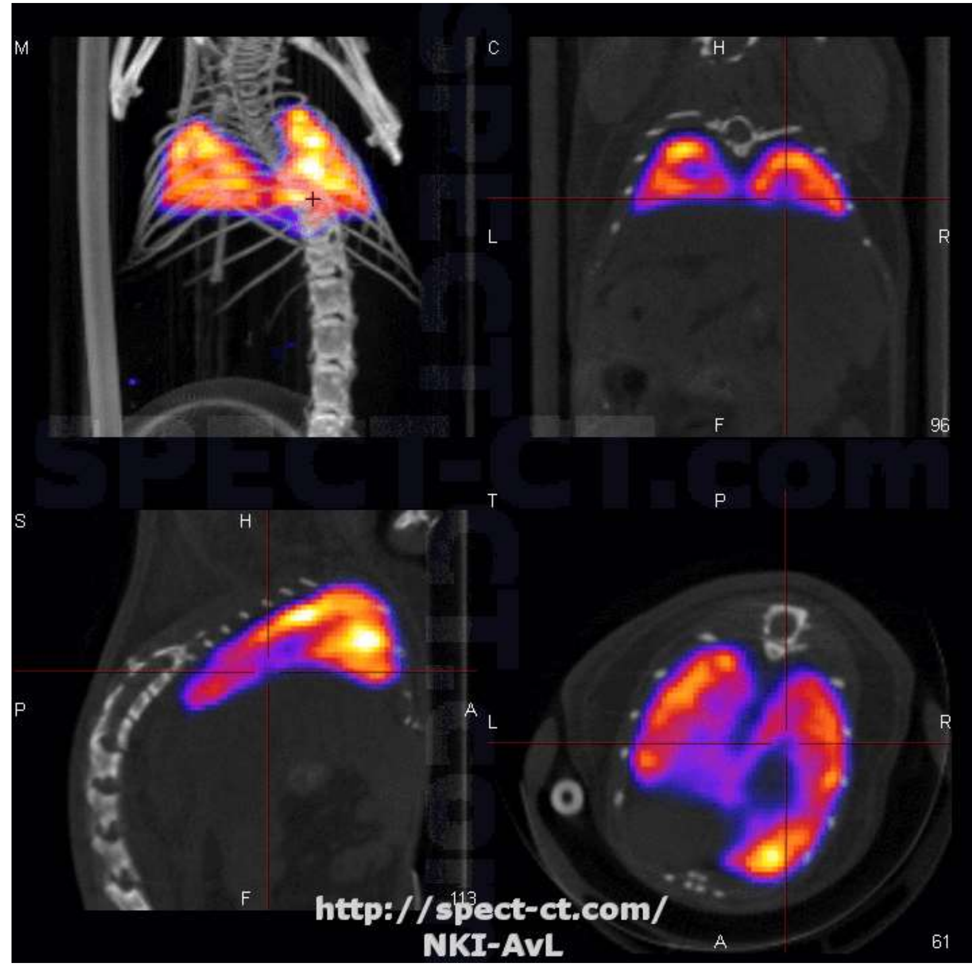
Small animal imaging



New generation of small animal SPECT

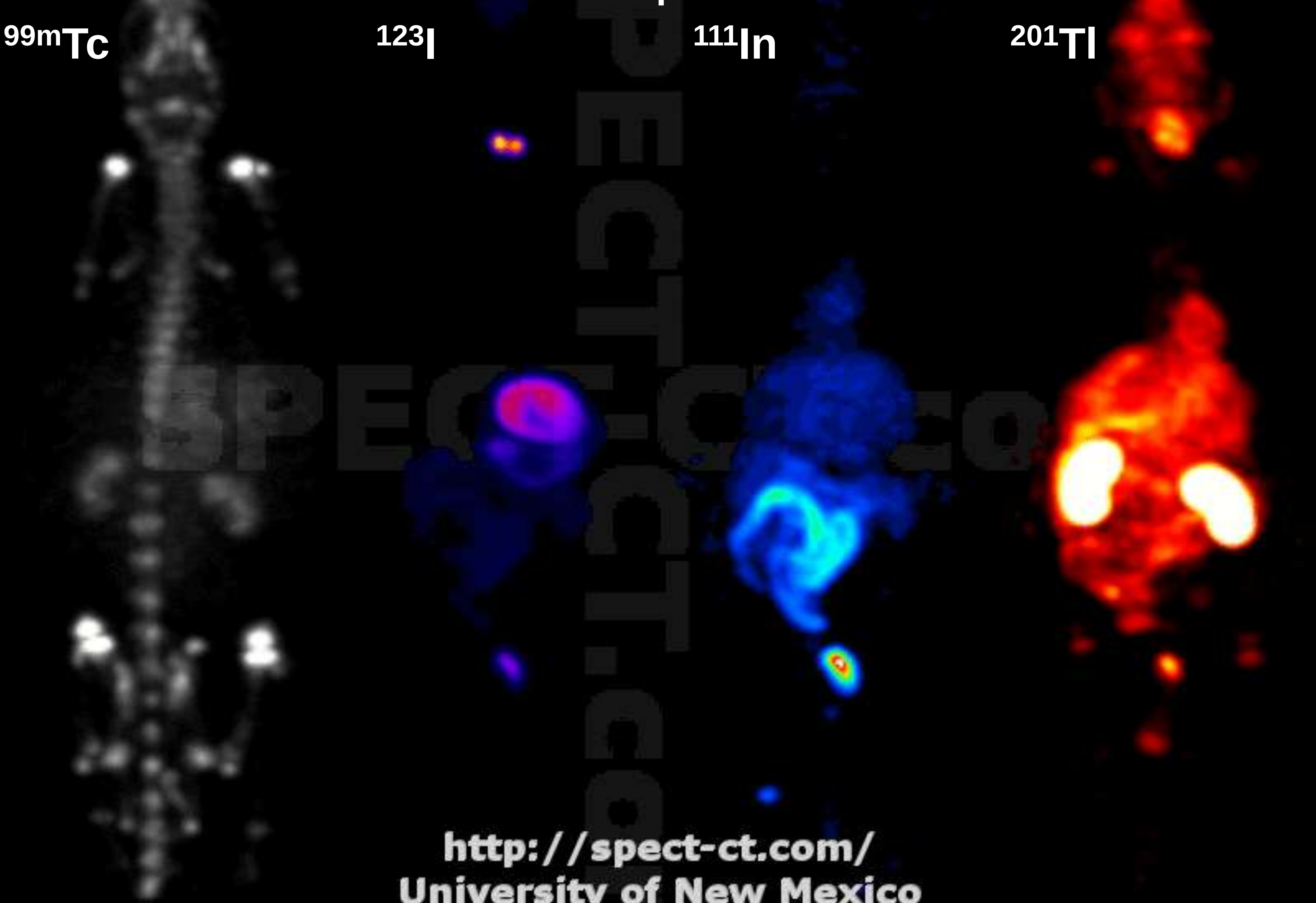






systematic biodistribution studies with different radiotracers become possible with dedicated small animal SPECT

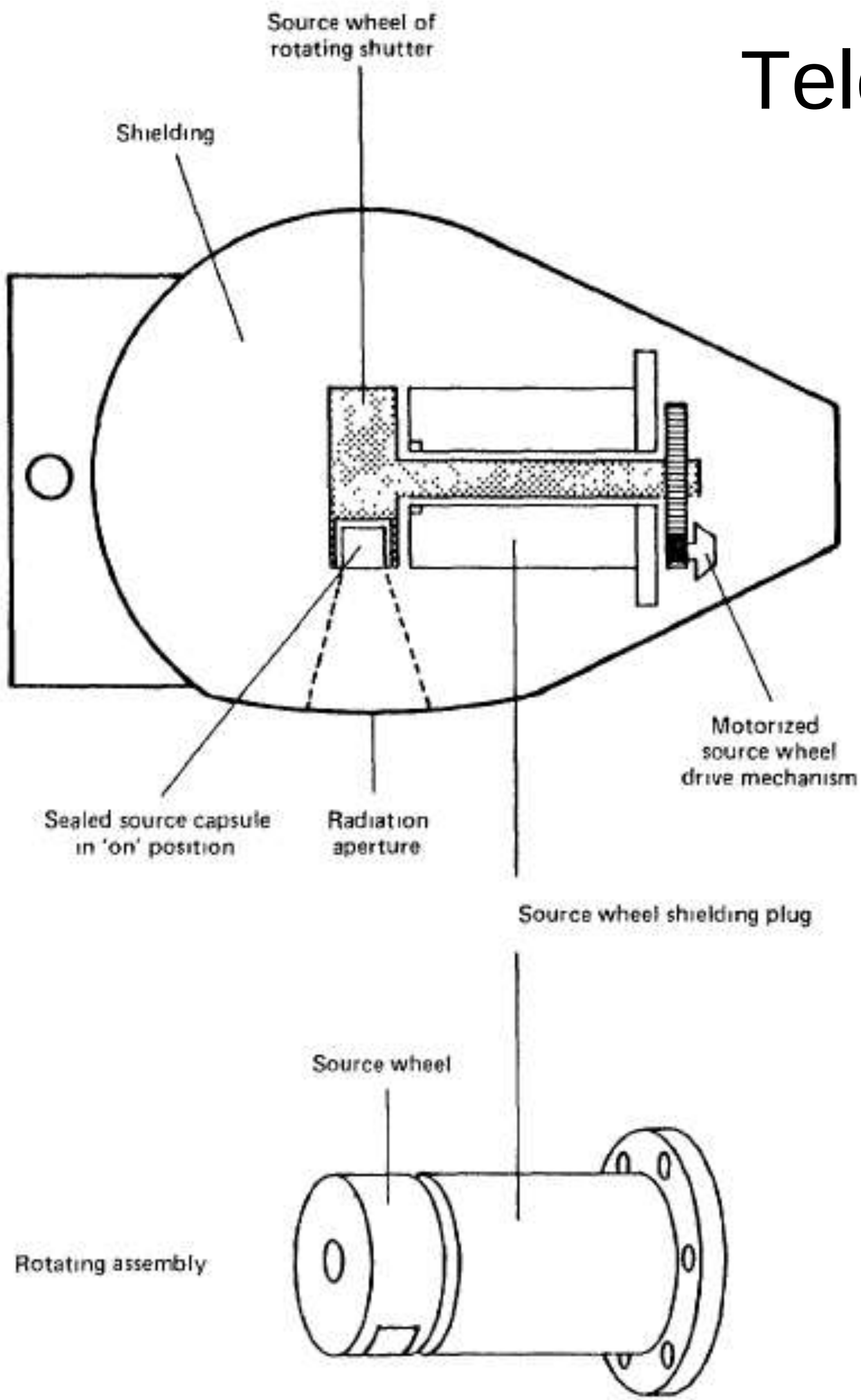
Multi-Isotope SPECT

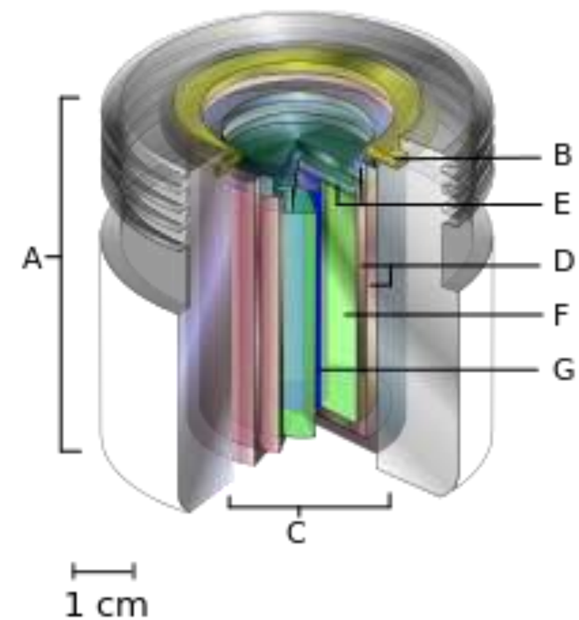


From diagnostics

to therapy

Teletherapy units

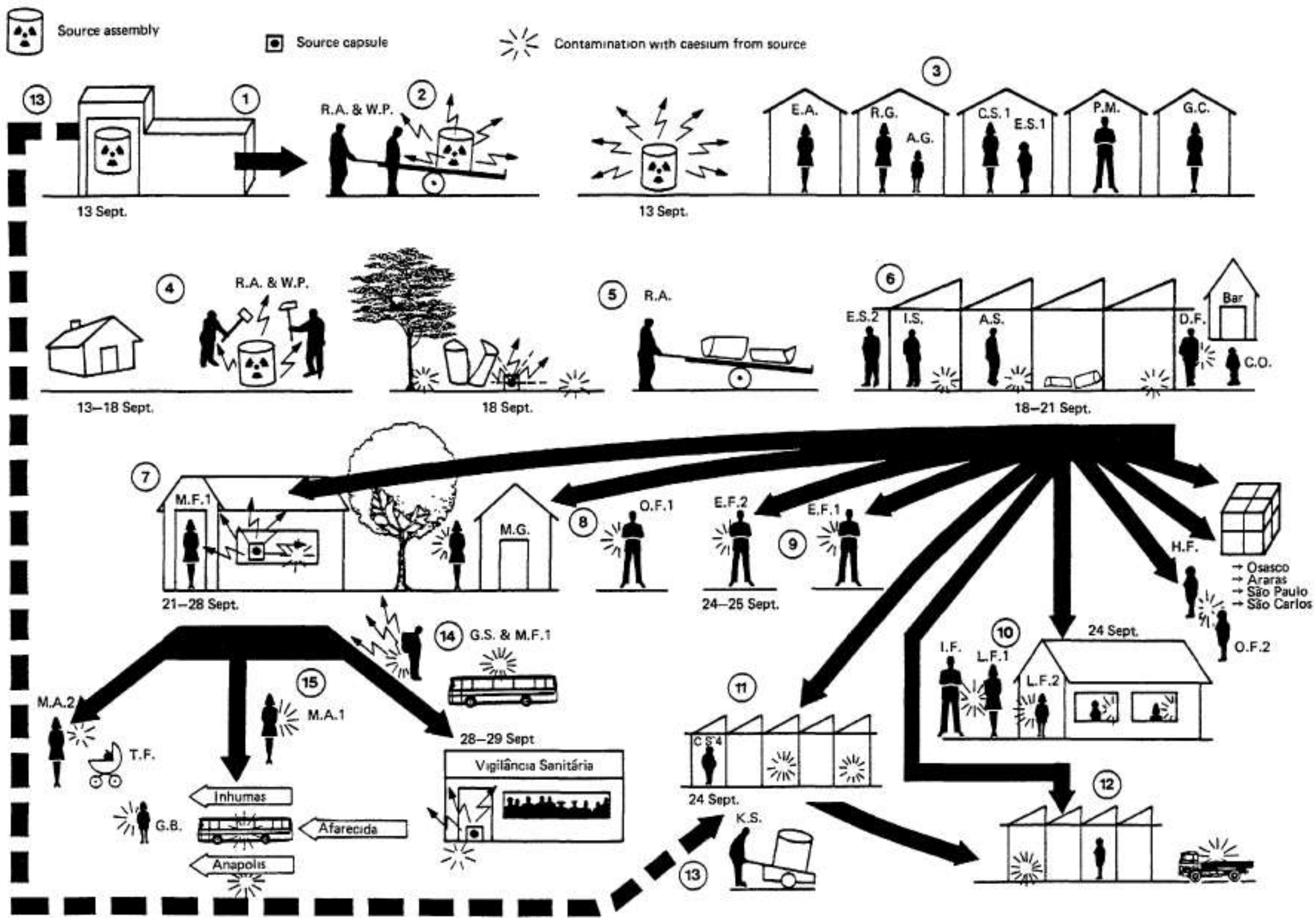




"Cobalt-bomb" or "Cesium-bomb"
50 – 100 TBq of ^{60}Co or ^{137}Cs
5 – 10 Gy/h at 1 m

Less operation and maintenance effort with respect to LINACs, BUT long-term legacy!

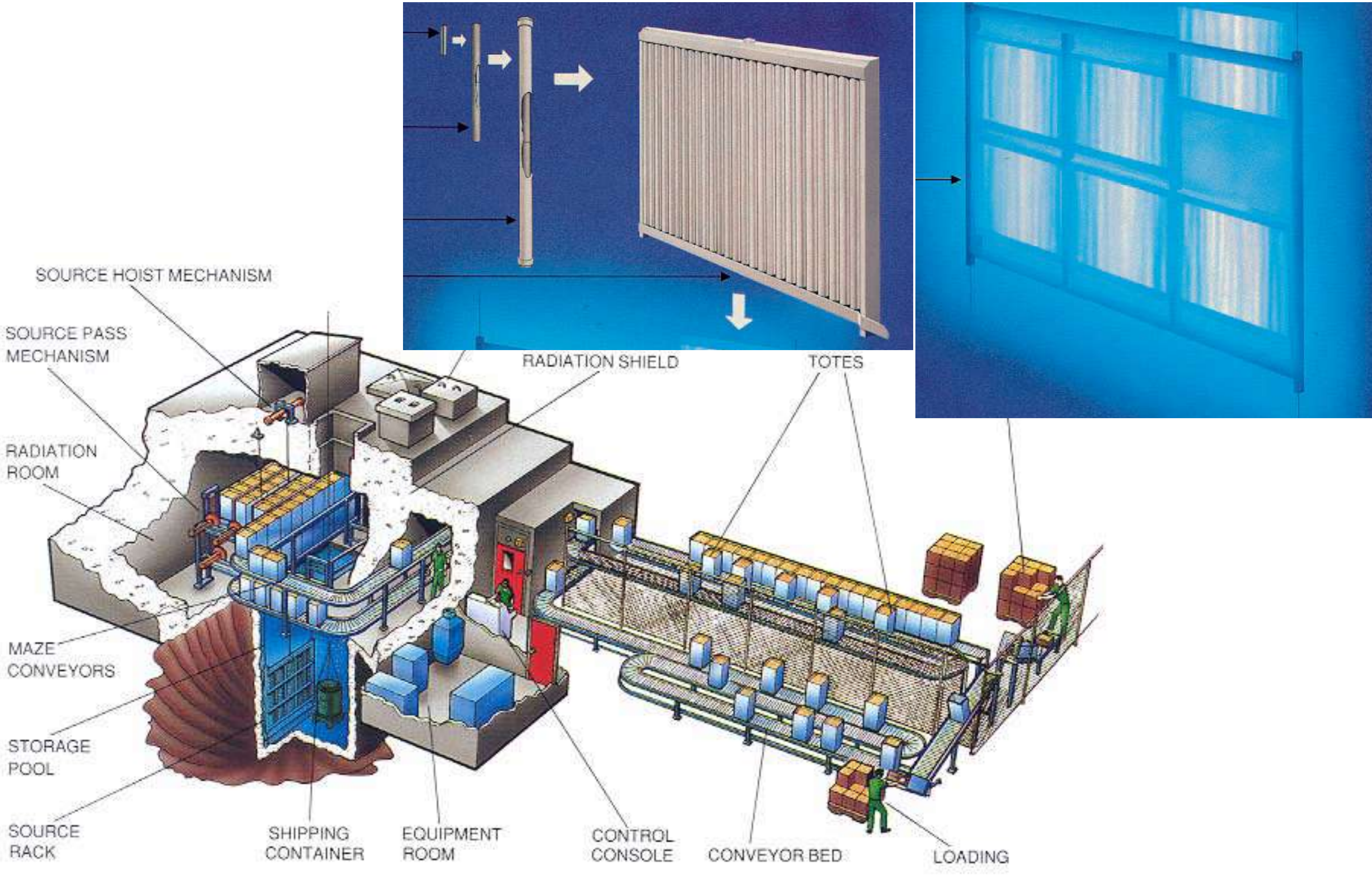
Civilian radiation accidents



Goiania, Ciudad Juarez, Samut Prakan, etc.

10. *A hole is made to remove a radiation hot spot giving a dose rate of 0.5 $Sv \cdot h^{-1}$.*

Parenthesis: Radiation Sterilization of Medical Devices

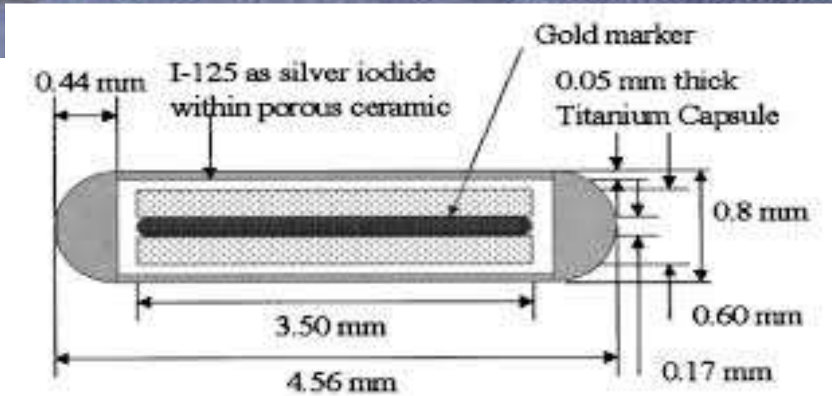


1 MCi = 37 PBq ^{60}Co sterilizes 650 kg/hour at 25 kGy

Brachytherapy

High Dose Rate (HDR) brachytherapy
short-term insertion of ^{60}Co, ^{137}Cs, ^{169}Yb or ^{192}Ir sources

Low Dose Rate (LDR) brachytherapy
long-term insertion of ^{32}P, ^{103}Pd, ^{125}I, ^{131}Cs, etc. sources (“seeds”)



Cancer and efficiency of treatments

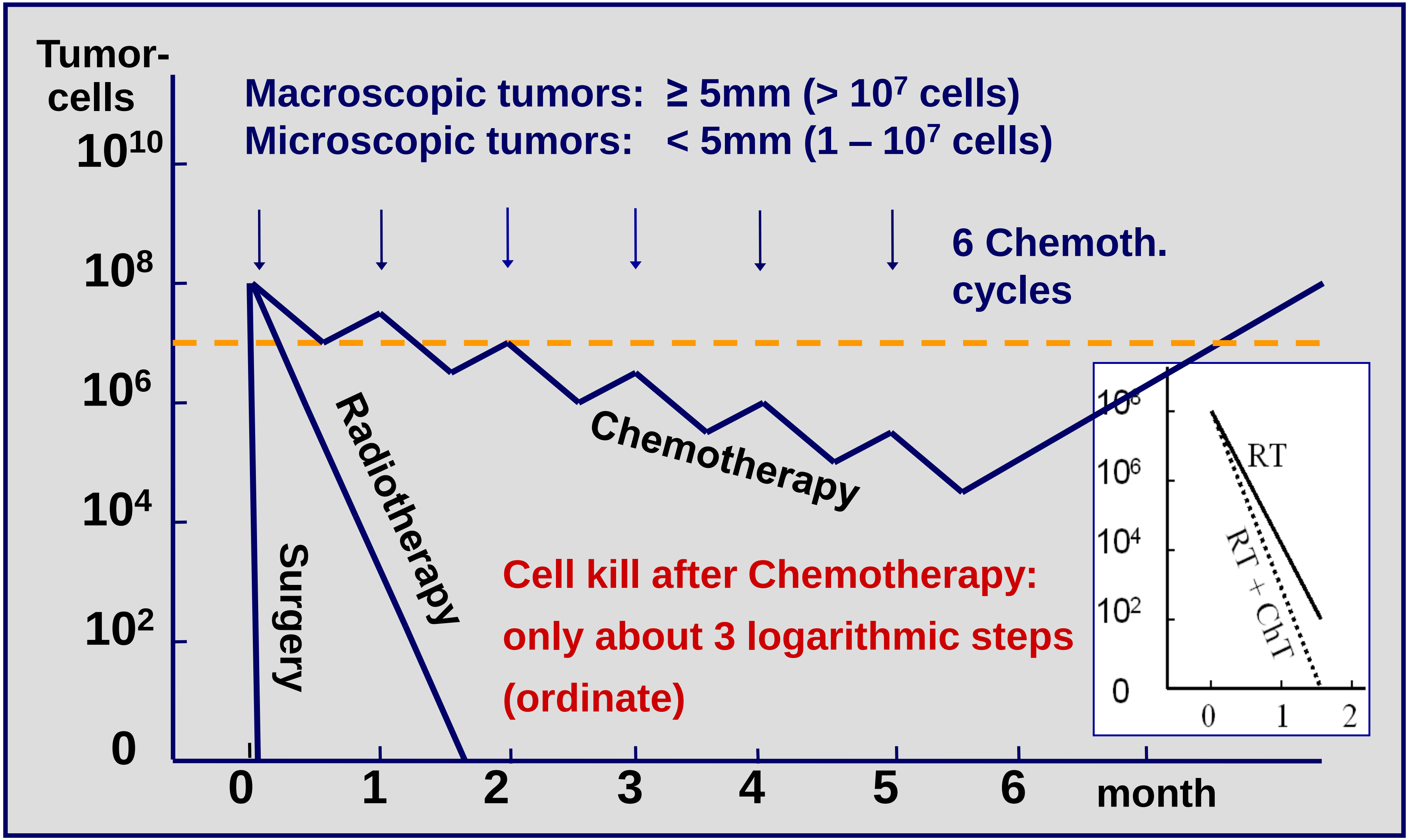
At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	**58%**	**42%**	**100%**
Cured by:			
Surgery	**22%**		
Radiation therapy	**12%**		
Surgery+radiation therapy	**6%**		
All other treatments and combinations incl. chemotherapy		**5%**	
Fraction cured	**69%**	**12%**	**45%**

Over one million deaths per year from cancer in EU.

⇒ improve early diagnosis

⇒ improve systemic treatments

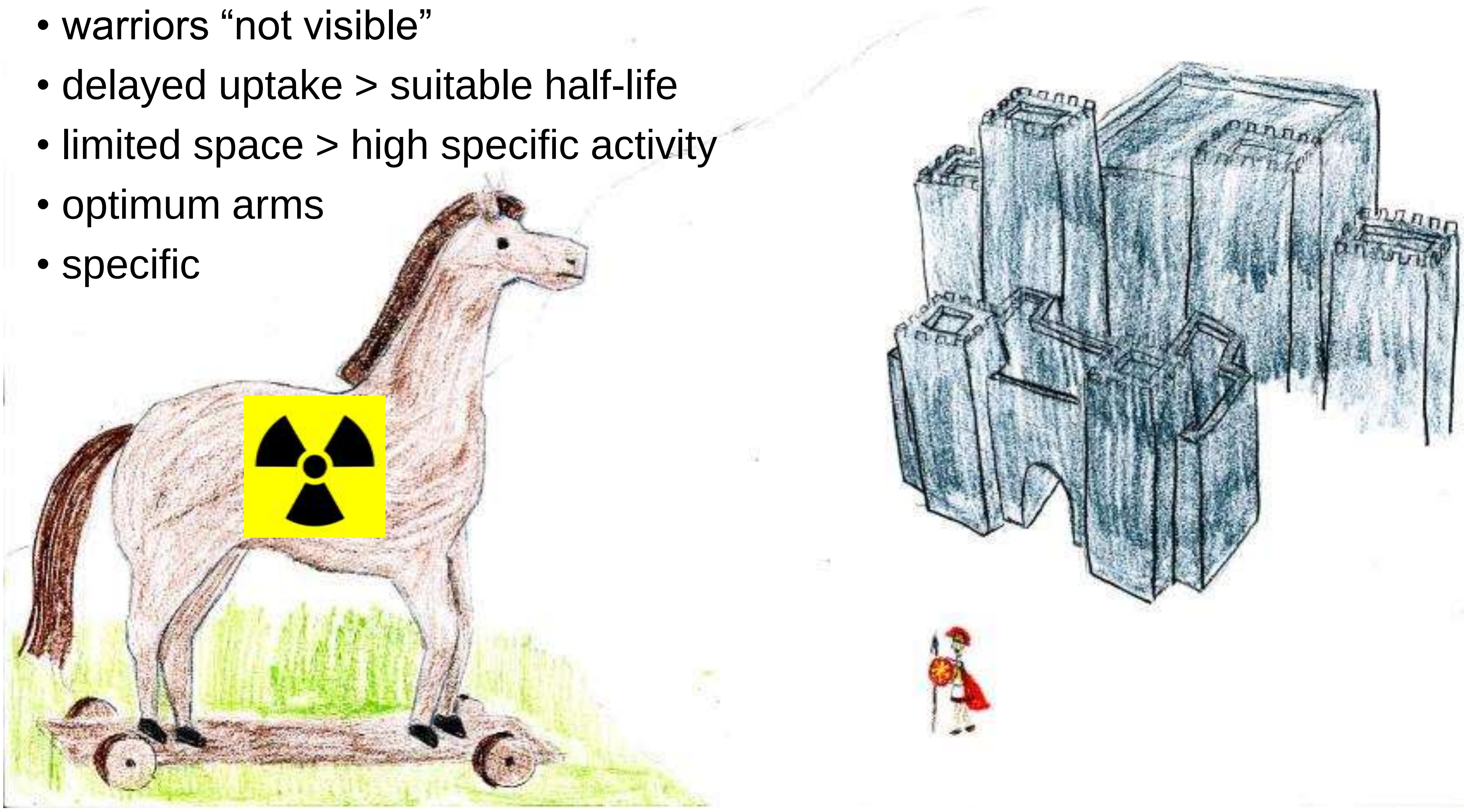
Comparison of Therapies



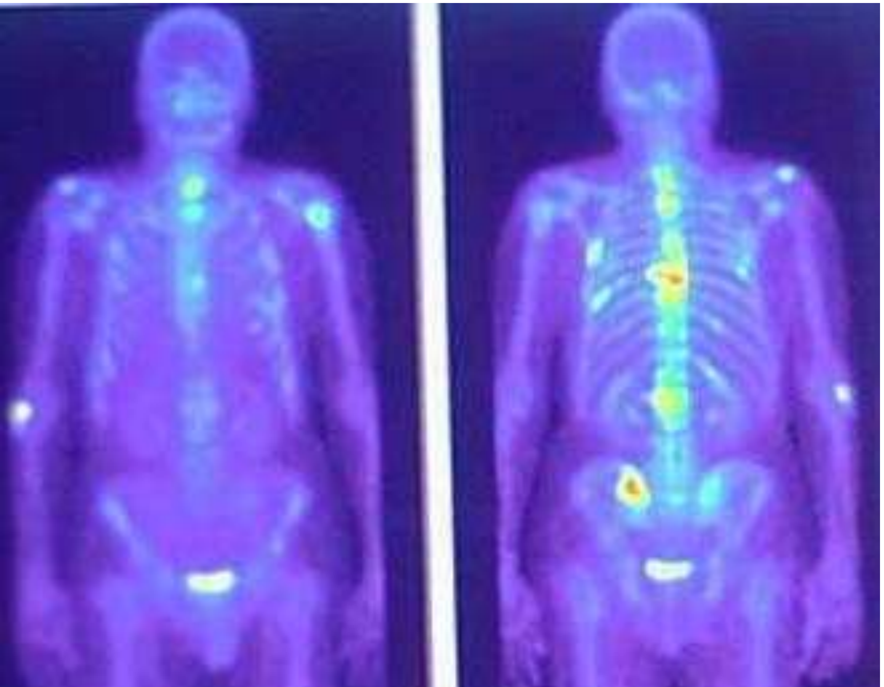
(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

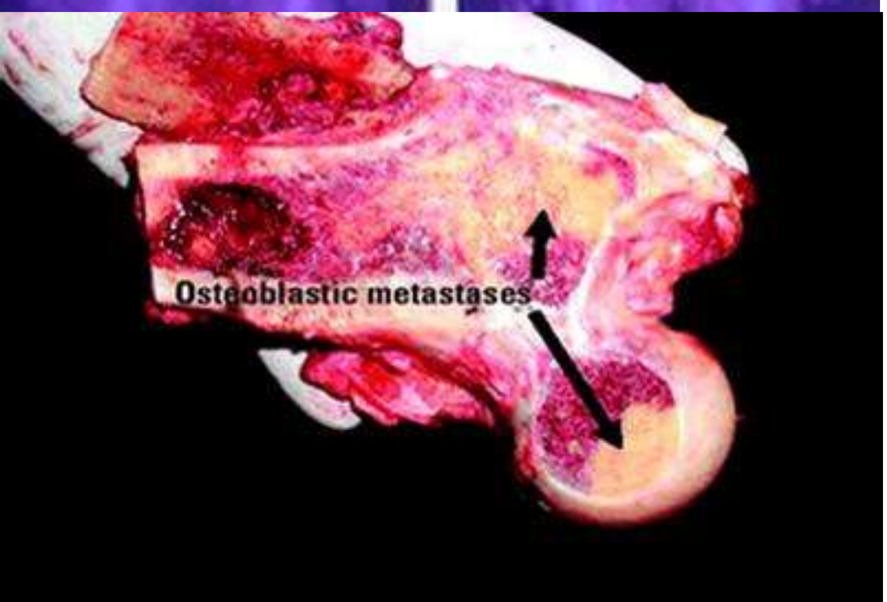
The principle of targeted therapies

- “attractive” vector > high uptake by the target
- transportable
- good in-vivo stability
- warriors “not visible”
- delayed uptake > suitable half-life
- limited space > high specific activity
- optimum arms
- specific



Metabolic targeting





Thyroid cancer

$^{123}I^-$ for imaging

$^{131}I^-$ for therapy

Bone metastases

1.5 million patients world-wide

^{99m}Tc-MDP for SPECT imaging

$^{18}F^-$ for PET imaging

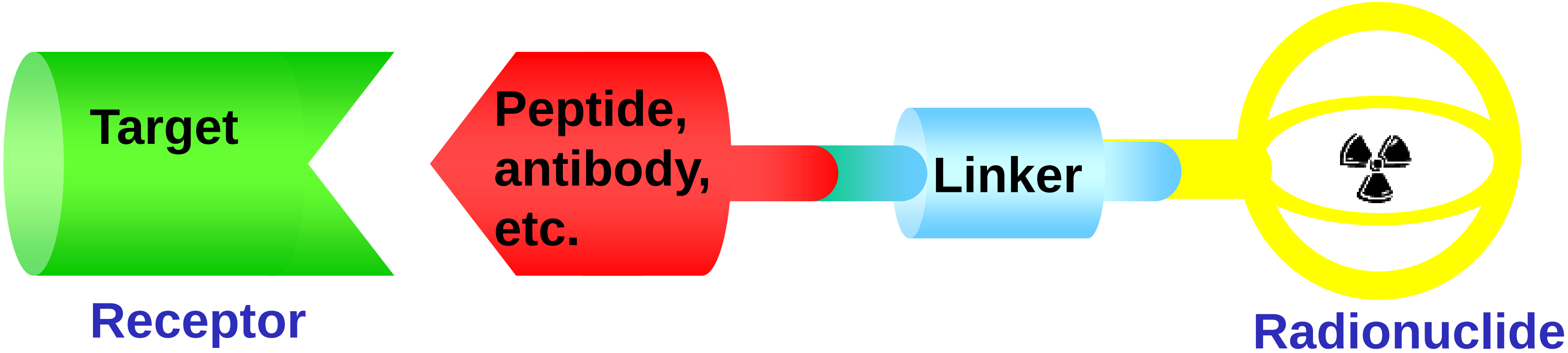
Therapy

^{153}Sm-EDTMP (Quadramet)

$^{89}Sr^{2+}$ (Metastron)

$^{223}Ra^{2+}$ (Xofigo/Alpharadin)

Multidisciplinary collaboration to fight cancer



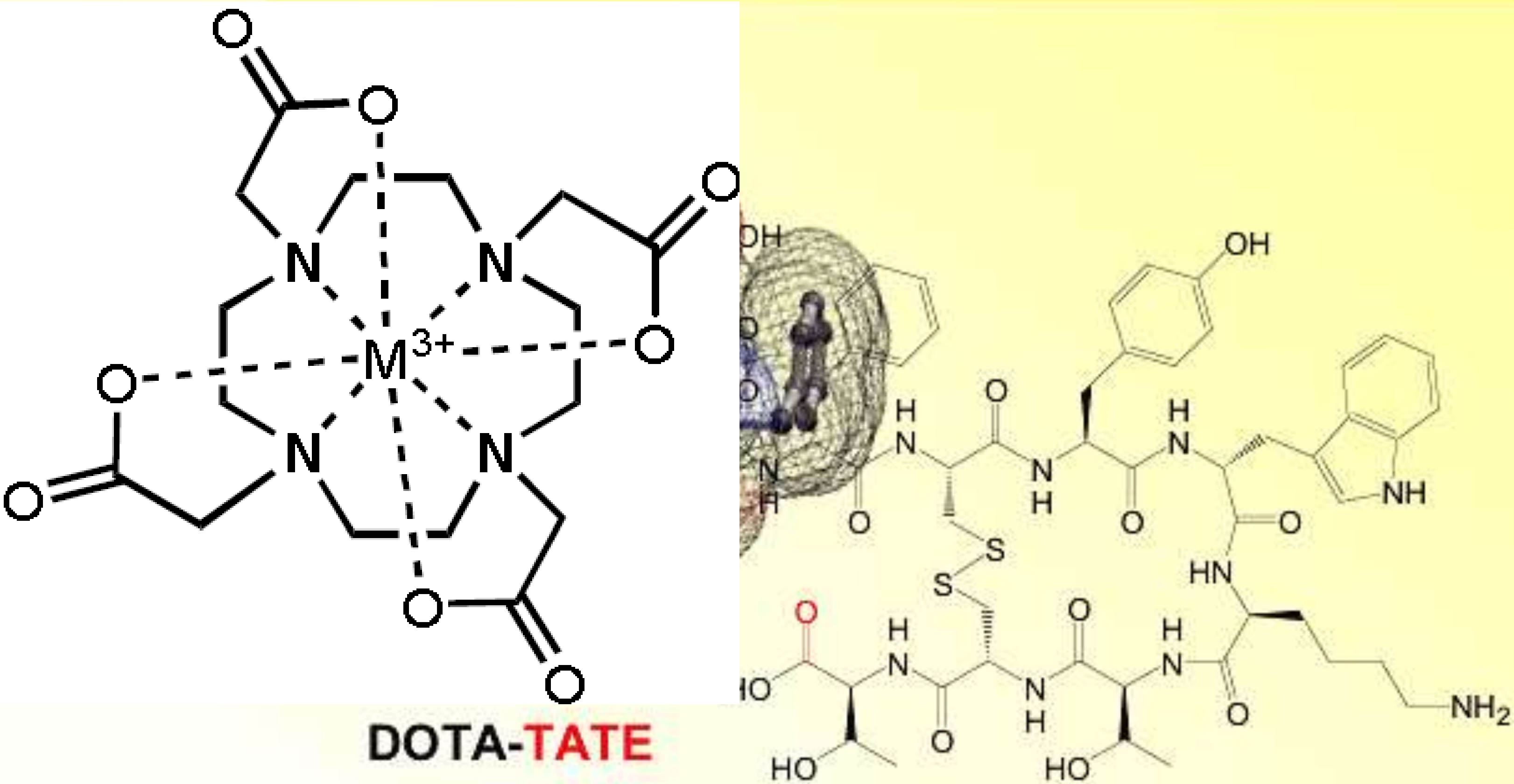
Immunology
Structural biology

Coordination chemistry

Nuclear physics and radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE



1,4,7,10-tetraazacyclododecantetraacetate

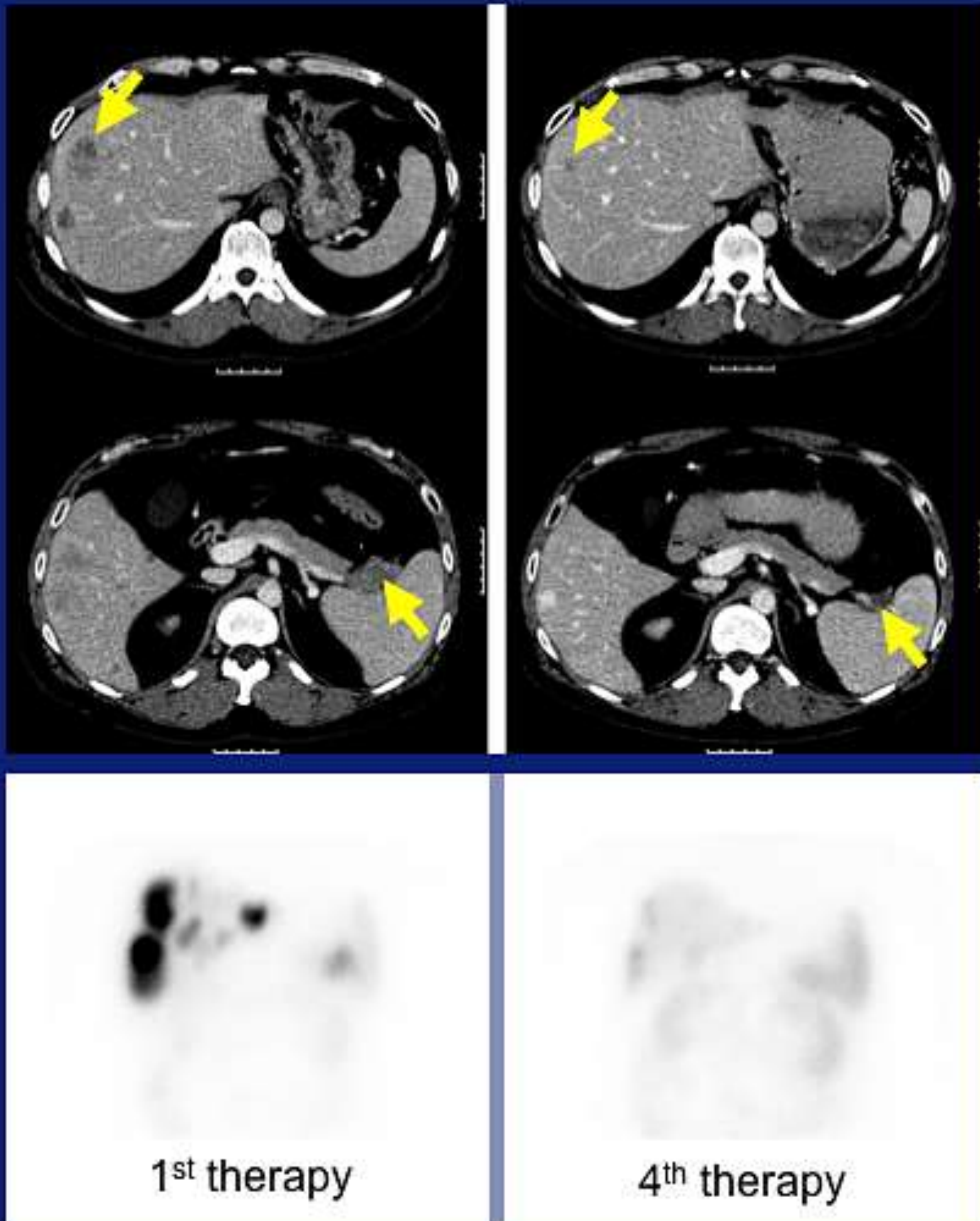
^{111}In ^{90}Y

^{67}Ga ^{177}Lu

^{68}Ga ^{213}Bi

IC_{50} (Y^{III}) = 1.6 ± 0.4 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

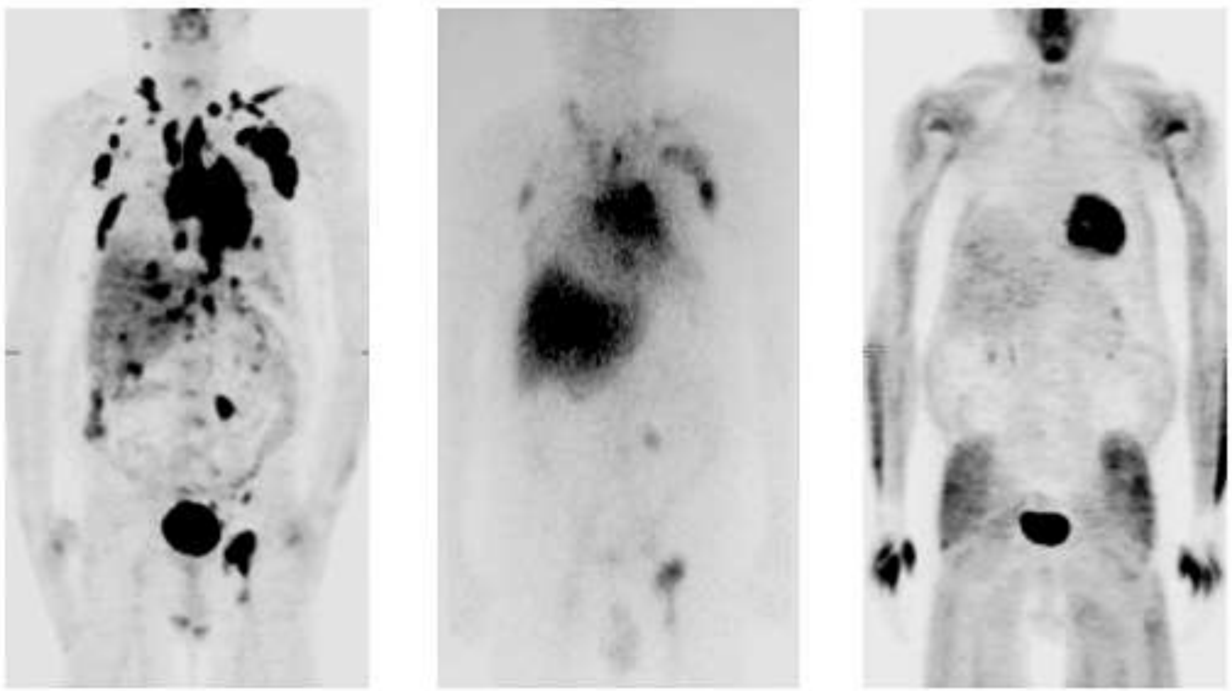
Partial remission

Roelf Valkema, EANM-2008.

Lymphoma therapy: RITUXIMAB+^{177}Lu

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

^{18}FDG PET | ^{177}Lu-Scan | ^{18}FDG PET



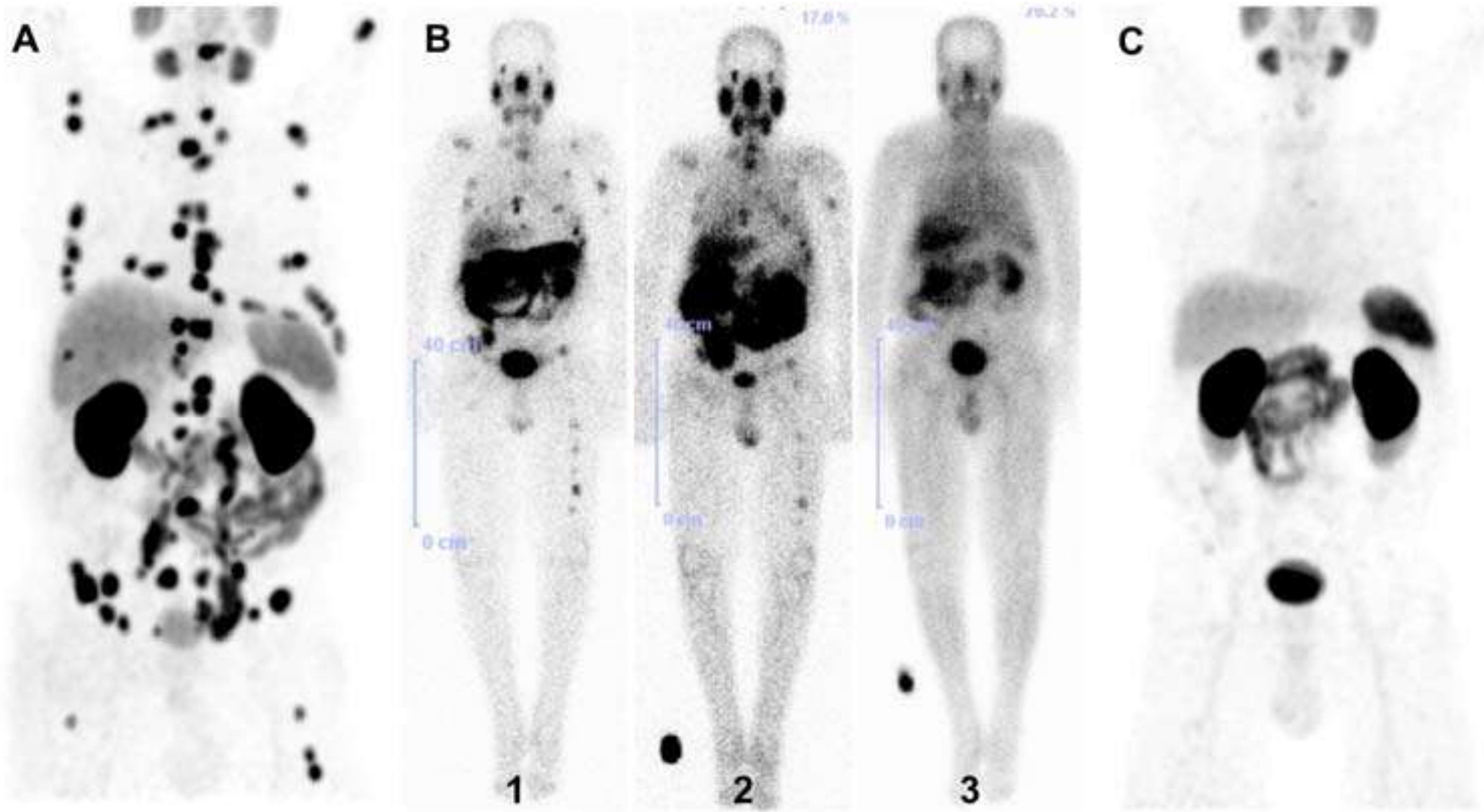
Still in CR

1.9.2002 | 13.9.2002 | 15.11.2002 | 15.9.2009

F. Forrer et al., J Nucl Med 2013;54:1045.

University Hospital Basel, CH

^{177}Lu-radioligand therapy of advanced prostate cancer



R.P. Baum et al., J Nucl Med 2016;57:1006.

C. Kratochwil et al., J Nucl Med 2016;57:1170.

K. Rahbar et al., J Nucl Med 2017;58:85.

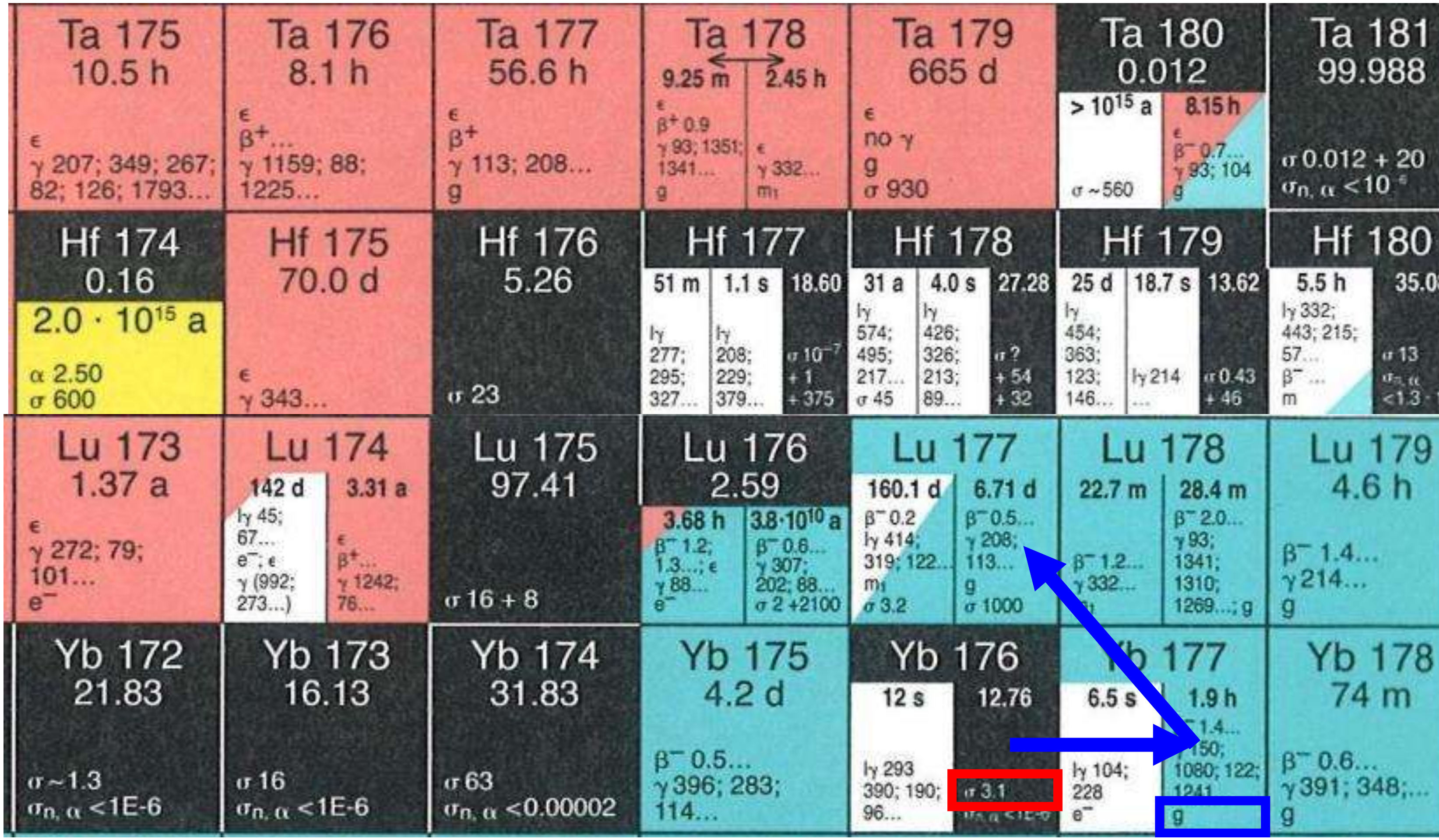
Radionuclides for targeted radionuclide therapy

Radio-nuclide	Half-life (d)	E mean (keV)	Eγ (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

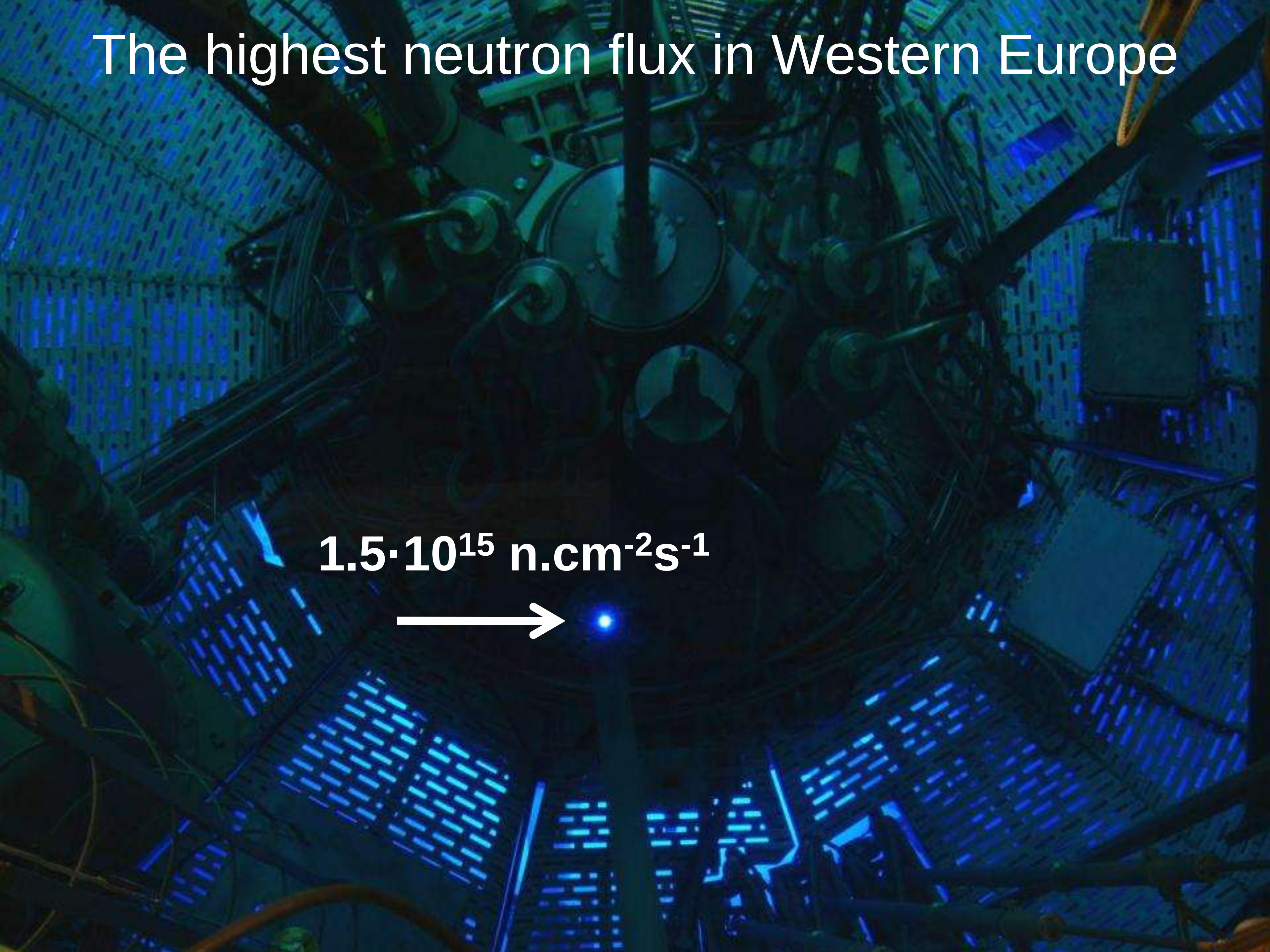
Emerging isotope

"Clean" production route to ^{177}Lu



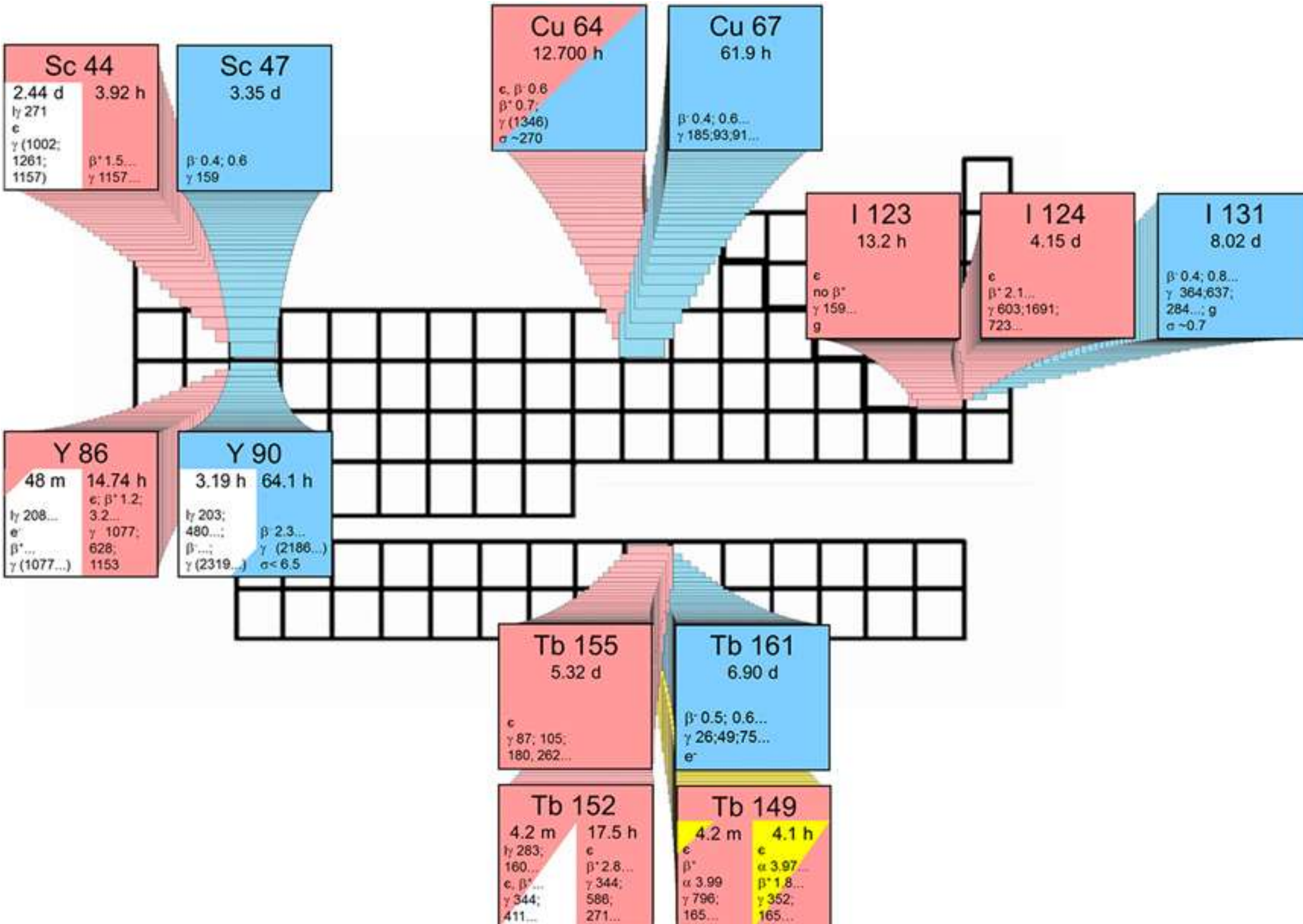
- **Free of long-lived isomer**
- **Non-carrier-added quality**
- **Requires high-flux reactor and advanced radiochemistry**

The highest neutron flux in Western Europe

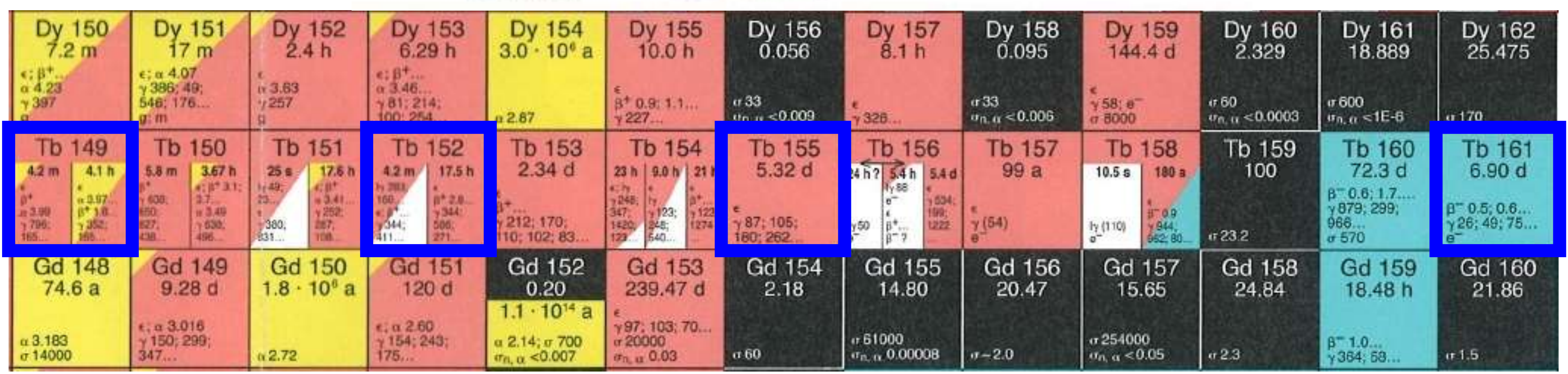


The rising star for therapy

Matched pairs for theranostics

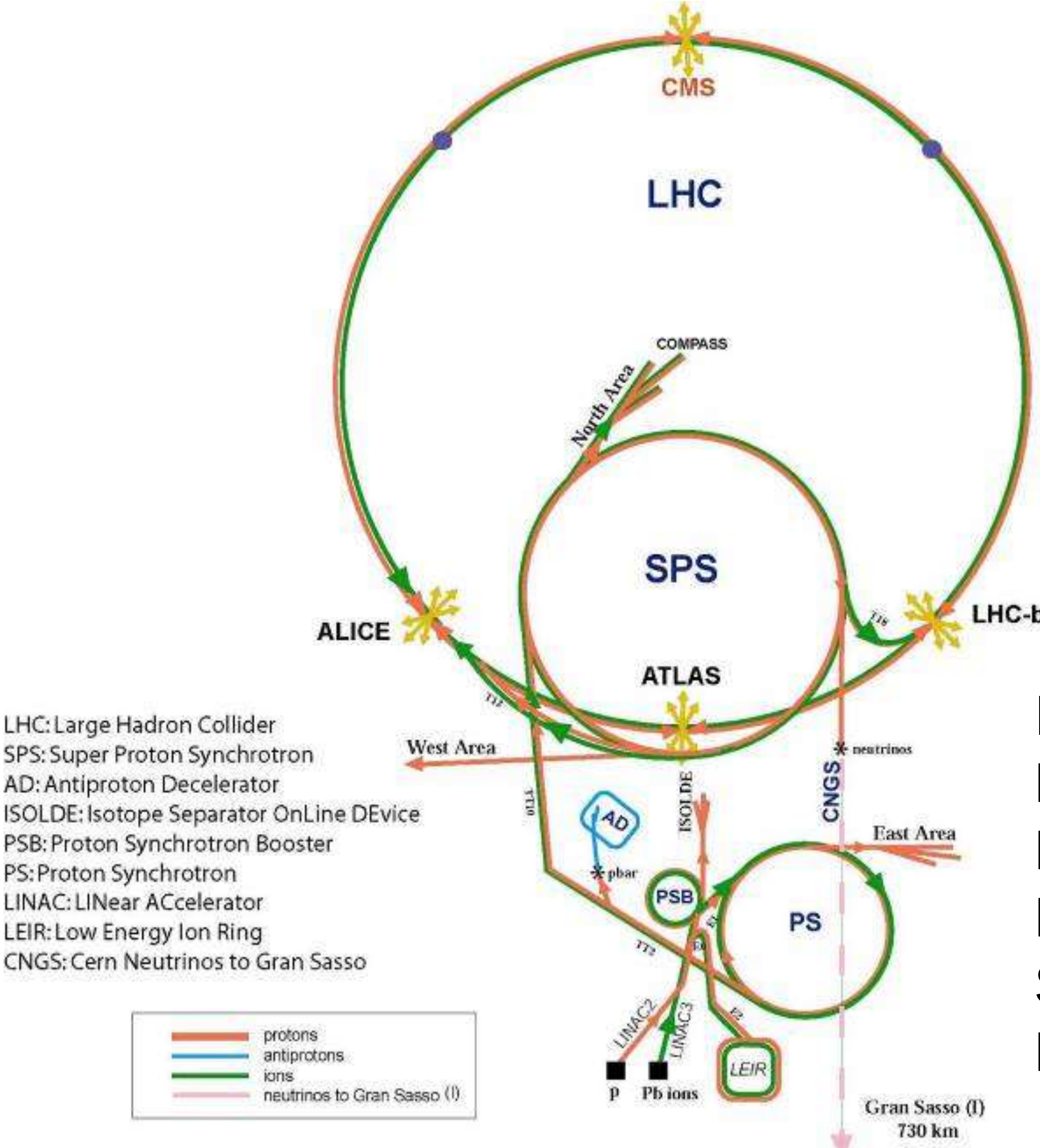


Terbium: a unique element for nuclear medicine



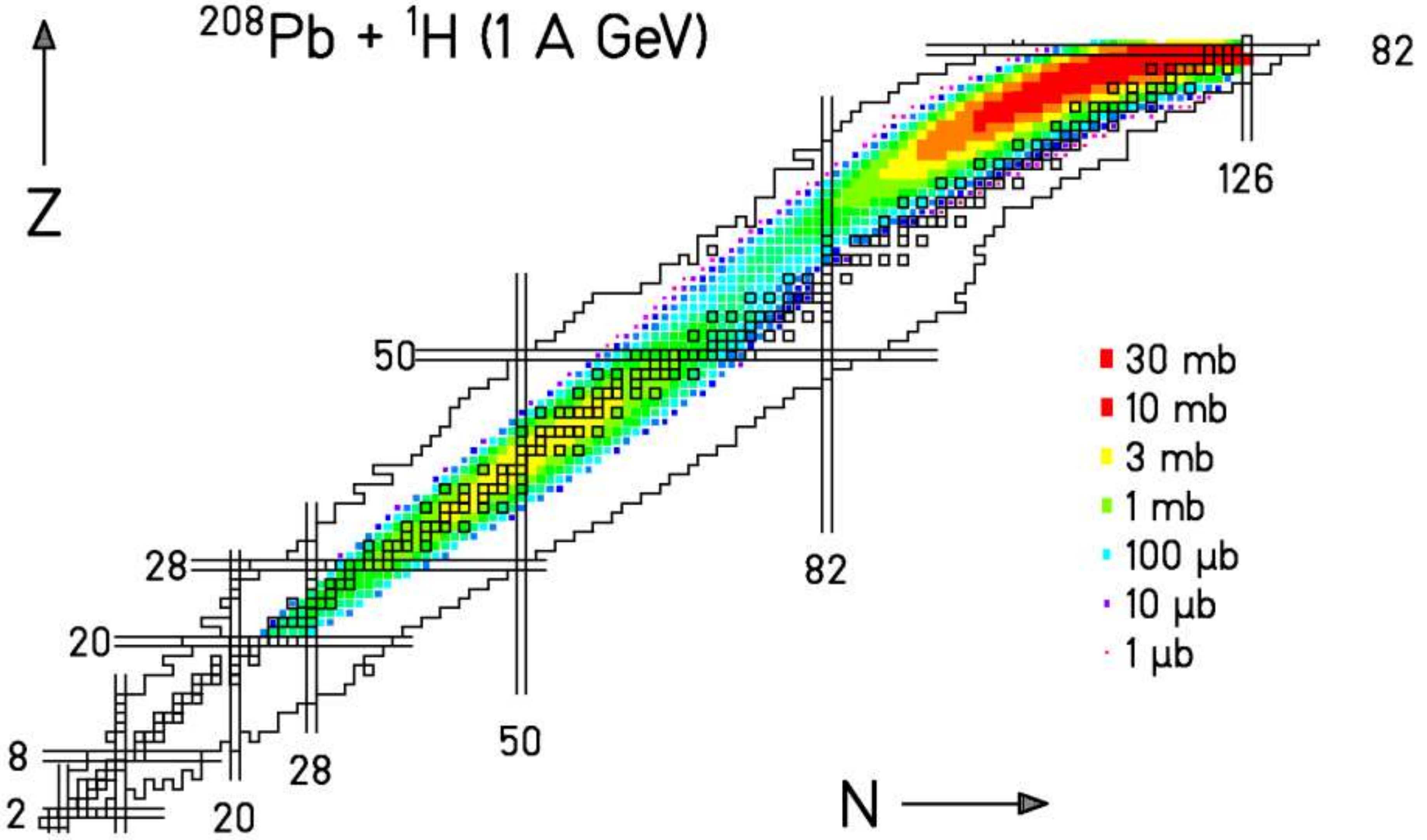
Dy 150 7.2 m	Dy 151 17 m	Dy 152 2.4 h	Dy 153 6.29 h	Dy 154 $3.0 \cdot 10^6$ a	Dy 155 10.0 h	Dy 156 0.056	Dy 157 8.1 h	Dy 158 0.095	Dy 159 144.4 d	Dy 160 2.329	Dy 161 18.889	Dy 162 25.475
Tb 149 4.2 m / 4.1 h	Tb 150 5.8 m / 3.67 h	Tb 151 25 s / 17.6 h	Tb 152 4.2 m / 17.5 h	Tb 153 2.34 d	Tb 154 23 h / 9.0 h / 21 h	Tb 155 5.32 d	Tb 156	Tb 157 99 a	Tb 158 10.5 s / 180 a	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 $1.8 \cdot 10^6$ a	Gd 151 120 d	Gd 152 0.20 / $1.1 \cdot 10^{14}$ a	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

The accelerator complex of CERN



Ion source	90 keV
LINAC2	50 MeV
PSB	1.4 GeV
PS	25 GeV
SPS	450 GeV
LHC	6500 GeV

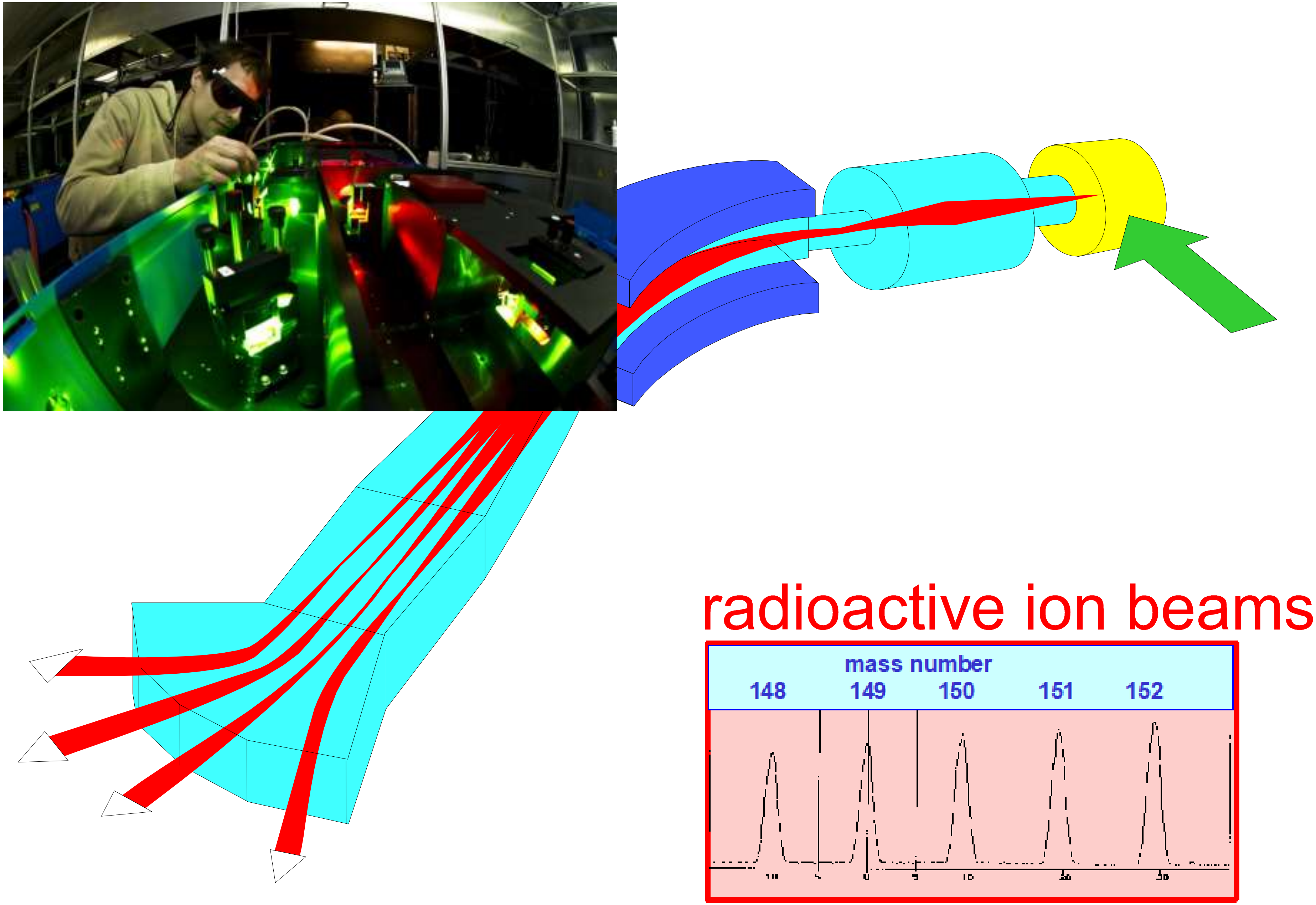
Spallation + Fragmentation + Fission



W. Wlazło et al., Phys. Rev. Lett. 84 (2000) 5736.

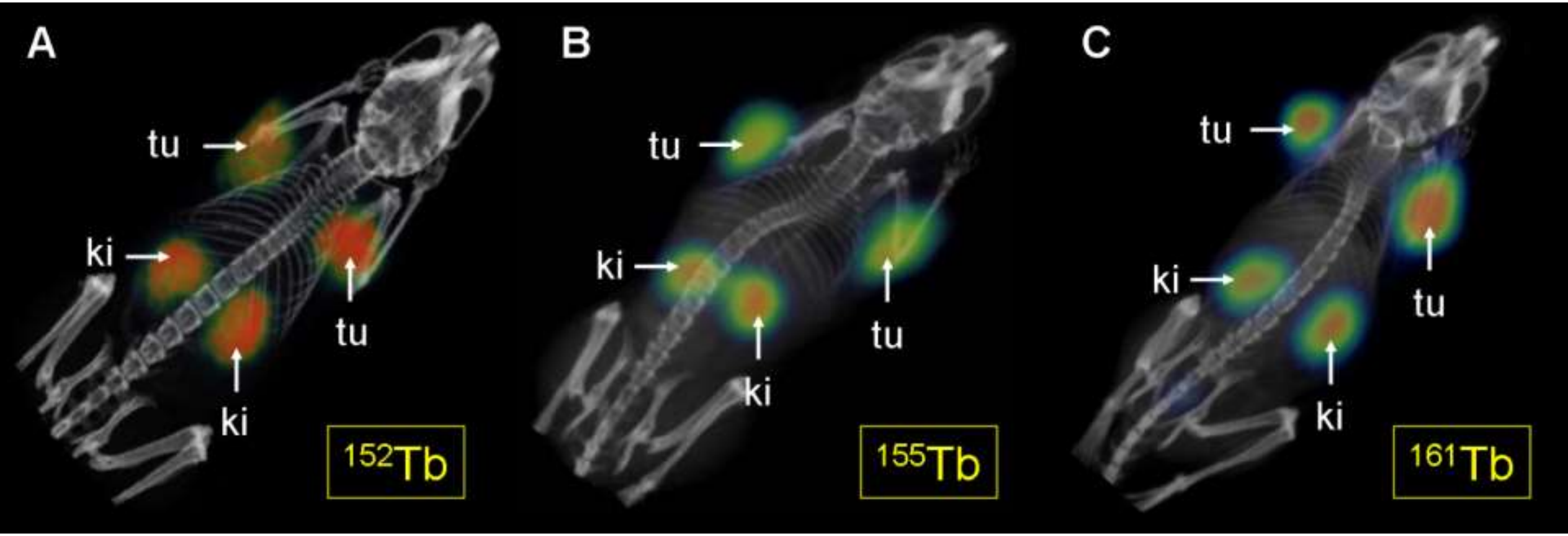
T. Enqvist et al., Nucl. Phys. A 686 (2001) 481.

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



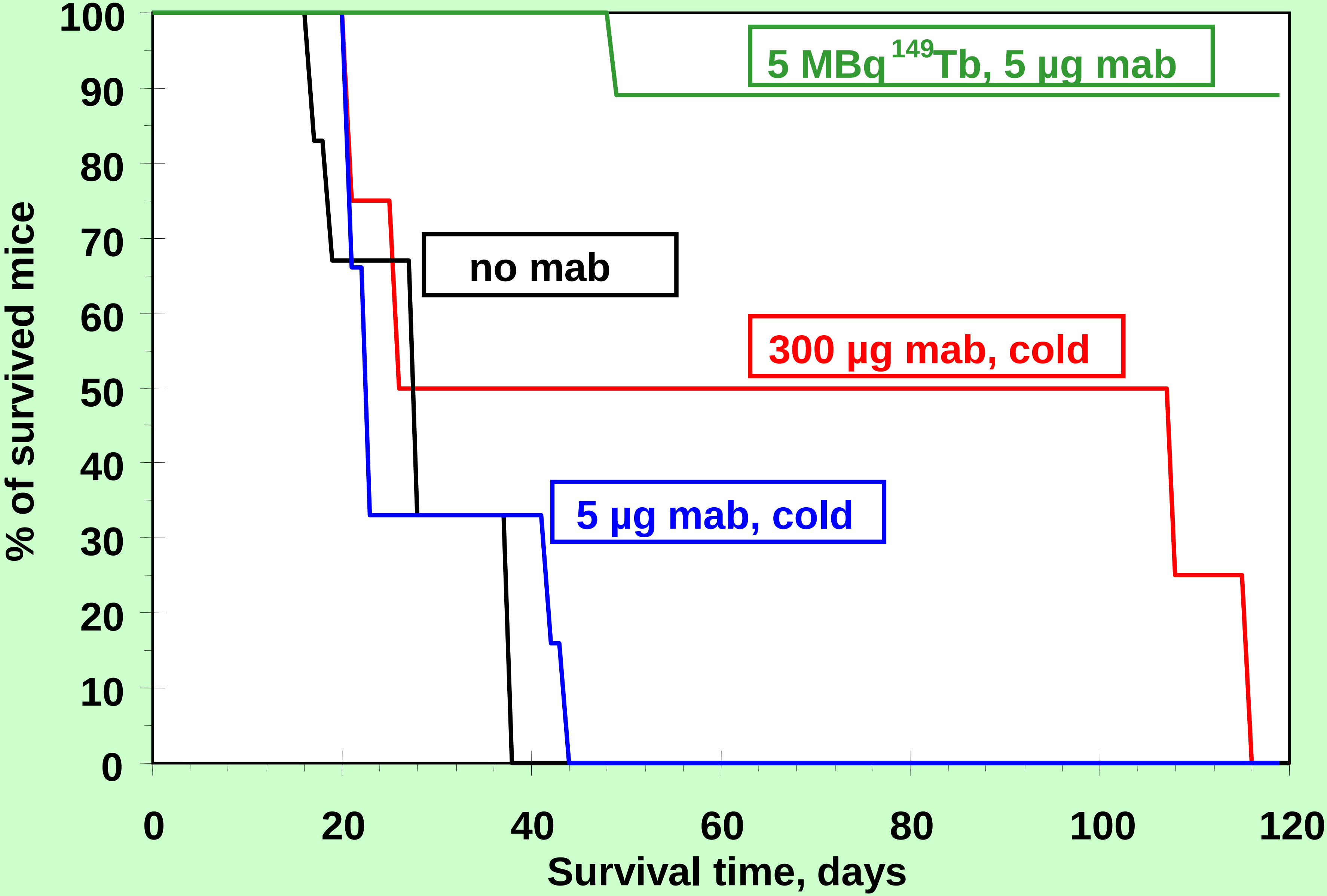
Theranostics with terbium isotopes

PET *SPECT* *SPECT*



IS528 Collaboration: C. Müller et al., J. Nucl. Med. 2012;53:1951.

Preclinical study with lymphoma mouse model



G.J. Beyer et al., Eur J Nucl Med Molec Imaging 2004:31;547.

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  http://www.nupecc.org/npmed/npmed2014.pdf

Many reports and guidelines from IAEA Vienna (free download):

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- Cyclotron Produced Radionuclides: Principles and Practice, IAEA Vienna 2008, Technical Report 465.
- Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods, IAEA Vienna 2009, Technical Report 468.
- Lectures on Theranostics by Richard Baum:

  https://www.youtube.com/watch?v=Z0TlXH2dVi8

  https://www.youtube.com/watch?v=S74LNxXOaSw
- (Free) medical review papers from http://pubmed.gov
- Information on on-going clinical trials: http://clinicaltrials.gov