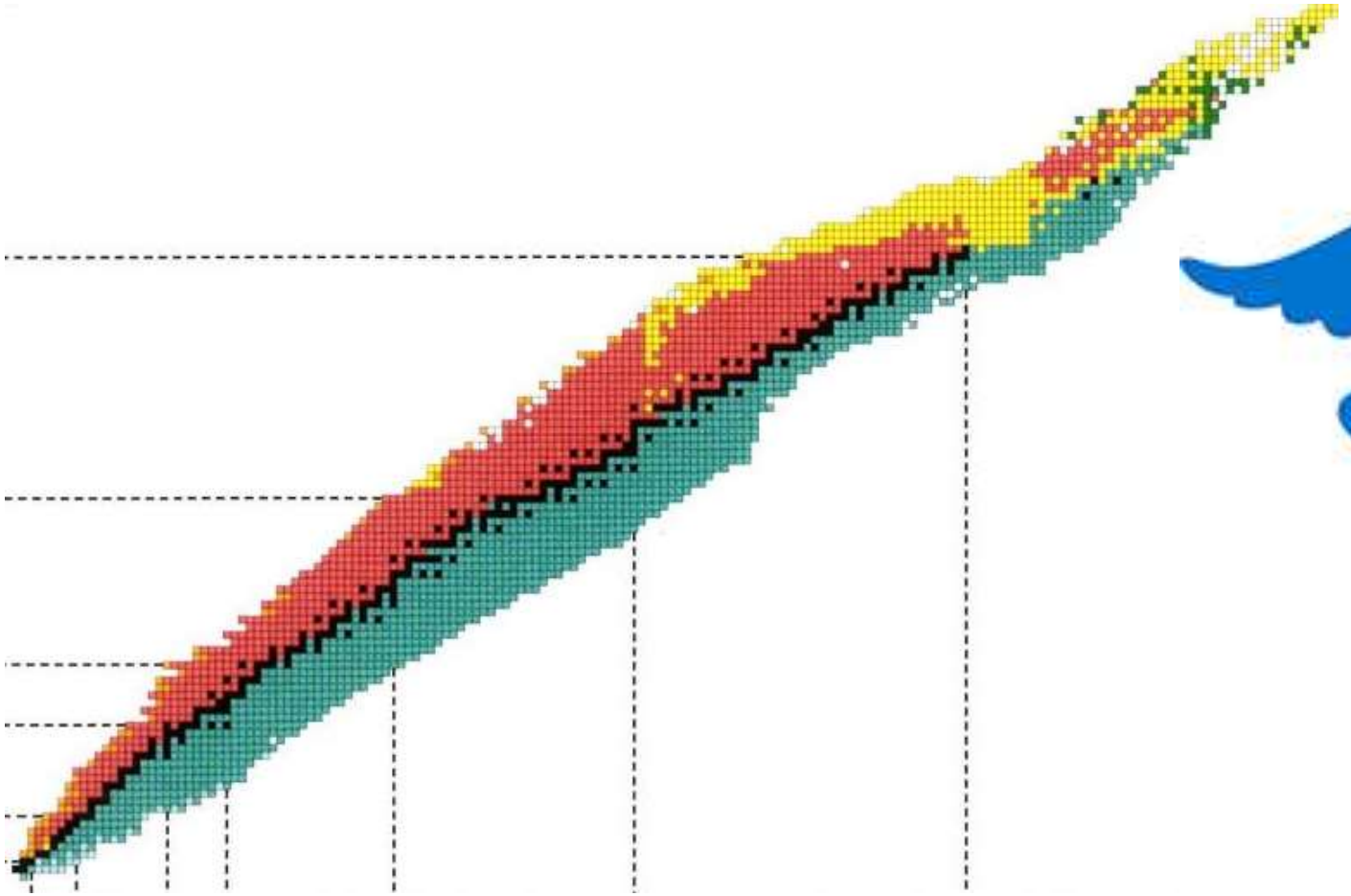
Medical Isotope Production



Ulli Köster

ILL & UGA, Grenoble, France

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UNIVERSITÉ Grenoble Alpes

Theranostics
=
Personalized medicine
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Precision medicine

Cure

Companion diagnostic

Therapy

Symptomatic treatment

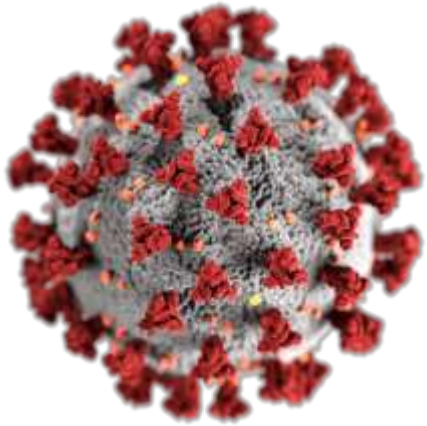
Diagnostic

Prevention

“Medical”

MD (Miracle Drug)

MD’s efficacy predictor



Theranostics
=
Personalized medicine
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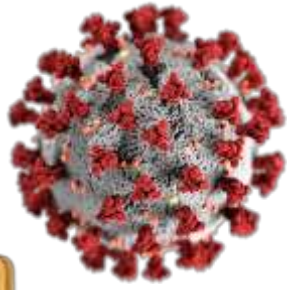
Precision medicine

“Medical”



Cure

10k **Miracle Drug** *  = 0.85 G$

Companion diagnostic

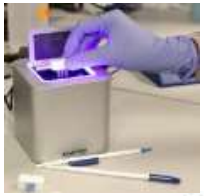
25k **MD’s efficacy predictor** *  = 0.08 G$

Therapy

25k  *  = 0.08 G$

Symptomatic treatment

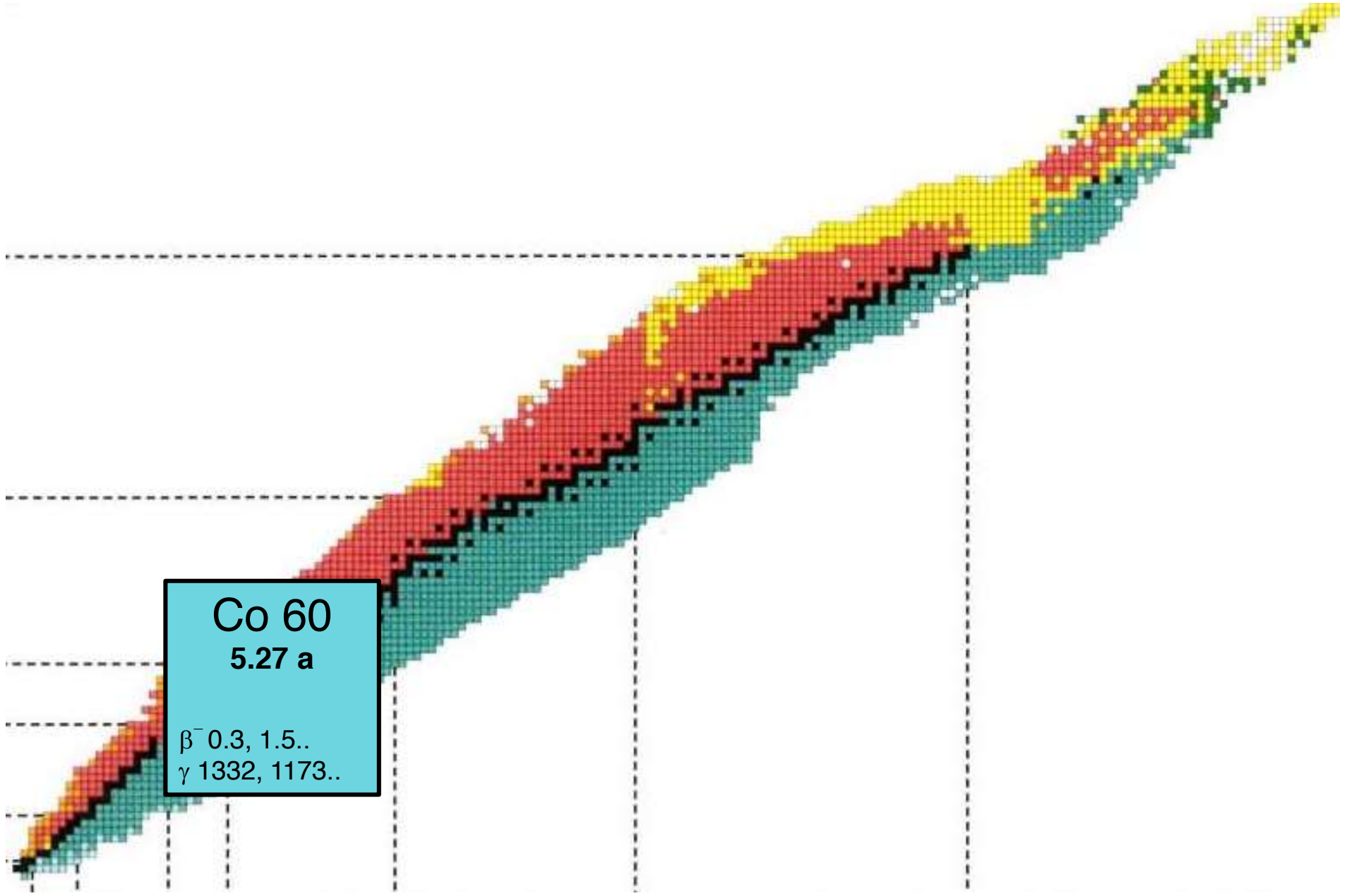
Diagnostic

20M  *  = 1 G$

Prevention

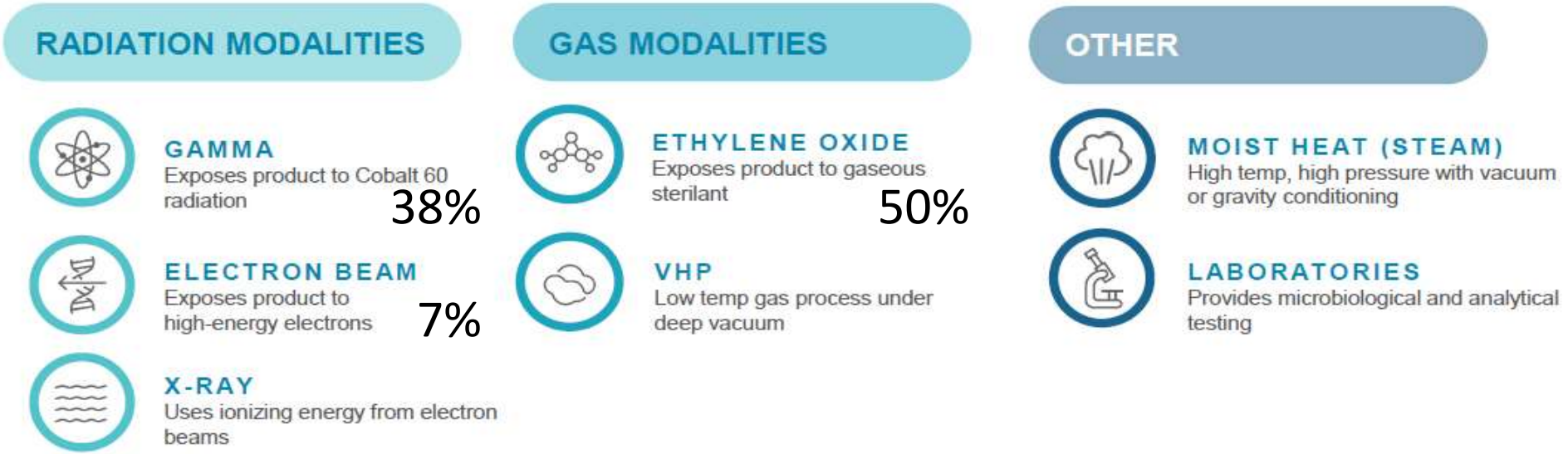
38M * 500  *  = 2 G$

Radionuclides for Medicine



Radiation sterilization of medical material

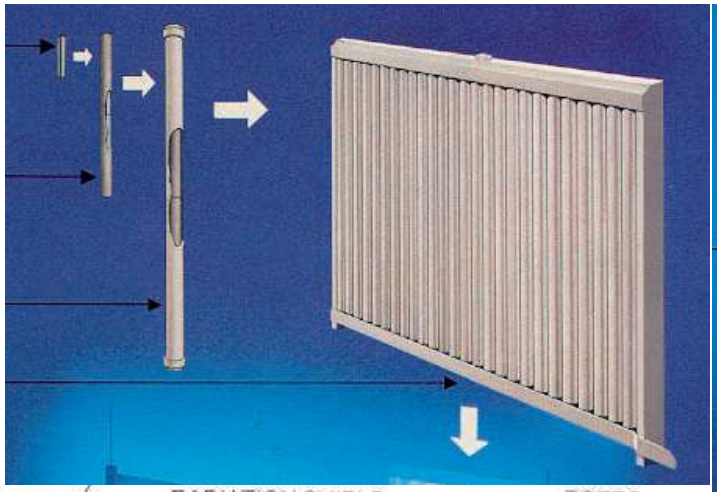
- Single use consumables (surgical threads, gloves, etc.)
- Human tissues
- Implantable devices
- Pharmaceuticals

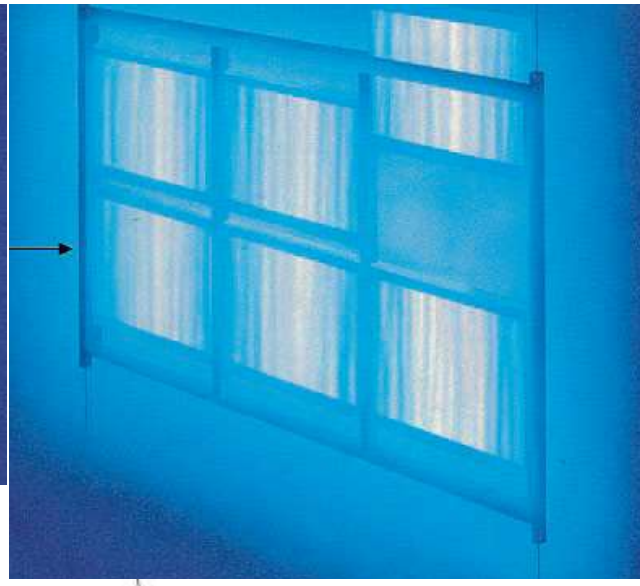


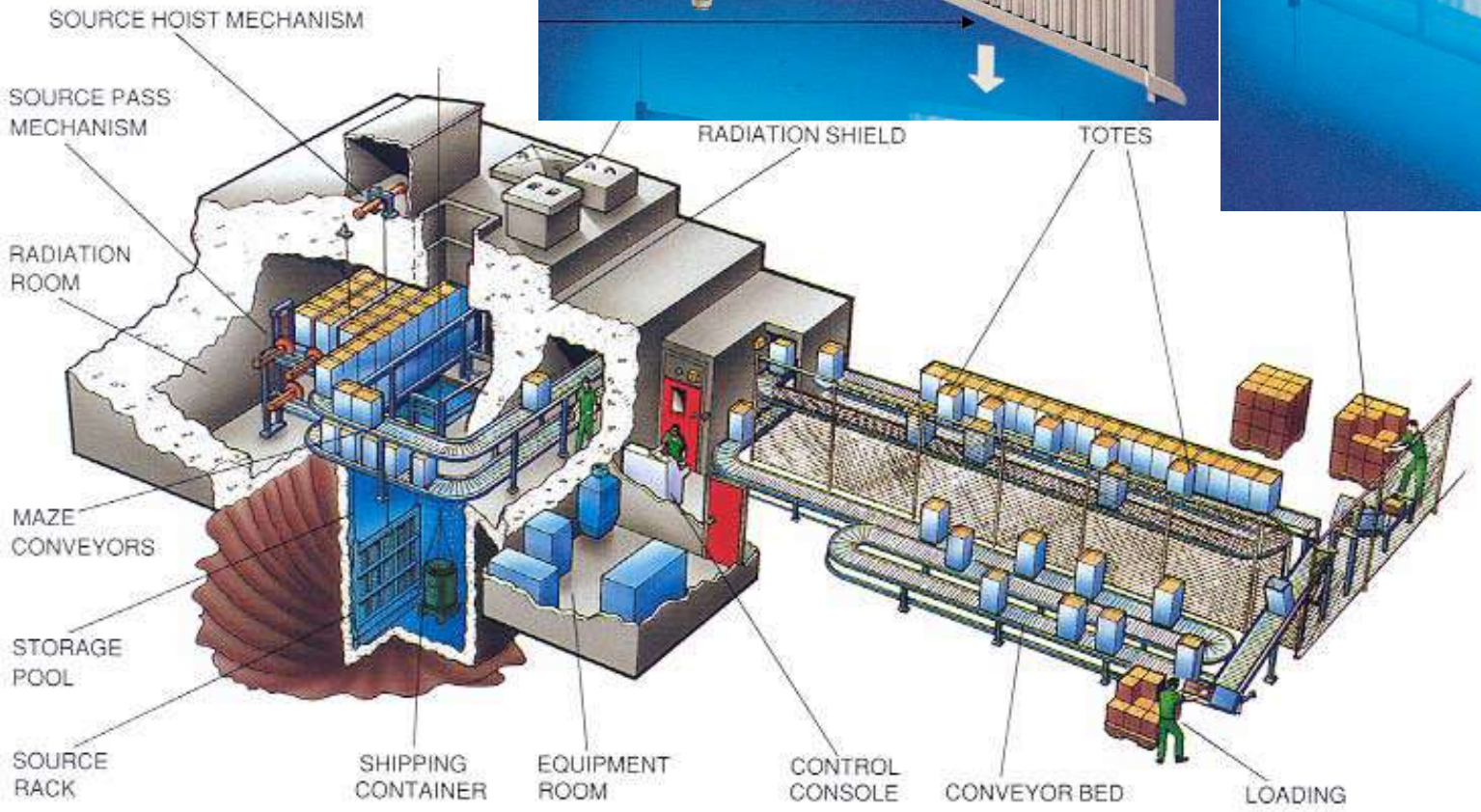
Market for gamma ray sterilization: $\approx$ 1 G$/year

Total ^{60}Co activity in use: $\approx 10^{19}$ Bq $\approx$ 0.3 GCi

Radiation Sterilization of Medical Devices







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

Theranostics
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Personalized medicine
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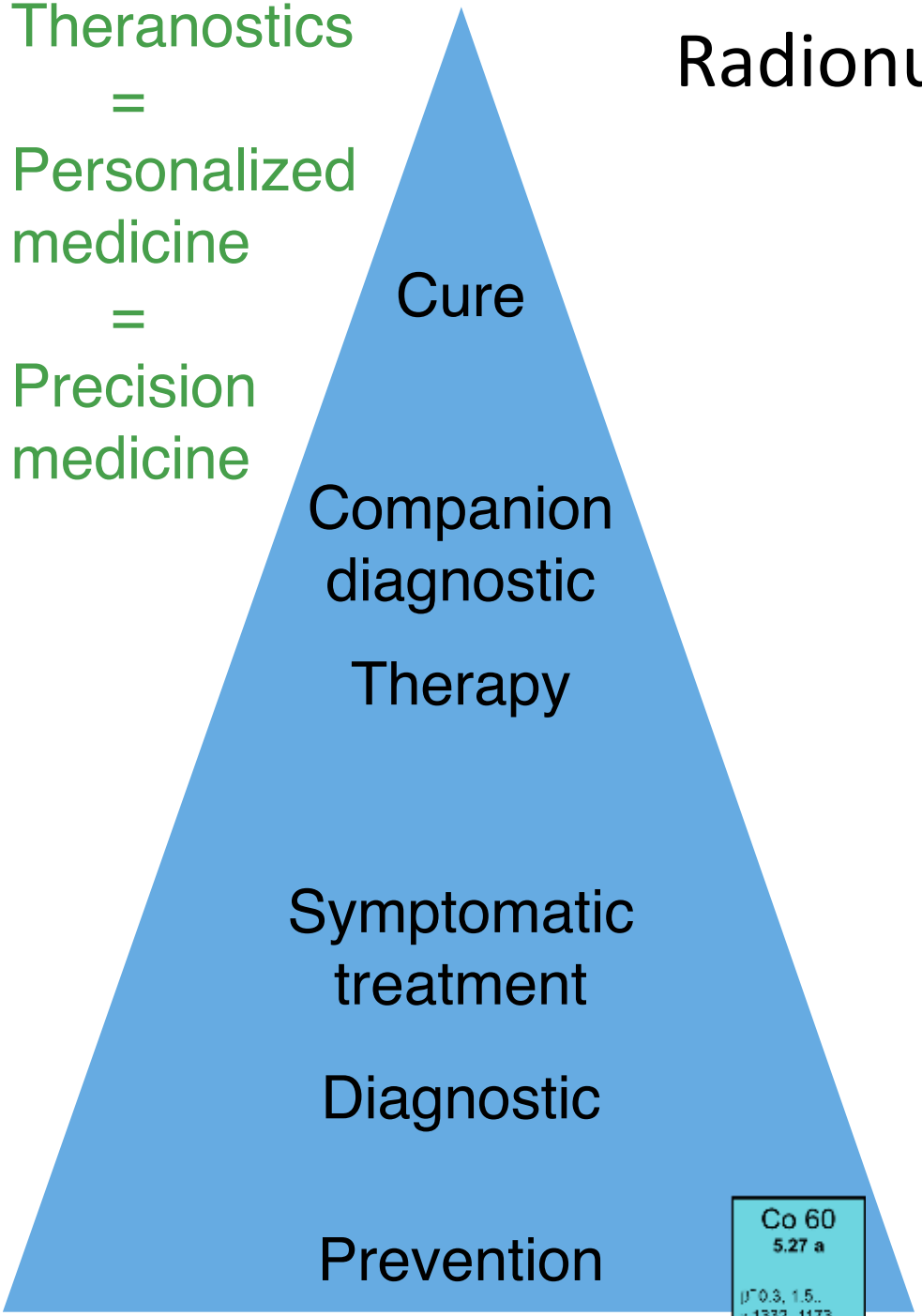
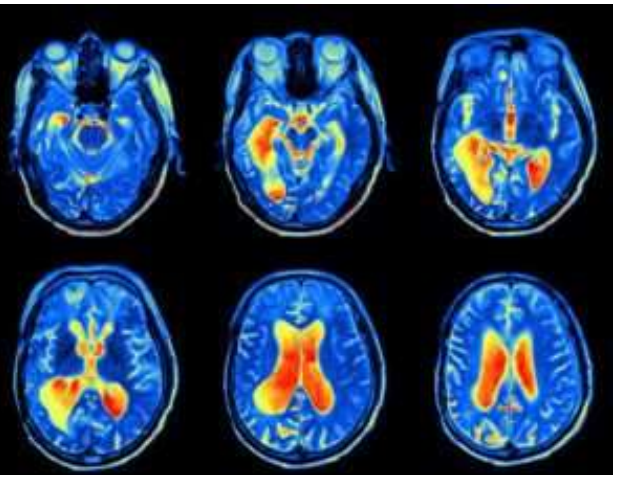
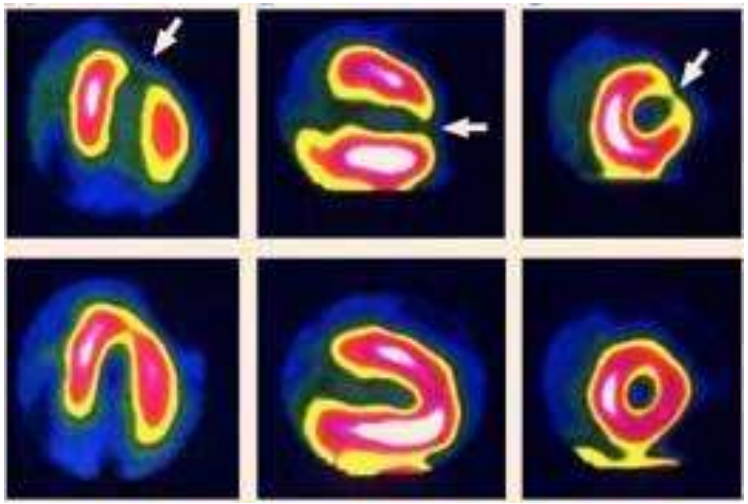
Precision medicine

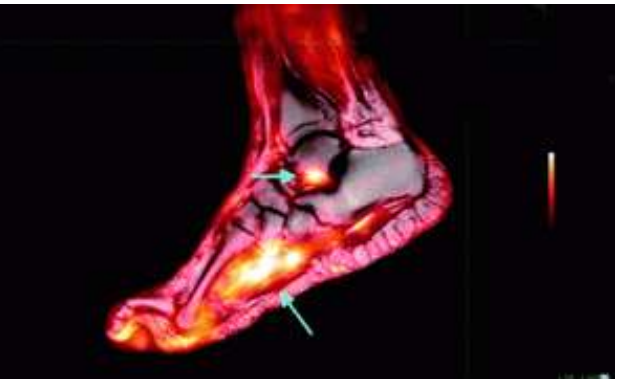
Radionuclides

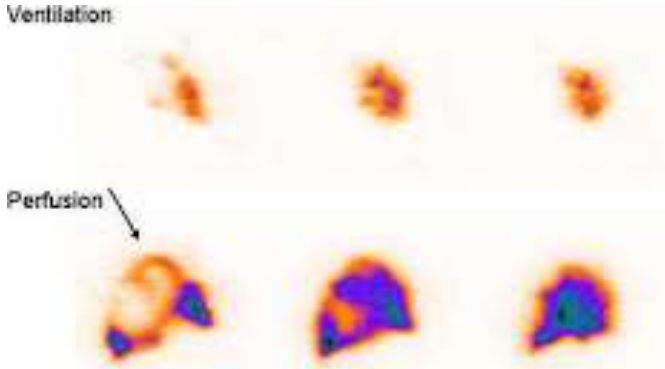


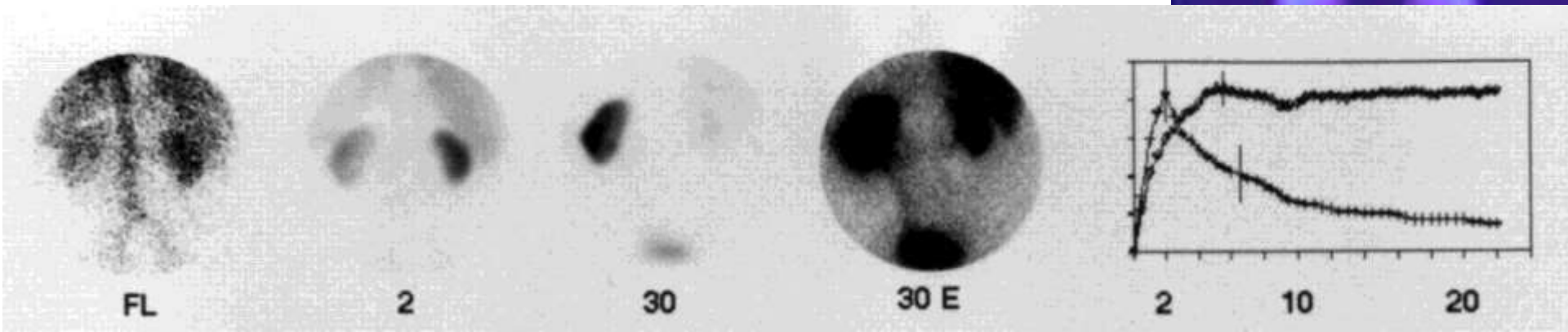
Molecular imaging











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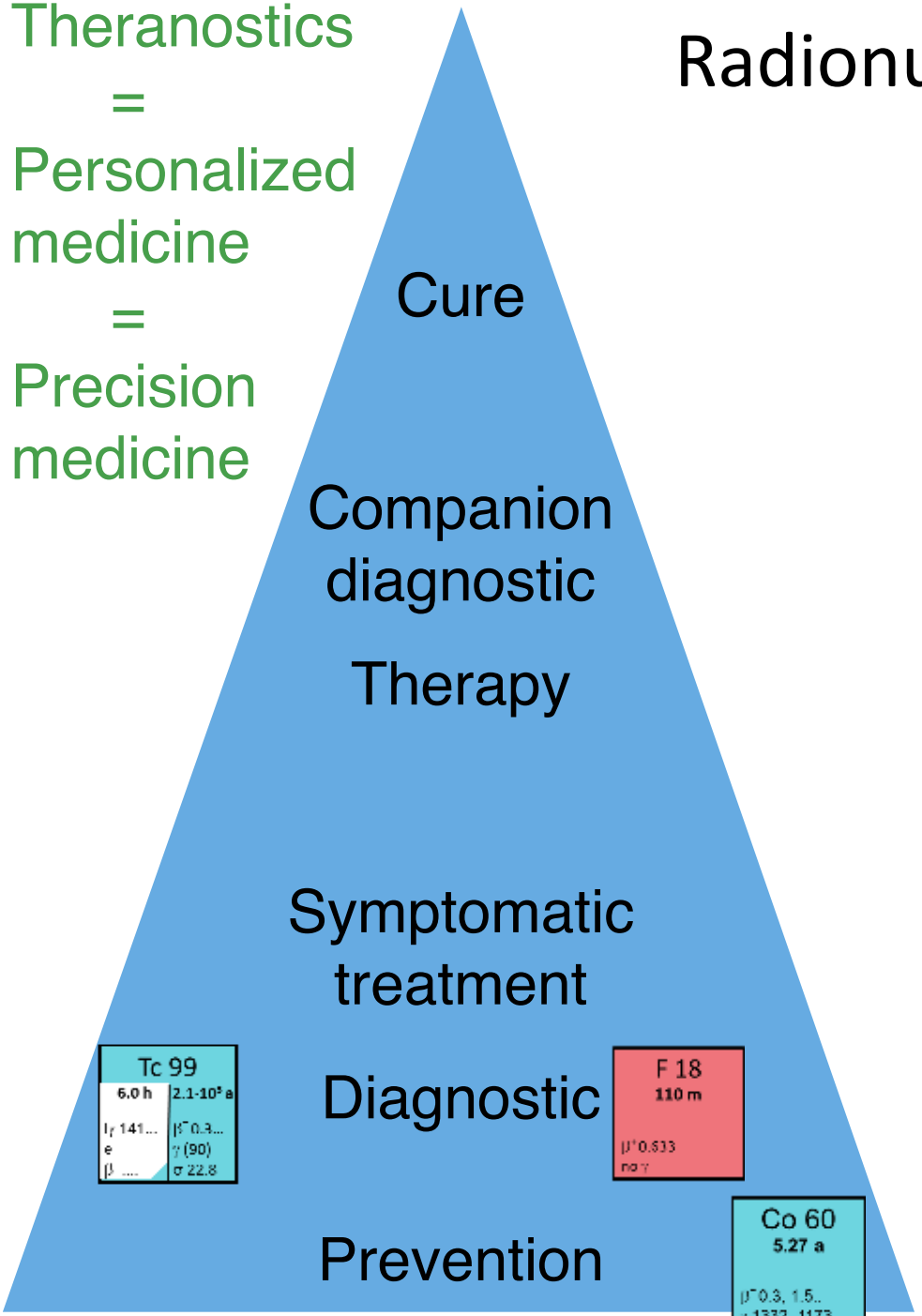
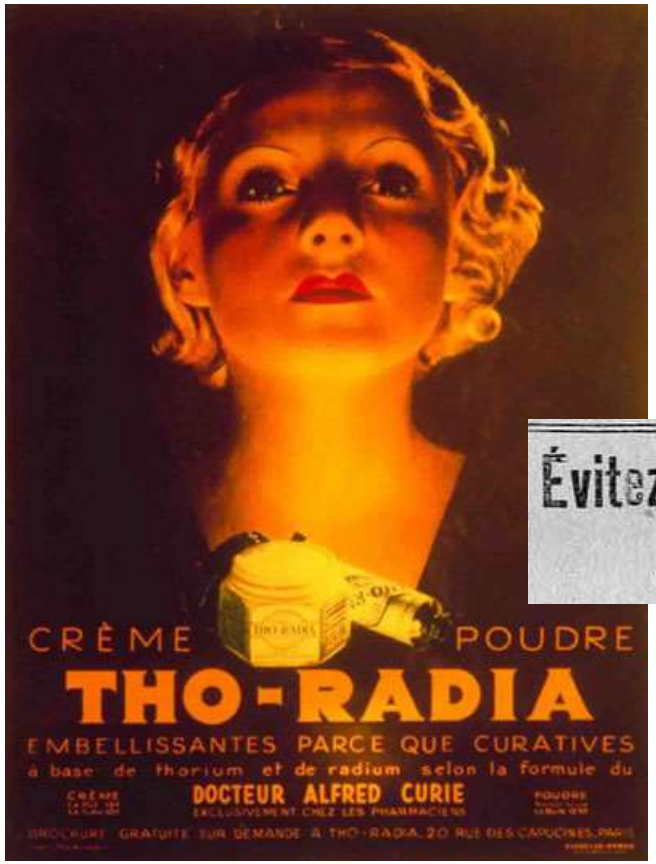
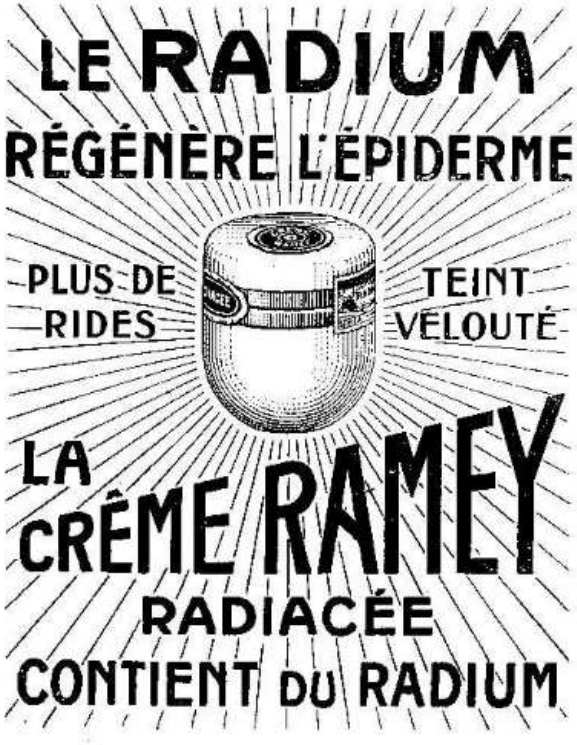
Radionuclides



Discontinued radium applications





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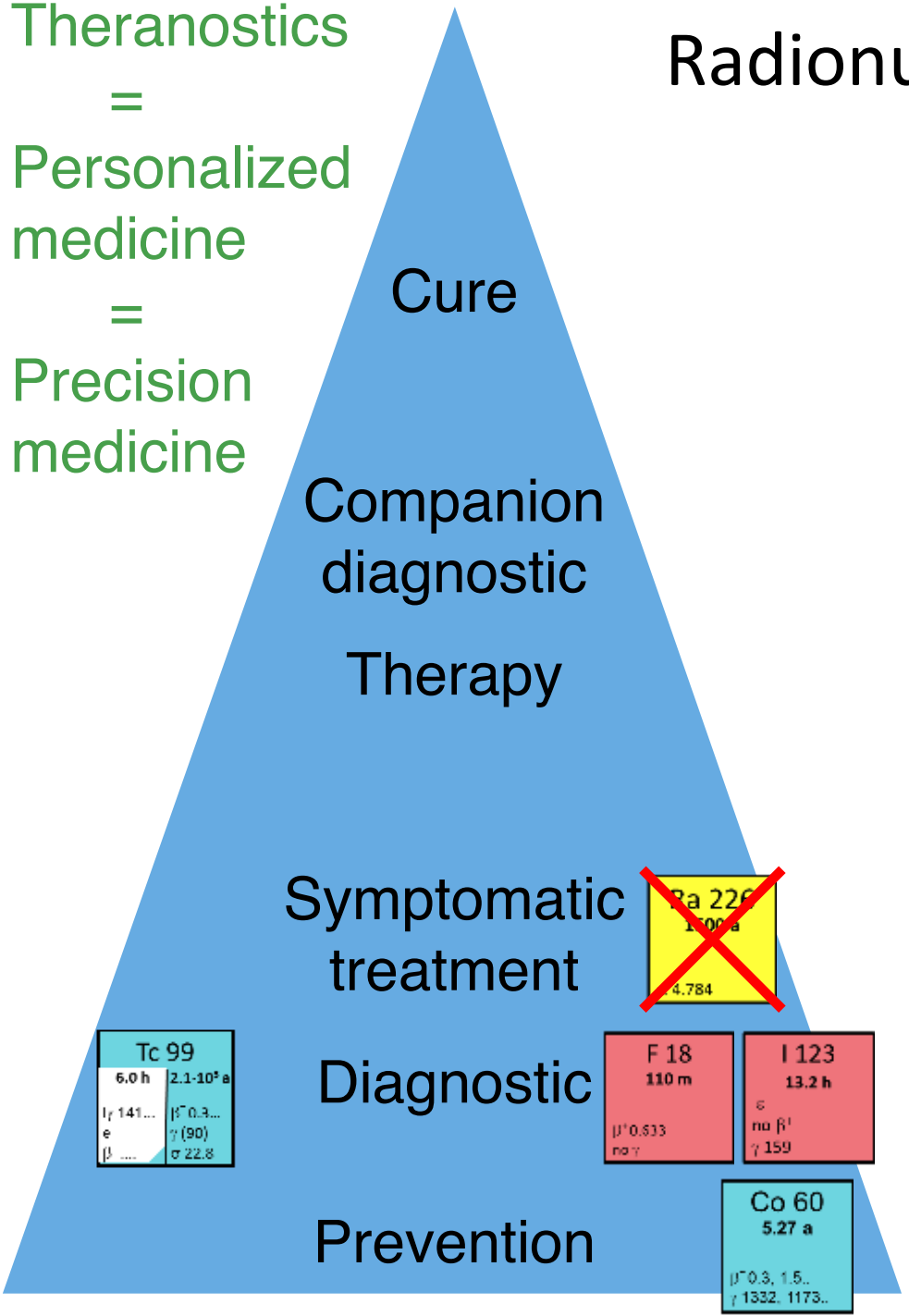
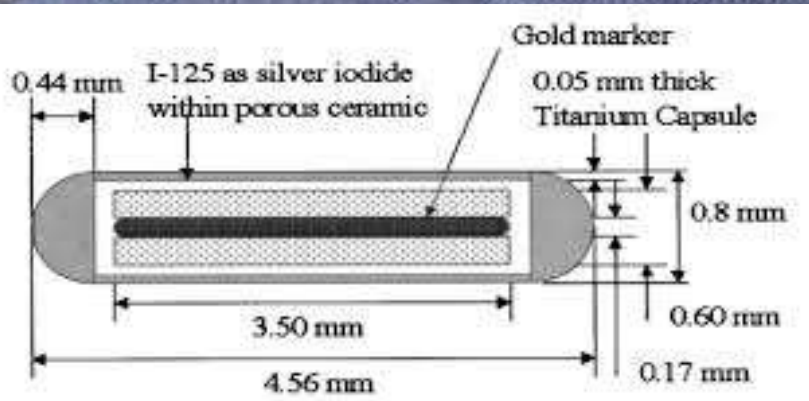
Radionuclides



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”)



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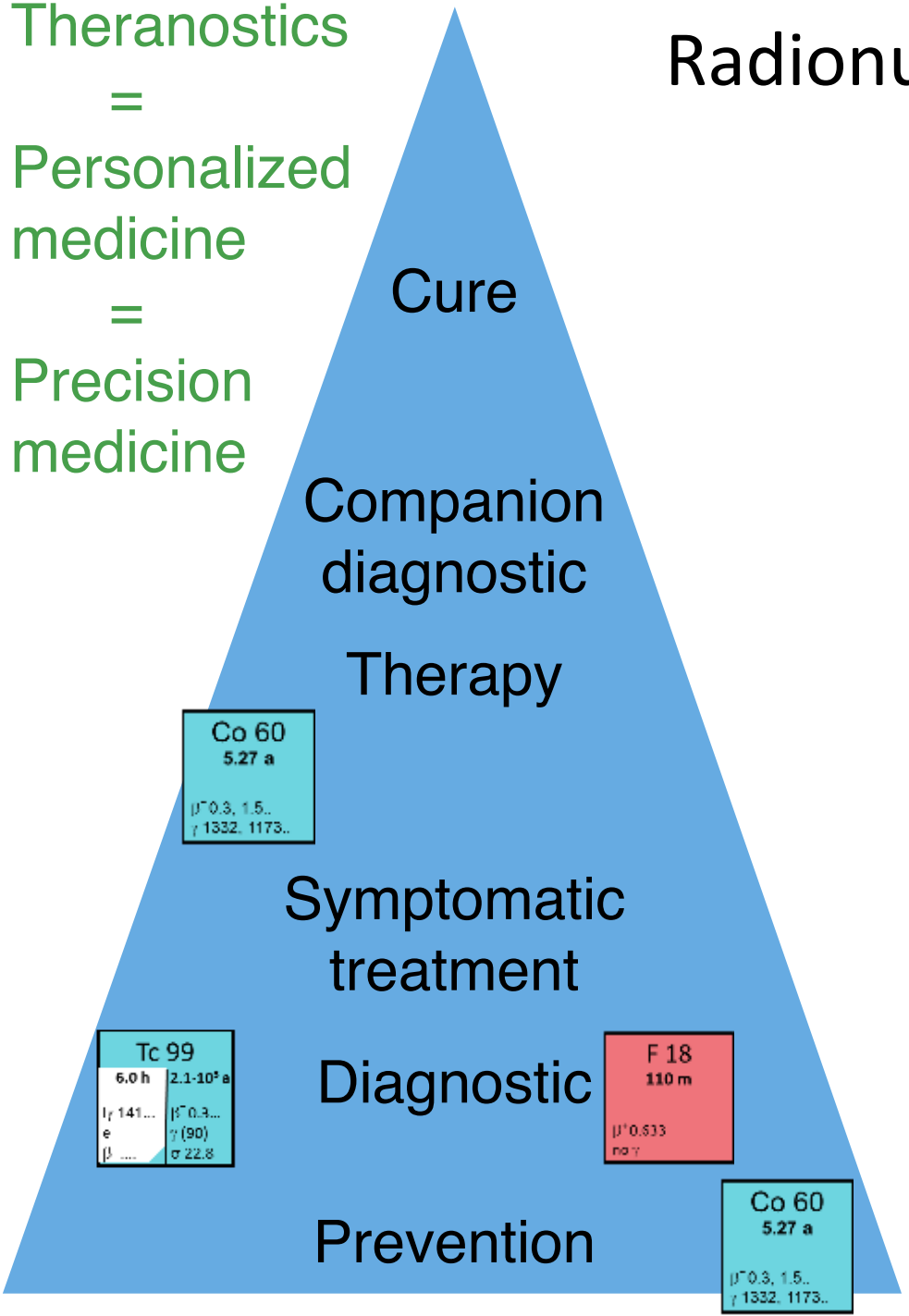
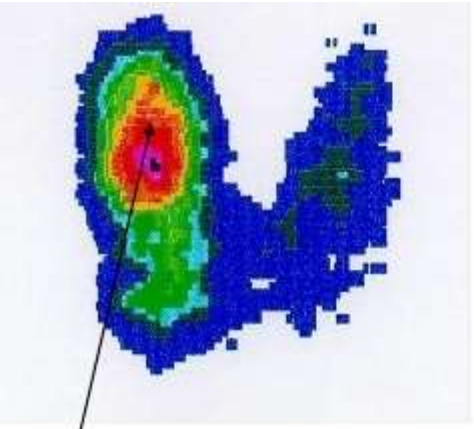
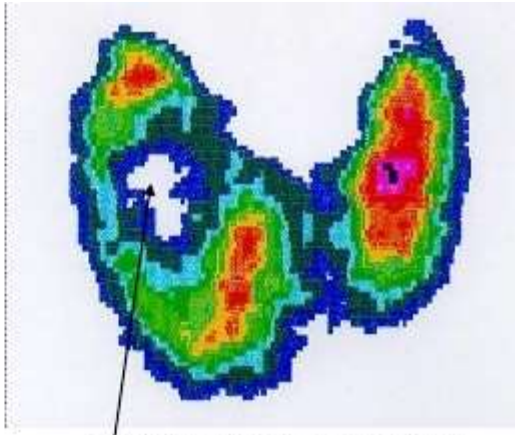
Radionuclides



Thyroid scintigraphy and therapy



Hot nodule – Rt. lobe



Cold nodule – Rt. lobe

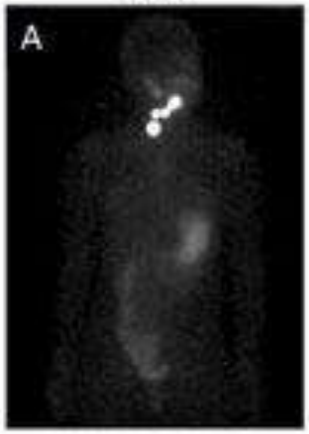
I 123
13.2 h
ε
no β^+
γ 159

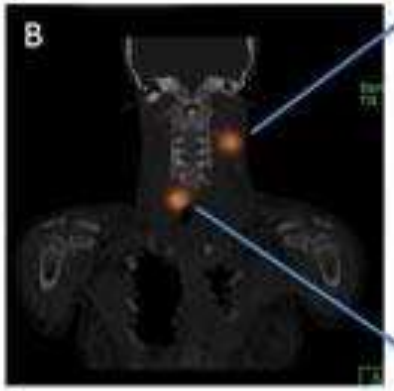
I 131
8.0 d

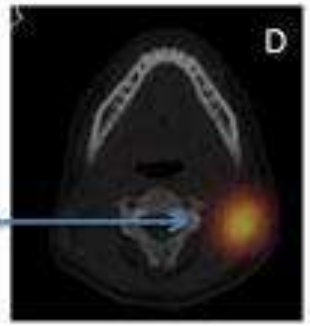
β^- 1.0, 1.8,…
γ 364, 637…

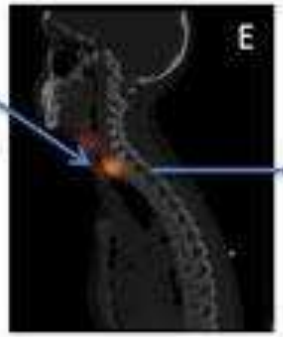
123-I Diagnostic Whole Body Scan

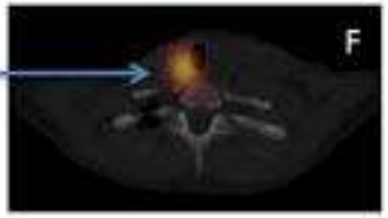
123-I DxWBS with SPECT-CT











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

(papillary) thyroid cancer has the **highest survival** of all malignant cancers !

Theranostics
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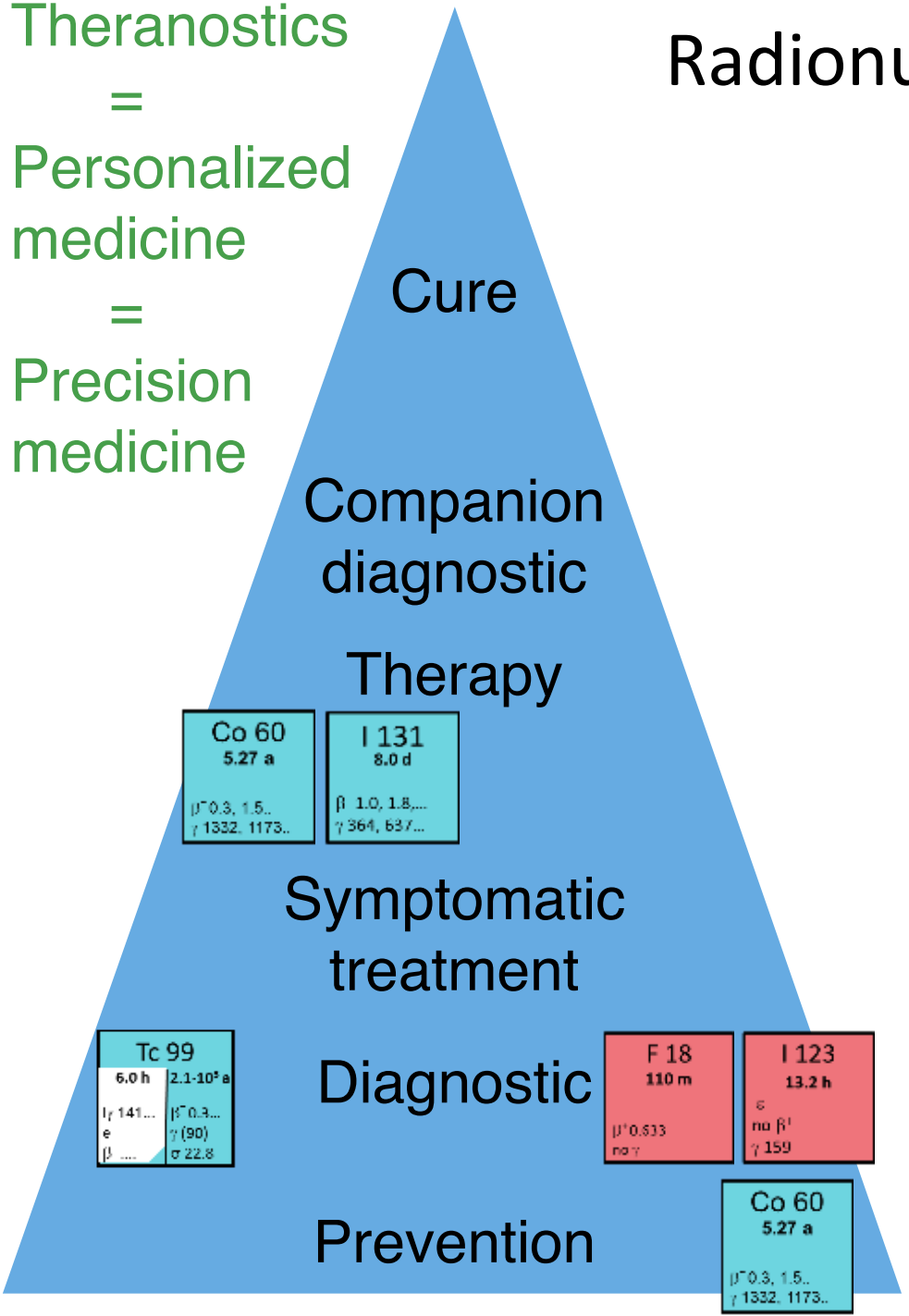
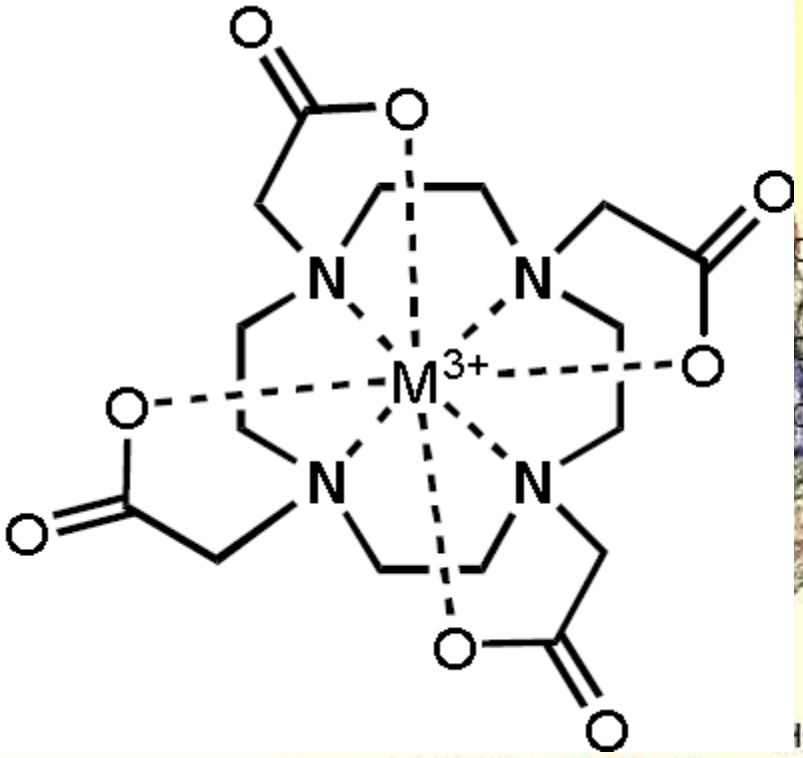
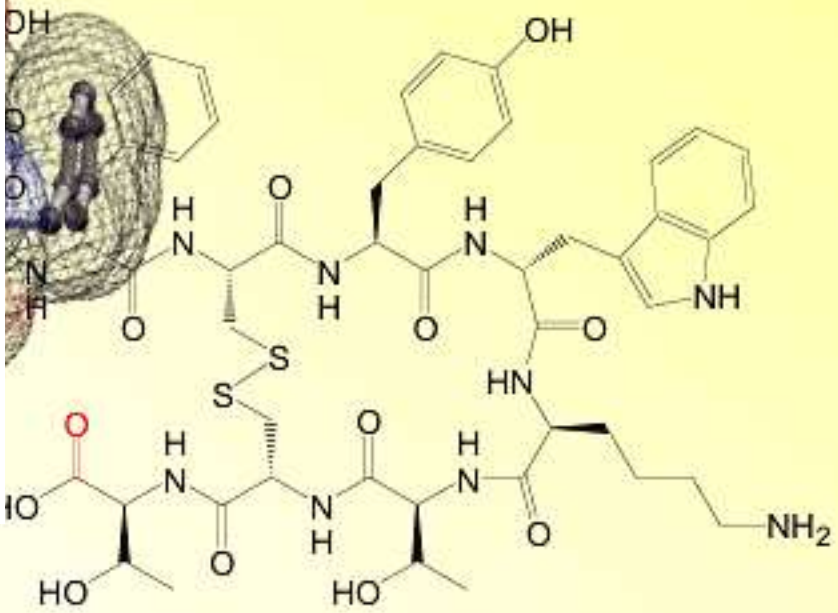
Radionuclides



How can one treat such patients?

Structural Formula of DOTA-TOC/TATE





DOTA-TATE

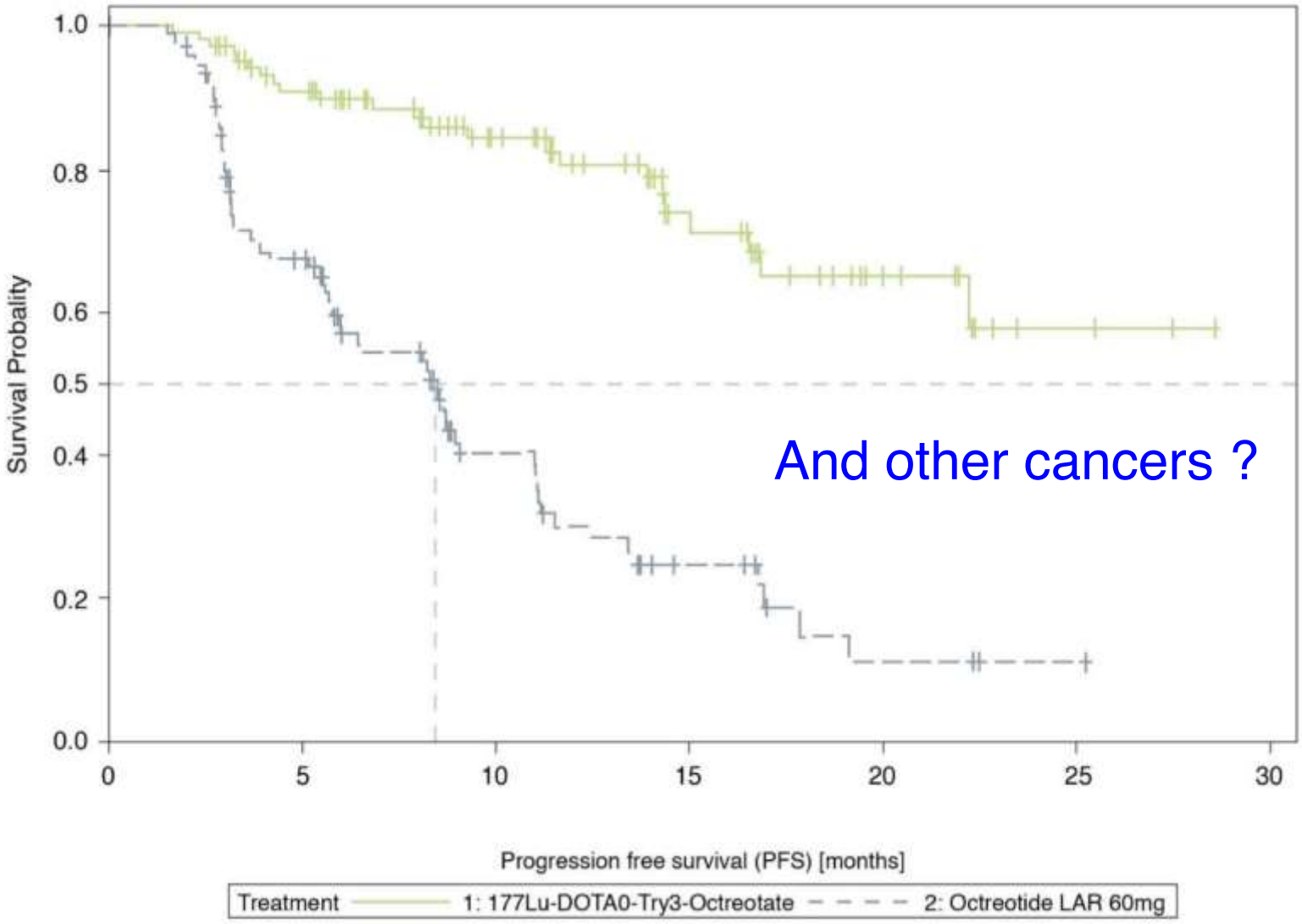
1,4,7,10-tetraazacyclododecantetraacetate

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

IC_{50} (Y^{III}) = 1.6 ± 0.4 nM

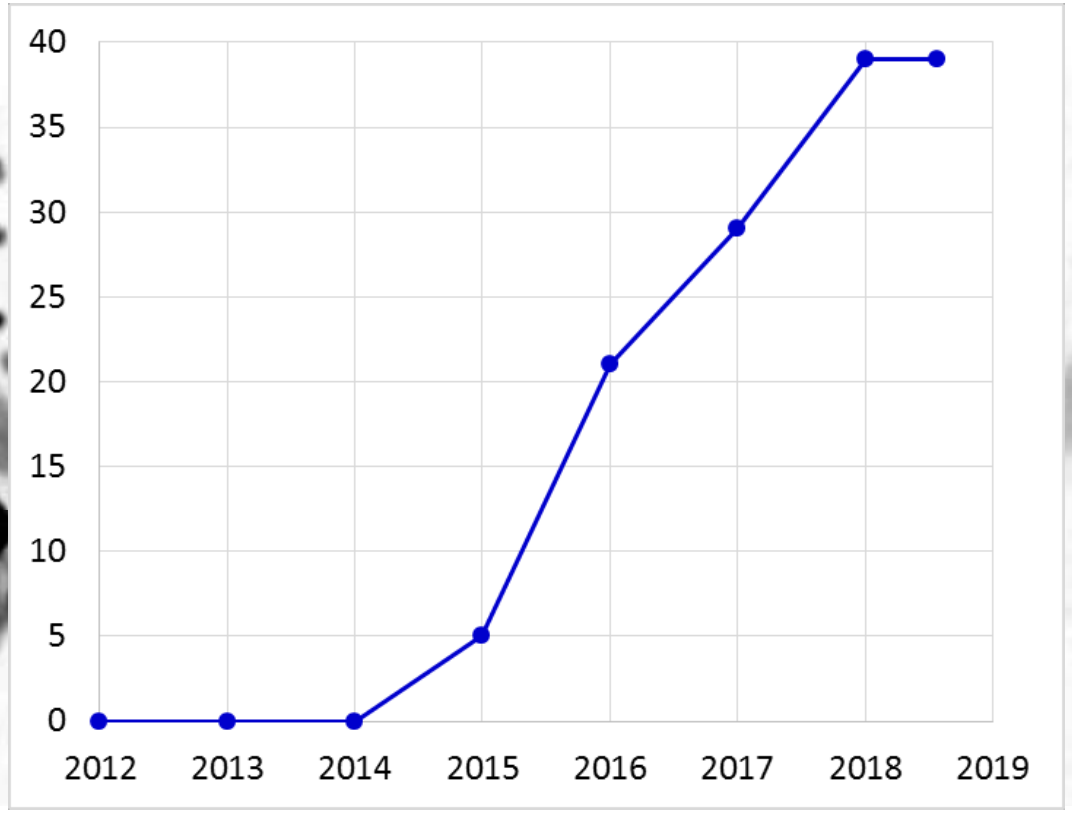
Helmut Maecke, EANM-2007.

^{177}Lu-Peptide Receptor Radionuclide Therapy of midgut neuroendocrine tumors



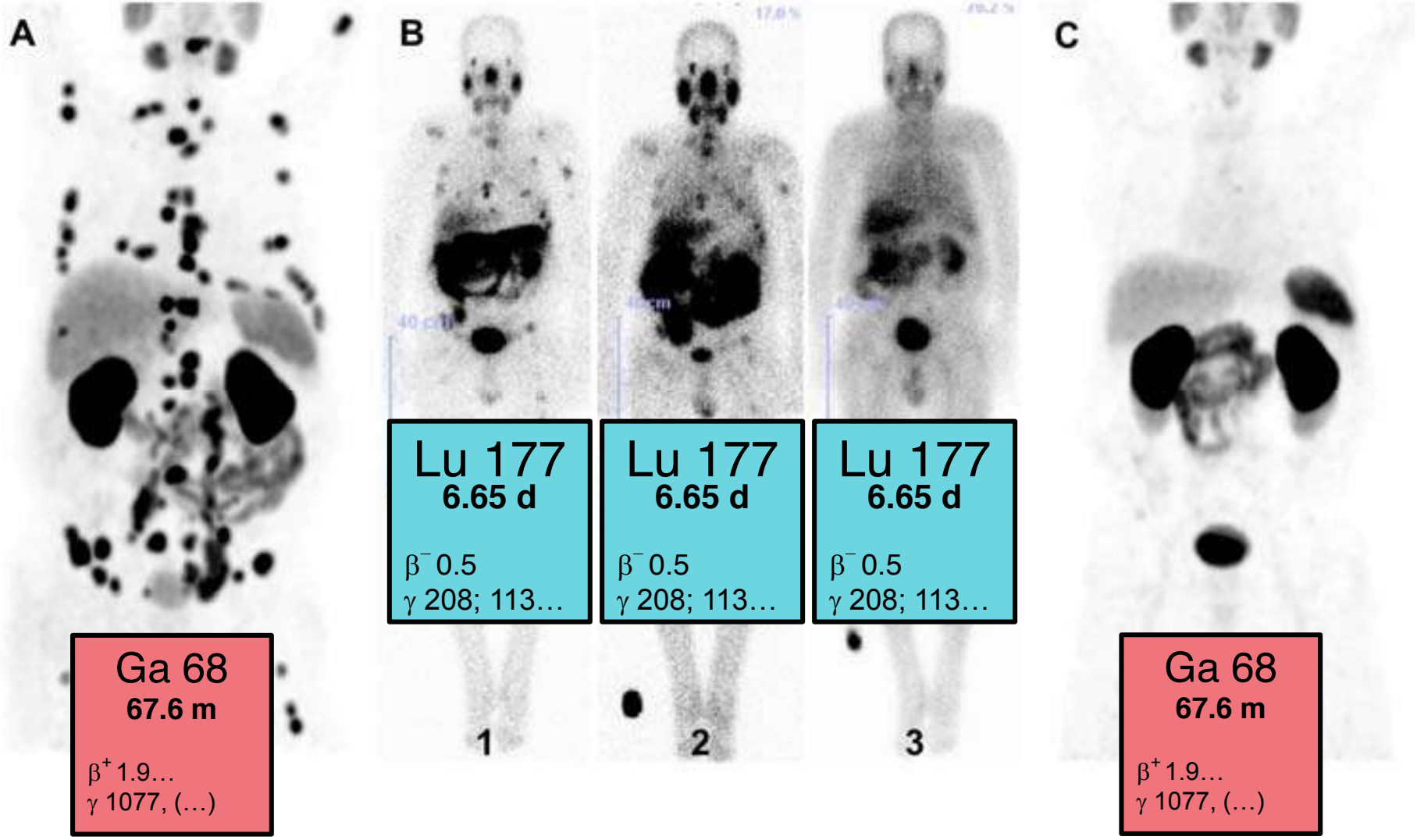
J. Strosberg et al., N Engl J Med 2017;376:125.

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

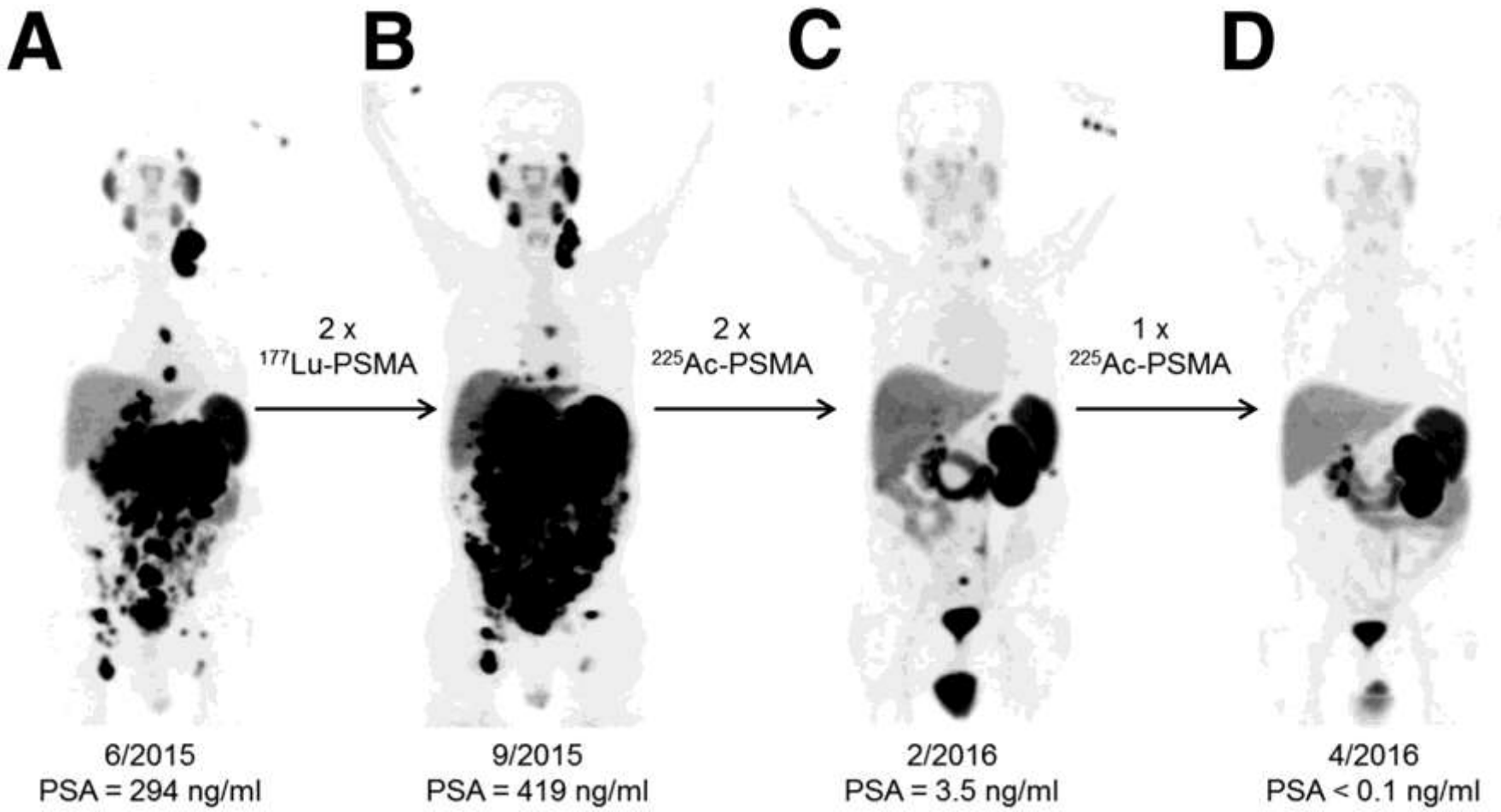


C. Kratochwil et al., Eur J Nucl Med Mol Imaging 2015;42:987.
R.P. Baum et al., J Nucl Med 2016;57:1006.
C. Kratochwil et al., J Nucl Med 2016;57:1170.
K. Rahbar et al., J Nucl Med 2017;58:85.
M.S. Hofman et al., Lancet Oncol 2018;19:825.
M.M. Heck et al., Eur Urol 2019;75:920.
T.W. Barber et al., J Nucl Med 2019; 60:955.

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

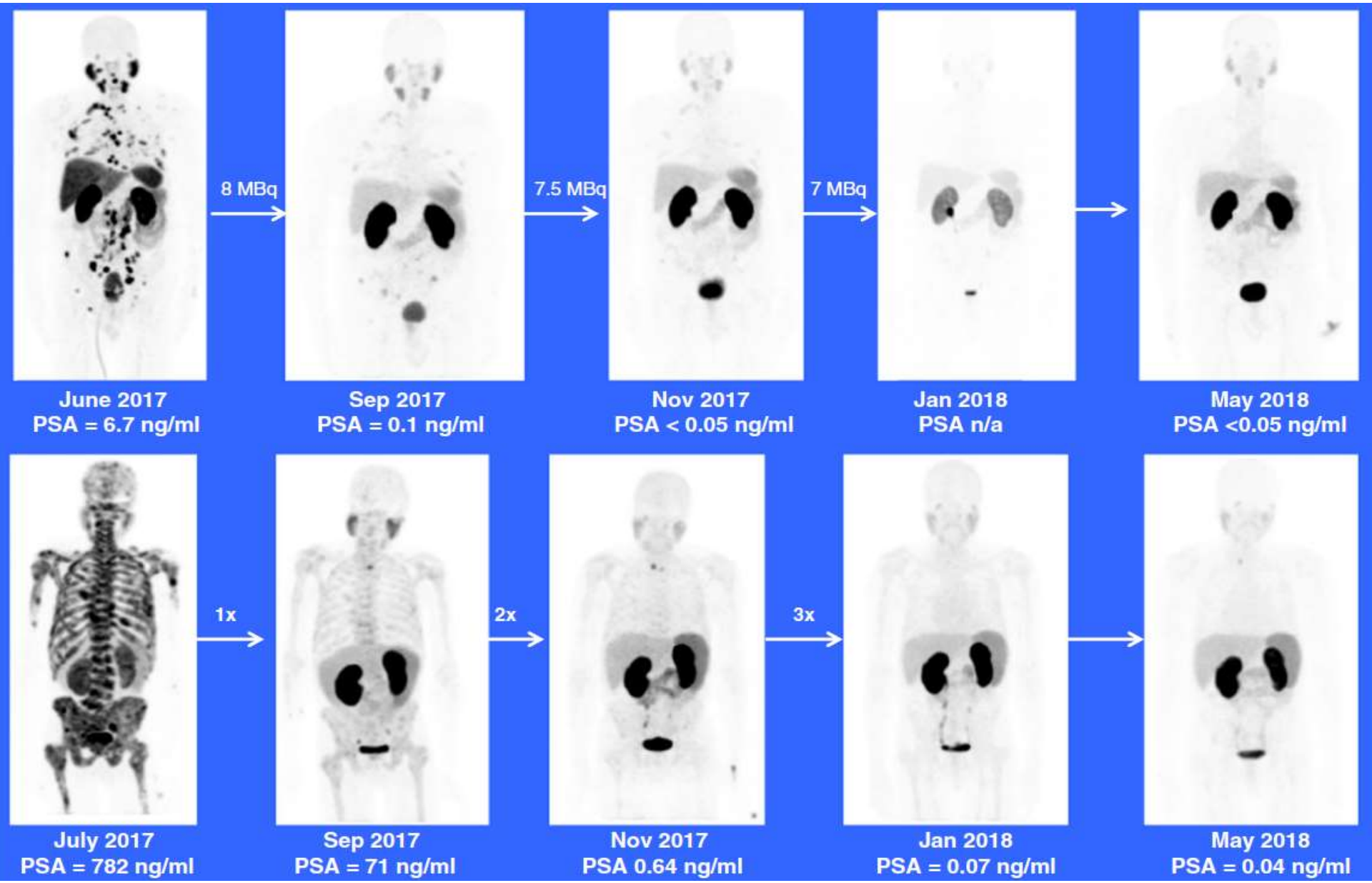


Targeted therapy with ^{225}Ac



C. Kratochwil et al. J Nucl Med 2016;57:1941.

Targeted therapy with ^{225}Ac



M. Sathekge et al., EJNMMI 2019;46:129.

Theranostics
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Personalized medicine
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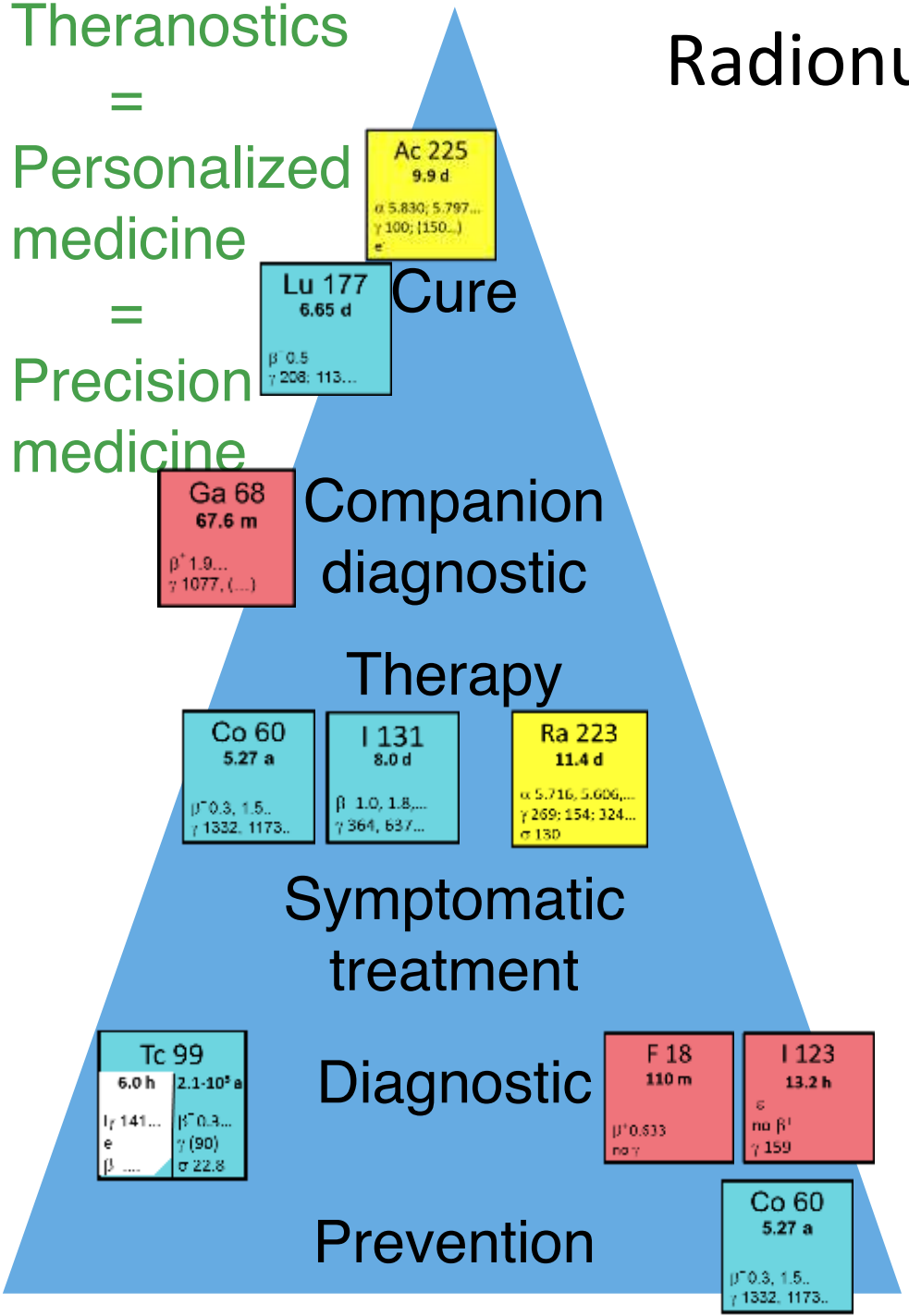
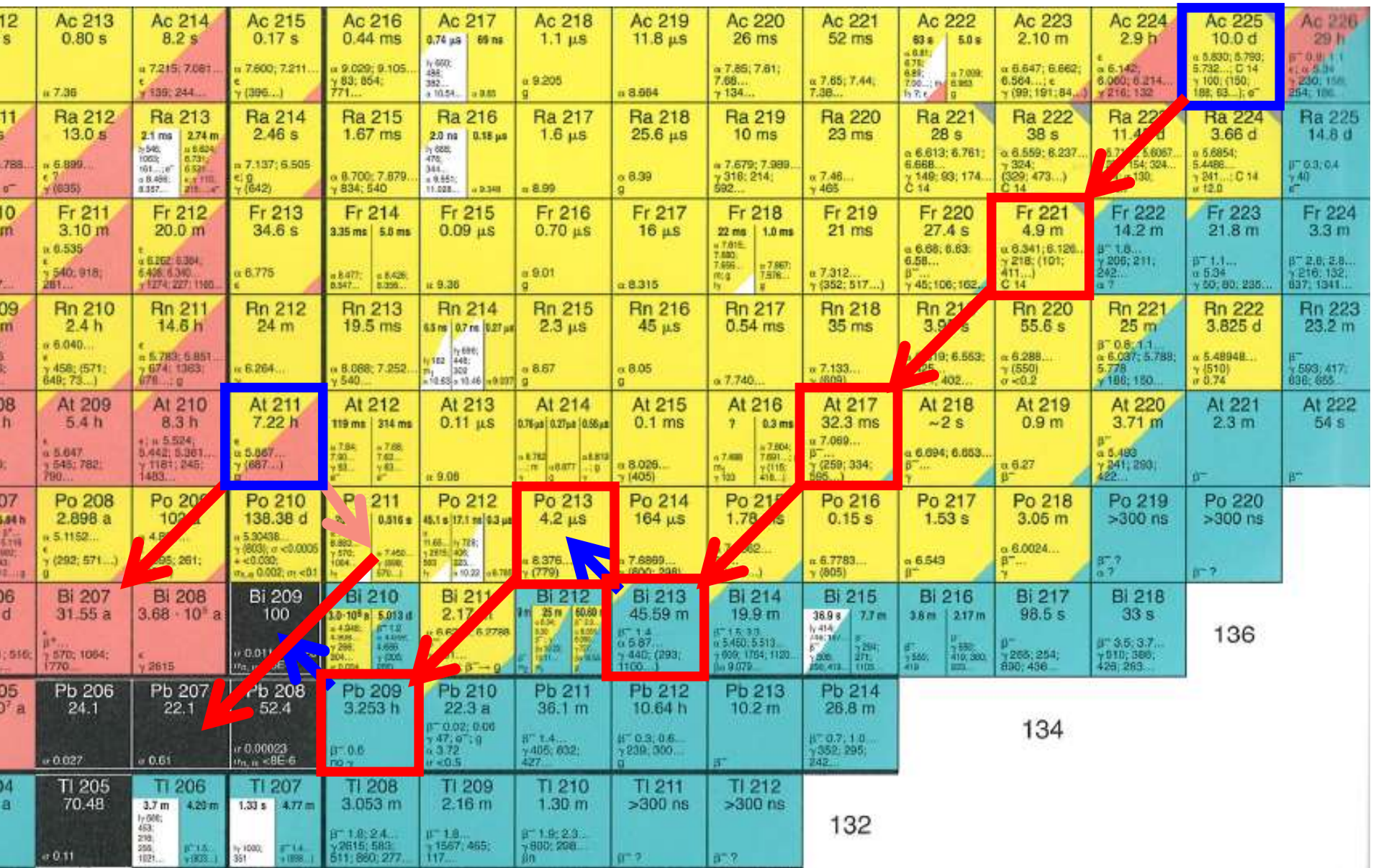
Precision medicine

Radionuclides



Isotopes for targeted alpha therapy



Theranostics

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Personalized medicine

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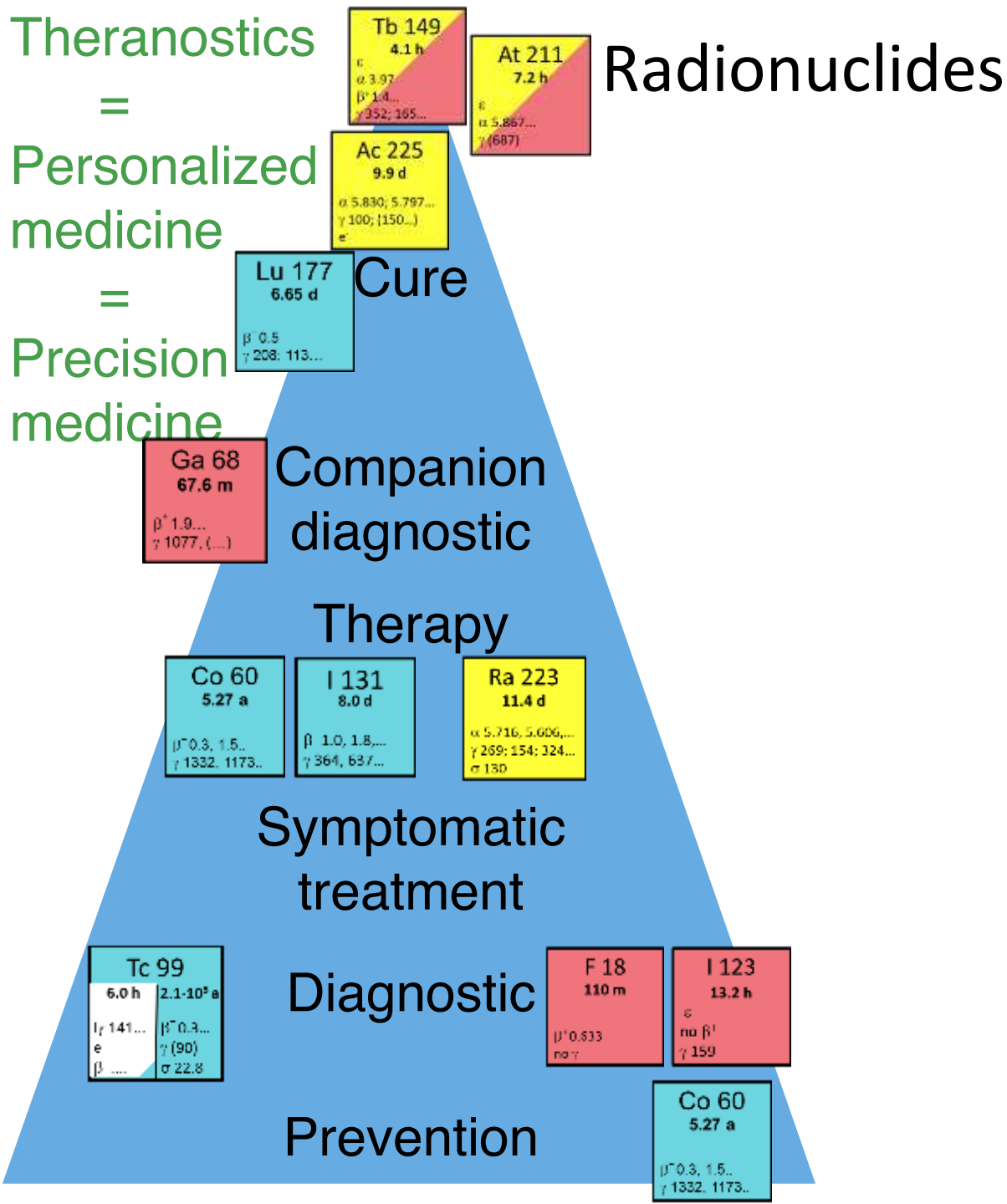
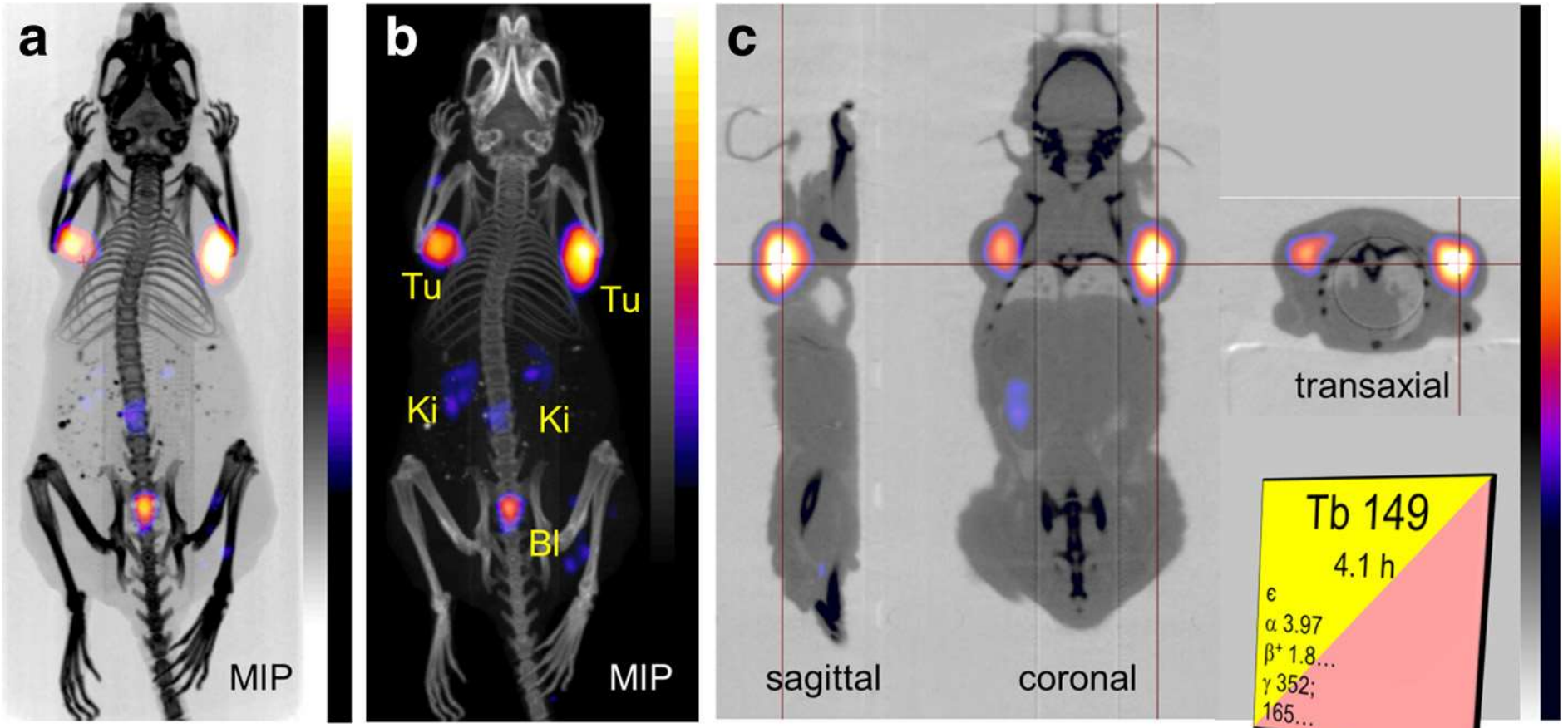
Precision medicine



Alpha-PET with ^{149}Tb



7 MBq ^{149}Tb-DOTANOC 2 h p.i.

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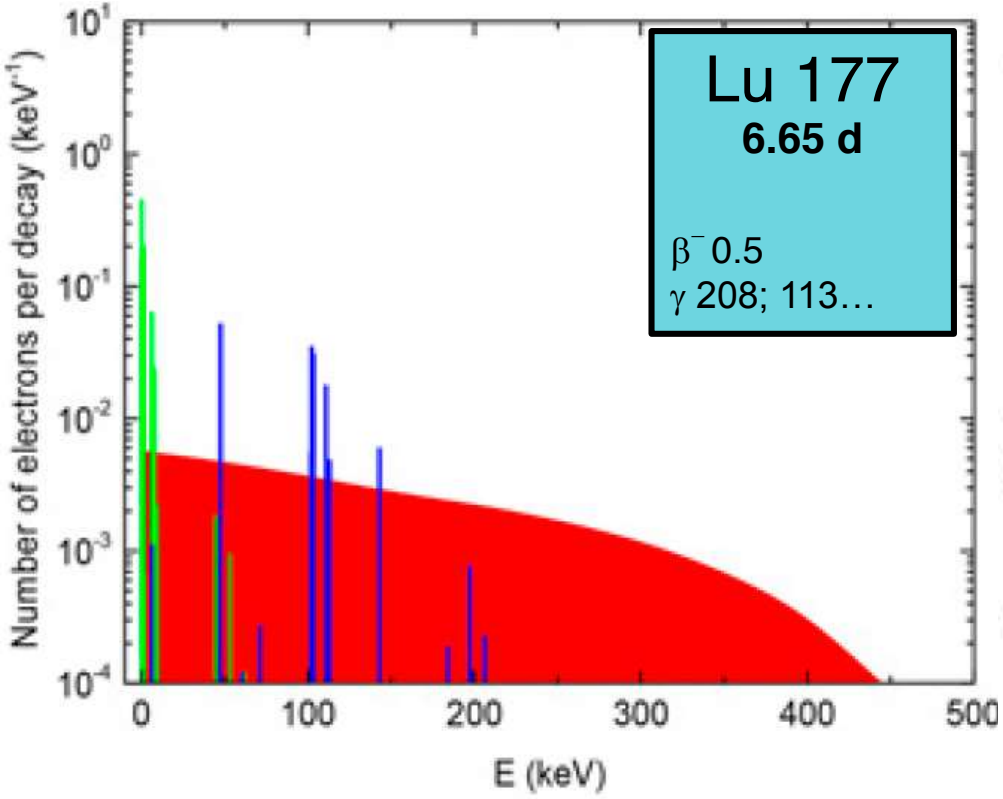
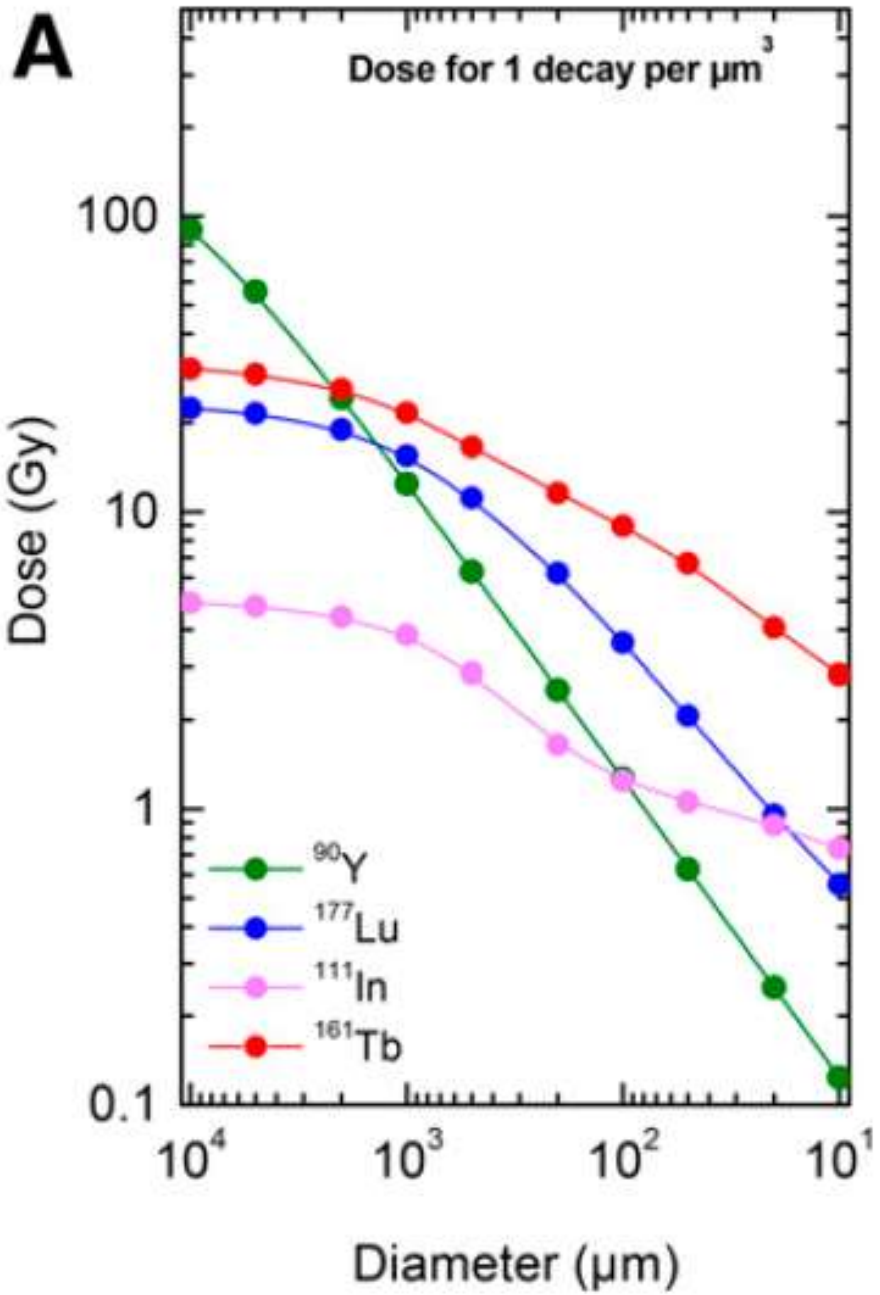
C. Müller et al. EJNMMI Radiopharm Chem 2016;1:5.

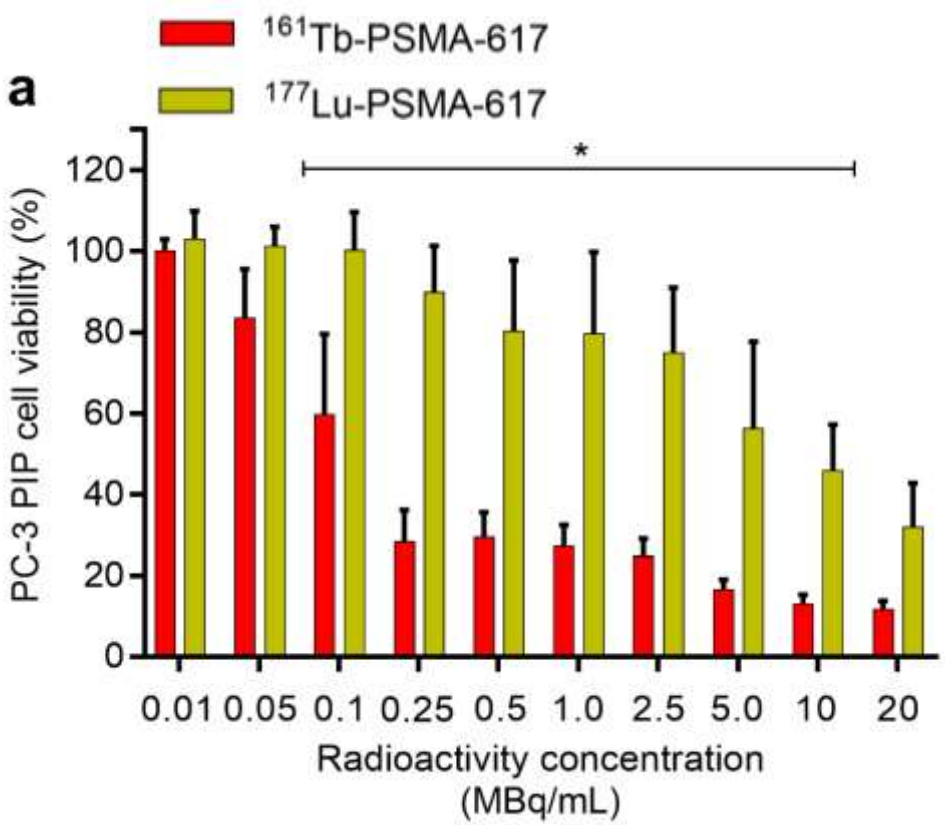
^{161}Tb versus ^{177}Lu

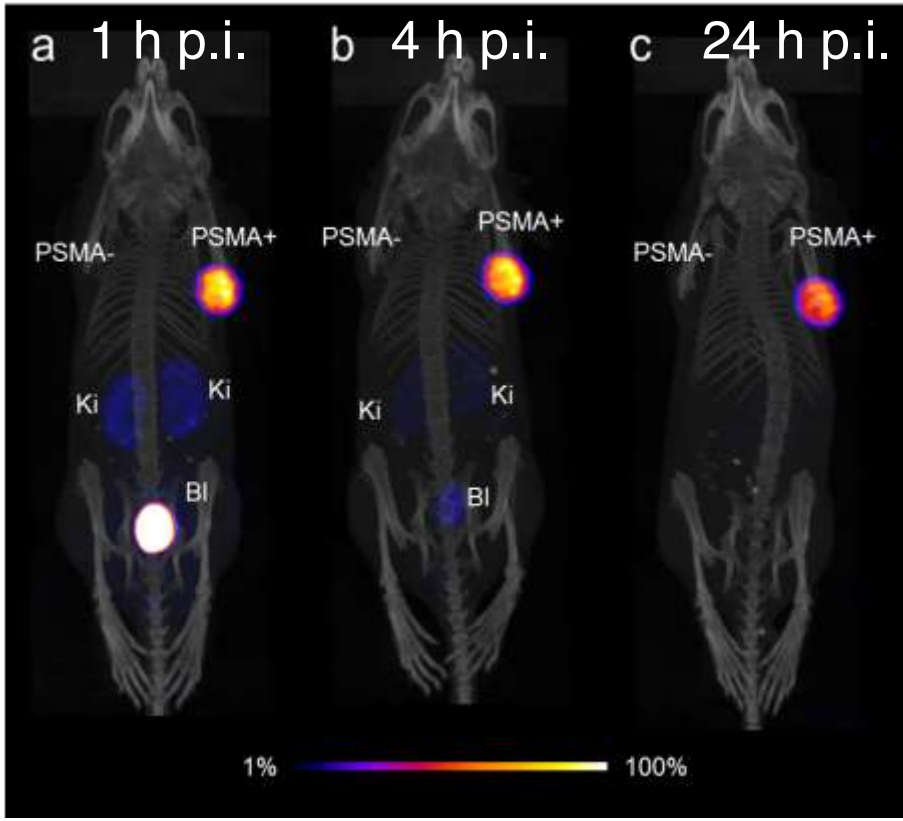




E. Hindié et al., J Nucl Med 2016;57:759.

Terbium-161 for PSMA-targeted radionuclide therapy of prostate cancer





C. Müller et al., Eur J Nucl Med Mol Imaging 2019;46:1919.

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UNIVERSITY OF GOTHENBURG

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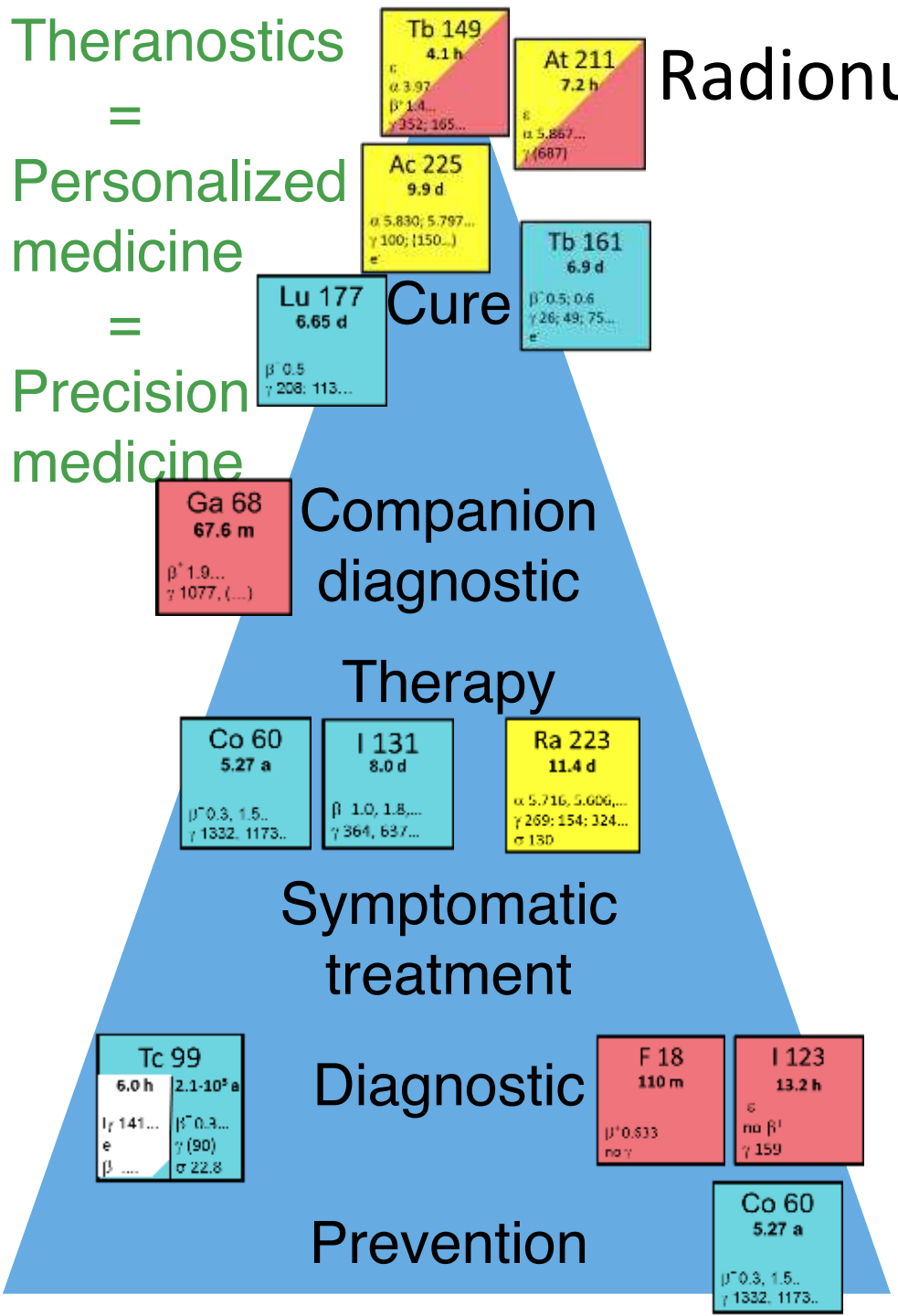
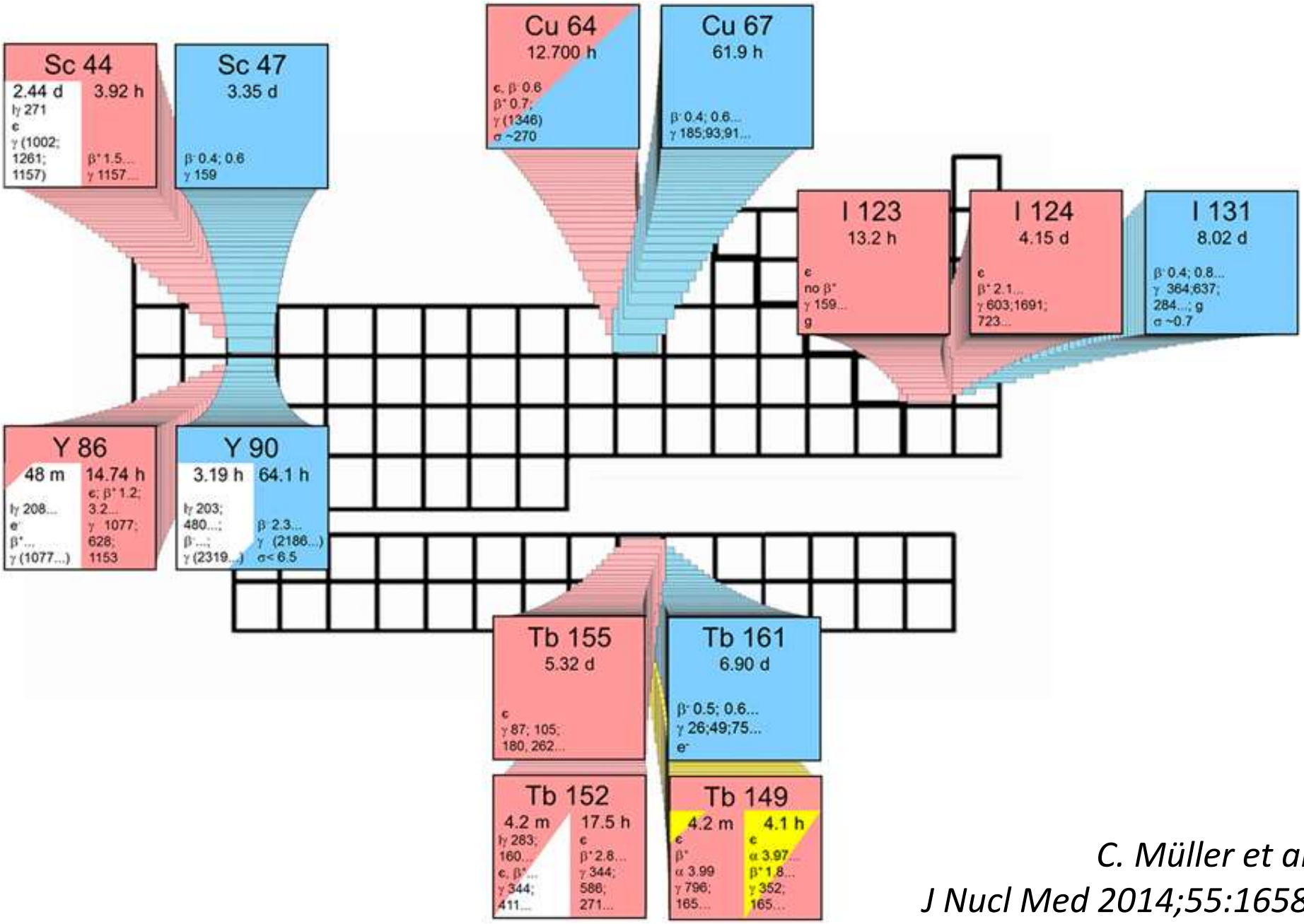


Radionuclides

Matched pairs for theranostics

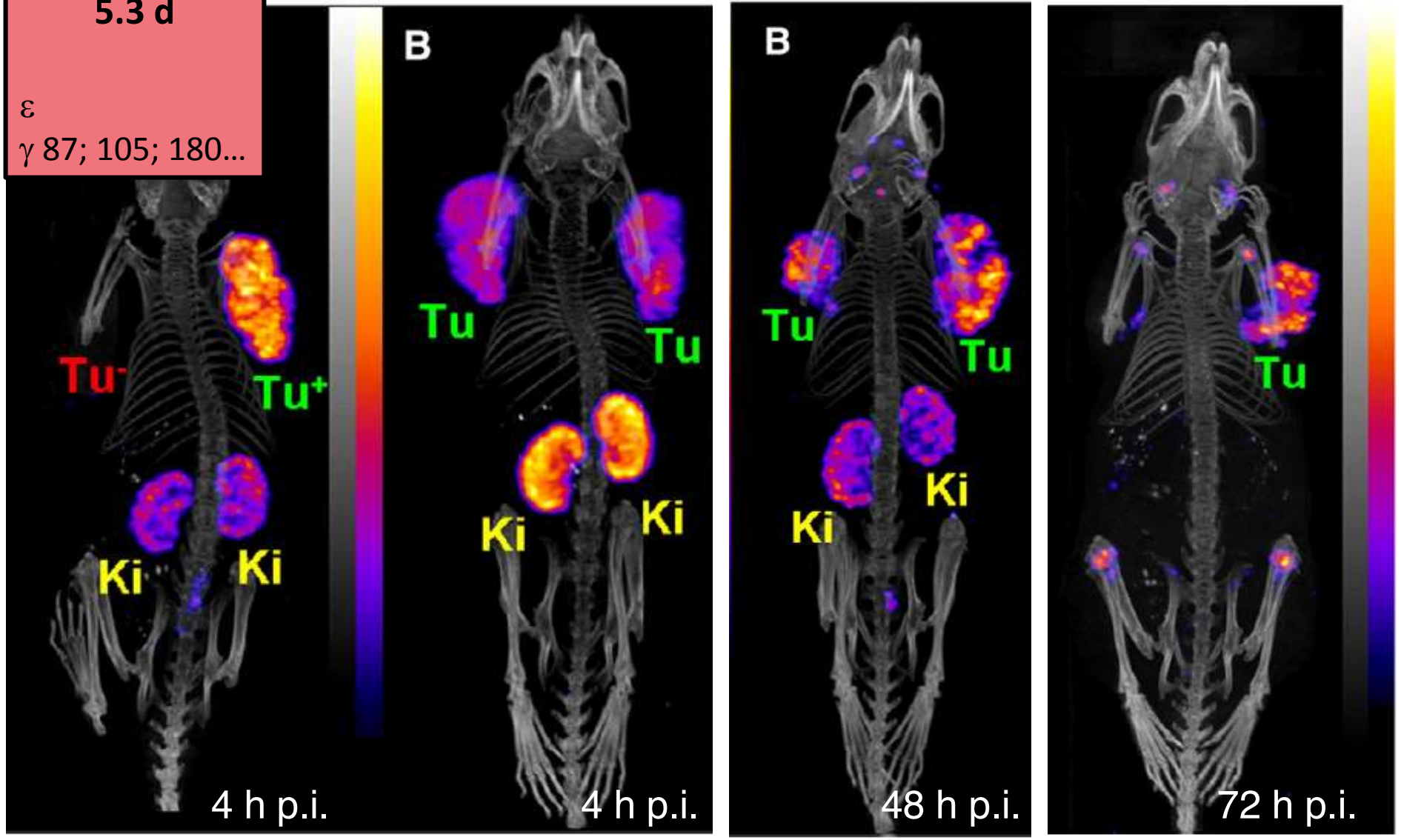


C. Müller et al.
J Nucl Med 2014;55:1658.

^{155}Tb for SPECT

Tb 155
5.3 d

ε
γ 87; 105; 180…



minigastrin
A431 tumor

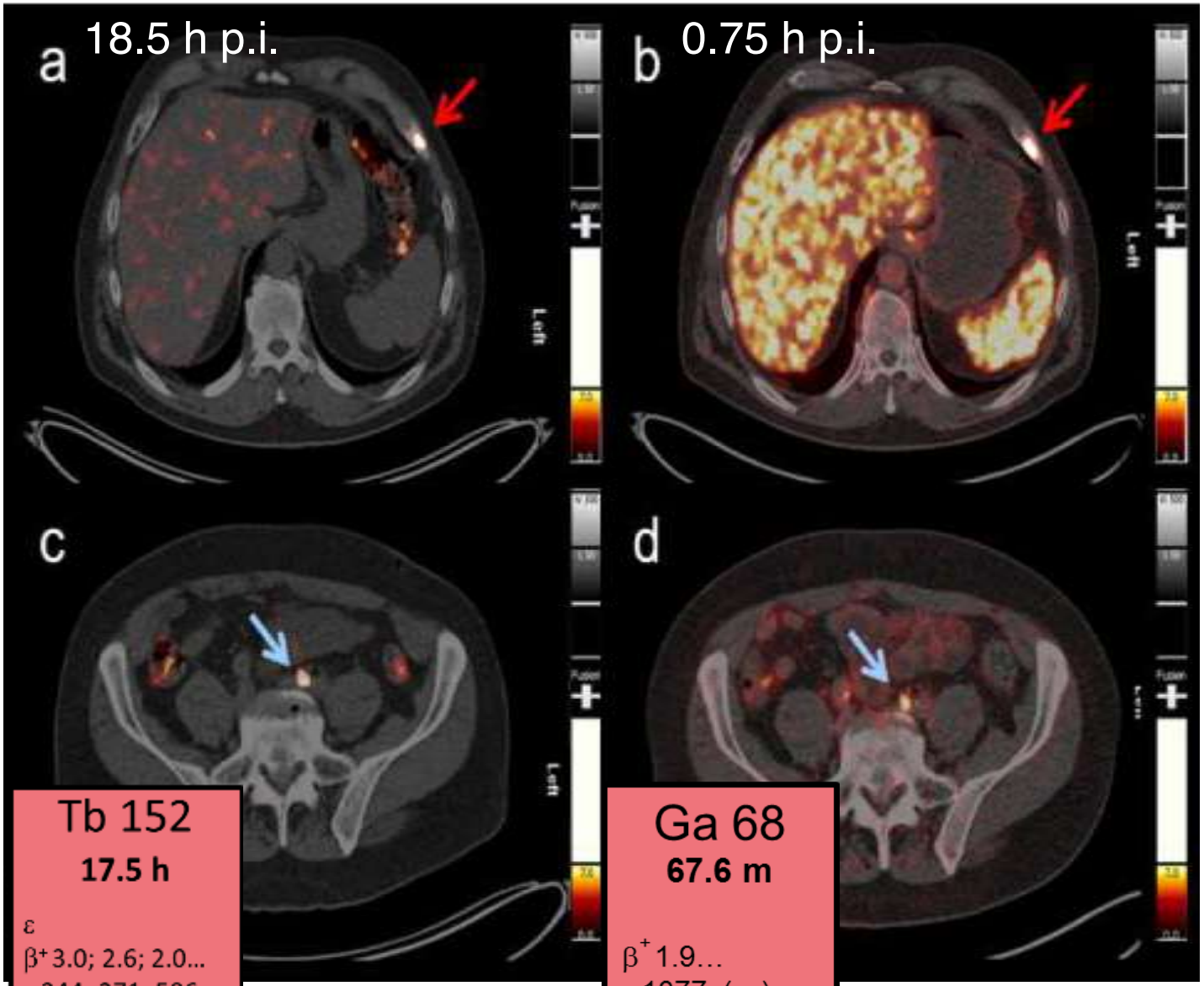
DOTATATE
A431 tumor

cm09
IGROV-1 tumor

chCE7
SKOV-3ip tumor

C. Müller et al. Nucl Med Biol 2014;41:e58.

First-in-human study with ^{152}Tb-PSMA-617



Zentralklinik Bad Berka

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C. Müller et al. EJNMMI Research 2019;9:68.

Terbium: the Swiss knife for nuclear medicine

Tb 155
5.3 d

ε
γ 87; 105; 180…
e^-

Tb 152
17.5 h

ε
β^+ 3.0; 2.6; 2.0…
γ 344; 271; 586…

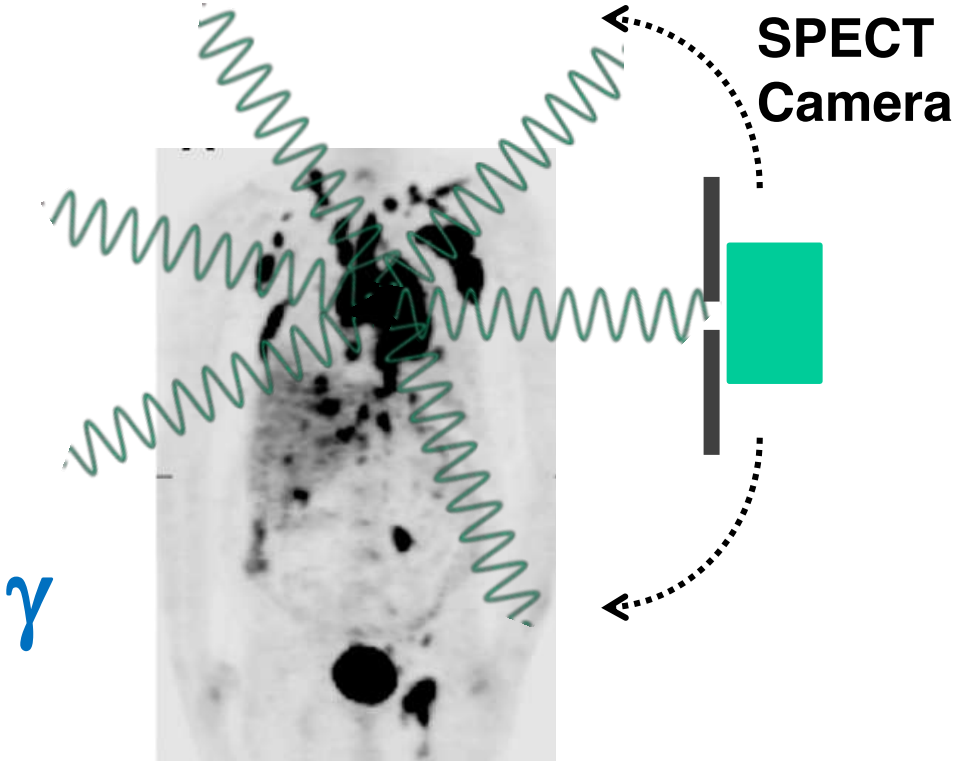
Tb 161
6.9 d

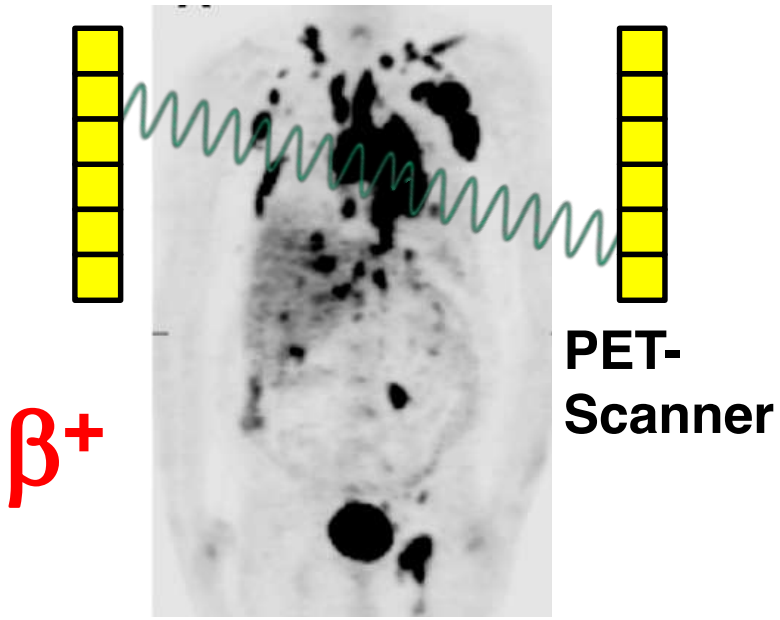
β^- 0.5; 0.6
γ 26; 49; 75…
e^-

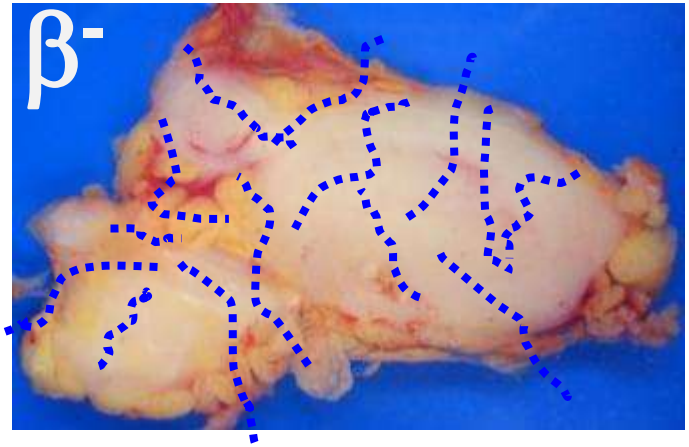
Tb 149
4.1 h

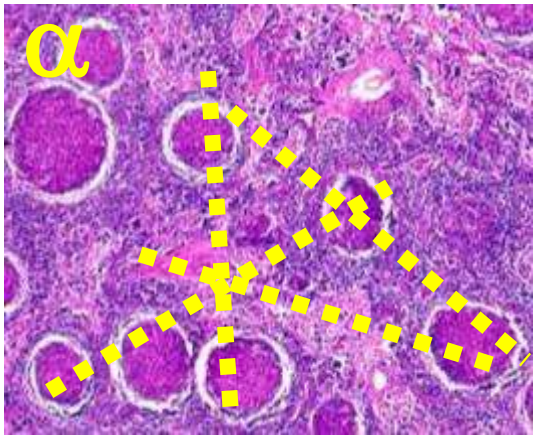
ε
α 3.97
β^+ 1.4…
γ 352; 165…

The Nuclear Medicine Alphabet

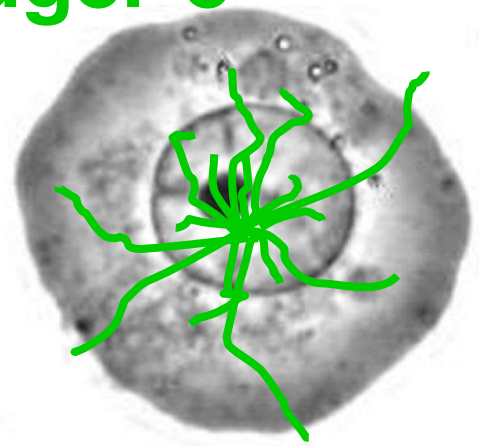




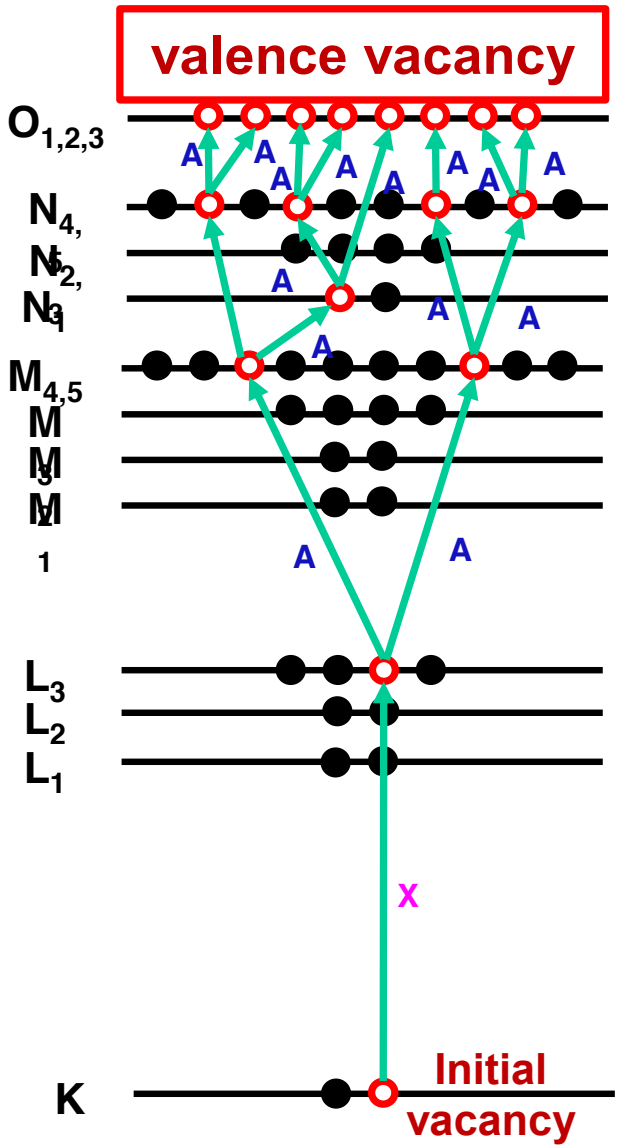




Auger-e-

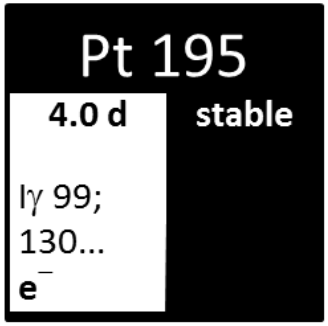


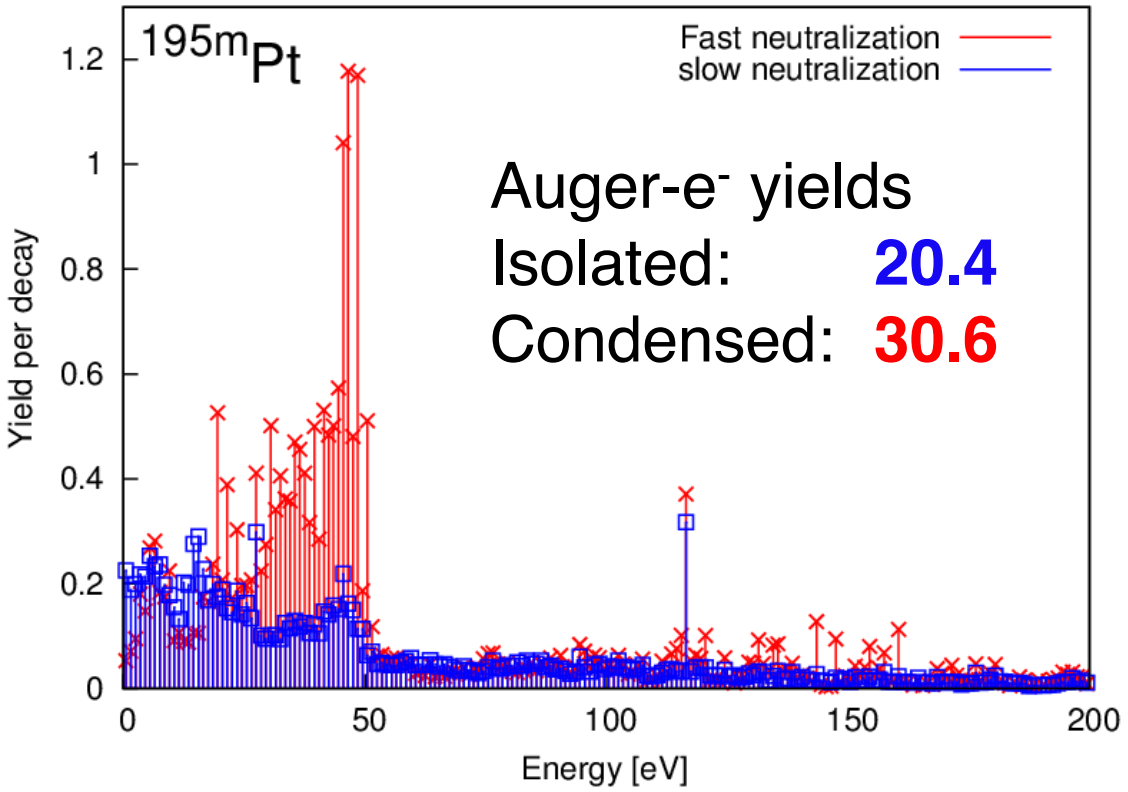
BrIccEmis: Simulation of Auger electron spectra



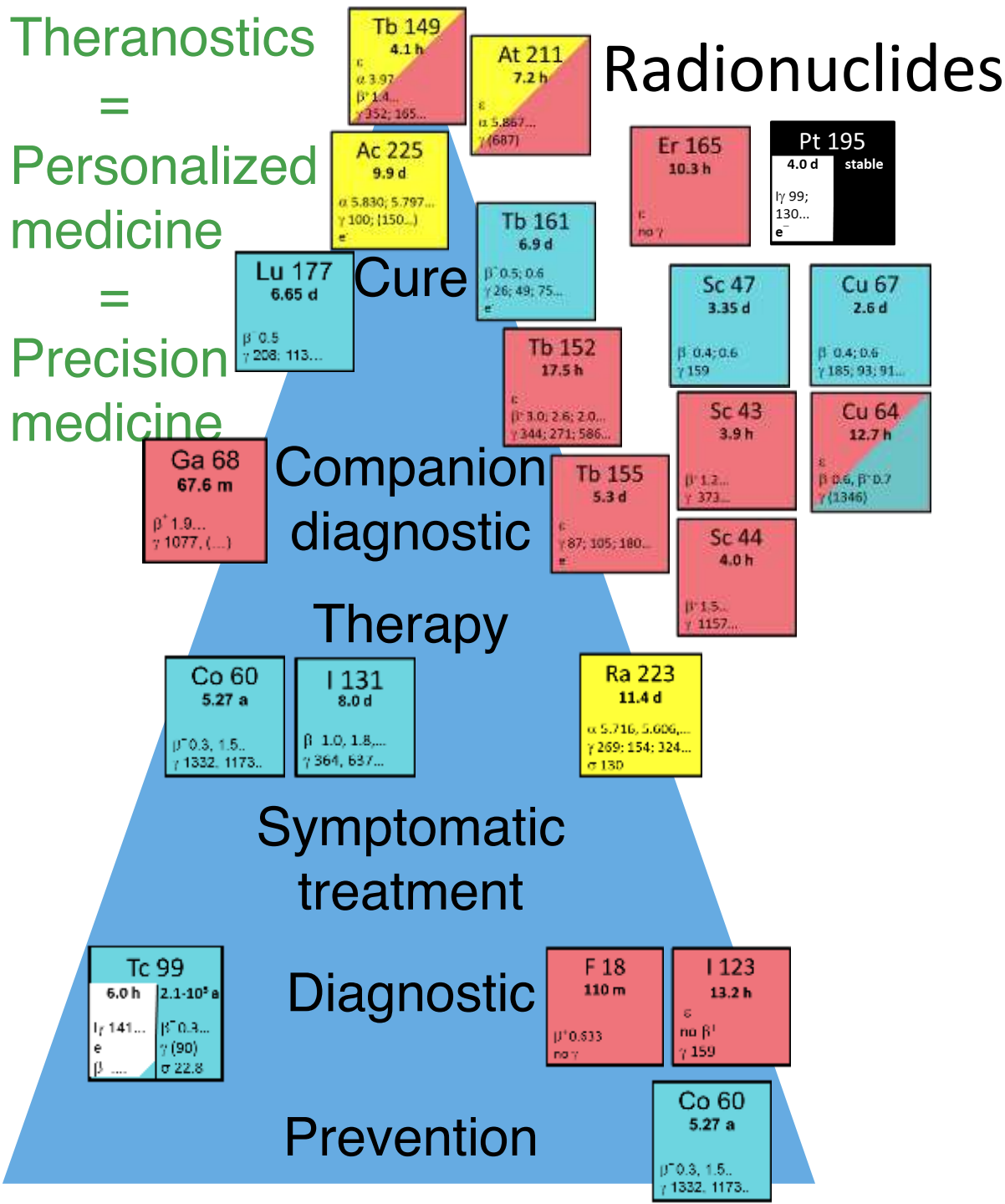
Two approaches:

1. No neutralization during Auger cascade **(slow)** isolated atom
2. Valence vacancy immediately neutralized **(fast)** condensed phase





Boon Quan Lee et al., Int J Radiat Biol 2016;92:641. and priv. comm.


Theranostics
=
Personalized medicine
=
Precision medicine
Radionuclides
Tb 149
4.1 h
α 3.97
β+ 1.4...
γ 352; 165...
At 211
7.2 h
ε
α 5.867...
γ (687)
Ac 225
9.9 d
α 5.830; 5.797...
γ 100; (150...)
e⁻
Er 165
10.3 h
ε
no γ
Pt 195
4.0 d
stable
Iγ 99; 130...
e⁻
Tb 161
6.9 d
β⁻ 0.5; 0.6
γ 26; 49; 75...
e⁻
Lu 177
6.65 d
β⁻ 0.5
γ 208; 113...
Cure
Sc 47
3.35 d
β⁻ 0.4; 0.6
γ 159
Cu 67
2.6 d
β⁻ 0.4; 0.6
γ 185; 93; 91...
Tb 152
17.5 h
ε
β+ 3.0; 2.6; 2.0...
γ 344; 271; 586...
Sc 43
3.9 h
β+ 1.2...
γ 373...
Cu 64
12.7 h
ε
β⁻ 0.6, β+ 0.7
γ (1346)
Ga 68
67.6 m
β+ 1.9...
γ 1077, (...)
Companion diagnostic
Tb 155
5.3 d
ε
γ 87; 105; 180...
e⁻
Sc 44
4.0 h
β+ 1.5...
γ 1157...
Therapy
Co 60
5.27 a
β⁻ 0.3, 1.5...
γ 1332, 1173...
I 131
8.0 d
β 1.0, 1.8,...
γ 364, 637...
Ra 223
11.4 d
α 5.716, 5.606,...
γ 269; 154; 324...
σ 130
Symptomatic treatment
Tc 99
6.0 h
Iγ 141...
e
β ....
2.1·10⁵ a
β⁻ 0.3...
γ (90)
σ 22.8
Diagnostic
F 18
110 m
β+ 0.633
no γ
I 123
13.2 h
ε
no β+
γ 159
Prevention
Co 60
5.27 a
β⁻ 0.3, 1.5...
γ 1332, 1173...

Prospects of targeted radionuclide therapies ?

2014	Algeta	⇒ Bayer	2.4 G$
2018	AAA	⇒ Novartis	3.9 G$
2018	Sirtex	⇒ CGE/CDH	1.4 G$
2019	Endocyte	⇒ Novartis	2.1 G$
2019	Blue Earth	⇒ Bracco	0.5 G$
2019	BTG	⇒ Boston Scientific	4.2 G$
Sum over 5 years			**14.5 G$**

Bayer HealthCare

NOVARTIS

远大健康

CGE HEALTHCARE

Boston Scientific

Advancing science for life™

SANOFI

oranomed

Theranostics

=

Personalized medicine

=

Precision medicine

Radionuclides

Cure

Companion diagnostic

Therapy

Symptomatic treatment

Diagnostic

Prevention

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α 3.97
β+ 1.4...
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α 5.830; 5.797...
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Pt 195
4.0 d | stable
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ε
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σ 130

Tc 99
6.0 h | 2.1·10⁵ a
Iγ 141...
e
β ....
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γ (90)
σ 22.8

F 18 110 m
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no γ

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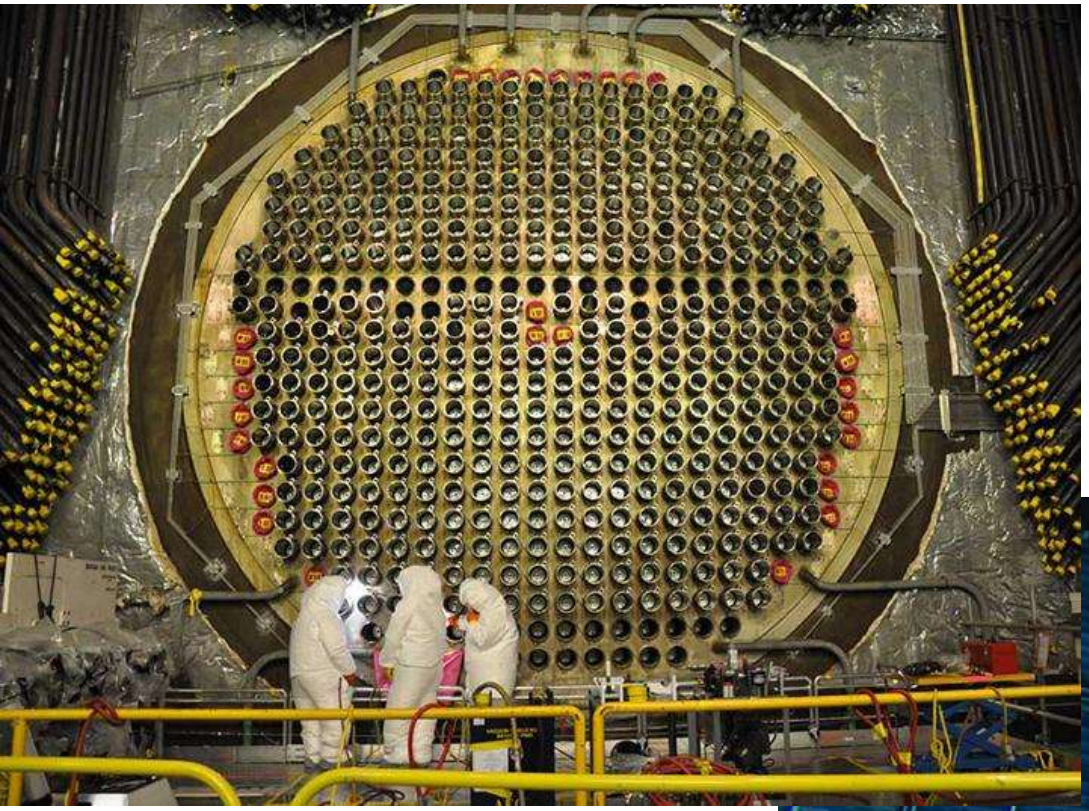
^{60}Co production in CANDU reactors

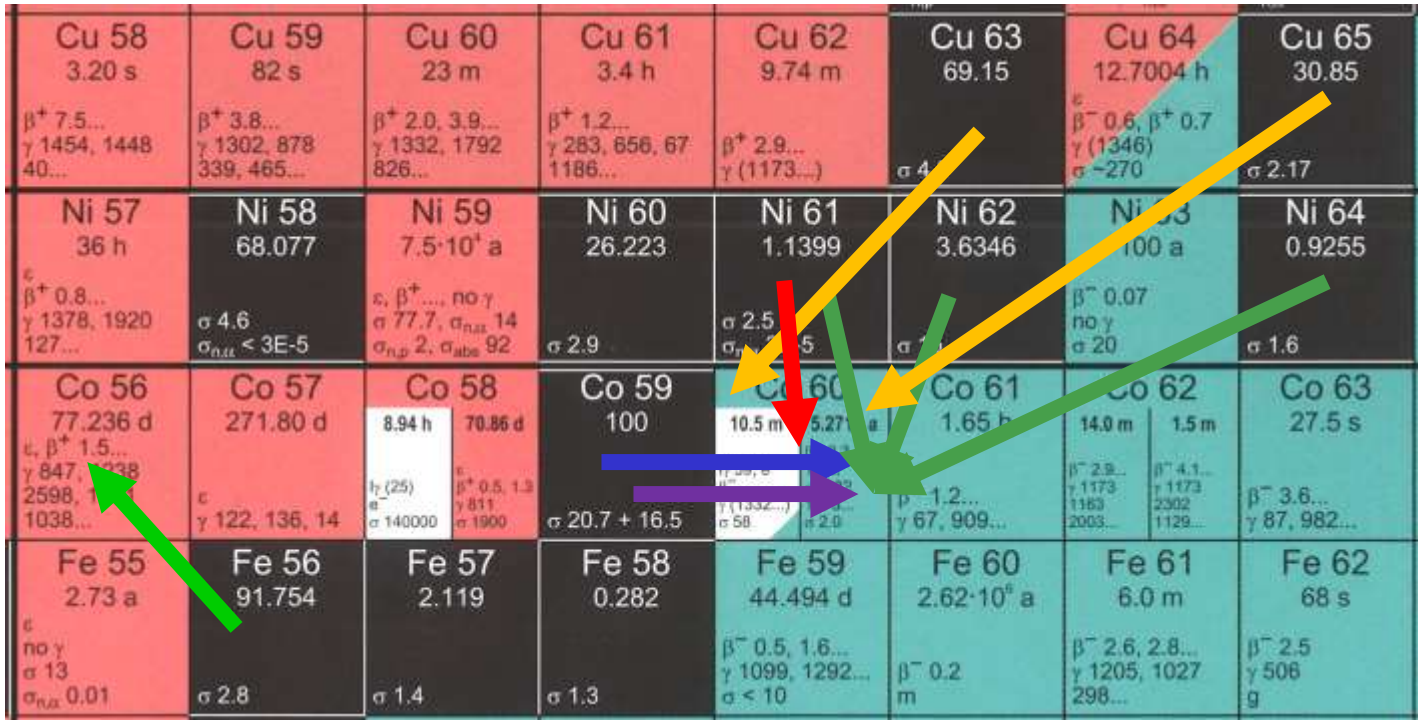


$\Phi \approx 1E14\ cm^{-2}s^{-1}$ over many m^2

"particle current" $\approx 16\ p\mu A/cm^2$

Total "particle current" ≈ 40 A
easily usable >> 100 mA

Different ways to ^{60}Co (as a theoretical case study)



^{59}Co(n,γ)^{60}Co: 1 n ≈ 1 atom ^{60}Co

^{59}Co(d,p)^{60}Co: 40 MeV d ≈ 1.2E-3 ^{60}Co

^{nat}Ni(p,*)^{60}Co: 30 MeV p < 1E-5 ^{60}Co

^{nat}Fe(p,*)^{56}Co: 30 MeV p ≈ 1.2E-3 ^{56}Co

^{nat}Cu(p,*)^{60}Co: 500 MeV p ≈ 0.015 ^{60}Co

^{nat}Ni(γ,*)^{60}Co: 30 MeV e^{-} < 1E-6 ^{60}Co

"160 mA" = 1 EBq ^{60}Co

25000x SPIRAL2 = 1 EBq ^{60}Co

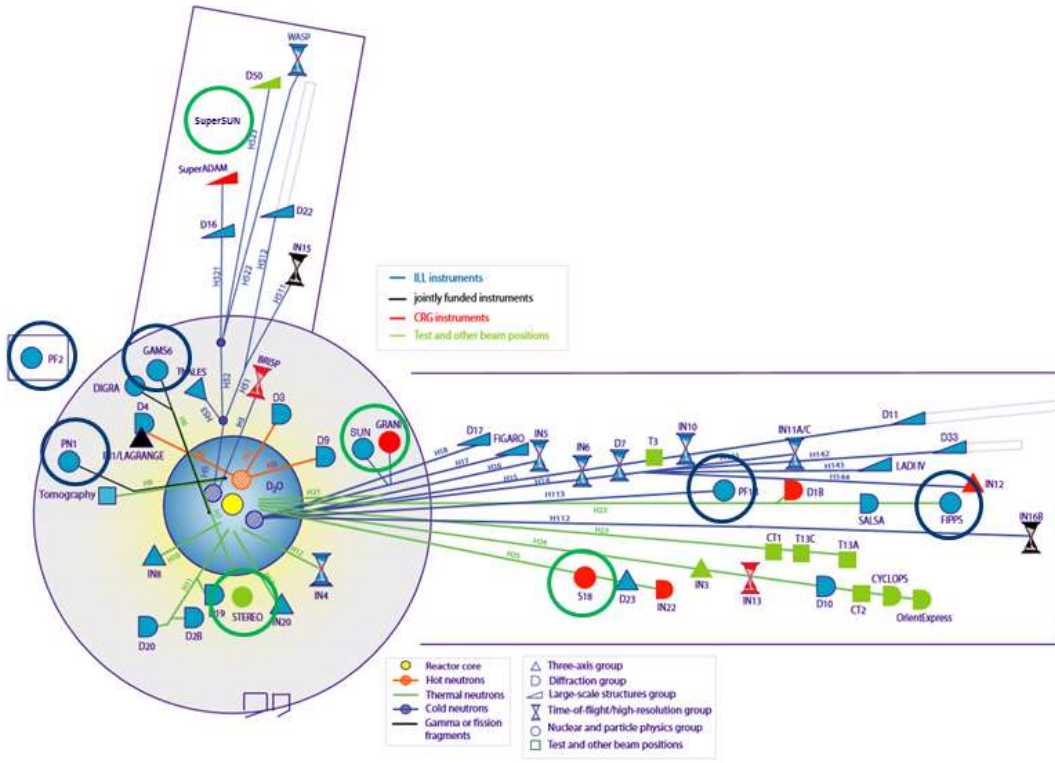
70000x TR30 = 1 EBq ^{60}Co equiv.

100000x main cyc. = 1 EBq ^{60}Co

^{177}Lu:
The “gold standard” for radionuclide therapy

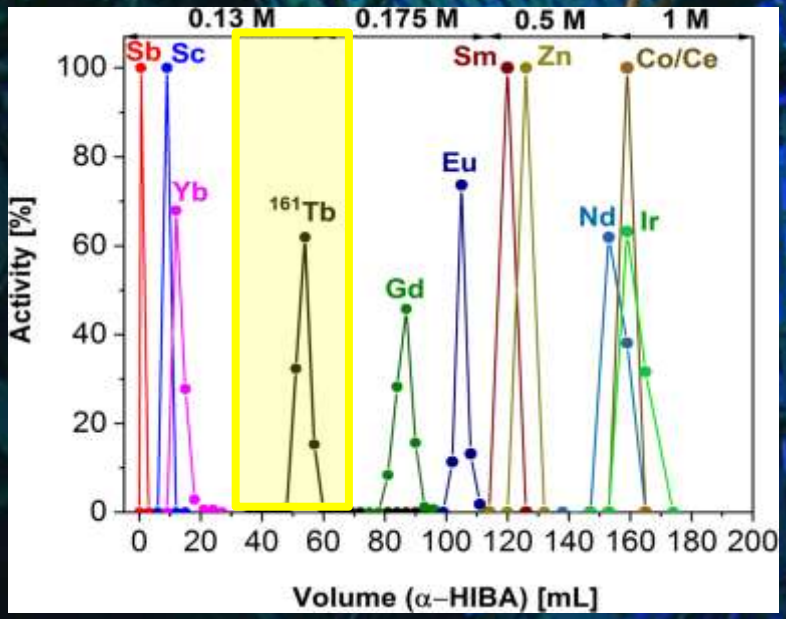
Institut Laue-Langevin 2018:

- ≈ **1600** scientific users at ILL
- ≈ **4000** patients get ^{177}Lu from ILL



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

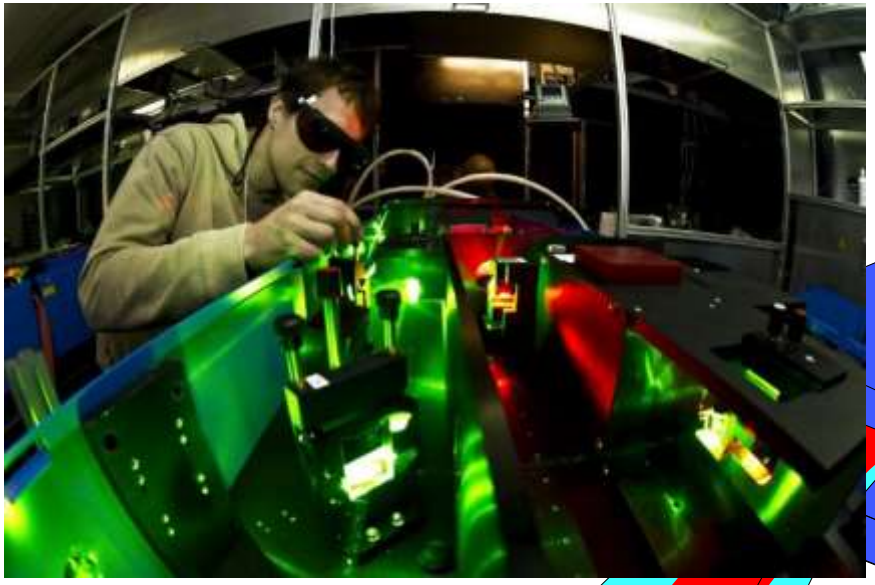
Dy 160 2.329 σ 60 $\sigma_{n,\alpha}$ <0.0003	Dy 161 18.889 σ 600 $\sigma_{n,\alpha}$ <1E-6	Dy 162 25.475 σ 170	Dy 163 24.896 σ 120 $\sigma_{n,\alpha}$ <2E-5	Dy 164 28.260 σ 1610 + 1040
Tb 159 100 σ 23.2	Tb 160 72.3 d β⁻ 0.6; 1.7.... γ 879; 299; 966... σ 570	Tb 161 6.90 d β⁻ 0.5; 0... γ 26; 49; ... e⁻	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 at ILL & Necsa, chemical separation at PSI

N. Gracheva et al., EJNMMI Radiopharm Chem 2019;4:12.

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



radioactive ion beams

Efficient parallel operation

HRS setup

ISOLTRAP

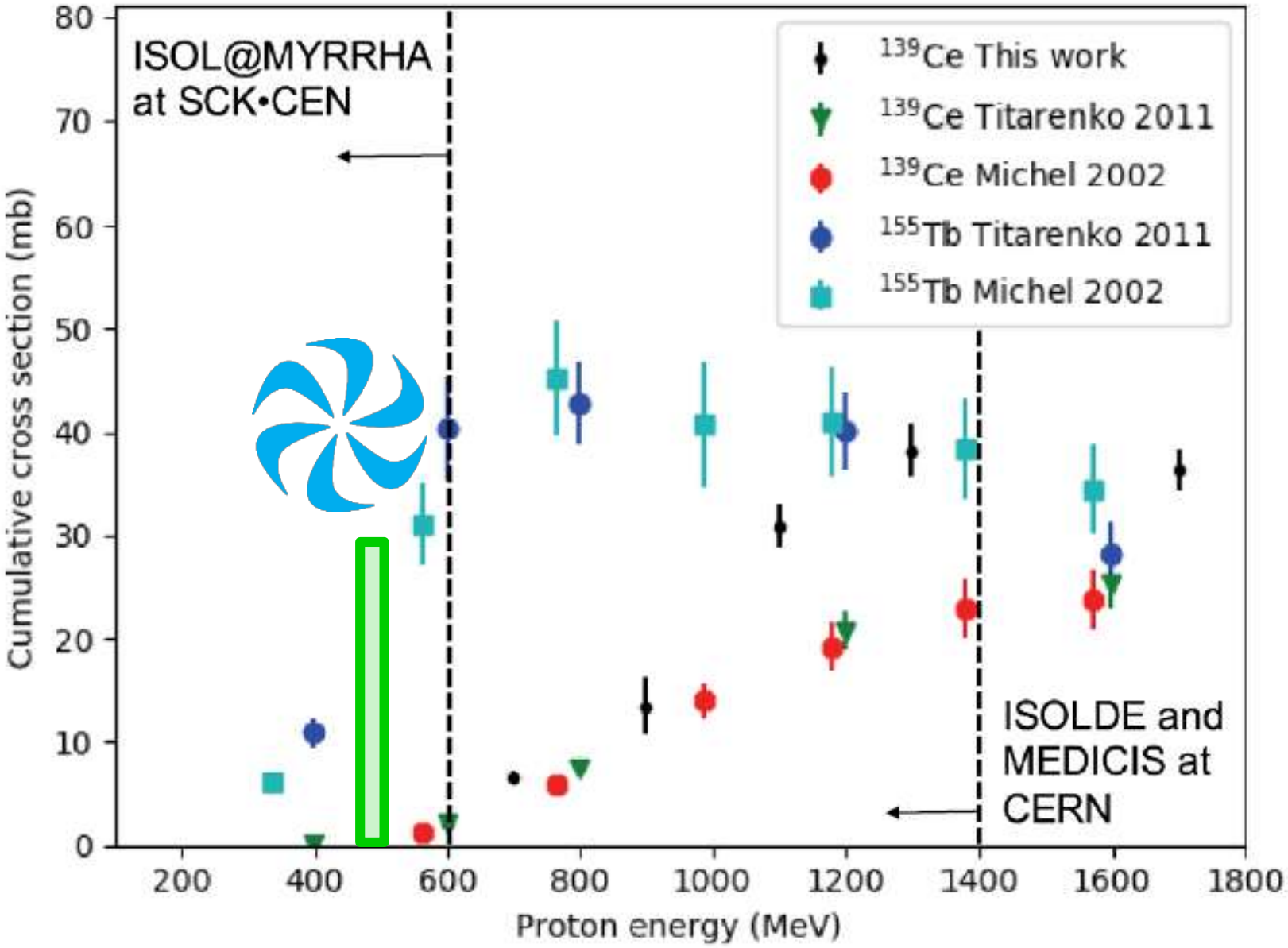
^{152}Tb

^{149}Tb

^{155}Tb

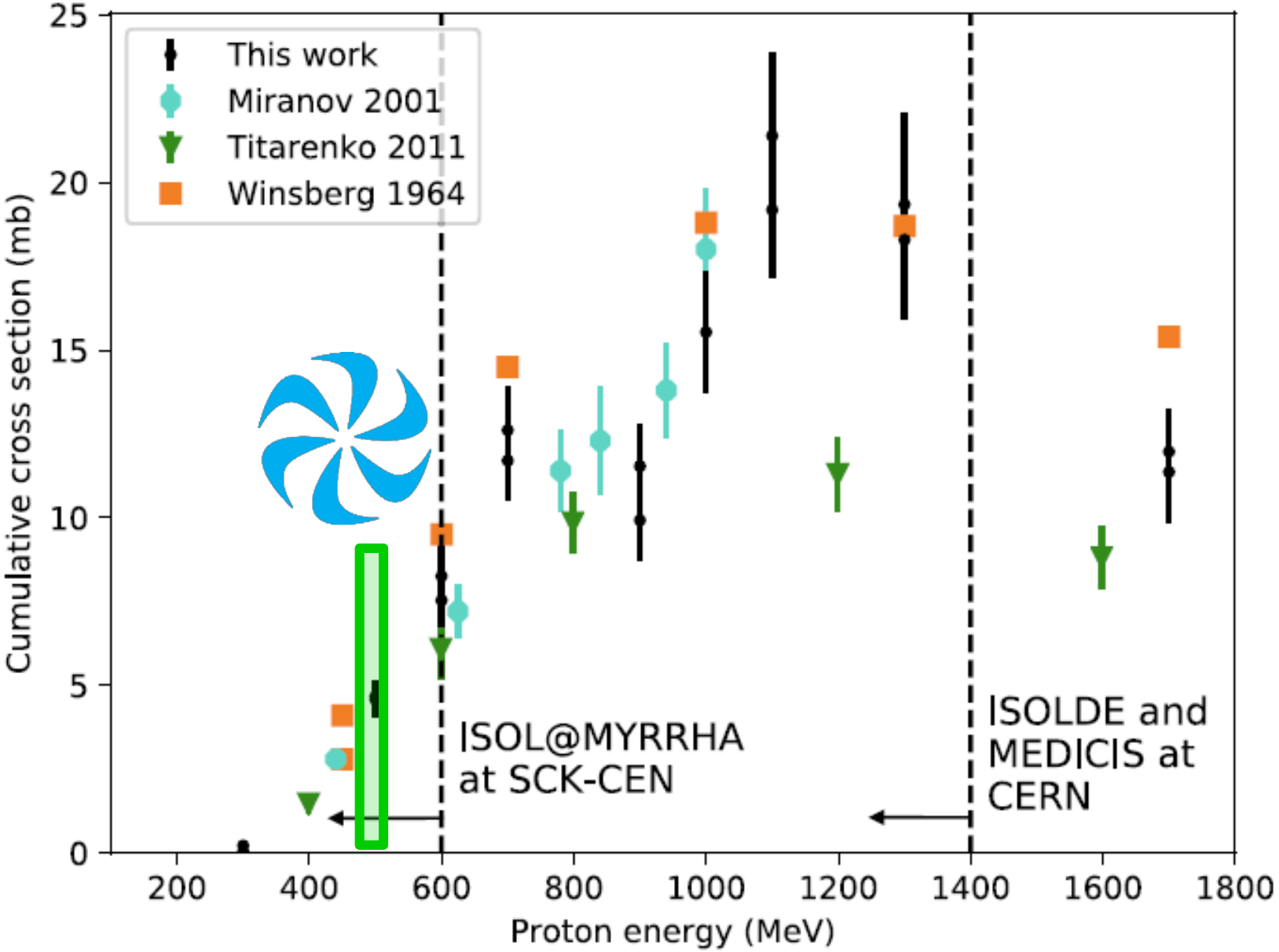
a very useful beam dump !

Spallation cross-sections: ^{155}Tb vs. ^{139}Ce



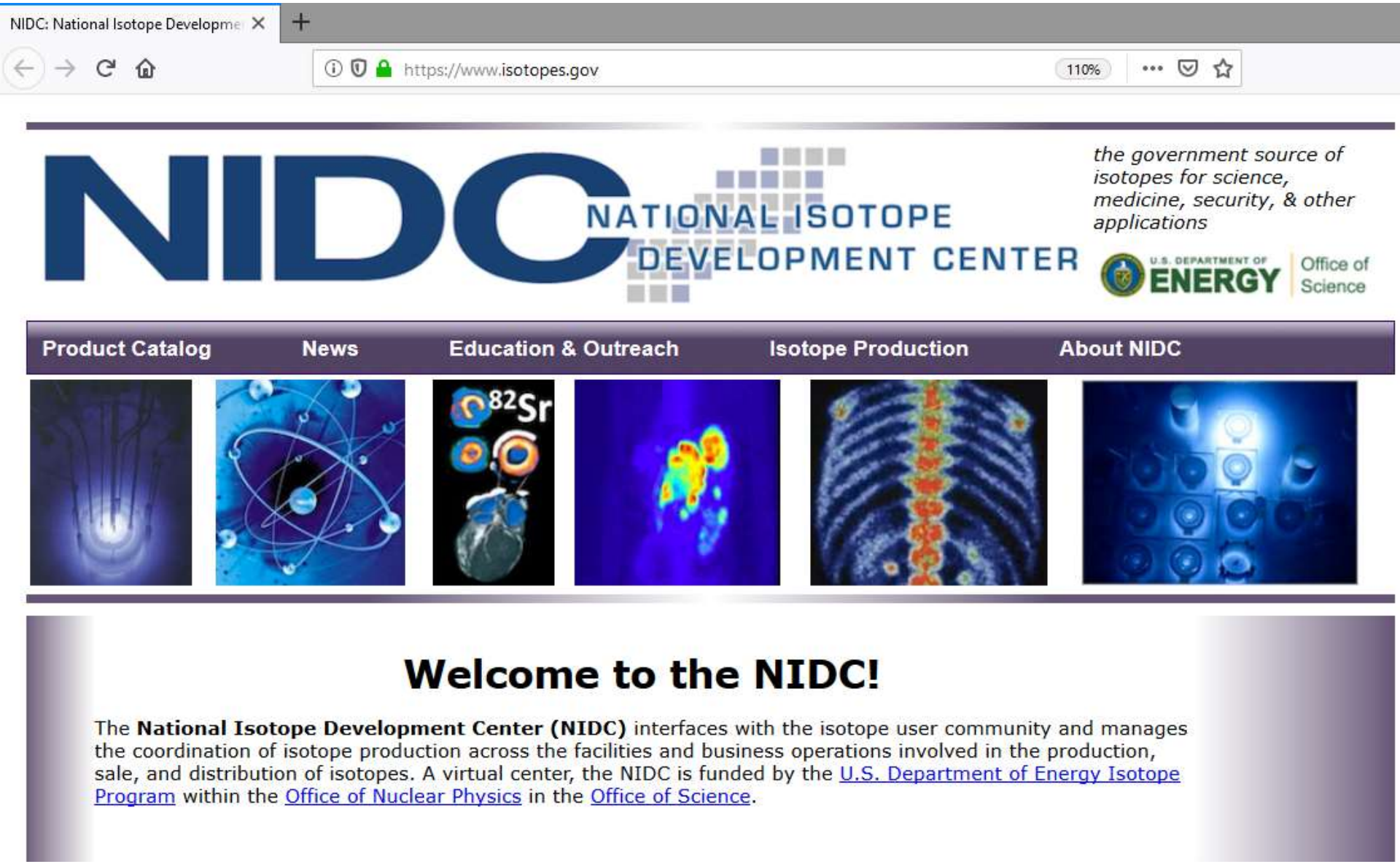
H Verhoeven et al, Nucl Instrum Meth 2020;B463:327.

Spallation cross-sections: ^{149}Tb vs. ^{133}Ce

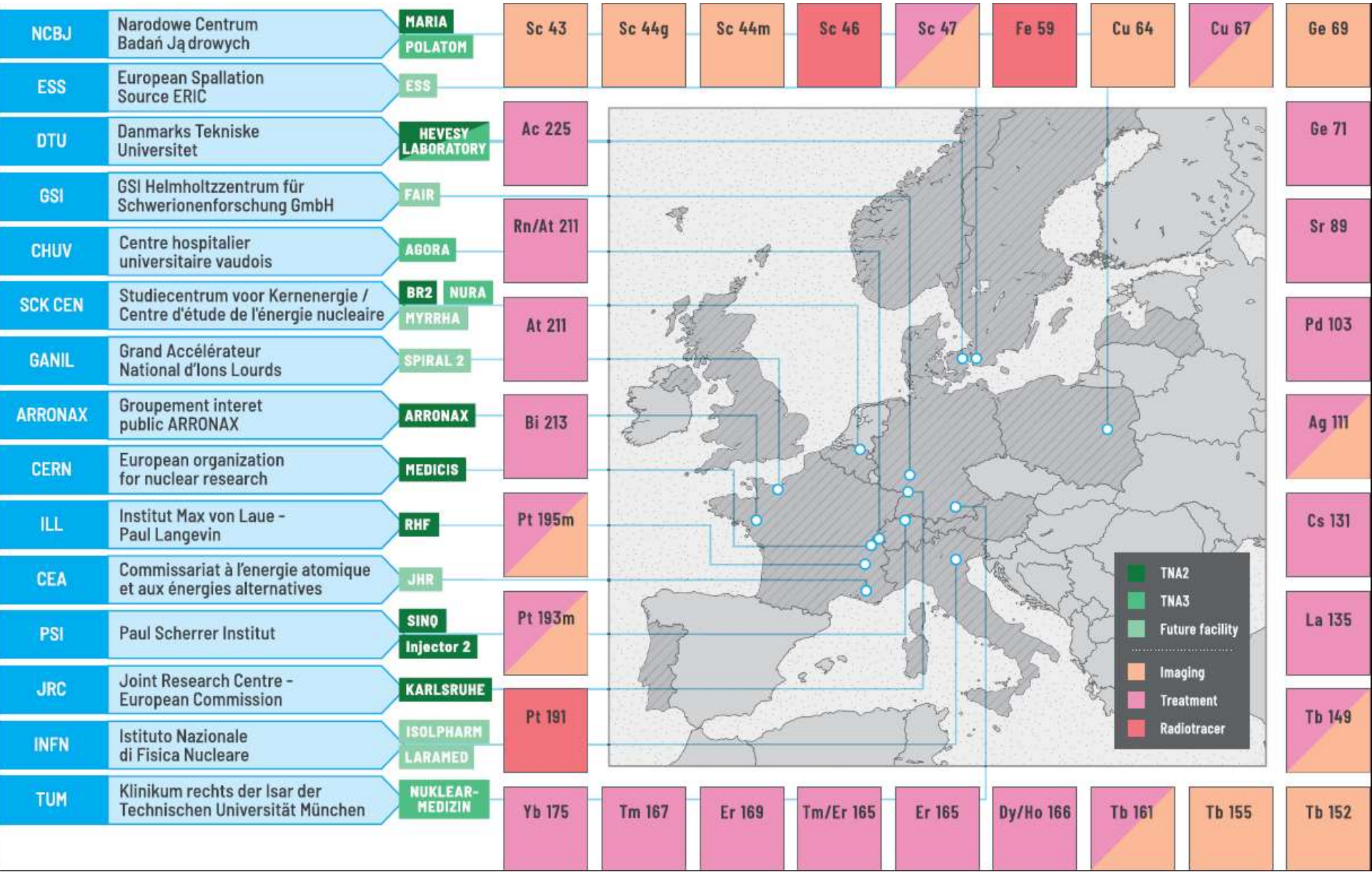


H Verhoeven et al, Nucl Instrum Meth 2020;B463:327.

A great model: the US DOE Isotope Program



Proposed EU project PRISMAP: **PR**oduction of high purity **I**sotopes by mass **S**eparation for **M**edical **Ap**plication



Summary and Outlook

- Targeted Radionuclide Therapies (TRT) are transforming nuclear medicine
- Bright future for Theranostics, in particular in oncology
- NP research infrastructures can play an important role for supply of EMERGING and UNCONVENTIONAL radionuclides ($^{149/152/155/161}$Tb, ^{211}At, ^{67}Cu, $^{193m/195m}$Pt, …)
- but medical applications using these radionuclides must be developed in parallel
- Research infrastructures are NOT competitive in production of “industrial” radionuclides
- PRISMAP: a European Isotope Development Center !

Specific ideas/wishes for TRIUMF

1. Logic choices for ISAC:

- Tb isotopes and other n-deficient lanthanides (Auger)
- ^{225}Ac, ^{211}Rn/^{211}At
- regular harvesting of R&D isotopes
- needs shielded collection position(s)!

2. Prospects for ARIEL

- ^{226}Ra(γ,n)^{225}Ra(β^-)^{225}Ac, Zn(γ,p)^{67}Cu..

3. Alpha beams (30-40 MeV)

- for production of ^{211}At, ^{43}Sc, ^{117m}Sn, ^{195m}Pt, ^{193m}Pt, etc.
- NO ^{4}He beams in Canada: cyclotron or LINAC prototype?

4. Synergies with laser spec., hyperfine interactions

- fundamental spectroscopy of At-molecules
- TDPAC for chelator/labelling development (cf. β-NMR)