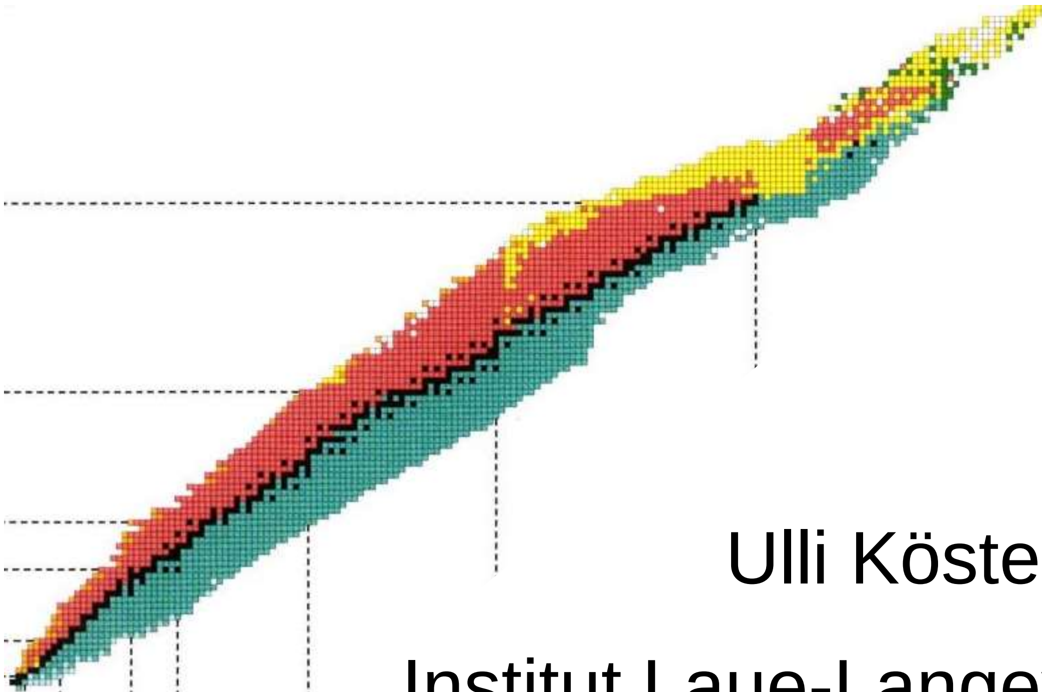
ENSAR2-RITMI activities for improved supply of theranostic nuclides



Ulli Köster

Institut Laue-Langevin & UGA
Grenoble, France

NEUTRONS FOR SOCIETY

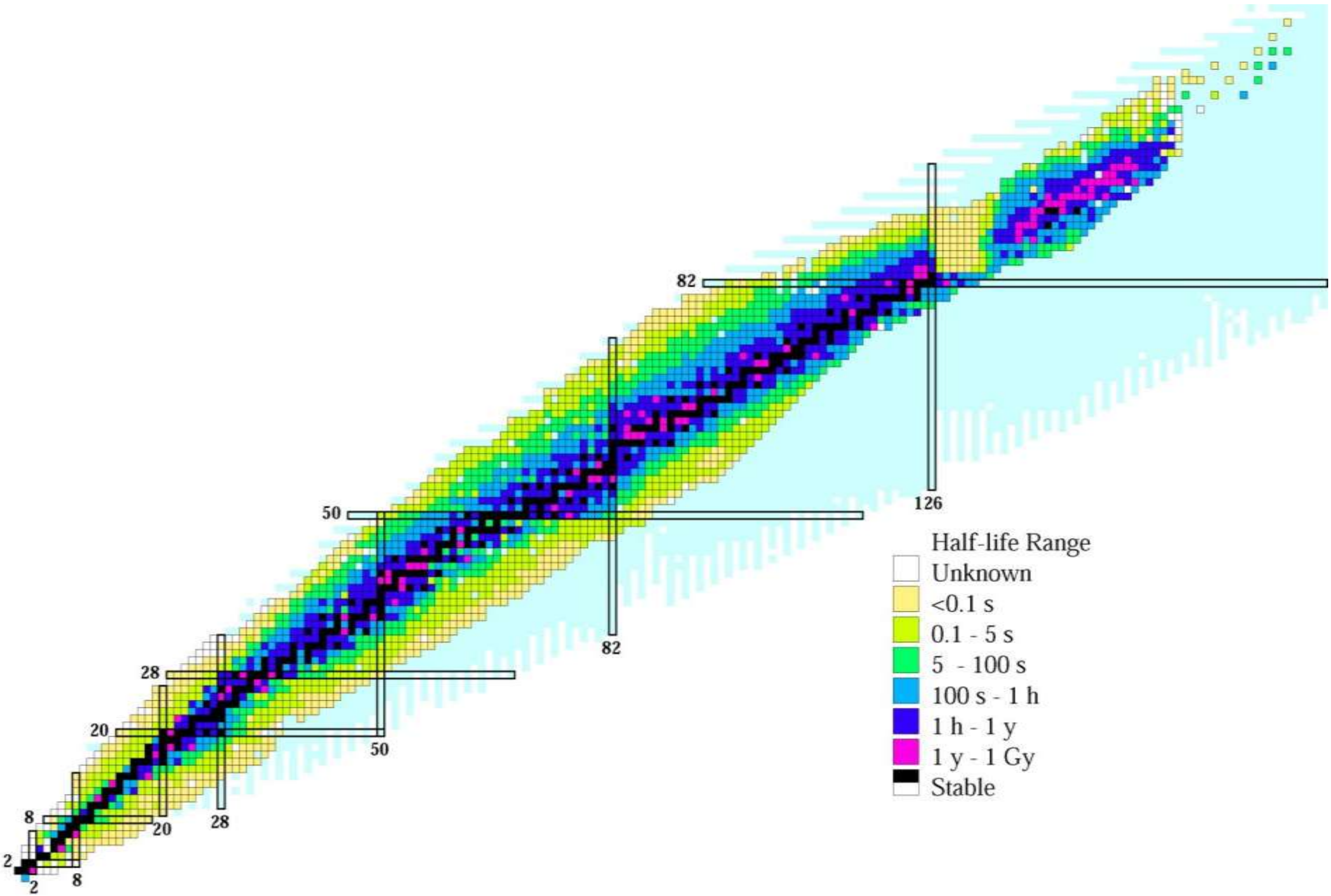
ENSAR2

UNIVERSITÉ Grenoble Alpes

Different medical disciplines and professions

Physician	medical doctor (MD)
Radiology	uses X-rays (CT) or MRI for imaging
Radiation therapy	uses closed radioactive sources or electron/Bremsstrahlung beams or hadron beams for irradiation
Nuclear medicine	uses open radioactive sources for imaging or therapy
Technologist	maintains instruments, places patients
Medical physics	calculates and measures doses
Radiochemist	prepares radioisotopes for nuclear medicine
Radiopharmacist	prepares injectable radiolabeled molecules

Nuclear physicist perspective

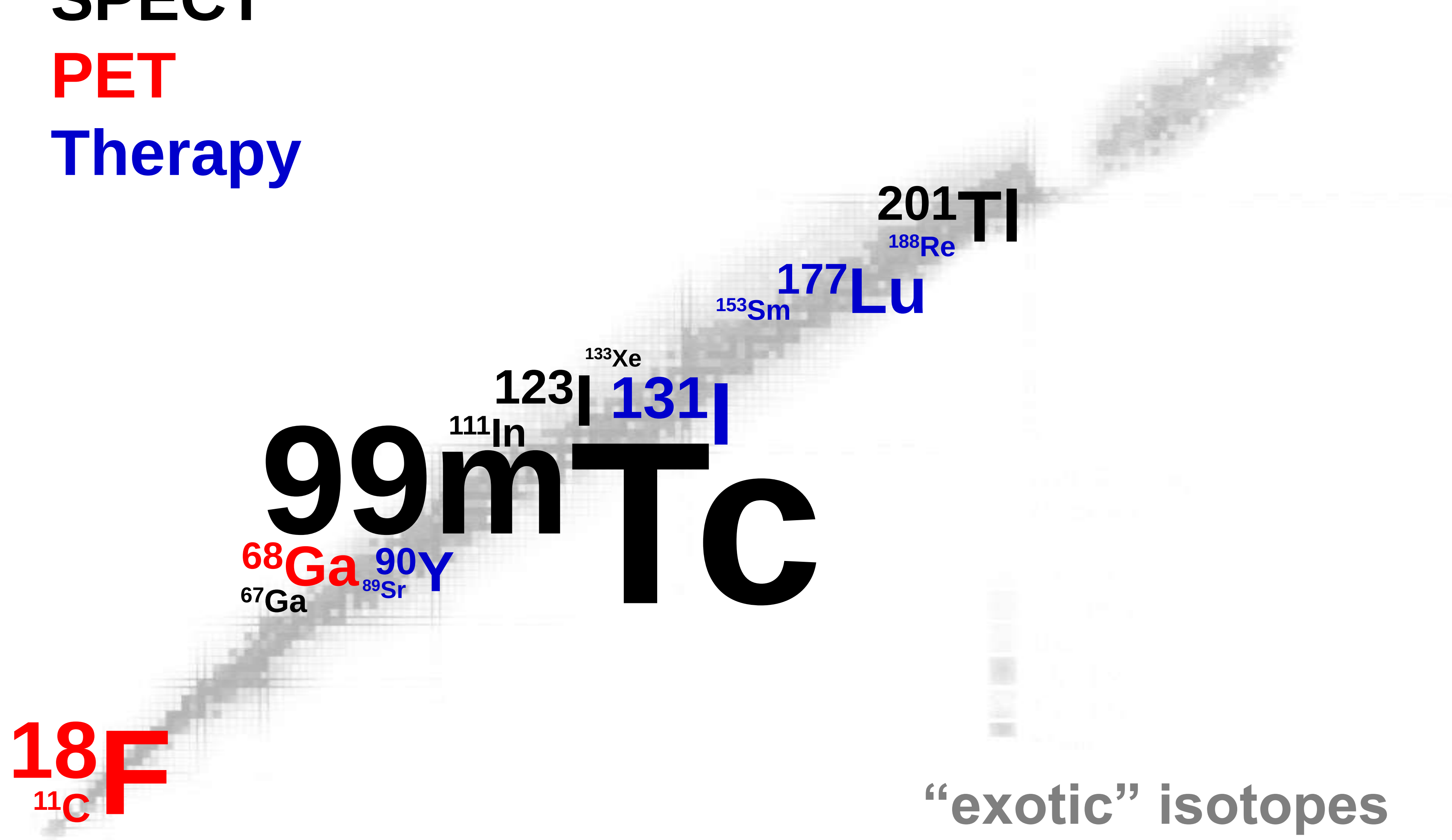


Nuclear medicine perspective

SPECT

PET

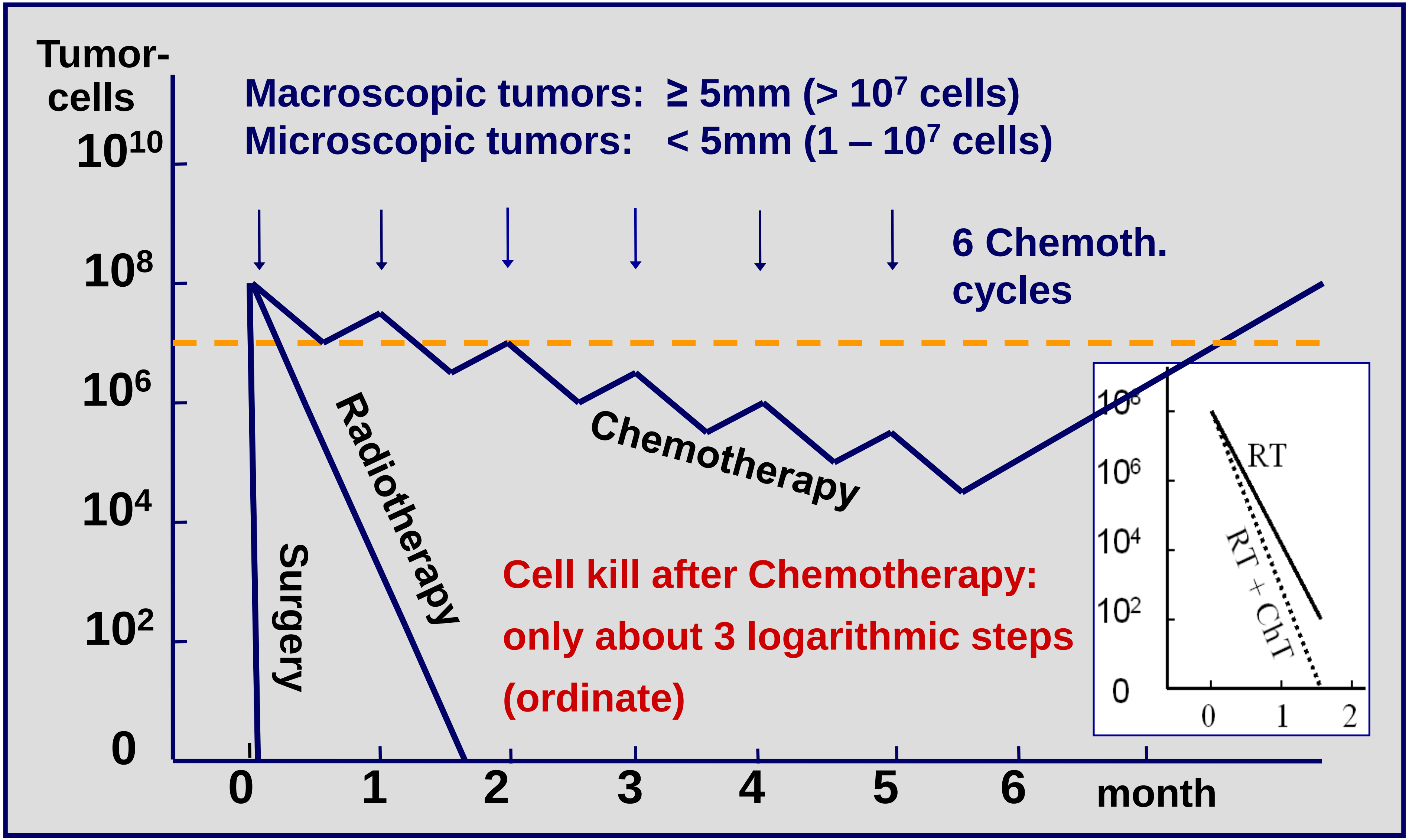
Therapy



From diagnostics

to therapy

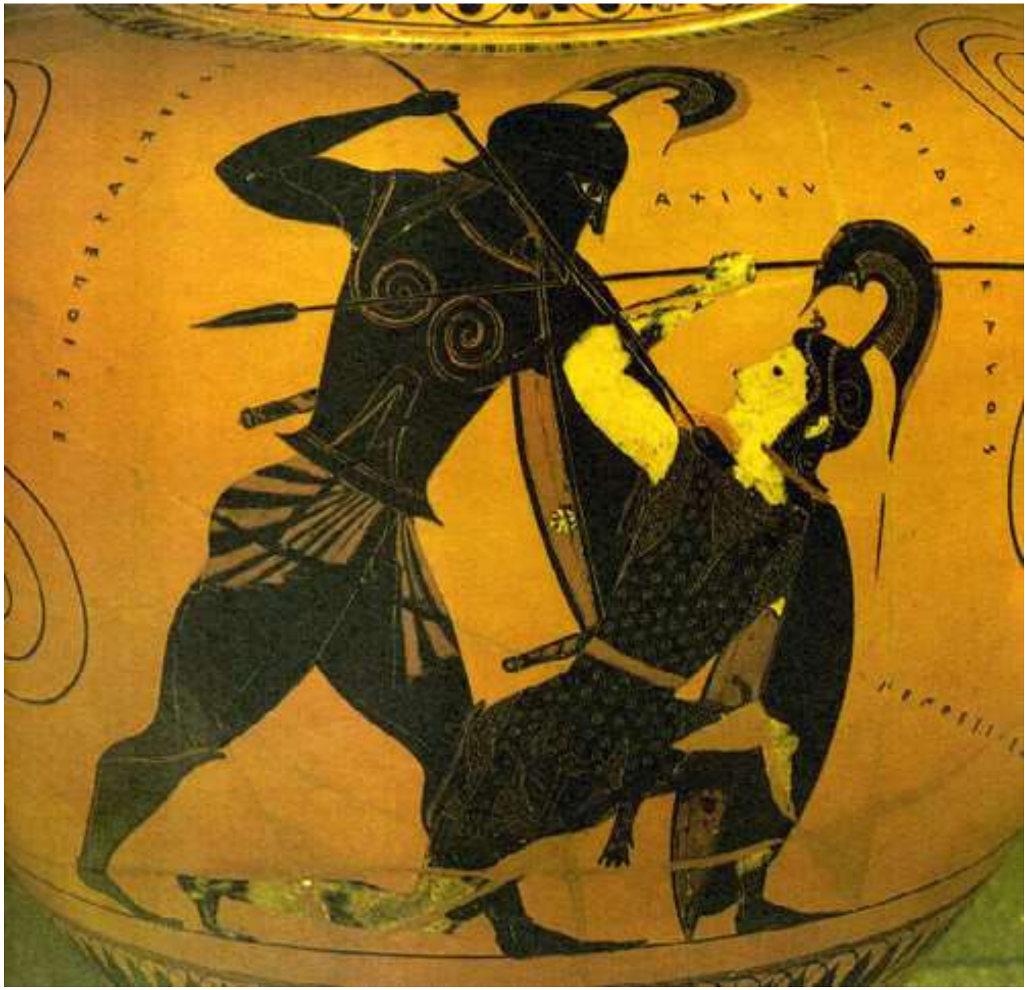
Comparison of Cancer Therapies



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

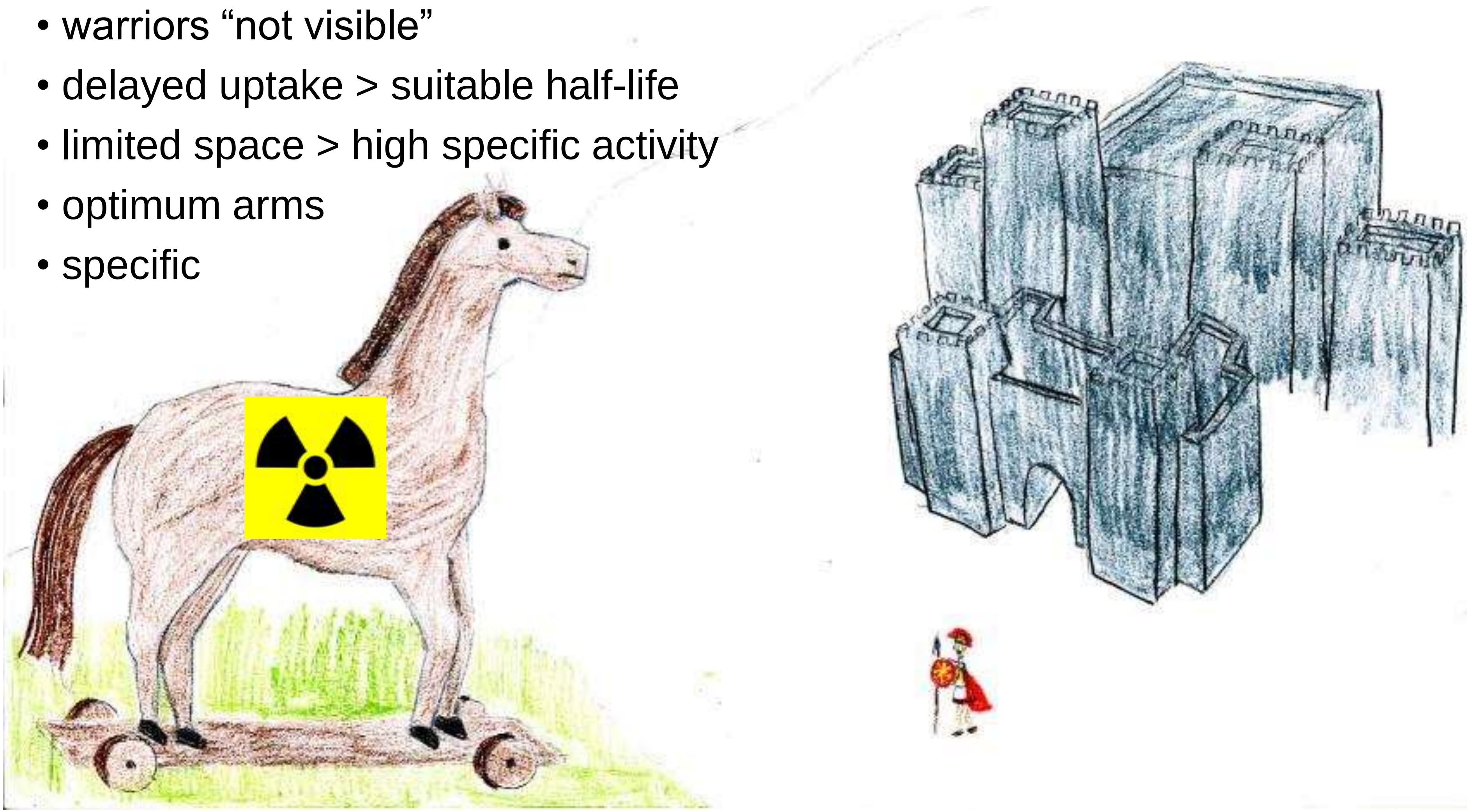
Question: How to treat such patients?

Learning from history

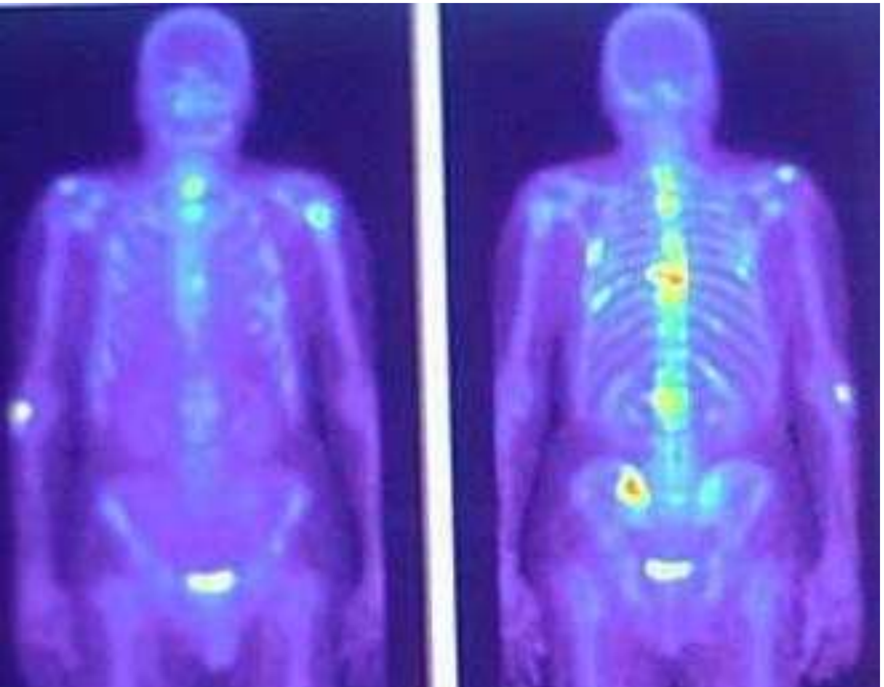


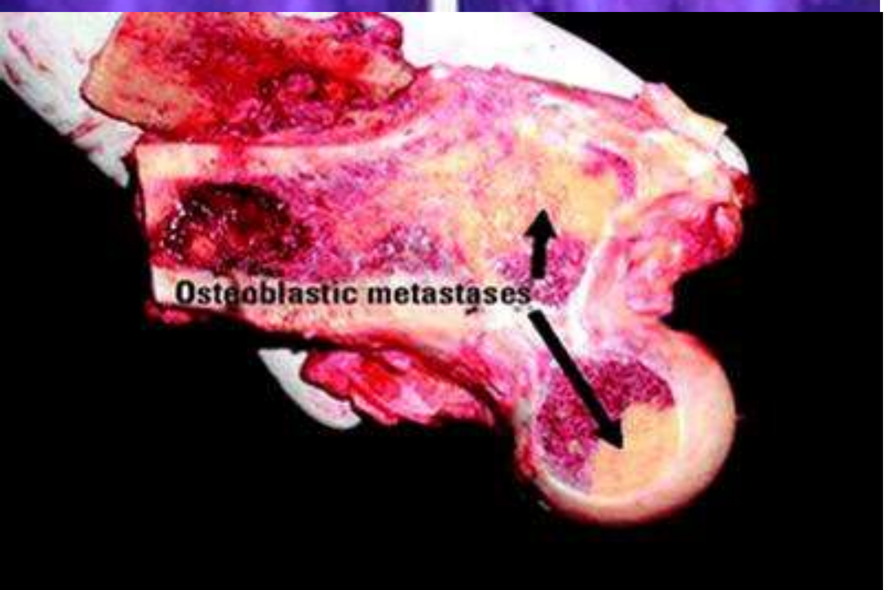
The principle of targeted therapies

- “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

Imaging

^{99m}Tc-MDP for SPECT

$^{18}F^-$ for PET

Therapy

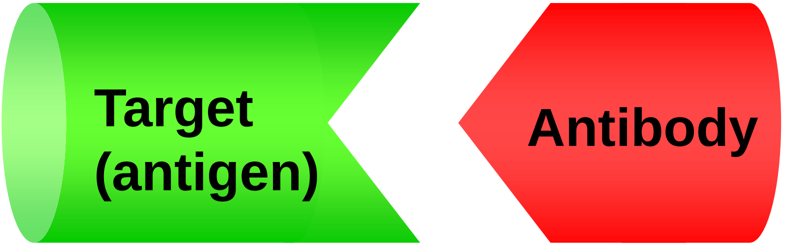
^{153}Sm-EDTMP (*Quadramet*)

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

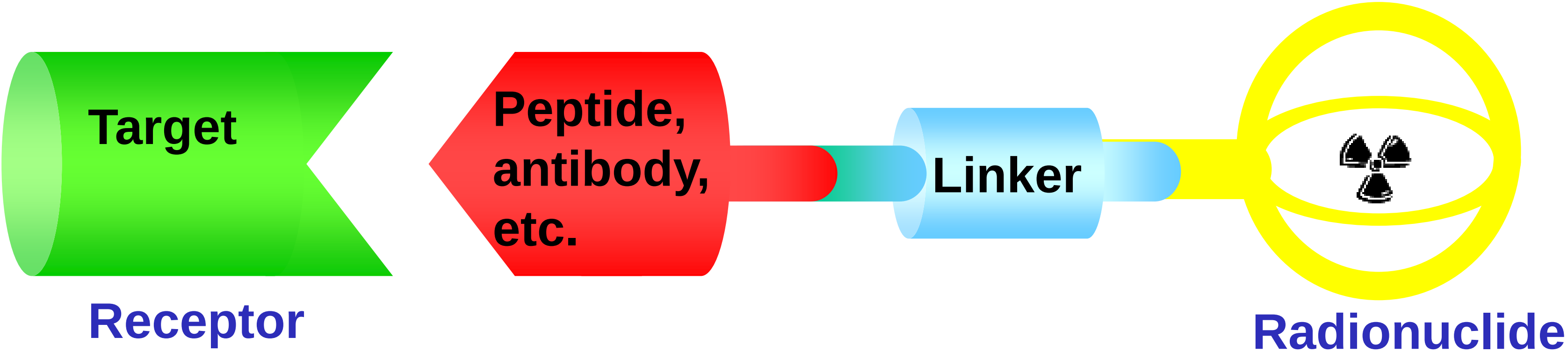
$^{223}Ra^{2+}$ (*Xofigo*)

^{177}Lu-BPAMD

Immunology approach



Multidisciplinary collaboration to fight cancer



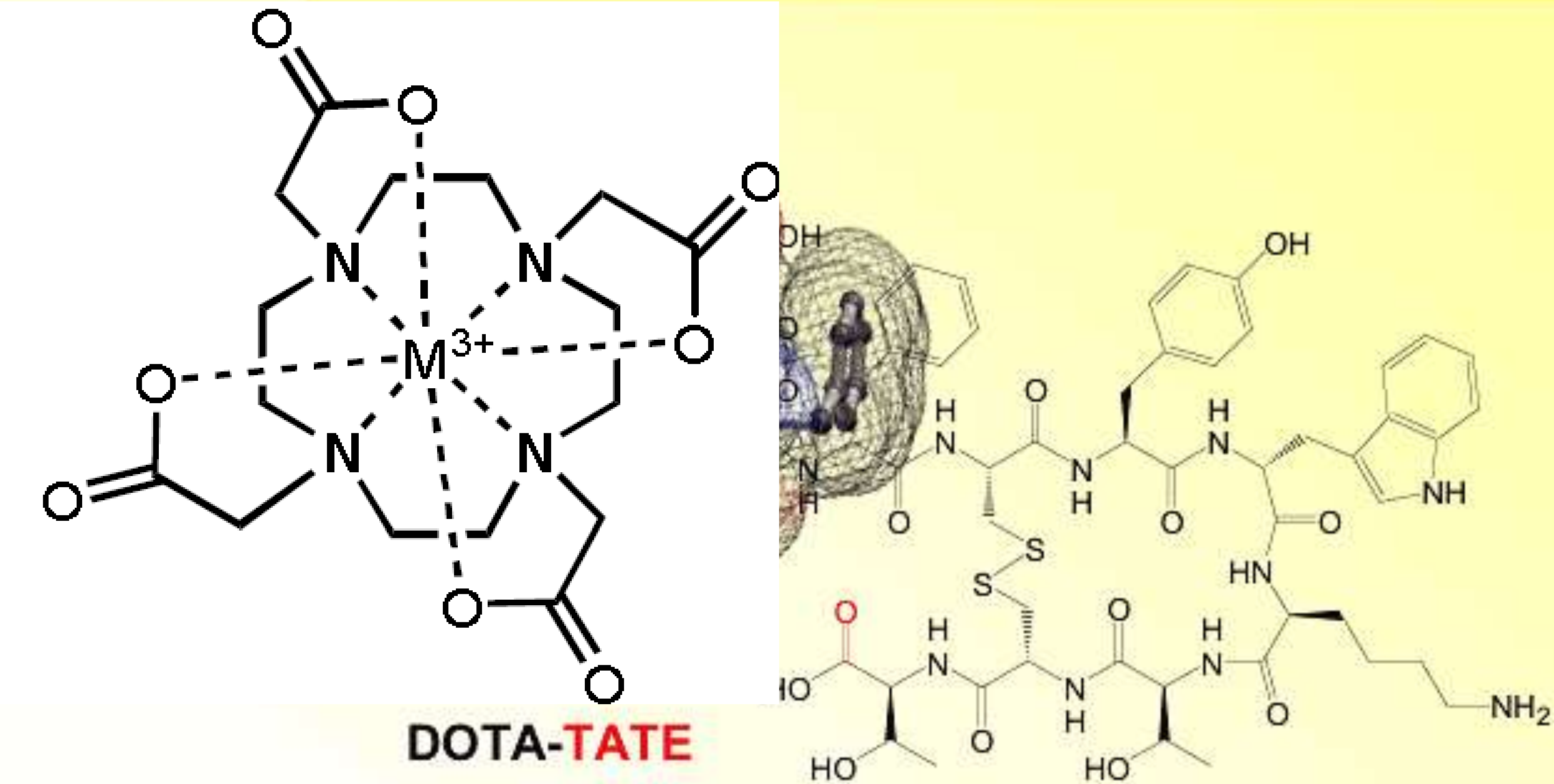
Immunology
Structural biology

Coordination chemistry

Nuclear physics and radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE



DOTA-TATE

1,4,7,10-tetraazacyclododecantetraacetate

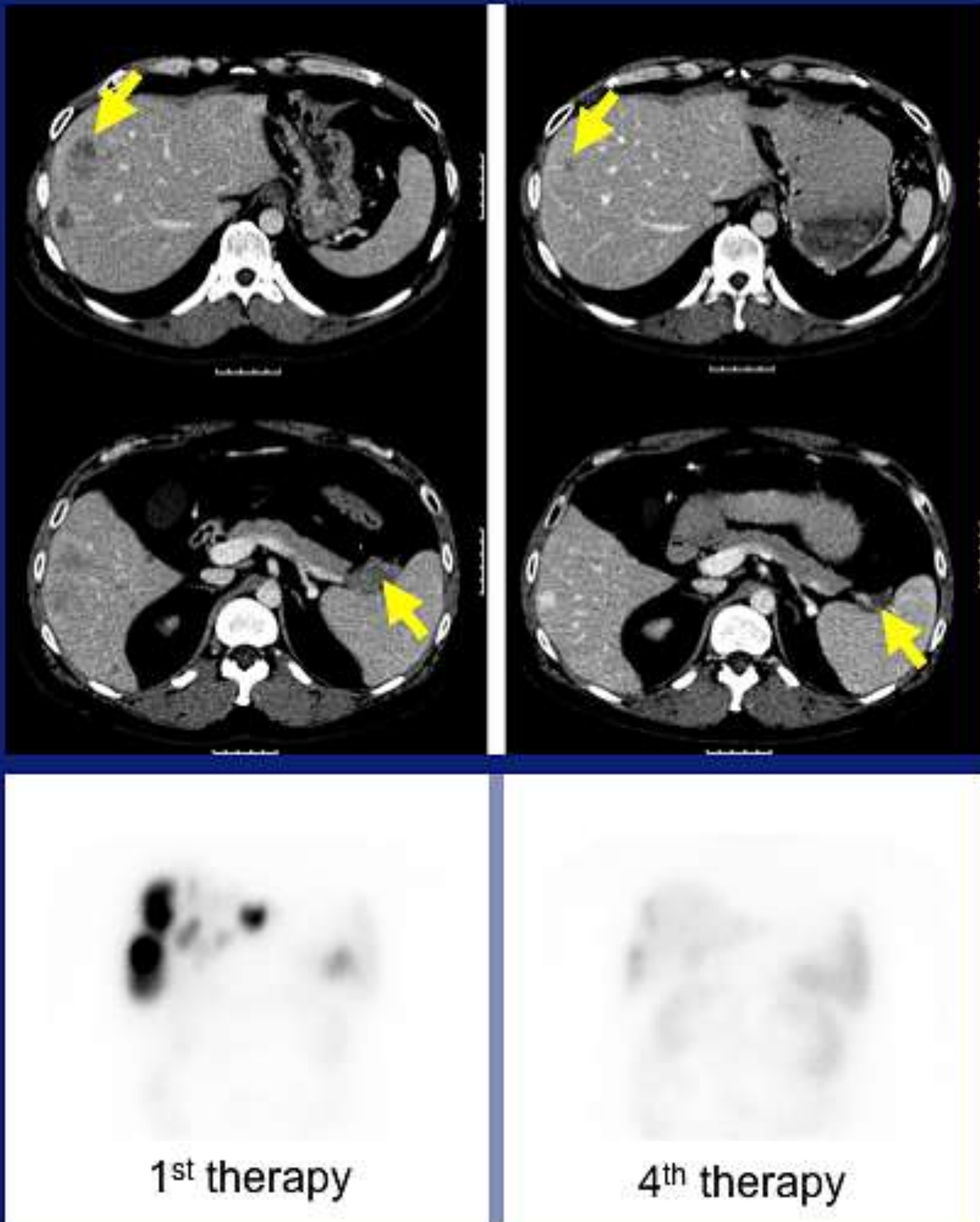
^{111}In ^{90}Y

^{67}Ga ^{177}Lu

^{68}Ga ^{213}Bi

IC_{50} (Y^{III}) = 1.6 ± 0.4 nM

Helmut Maecke, EANM-2007.



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

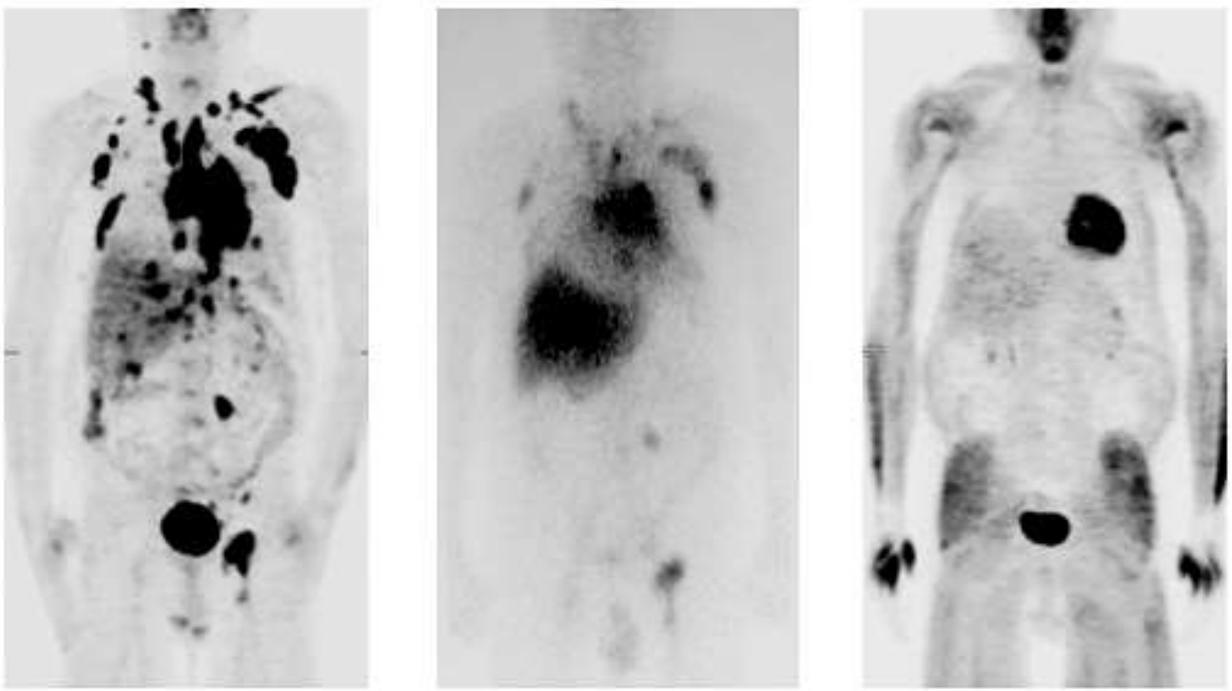
Partial remission

Roelf Valkema, EANM-2008.

Lymphoma therapy: RITUXIMAB+^{177}Lu

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

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

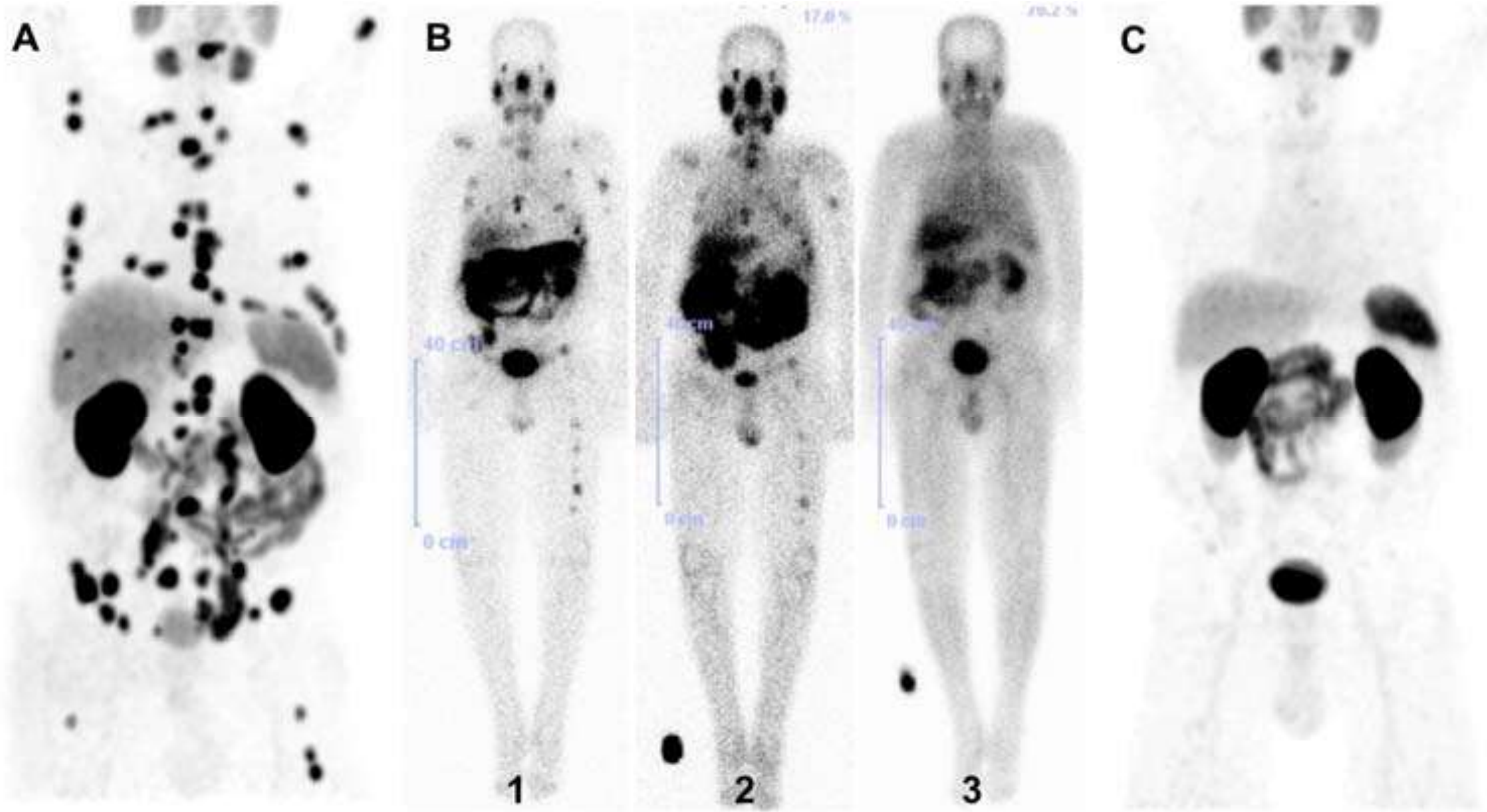


1.9.2002	13.9.2002	15.11.2002	Still in CR 15.9.2009

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

University Hospital Basel, CH

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

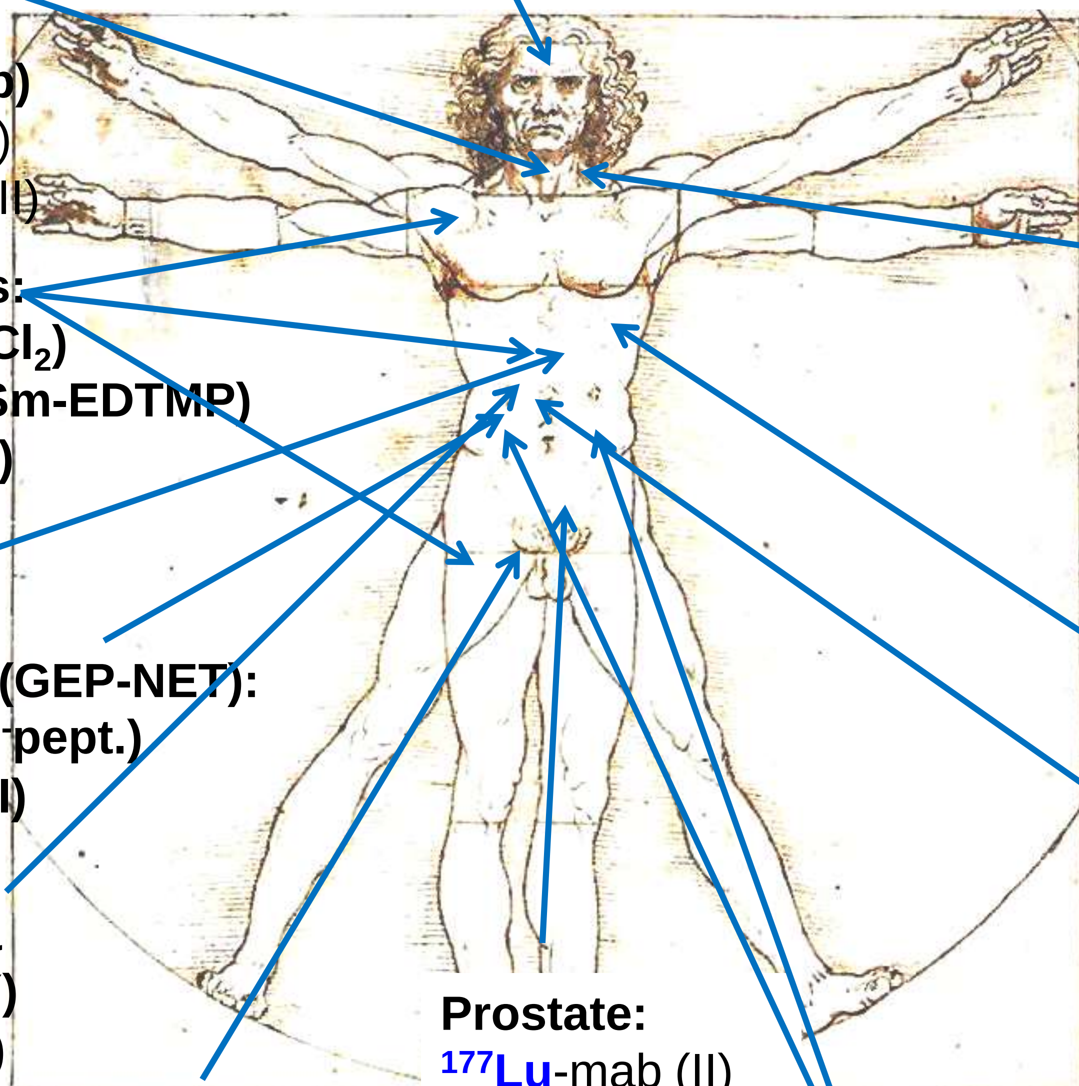


R.P. Baum et al., J Nucl Med 2016;57:1006.

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

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

Targeted radionuclide therapies in the clinic



Thyroid: $^{131}I^-$

Lymphoma:
Zevalin® (^{90}Y-mab)
Bexxar® (^{131}I-mab)
^{131}I/^{177}**Lu**-mabs (I/II)

Bone metastases:
Metastron® ($^{90}SrCl_2$)
Quadramet® (^{153}Sm-EDTMP)
Xofigo® ($^{223}RaCl_2$)

Neuroblastoma:
^{131}I-MIBG

Neuroendocrine (GEP-NET):
Lutathera® (^{177}Lu-pept.)
^{177}Lu-peptides (III)

Liver (HCC):
Theraspheres® &
SIRspheres® (^{90}Y)
^{188}Re-Lipiodol (II)
^{166}Ho-microspheres
^{177}**Lu**-vitamin B7 (I)

Colon & rectum:
^{131}I-mab (II)

Prostate:
^{177}**Lu**-mab (II)
^{177}Lu-PSMA (II)
^{225}Ac-PSMA (I)

Kidneys (RCC):
^{90}Y/^{177}**Lu**-mab (II)

Melanoma:
^{213}Bi-mab(I)

Brain: ^{90}Y-mab ,^{131}I-mab (I/II), ^{211}At-mab (I), ^{213}Bi-pept.(I)

Leukemia, myeloma:
^{131}Y-mab (III),
^{213}Bi/^{225}Ac-mab (II)

Medullary Thyroid:
^{131}I-mab (II)
^{177}**Lu**-pept. (I)

Breast:
^{90}Y-mab, $^{131}I^-$ (II),
^{212}Pb-mab (I)
^{177}**Lu**-mab (I)

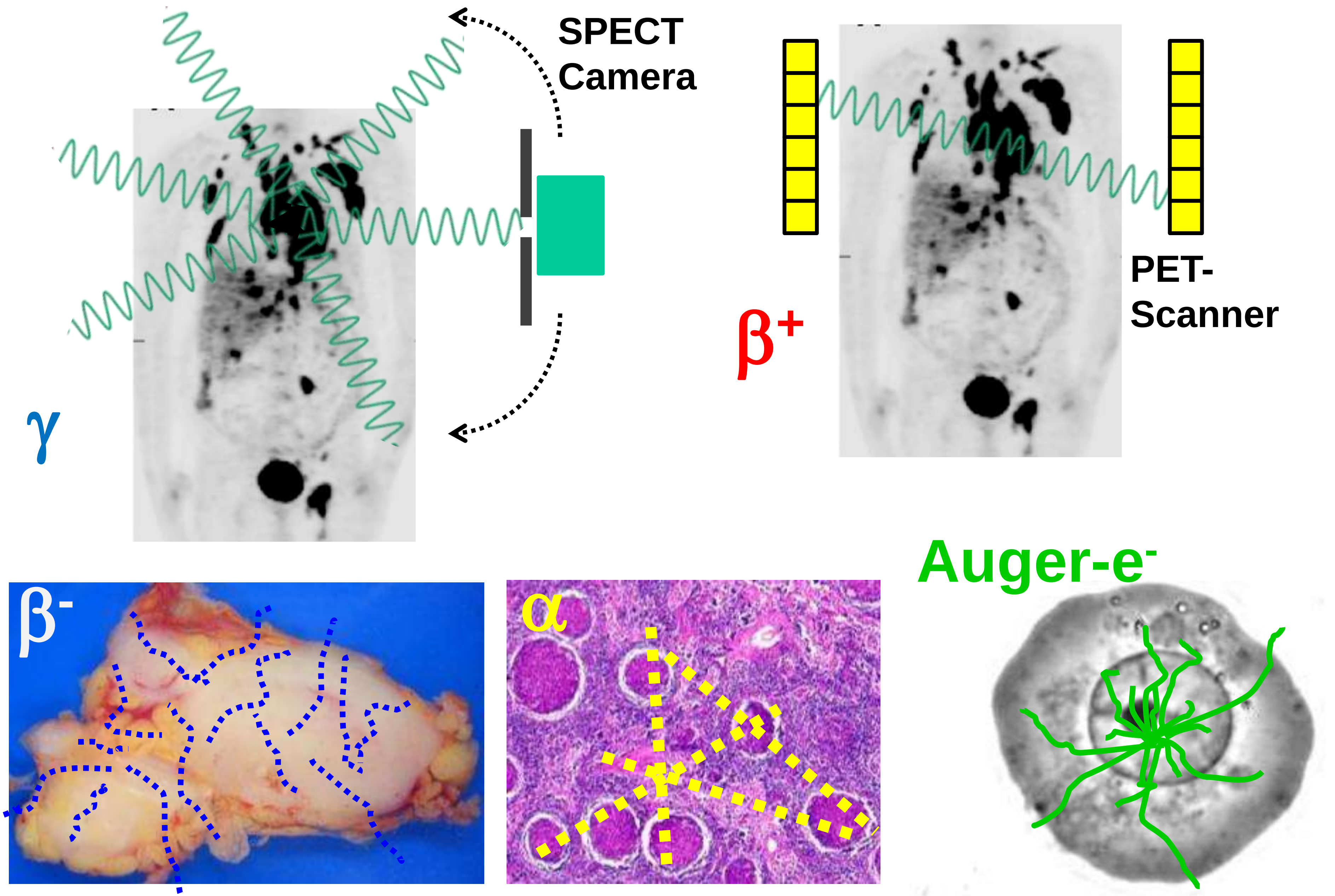
Lung (SCLC):
^{177}**Lu**-mab (II)

Pancreas:
^{90}Y-mab (III)

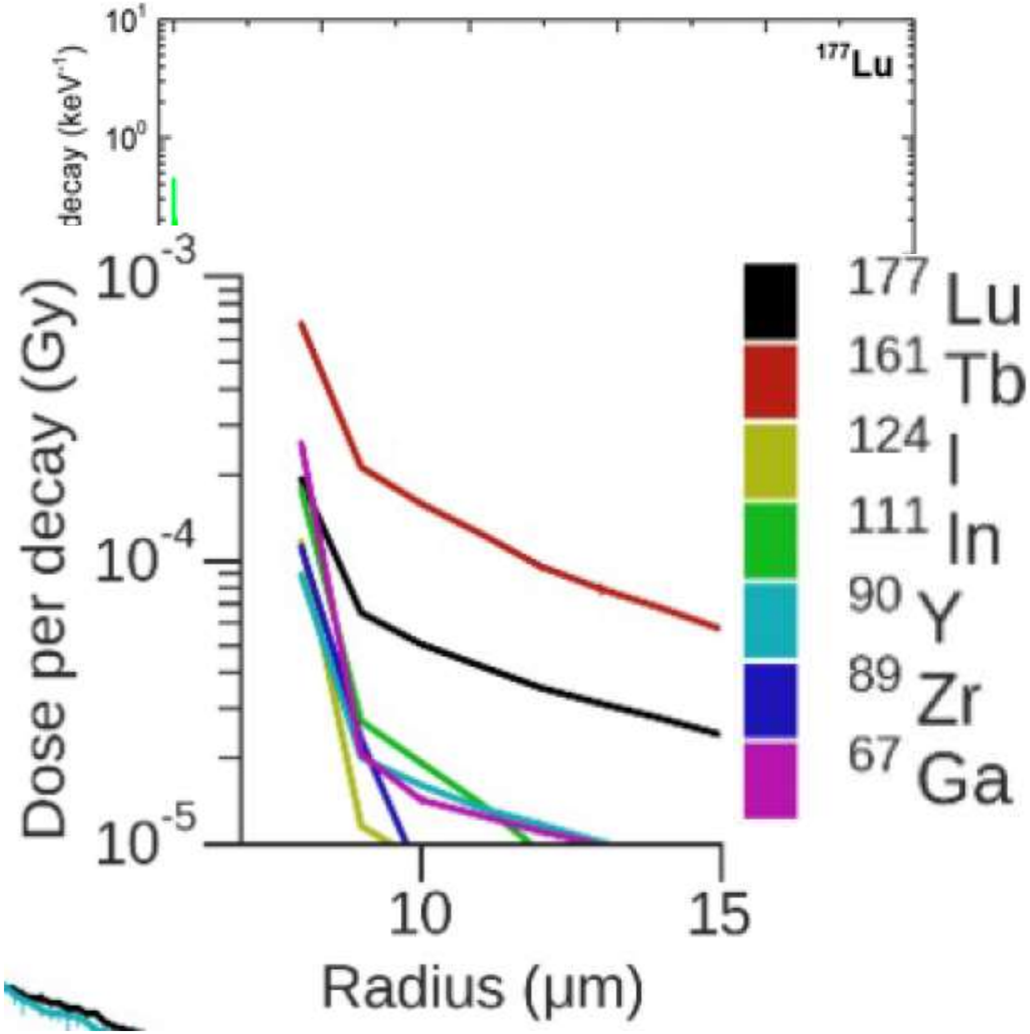
Ovary:
^{212}Pb-mab (I)
^{90}Y/^{177}**Lu**-mab

The rising star for therapy

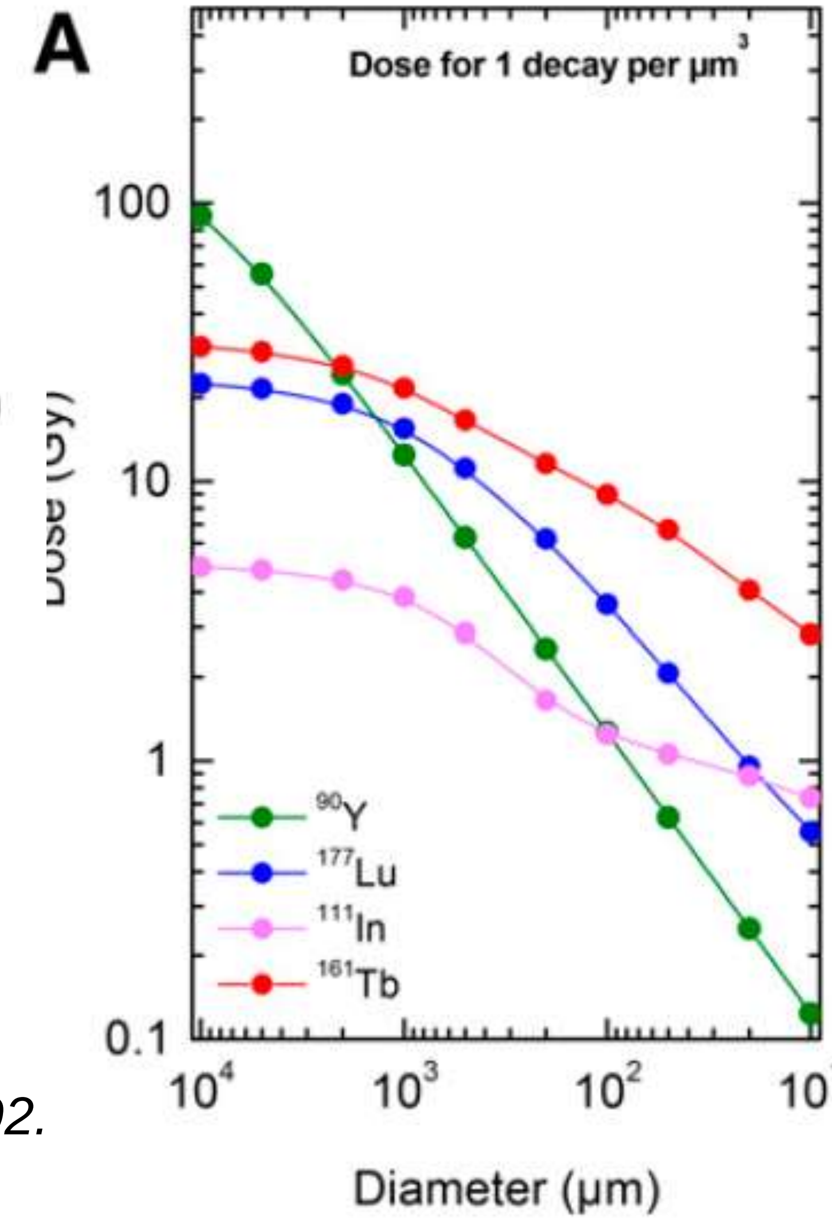
The Nuclear Medicine Alphabet



^{161}Tb versus ^{177}Lu

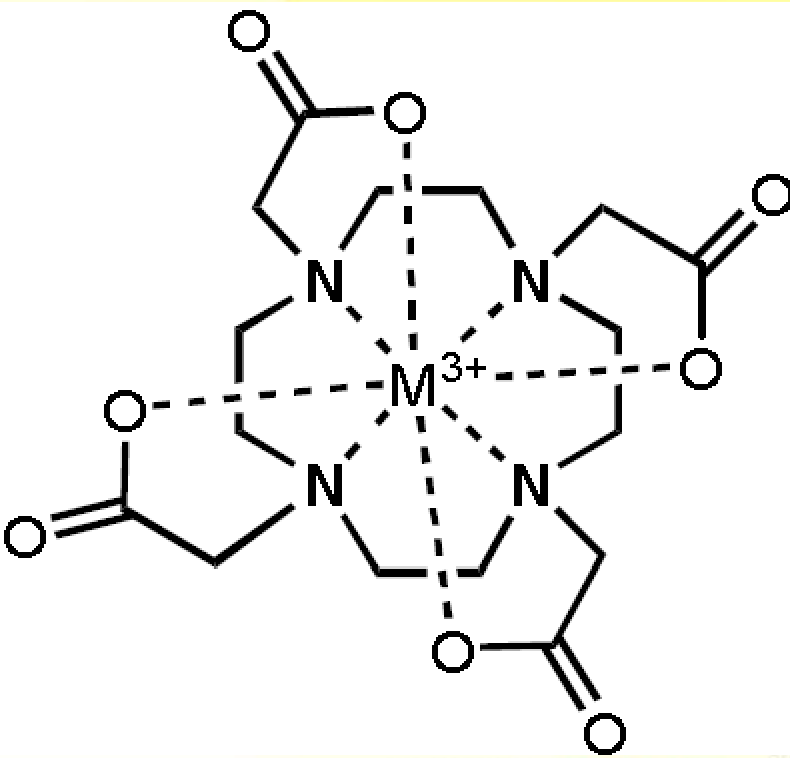


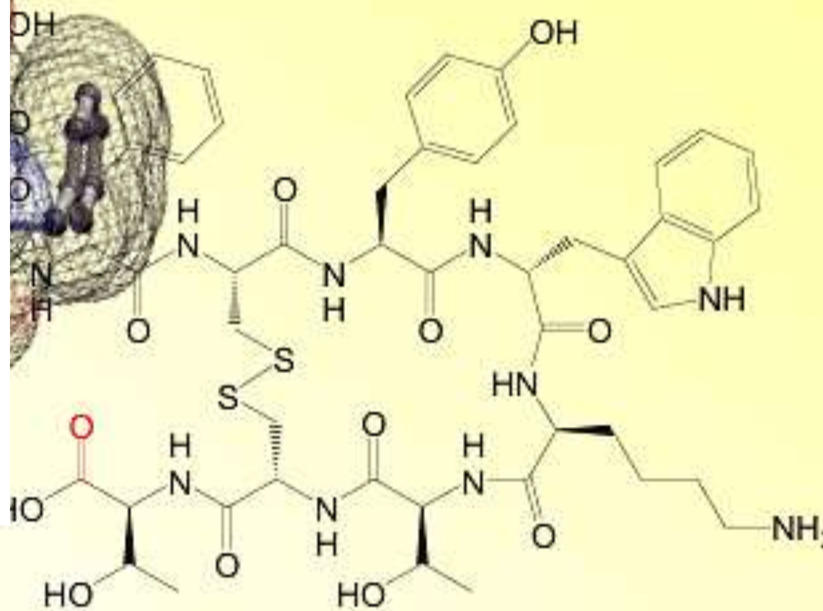
N. Falzone et al., *Theranostics 2018;8:292.*



E. Hindié et al., JNM 2016;57:759.

Structural Formula of DOTA-TOC/TATE





DOTA-TATE

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^{67}Ga	^{177}Lu
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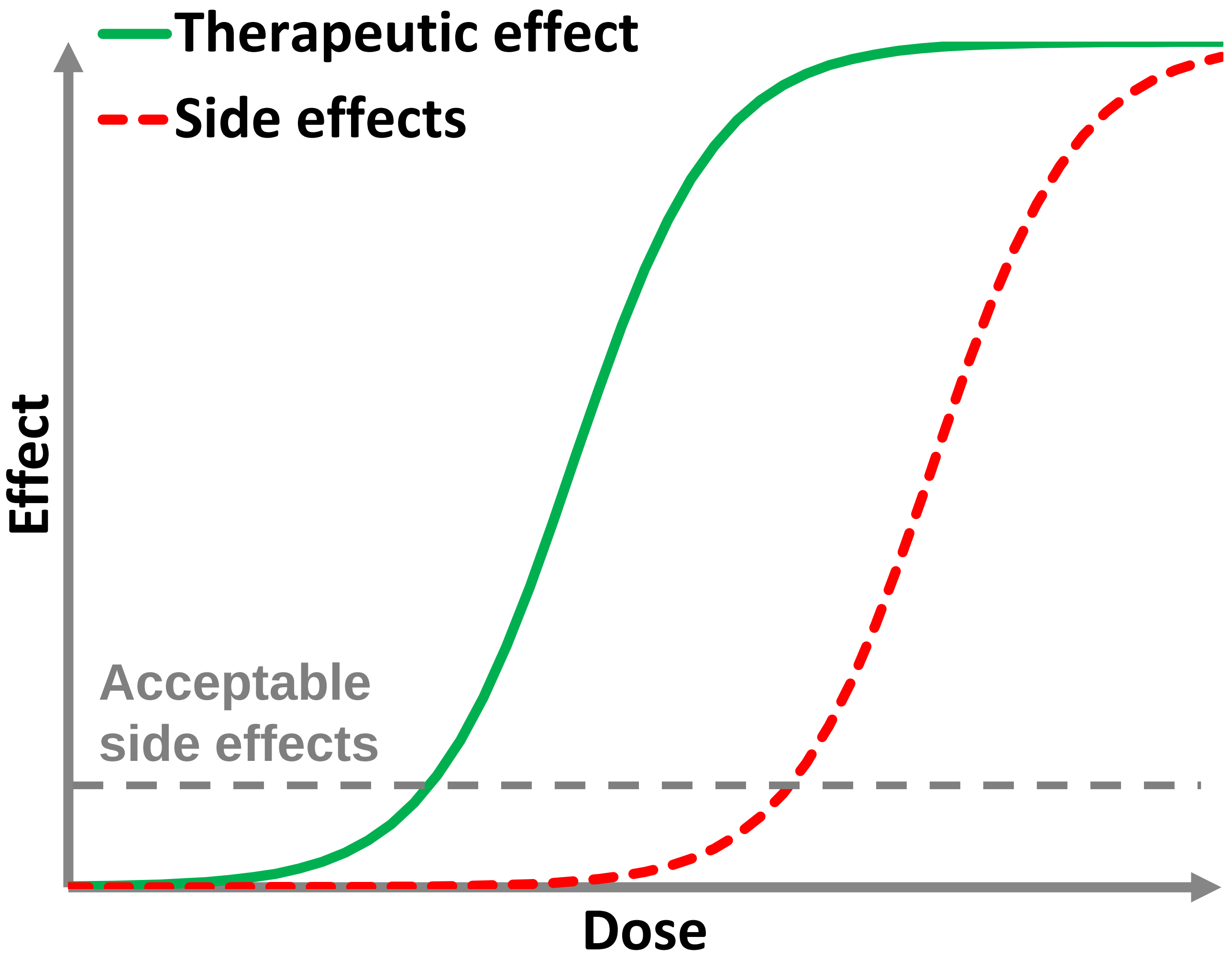
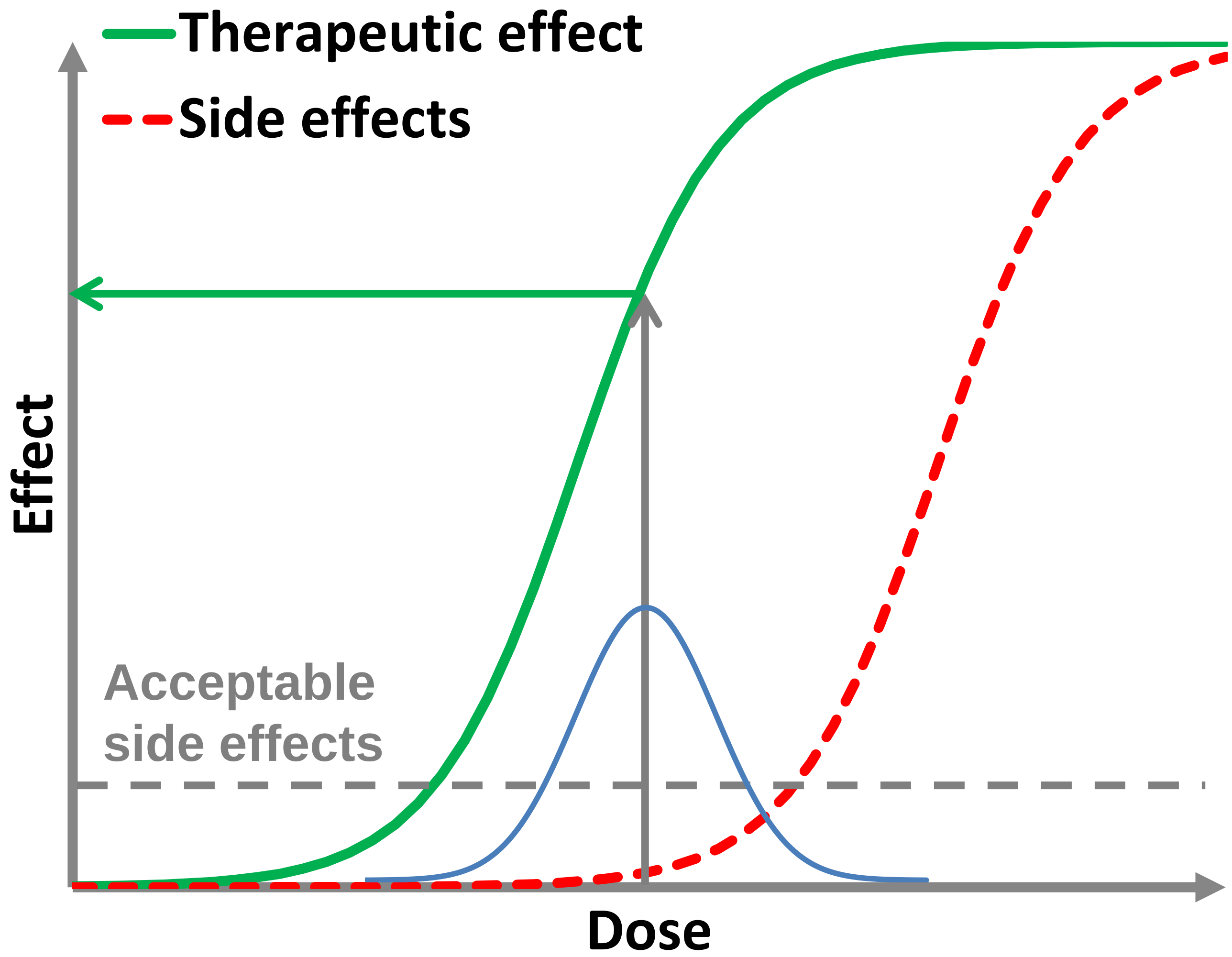
IC_{50} (Y^{III}) = 1.6 ± 0.4 nM

Helmut Maecke, EANM-2007.

Therapeutic window

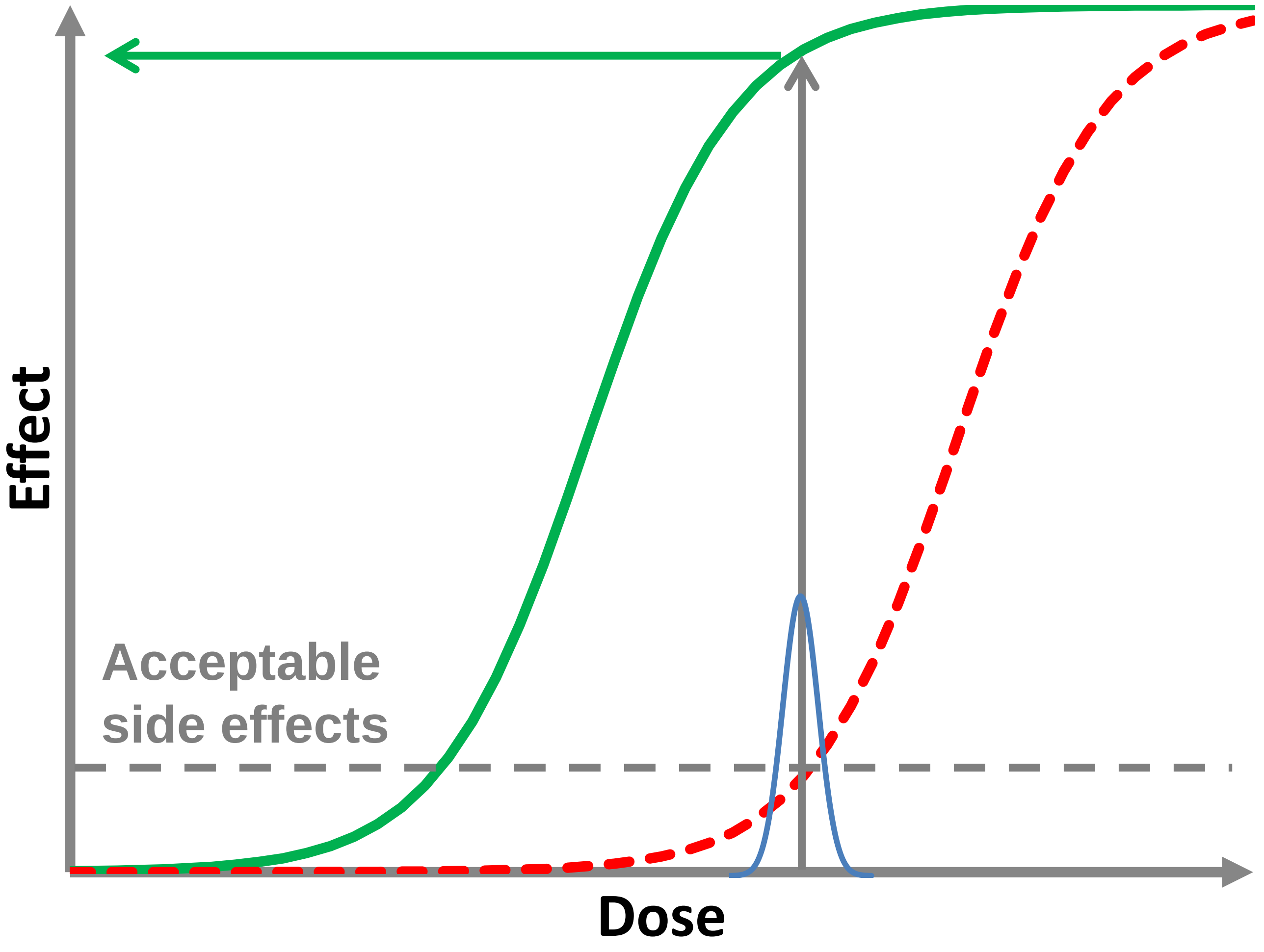


Theranostics



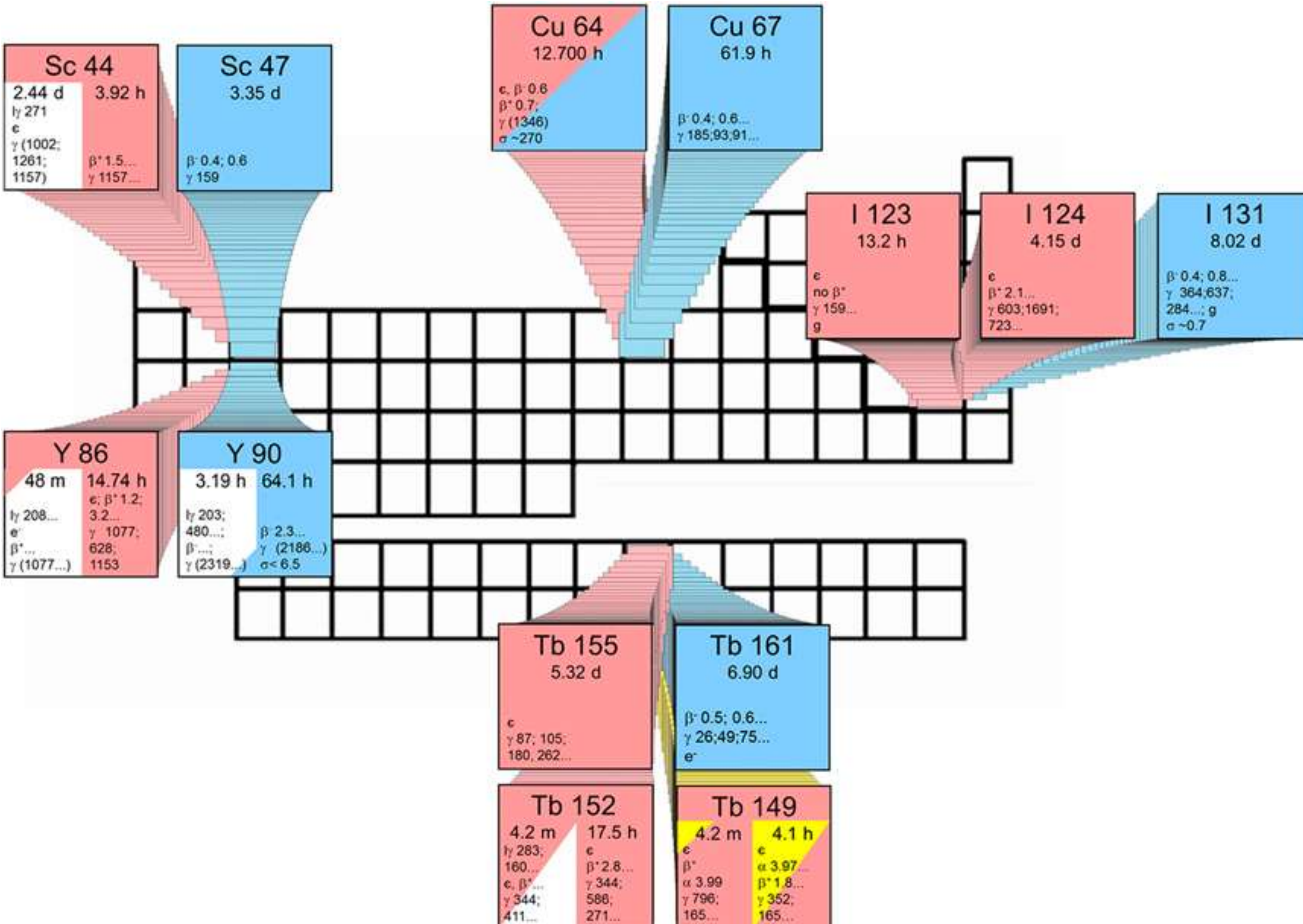
Accurate dosimetry is essential for optimum use of the therapeutic window.

Theranostics



Accurate dosimetry is essential for optimum use of the therapeutic window.

Matched pairs for theranostics

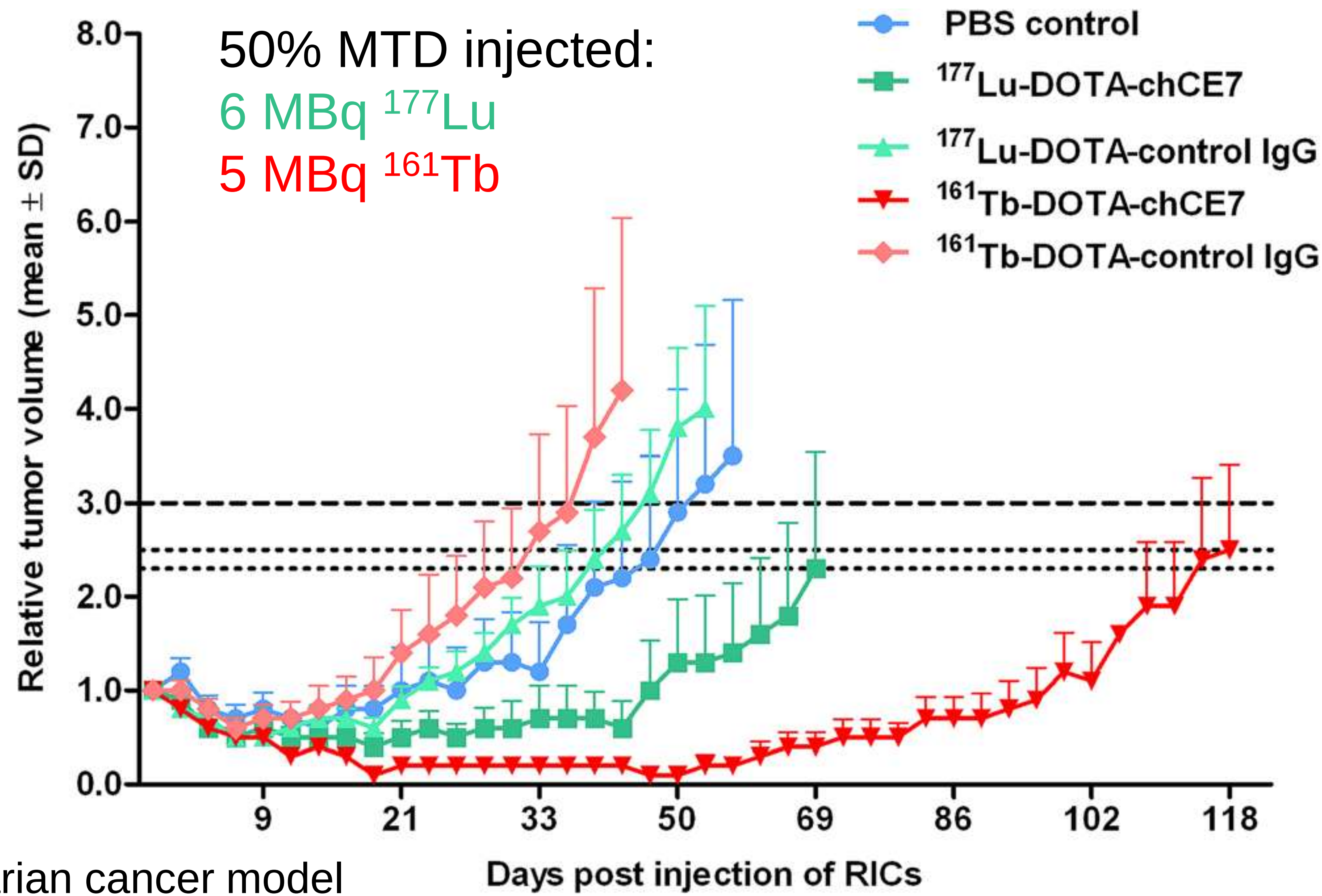


Production of non-carrier-added ^{161}Tb

Irradiation in high flux reactor, then chemical separation

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

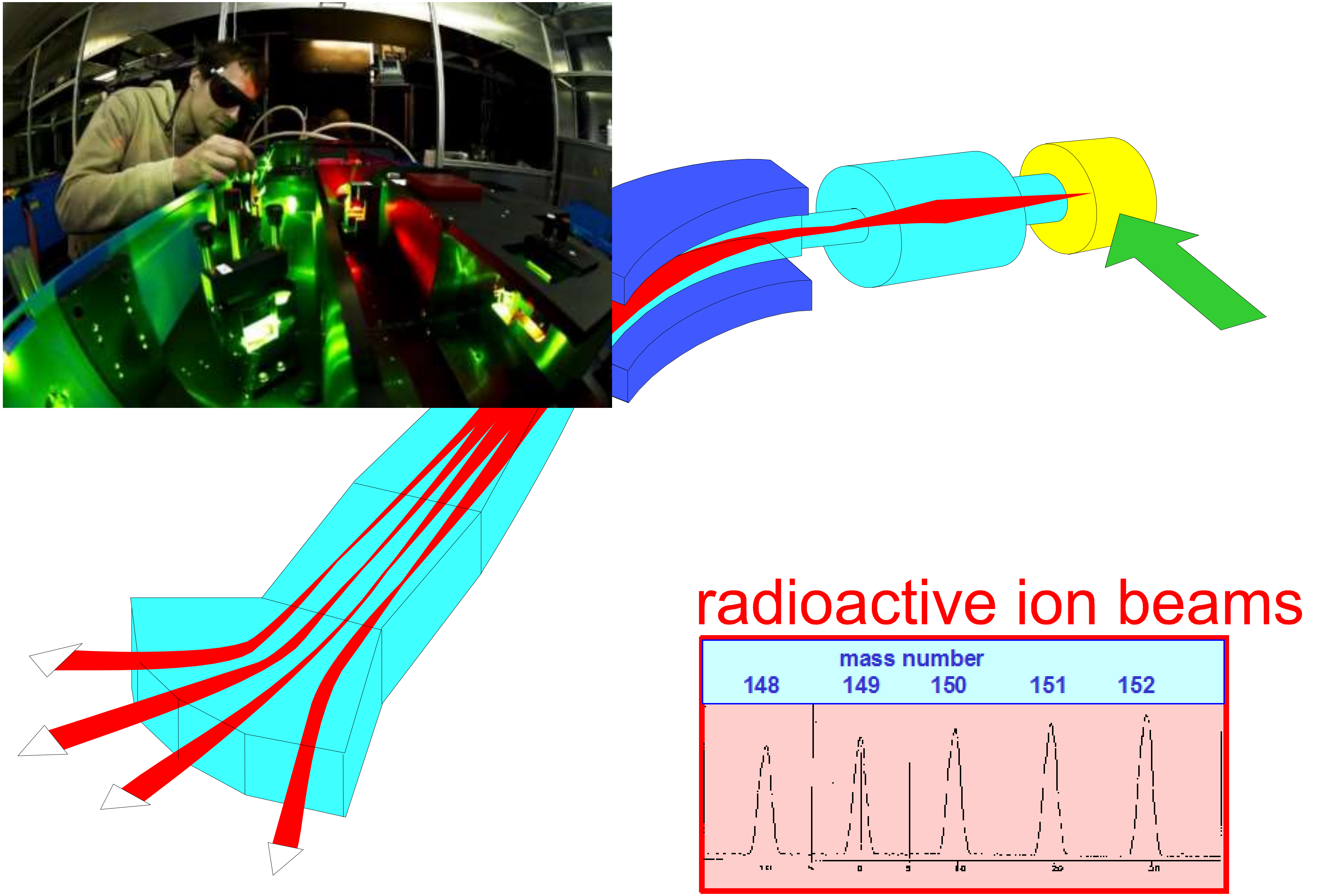
Therapeutic efficacy of ^{161}Tb-RIT vs. ^{177}Lu-RIT



ovarian cancer model

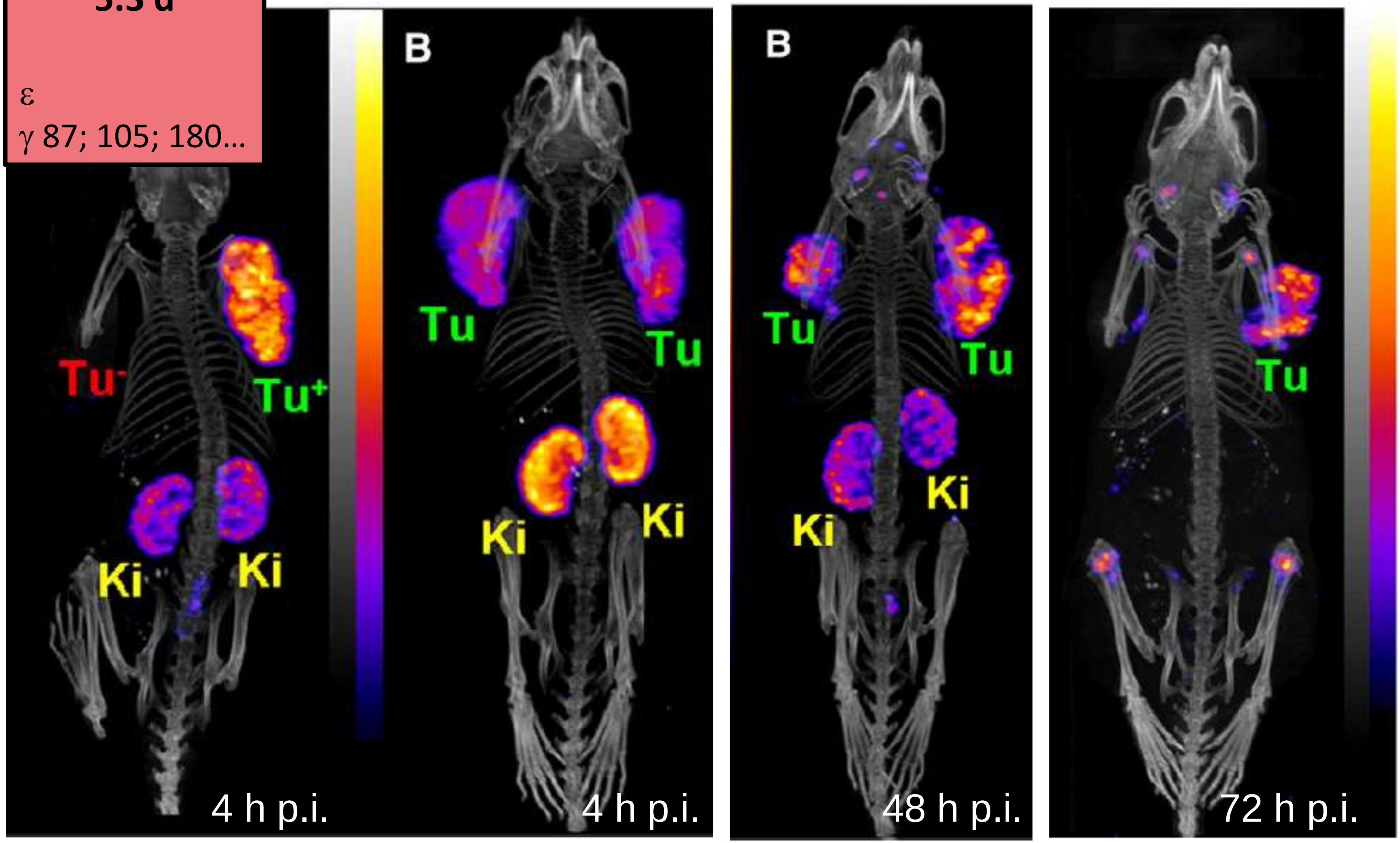
J. Grünberg et al. Eur J Nucl Med Mol Imaging 2014;41:1907.

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



^{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

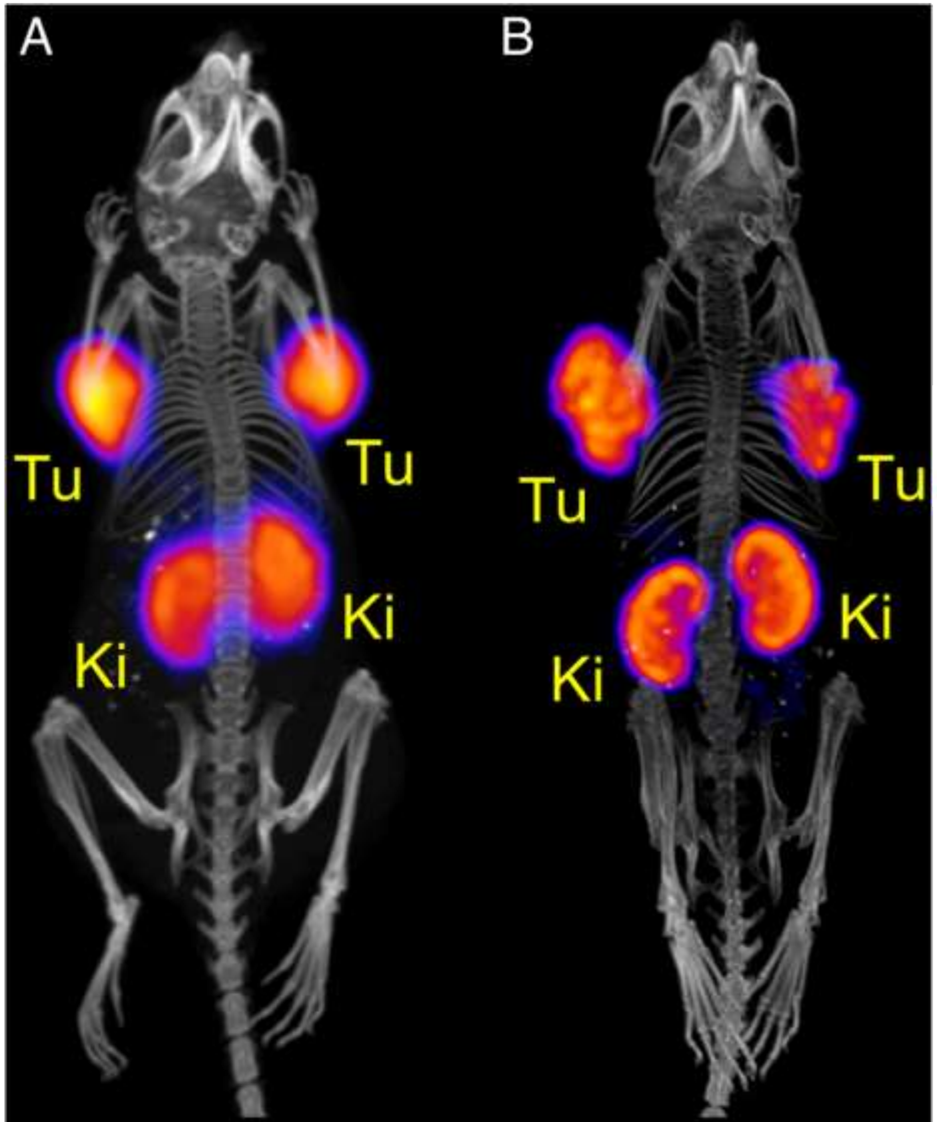
C. Müller et al. Nucl Med Biol 2014;41:e58.

^{152}Tb well matched for ^{177}Lu/^{161}Tb-PRRT dosimetry

Tb 152

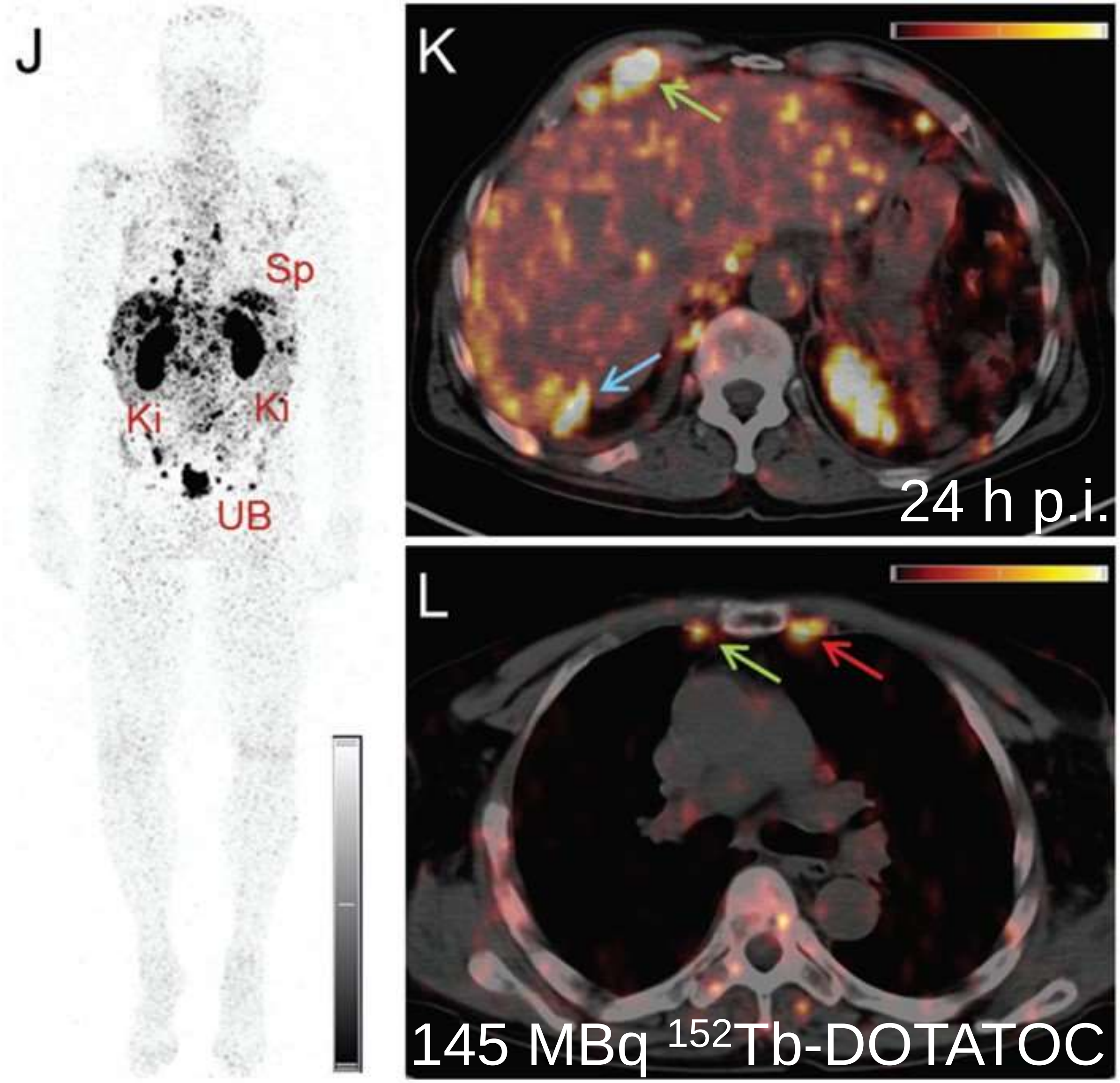
17.5 h

ε
β^+ 3.0; 2.6; 2.0…
γ 344; 271; 586…



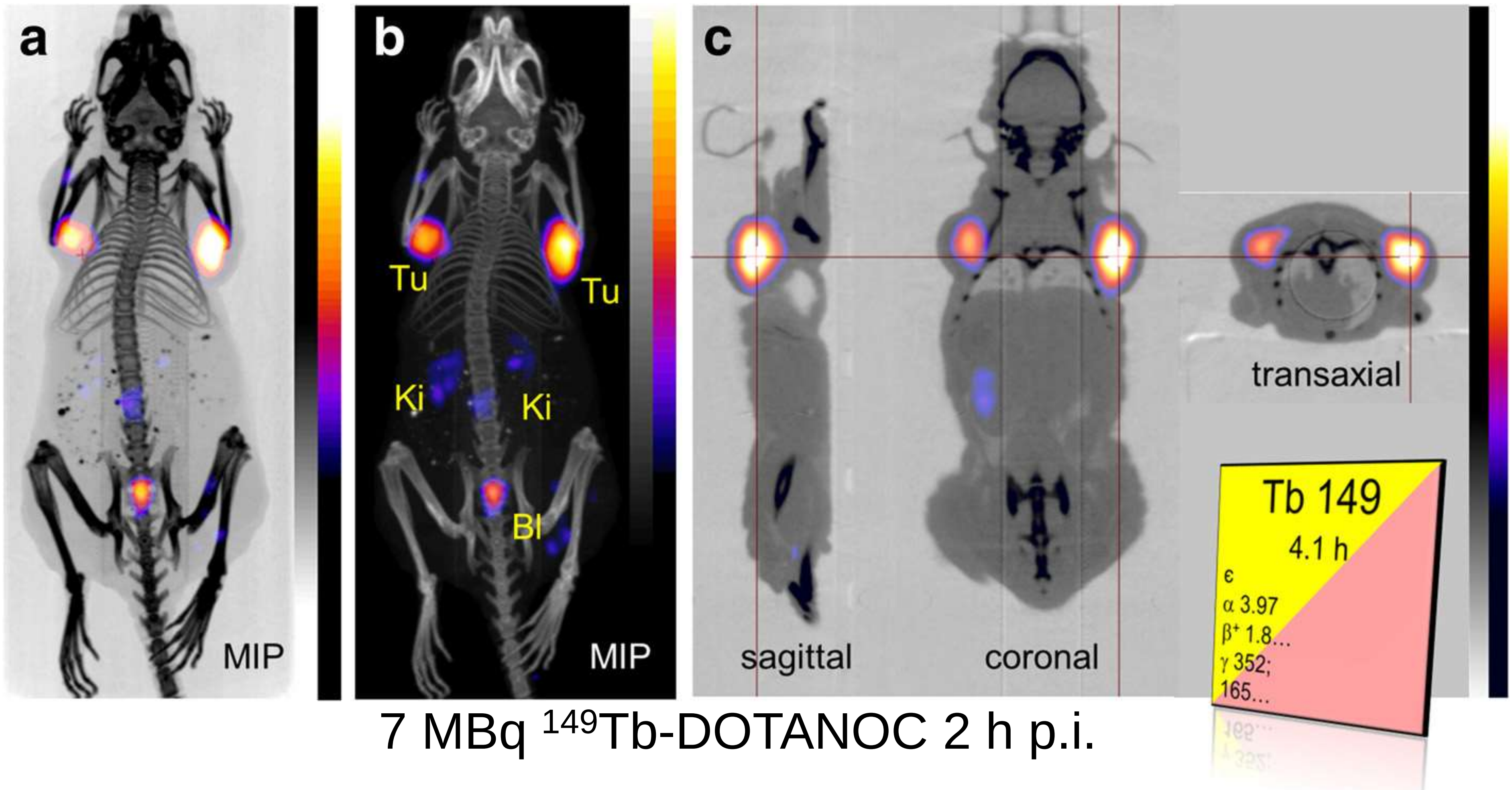
C. Müller et al. EJNMMI Research 2016;6:35.

First-in-human study with ^{152}Tb-DOTATOC



R.P. Baum et al. Dalton Transactions 2017;46:14638.

Alpha-PET with ^{149}Tb

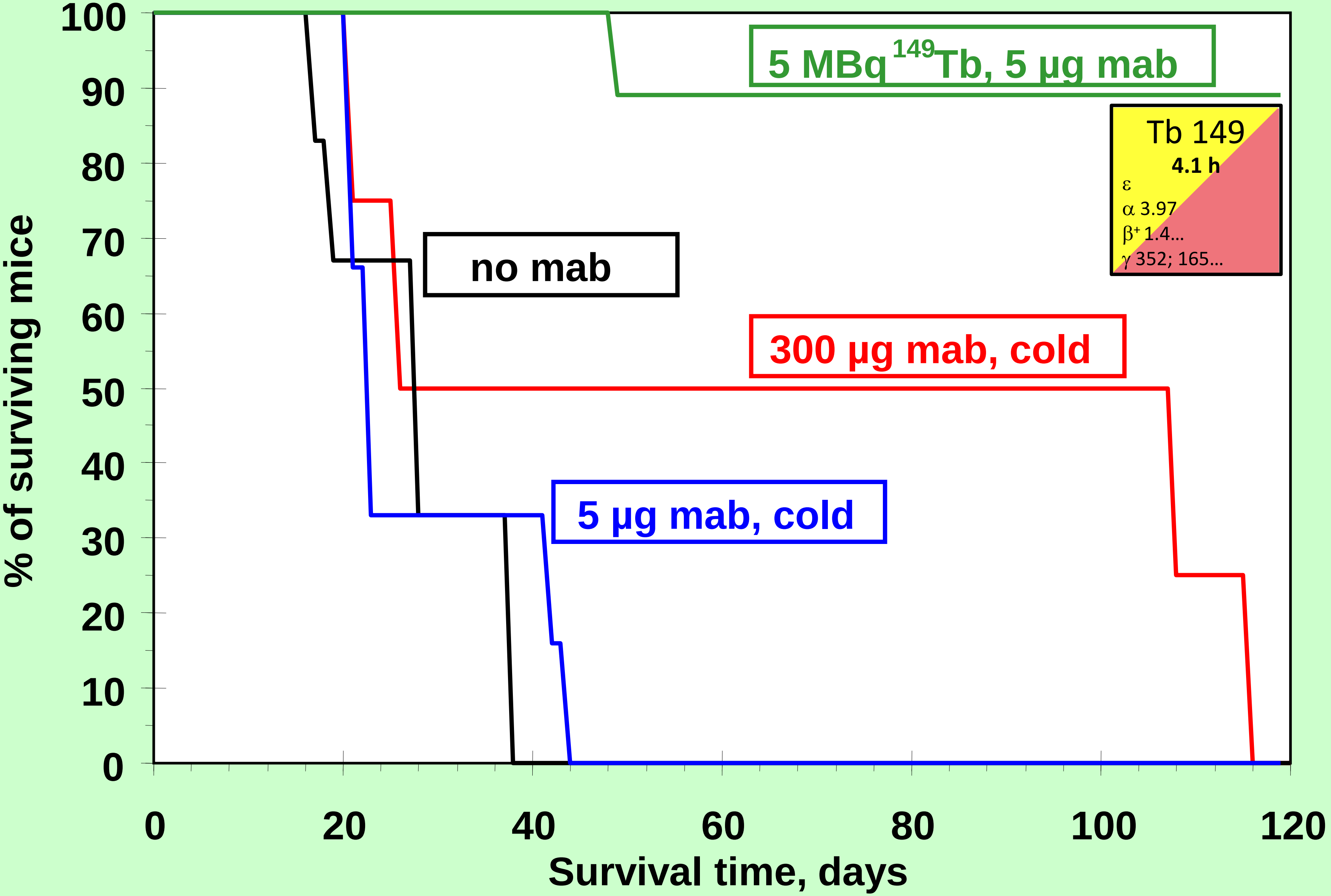


7 MBq ^{149}Tb-DOTANOC 2 h p.i.

ISOLDE · PAUL SCHERRER INSTITUT PSI · ETH zürich · ILL NEUTRONS FOR SOCIETY · u^b UNIVERSITÄT BERN · ENSAR European Nuclear Science and Applications Research

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

^{149}Tb-rituximab in lymphoma mouse model



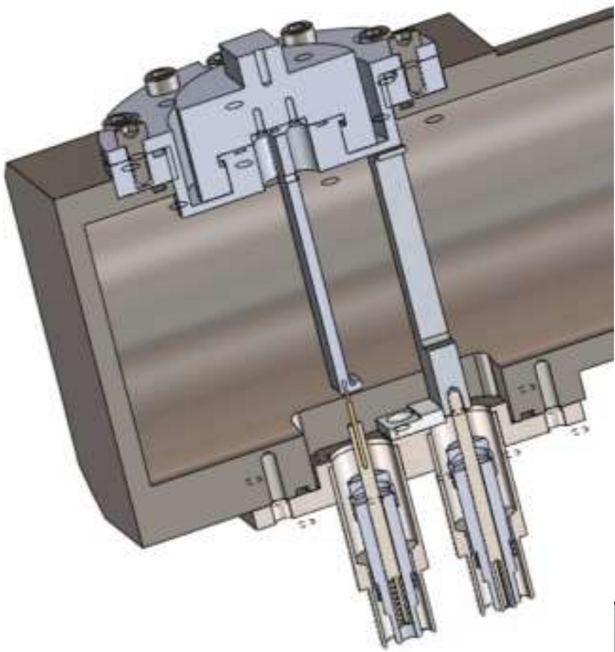
G.J. Beyer et al., Eur J Nucl Med Molec Imaging 2004;31:547.

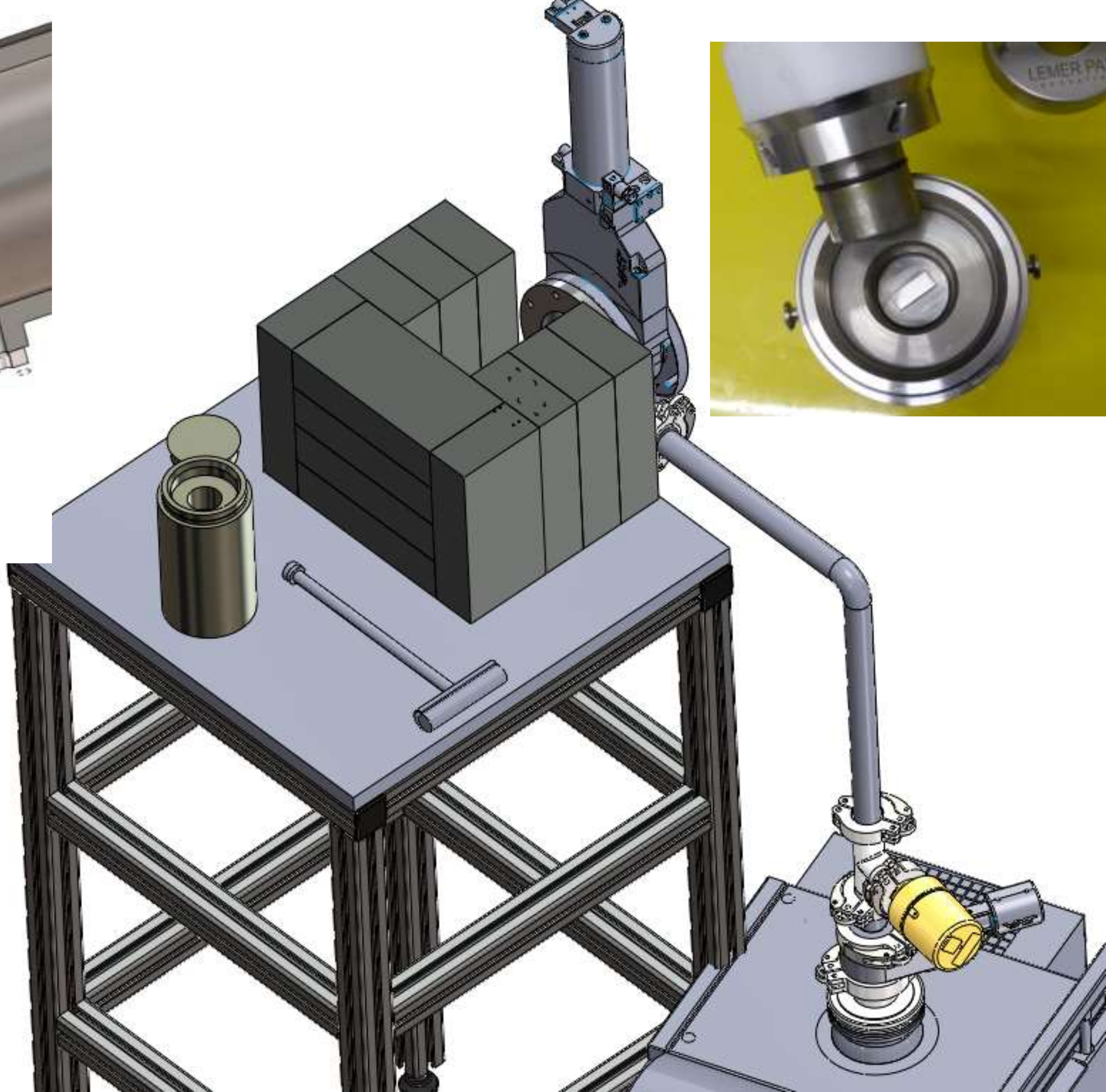
Terbium: a unique element for nuclear medicine

IS528: Novel diagnostic and therapeutic radionuclides for the development of innovative radiopharmaceuticals

Anu Airaksinen, Martina Benesova, Thomas Cocolios, David Cullen, Gilles de France, Andrew Fenwick, Kelly Ferreira, Hanna Frånberg, Catherine Ghezzi, Nadezda Gracheva, Ferid Haddad, Kerttuli Helariutta, Peter Ivanov, Ulrika Jakobsson, Mikael Jensen, Karl Johnston, Steven Judge, Ulli Köster, Gilles Montavon, Cristina Müller, Bernd Pichler, Jean-Pierre Pouget, Andrew Robinson, Anna-Maria Rolle, Roger Schibli, Gregory Severin, Jill Tipping, Andreas Türler, Christoph Umbricht, Stefan Wiehr, Nick van der Meulen, Etienne Vermeulen

Shielded ENSAR2 collection chamber





ISOLDE

NEUTRONS FOR SOCIETY

ARRONAX

ENSAR2

Transport limitations (ADR, IATA)

BASIC RADIONUCLIDE VALUES FOR UNKNOWN RADIONUCLIDES OR MIXTURES

Radioactive contents	A_1 TBq	A_2 TBq	Activity concentration for exempt material Bq/g
Only beta or gamma emitting nuclides are known to be present	0.1	0.02	1×10^{1}
Alpha emitting nuclides but no neutron emitters are known to be present	0.2	9×10^{-5}	1×10^{-1}

20 GBq ^{161}Tb, 90 MBq ^{149}Tb

CERN
CH1211 Geneva 23
Switzerland

EDMS NO.	REV.	VALIDITY
1221502	**2.1**	**Released**

REFERENCE
CERN-DGS-2012-046-RP-TN

HSE Unit

Calculation of A2 values for short-lived radionuclides produced at the ISOLDE experiment at CERN

IAEA

2016: IAEA TRANSSC will include
^{161}Tb (**A2=0.7 TBq**) and
^{149}Tb (**A2=0.8 TBq**) in SSR6 update

Boundary conditions for ENSAR2-RITMI (2013)

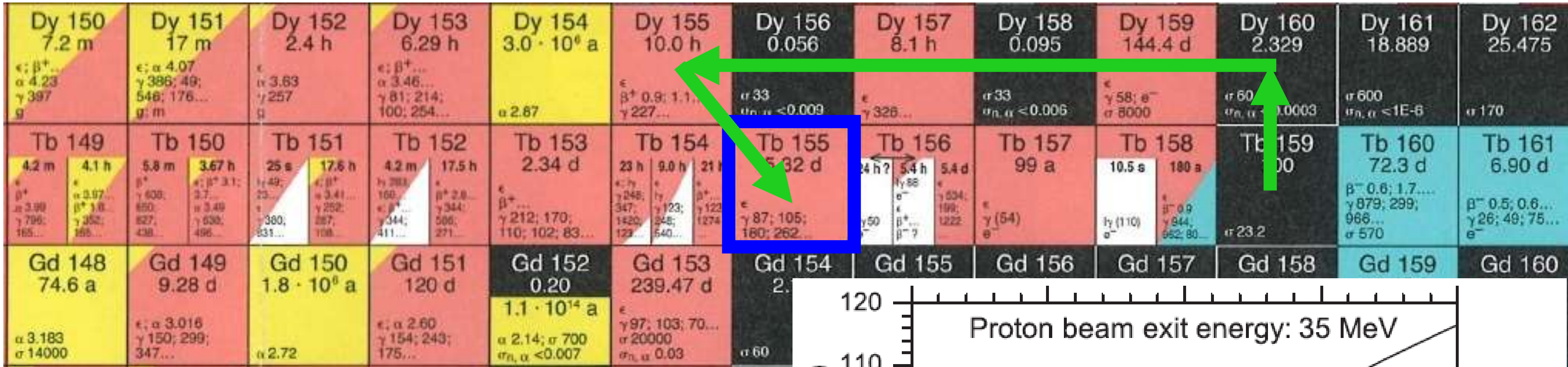
focus on particular strengths of ENSAR2 facilities

- protons >> 30 MeV
- beams of alphas and heavier ions
- ISOL target technology
- mass separation

$\Rightarrow$ focus on alpha emitters: highest “value” per # of atoms

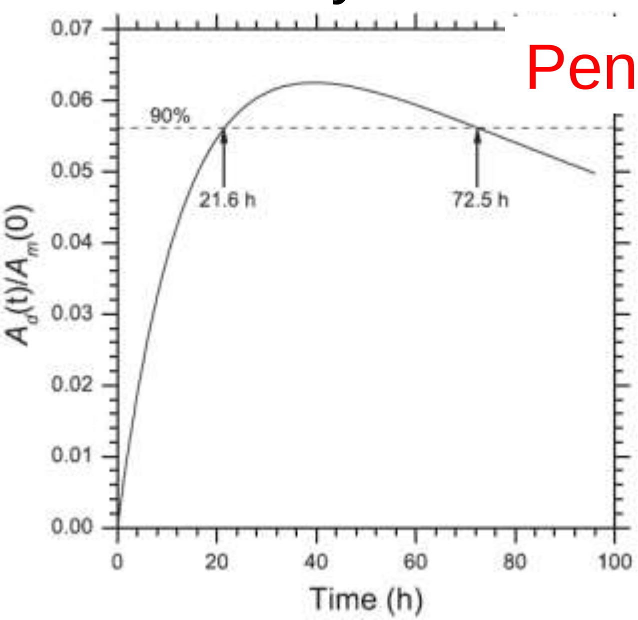
and production of Sc isotopes with alpha beams

Radionuclidic purity without mass separation ?

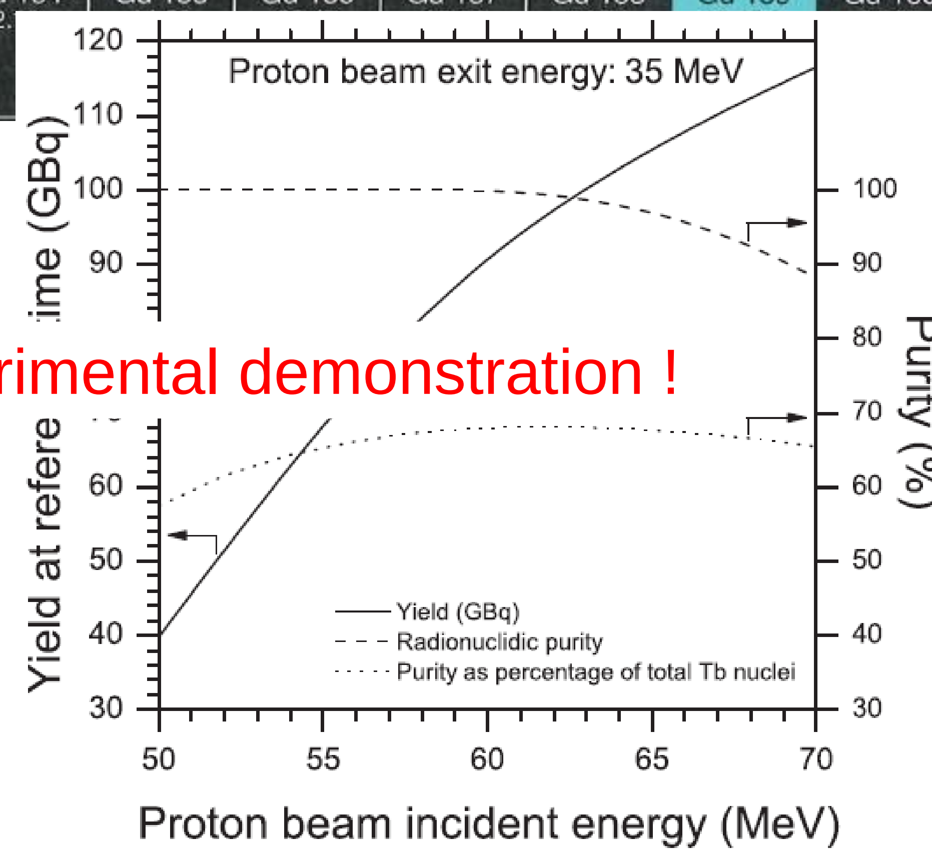


$^{159}Tb(p,5n)^{155}Dy$ ≈60 MeV p

$^{155}Dy > ^{155}Tb$



Pending experimental demonstration !



G.F. Steyn et al., Nucl. Instr. Meth. B 2014;319:128.

Which theranostic isotopes will we use in future ?

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 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...

At 211
7.2 h
ε
α 5.867...
γ (687)

Ac 225
10.0 d
α 5.830; 5.797...
γ 100; (150...)
e^-

Tb 149
4.1 h
ε
α 3.97
β^+ 1.4...
γ 352; 165...

Sc 43
3.9 h
β^+ 1.2...
γ 373...

Cu 61
3.4 h
β^+ 1.2...
γ 283; 656; 67; 1186...

Tb 152
17.5 h
ε
β^+ 3.0; 2.6; 2.0...
γ 344; 271; 586...

Ga 68
1.1 h
ε
β^+ 1.9...
γ 1077; (1833...)

I 124
4.15 d
ε
β^+ 2.1...
γ 603; 1691...

Zr 89
3.3 d
ε
β^+ 0.9
γ (1713)
m

Sc 44
4.0 h
β^+ 1.5...
γ 1157...

Cu 64
12.7 h
ε
β^- 0.6, β^+ 0.7
γ (1346)

Tb 155
5.3 d
ε
γ 87; 105; 180...
e^-

In 111
2.8 d
ε
γ 245; 171...

I 123
13.2 h
ε
γ 159...

Radionuclides for RIT and PRRT

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

cross-fire

Estab-lished isotopes

Emerging isotopes

R&D isotopes: supply-limited!

localized

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


ENSAR(x) facilities provide unique features and technology, also useful for innovative radiopharmaceuticals.