Radionuclides for medical applications

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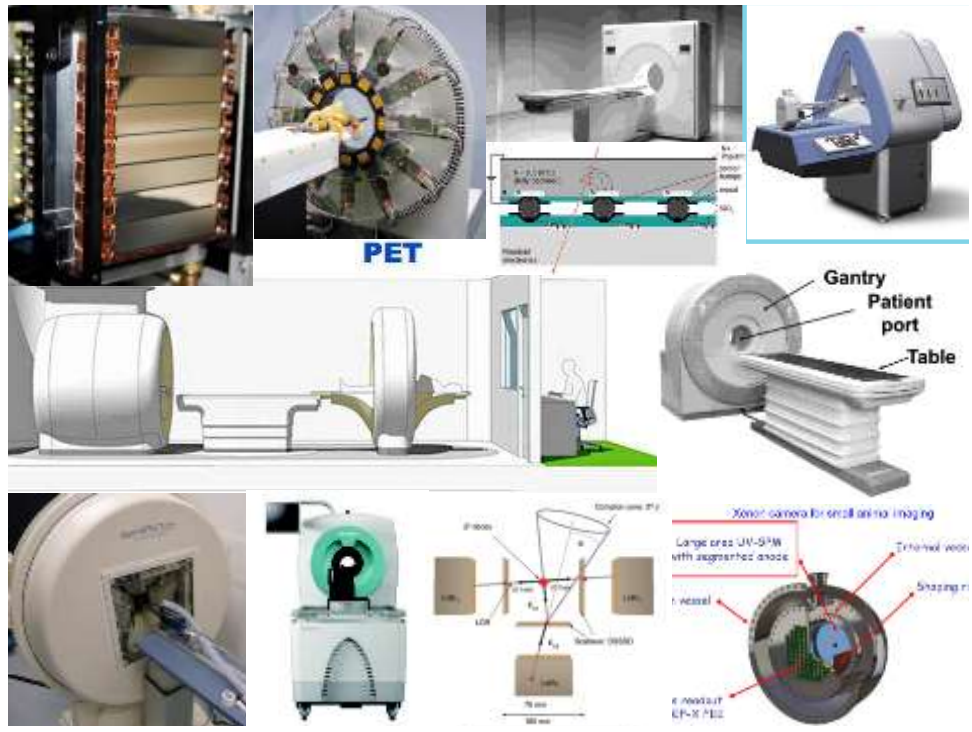
EuNPC

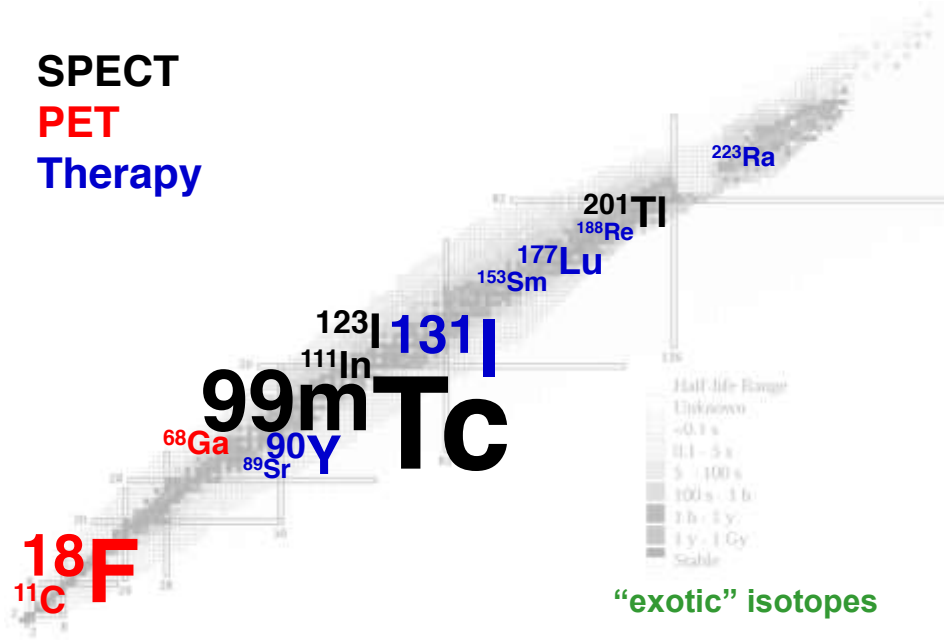
1 September 2015



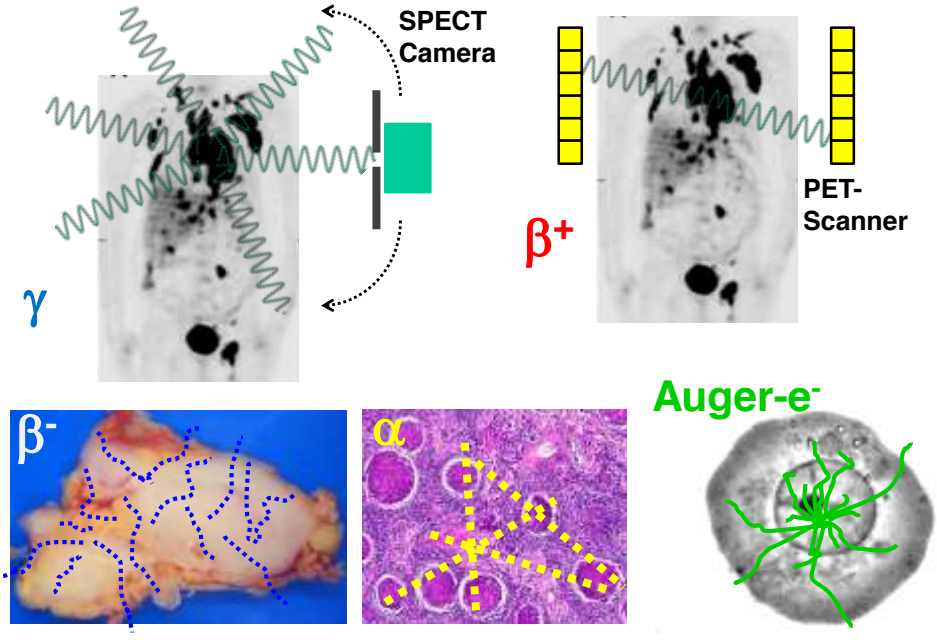
Don’t forget the fuel!

Radioisotopes: the “fuel” for nuclear medicine

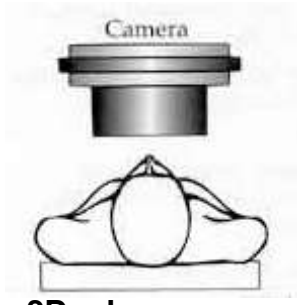
The chart of nuclides: nuclear medicine perspective



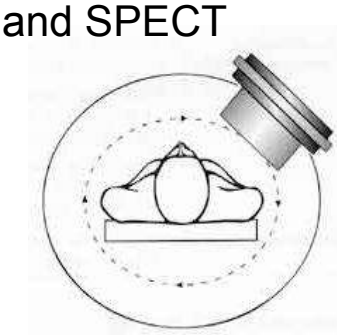
The Nuclear Medicine Alphabet



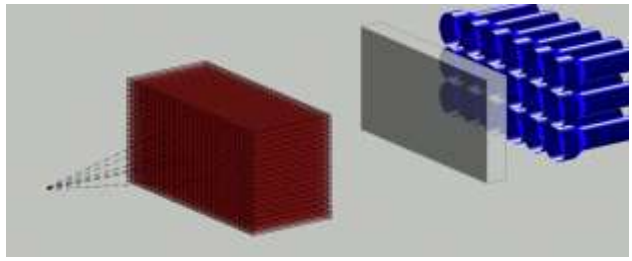
Scintigraphy and SPECT



2D: planar scan (Gamma camera)



3D: SPECT: Single Photon Emission Computer Tomography



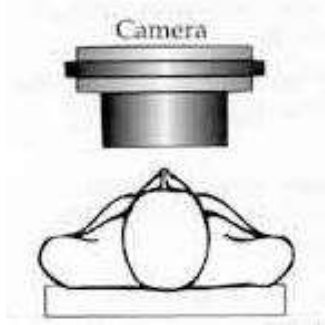
E_γ > 60 keV
E_γ < 400 keV

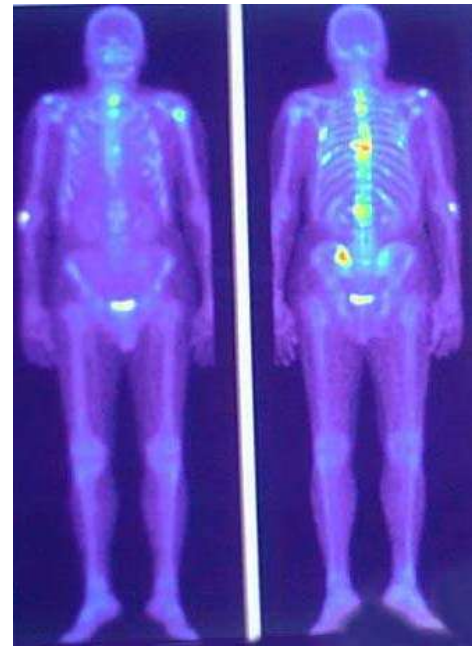
^{99m}Tc: ideal for SPECT and gamma cameras

Ru 98 1.87	Ru 99 12.76	Ru 100 12.60	Ru 101 17.06	Ru 102 31.55
σ <8	σ 4	σ 5.8	σ 5	σ 1.2
Tc 97	Tc 98 $4.2 \cdot 10^6$ a	Tc 99 6.0 h / $2.1 \cdot 10^5$ a	Tc 100 15.8 s	Tc 101 14.2 m
92.2 d / $4.0 \cdot 10^6$ a	β⁻ 0.4 γ 745; 652 σ 0.9 + ?		β⁻ 3.4... ε γ 540; 591...	β⁻ 1.3... γ 307; 545...
Mo 96 16.68	Mo 97 9.56	Mo 98 24.19	Mo 99 66.0 h	Mo 100 9.67
σ 0.5	σ 2.5	σ 0.14	β⁻ 1.2... γ 740; 182; 778... m; g	$1.15 \cdot 10^{19}$ a 2β⁻ σ 0.19

- 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

Bone metastases

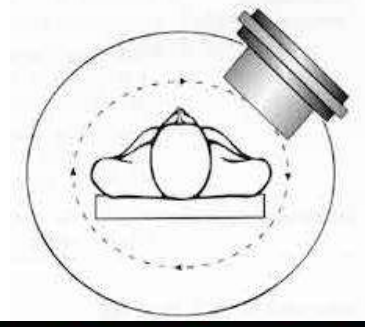


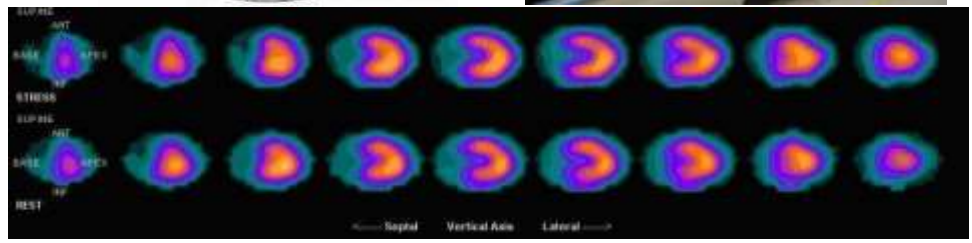


- planar or SPECT scan for bone metastases
- differentiate between local and generalized disease
- decide on treatment options: surgery or radiation therapy versus systemic therapy

Ischemic heart disease

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



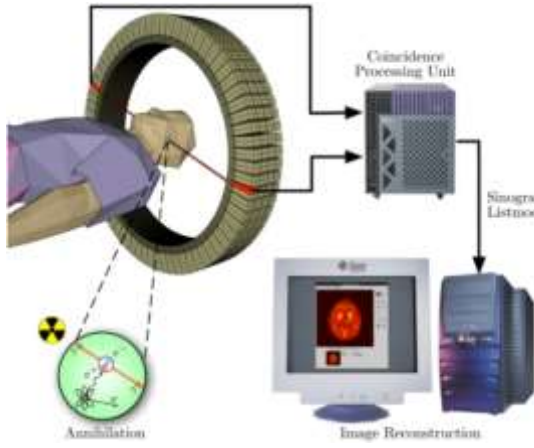


Nuclear cardiology procedures per capita

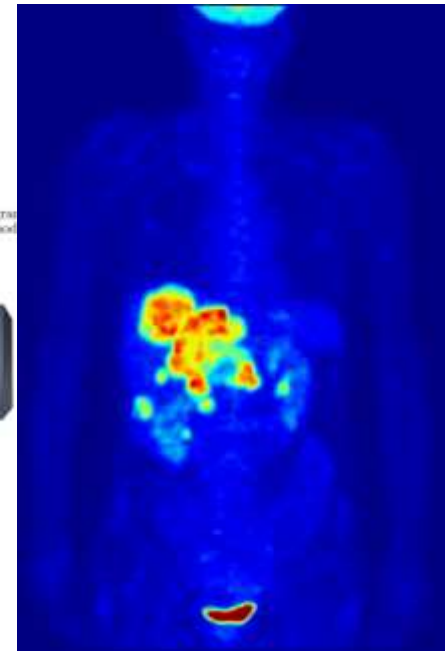
2007: 8.54M myocardial perfusion SPECT procedures reimbursed in the USA

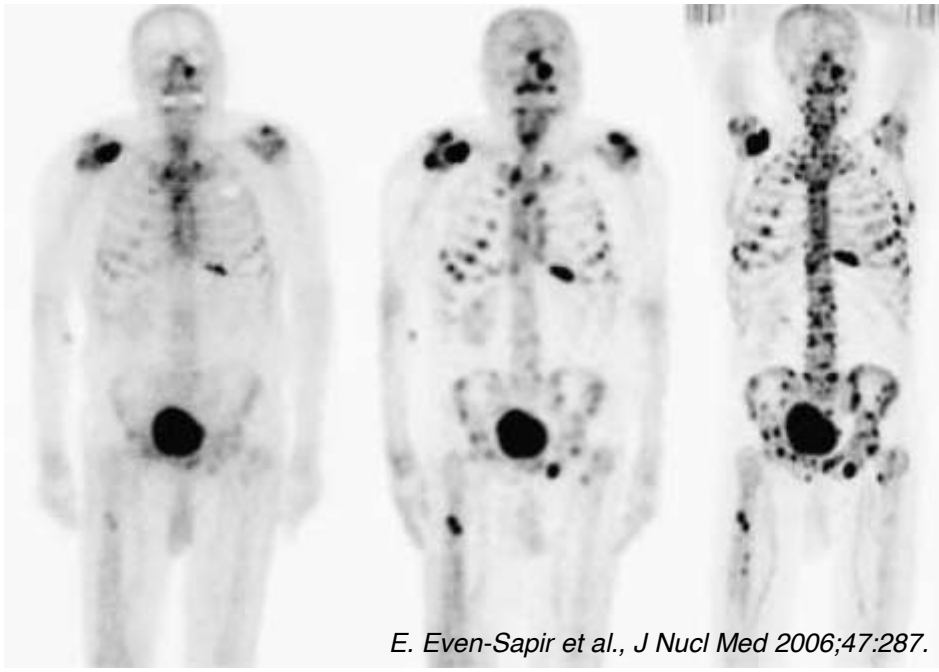
J.V. Vitola et al., J Nucl Cardiol 2009;16:956.

Positron Emission Tomography



^{18}F-Fluorodeoxyglucose (FDG)





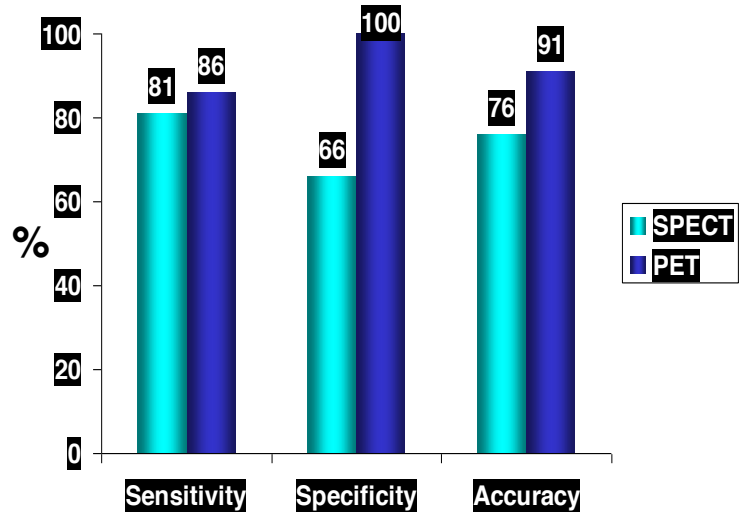
E. Even-Sapir et al., J Nucl Med 2006;47:287.

^{99m}Tc-MDP planar ^{99m}Tc-MDP SPECT ^{18}F^{-} PET

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	**Mother isotope:**	0.74	3.2
F-18	1.83		0.25	0.7
Ga-68	1.13	**271 d**	0.83	3.8
Rb-82	0.02	**25 d**	3.38	20

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



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

Facilities producing ^{82}Sr

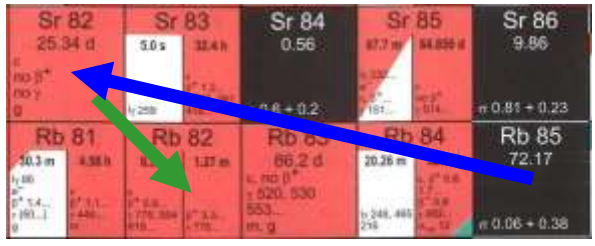
BNL, USA – 200 MeV, 100 μA

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

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

ARRONAX, France – 70 MeV, < 750 μA

SPES, Italy – 70 MeV, < 1000 μA

Zevacor, USA – 70 MeV, < 750 μA

ZDNM, Russia – 70 MeV, < 750 μA

Cancer and efficiency of treatments

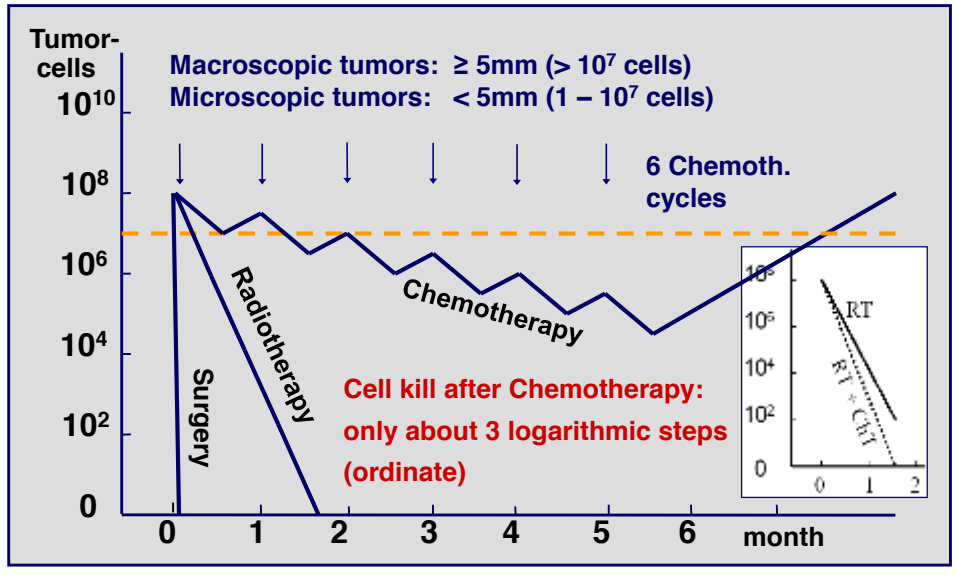
At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	58%	42%	100%
Cured by:			
Surgery	22%		
Radiation therapy	12%		
Surgery + radiation therapy	6%		
All other treatments and combinations incl. chemotherapy		5%	
Fraction cured	69%	12%	45%

Over one million deaths per year from cancer in EU.

⇒ improve early diagnosis

⇒ improve systemic treatments

Comparison of Therapies

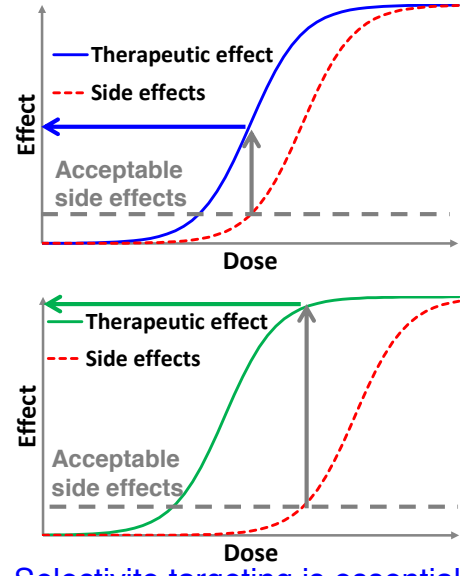


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

Targeted therapies

Paracelsus (1493-1541)

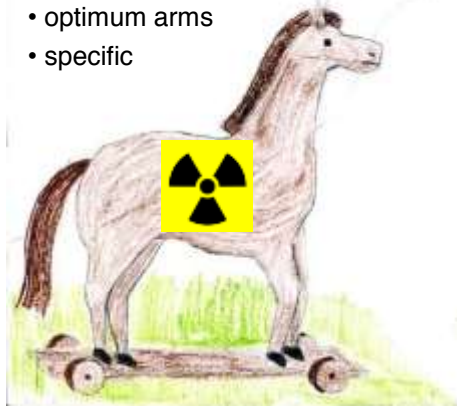
"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous."

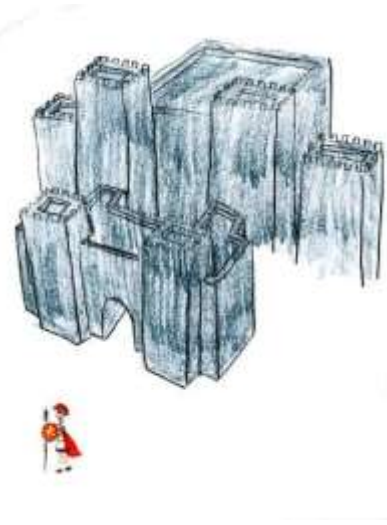


Selectivite targeting is essential to widen the therapeutic window!

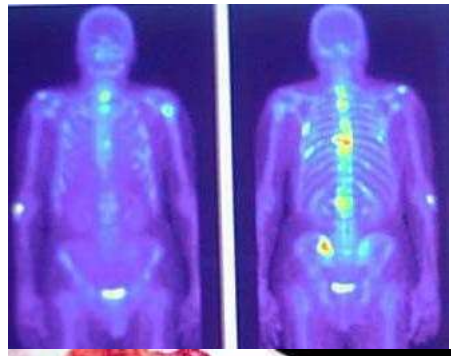
The principle of targeted therapies

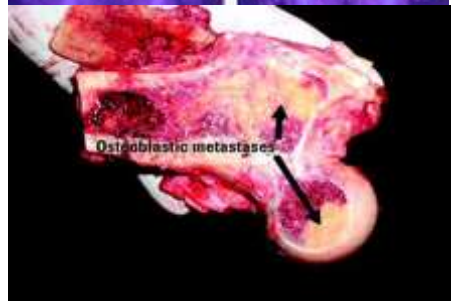
- “attractive” vector > high uptake by the target
- transportable
- good in-vivo stability
- warriors “not visible”
- delayed uptake > suitable half-life
- limited space > high specific activity
- optimum arms
- specific





Metabolic targeting





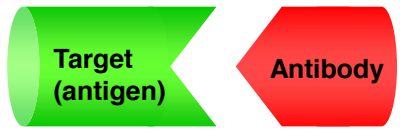
Thyroid cancer
$^{123}I^-$ for imaging
$^{131}I^-$ for therapy

Bone metastases
1.5 million patients world-wide

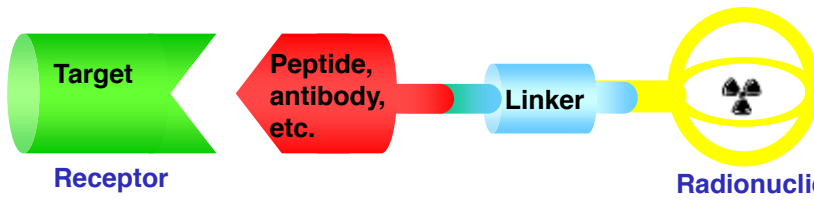
^{99m}Tc-MDP for SPECT imaging
$^{18}F^-$ for PET imaging

Therapy
^{153}Sm-EDTMP (Quadramet)
$^{89}Sr^{2+}$ (Metastron)
$^{223}Ra^{2+}$ (Xofigo/Alpharadin)

Immunology approach



Multidisciplinary collaboration to fight cancer



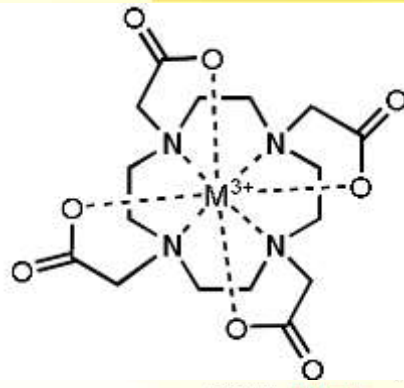
Immunology
Structural biology

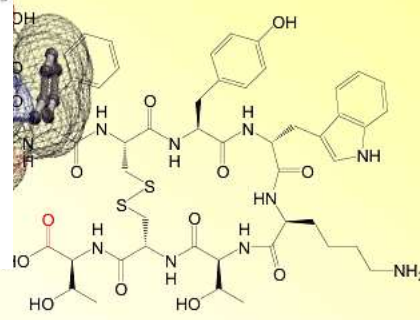
Coordination chemistry

Nuclear physics and radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE





DOTA-TATE

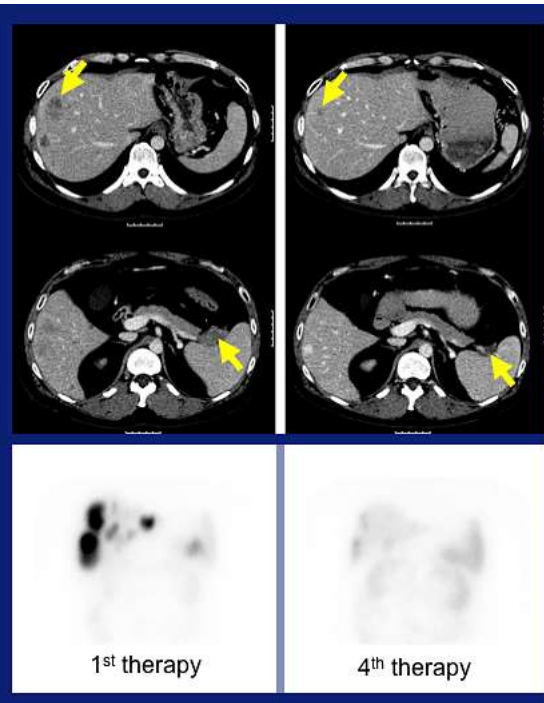
1,4,7,10-tetraazacyclododecantetraacetate

^{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.

Universitätsspital Basel



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.

What success does PRRT offer?

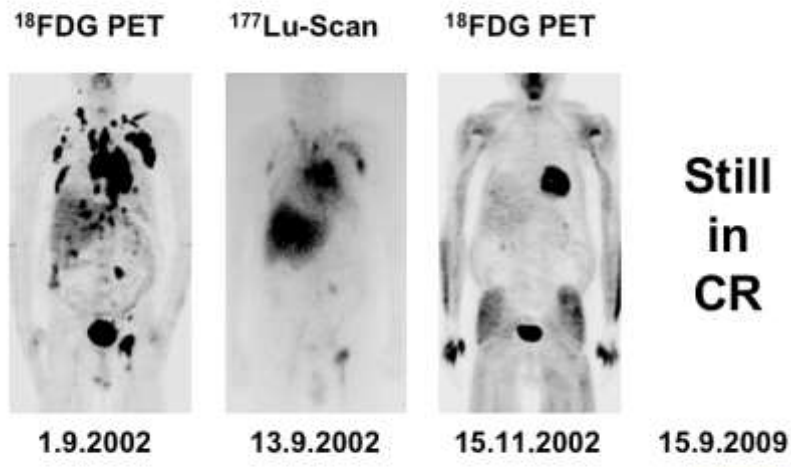
- ✓ CR+ PR + MR in about 50% of patients: YES
- ✓ Reduce symptoms and improve quality of life: YES
- ✓ Increase survival time: YES
- ✓ Safety and tolerability: YES

Roelf Valkema, EANM-2008.

Erasmus MC

Lymphoma therapy: RITUXIMAB+^{177}Lu

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



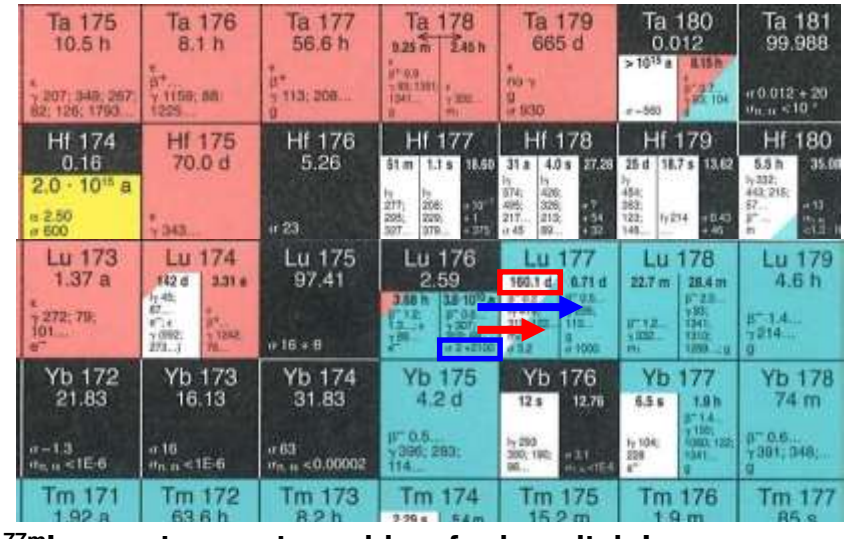
F. Forrer et al., J Nucl Med 2013;54:1045.

University Hospital Basel, CH

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	Established isotopes
I-131	8.0	182 β	364 (82%)	3 mm	
Lu-177	6.7	134 β	208 (10%) 113 (6%)	2 mm	Emerging isotope

Production of ^{177}Lu



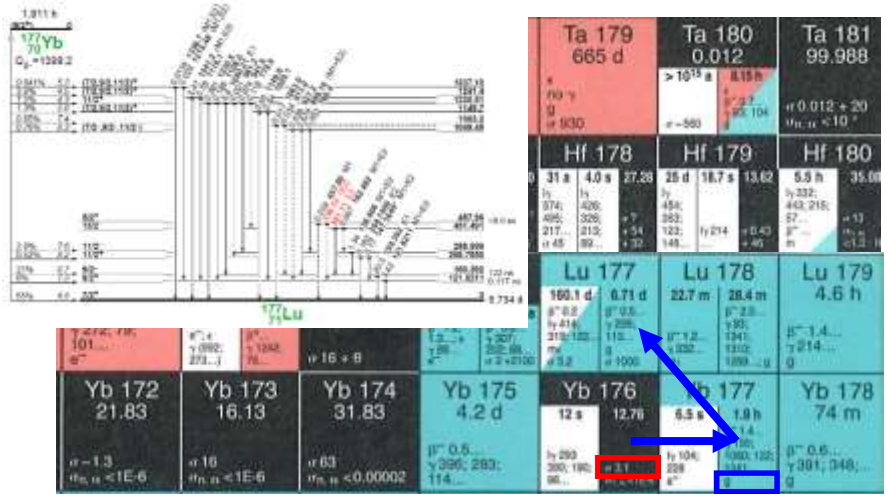
^{177m}Lu creates waste problem for hospitals!

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 !"

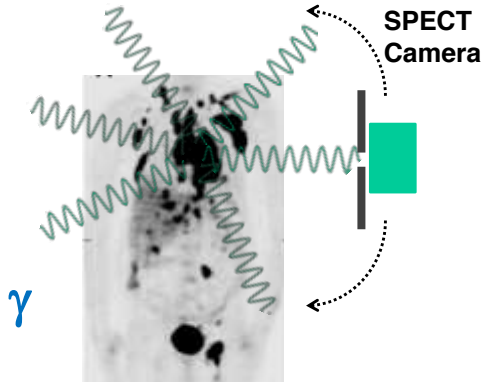
"Clean" production route to ^{177}Lu

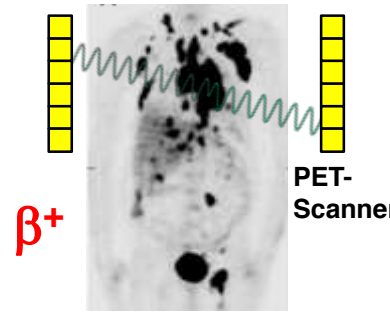


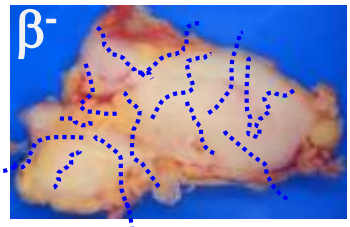
- **Free of long-lived isomer**
- **Non-carrier-added quality**
- **Requires high-flux reactor and advanced radiochemistry**

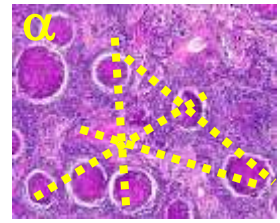
The rising star
for therapy

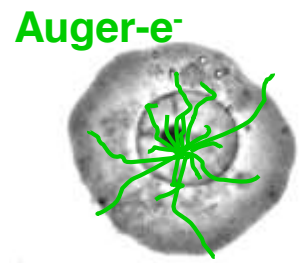
The Nuclear Medicine Alphabet



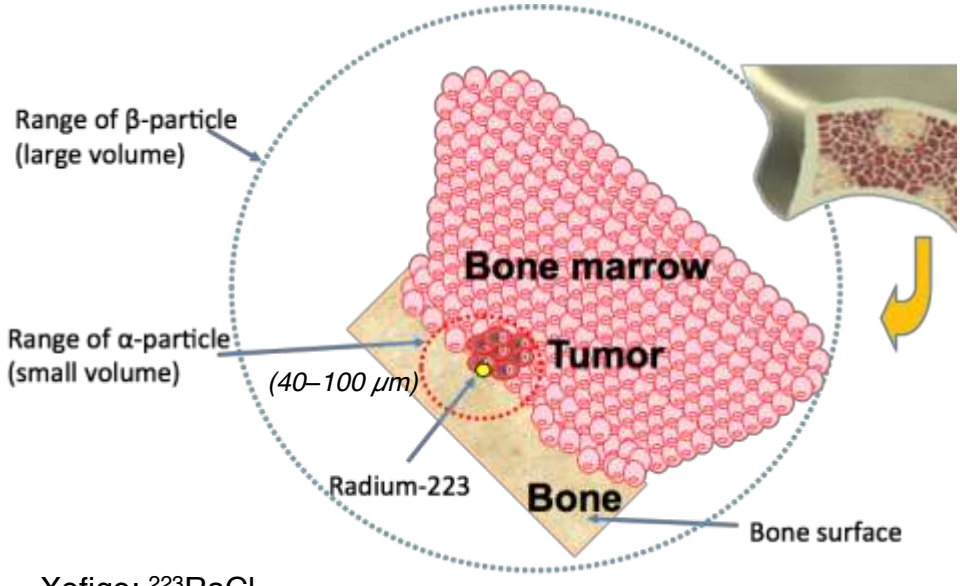








Alpha versus beta for therapy



Xofigo: $^{223}RaCl_2$

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

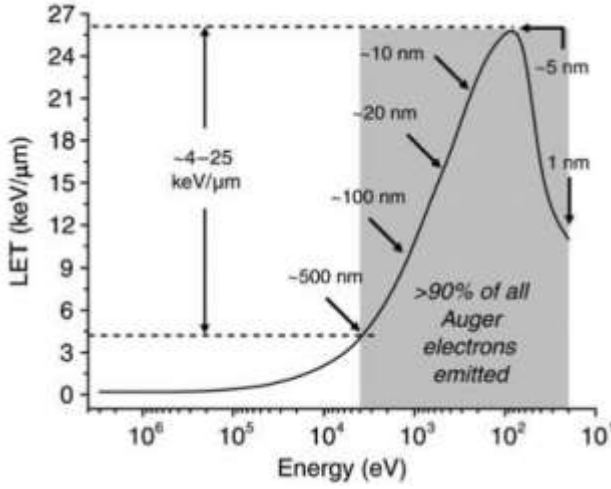
Emerging isotopes

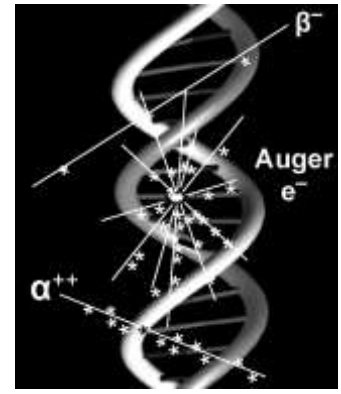
R&D isotopes: supply-limited!

localized

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

Radiobiological effectiveness of Auger electrons





A.I. Kassis, Rad. Prot. Dosimetry 2011;143:241.

Auger therapy ?

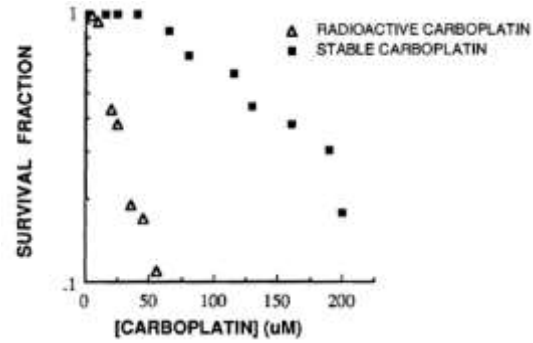
^{194}Pt(n,g)^{195m}Pt < 0.1 b
^{195m}Pt(n,X) 13000 b
<50 MBq/mg with thermal n

about 30 Auger electrons/decay

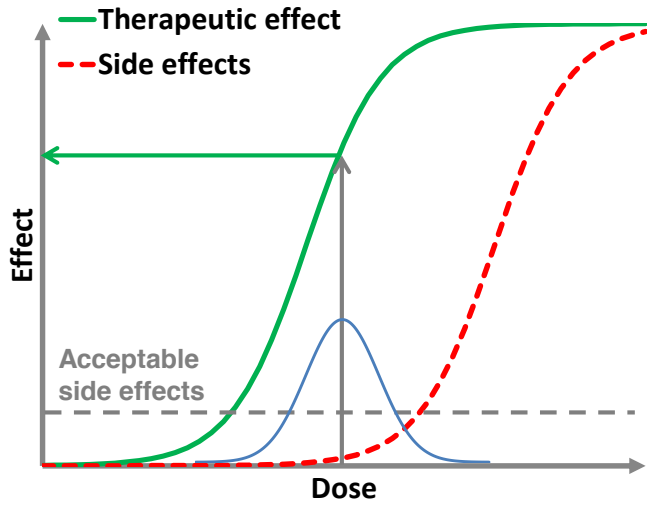
M.T. Azure et al., AAPM Symp 1992;8:336.
J.D. Willins, G. Sgouros, J Nucl Med 1995;36:315.

Combined chemo-radiotherapy may overcome resistance to chemotherapy!

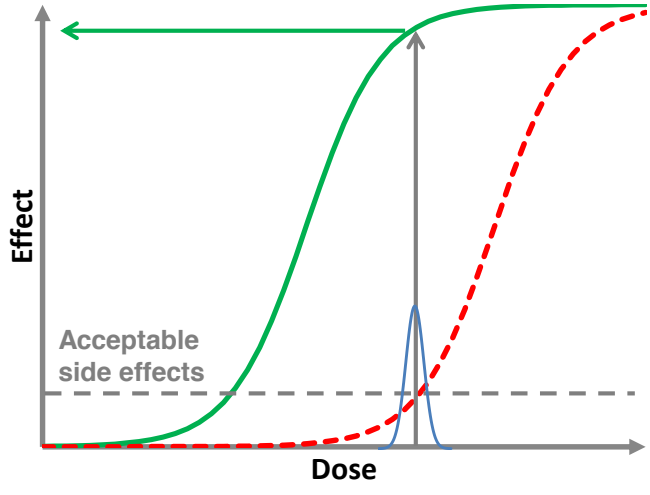
Cancer cell survival



Theranostics

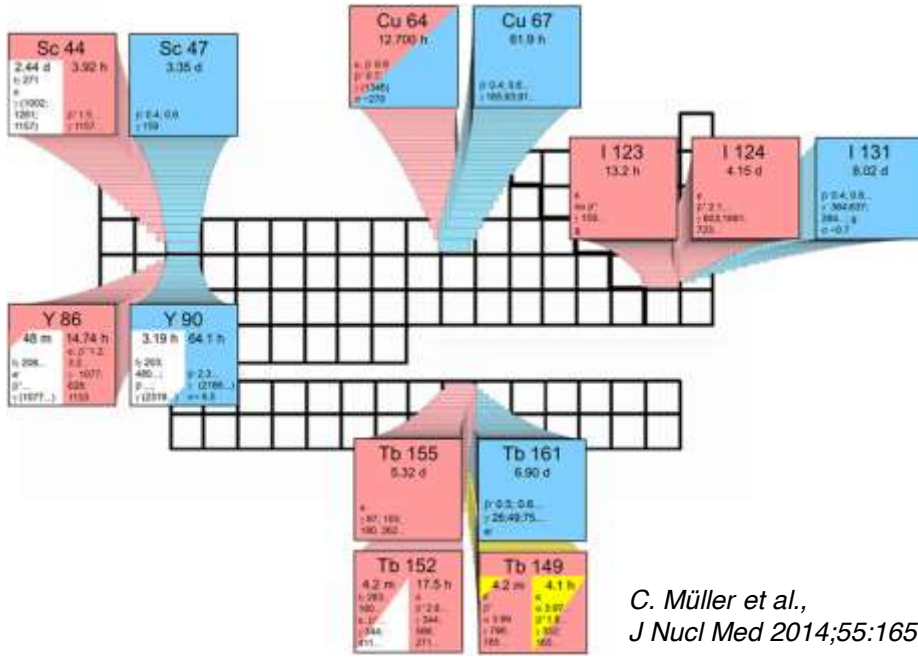


Theranostics



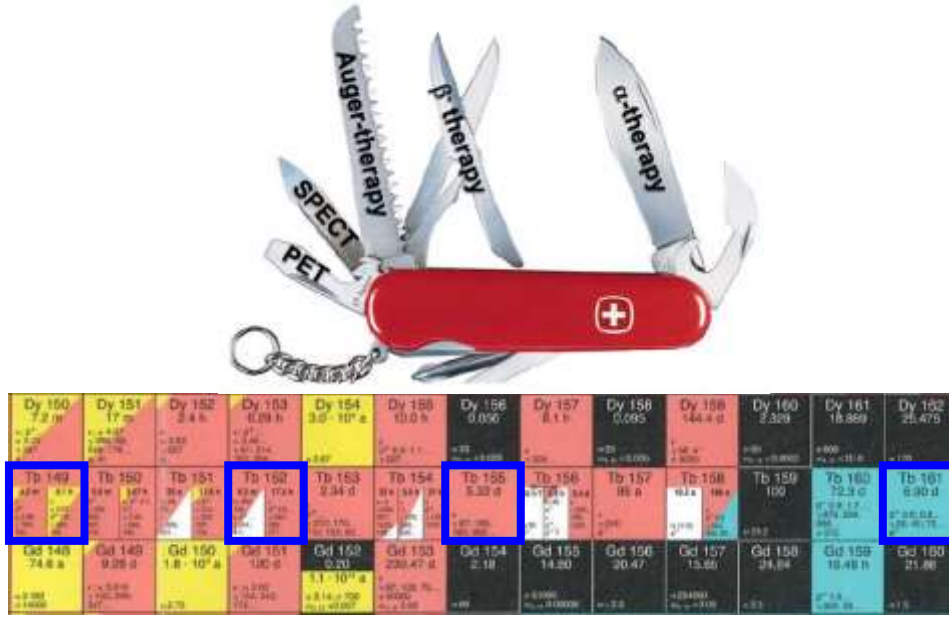
Accurate dosimetry is essential for optimum use of the therapeutic window.

Matched pairs for theranostics

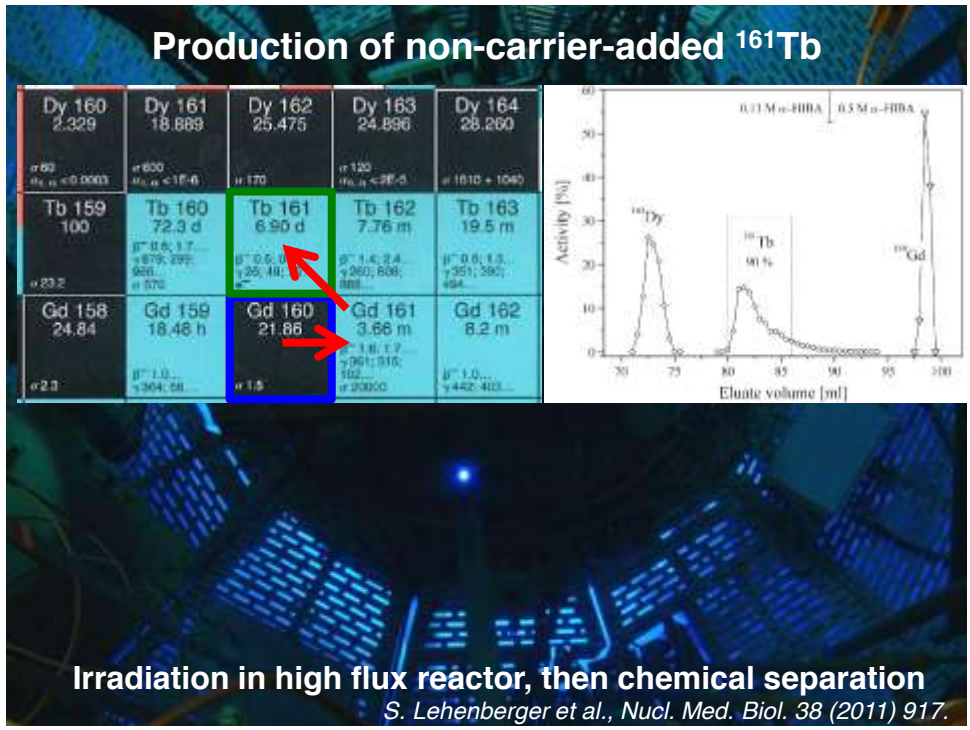


C. Müller et al.,
J Nucl Med 2014;55:1658.

Terbium: a unique element for nuclear medicine



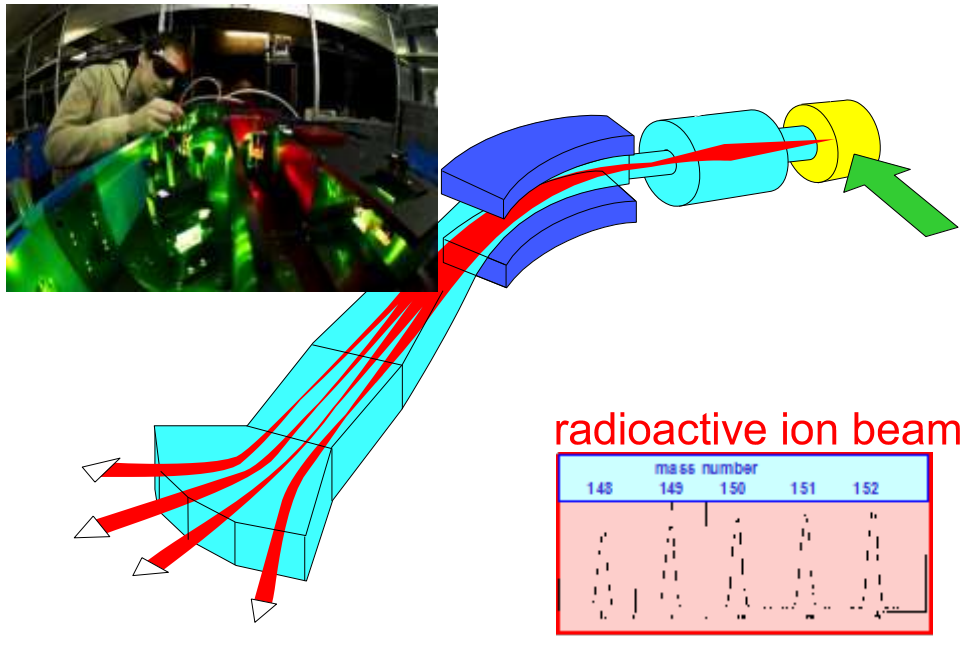
Production of non-carrier-added ^{161}Tb



Irradiation in high flux reactor, then chemical separation

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

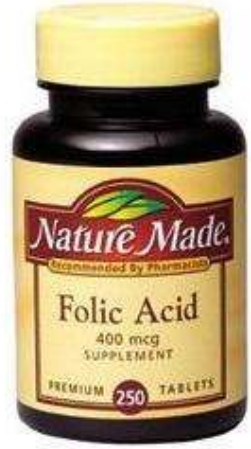
^{149,152,155}Tb from CERN-ISOLDE



Folate-receptor positive cancers

Frequent overexpression of folate receptor in cancer of:

- ovaries
- cervix uteri
- lung
- kidney
- brain
- colon
- breast
- leukemia

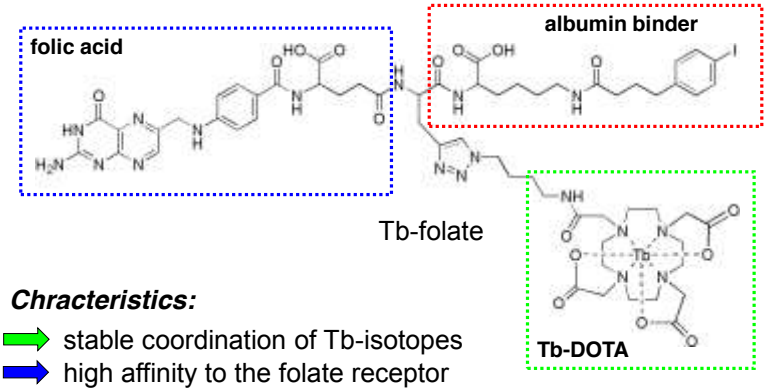


folic acid = vitamine B9

C. Müller, Curr. Pharmaceut. Design 2012;18:1058.

Tumor Tageting Agent for Tb-Coordination

Chemical Structure with 3 Functionalities



Tb-folate

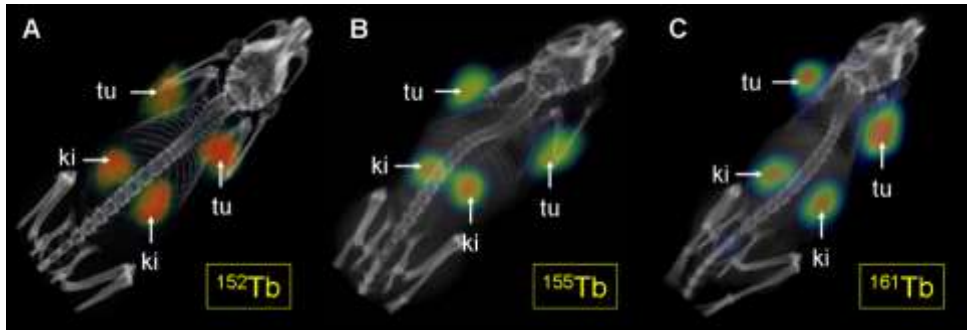
Chracteristics:

- stable coordination of Tb-isotopes
- high affinity to the folate receptor
- prolonged blood circulation time

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

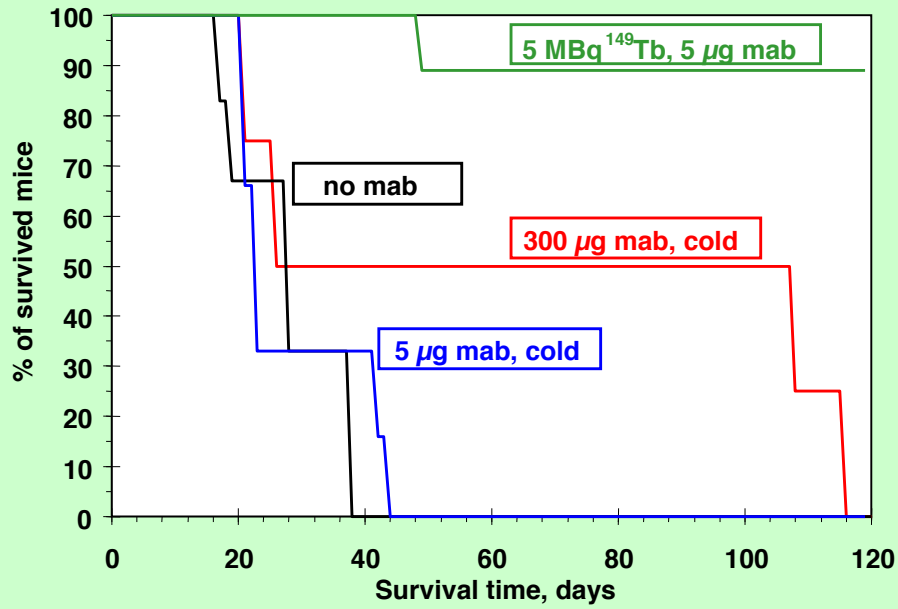
Theranostics with terbium isotopes

PET *SPECT* *SPECT*



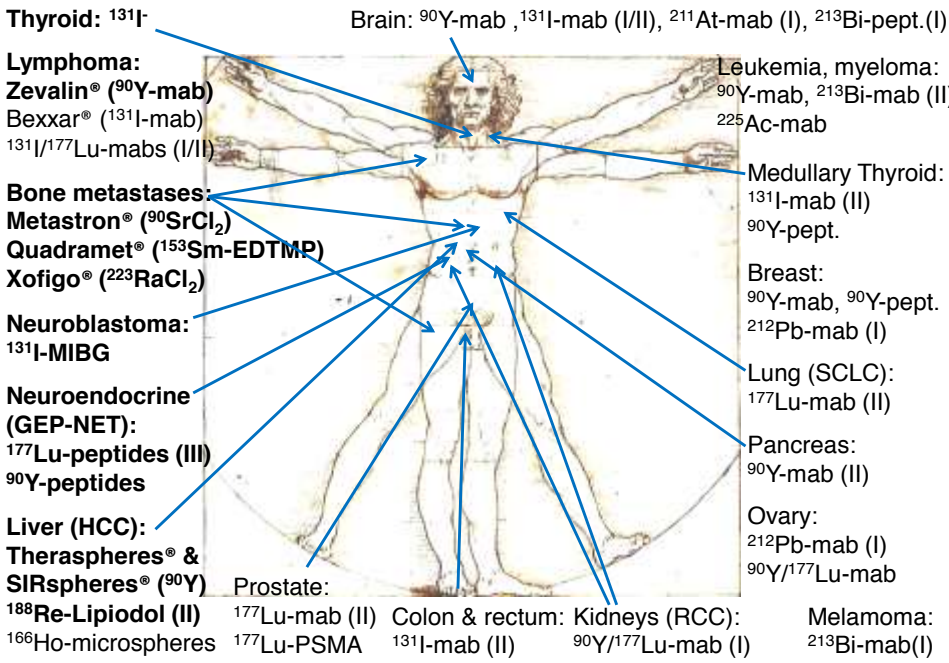
C. Müller et al., J Nucl Med 2012;53:1951.

Preclinical study with lymphoma mouse model



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

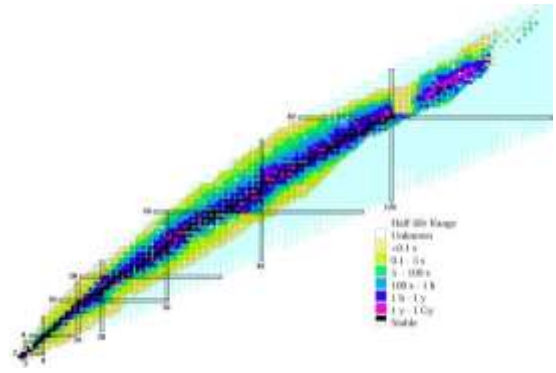
Targeted radionuclide therapies in the clinic



Paracelsus (1493-1541)

"Many have said of Alchemy, that it is for the making of gold and silver. For me such is not the aim, but to consider only what virtue and power may lie in medicines."

(Edwardes)



500 years later:

"Many have said of nuclear physics, that it is for the making of gold and silver (and other elements') isotopes. For us such is not the only aim, but also to consider what virtue and power may lie in it for medicine."

Bibliography

- Nuclear Physics for Medicine, NuPECC 2014
  http://www.nupecc.org/npmed/npmed2014.pdf
- Nuclear Medicine Physics. A Handbook for Teachers and Students, IAEA Vienna 2014, STI/PUB/1617.
- 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