Medical radioisotopes

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ESIPAP
8 March 2017


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


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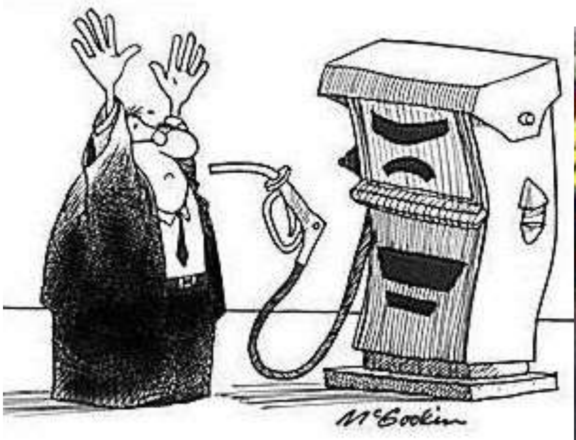
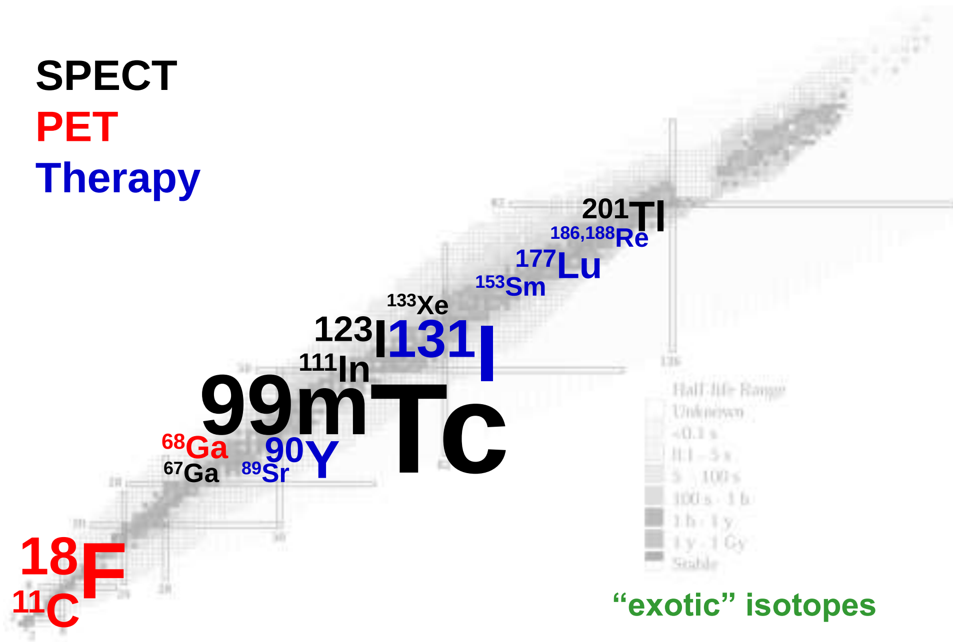
Don’t forget the fuel!



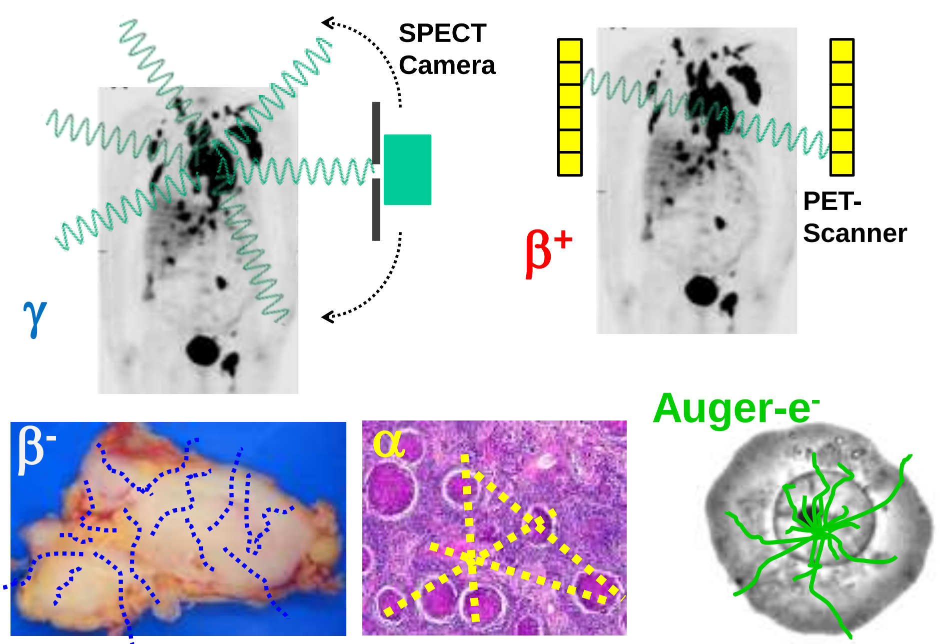
Radioisotopes: the “fuel” for nuclear medicine

1. What is the optimum fuel for an application ?
2. Are we using the optimum fuel today ?
3. Where does this fuel come from ?

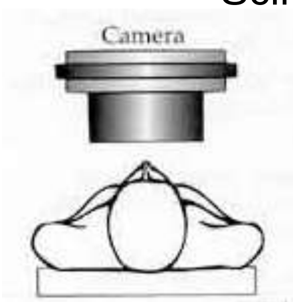
The chart of nuclides – nuclear medicine perspective

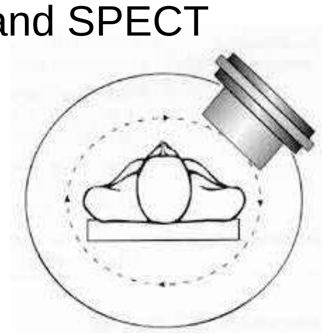


The Nuclear Medicine Alphabet



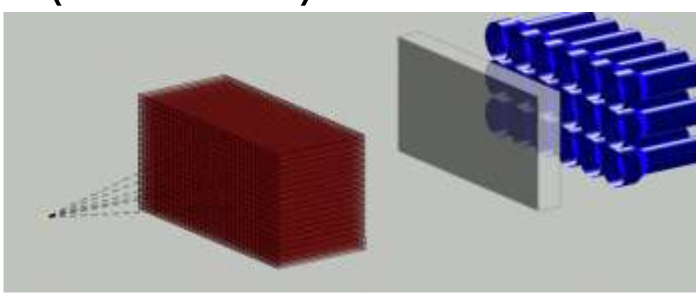
Scintigraphy and SPECT



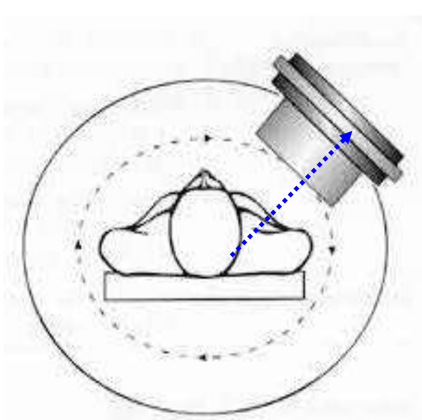


2D: planar scan (Gamma camera)

3D: SPECT: Single Photon Emission Computed Tomography



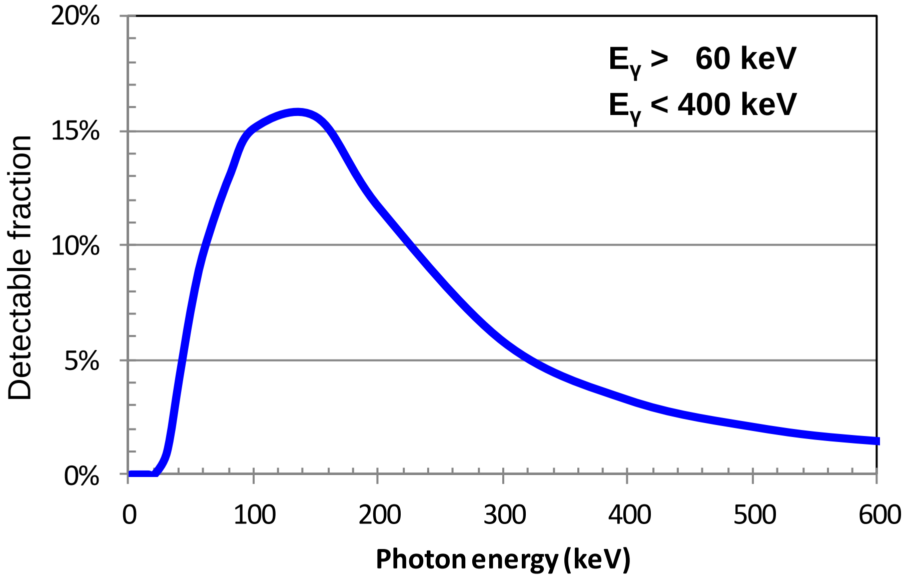
Ideal gamma ray energy for scintigraphy/SPECT?



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

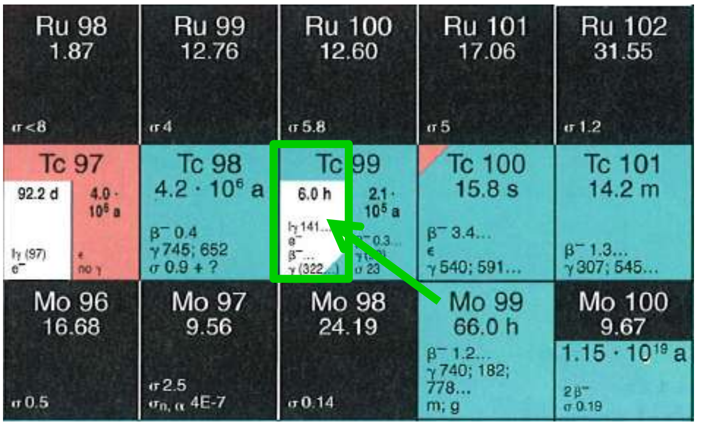
10 cm soft tissue
0.2 cm aluminium (detector encapsulation)
1 cm NaI

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

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

$$dN_{Mo}/dt = - \lambda_{Mo} N_{Mo}$$

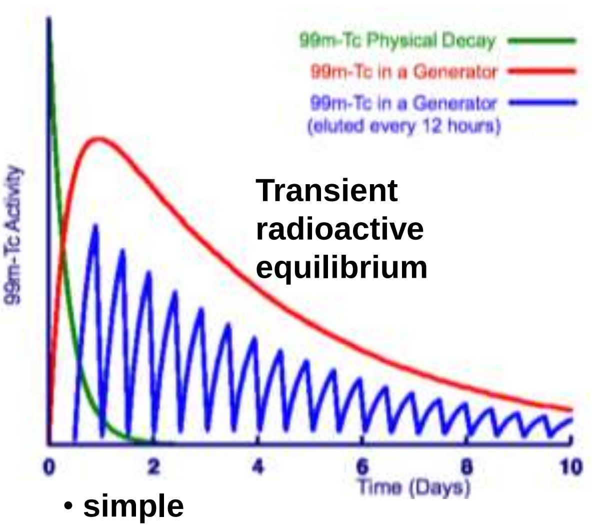
$$N_{Mo}(t) = N_{Mo}(0) \exp(- \lambda_{Mo} t)$$

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

$$dN_{Tc}/dt = \lambda_{Mo} N_{Mo} - \lambda_{Tc} N_{Tc}$$

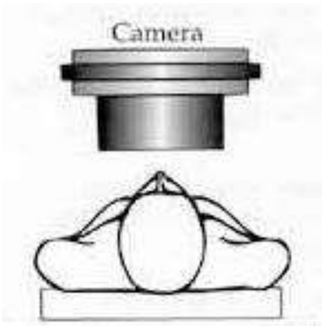
$$N_{Tc}(t) = N_{Tc}(0) \exp(- \lambda_{Tc} t) + \frac{\lambda_{Mo}}{\lambda_{Tc} - \lambda_{Mo}} N_{Mo} [\exp(- \lambda_{Mo} t) - \exp(- \lambda_{Tc} t)]$$

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

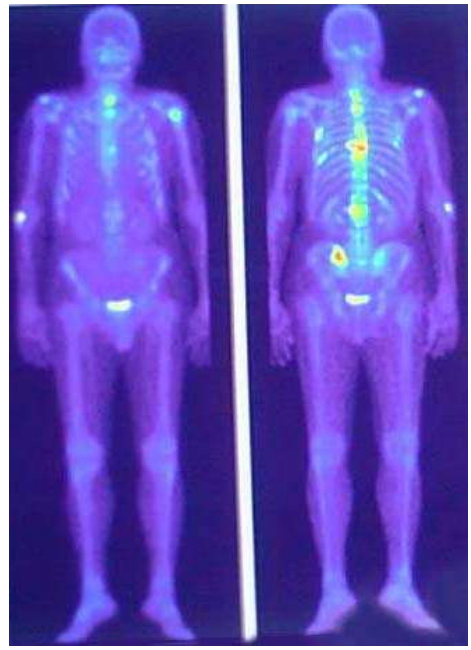


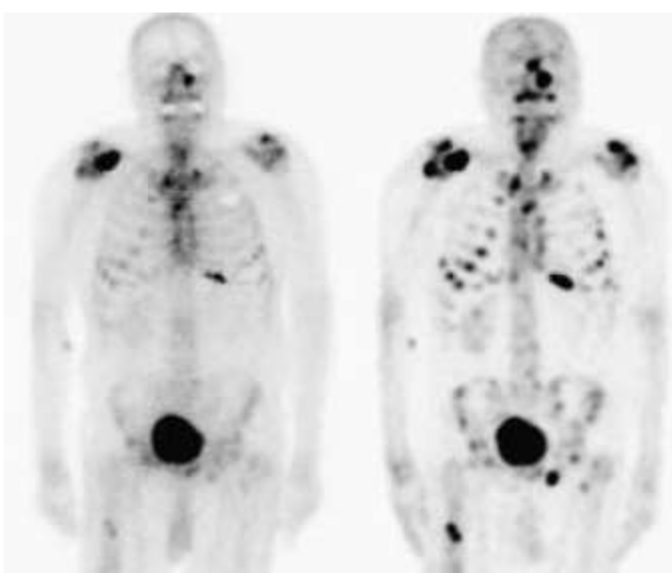
- **simple**
- **reliable**
- **portable**
- **self-shielded**

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



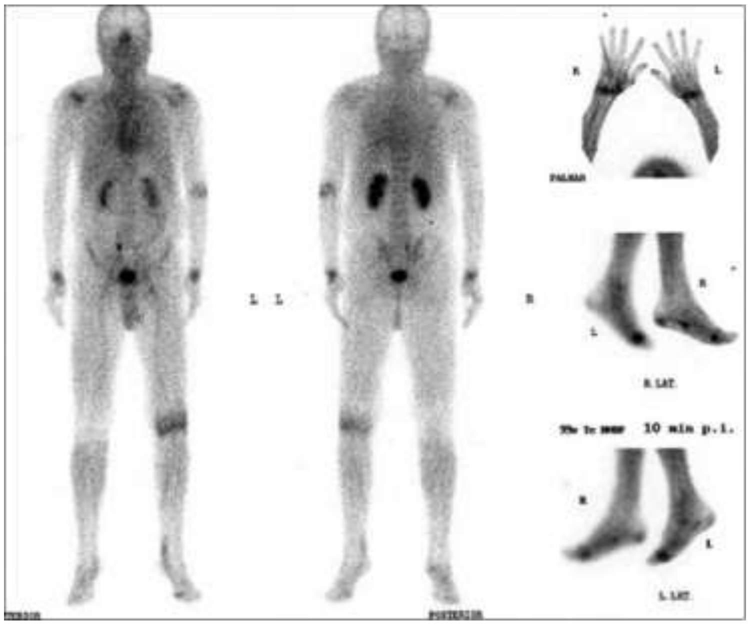


Bone scans: 35% of NM procedures in Europe

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

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

Rheumathoid arthritis

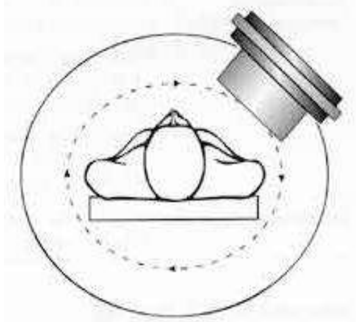


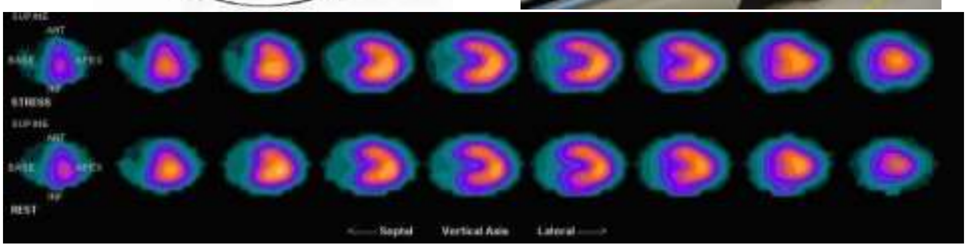
L. Knut, World J Nucl Med. 2015; 14:10.

Veterinary scintigraphy

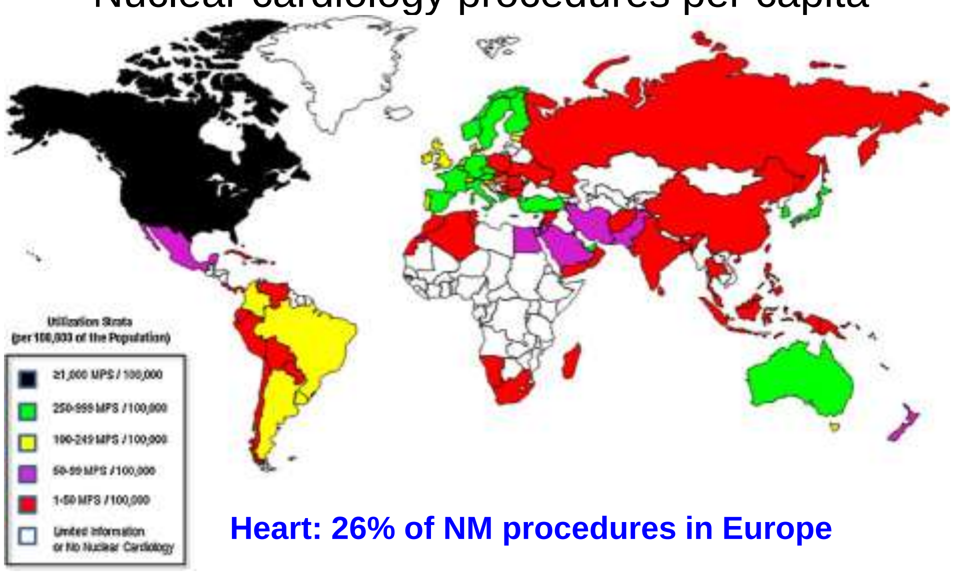
Ischemic heart disease

- 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

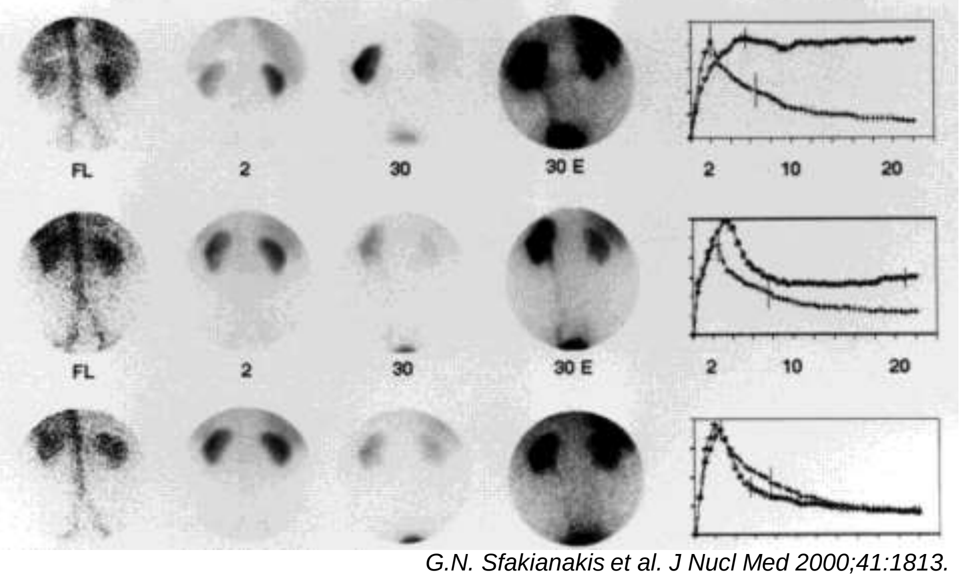
J.V. Vitola et al., J Nucl Cardiol 2009;16:956.

Ischemic heart disease

age-standardized death rates (per year):

US 1‰, UK/DE/DK/SE 0.9‰, CH/IT 0.6‰, FR 0.38‰

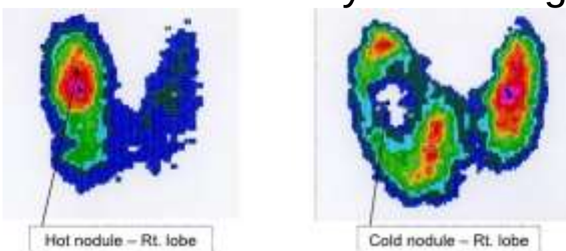
Scintirenography

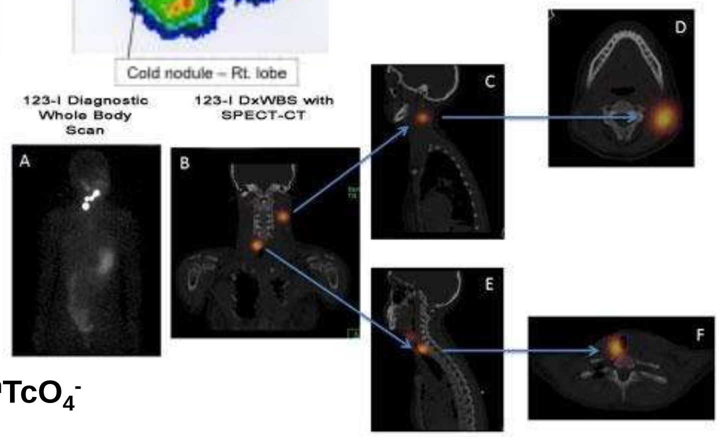


G.N. Sfakianakis et al. J Nucl Med 2000;41:1813.

Kidney: 13% of NM procedures in Europe

Thyroid scintigraphy



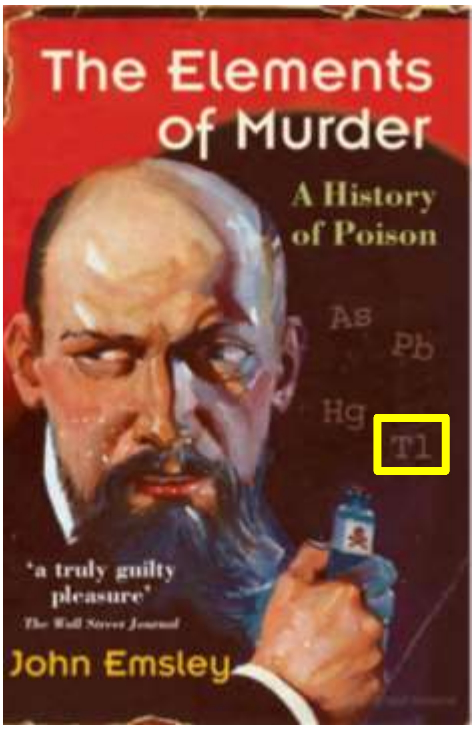


$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$

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^-

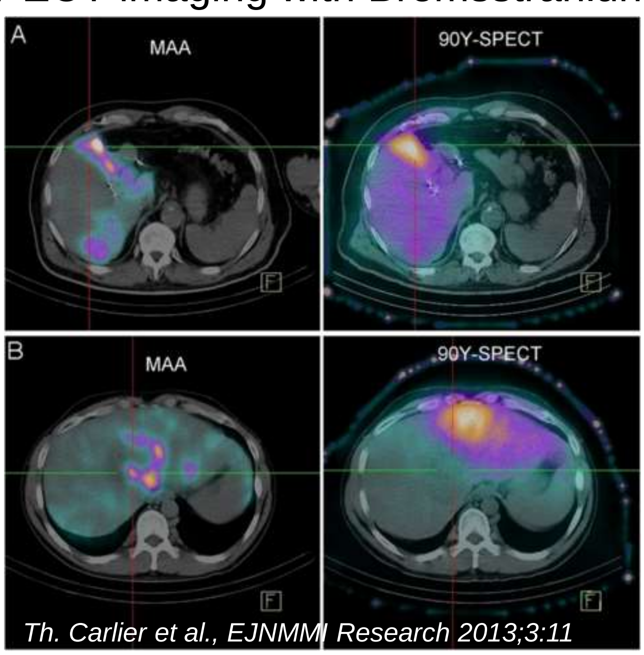


Thallium for patients ?

- 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!

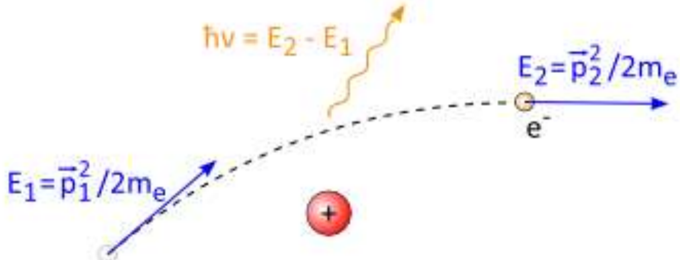
$A/m = \lambda N_A/M = N_A \ln(2)/(M \cdot T_{1/2})$
specific activity (Bq/g)

SPECT imaging with Bremsstrahlung



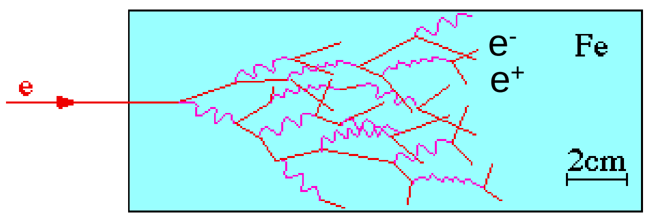
Th. Carlier et al., EJNMMI Research 2013;3:11

Bremsstrahlung

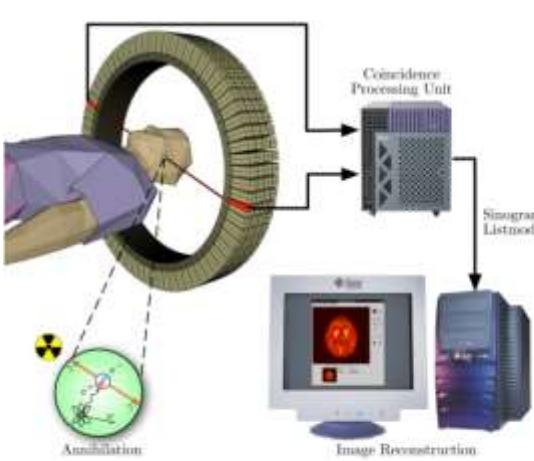


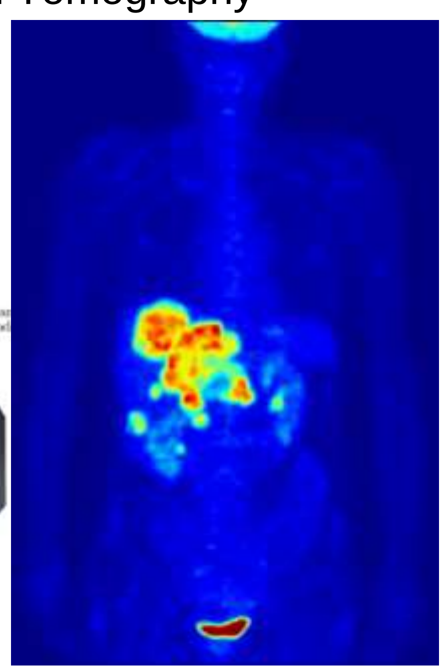
$$\left.\frac{dE}{dx}\right|_{BS} = -\frac{E}{X_0} \qquad X_0 \propto \frac{A}{Z^2} \quad \text{radiation length}$$

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



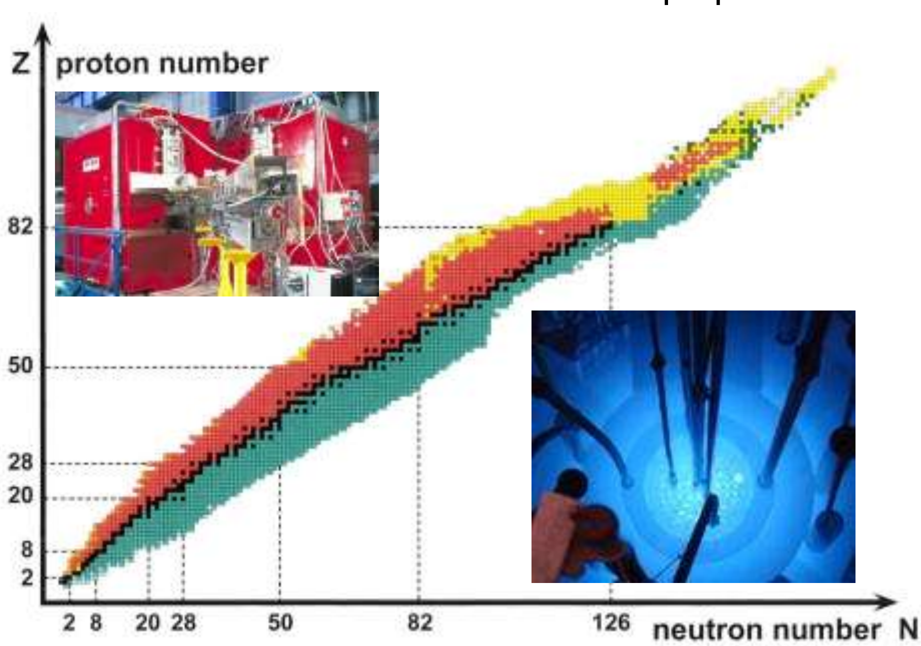
Positron Emission Tomography



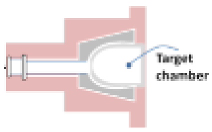


The Tordesillas meridian

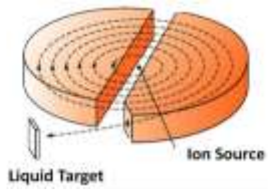
The Tordesillas meridian of radioisotope production



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

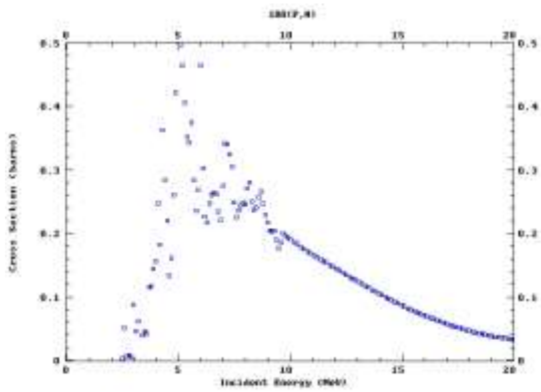


$H_2{}^{18}O$ (water)



Cyclotron irradiation

Transformation into FDG

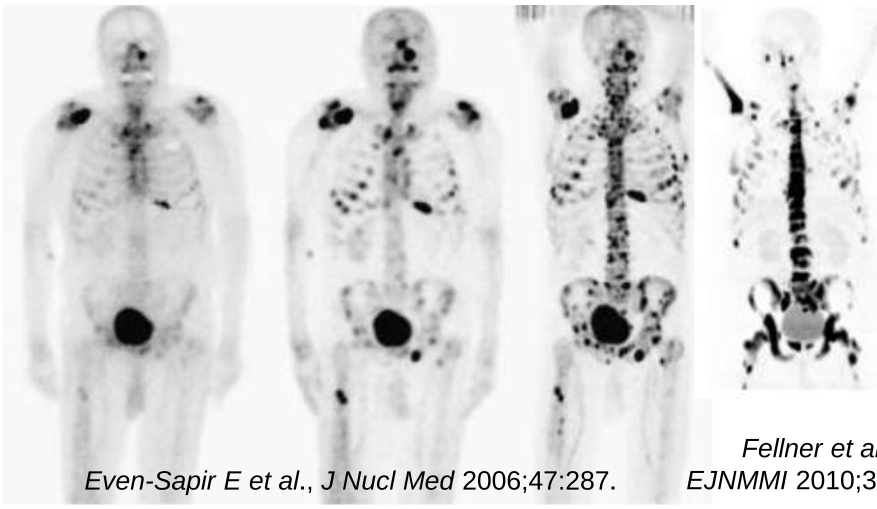


PET isotopes

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**

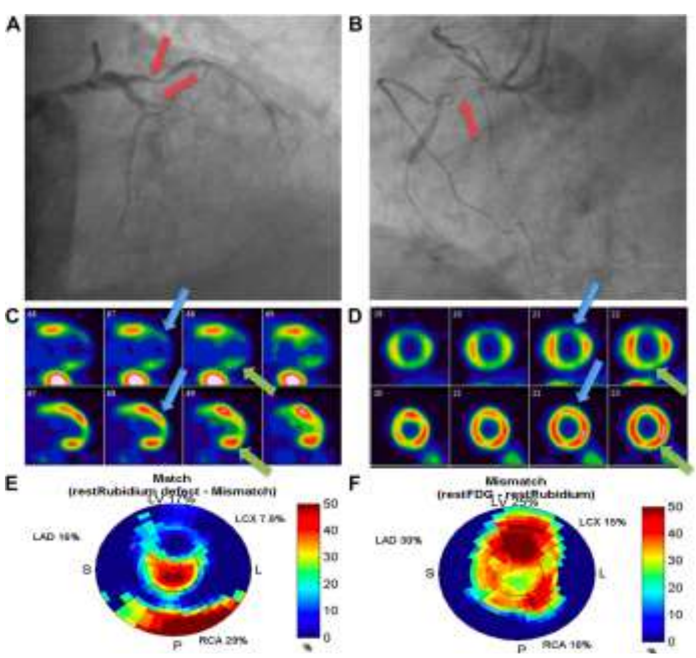
Transport of short-lived radioisotopes

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		0.74	3.2
F-18	1.83		0.25	0.7
Ga-68	1.13		0.83	3.8
Rb-82	0.02		3.38	20

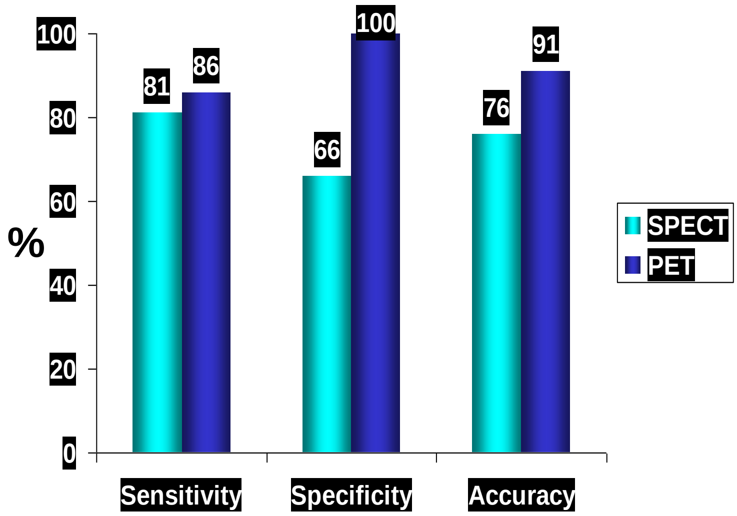
Mother isotope:
271 d
25 d

Cardiology applications



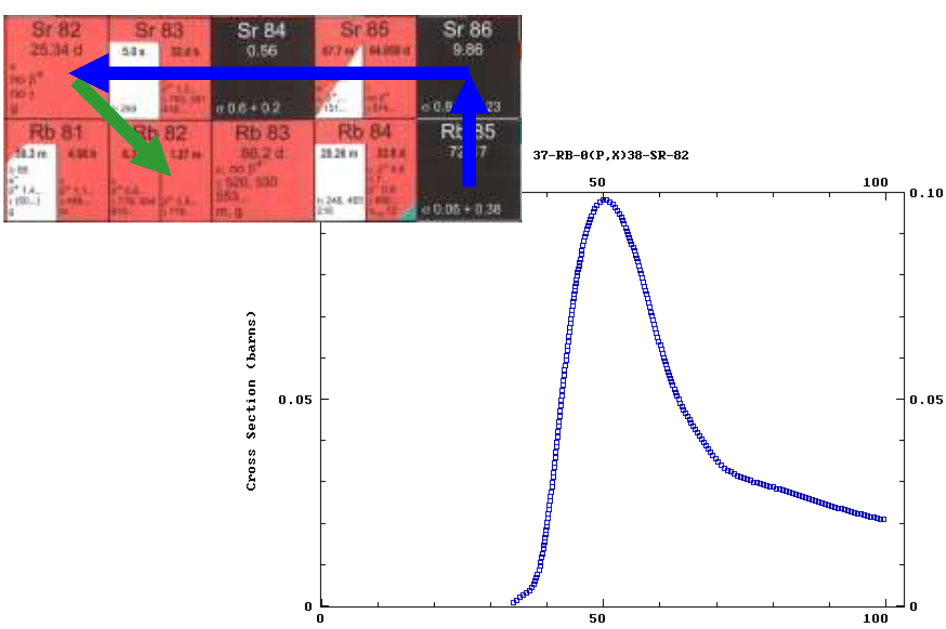
B.A. Mc Ardle, Can. J. Cardiology 29 (2013) 399.

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

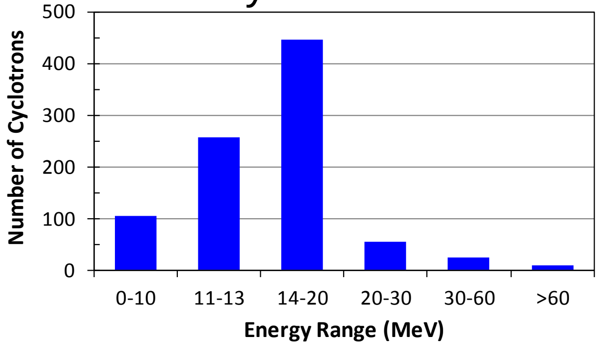


Bateman et al, J Nucl Cardiol 2006;13:24.

^{82}Sr production



Cyclotrons: the work horses



11 MeV 18 MeV 30 MeV 70 MeV

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

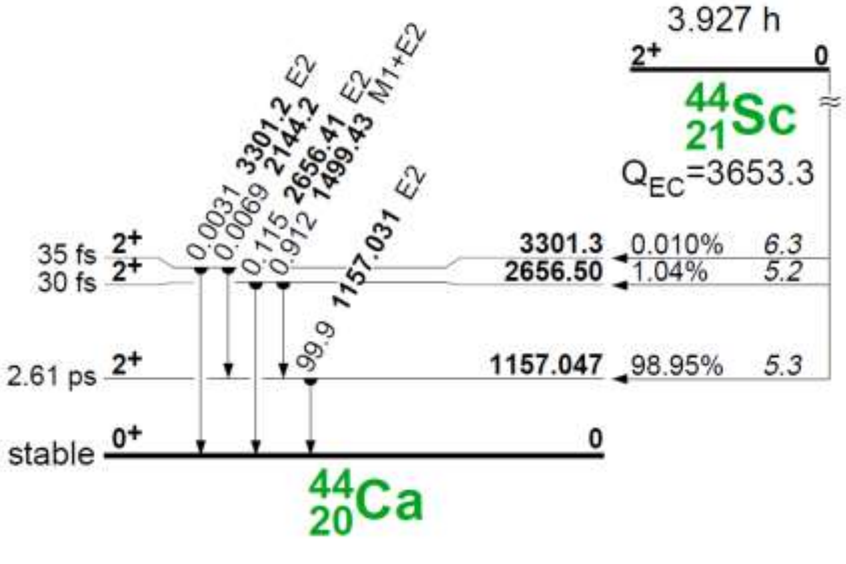
SPES, Italy – 70 MeV, < 1000 µA

Zevacor, USA – 70 MeV, < 750 µA

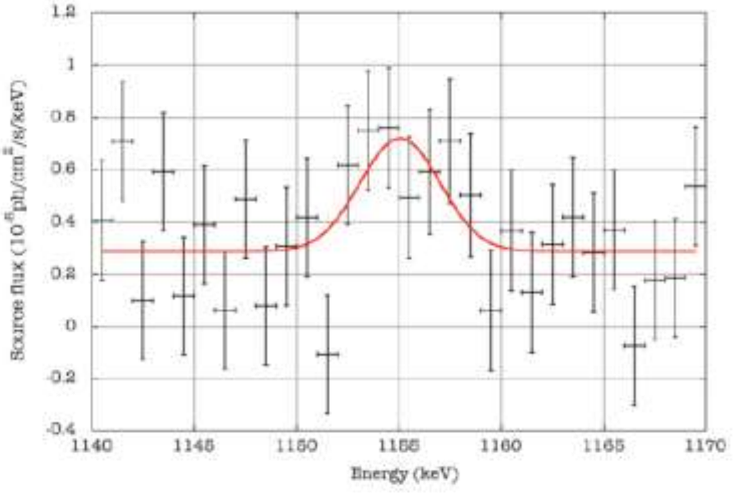
ZDNM, Russia – 70 MeV, < 750 µA

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	

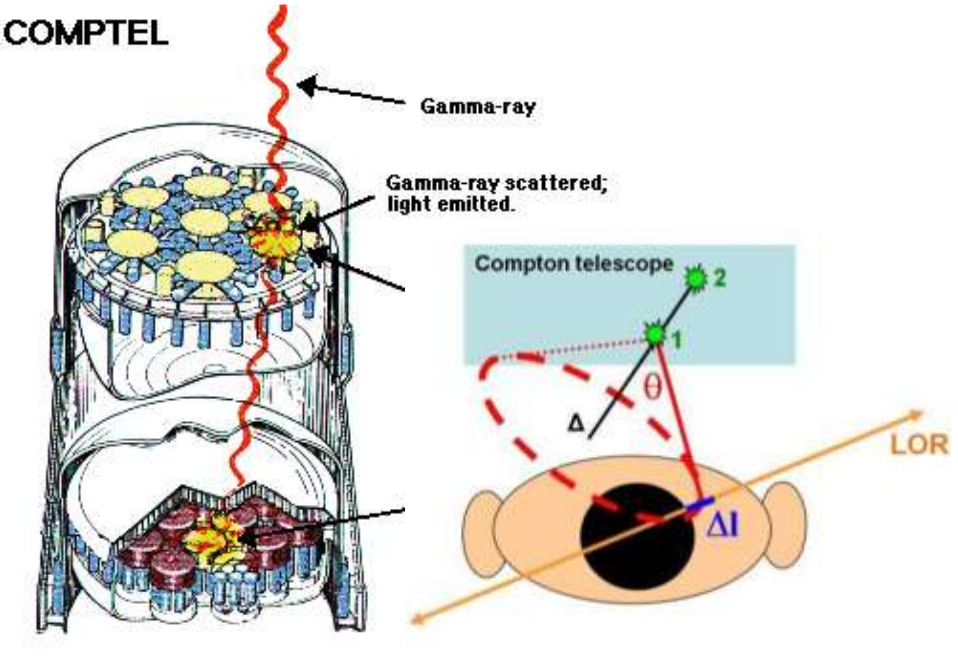


^{44}Sc in the universe

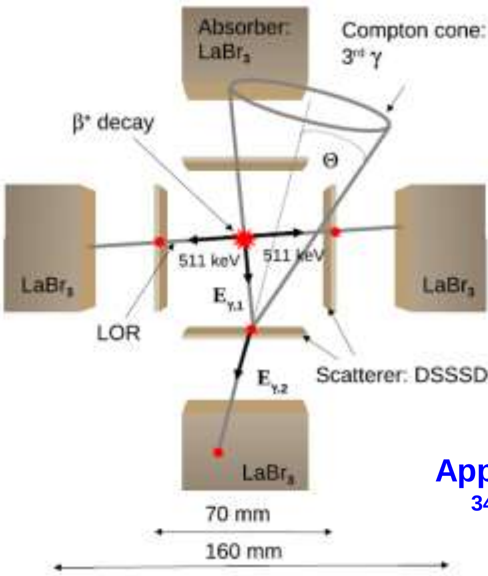


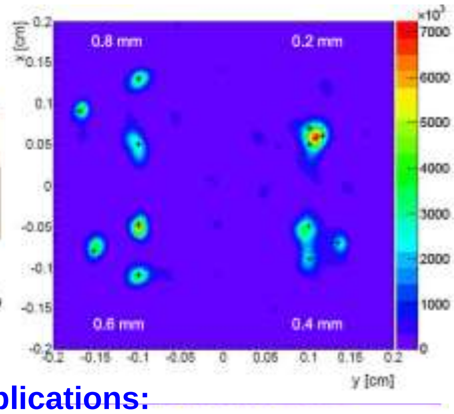
M. Leising, R. Diehl, PoS 2009.

Compton telescope



3-photon-camera: PET-SPECT





Applications:

^{34m}Cl, ^{44}Sc, ^{44m}Sc, ^{52}Mn, ^{52m}Mn, ^{86}Y, ^{94g}Tc, ^{94m}Tc, ^{124}I, ^{10}C, ^{14}O

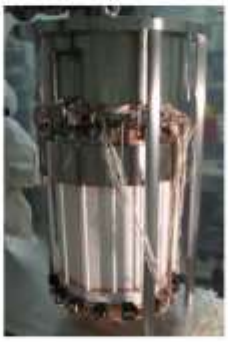
C. Lang et al. JINST 2014;9:P01080.

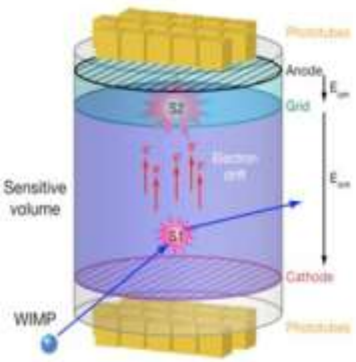
Alternative detector

a more efficient Compton scatterer than Si ?

with large sensitive volume ?

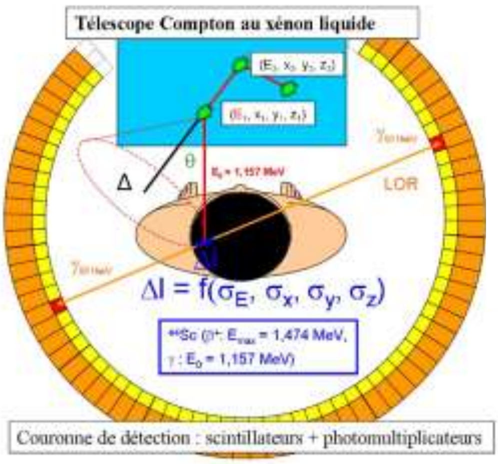
100 kg LXe dual-phase TPC

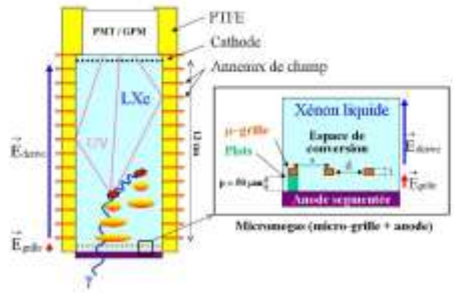




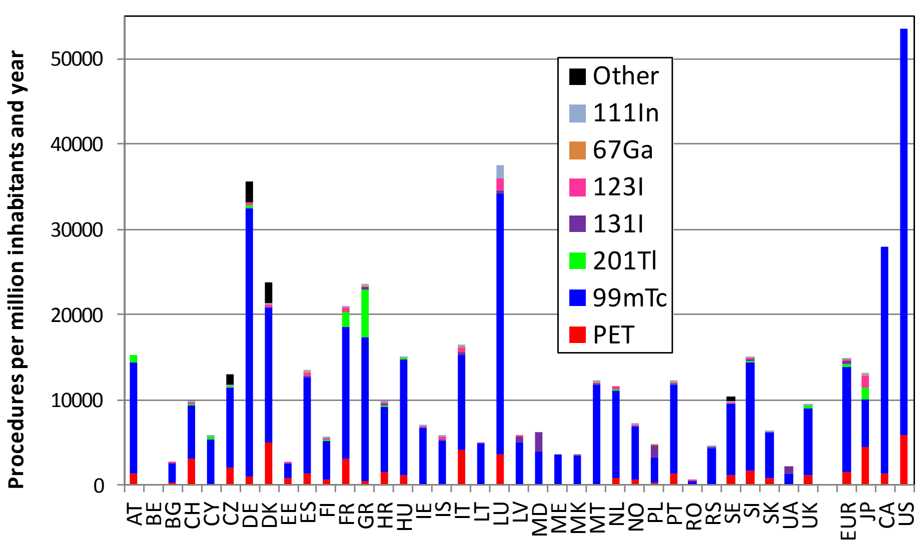
Johann Collot collot@in2p3.fr http://lpsc.in2p3.fr/collot UGA 6/33

XEMIS2 Xenon-TPC



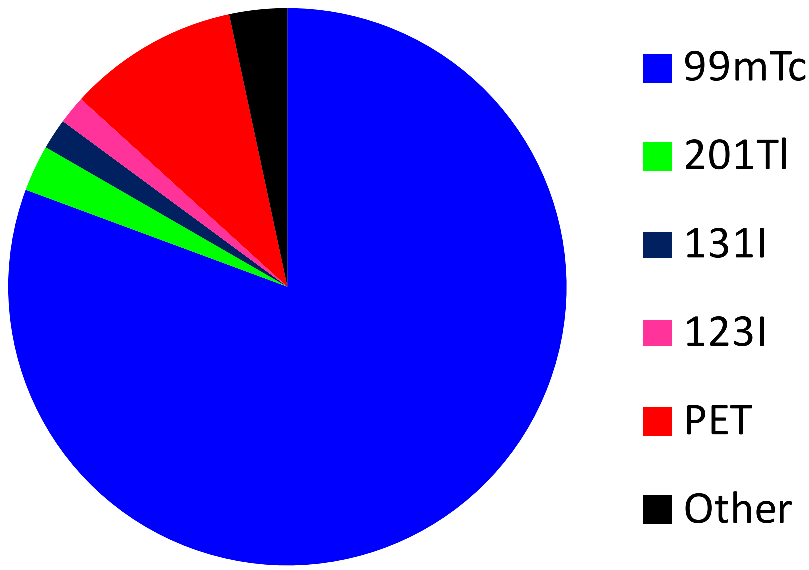


Statistics of radionuclide use in Europe



Use of diagnostic isotopes in Europe, USA, Canada and Japan

Cumulative use of diagnostic isotopes in Europe

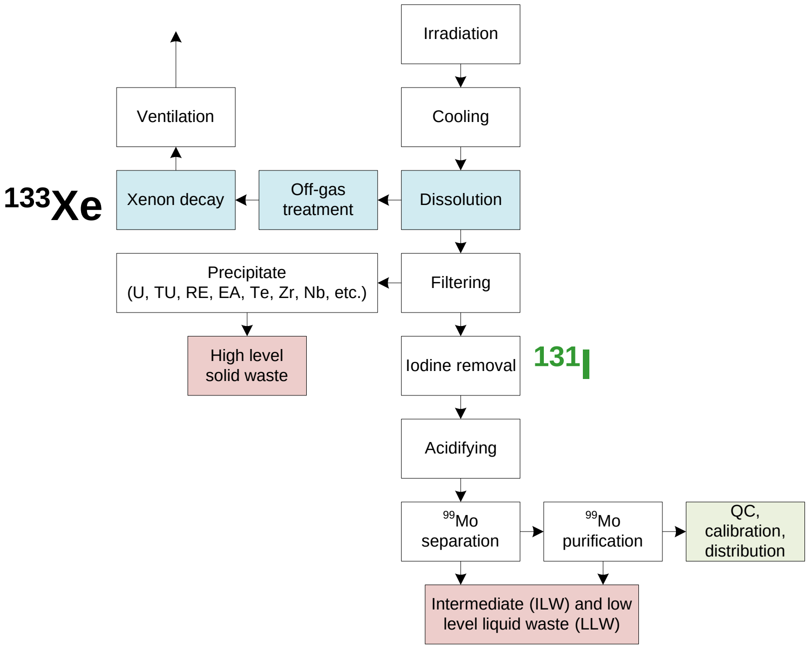


Fission production

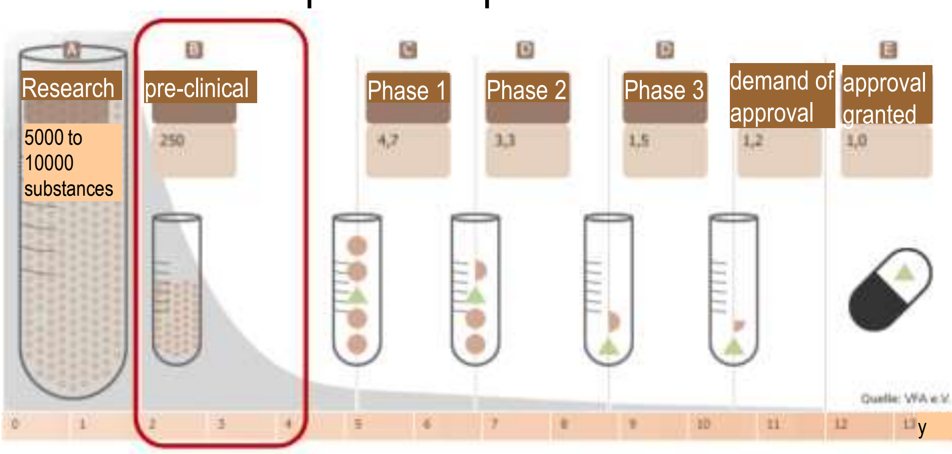
After irradiation, decay and chemical processing:

^{99}Mo/^{all}Mo ≈ 10%, i.e. 10% of theoretical specific activity 480 kCi/g

Extraction of fission-moly



Development of pharmaceuticals



Screening in vitro tests
animal exp.

tests with humans

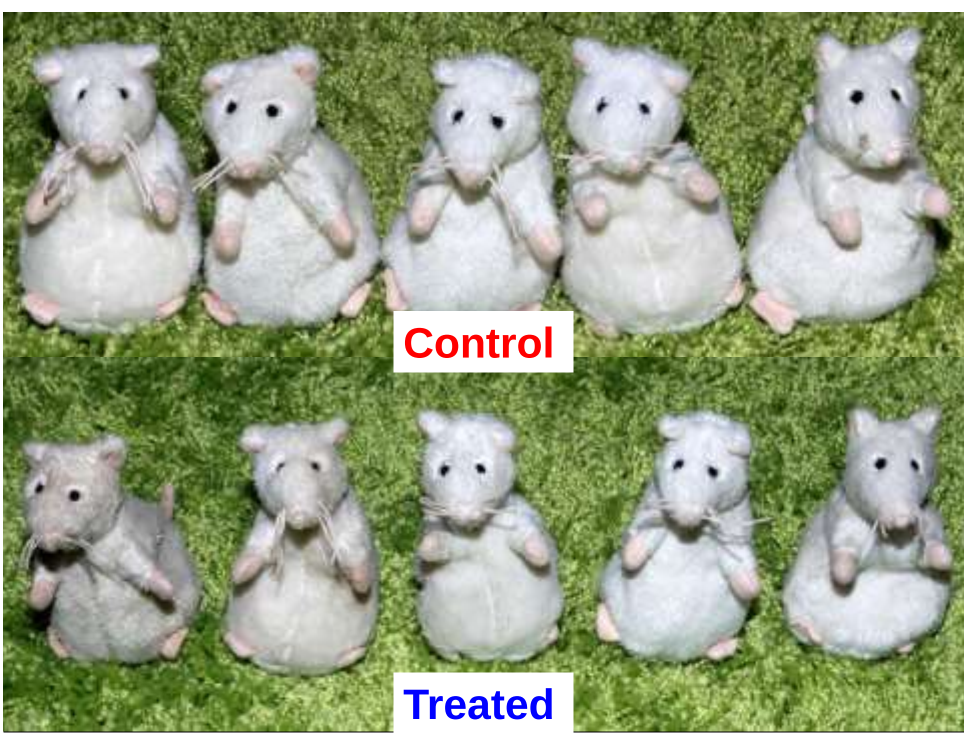
toxicity wanted effect comparison
side effects with standard

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

Pre-clinical studies (1)

Pre-clinical studies (2)

Pre-clinical studies (3)



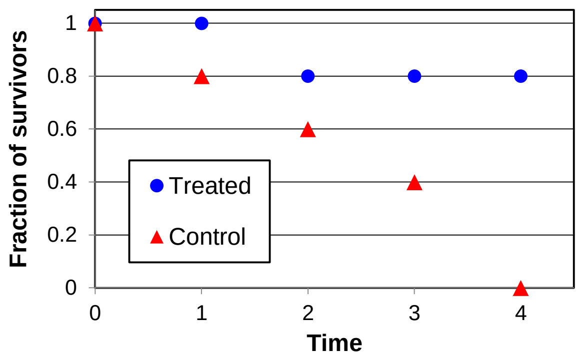

Control
Treated


Control
Treated


Control
Treated


Control
Treated

Survival curve

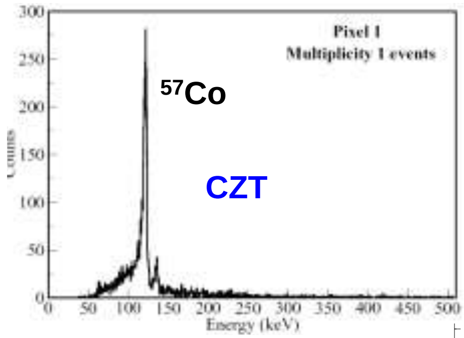


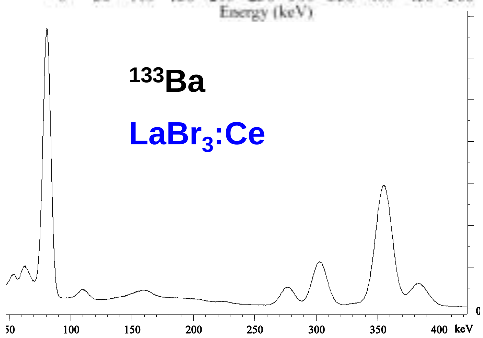
- **medium survival time, median survival time, survival benefit**
- **shows final benefit but not detailed mechanism**

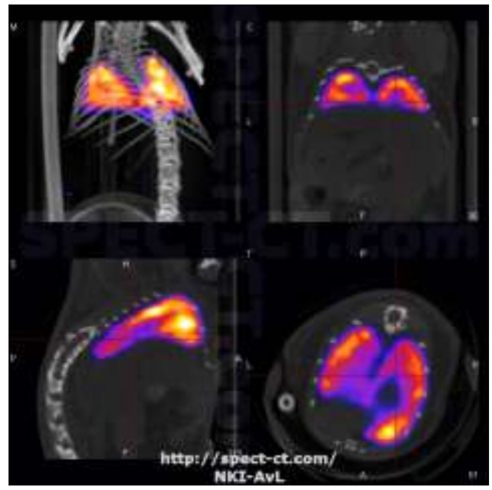
- **more information from bio-distribution studies**
- **preferentially on-line with suitable radiotracers and small animal SPECT or PET**

Small animal imaging

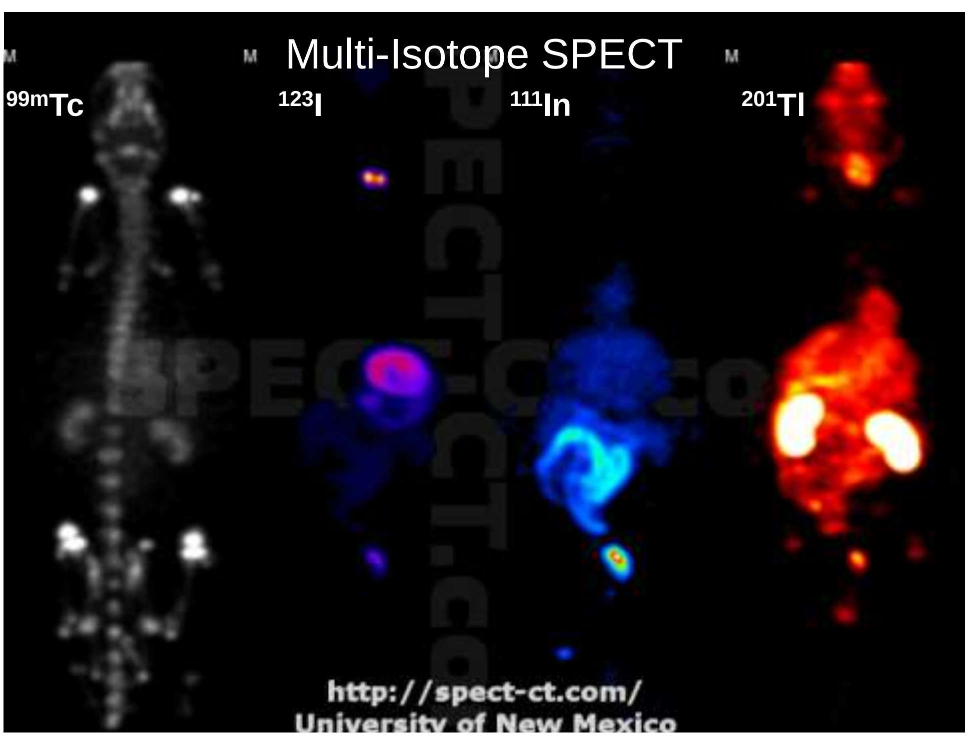
New generation of small animal SPECT







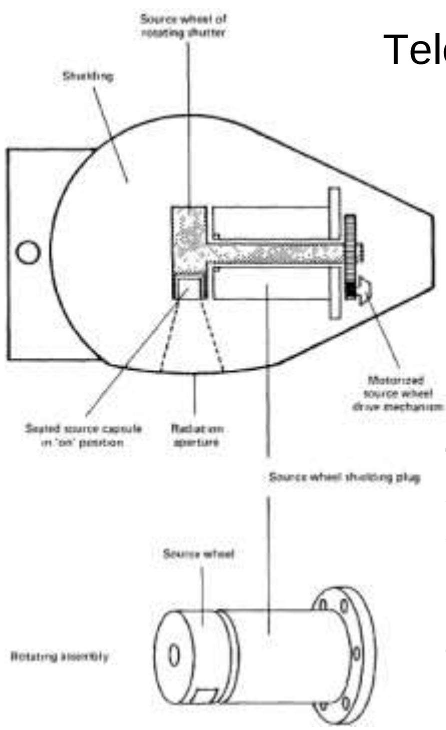
systematic biodistribution studies with different radiotracers become possible with dedicated small animal SPECT

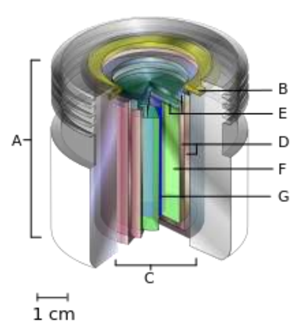


From diagnostics

to therapy

Teletherapy units

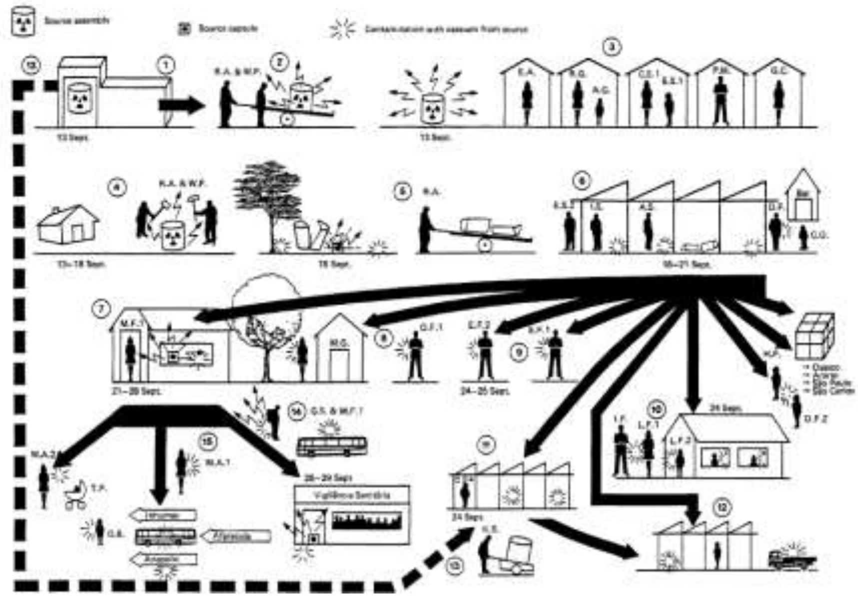




“Cobalt-bomb” or “Cesium-bomb”
50 – 100 TBq of ^{60}Co or ^{137}Cs
5 – 10 Gy/h at 1 m

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

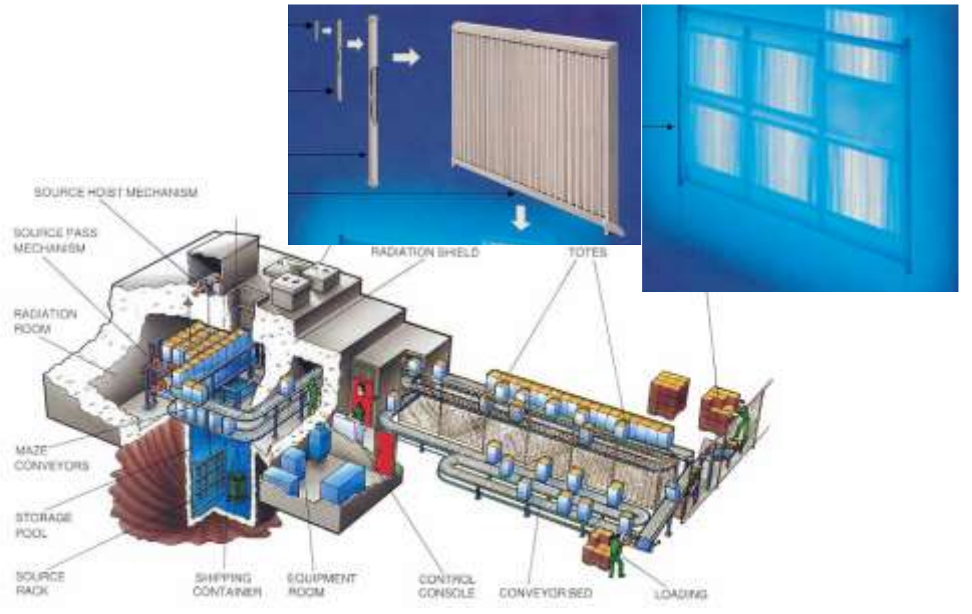
Civilian radiation accidents



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

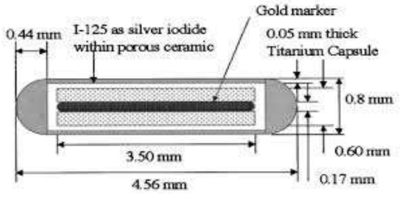


1 MCi = 37 PBq ^{60}Co sterilizes 650 kg/hour at 25 kGy

Brachytherapy

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

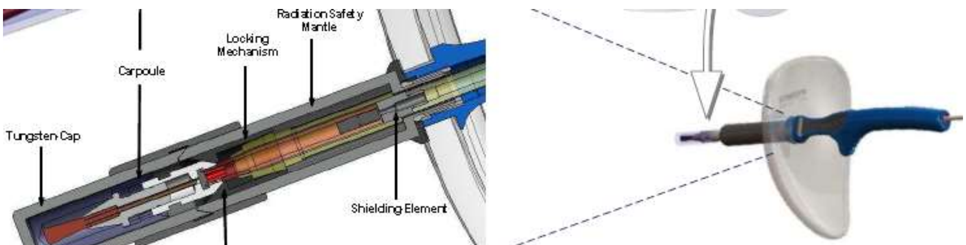
Low Dose Rate (LDR) brachytherapy long-term insertion of ^{32}P, ^{103}Pd, ^{125}I, ^{131}Cs, etc. sources ("seeds")



Rhenium skin cancer therapy

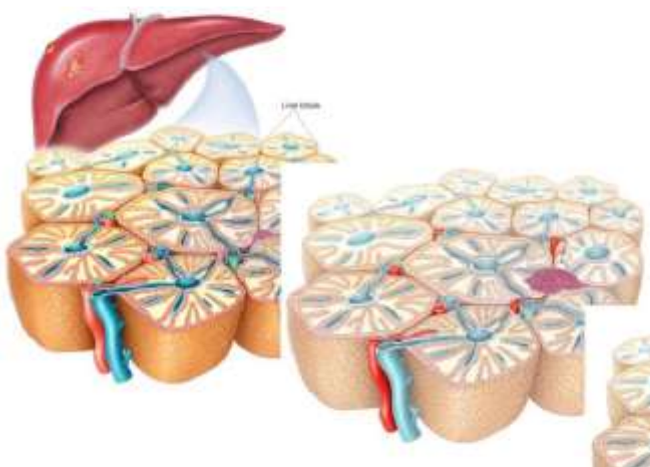
non-melanoma skin cancer:

- basal cell carcinoma and squamish cell carcinoma
- in the Alps 20-30% lifetime risk to develop skin cancer

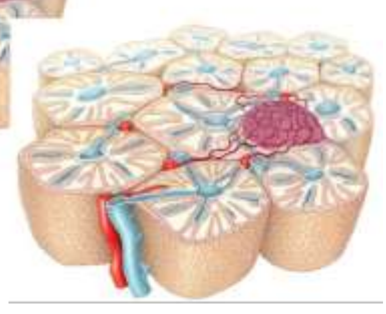


A.F. Sedda et al., Clin Exp Dermatol 2008;33:745.

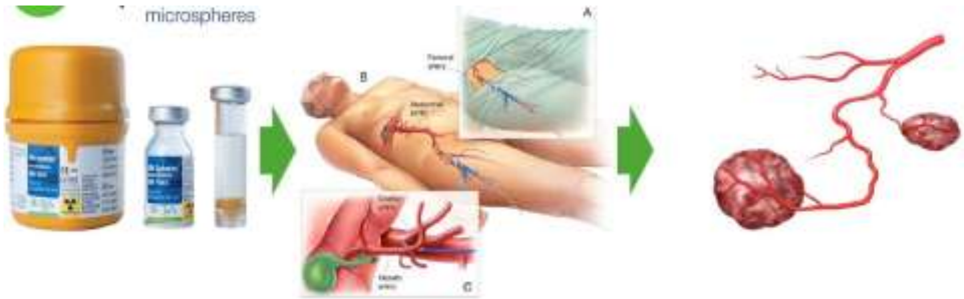
Liver cancer and liver metastases



Liver cancer and liver metastases triggers angiogenesis (supply path from artery)

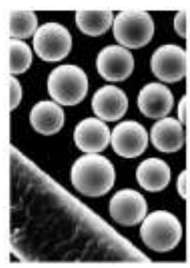


Selective Internal Radiation Therapy (SIRT)



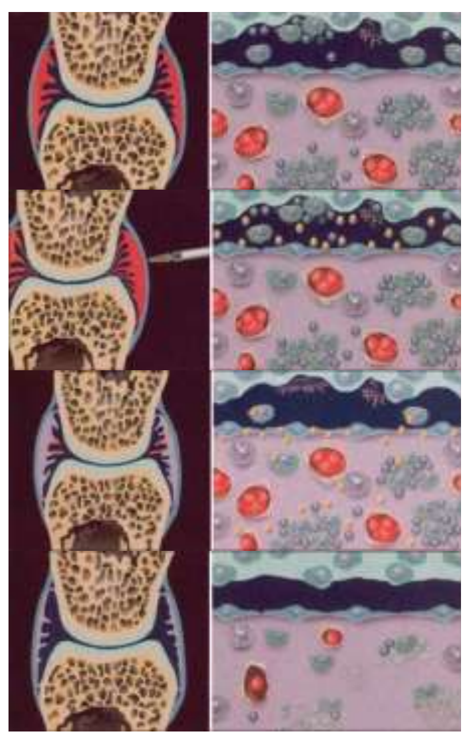
Radioembolization cuts supply lines of cancer while healthy liver remains supplied by port vein

^{90}Y-polymer or ^{90}Y-glass microspheres or ^{188}Re-Lipiodol



Y-90 glass microspheres comparison to human hair (8 µm diameter)

Radiosynovectomy (radiosynoviorthesis)



Injection of radionuclide colloids

Knee: ^{90}Y (185 MBq)

Ankle/elbow/shoulder/wrist/hip:

^{186}Re (74-111 MBq)

Finger: ^{169}Er (15-37 MBq)

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

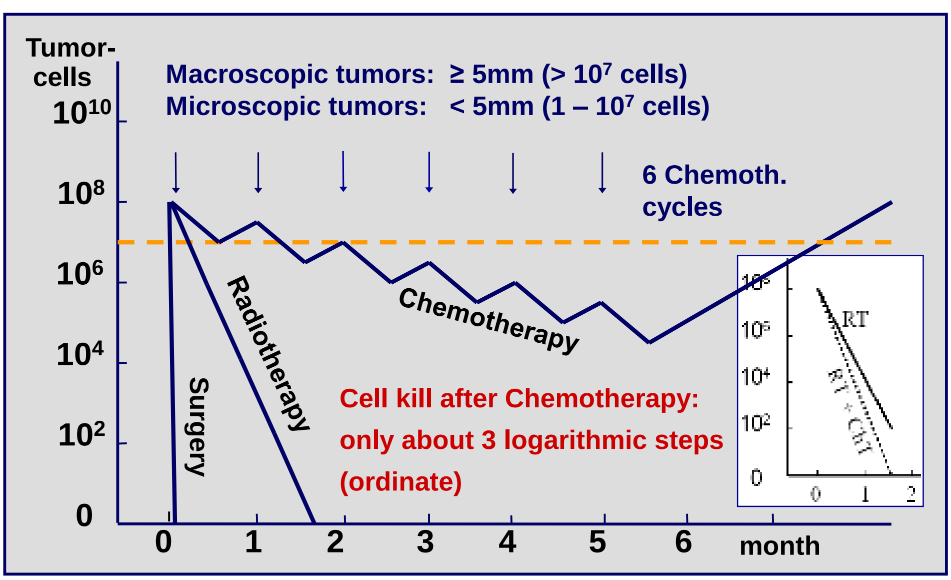
Cancer and efficiency of treatments

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

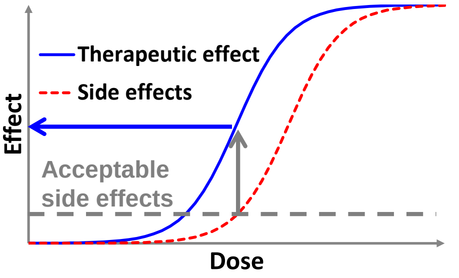


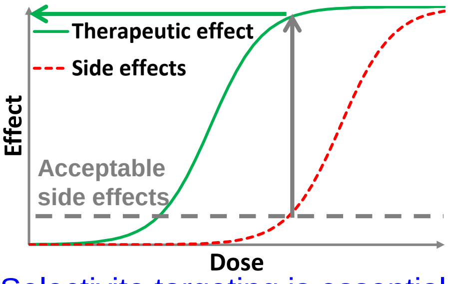
(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie Prof. Molls

Targeted therapies

Paracelsus (1493-1541)
"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous."



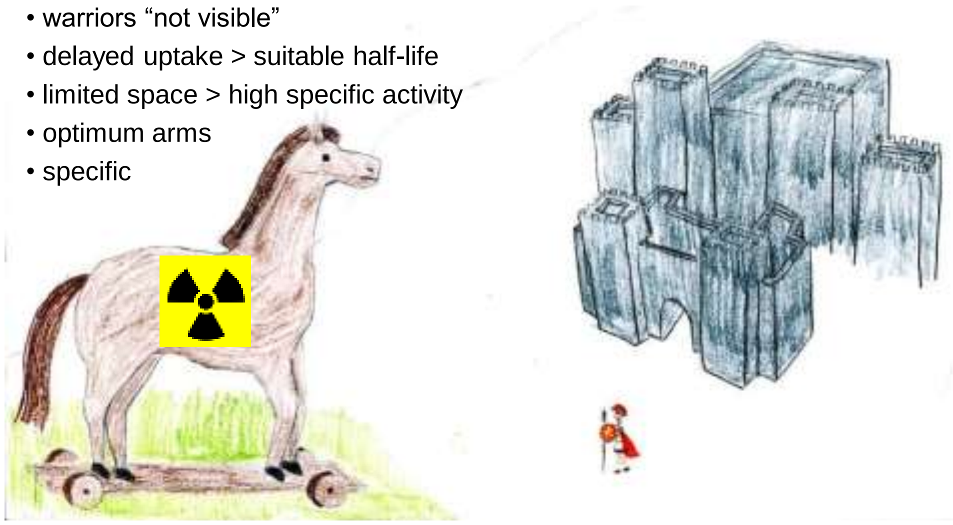


Selectivite targeting is essential to widen the therapeutic window!

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

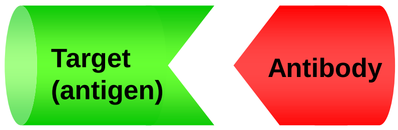
Thyroid cancer
$^{123}I^-$ for imaging
$^{131}I^-$ for therapy

Bone metastases
1.5 million patients world-wide

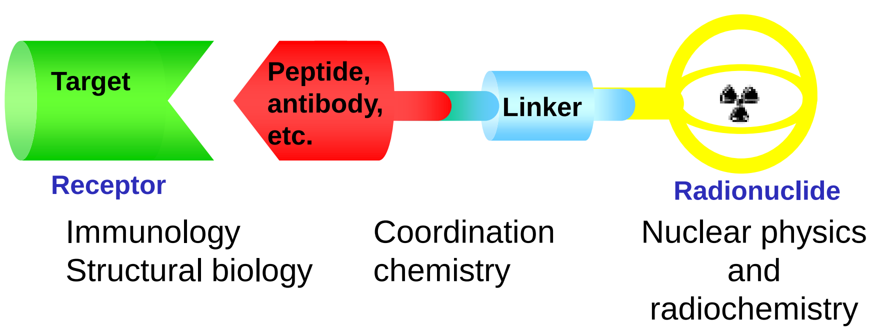
^{99m}Tc-MDP for SPECT imaging
$^{18}F^-$ for PET imaging

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

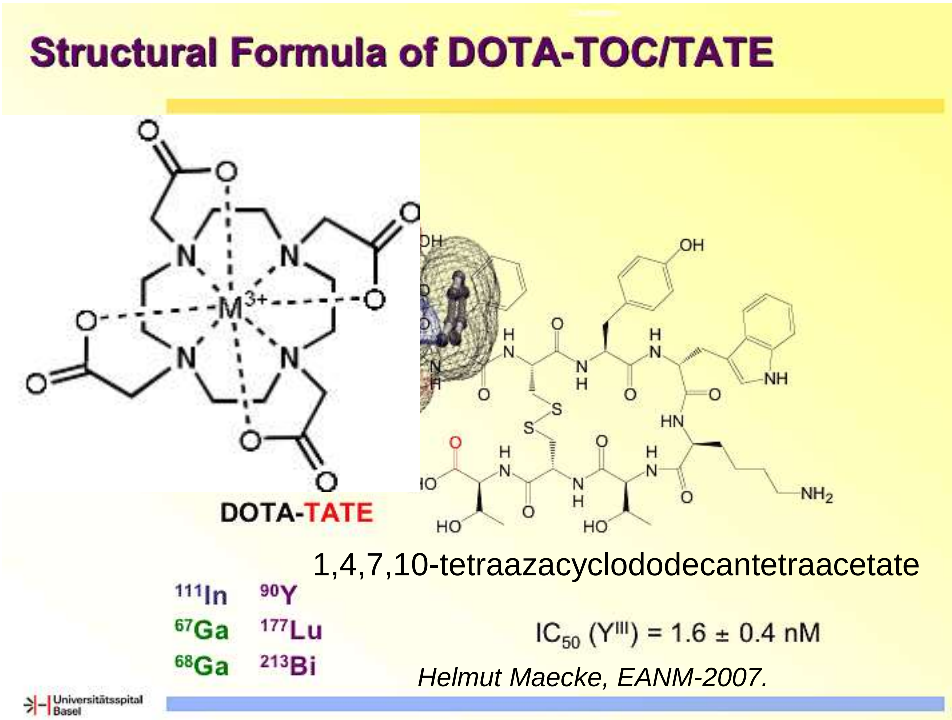
Immunology approach

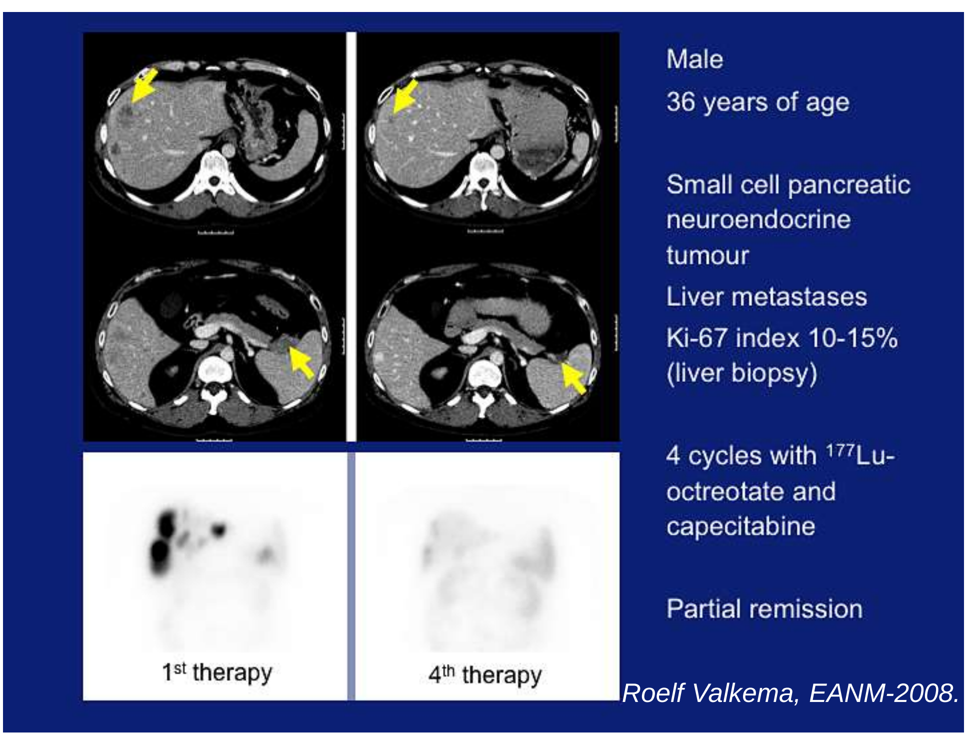


Multidisciplinary collaboration to fight cancer



Nuclear medicine and medical physics


Structural Formula of DOTA-TOC/TATE
DOTA-TATE
1,4,7,10-tetraazacyclododecantetraacetate
111In 90Y
67Ga 177Lu
68Ga 213Bi
IC50 (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 177Lu-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

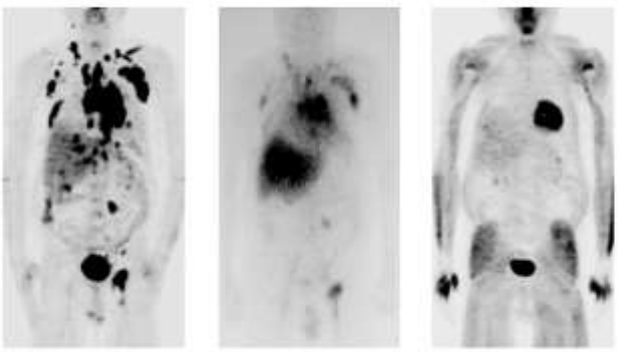
Roelf Valkema, EANM-2008.

Erasmus MC

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	15.9.2009

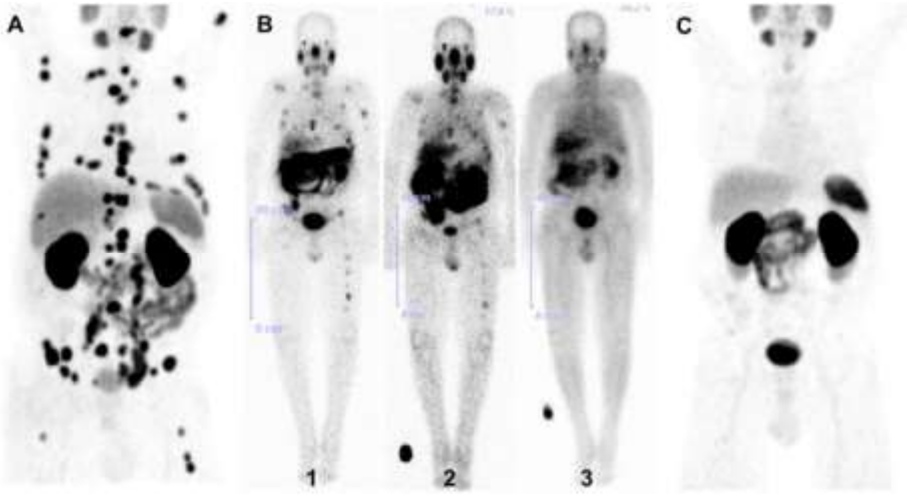


Still in CR

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

University Hospital Basel, CH

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

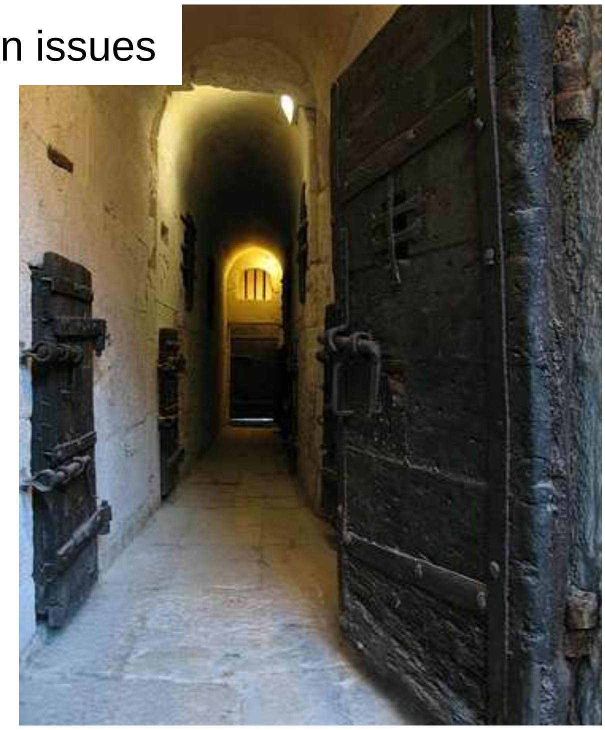


R.P. Baum et al., J Nucl Med 2016;57:1006.
C. Kratochwil et al., J Nucl Med 2016;57:1170.
K. Rahbar et al., J Nucl Med 2017;58:85.

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**	**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**

^{131}I: radioprotection issues



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

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

"hot zone" (IAEA/NRCP)

requires dedicated shielded treatment rooms

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

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

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**
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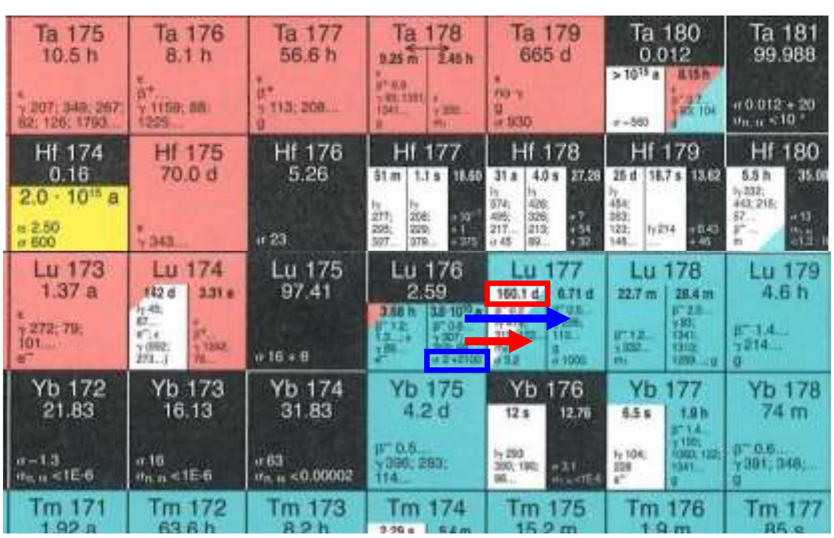
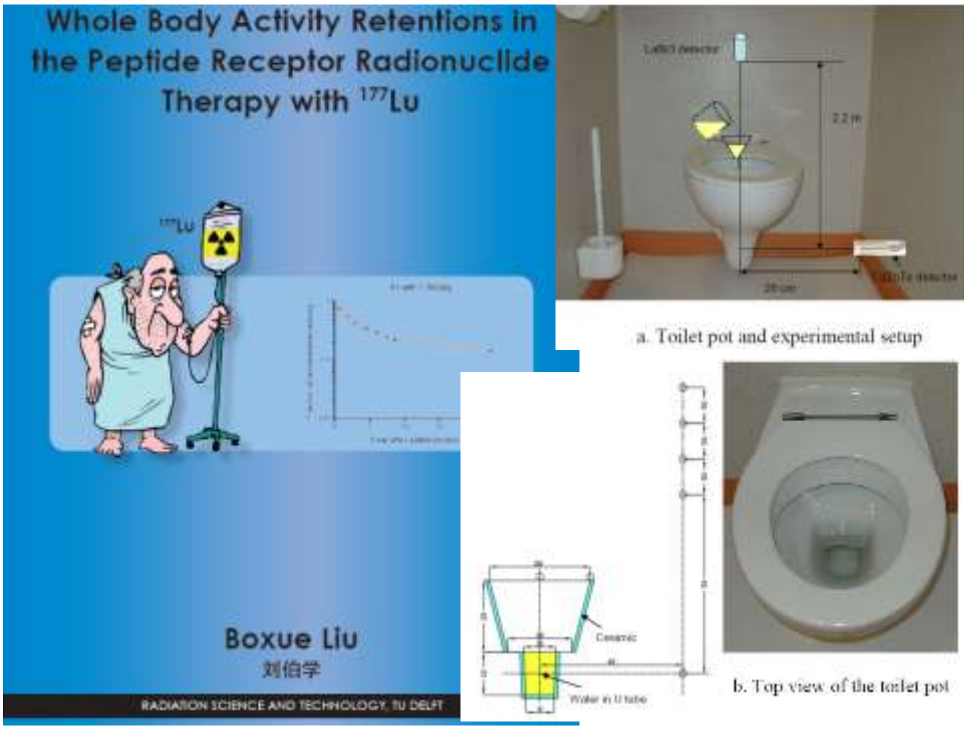
Production of ^{177}Lu



Waste problem for hospitals!

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



“Clean” production route to ^{177}Lu

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

NEUTRONS FOR SCIENCE

itg isotope technologies Garching GmbH

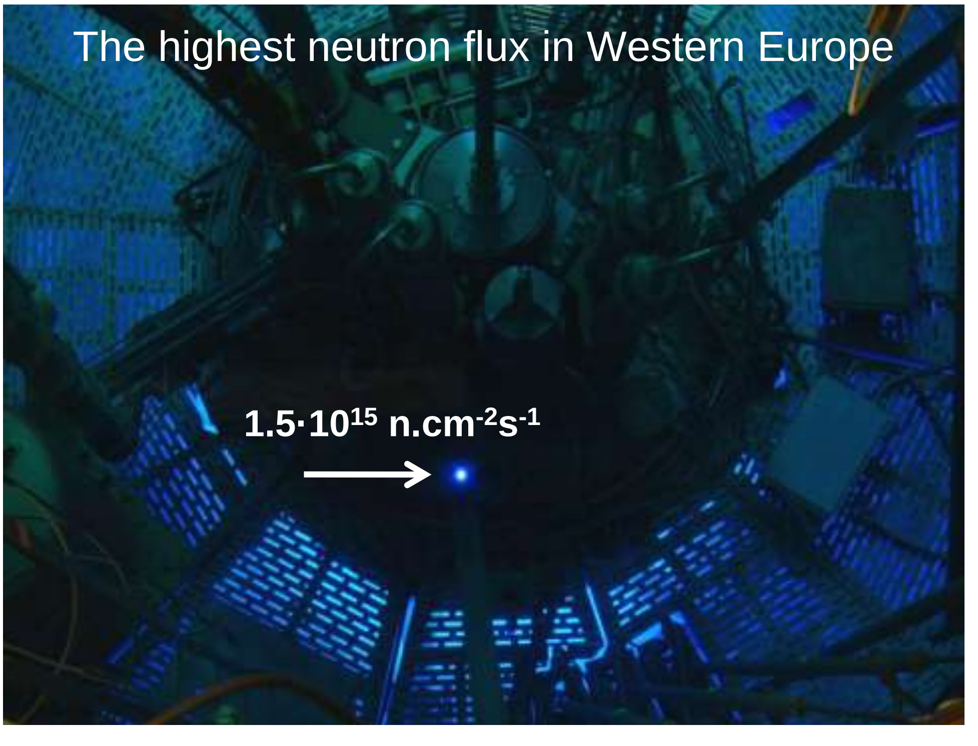
The history of lutetium separation

1878 Separation of Yb
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 and LYSO 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



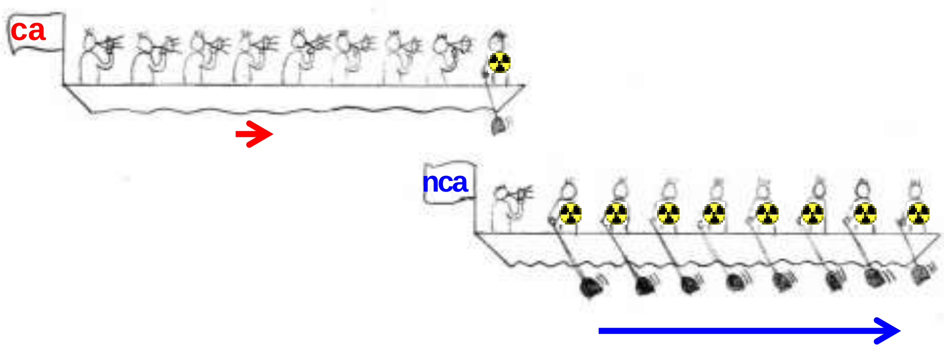
The rising star
for therapy

Specific activity

Physical quantity describing the activity per mass (GBq/mg, Ci/mg),

For mixtures it quantifies the ratio of radioactive atoms to all atoms (including stable ones).

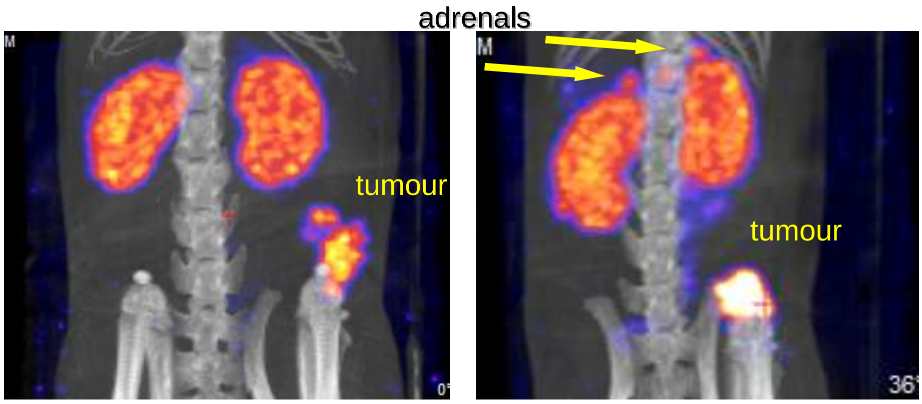
Carrier added vs. non-carrier added




Saturation of selective receptors per cell

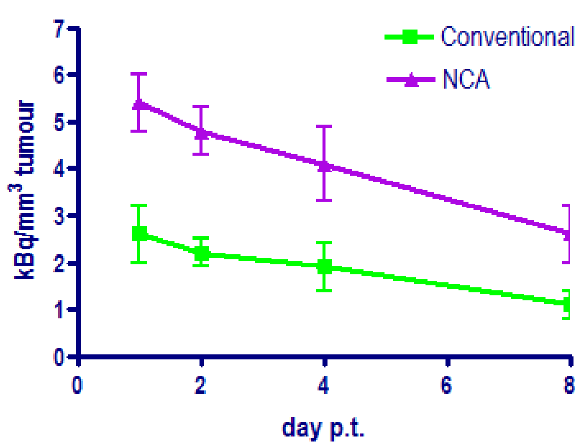
SPECT/CT day 1 p.t. Lu-octreotate

Conv. ^{177}Lu-octreotate, 11 µg NCA ^{177}Lu-octreotate, 2 µg



M. de Jong

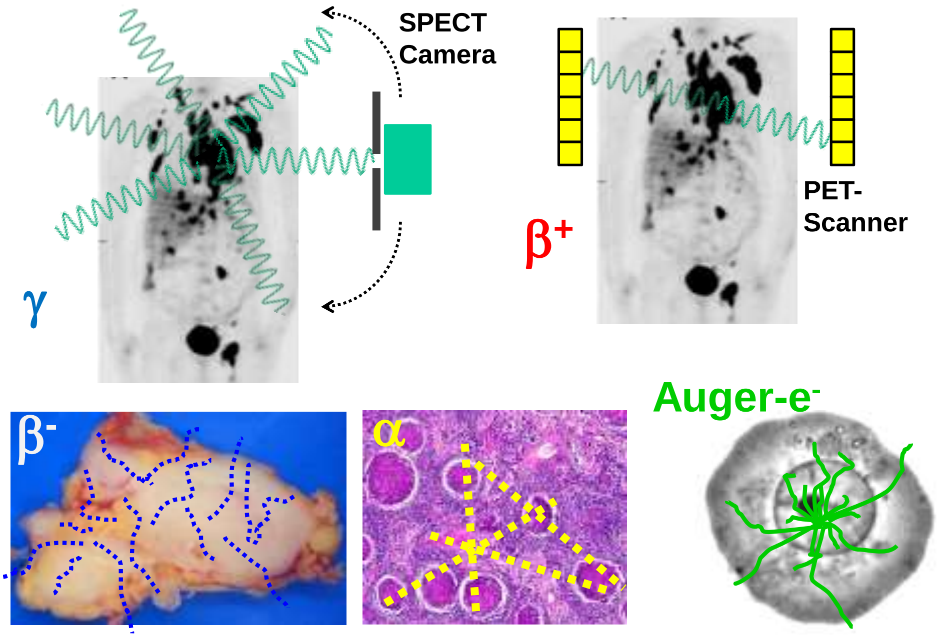
Tumour uptake, based on SPECT quantification



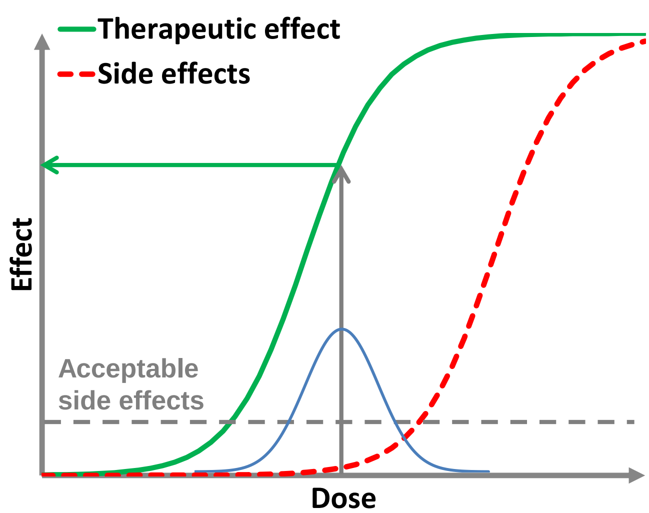
NCA ^{177}Lu-octreotate: ~2x higher tumour uptake
➔ 70 vs. 35 Gy tumour dose

M. de Jong

The Nuclear Medicine Alphabet

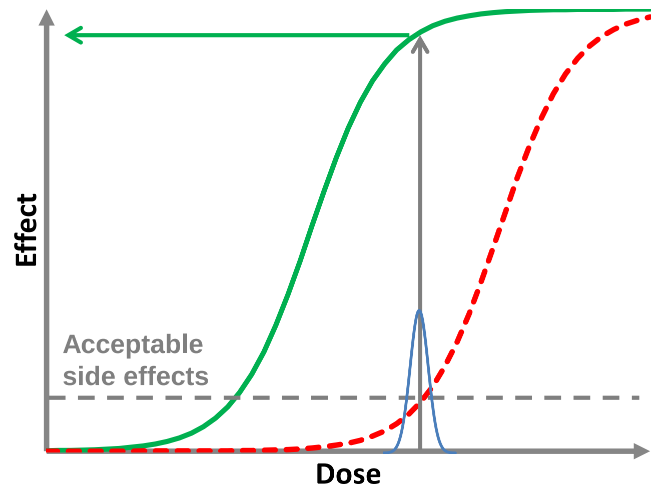


Theranostics



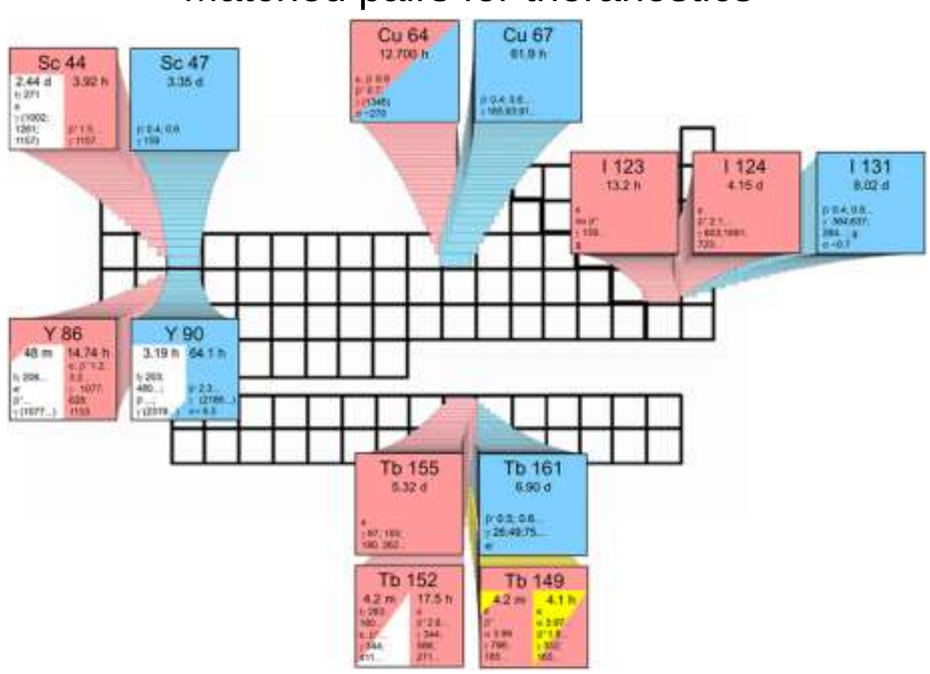
Accurate dosimetry is essential for optimum use of the therapeutic window.

Theranostics



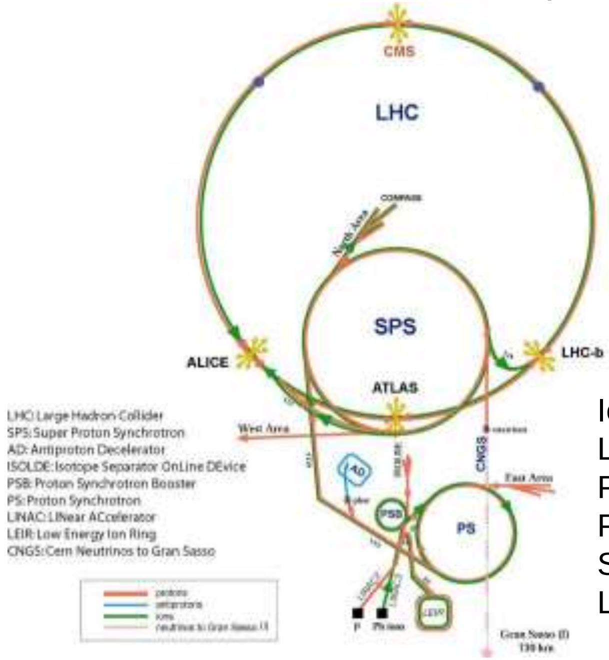
Accurate dosimetry is essential for optimum use of the therapeutic window.

Matched pairs for theranostics



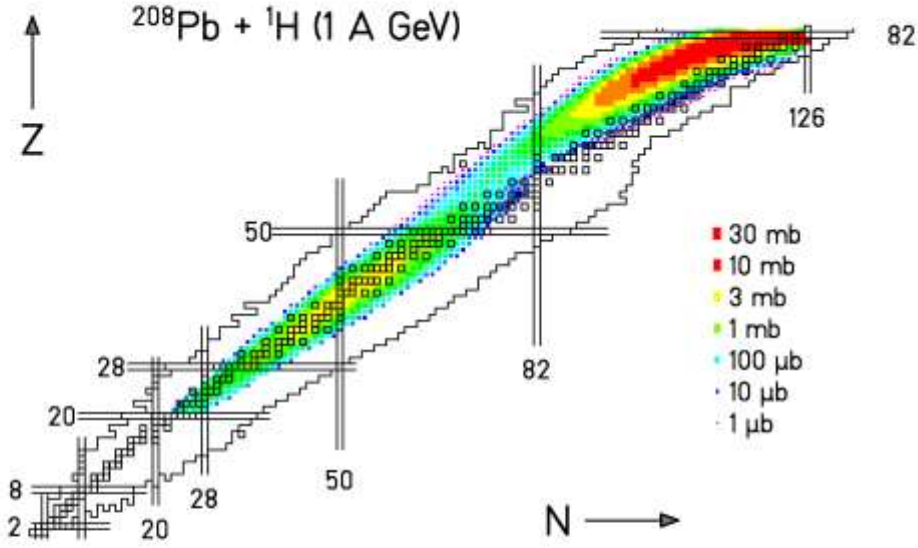
Terbium: a unique element for nuclear medicine

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

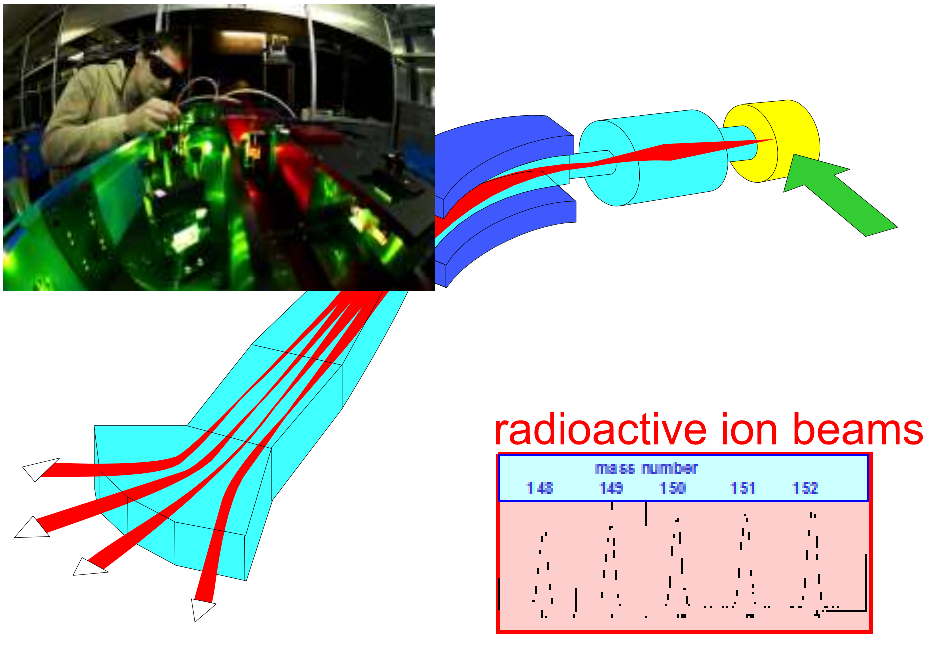
Spallation + Fragmentation + Fission



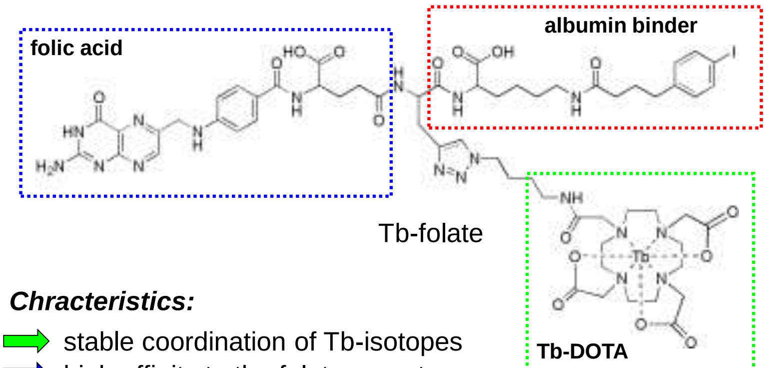
W. Wlazło et al., Phys. Rev. Lett. 84 (2000) 5736.

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

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



Tumor Tageting Agent for Tb-Coordination Chemical Structure with 3 Functionalities

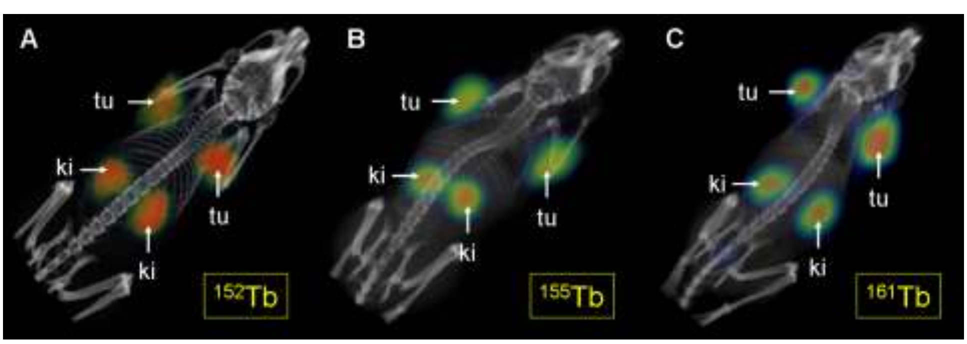


Chracteristics:

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

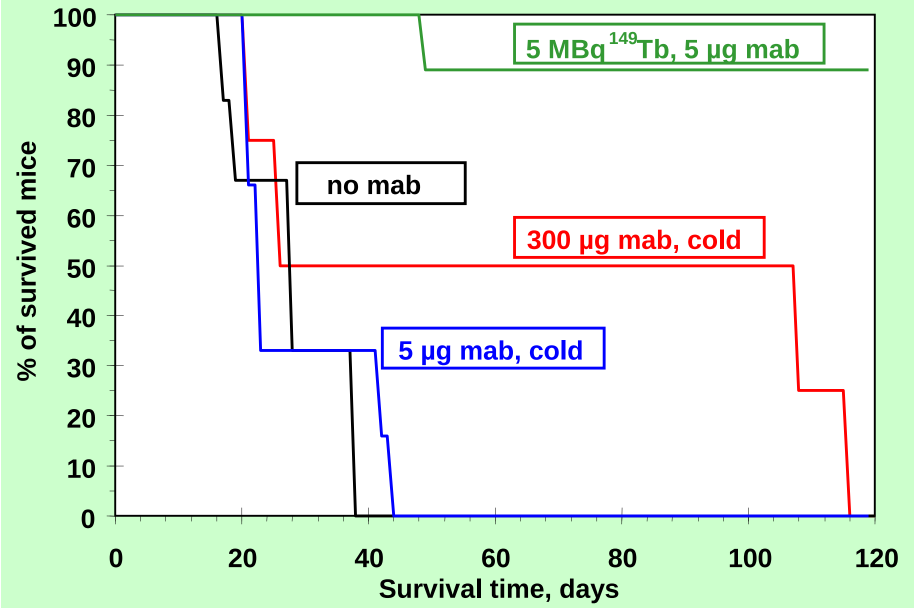
Theranostics with terbium isotopes

PET *SPECT* *SPECT*



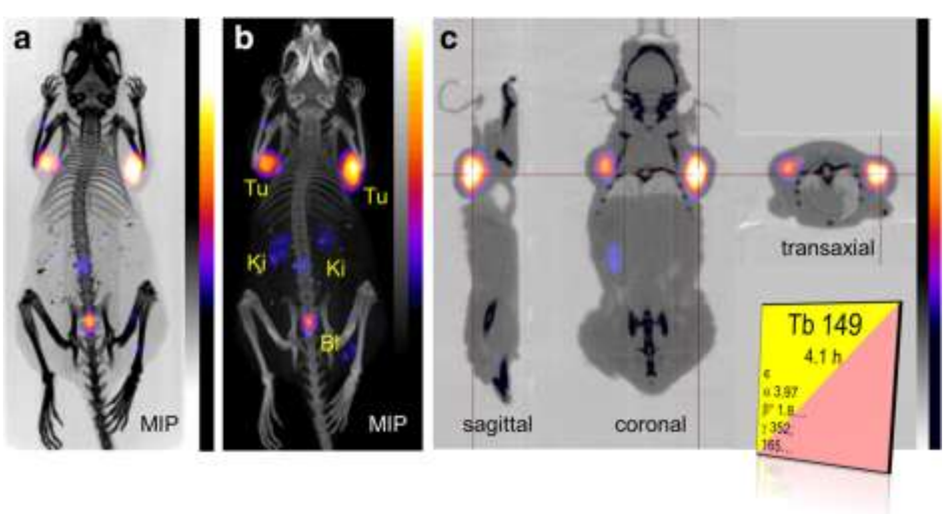
IS528 Collaboration: C. Müller et al., J. Nucl. Med. 2012;53:1951.

Preclinical study with lymphoma mouse model



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

Alpha-PET with ^{149}Tb



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

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 ↑ / ↓ **localized**

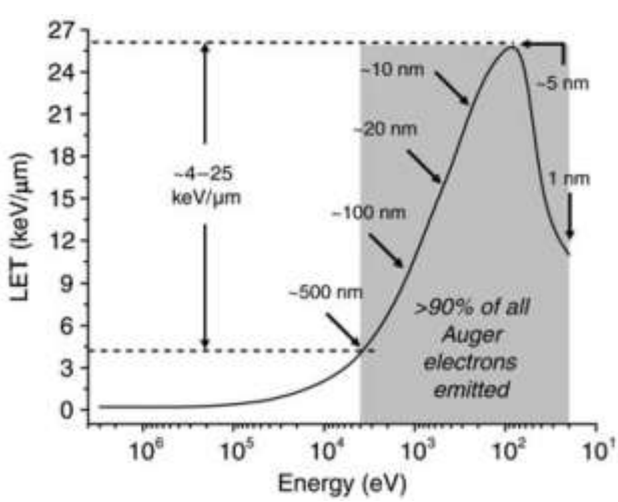
Established isotopes

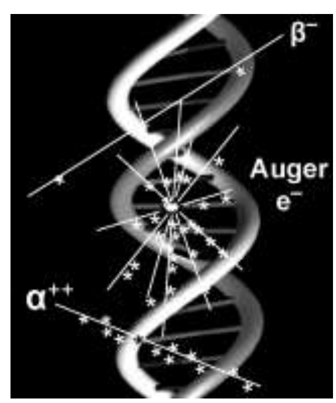
Emerging isotopes

R&D isotopes: supply-limited!

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

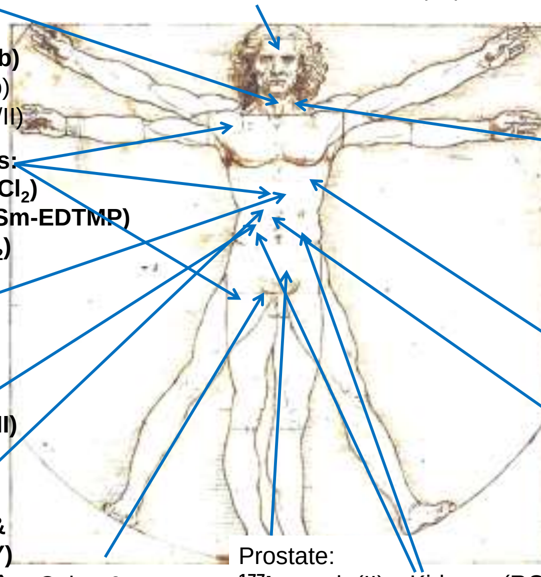
Radiobiological effectiveness of Auger electrons





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

Targeted radionuclide therapies in the clinic



Thyroid: ^{131}I^{-}

Brain: ^{90}Y-mab, ^{131}I-mab (I/II), ^{211}At-mab (I), ^{213}Bi-pept.(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):
^{177}Lu-peptides (III)

Liver (HCC):
Theraspheres® &
SIRspheres® (^{90}Y)
^{188}Re-Lipiodol (II)
^{166}Ho-microspheres

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

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

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

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

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

Medullary Thyroid:
^{131}I-mab (II)
^{90}Y/^{177}**Lu**-pept.

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

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

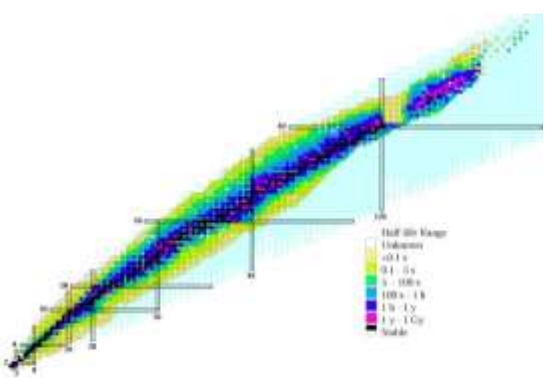
Pancreas:
^{90}Y-mab (III)

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

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."

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