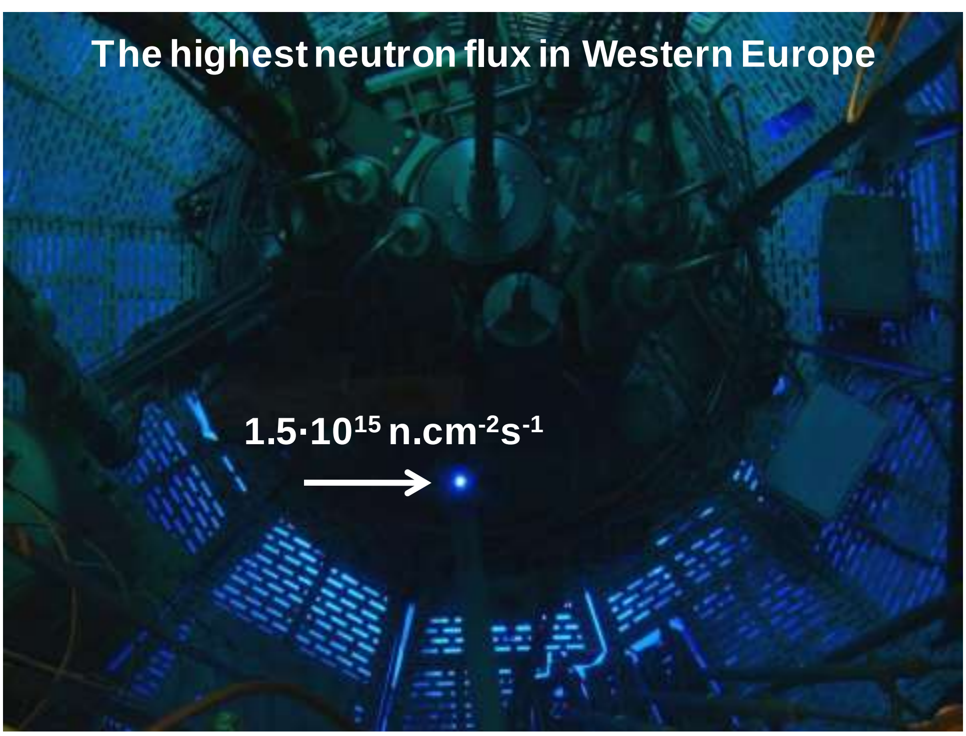
(Medical) applications or radioisotopes

Ulli Köster

Institut Laue-Langevin, Grenoble

CERN Accelerator School

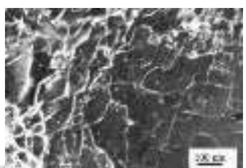
3 June 2015

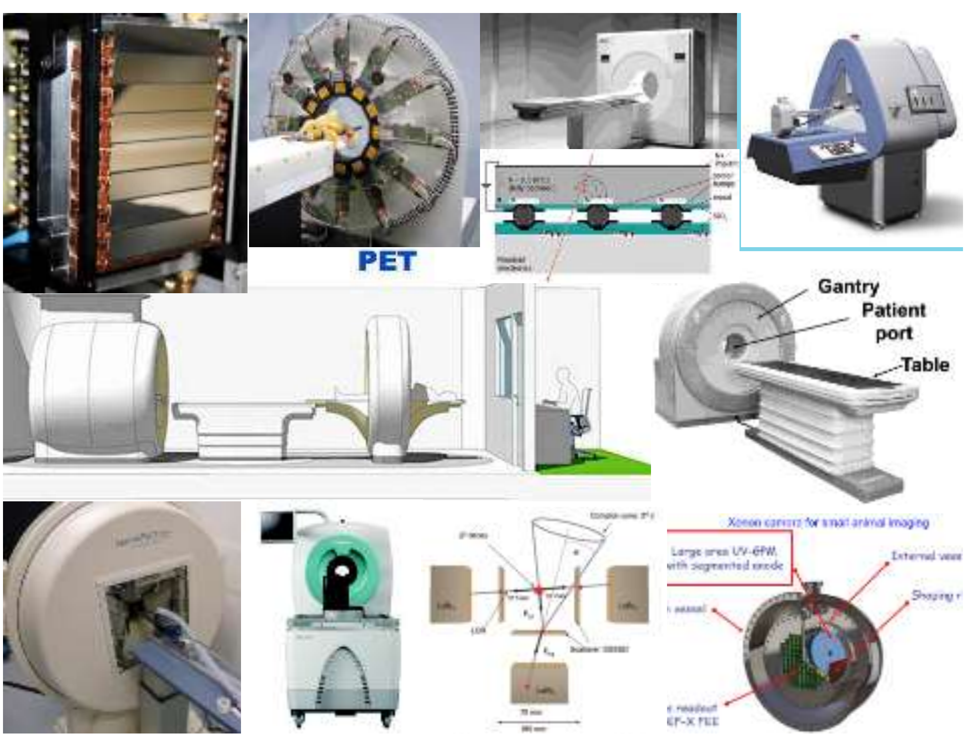


Research reactors are multi-use facilities

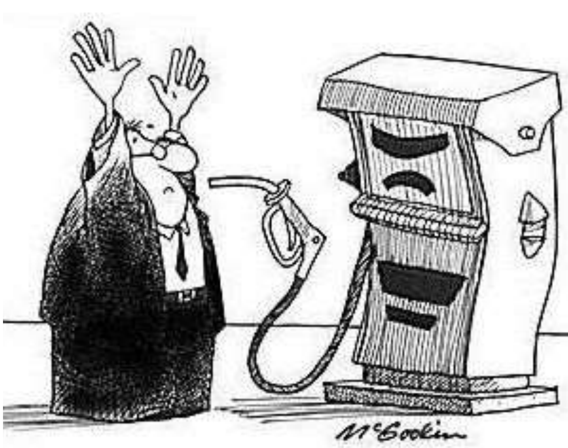
Neutron scattering
Neutron radiography
Nuclear physics
Neutron physics
Fuel testing
Materials irradiation
NTD silicon
Neutron activation analysis
Radioisotope production
etc.







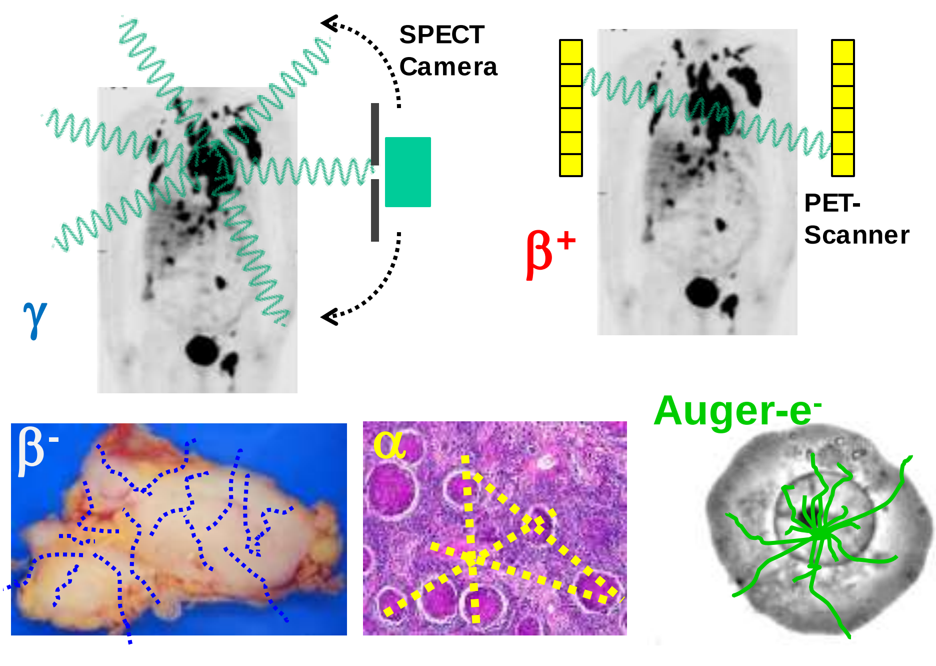
Don’t forget the fuel!



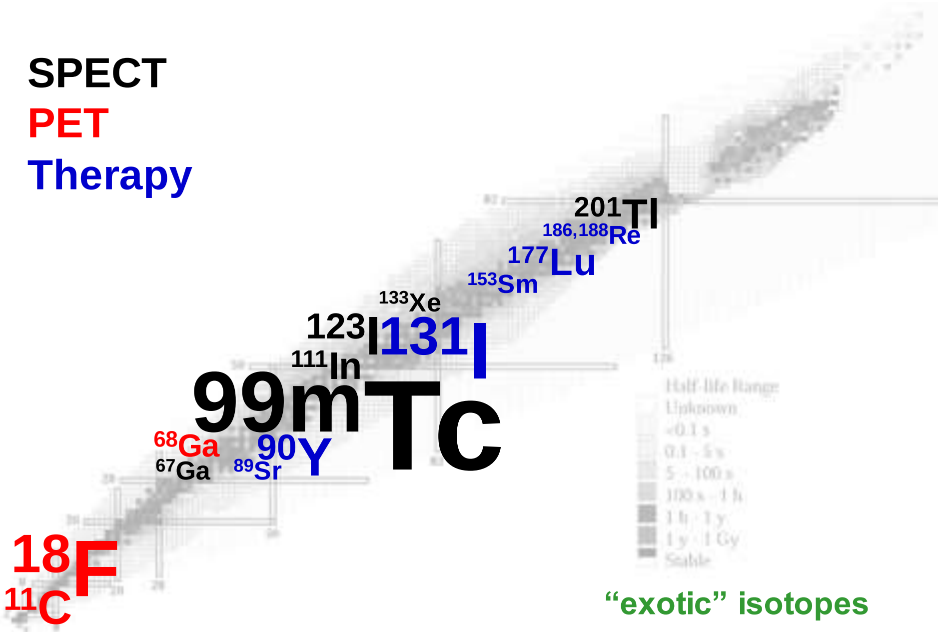
Radioisotopes: the “fuel” for nuclear medicine

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

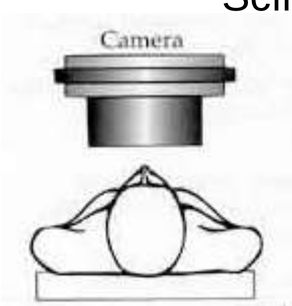
The Nuclear Medicine Alphabet



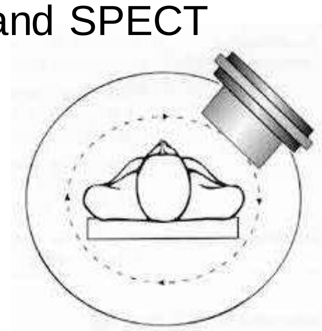
The chart of nuclides – nuclear medicine perspective



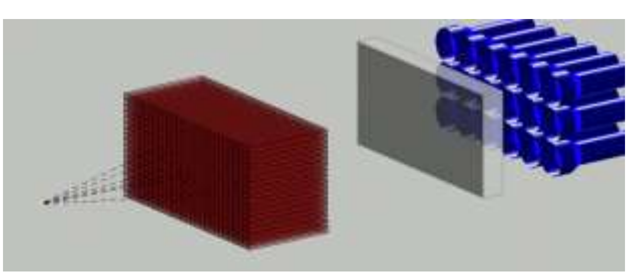
Scintigraphy and SPECT



2D: planar scan (Gamma camera)

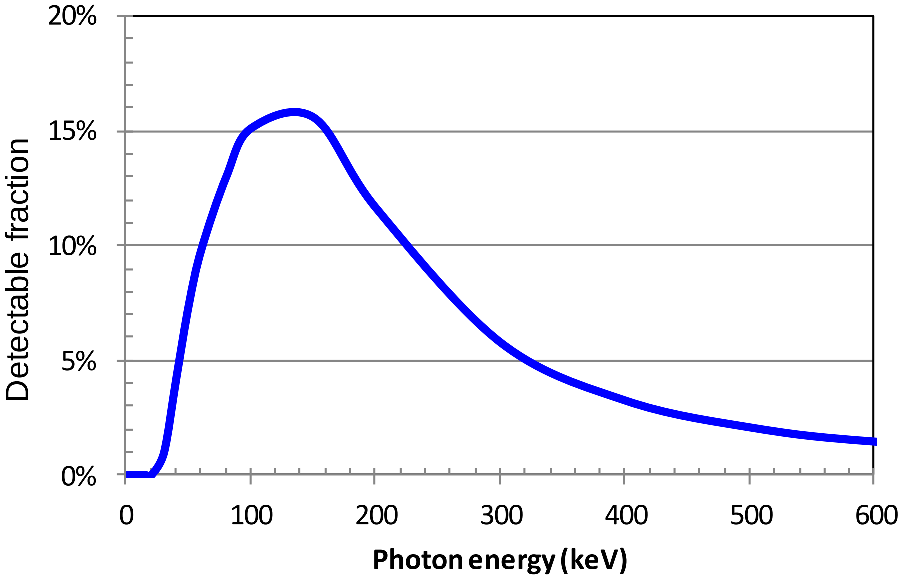


3D: SPECT: Single Photon Emission Computer Tomography



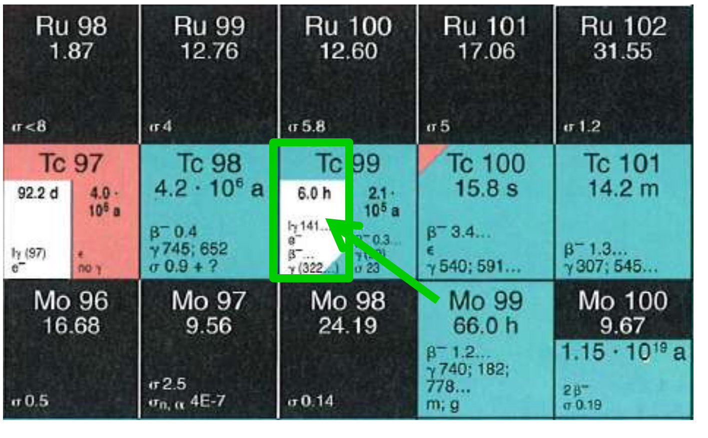
$E_\gamma >$ 60 keV
$E_\gamma <$ 400 keV

Ideal gamma ray energy for scintigraphy/SPECT



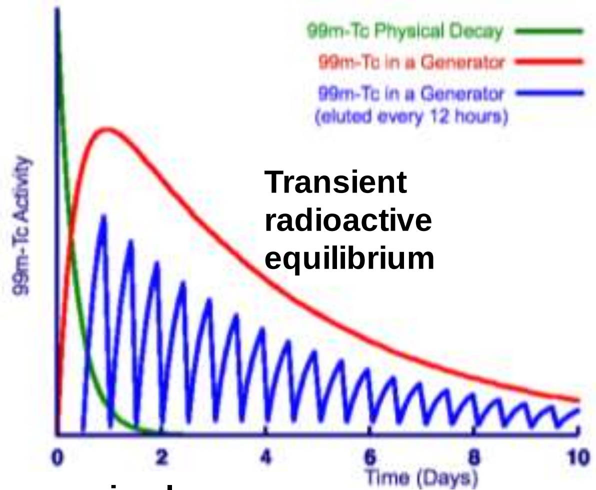
10 cm soft tissue, 0.2 cm aluminium (detector encapsulation), 1 cm NaI

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



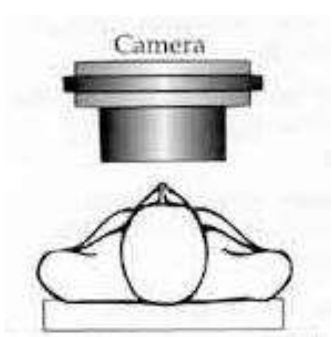
- IT with 89% 140.5 keV gamma ray, $T_{1/2}$ = 6 h
- decays to quasi-stable daughter
- ^{99m}Tc fed in 88% of β^- decays of ^{99}Mo, $T_{1/2}$ = 66 h
- produces nearly carrier-free product

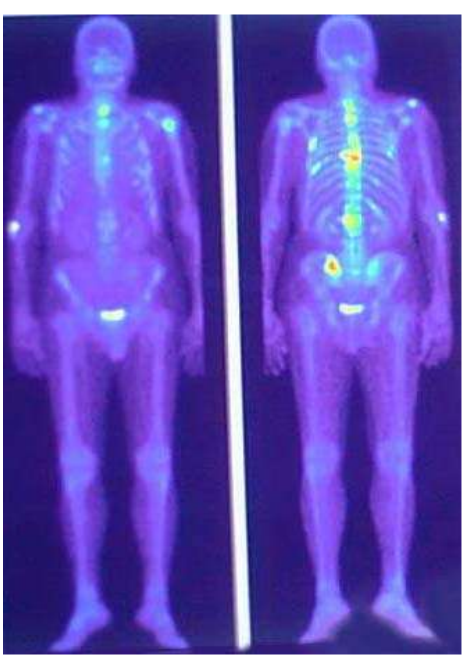
$^{99}Mo/^{99m}Tc$ generator



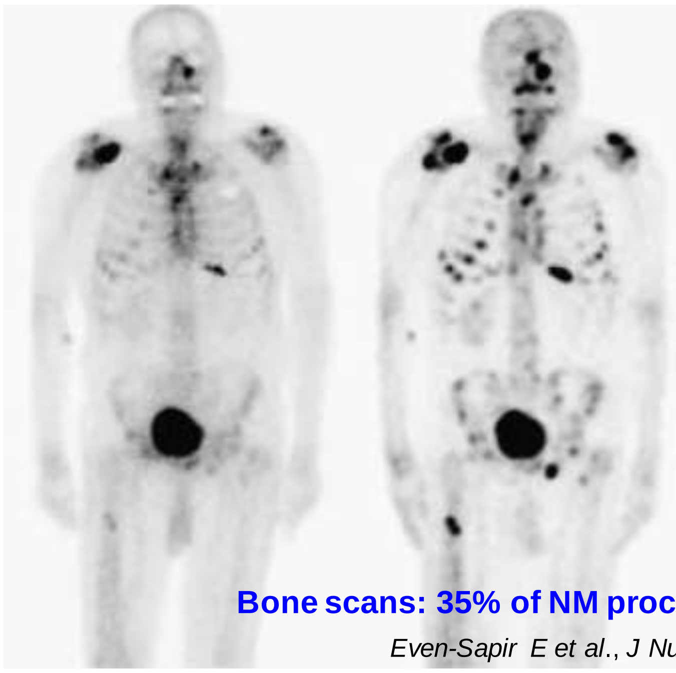
- simple
- reliable
- portable
- self-shielded

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

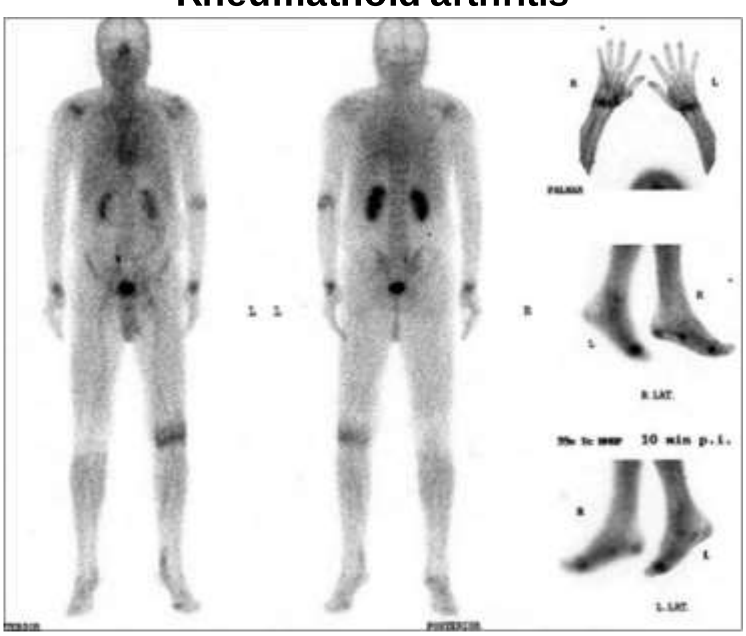


Bone scans: 35% of NM procedures in Europe

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

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

Rheumathoid arthritis

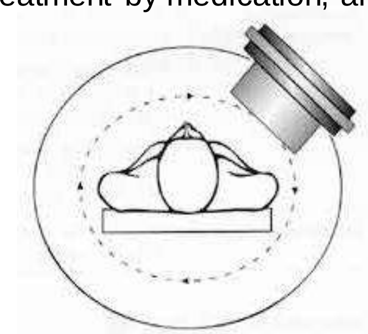


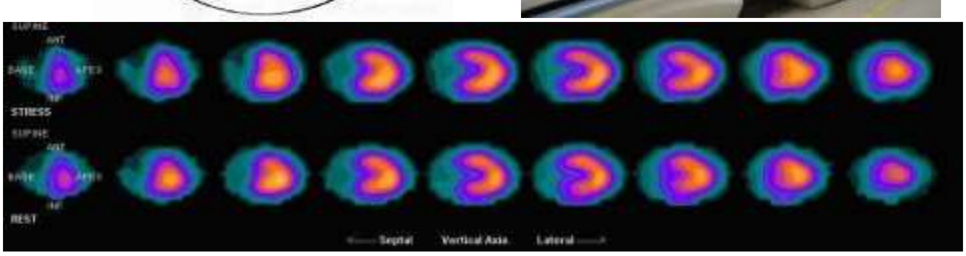
L. Knut, World J Nucl Med. 2015; 14:10.

Veterinary scintigraphy

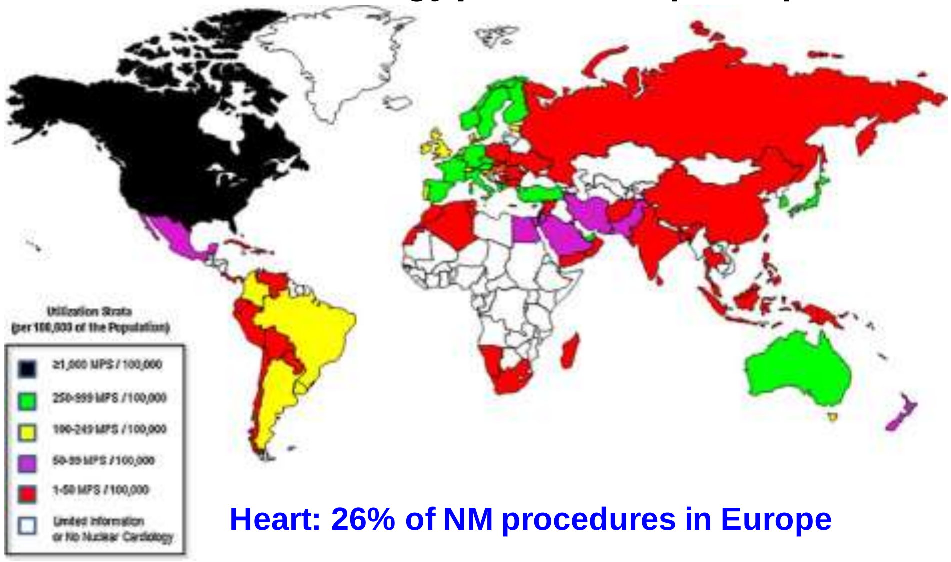
Ischemic heart disease

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





Nuclear cardiology procedures per capita

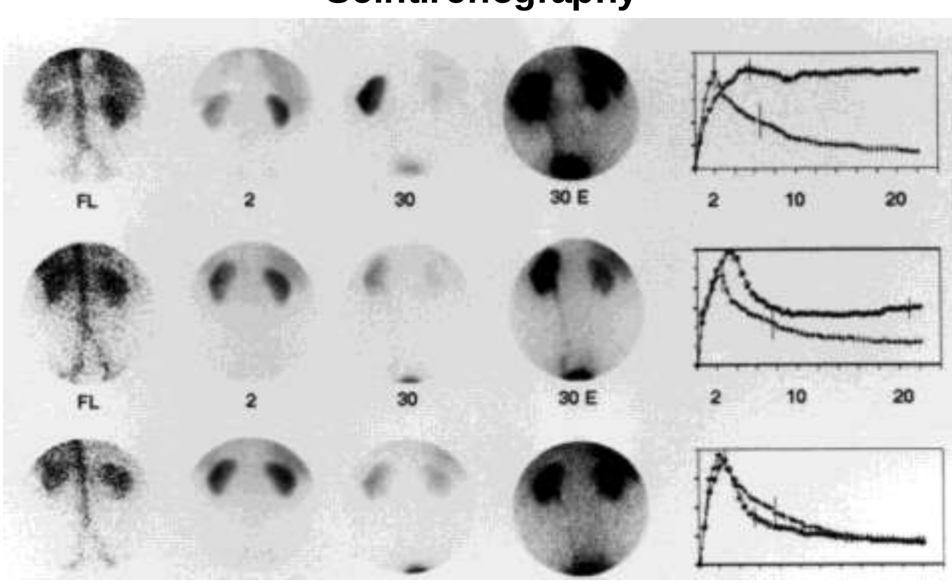


Heart: 26% of NM procedures in Europe

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

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

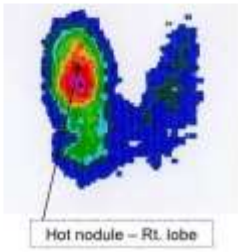
Scintirenography

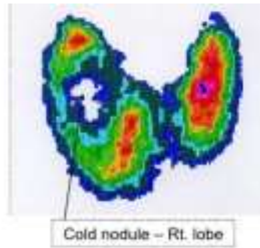


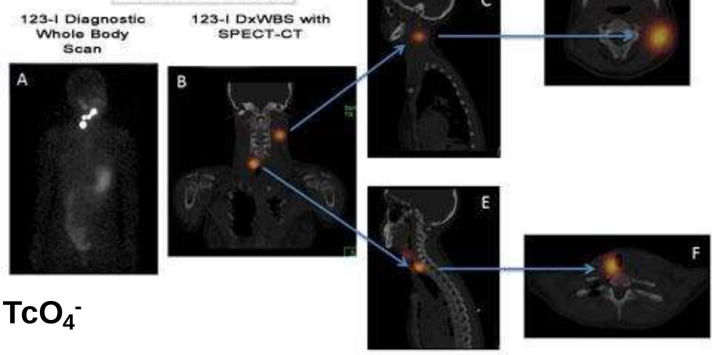
G.N. Sfakianakis et al. J Nucl Med 2000;41:1813.

Kidney: 13% of NM procedures in Europe

Thyroid scintigraphy





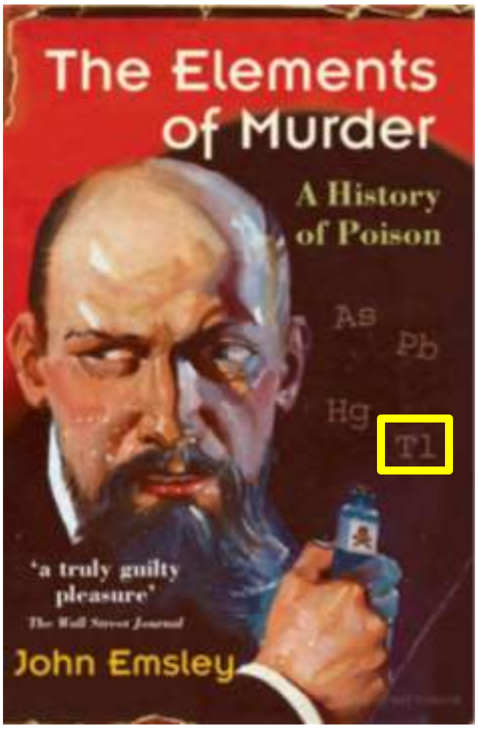


$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$

Thyroid: 12% of NM procedures in Europe

SPECT isotopes

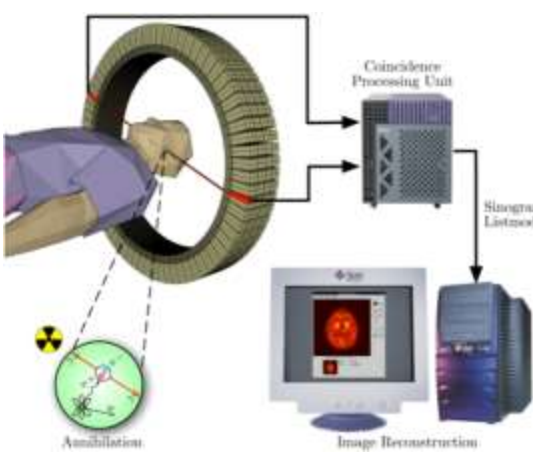
Radio-nuclide	Half-life (h)	Eγ (keV)	Iγ (%)	Decay type
Ga-67	78	93 185	42 21	EC
Kr-81m	0.004	190	64	IT
Tc-99m	6	141	89	IT
In-111	67	171 245	91 94	EC
I-123	13	159	83	EC
Xe-133	126	81	38	β^-
Tl-201	73	70 167	59 10	EC
I-131	192	364	82	β^-
Lu-177	161	113 208	6 10	β^-

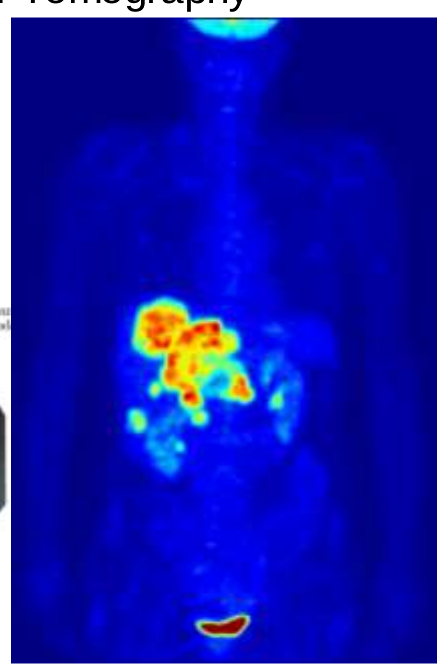


Thallium for patients ?

- 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!

Positron Emission Tomography

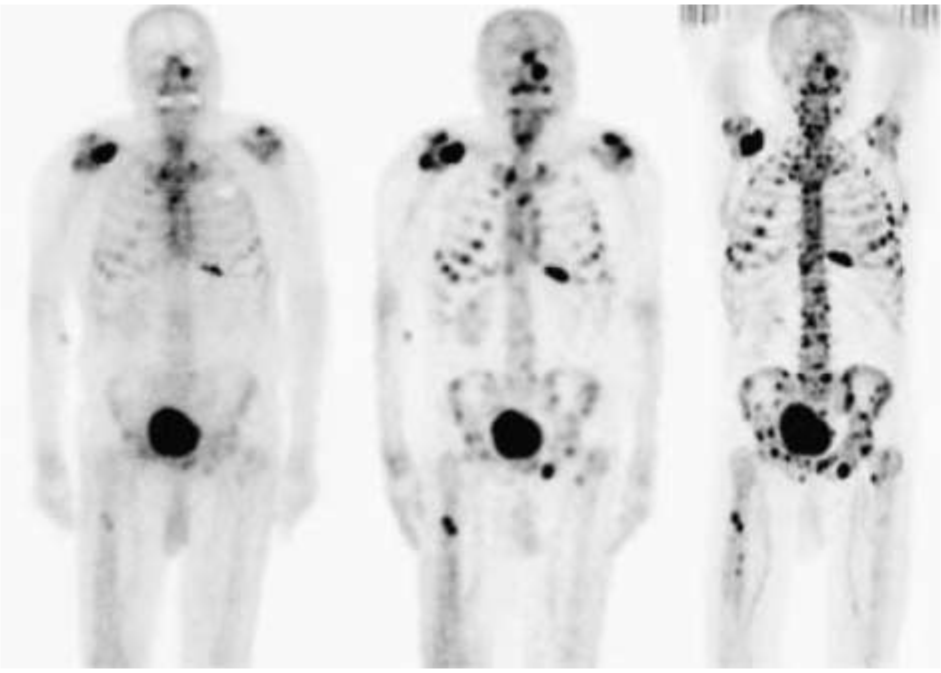




PET isotopes

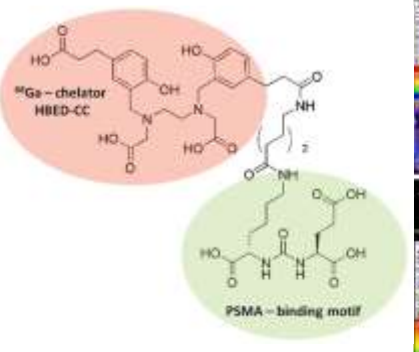
Radio-nuclide	Half-life (h)	Intensity β⁺ (%)	E mean (MeV)	Range (mm)
C-11	0.34	99.8	0.39	1.3
N-13	0.17	99.8	0.49	1.8
O-15	0.03	99.9	0.74	3.2
F-18	1.83	96.7	0.25	0.7
Ga-68	1.13	89.1	0.83	3.8
Rb-82	0.02	95.4	3.38	20

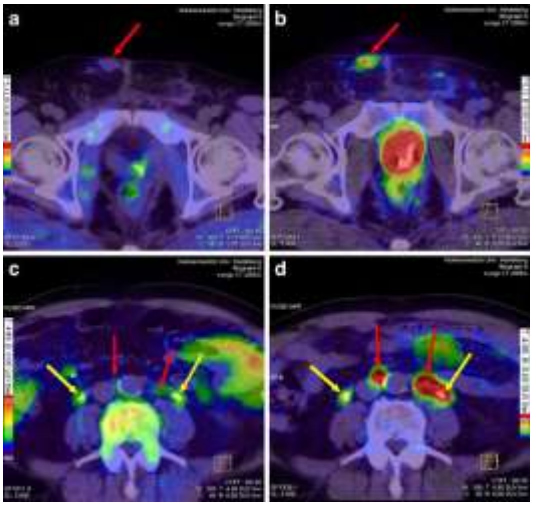
^{18}F-Fluorodeoxyglucose (FDG)



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

Imaging of prostate cancer lesions





^{18}F-choline ^{68}Ga-PSMA-ligand

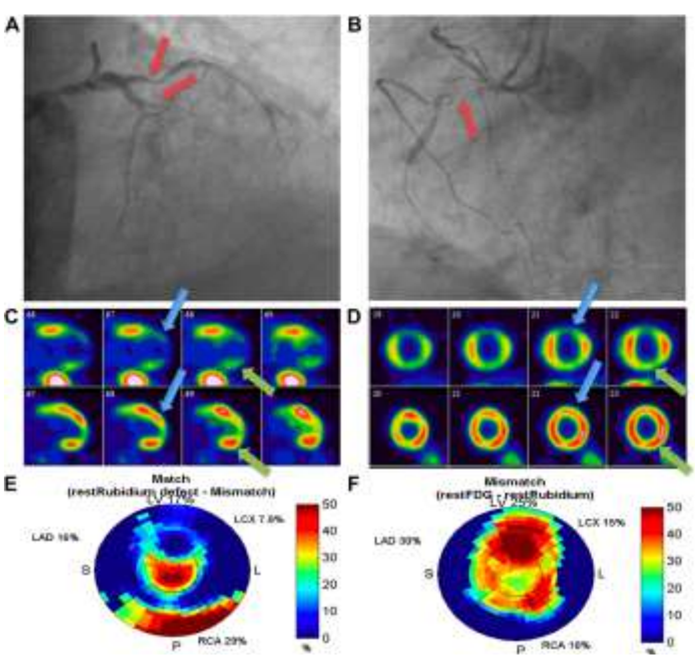
M Eder et al. Bioconjugate Chem 2012, 23:688.
Ali Afshar-Oromieh et al. Eur J Nucl Med Mol Imaging 2014, 41:11.

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

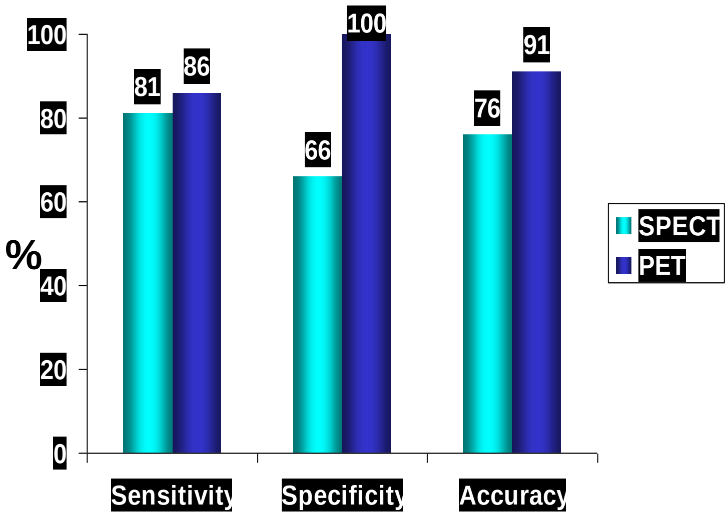
Mother isotope:
271 d
25 d

Cardiology applications



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

Diagnostic Accuracy: PET vs SPECT

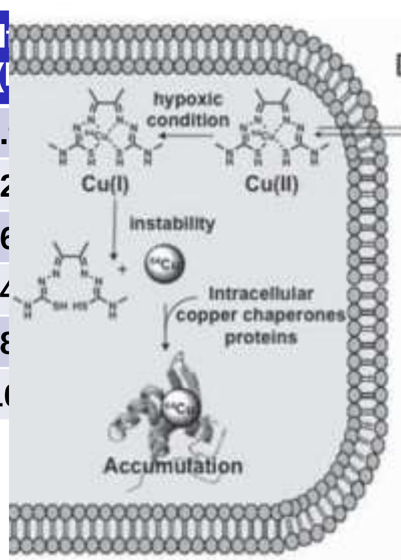


Bateman et al, J Nucl Cardiol 2006;13:24.

^{99m}Tc-SPECT
vs.
^{201}Tl-SPECT
vs.
^{82}Rb-PET
vs.
$^{13}NH_3$-PET
vs.
$^{15}OH_2$-PET
vs.
Coronary CT
vs.
MRI
vs.
echography

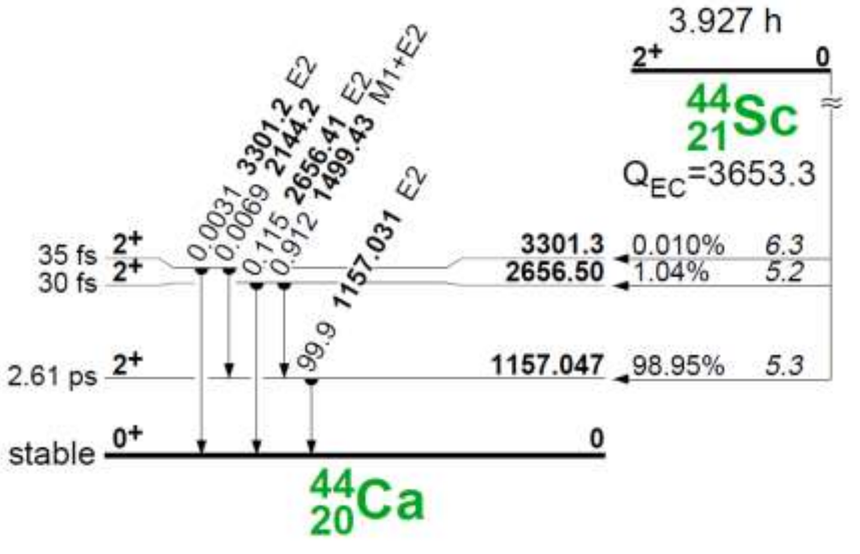
Longer-lived PET isotopes

Radio-nuclide	Hal ((	ange (mm)
Sc-44	3.	2.5
Cu-64	12	0.8
Br-76	16	6
Y-86	14	2.6
Zr-89	78	1.4
I-124	10	3.8

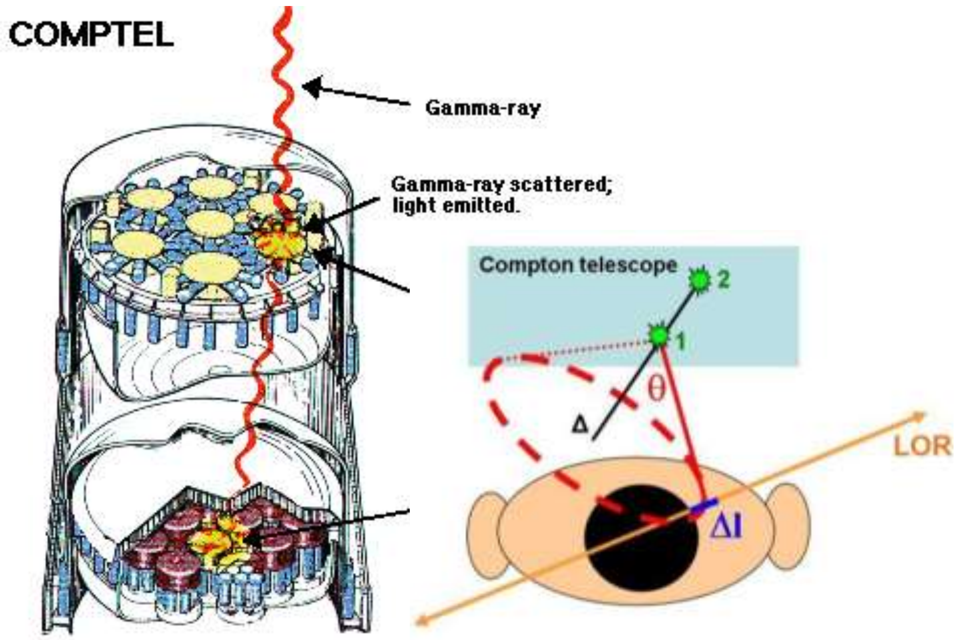


Longer-lived PET isotopes

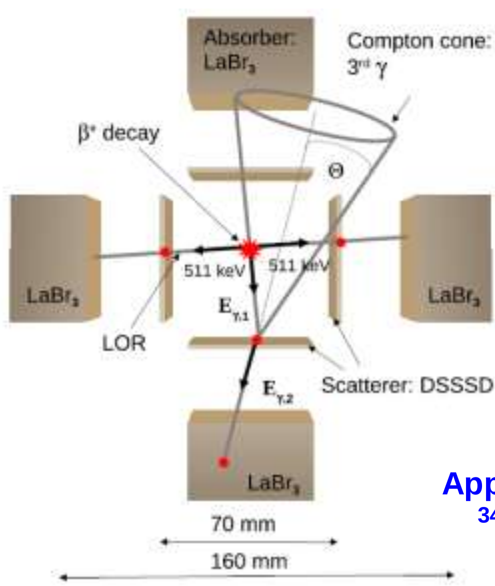
Radio-nuclide	Half-life (h)	Branching ratio β^+ (%)	Branching ratio γ (%)	h_{10} (mSv/h/GBq)
Sc-44	3.97	94.3	101	0.324
Cu-64	**12.7**	**17.6**	**0.5**	**0.03**
Y-86	14.7	31.9	320	0.515
Zr-89	**78.4**	**22.7**	**100**	**0.182**
I-124	**100.2**	**22.8**	**99**	**0.17**
Tb-152	17.5	17	142	

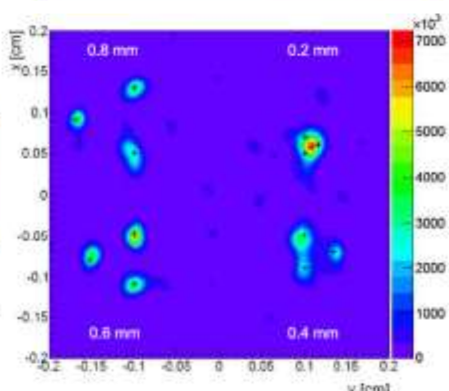


Compton telescope



3-photon-camera: PET-SPECT



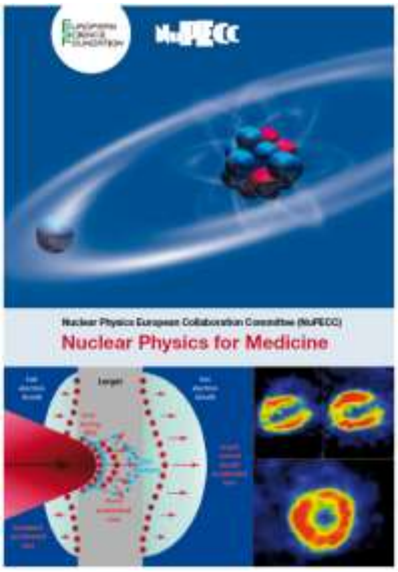


Applications:

^{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.

NuPECC: Nuclear Physics for Medicine
Chapter III: Radioisotope Production



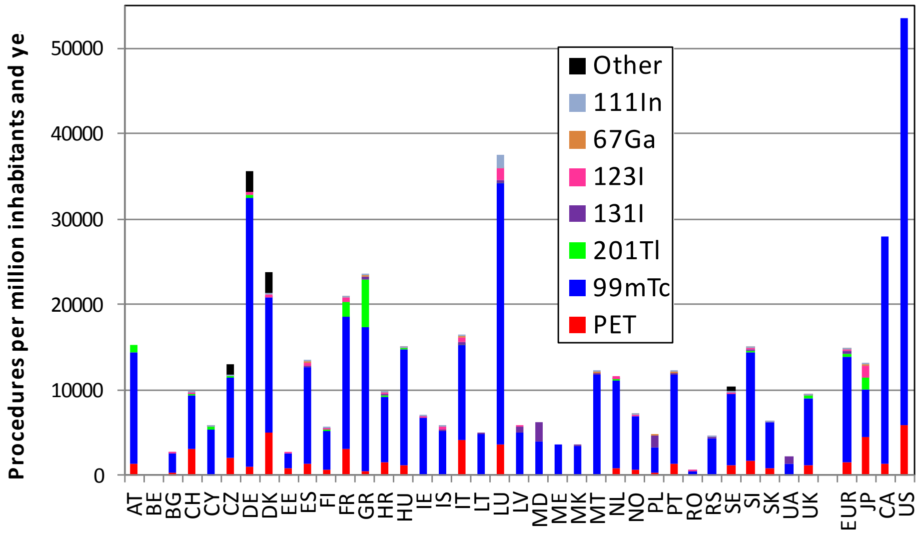
Marie-Claire Cantone, Italy – *convener*
Ferid Haddad, France
Sotirios Harissopoulos, Greece
Mikael Jensen, Denmark
Ari Jokinen, Finland – *NuPECC liaison*
Itzhak Kelson, Israel
Ulli Köster, France – *convener*
Ondrej Lebeda, Czech Republic
Bernard Ponsard, Belgium
Uli Ratzinger, Germany
Thierry Stora, Switzerland
Ferenc Tarkanyi, Hungary
Piet Van Duppen, Belgium – *NuPECC liaison*

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

Statistics data from DDM2 report and:

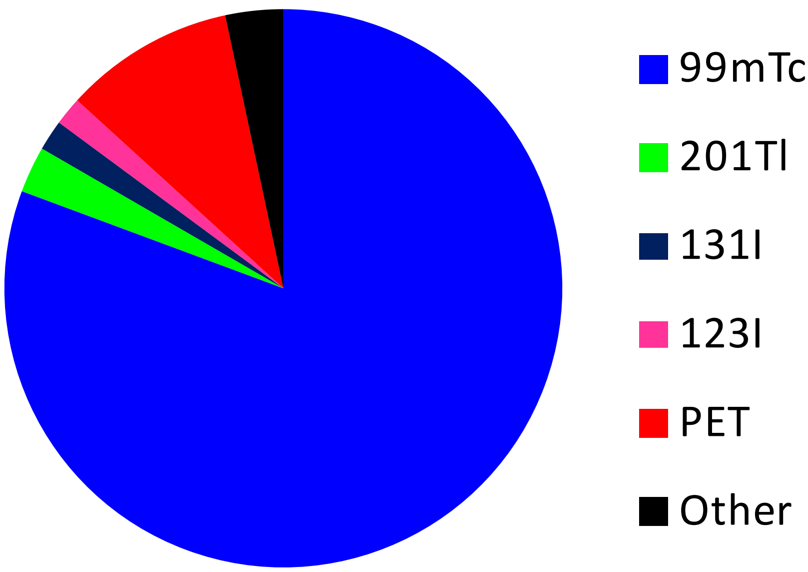
Bernard Aubert (IRSN France)
Ursula Bär (Federal Statistical Office, Germany)
Dieter Cernohorski (Federal Office of Economics and Export Control, Germany)
Panicos Demitriades (Department of Labour Inspection, Cyprus)
Andrejs Dreimanis (State Environmental Service, Latvia)
Marisa España Lopez (H.U. de la Princesa, Madrid)
Cécile Etard (IRSN France)
Karlheinz Haug (Bavarian State Office for Environment)
Jörg Kotzerke (DGN & TU Dresden, Germany)
Leszek Krolicki (Medical Univ. of Poland)
Reto Linder (Federal Office of Public Health, Bern, Switzerland)
Dietmar Noßke (Federal Office for Radiation Protection, Germany)
Sigrid Richter (Bavarian State Office for Environment)
Anthony Samuel (Mater Dei Hospital, Malta)
Elena Shubina (Environmental Board, Estonia)
Damijan Škrk (Slovenian Radiation Protection Administration)
Pedro Teles (IST/ITN Portugal)
Gertrud Vierkant (Federal Statistical Office, Germany)
Stavroula Vogiatzi (Greek Atomic Energy Commission)
the State Institute for Drug Control Czech Republic
the State Institute of Radiation Protection Denmark
the Japan Radioisotope Association
Consejo de Seguridad Nuclear (Spain)

Statistics of radionuclide use in Europe

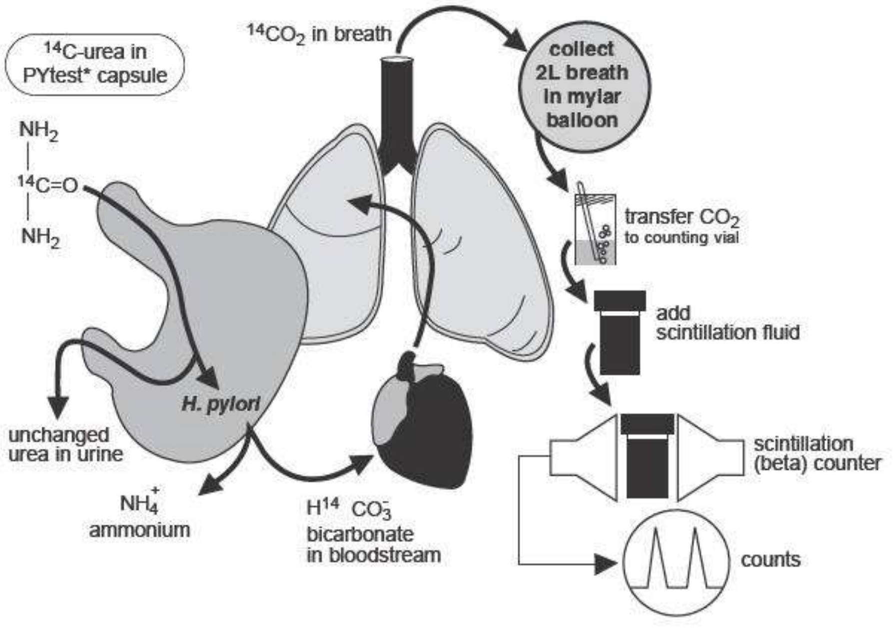


Use of diagnostic isotopes in Europe, USA, Canada and Japan

Cumulative use of diagnostic isotopes in Europe

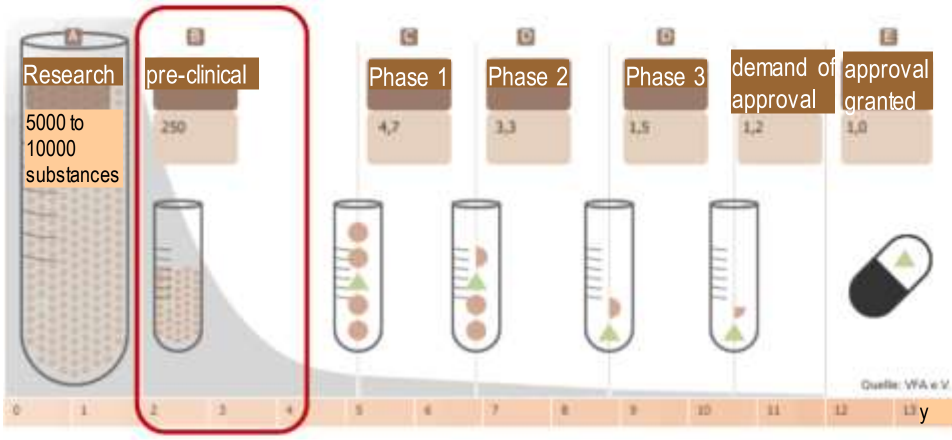


Radiotracer diagnostics without imaging



Molecular imaging without patients?

Development of pharmaceuticals



Screening | in vitro tests, animal exp. | tests with humans

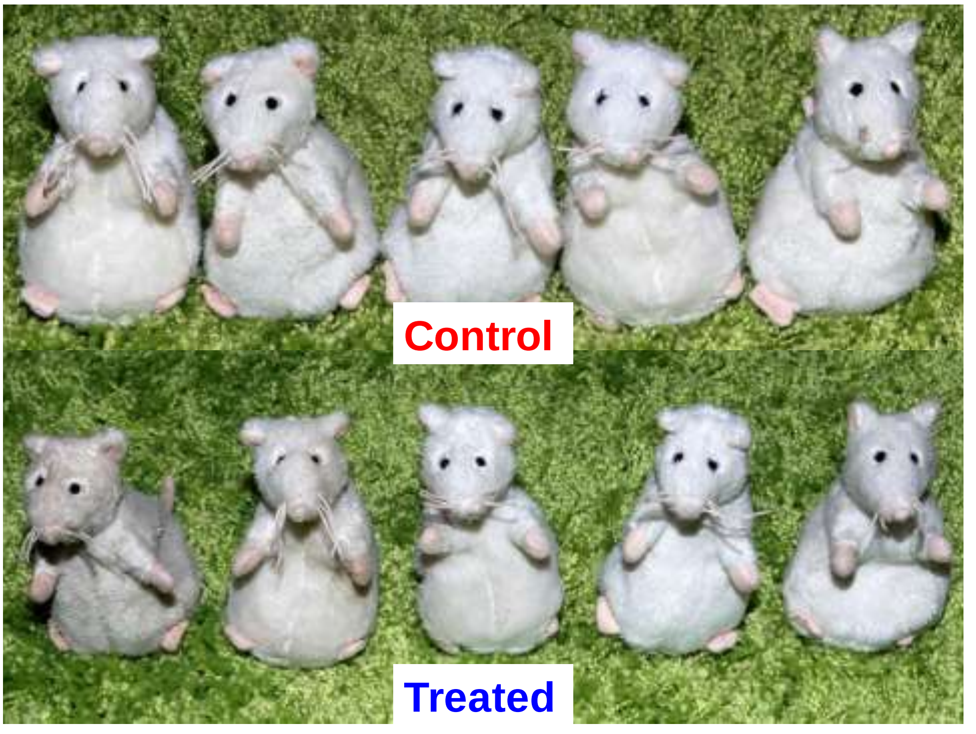
toxicity, side effects | wanted effect | comparison with standard

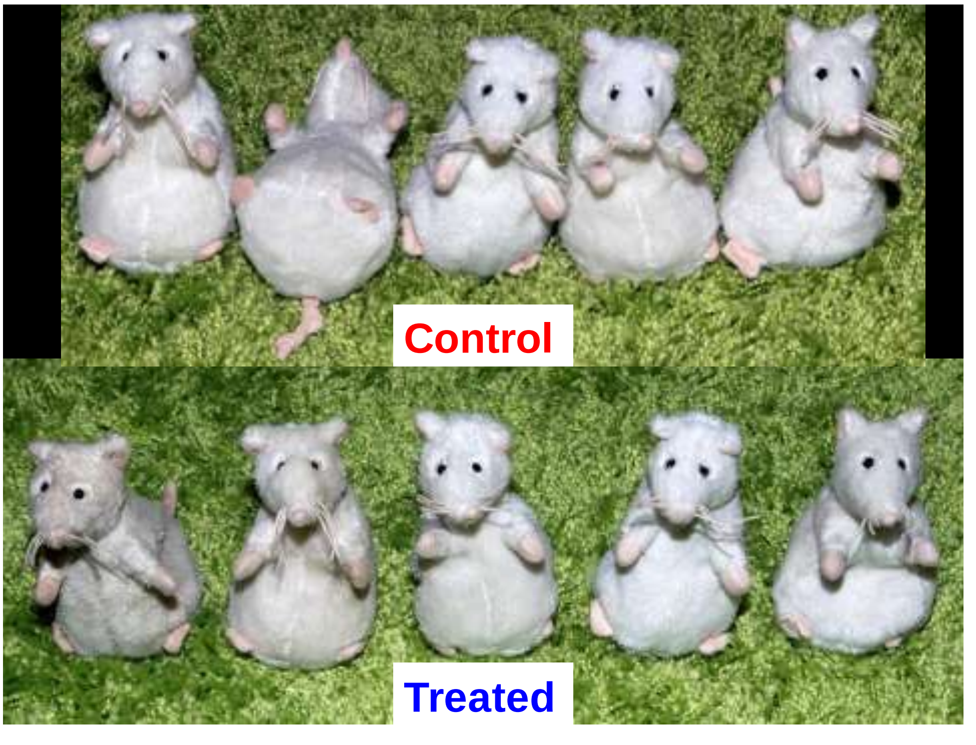
20-80 healthy volunteers | 100-300 patients | x00-x000 patients

Pre-clinical studies (1)

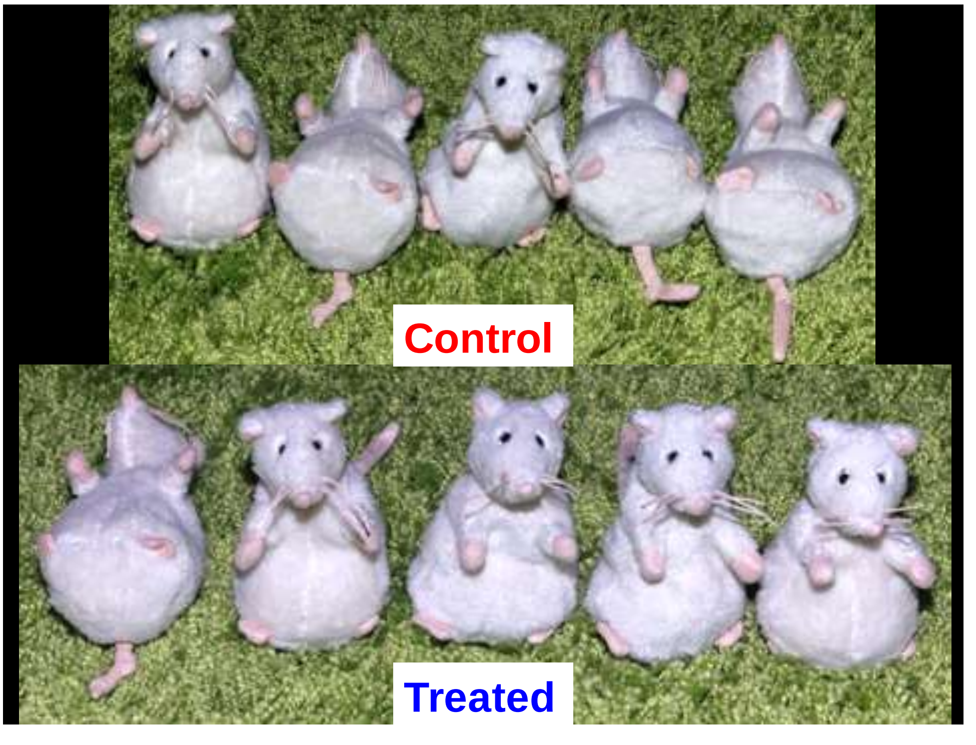
Pre-clinical studies (2)

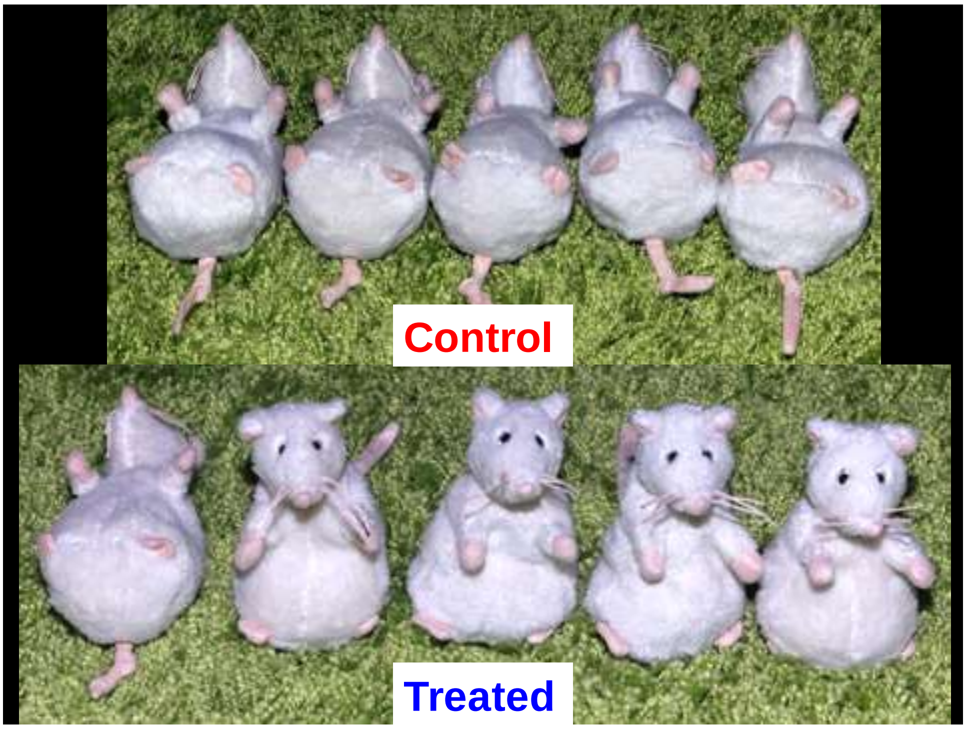
Pre-clinical studies (3)

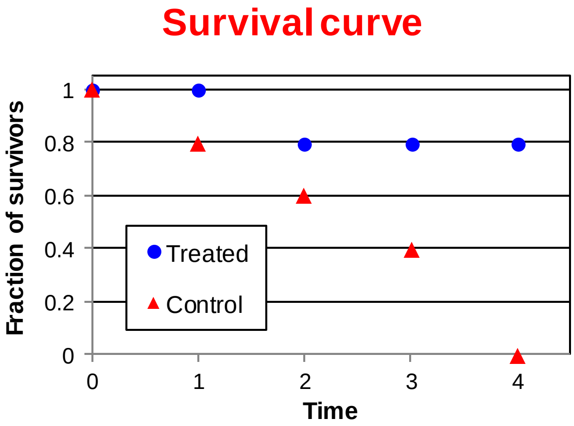

Control
Treated


Control
Treated


Control
Treated


Control
Treated

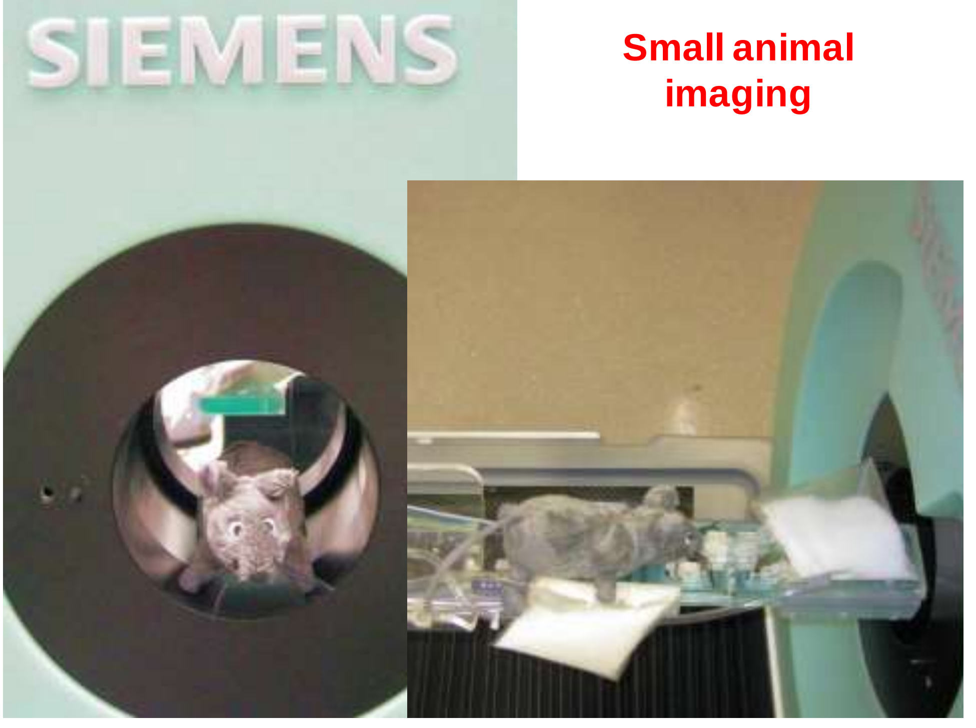




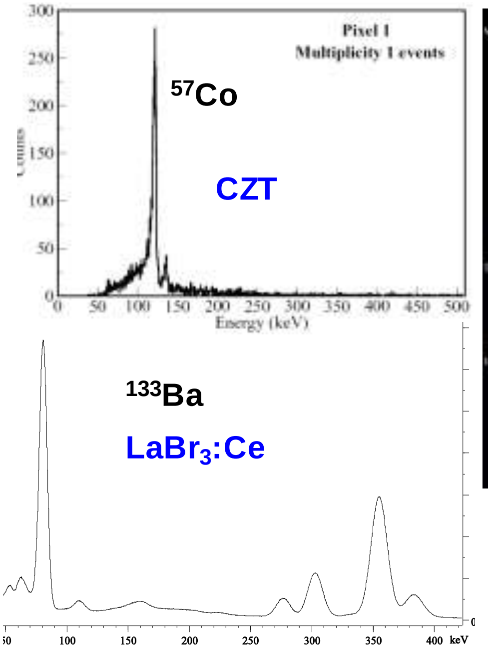
- medium survival time, median survival time, survival benefit
- shows final benefit but not detailed mechanism

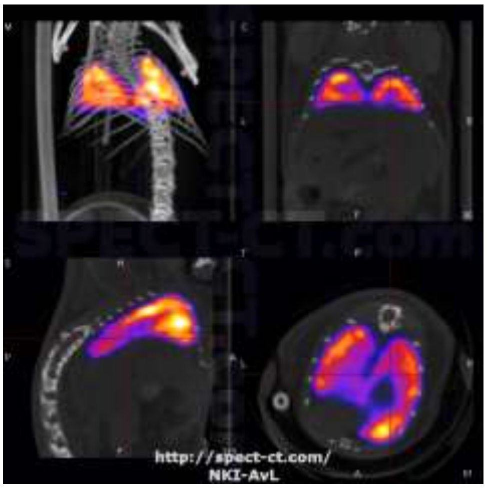
- more information from bio-distribution studies
- preferentially on-line with suitable radiotracers and small animal SPECT or PET

Small animal imaging

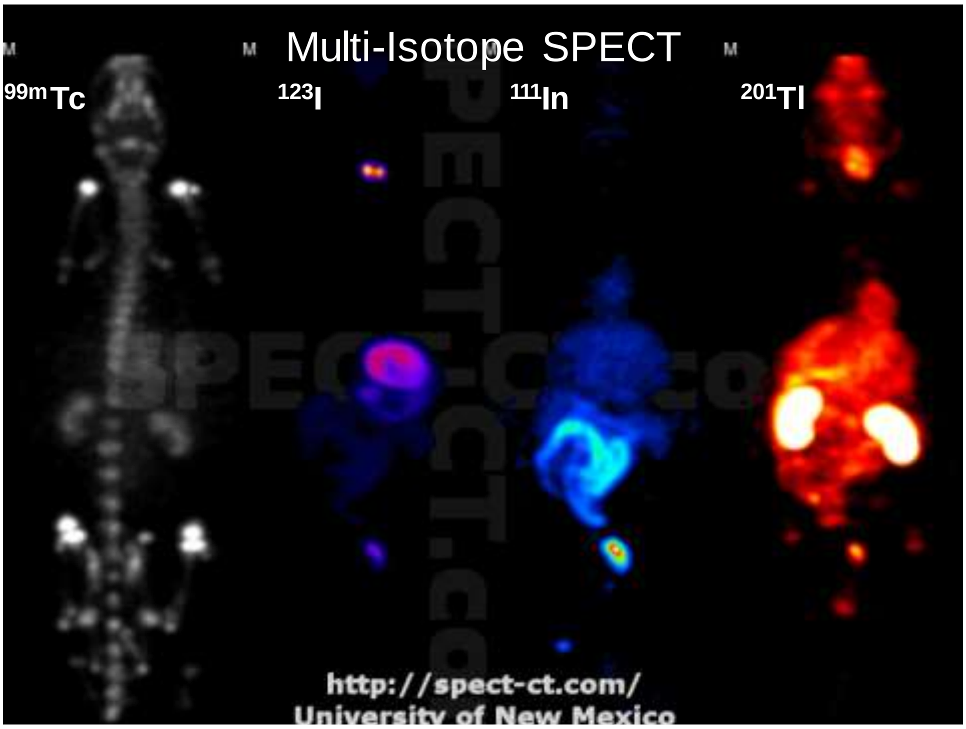


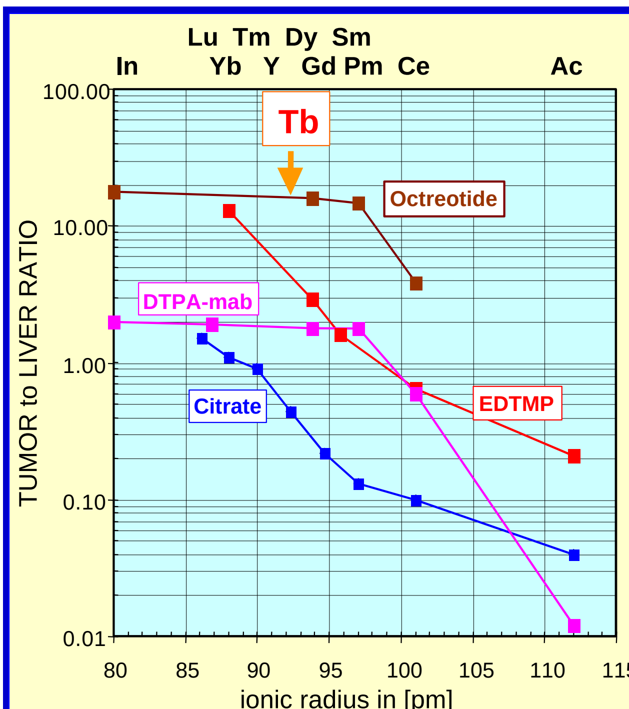
New generation of small animal SPECT





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





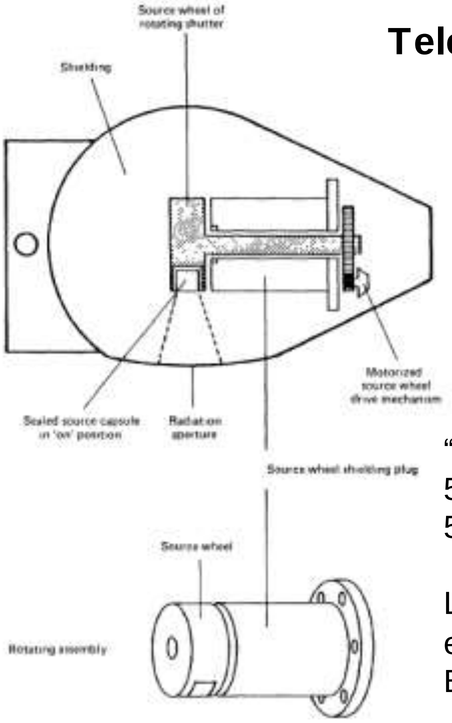
Comparison
of the
bio-distribution
of different
tumor seeking tracers
labeled with
radio-lanthanides, ^{225}Ac and ^{111}In

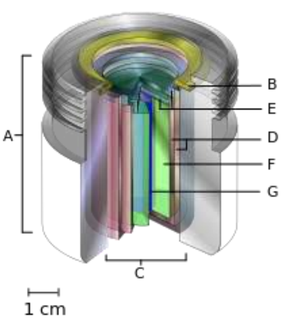
free chelates:
Citrate
EDTMP
specific tracers:
Octreotide
and
Mab
Linker:
Aminobenzyl-DTPA

G.J.Beyer, Hyperfine Interactions ***129*** *(2000) 529.*

From diagnostics to therapy

Teletherapy units

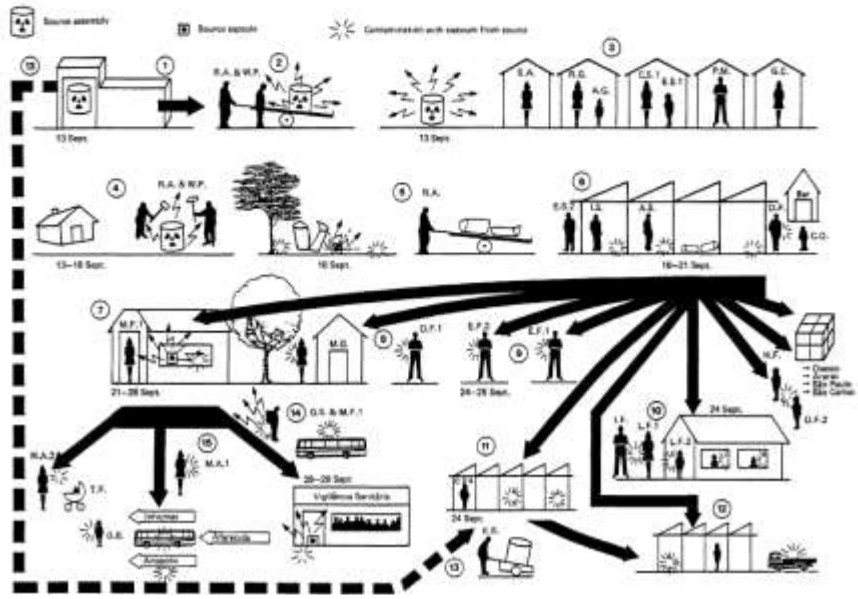




"Cobalt-bomb" or "Cesium-bomb"
50 – 100 TBq of ^{60}Co or ^{137}Cs
5 – 10 Gy/h at 1 m

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

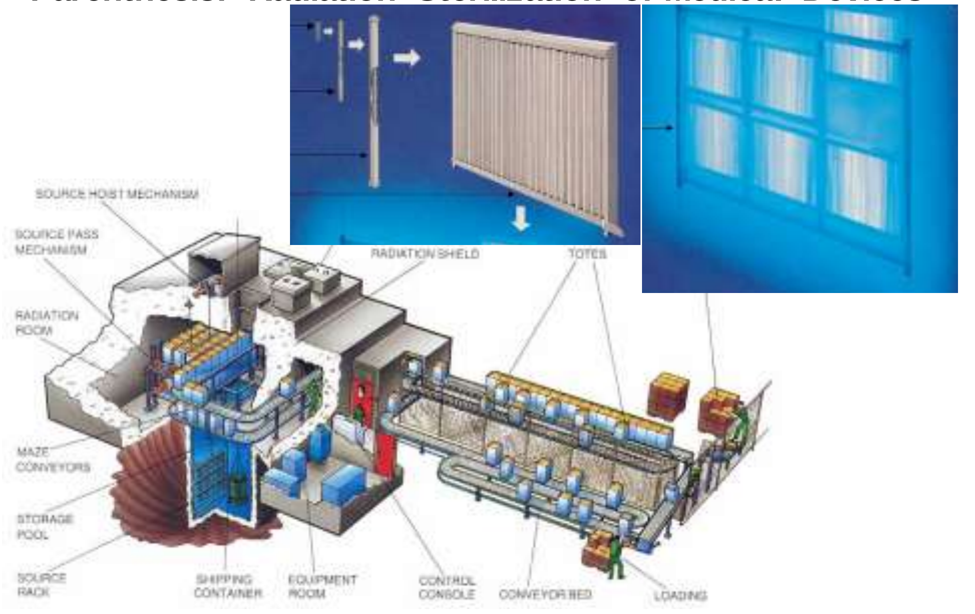
Civilian radiation accidents



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

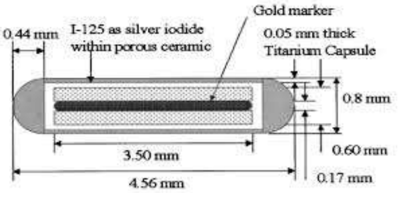


1 MCi = 37 PBq ^{60}Co sterilizes 650 kg/hour at 25 kGy

Brachytherapy

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

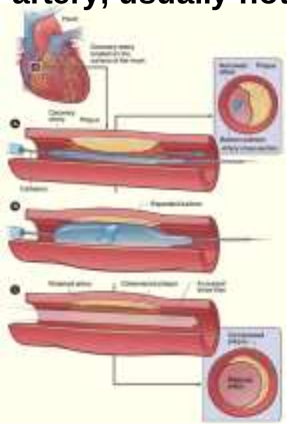
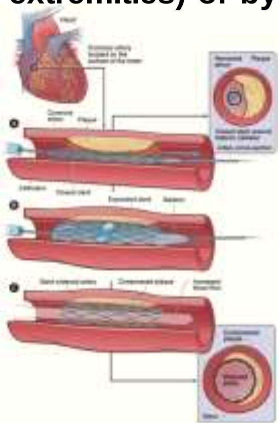
Low Dose Rate (LDR) brachytherapy long-term insertion of ^{32}P, ^{103}Pd, ^{125}I, ^{131}Cs, etc. sources ("seeds")



Historically also ampoules with ^{226}Ra, ^{222}Rn or ^{210}Po were used for brachytherapy.

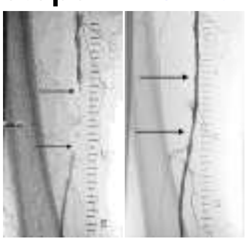
Stenosis

- constriction of blood vessels (due to diabetis mellitus, high blood pressure, high chloresterol level, nicotine consumption); 4.5 million patients in Germany
- arteries opened by balloon dilatation (angioplasty), sometimes with placement of stent (mainly coronary artery, usually not in extremities) or bypass operation

Rhenium-PTA

- frequent restenosis within few months due to deposition of vascular smooth muscle cells in intima (NIHA)
- repeated restenosis may lead to amputation of extremity: 60000 amputations/year in Germany (70% due to diabetis)
- alternative: PTA (percutaneous transluminal angioplasty), i.e. irradiation of cells after balloon dilatation prevents restenosis ⇒ ideal isotope ^{188}Re with high concentration

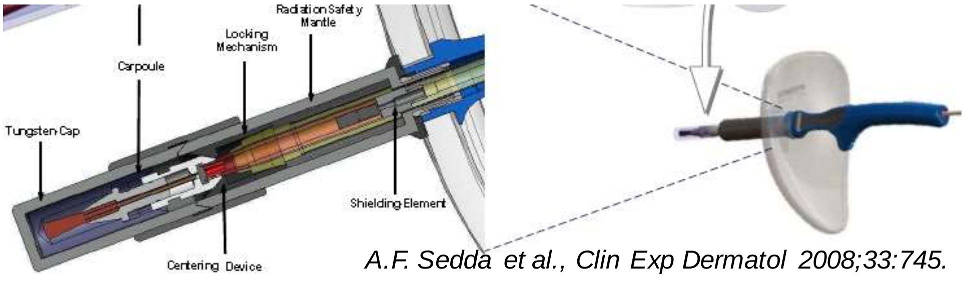

- clinical study in Augsburg: 13% restenosis in 16 months versus usually 50-75% in 6 months

W.A. Wohlgemuth et al., J Cardiovascular Surgery 2010;51:573.

Rhenium skin cancer therapy

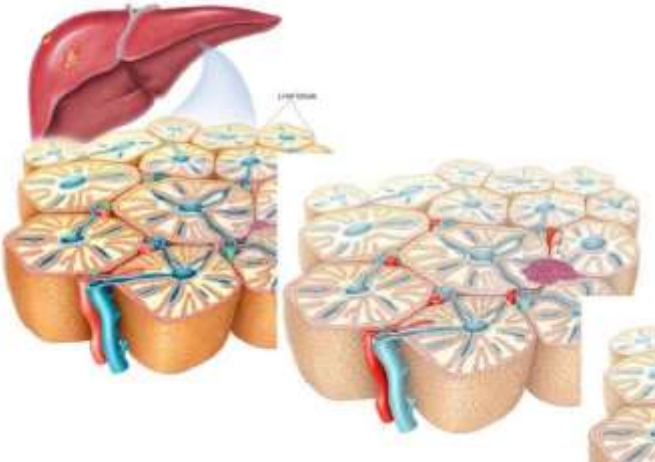
non-melanoma skin cancer:

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

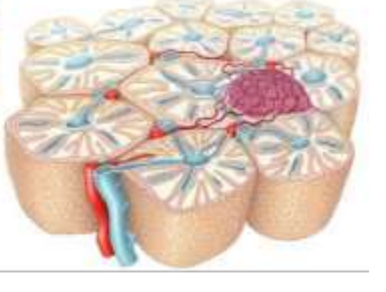


A.F. Sedda et al., Clin Exp Dermatol 2008;33:745.

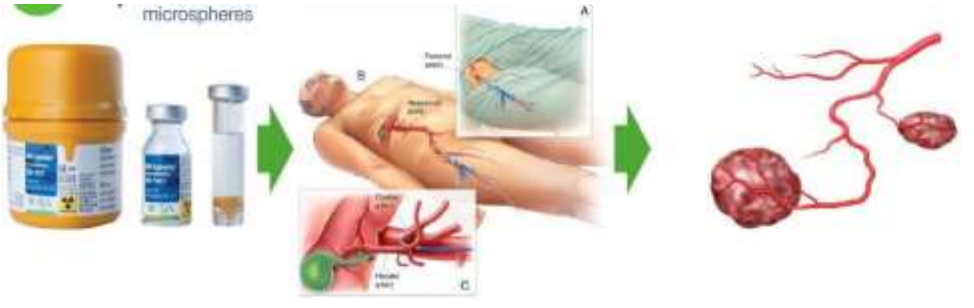
Liver cancer and liver metastases



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

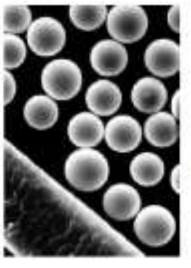


Selective Internal Radiation Therapy (SIRT)



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

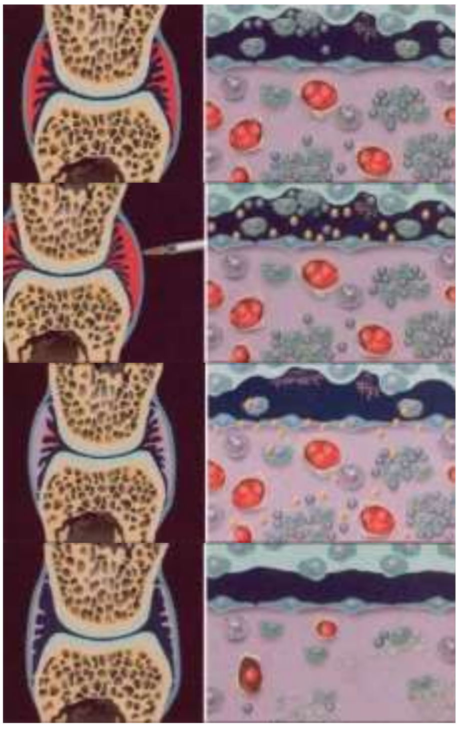
Knee: ^{90}Y (185 MBq)

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.



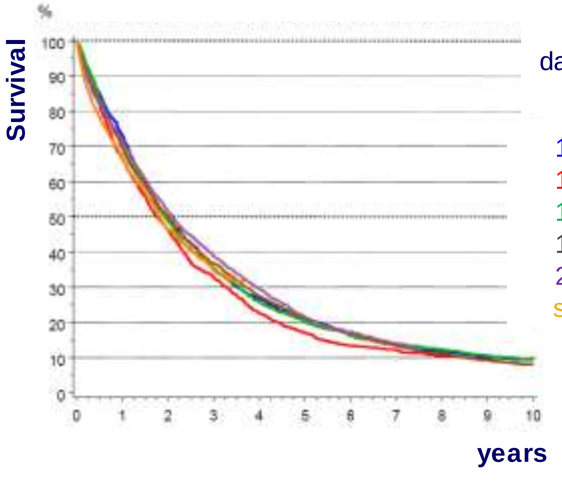
Cancer and efficiency of treatments

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

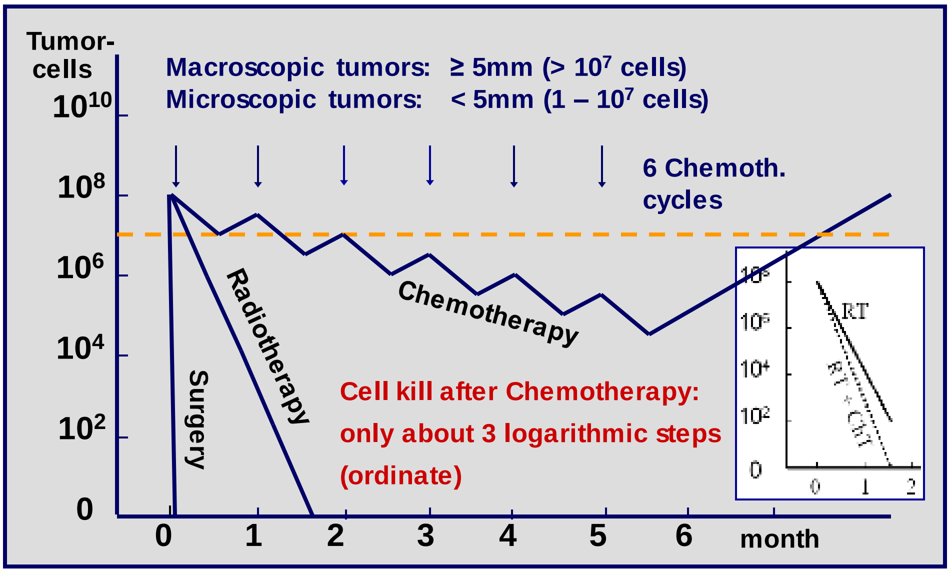
Mammary Carcinoma
Survival time since diagnosis of metastases



Results for 6 time periods
data from tumor centre Munich
n = 9228

1980-1984
1985-1989
1990-1994
1995-1999
2000-2003
since 2004

Comparison of Therapies

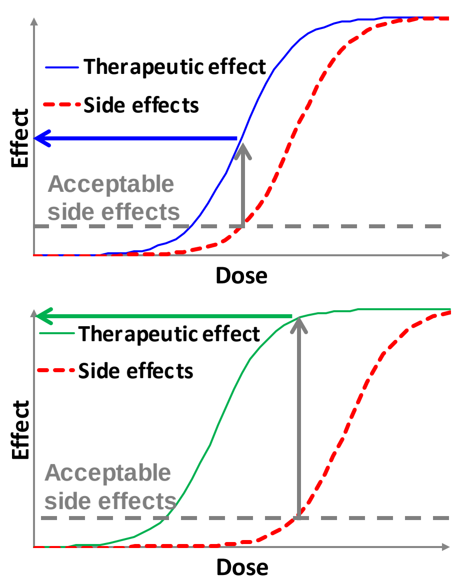


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

Targeted therapies

Paracelsus (1493-1541)

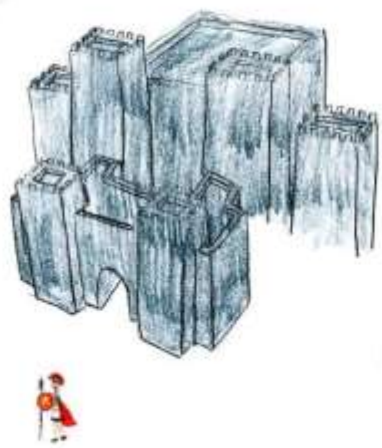
"All things are poison, and nothing is without poison; only the dose permits something not to be poisonous."



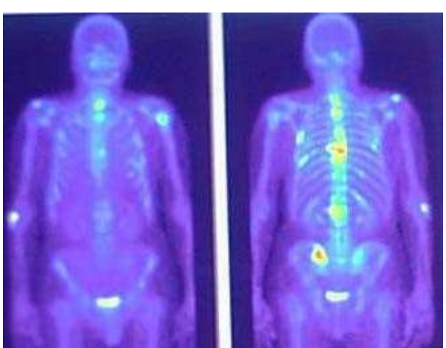
Selectivite targeting is essential to widen the therapeutic window!

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



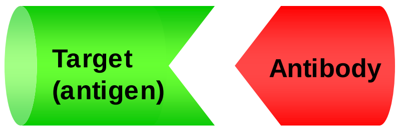
Thyroid cancer
$^{123}I^-$ for imaging
$^{131}I^-$ for therapy

Bone metastases
1.5 million patients world-wide

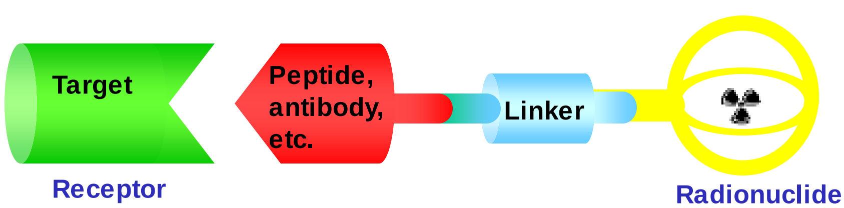
^{99m}Tc-MDP for SPECT imaging
$^{18}F^-$ for PET imaging

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

Immunology approach



Multidisciplinary collaboration to fight cancer



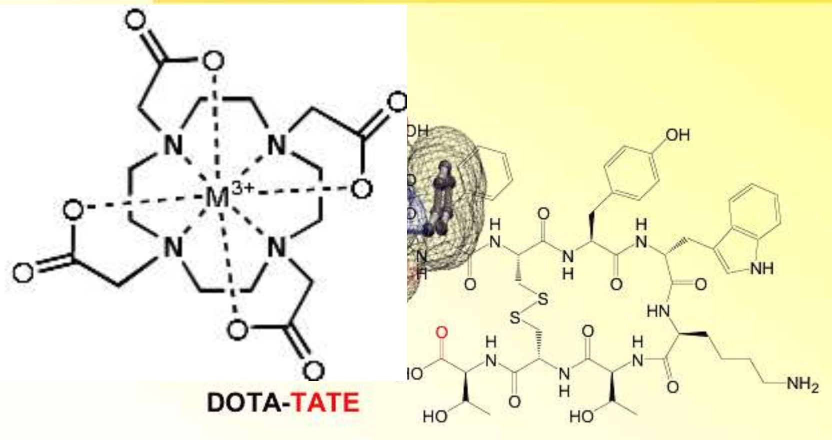
Immunology
Structural biology

Coordination
chemistry

Nuclear physics
and
radiochemistry

Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE



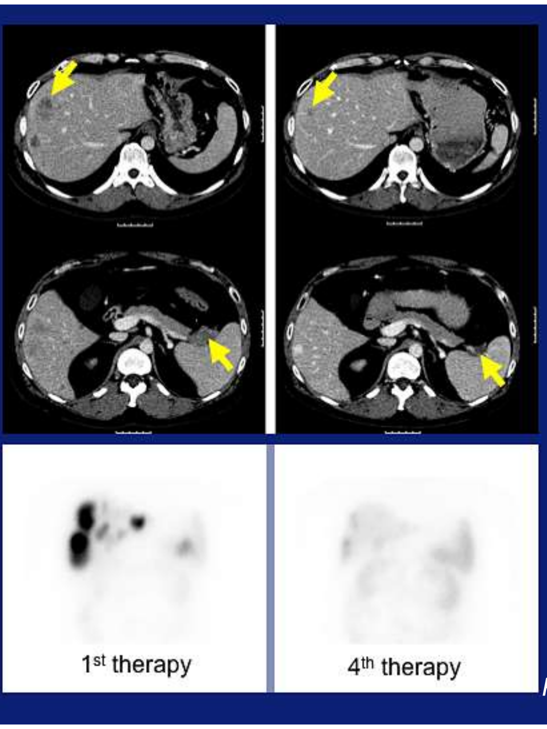
1,4,7,10-tetraazacyclododecantetraacetate

^{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?

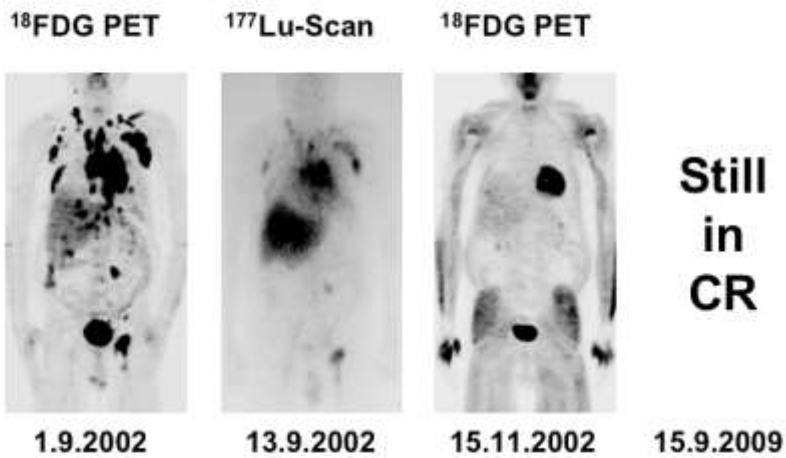
- ✓ CR+ PR + MR in about 50% of patients: YES
- ✓ Reduce symptoms and improve quality of life: YES
- ✓ Increase survival time: YES
- ✓ Safety and tolerability: YES

Roelf Valkema, EANM-2008.

Erasmus MC

Lymphoma therapy: RITUXIMAB+^{177}Lu

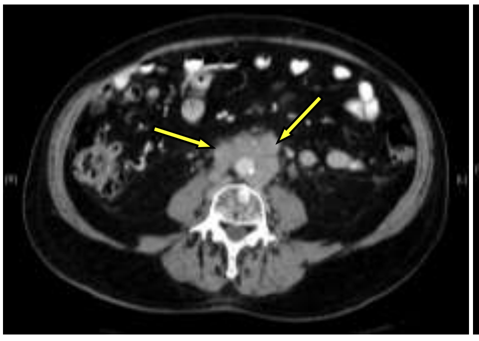
E.B., 1941 (m): UPN 6

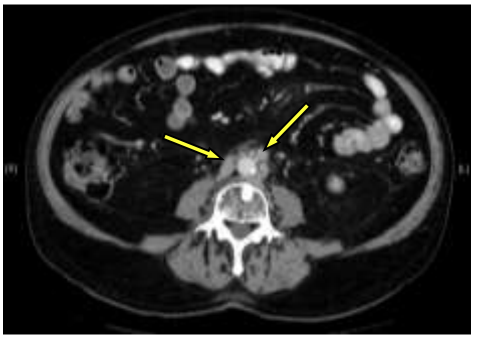


F. Forrer et al., J Nucl Med 2013;54:1045.

University Hospital Basel, CH

Radioimmunotherapy of advanced prostate cancer





8 Oct 2010:
before RIT

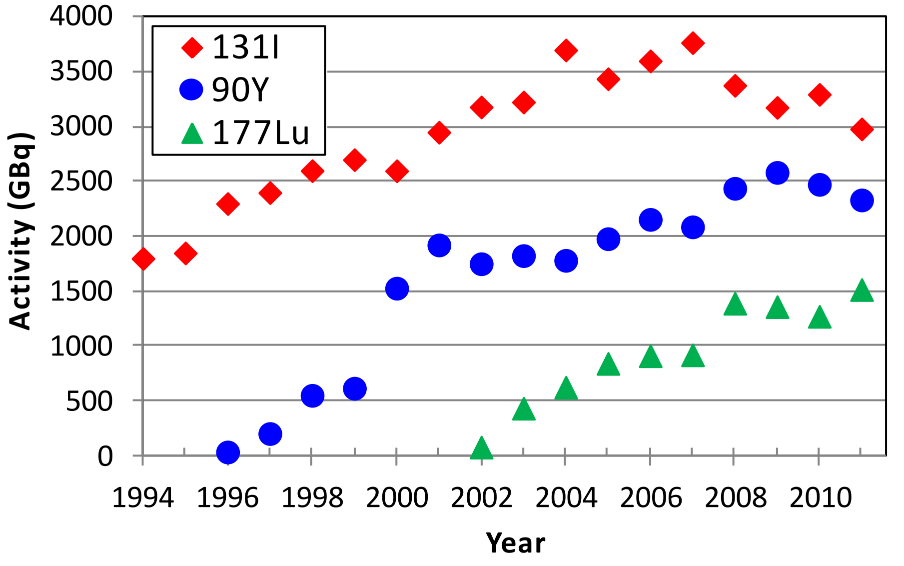
28 Jan 2011:
after RIT with ^{177}Lu+J591
Massive reduction of the size of metastases

Cornell Univ., ATLAB Pharma Nantes

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**

Evolution of use of therapeutic isotopes in Switzerland



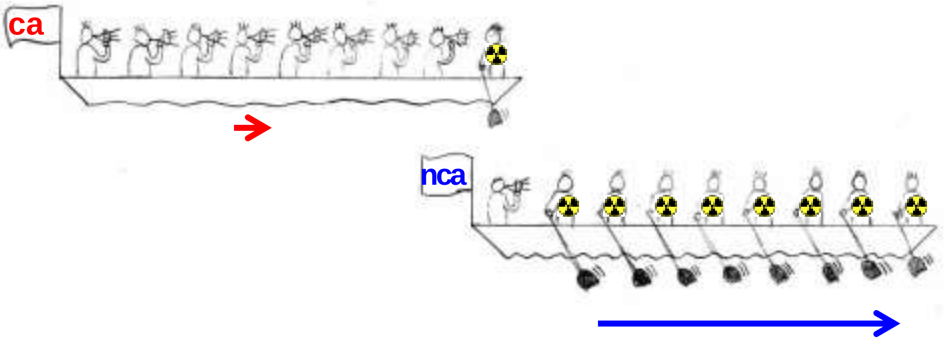
The rising star for therapy

Specific activity

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

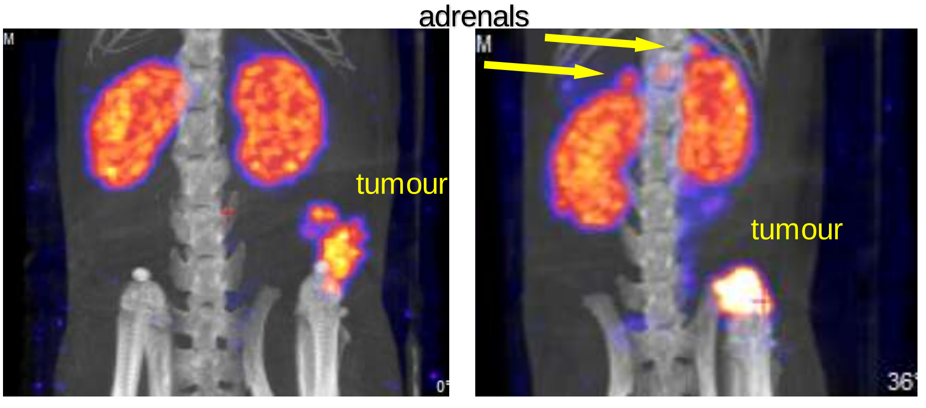
basically the ratio of radioactive atoms to all atoms (including stable ones).

Carrier added vs. non-carrier added



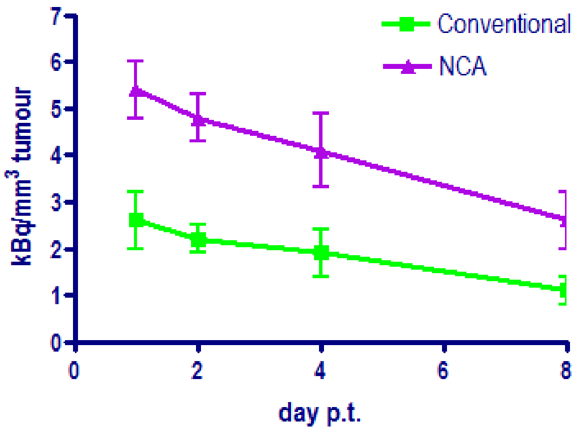
SPECT/CT day 1 p.t. Lu-octreotate

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



M. de Jong, ICTR-PHE 2012

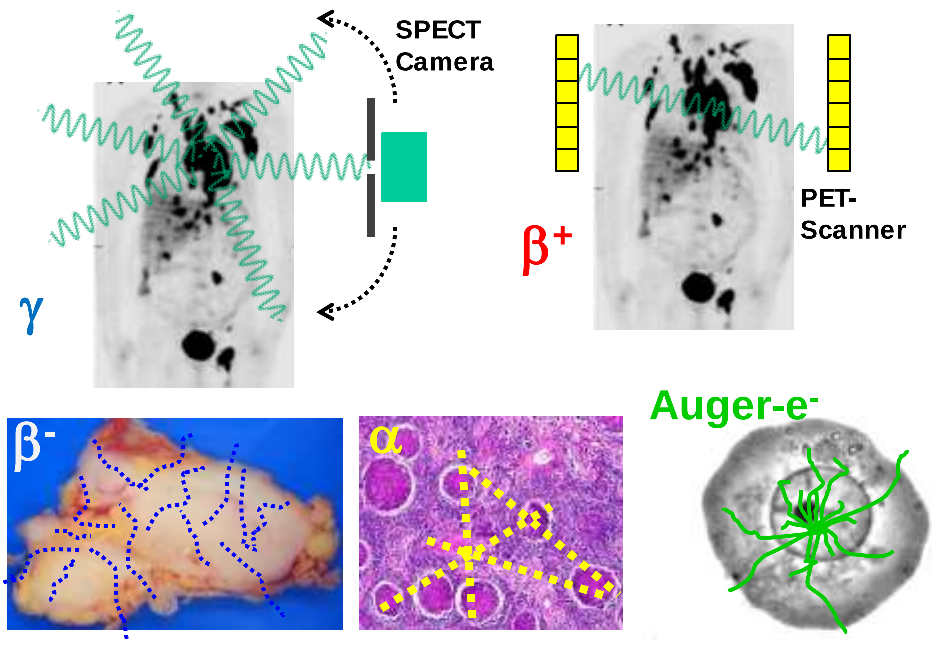
Tumour uptake, based on SPECT quantification



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

M. de Jong, ICTR-PHE 2012

The Nuclear Medicine Alphabet

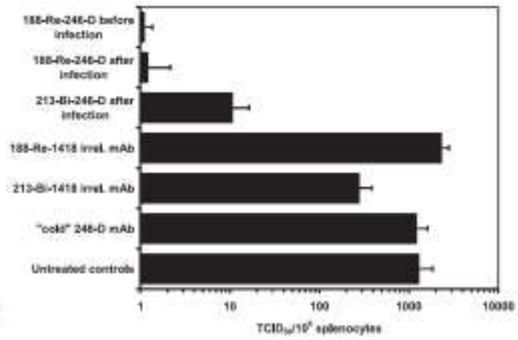


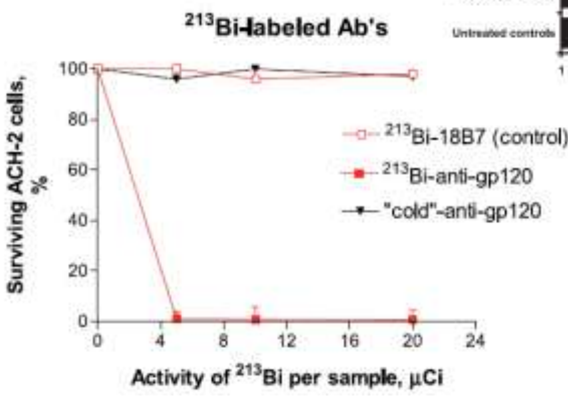
Radio-nuclide	Half-life	Daugh-ters	Half-life	Cumulative α/decay	E_{α} mean (MeV)	Range (μm)
Tb-149	4.1 h			0.17	3.97	25
Pb-212	*10.6 h*	Bi-212 Po-212	1.01 h 0.3 μs	1	7.74	65
Bi-212	1.01 h	Po-212	0.3 μs	1	7.74	65
Bi-213	*0.76 h*	Po-213	4 μs	1	8.34	75
At-211	7.2 h	Po-211	0.5 s	1	6.78	55
Ra-223	11.4 d	Rn-219 Po-215 *Pb-211* Bi-211	4 s 1.8 ms *0.6 h* 130 s	4	6.59	>50
Ra-224	3.66 d	Rn-220 Po-216 *Pb-212* Bi-212	56 s 0.15 s *10.6 h* 1.01 h	4	6.62	>50
Ac-225	10.0 d	Fr-221 At-217 *Bi-213* Po-213	294 s 32 ms *0.76 h* 4 μs	4	6.88	>50

Isotopes for targeted alpha therapy

High LET radiation, also for non-oncology applications

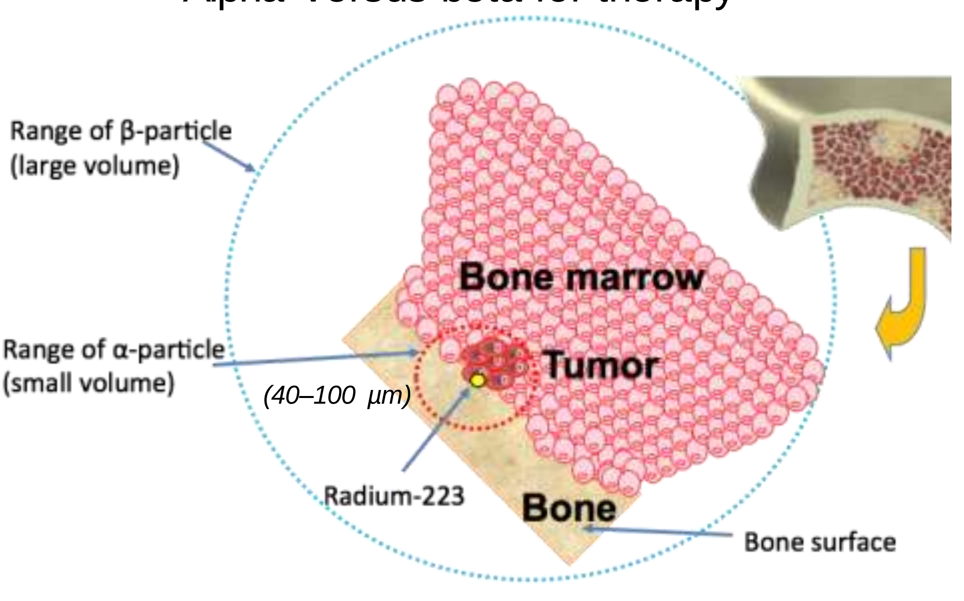
- Serious infections
- Fungal diseases
- HIV
- Anthrax



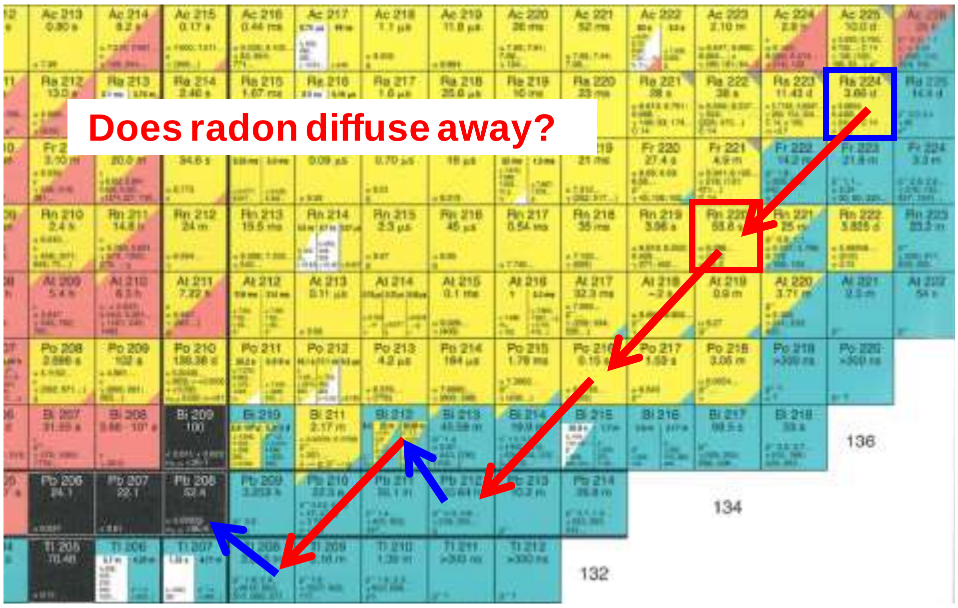


E. Dadachova et al.
PLoS Med 2006;3:e427.
PLoS One 2012;7:e31866.
Microbiol Spectr 2014;2:23.

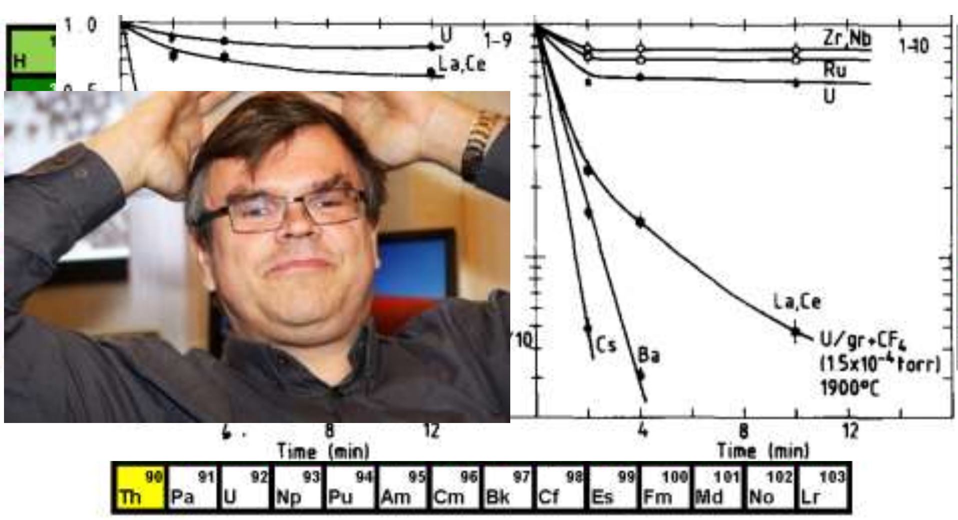
Alpha versus beta for therapy



Isotopes for targeted alpha therapy



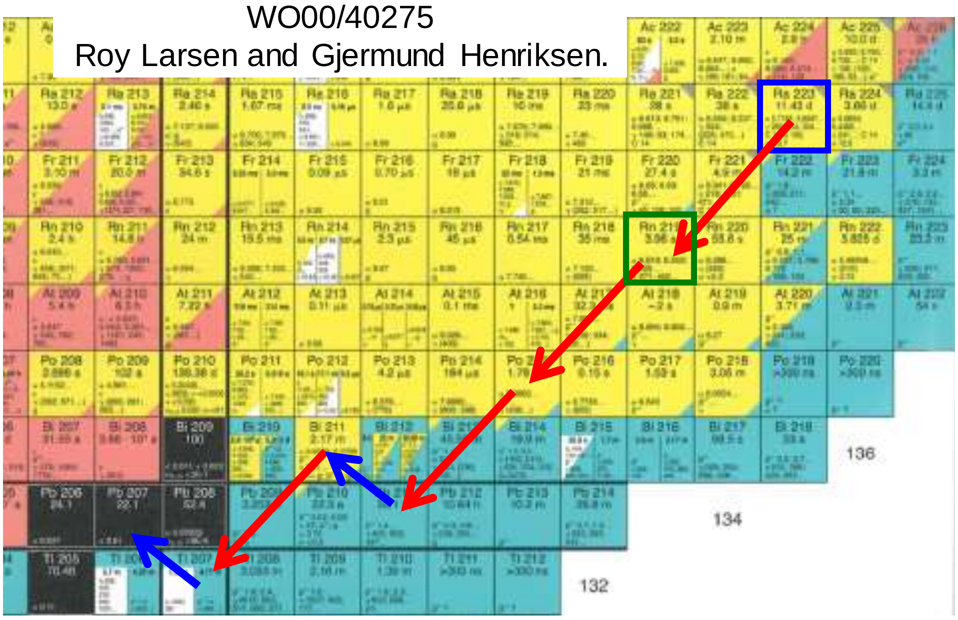
Radioisotopes available at ISOLDE-CERN



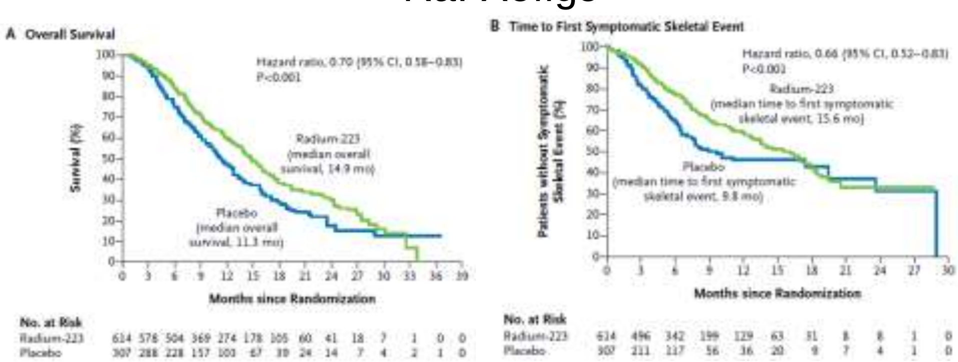
Diffusion and release measurements to develop new beams

e.g. *P. Hoff et al., NIM 221 (1984) 313.*

Isotopes for targeted alpha therapy



^{223}Ra: Xofigo

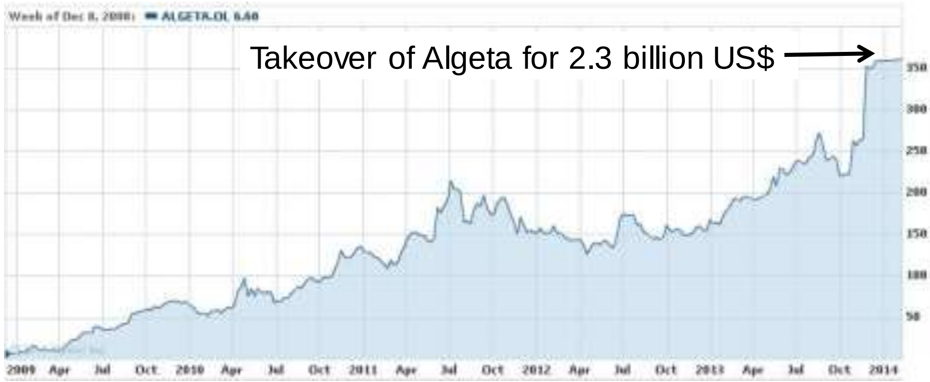


C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Prospects of targeted alpha therapies ?



Bayer HealthCare

SANOFI

AREVA Med
212Pb for Powerful Targeted Therapies

Roche

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

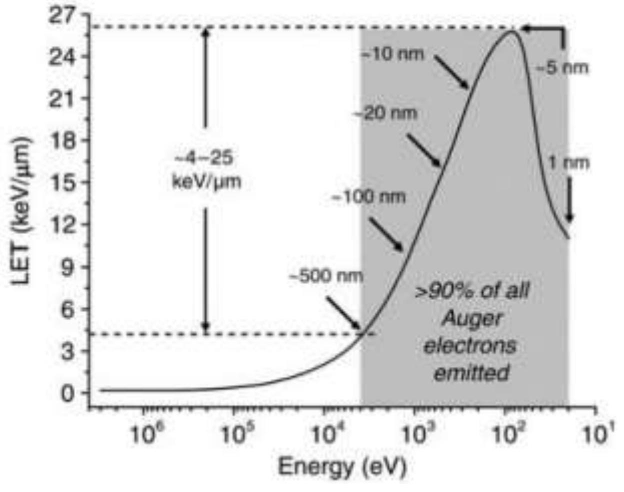
Estab-lished isotopes

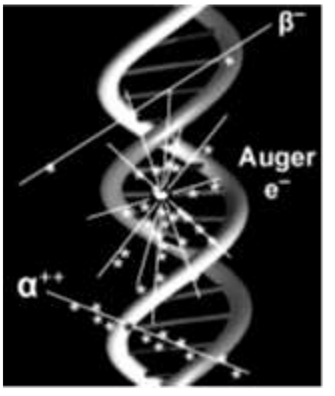
Emerging isotopes

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





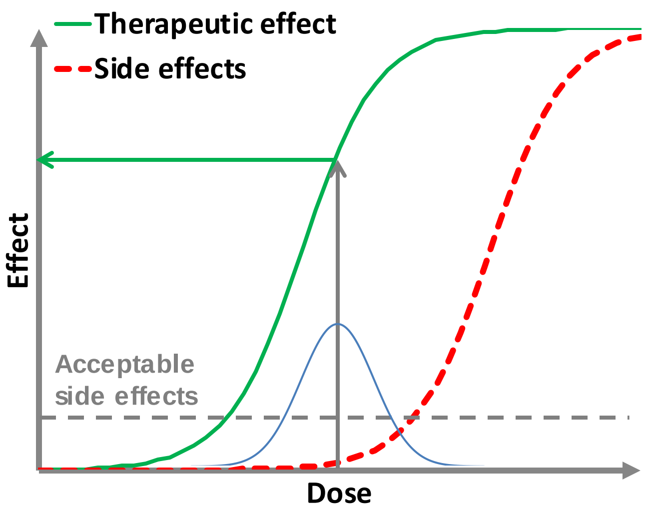
A.I. Kassis, Rad. Prot. Dosimetry 2011;143:241.

Auger therapy: a long-term project

The ideal agent for cancer therapy would consist of heavy elements capable of emitting radiations of molecular dimensions, which could be administered to the organism and selectively fixed in the protoplasm of cells one seeks to destroy. While this is perhaps not impossible to achieve, the attempts so far have been unsuccessful.

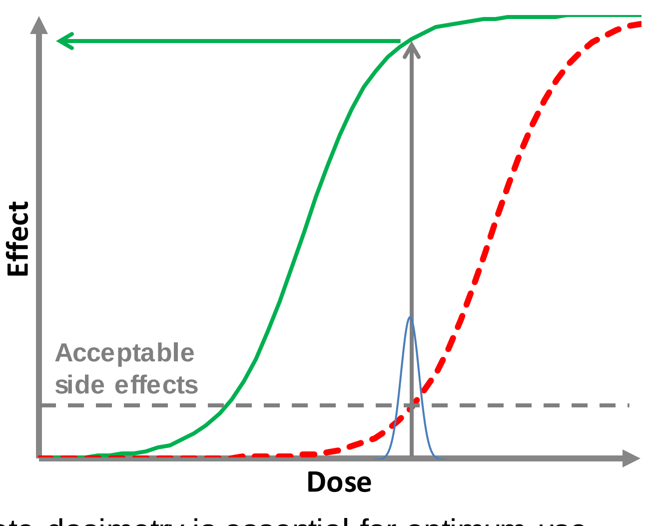
*C. Regaud, A. Lacassagne, Radiophysiologie et Radiotherapie **1927**;1:95.*

Theranostics



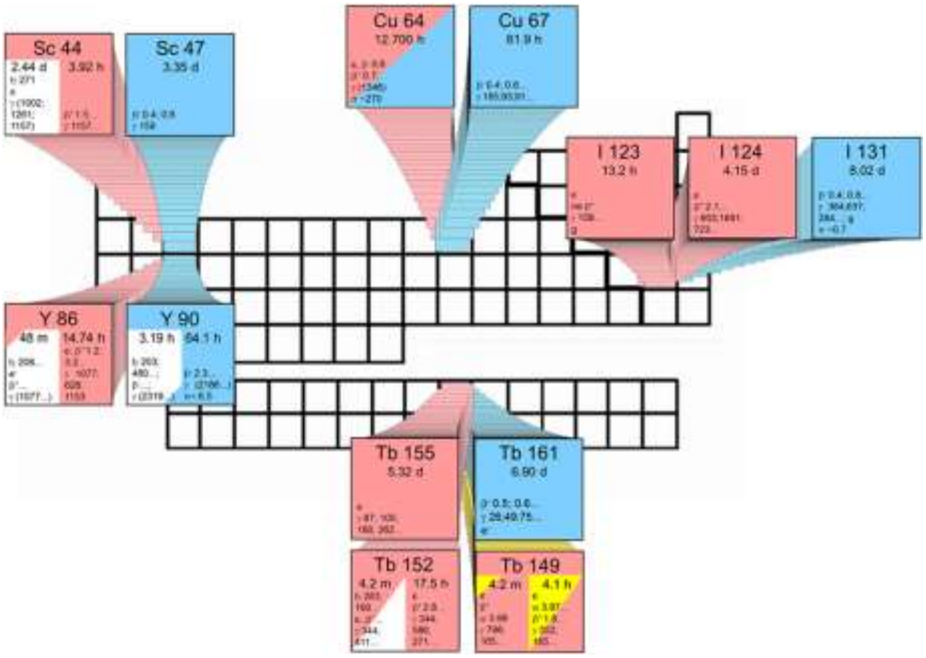
Accurate dosimetry is essential for optimum use of the therapeutic window.

Theranostics



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

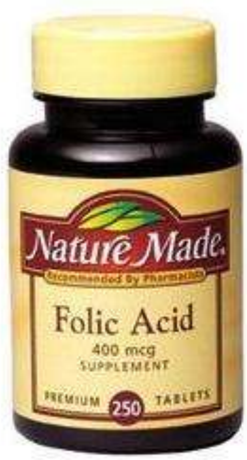
Matched pairs for theranostics



Folate-receptor positive cancers

Frequent overexpression of folate receptor in cancer of:

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



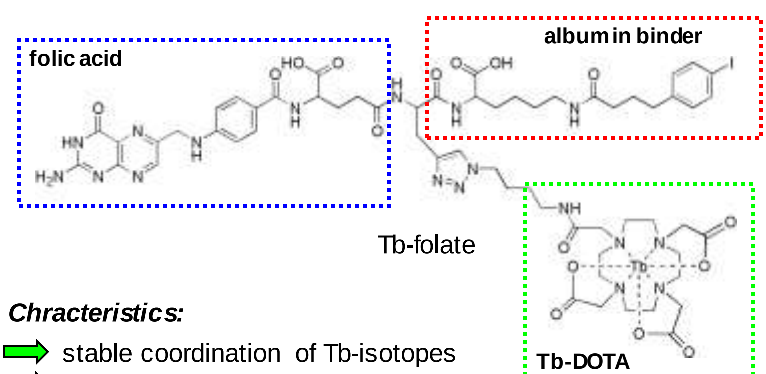
folic acid = vitamine B9

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

Terbium: a unique element for nuclear medicine

Tumor Tageting Agent for Tb-Coordination

Chemical Structure with 3 Functionalities

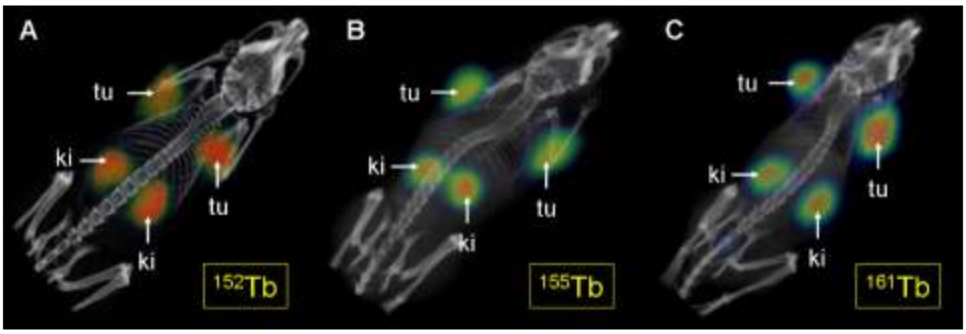


Chracteristics:

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

Theranostics with terbium isotopes

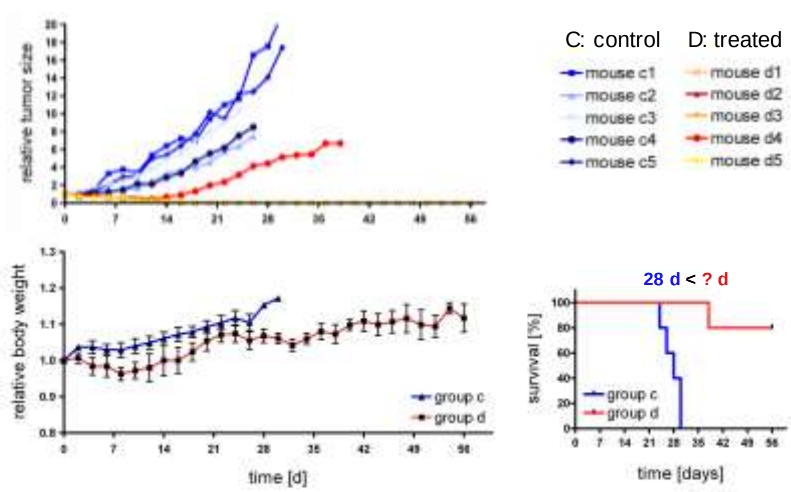
PET *SPECT* *SPECT*



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

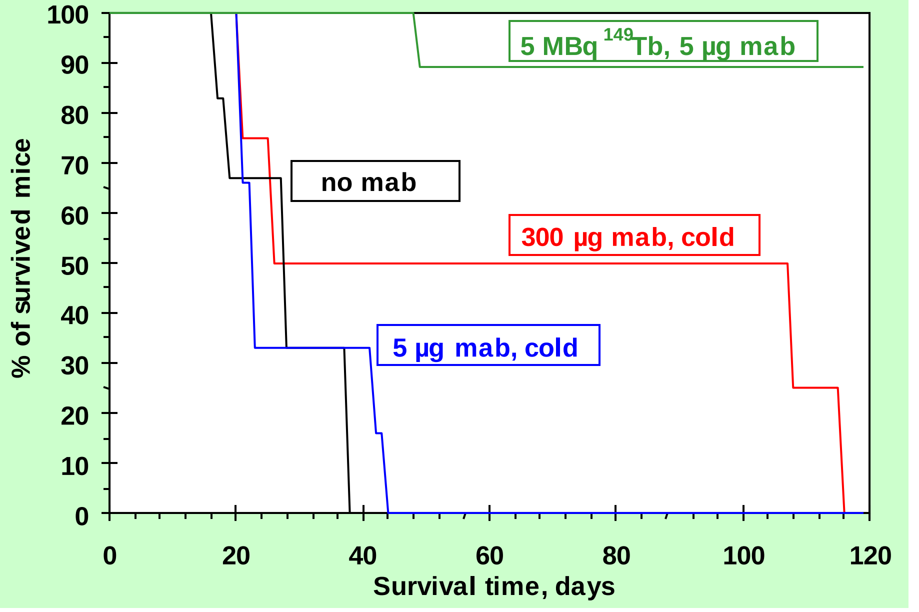
Targeted Beta Radionuclide Therapy

KB Tumor-Bearing Mice Treated with ^{161}Tb-Folate



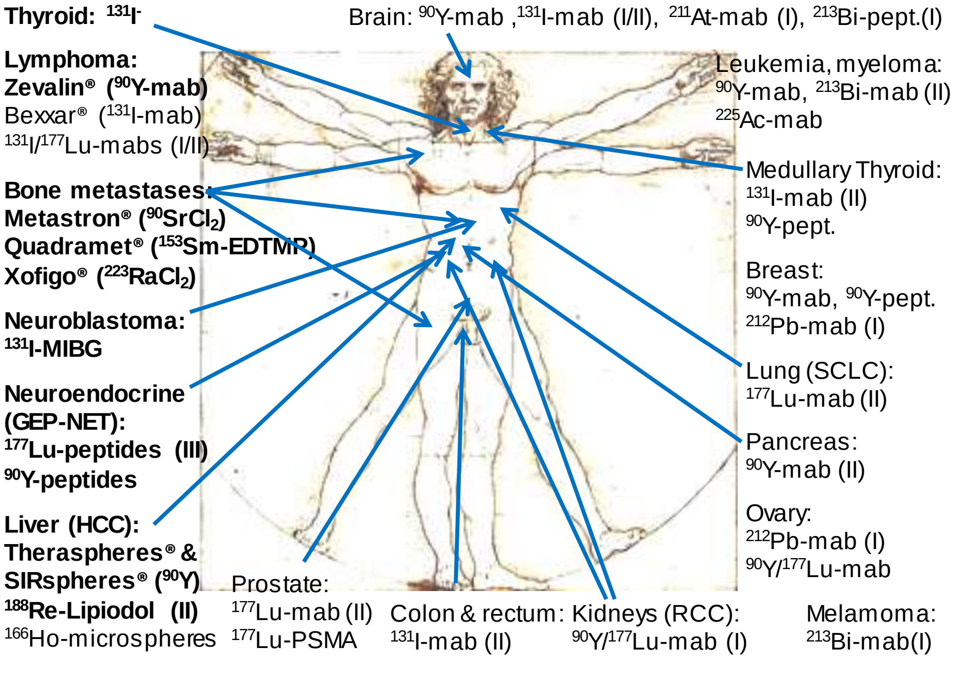
IS528 Collaboration: C. Müller et al., J. Nucl. Med. 2012;53:1951.

Preclinical study with lymphoma mouse model



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

Targeted radionuclide therapies in the clinic



Cost effectiveness ?

2010 TARMED prices:

650 mg rituximab 3939 CHF

1x Zevalin 24330 CHF
(^{90}Y-anti-CD20-ibritimumab)

6.2x more expensive?

16x rituximab 63024 CHF

1x Zevalin is >2.6x cheaper!

*“**A single infusion of ZEVALIN matched roughly 16 infusions of rituximab in terms of achieving the same increase in progression free survival.** I leave it up to the audience to draw conclusions about cost effectiveness. Thus, in conclusion, RIT represents the most effective single drug in the treatment of follicular NHL.”*

Dr. Anton Hagenbeek, the Academic Medical Center, Amsterdam, NL, on "*Controversies in Follicular Lymphomas”*

Which radionuclides will we need for medicine in 2030 ?

Today 30 million clinical applications per year !

BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel M. Schaeffer, Head
BNL Patent Office

SUBJECT: P-701 and P-702 - PREPARATION OF CARRIER-FREE MOLYBDENUM AND OF TECHNETIUM FROM FISSION PRODUCTS

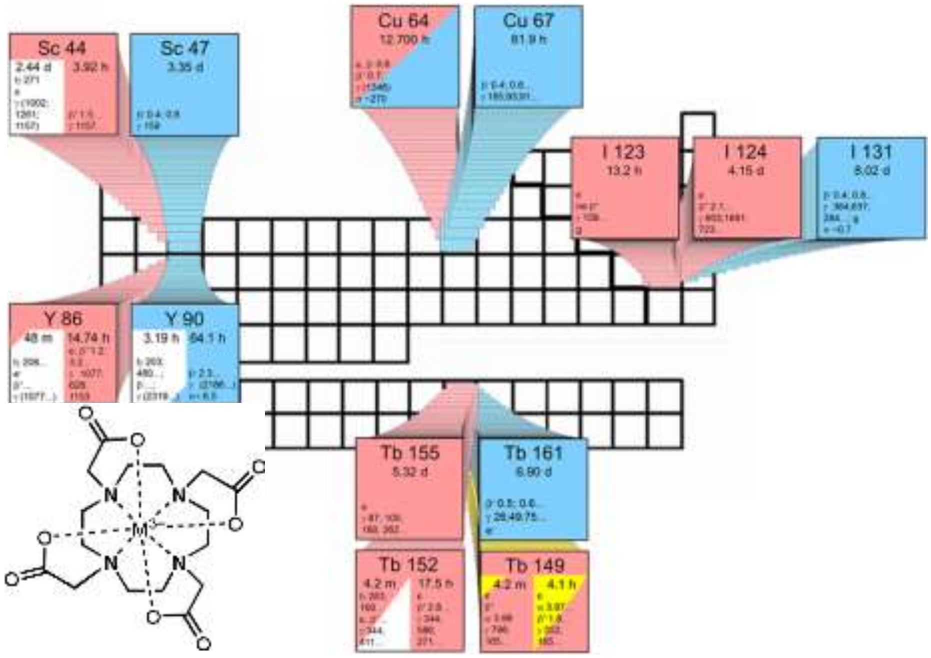
The New York Patent Group has carefully studied the information available relative to the above-identified item. The AEC does not at present desire to prepare a patent application on this item for the following reason:

"The method of producing carrier-free molybdenum-99 from fission products is disclosed in U. S. Patent Application S.N. 732,108, Green, Powell, Samos & Tucker (BNL Pat No. 58-17). It is noted that molybdenum-99 may be separated from its radioactive daughter, technetium-99, by absorption of a solution of molybdenum-99 on alumina and subsequent elution of its daughter with .1 nitric acid. While this method is probably novel, it appears that the product will probably be used mostly for experimental purposes in the laboratory. On this basis, no further patent action is believed warranted."

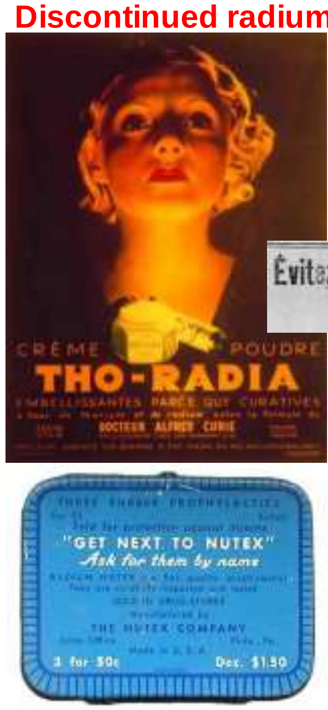
...

believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

Importance of chemical properties



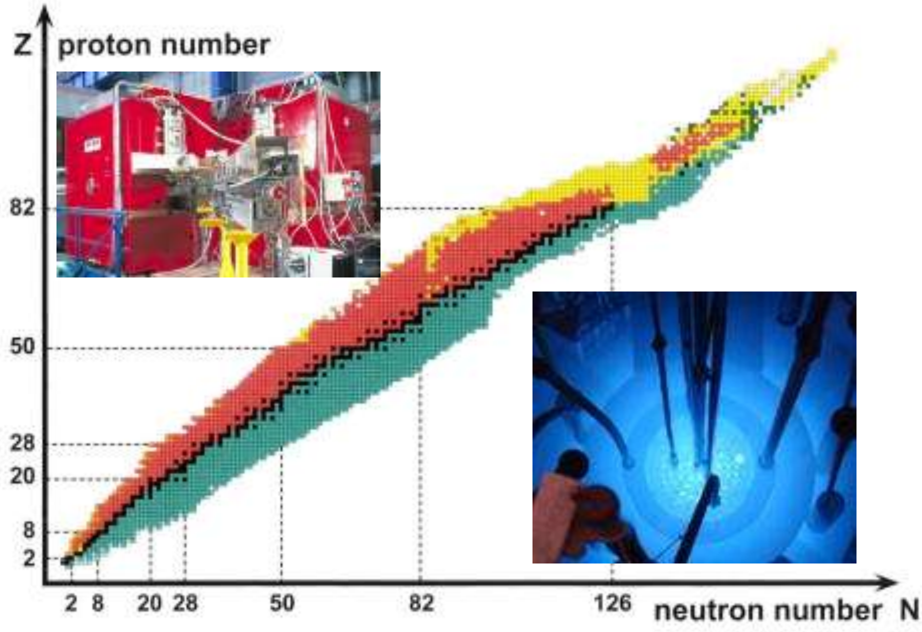
Discontinued radium applications



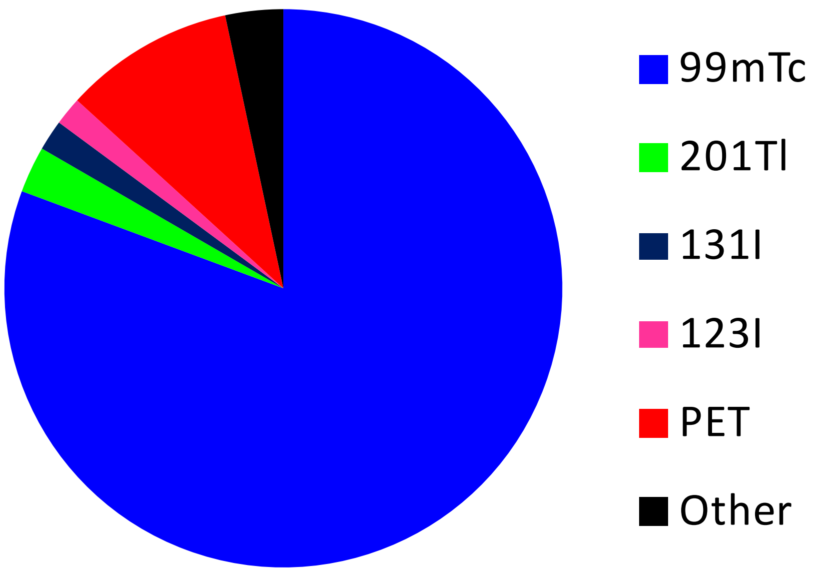
Radioisotope Production

The Tordesillas meridian

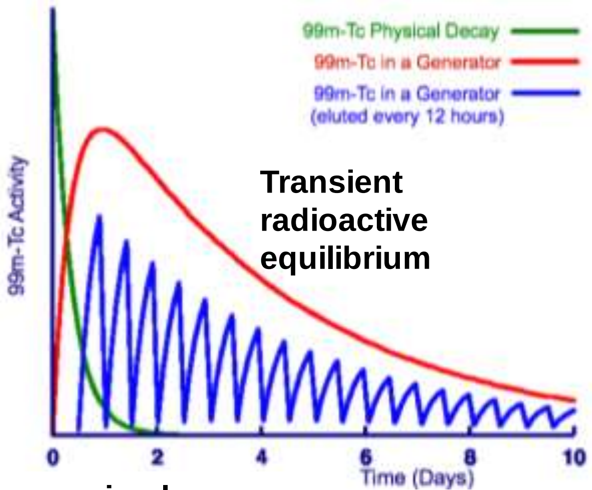
The Tordesillas meridian of radioisotope production



Cumulative use of diagnostic isotopes in Europe

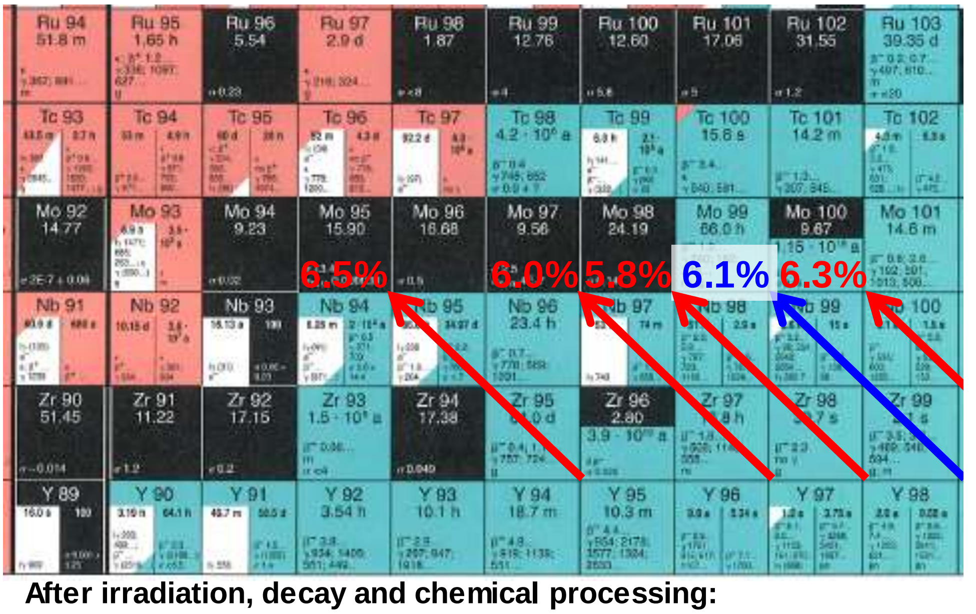


^{99}Mo/^{99m}Tc generator



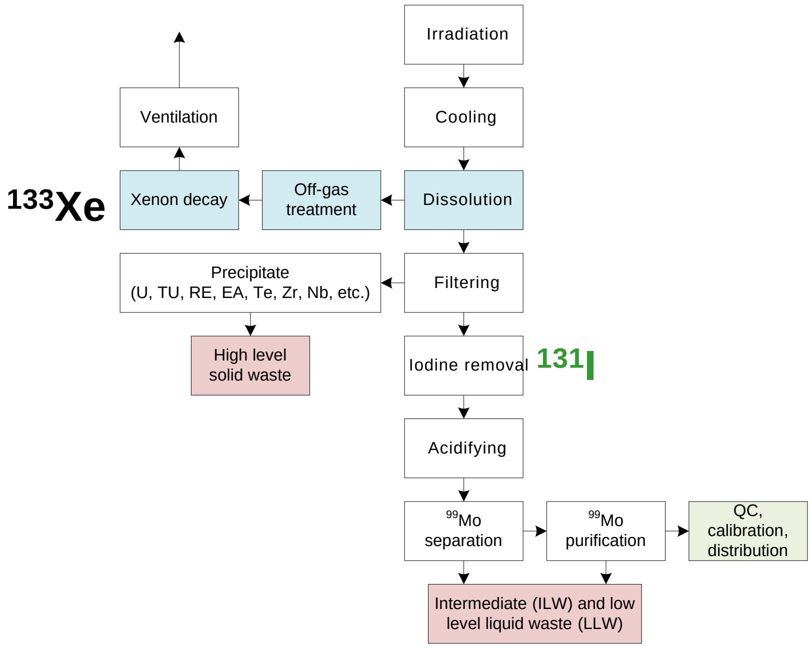
- simple
- reliable
- portable
- self-shielded

Fission production

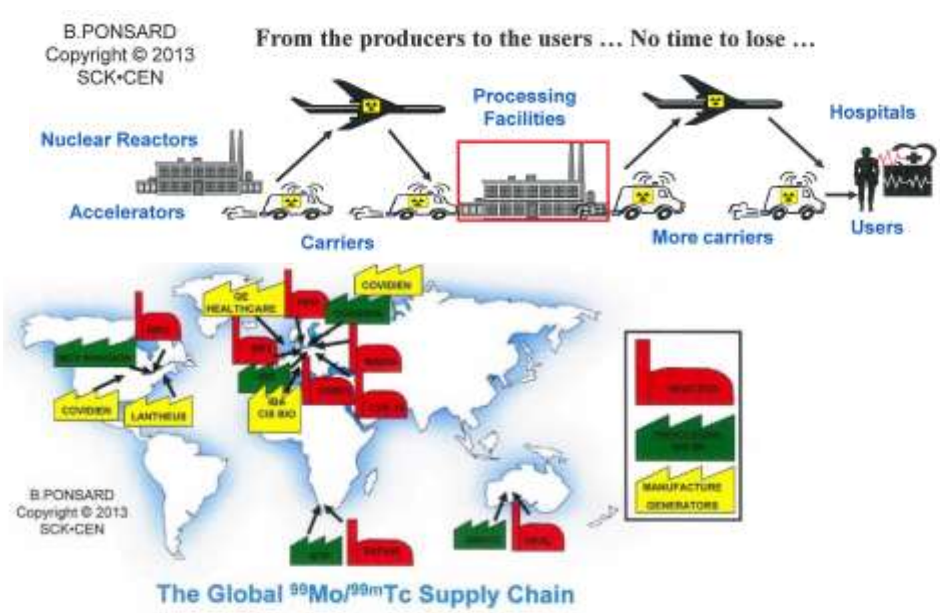


After irradiation, decay and chemical processing:
^{99}Mo/^{all}Mo ≈ 10%, i.e. 10% of theoretical specific activity 480 kCi/g

Extraction of fission-moly



The traditional supply chain of $^{99}Mo/^{99m}Tc$



European hospitals cope with Mo-99 supply crisis

Petten reactor shutdown disrupts nuclear medicine in 20 European countries and U.S. until mid-January

01 December 2008

MOLYBDENUM SUPPLY REVIEW

L'inquiétante pénurie d'isotopes pour l'imagerie

Le 02 septembre 2010 à 00h 00 par A. P.

Engpässe in der Tumormedizin

SPIEGEL

Krebsärzten gehen die Diagnosemittel aus

Isotopes médicaux - Crise mondiale à l'horizon

Aucune solution n'existe pour résoudre le problème d'approvisionnement

Pauline Gravel 23 mai 2009 Santé

We Need to Expand Medical Isotope Production!

Isotope shortage means a healthcare crisis

Los Angeles Times

The radioisotope is needed to scan for heart disease and cancer. Two nuclear reactors that produce it have been shut down, severely limiting the supply, and alternatives are scant.

L'OCDE s'inquiète des risques de pénurie d'isotopes médicaux

Isotope shortage to get worse with closing of more reactors

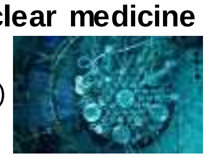
Mangel an medizinisch verwendbaren Isotopen

Frankfurter Allgemeine

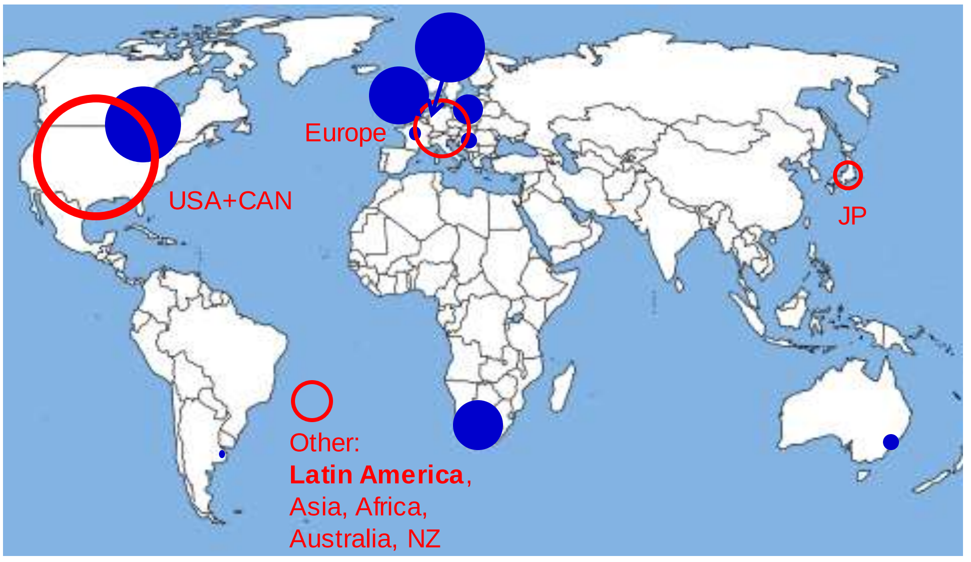
Szintigraphien fallen aus, für Februar droht der Notstand

Mo-99 crisis

The economy of the aviation industry and of nuclear medicine

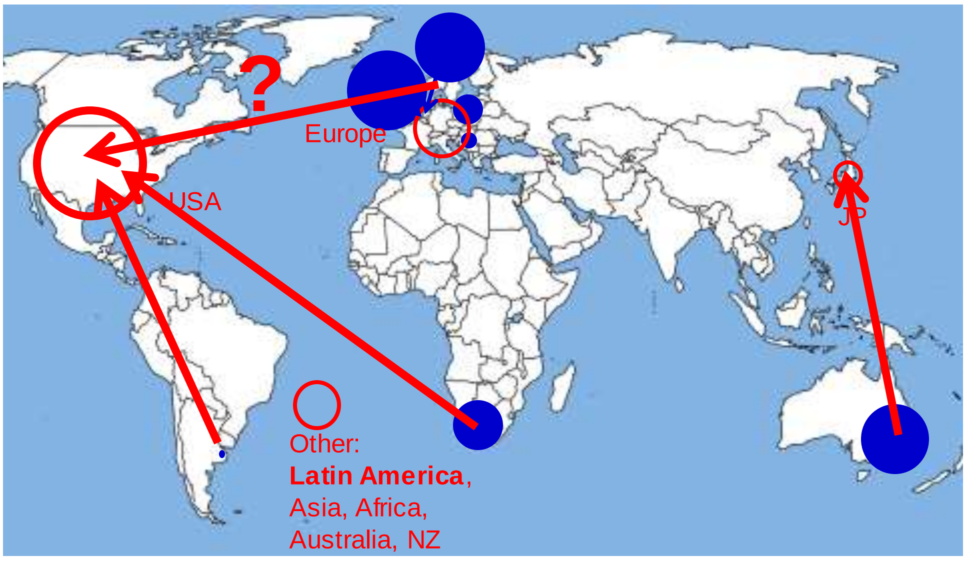
	19%	"Fuel" sourcing Reactor	 0.11% (0.26€)	
	5%	"Fuel" refinement Mo processing Generator	 0.67% (1.64€) 0.14% (0.34€)	
		Transport Radiopharmacy	 3.51% (8.62€)	
	17%	Equipment (amortization, maintenance, leasing, chartering)		
	31%	Personal costs	CH 2009: 760 € US 2014: 909 €	
Air France KLM, financial reports 2007-2012			Total 245.61€	*OECD-NEA, 2008*

2013: ^{99}Mo production capacity and demand



Circle diameter proportional to annual reactor capacity (blue) and demand (red).

2017: ^{99}Mo production capacity and demand



Diameter of circles proportional to annual reactor capacity and demand.

New research reactors

All ways lead to Rome; many ways lead to ^{99m}Tc

^{99}Mo production (for generator) — **direct ^{99m}Tc production**

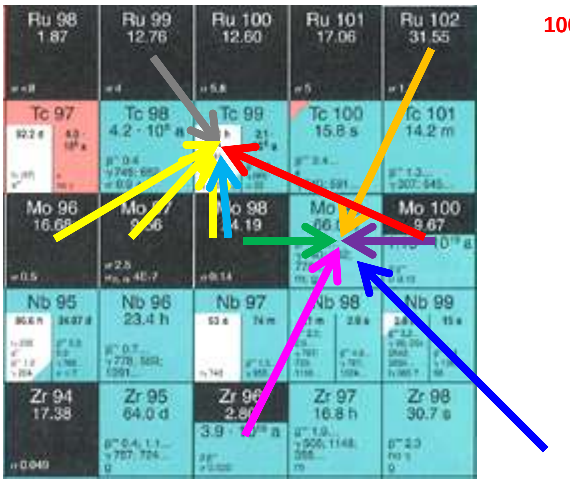
^{235}U(n_{th},f)
^{238}U(n_{fast},f)
^{238}U(γ,f)
^{238}U(p,f)

^{98}Mo(n,γ)
^{nat}Mo(n,γ)
^{100}Mo(d,p)

^{100}Mo(γ,n)
^{100}Mo(n,2n)
^{100}Mo(p,np)

^{96}Zr(α,n)

^{102}Ru(n,α)



^{100}Mo(p,2n)

^{nat}Mo(α,x)

^{98}Mo(d,n)

^{99}Ru(n,p)

The rising star for therapy

Production of ^{177}Lu

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 history of lutetium separation

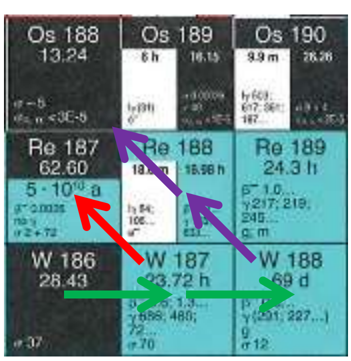
1878 Separation of Yb
by Jean-Charles Galissard de Marignac

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

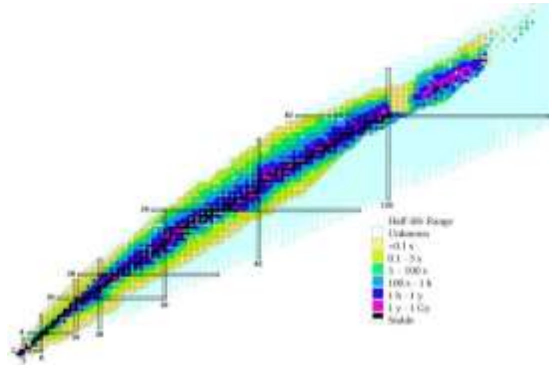
$^{188}W/^{188}Re$ generator



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

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

- Nuclear Medicine Physics. A Handbook for Teachers and Students, IAEA Vienna 2014, STI/PUB/1617.
- Cyclotron Produced Radionuclides: Principles and Practice, IAEA Vienna 2008, Technical Report 465.
- Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods, IAEA Vienna 2009, Technical Report 468.
- Lectures on Theranostics by Richard Baum:
  https://www.youtube.com/watch?v=Z0TlXH2dVi8
  https://www.youtube.com/watch?v=S74LNxXOaSw
- (Free) medical review papers from http://pubmed.gov
- Information on on-going clinical trials: http://clinicaltrials.gov