Medical applications of radioactivity

Ulli Köster
Institut Laue-Langevin, Grenoble
and Chair GIE, Université Grenoble Alpes

NEUTRONS FOR SOCIETY

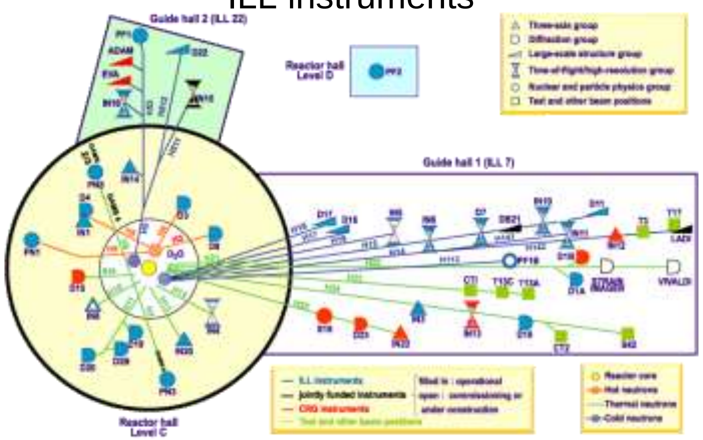
École Joliot Curie
25/26 September 2017

UNIVERSITÉ Grenoble Alpes

Institut Max von Laue – Paul Langevin

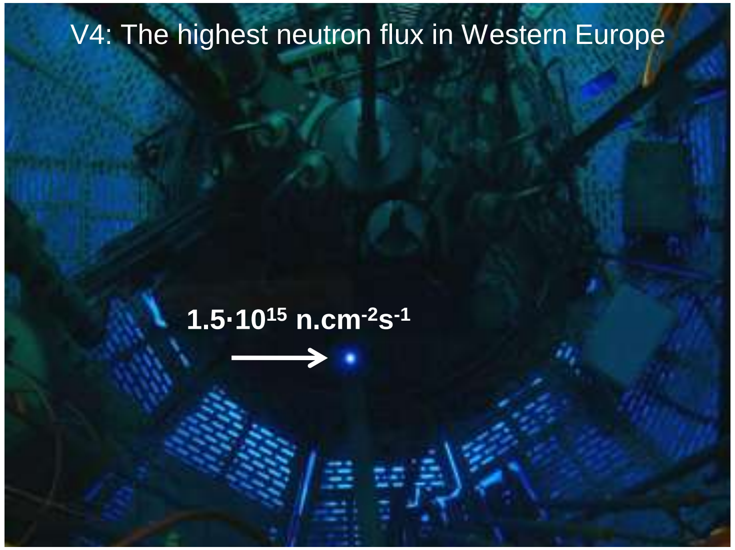
- founded 1967
- today governed by "associates" FR, DE, UK
- + member states: ES, CH, AT, IT, CZ, SE, BE, SK, DK, PL
- over 40 instruments, mainly for neutron scattering, but also some for nuclear and particle physics
- user facility: >1400 scientific visitors from 40 countries per year

ILL instruments



40 instruments running simultaneously for 150-200 days per year
Neutron beams: up to $2\cdot10^{10}$ $n.cm^{-2}s^{-1}$ flux, up to 320 cm^2 area

The LOHENGRIN fission fragment spectrometer


V4: The highest neutron flux in Western Europe
1.5·10^15 n.cm^-2s^-1


GIE: Grands Instruments Européens
CERN
iram
LPSC
Grenoble
EMFL
European Magnetic Field Laboratory
NEUTRONS FOR SOCIETY
ESRF
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IRM
PET


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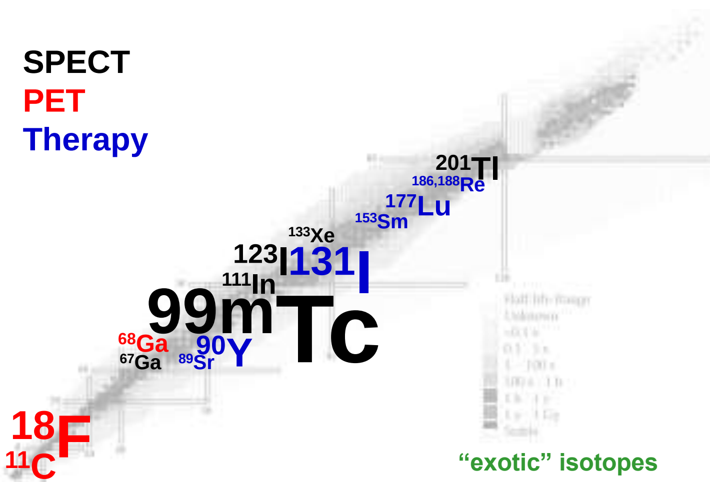
et accessoires
9–19 mars 2017
Genève
www.gims.swiss

Don’t forget the fuel!

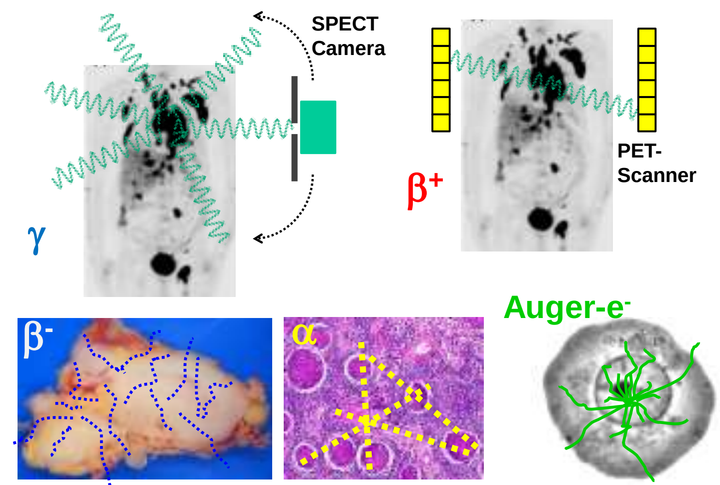
Radioisotopes: the “fuel” for nuclear medicine

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

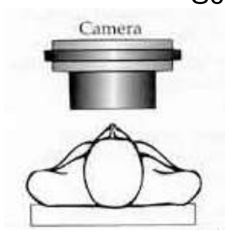
The chart of nuclides – nuclear medicine perspective



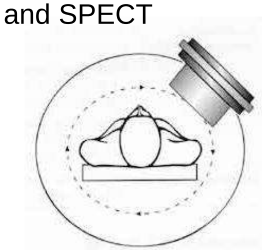
The Nuclear Medicine Alphabet



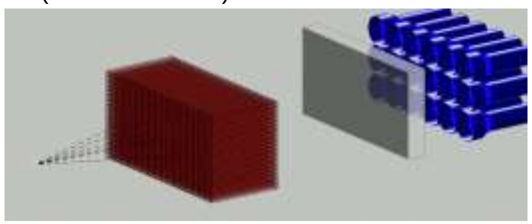
Scintigraphy and SPECT



2D: planar scan
(Gamma camera)

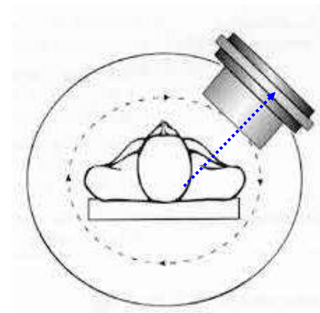


3D: SPECT: Single Photon Emission Computed Tomography



Anger camera

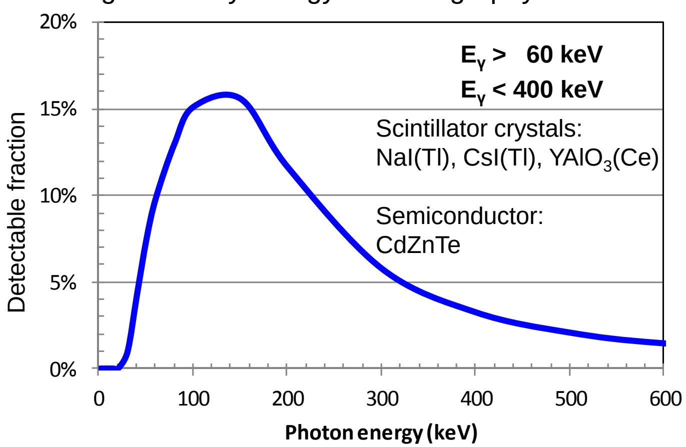
Ideal gamma ray energy for scintigraphy/SPECT?



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

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

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

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

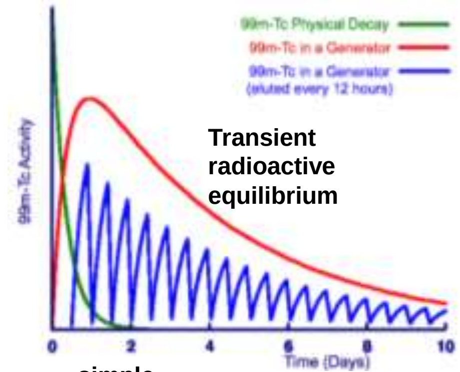
$N_{Mo}(t) = N_{Mo}(0)\exp(-\lambda_{Mo} t)$

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

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

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

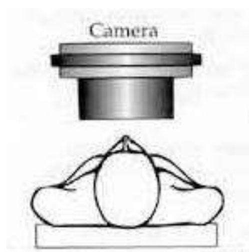
^{99}Mo/^{99m}Tc generator

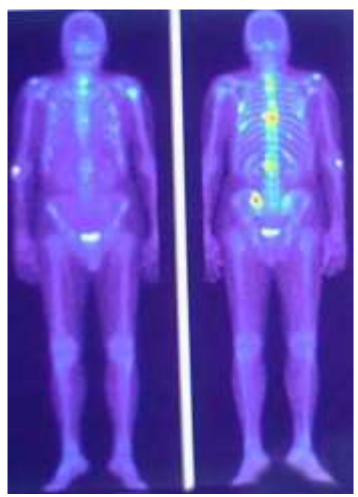


Transient radioactive equilibrium

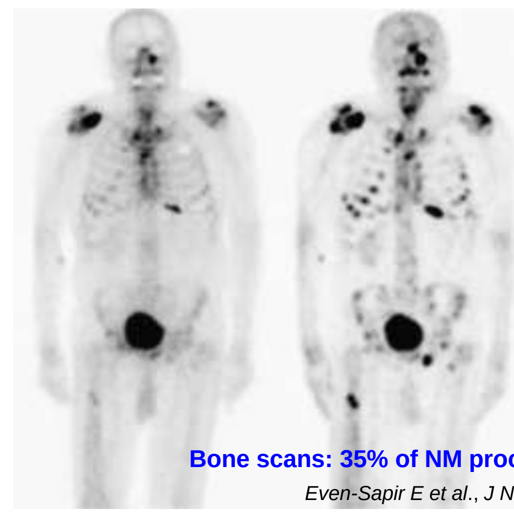
- **simple**
- **reliable**
- **portable**
- **self-shielded**

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

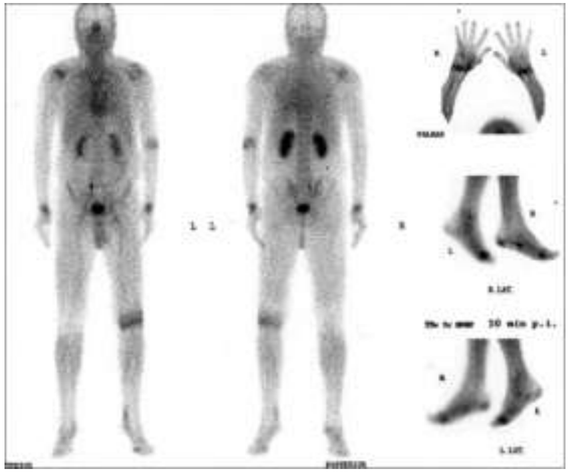


Bone scans: 35% of NM procedures in Europe

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

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

Rheumathoid arthritis

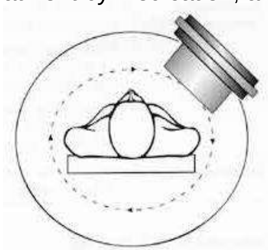


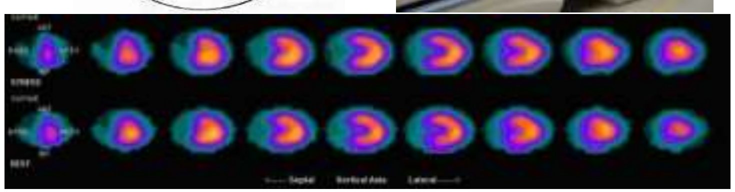
L. Knut, World J Nucl Med. 2015; 14:10.

Veterinary scintigraphy

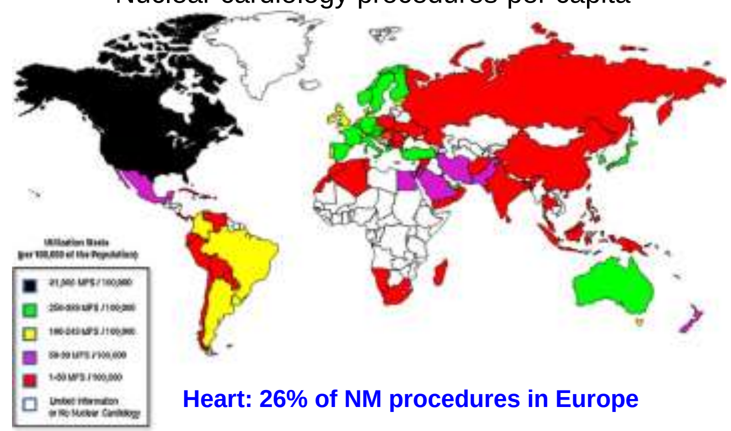
Ischemic heart disease

- 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

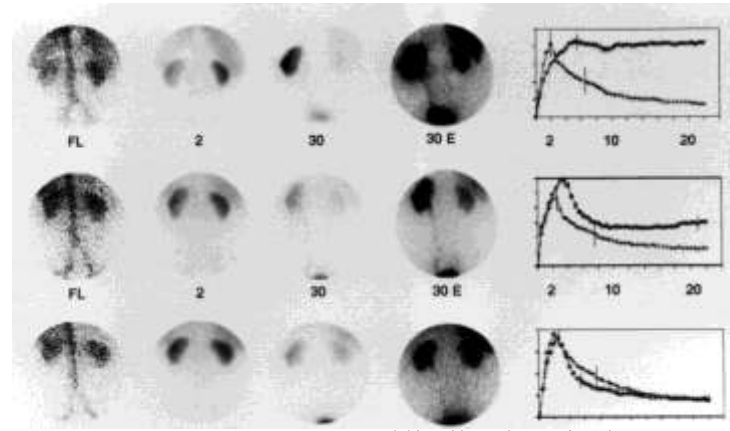
J.V. Vitola et al., J Nucl Cardiol 2009;16:956.

Ischemic heart disease

age-standardized death rates (per year):

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

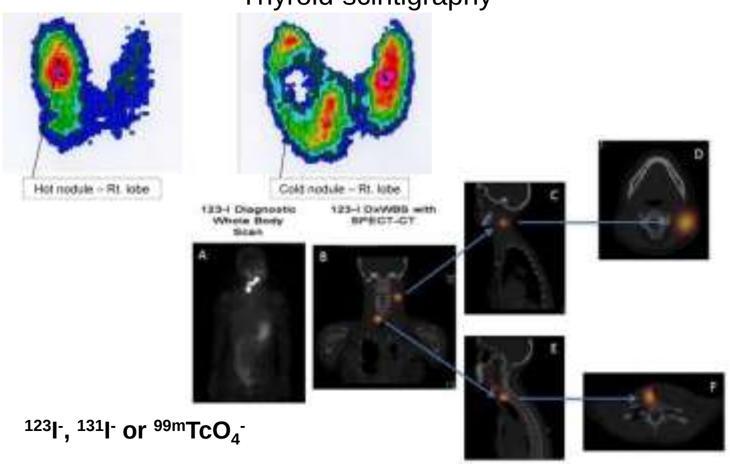
Scintirenography



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

Kidney: 13% of NM procedures in Europe

Thyroid scintigraphy

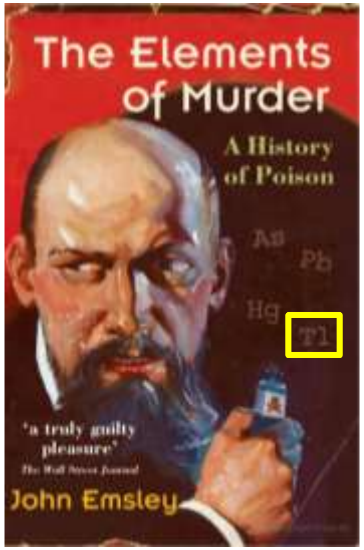


$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$

Thyroid: 12% of NM procedures in Europe

SPECT isotopes

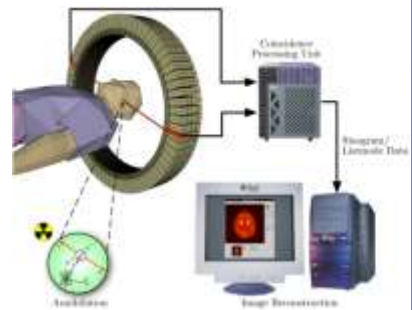
Radio-nuclide	Half-life (h)	Eγ (keV)	Iγ (%)	Decay type
Ga-67	78	93 185	42 21	EC
Kr-81m	0.004	190	64	IT
Tc-99m	6	141	89	IT
In-111	67	171 245	91 94	EC
I-123	13	159	83	EC
Xe-133	126	81	38	β^-
Tl-201	73	70 167	59 10	EC
I-131	192	364	82	β^-
Lu-177	161	113 208	6 10	β^-

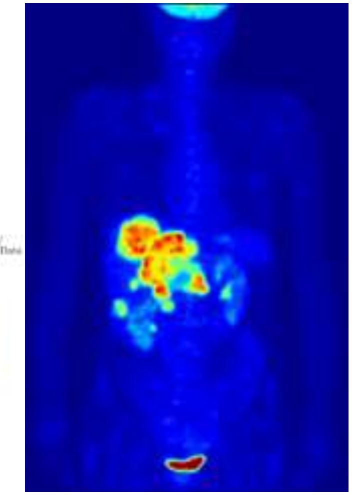


Thallium for patients ?

- 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!

Positron Emission Tomography



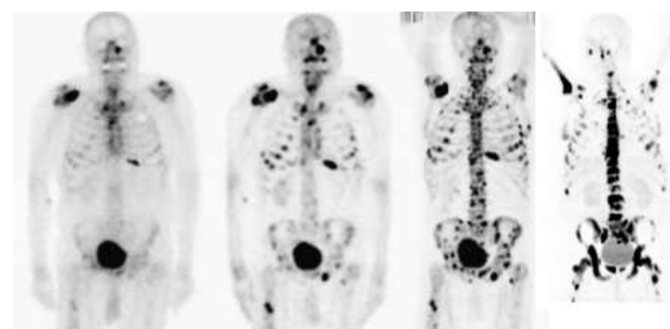


PET isotopes

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)

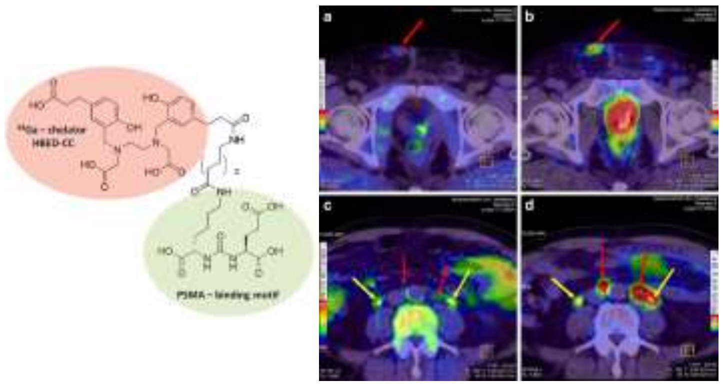
Bone scans for bone metastasis screening



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**

Imaging of prostate cancer lesions



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

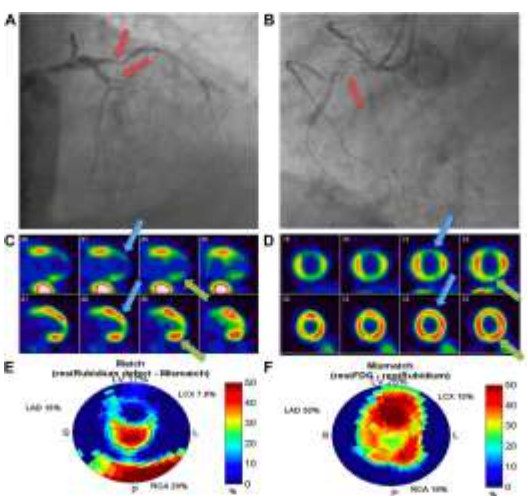
M Eder et al. Bioconjugate Chem 2012, 23:688.
Ali Afshar-Oromieh et al. Eur J Nucl Med Mol Imaging 2014, 41:11.

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

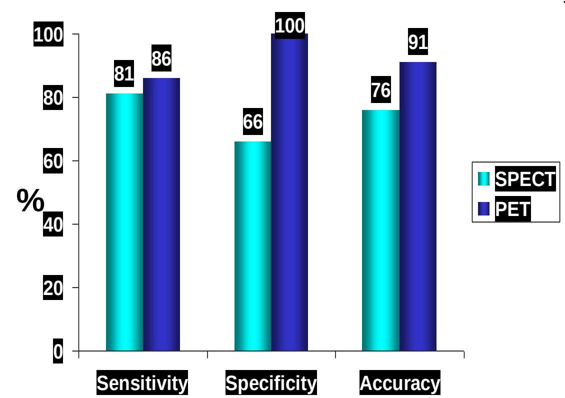
Mother isotope:
271 d
25 d

Cardiology applications



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

Diagnostic Accuracy: PET vs SPECT

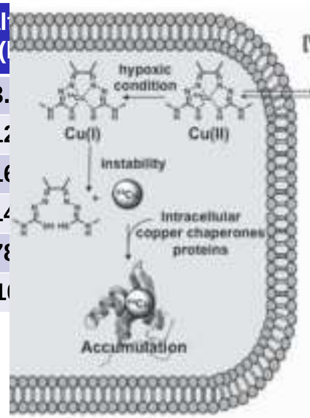


Bateman et al, J Nucl Cardiol 2006;13:24.

^{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

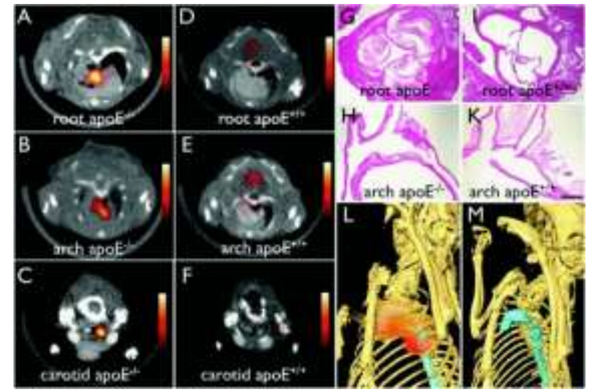
Longer-lived PET isotopes

Radio-nuclide	Hal (…	Range (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



Nanoparticle PET-CT Imaging of Macrophages in Inflammatory Atherosclerosis

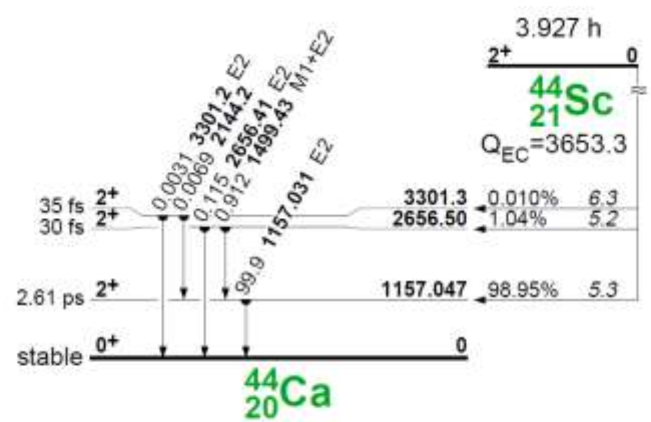
^{64}Cu-TNP



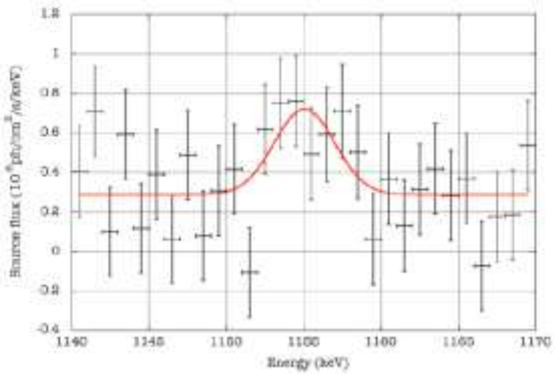
M Nahrendorf et al, Circulation 2008, 117:379.

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	

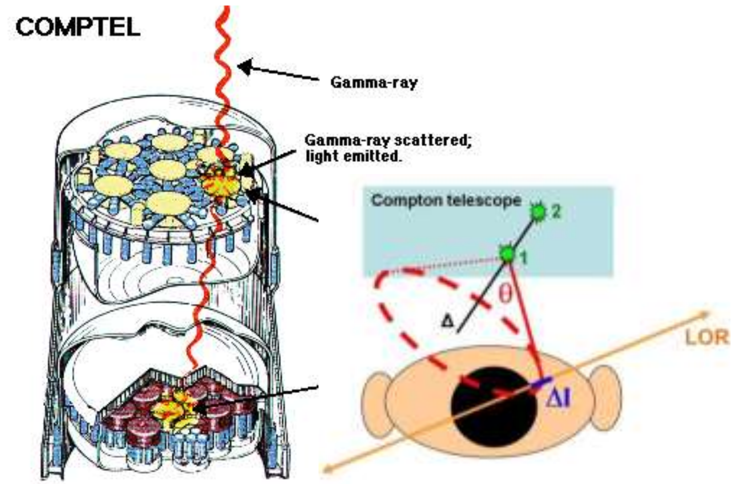


^{44}Sc in the universe

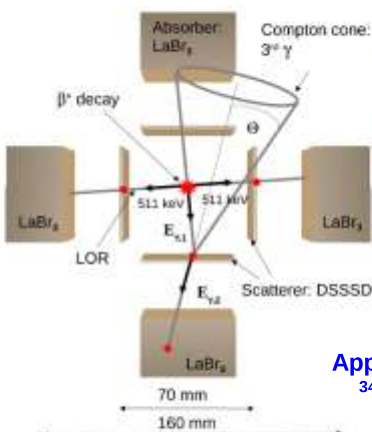


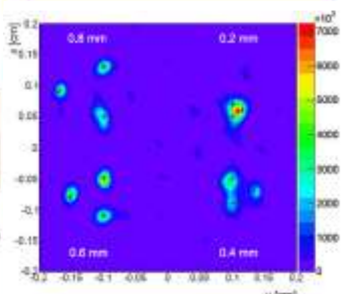
M. Leising, R. Diehl, PoS 2009.

Compton telescope



3-photon-camera: PET-SPECT

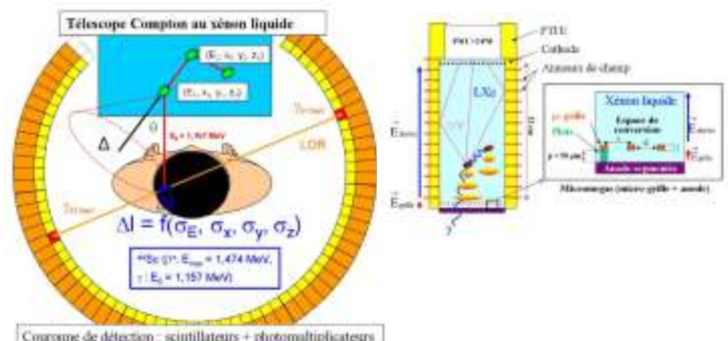




Applications:
^{34m}Cl, ^{44}Sc, ^{44m}Sc, ^{52}Mn, ^{52m}Mn,
^{86}Y, ^{94g}Tc, ^{94m}Tc, ^{124}I, ^{10}C, ^{14}O

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

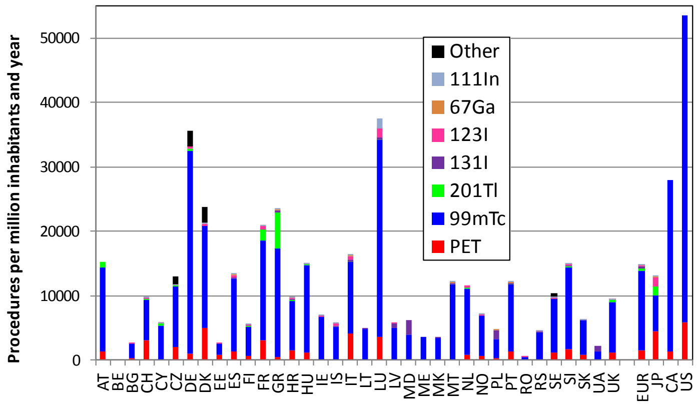
XEMIS2 Xenon-TPC



Subatech

L. Gallego Manzano et al. Nucl Instr Meth A 2015;787:89.

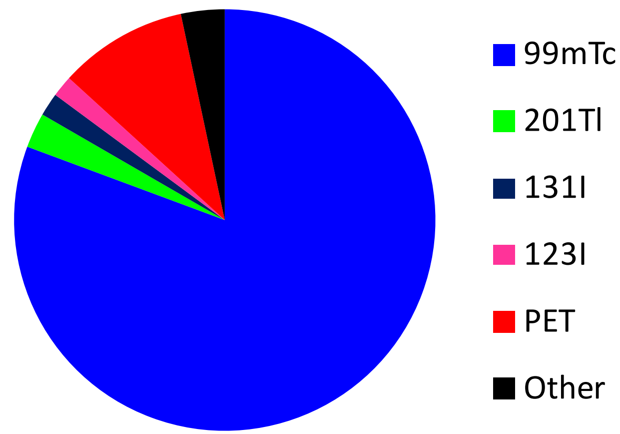
Statistics of radionuclide use in Europe



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

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

Cumulative use of diagnostic isotopes in Europe

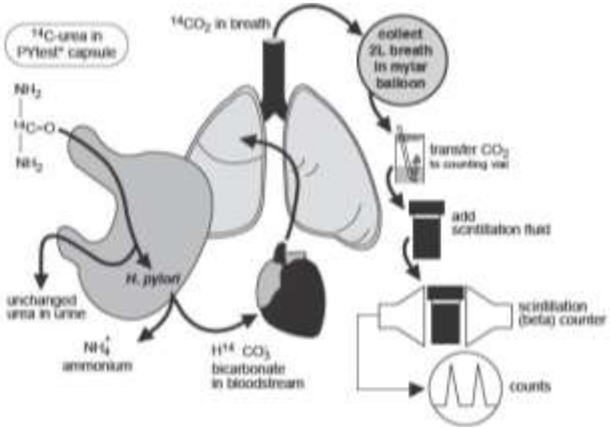


http://www.nupecc.org/npmed/npmed2014.pdf

Radiotracer diagnostics without imaging

Helicobacter pylori: chronic stomach inflation (ulcers, pain)
cause of 60-90% of all stomach cancers

111 kBq



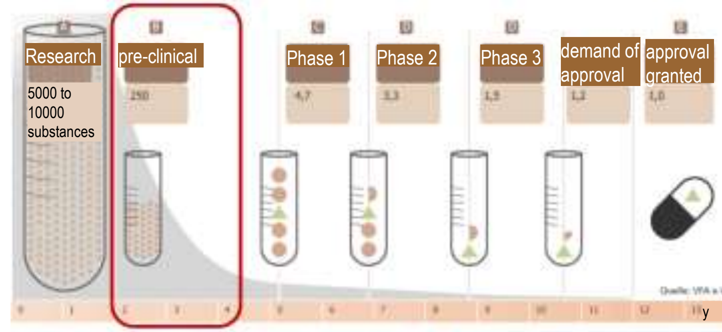
Why 111 kBq?

1 Ci = 37 GBq
1 mCi = 37 MBq
1 µCi = 37 kBq

3 µCi = 111 kBq

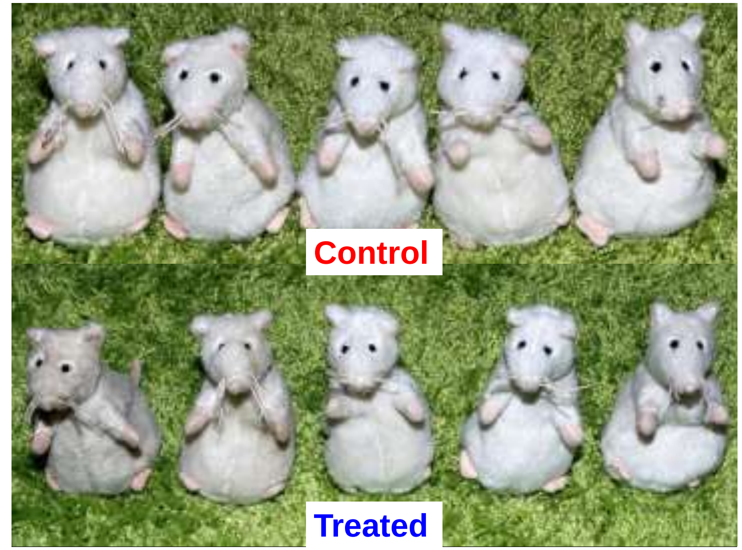
Molecular imaging without patients?

Development of pharmaceuticals

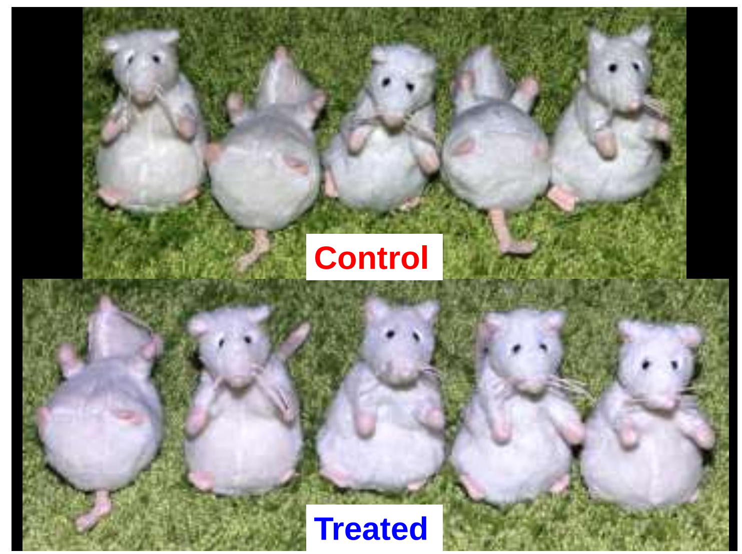


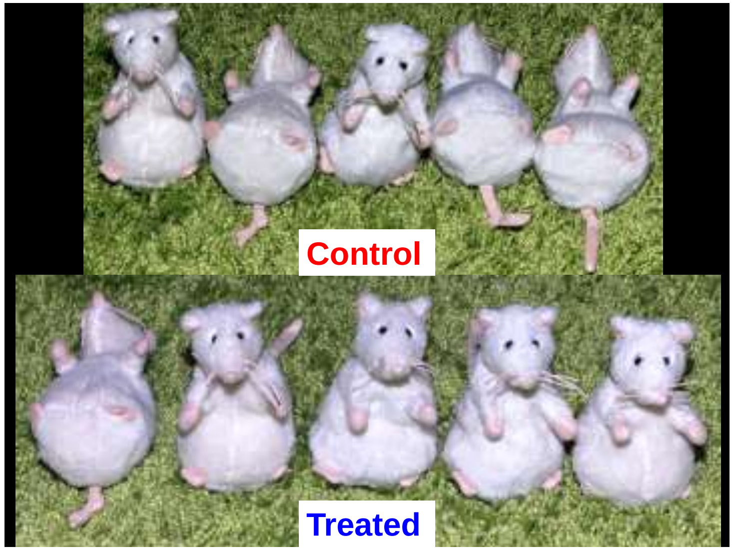
Screening **in vitro tests animal exp.** **tests with humans**

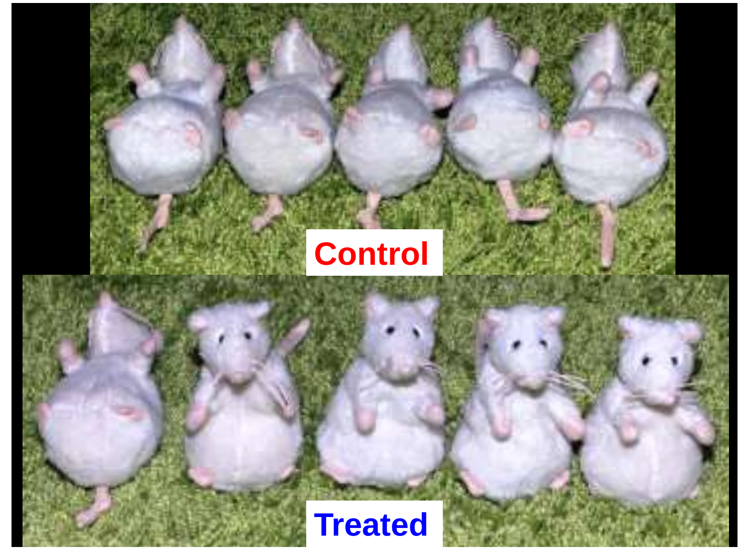
toxicity side effects	wanted effect	comparison with standard
20-80 healthy volunteers	100-300 patients	x00-x000 patients


Control
Treated

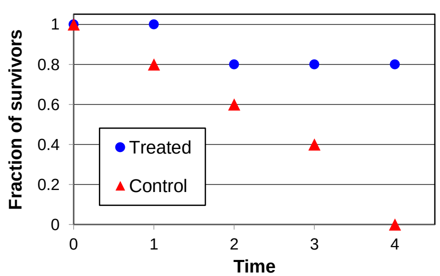

Control
Treated


Control
Treated





Survival curve

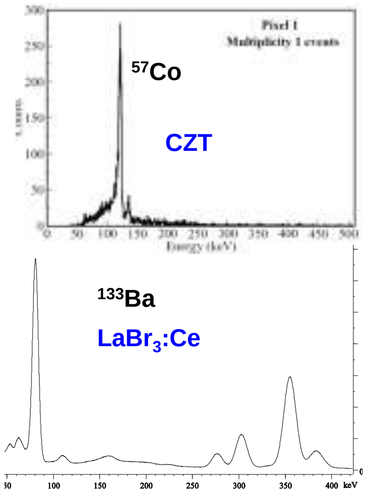


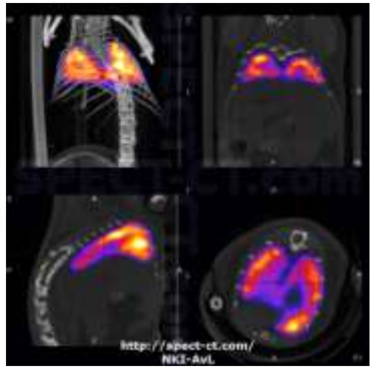
- medium survival time, median survival time, survival benefit
- shows final benefit but not detailed mechanism

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

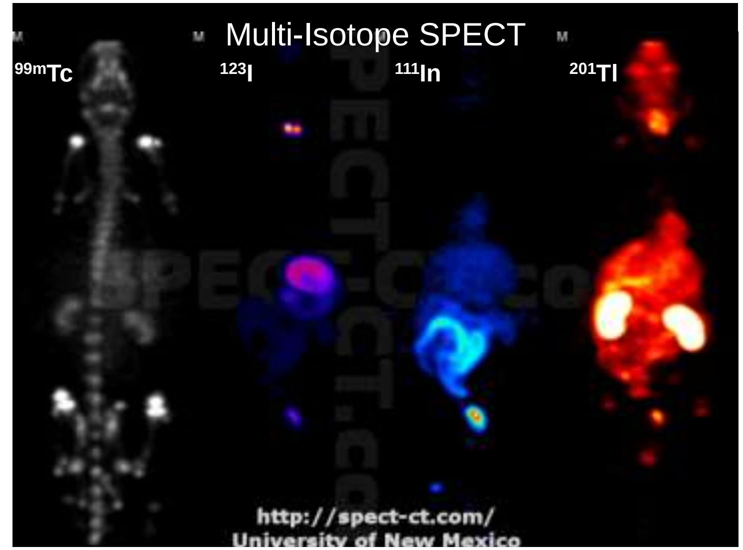
Small animal imaging

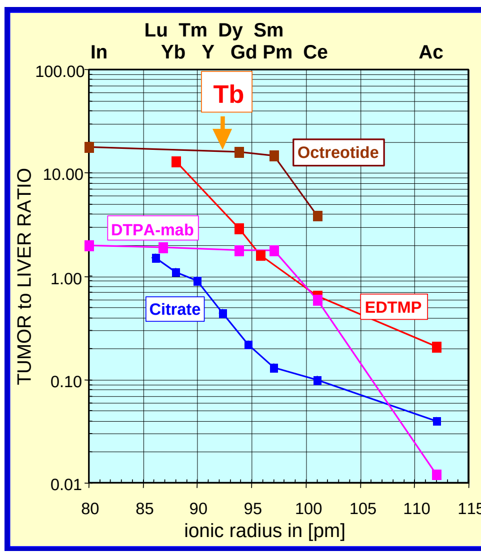
New generation of small animal SPECT





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





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

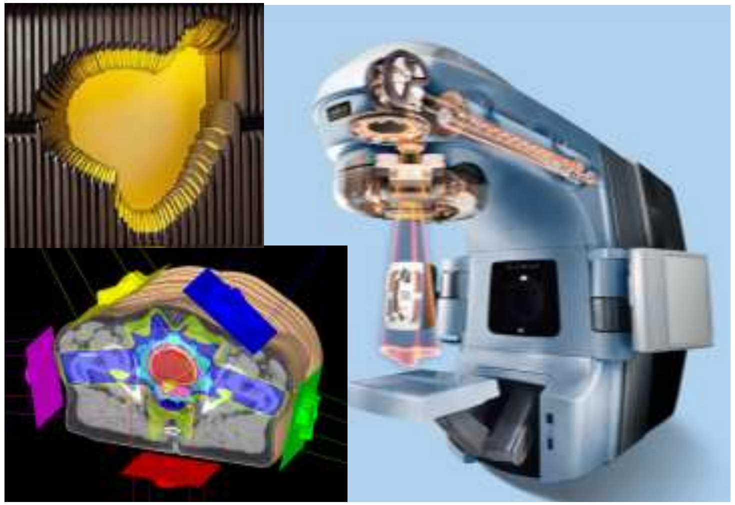
Linker:
Aminobenzyl-DTPA

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

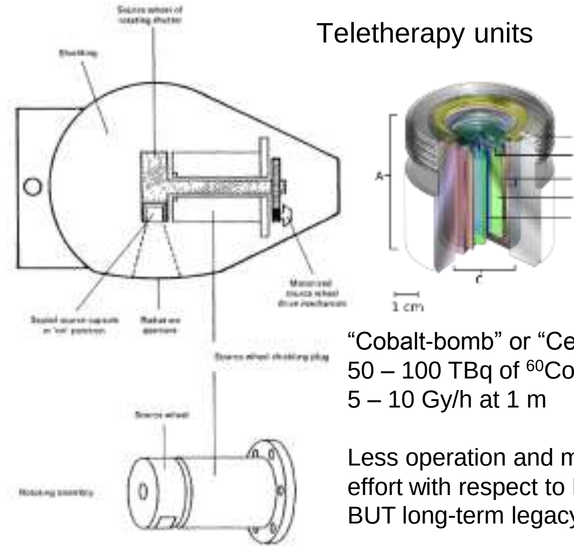
From diagnostics

to therapy

EBRT (External Beam Radiation Therapy)



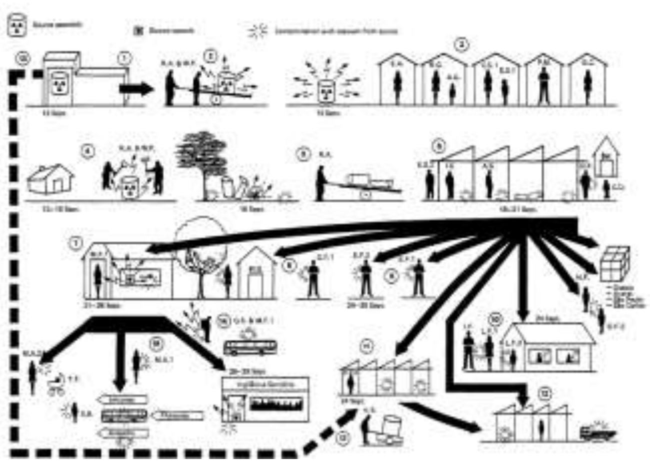
Teletherapy units



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

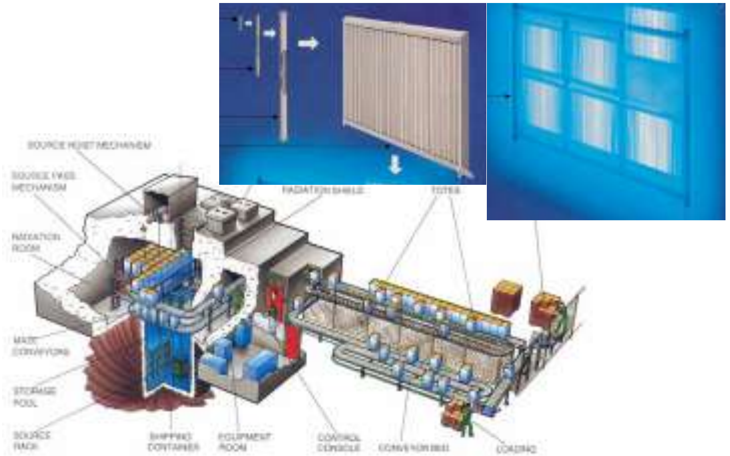
Less operation and maintenance effort with respect to LINACs, BUT long-term legacy!

Civilian radiation accidents



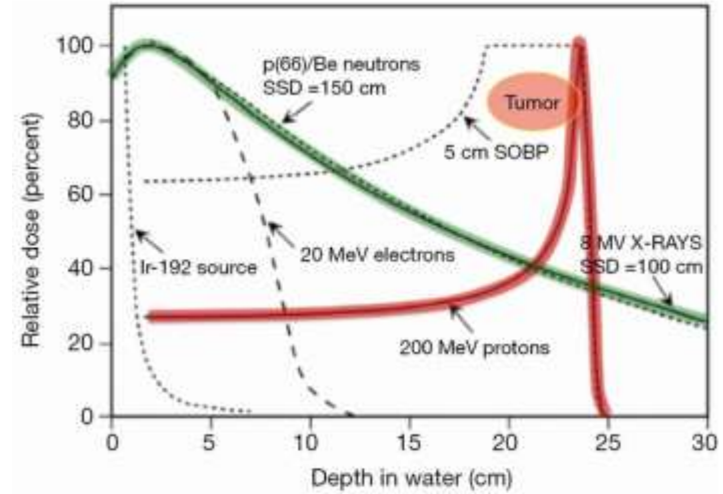
Goiania, Ciudad Juarez, Samut Prakan, etc.

Parenthesis: Radiation Sterilization of Medical Devices

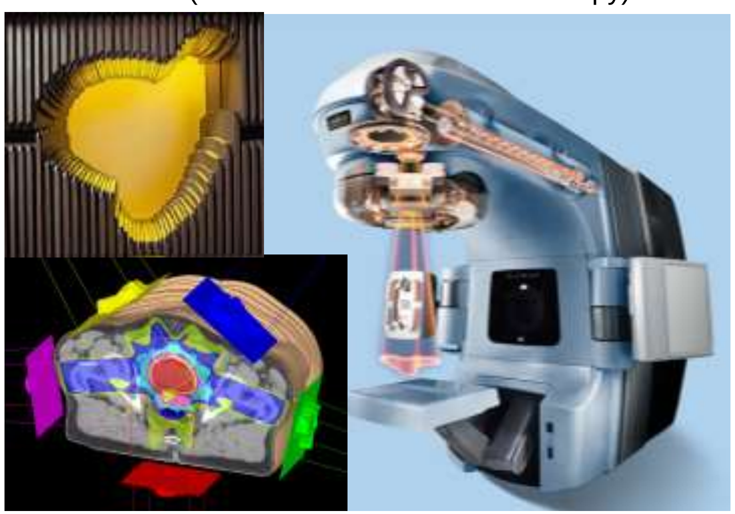


1 MCi = 37 PBq ^{60}Co sterilizes 650 kg/hour at 25 kGy

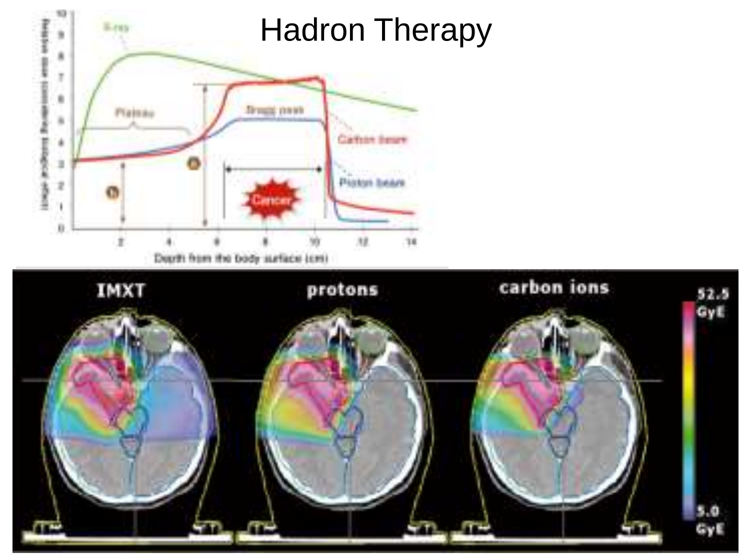
EBRT (External Beam Radiation Therapy)



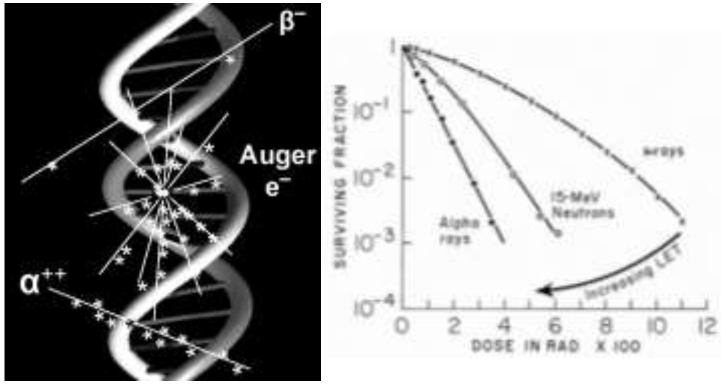
EBRT (External Beam Radiation Therapy)



Hadron Therapy

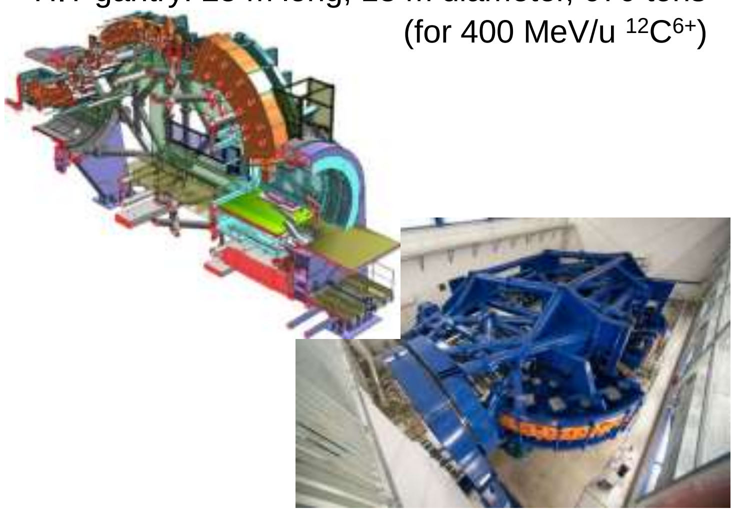


Effect of Linear Energy Transfer (LET) on cell survival

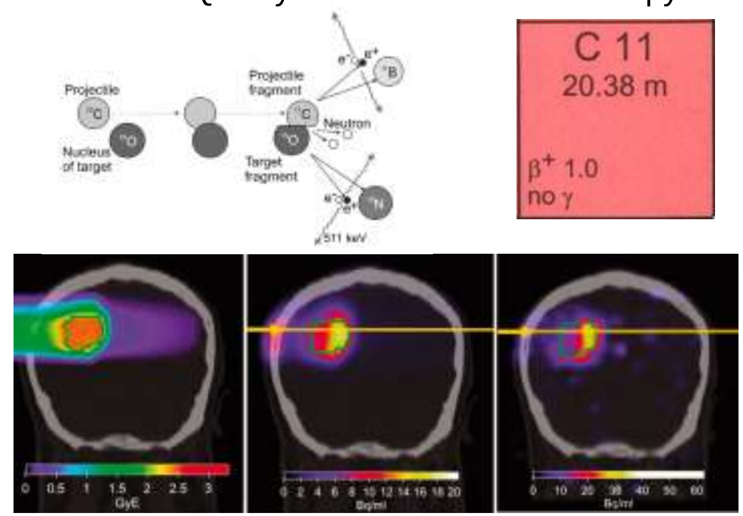


CNAO synchrotron: 78 m long, 25 m diameter (for 400 MeV/u $^{12}C^{6+}$)

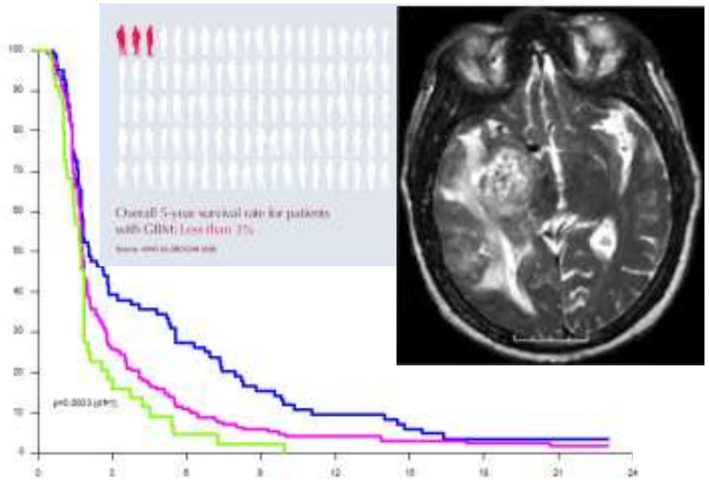
HIT gantry: 25 m long, 13 m diameter, 670 tons (for 400 MeV/u $^{12}C^{6+}$)



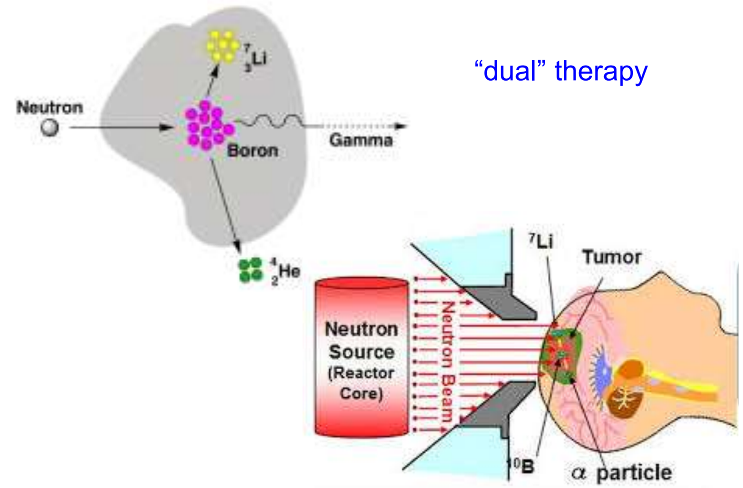
PET for Quality Control in Hadron Therapy



Glioblastoma multiforme



Boron Neutron Capture Therapy (BNCT)



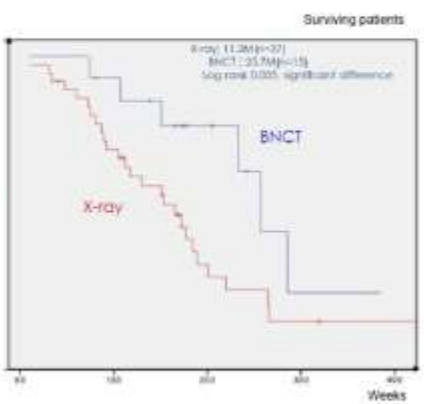
"dual" therapy

BNCT – does it work?

Glioblastoma treated at Tsukuba University

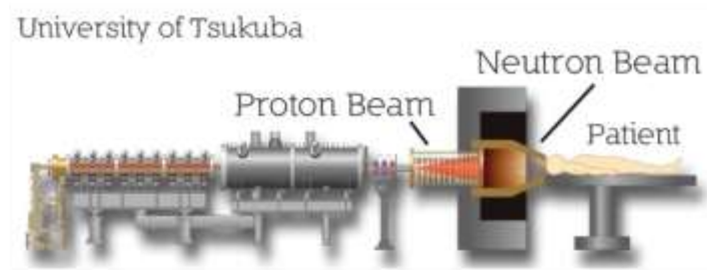
conventional radiotherapy vs. BNCT

Conclusion: Results for BNCT were significantly better,



Wolfgang Sauerwein, Univ. Hospital Essen

Accelerator production of epithermal neutron beams

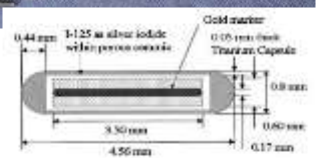


^{7}Li(p,n) or ^{9}Be(p,n) reactions with intense proton beams

Brachytherapy

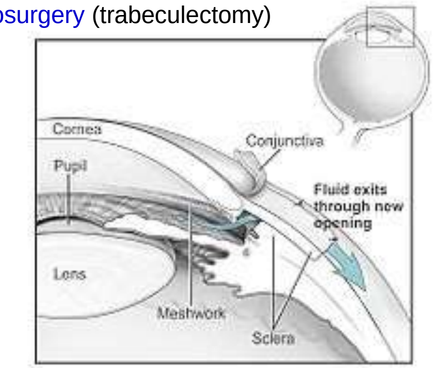
High Dose Rate (HDR) brachytherapy
short-term insertion of ^{60}Co, ^{137}Cs, ^{169}Yb or ^{192}Ir sources

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



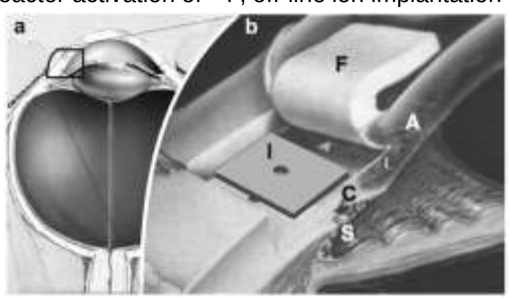
Glaucoma

- damage to optic nerve, often caused by high intraocular pressure (>30 mbar) ⇒ irreversible loss of vision
- incidence: 0.5% over 50 years, 10% over 80 years
- second leading cause of blindness
- treatment: filtering microsurgery (trabeculectomy)



Glaucoma

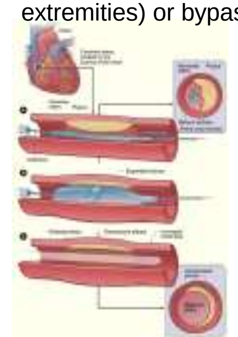
- hyperproliferation during wound healing closes channel ⇒ 30-40% failure in 5 years
- prevent by low-dose rate-brachytherapy (15 Gy at 1 mm in 7 d)
- 45 kBq of ^{32}P (14 d)
- ion-implanted at 2E12 ions/cm^2 into biodegradable polymer
- ^{32}P produced by reactor activation of ^{31}P, off-line ion implantation

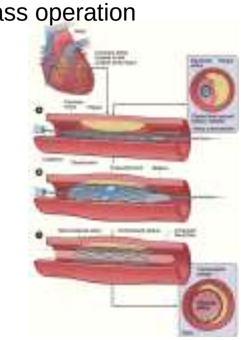


W. Assmann et al., Nucl. Instr. Meth. B257 (2007) 108.

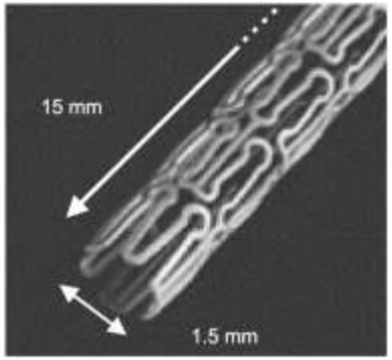
Stenosis

- 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

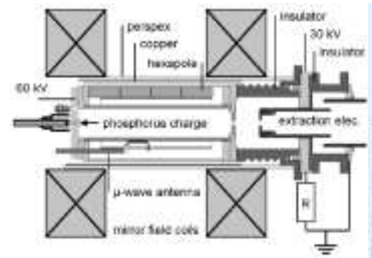


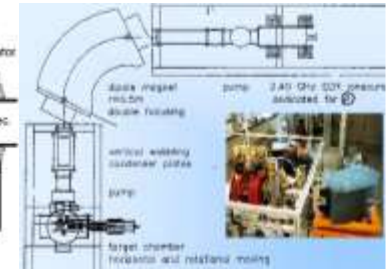


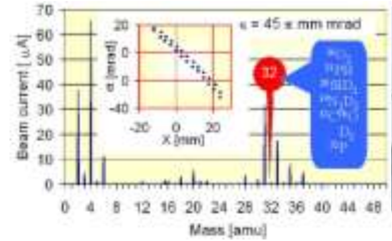
Radioactive ion implanted stents prevent restenosis

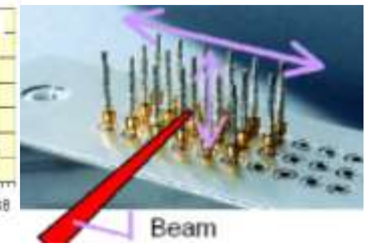


K. Schlösser and H. Schweickert, CAARI-16, AIP Conf. Proc. 576 (2001) 824.
A.M. Joussen et al., Int. J. Radiation Oncology Biol. Phys. 49 (2001) 817.
E. Huttel et al., Rev. Sci. Instr. 73 (2002) 825.
M.A. Golombeck et al., Nucl. Instr. Meth. B206 (2003) 495.
W. Ensinger et al., Surface and Coatings Technology 196 (2005) 288.



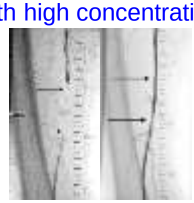






Rhenium-PTA

- 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

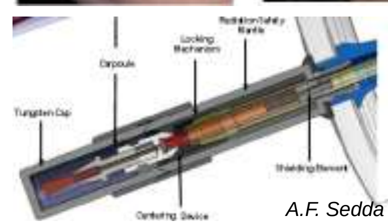

- clinical study in Augsburg: 13% restenosis in 16 months versus usually 50-75% in 6 months

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

Rhenium skin cancer therapy

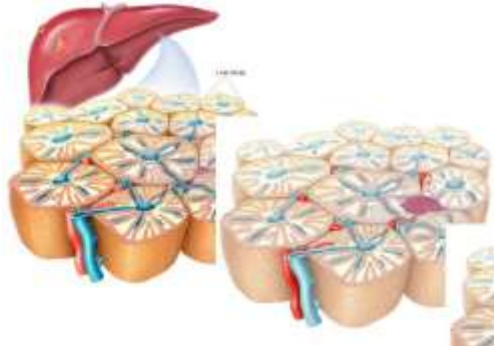
non-melanoma skin cancer:

- 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




Normal liver cells mainly supplied by portal vein. Liver cancer and liver metastases trigger angiogenesis (supply path from artery).

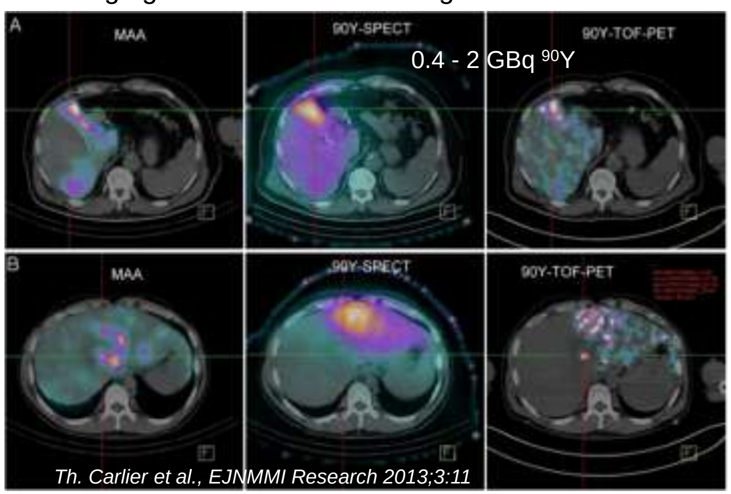
Selective Internal Radiation Therapy (SIRT)

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

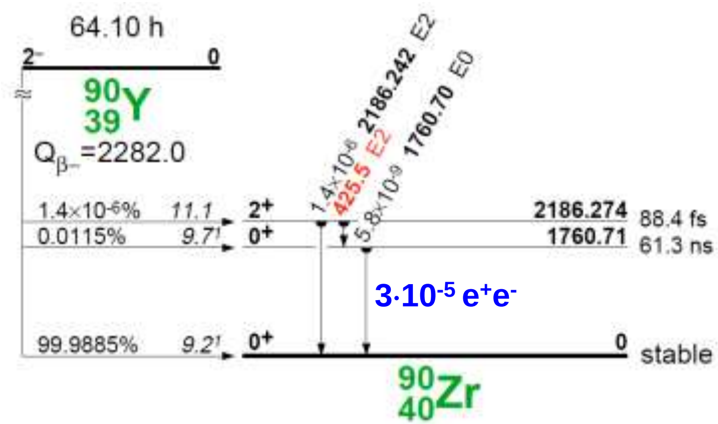
Y-90 glass microspheres comparison to human hair (8 µm diameter)

Imaging ^{90}Y via Bremsstrahlung-SPECT and PET



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

PET with a β^- emitter !



Different medical disciplines and professions

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

Radiosynovectomy (radiosynoviorthesis)

Injection of radionuclide colloids

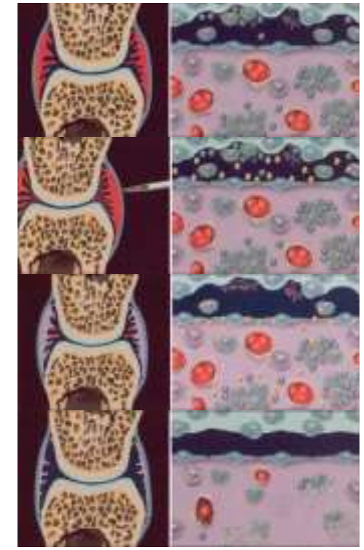
Knee: ^{90}Y (185 MBq)

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

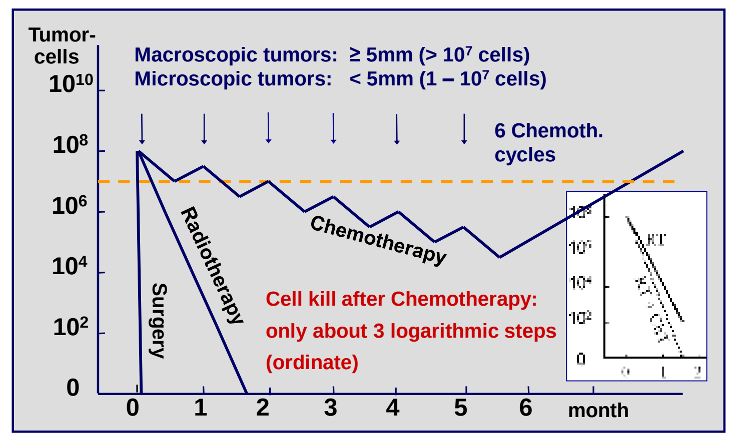
At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	**58%**	**42%**	**100%**
Cured by:			
Surgery	**22%**		
Radiation therapy	**12%**		
Surgery+radiation therapy	**6%**		
All other treatments and combinations incl. chemotherapy		**5%**	
Fraction cured	**69%**	**12%**	**45%**

Over one million deaths per year from cancer in EU.

⇒ improve early diagnosis

⇒ improve systemic treatments

Comparison of Therapies

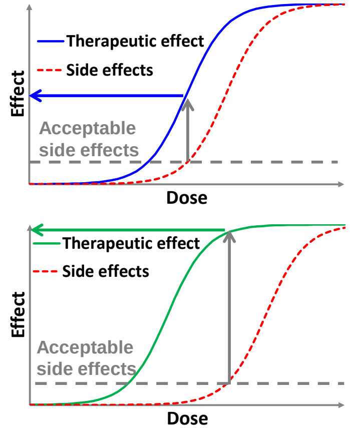


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie Prof. Molls

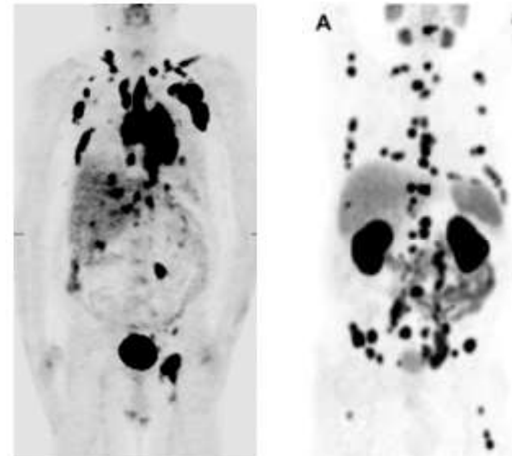
Targeted therapies

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!

How to treat such patients?



Learning from history

The principle of targeted therapies

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

Metabolic targeting

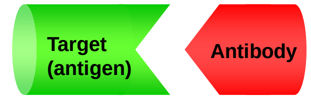
Thyroid cancer
$^{123}I^-$ for imaging
$^{131}I^-$ for therapy

Bone metastases
1.5 million patients world-wide

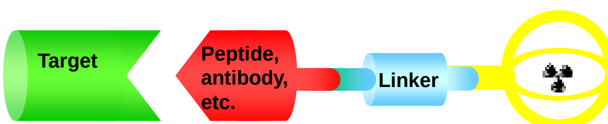
^{99m}Tc-MDP for SPECT imaging
$^{18}F^-$ for PET imaging

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

Immunology approach



Multidisciplinary collaboration to fight cancer

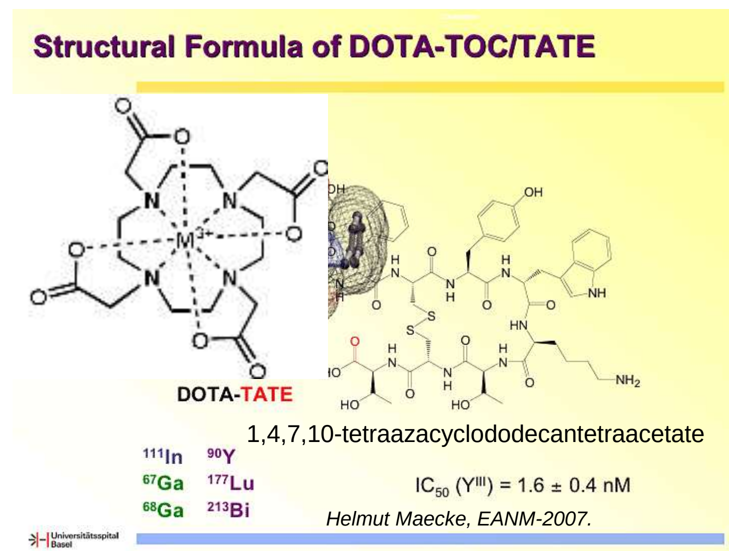


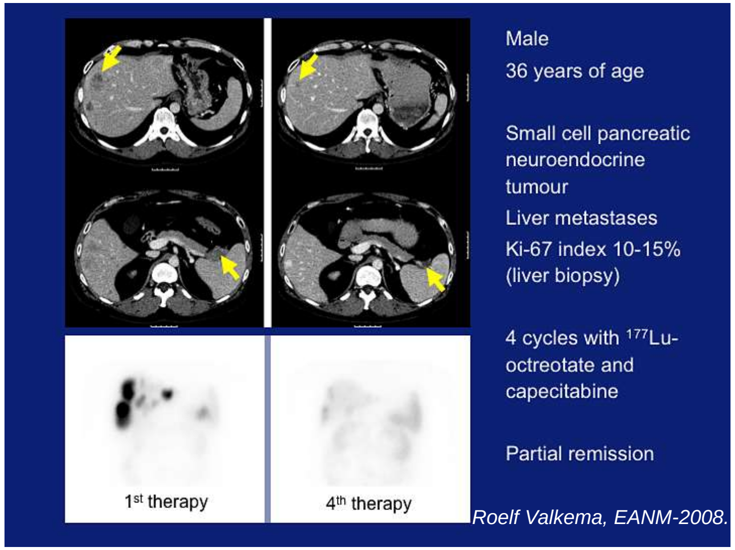
Receptor
Immunology
Structural biology

Coordination
chemistry

Radionuclide
Nuclear physics
and
radiochemistry

Nuclear medicine and medical physics





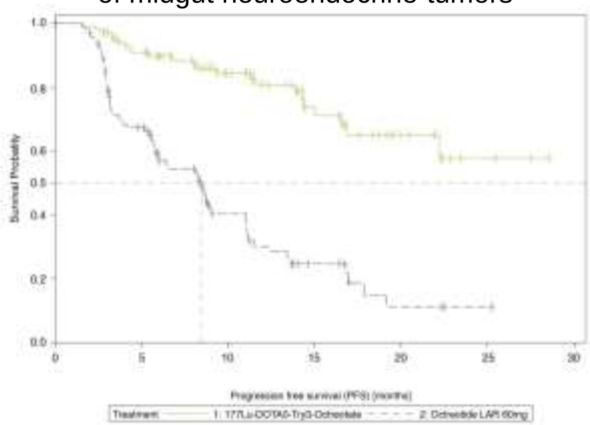
What success does PRRT offer?

- ✓ 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.

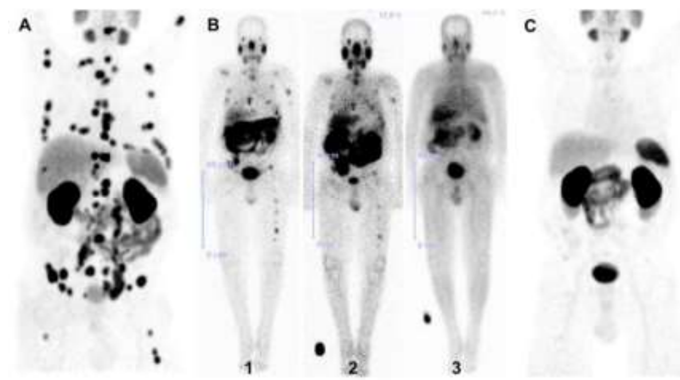
Erasmus MC

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



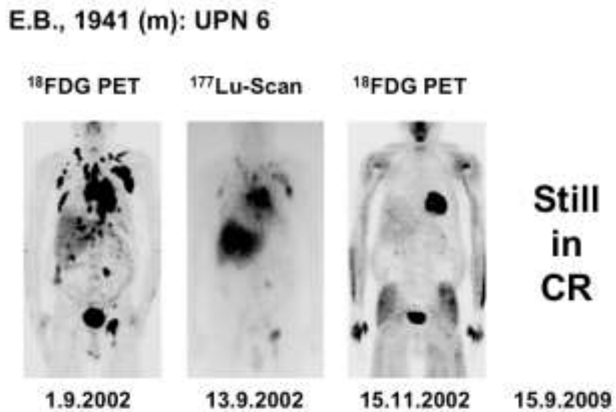
J. Strosberg et al., Results of the Phase III NETTER-1 Trial, ESMO, 27.9.2015

^{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.

Lymphoma therapy: RITUXIMAB+^{177}Lu



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

Cost effectiveness ?

2010 TARMED prices:

650 mg rituximab 3939 CHF — **16x rituximab 63024 CHF**

1x Zevalin 24330 CHF (^{90}Y-anti-CD20-ibritimumab) — **1x Zevalin is >2.6x cheaper!**

6.2x more expensive?

"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"*

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

Radionuclides for targeted radionuclide therapy

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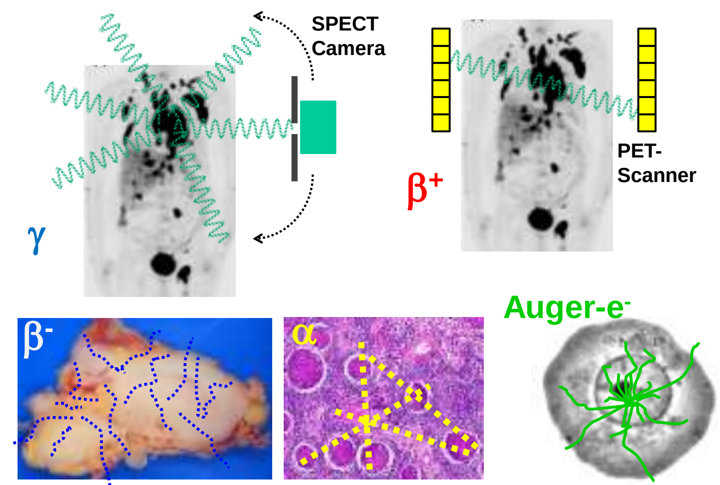
The rising star for therapy

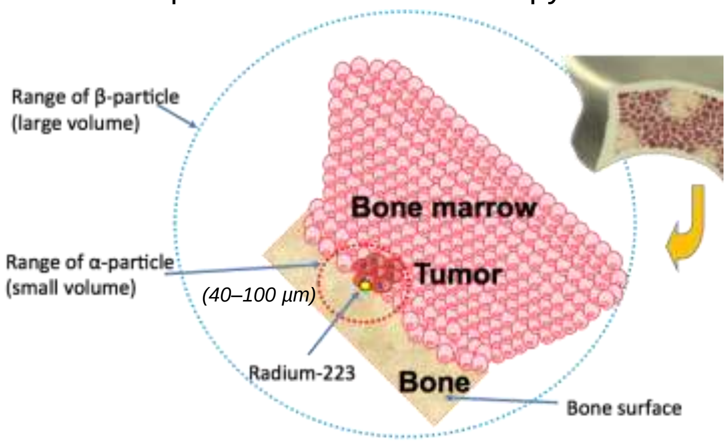
The Nuclear Medicine Alphabet



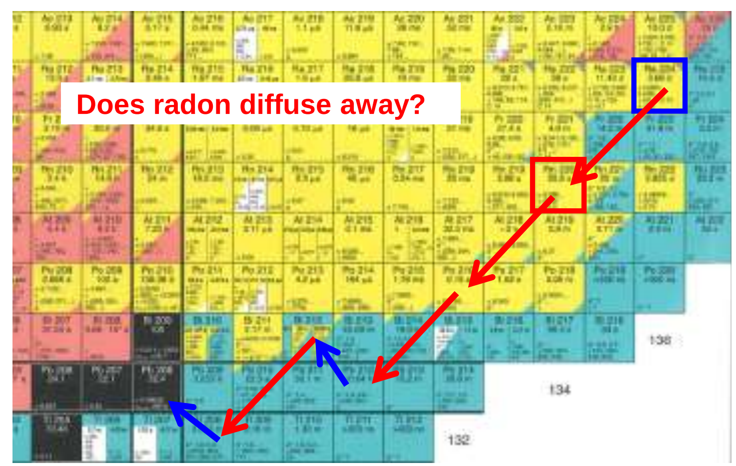
Radio-nuclide	Half-life	Daugh-ters	Half-life	Cumulative α/decay	E_α mean (MeV)	Range (μm)
Tb-149	4.1 h			0.17	3.97	25
Pb-212	*10.6 h*	Bi-212 Po-212	1.01 h 0.3 μs	1	7.74	65
Bi-212	1.01 h	Po-212	0.3 μs	1	7.74	65
Bi-213	*0.76 h*	Po-213	4 μs	1	8.34	75
At-211	7.2 h	Po-211	0.5 s	1	6.78	55
Ra-223	11.4 d	Rn-219 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

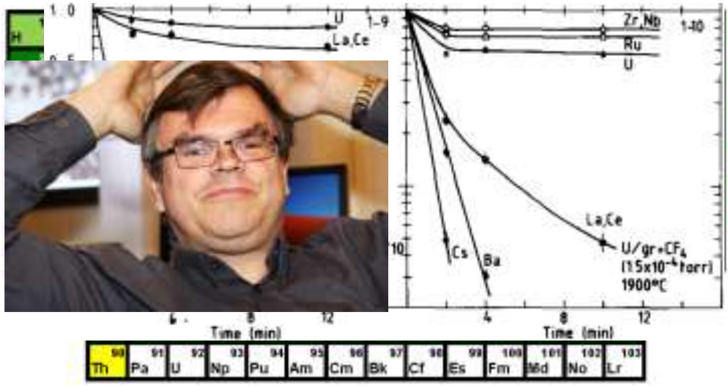
Alpha versus beta for therapy



Isotopes for targeted alpha therapy

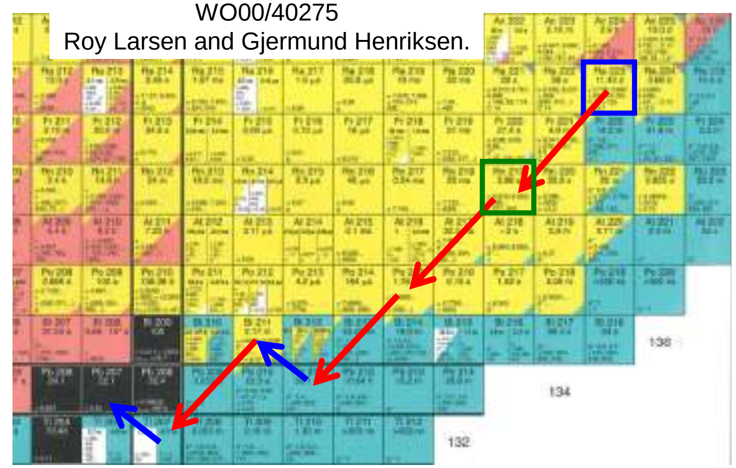


Radioisotopes available at ISOLDE-CERN

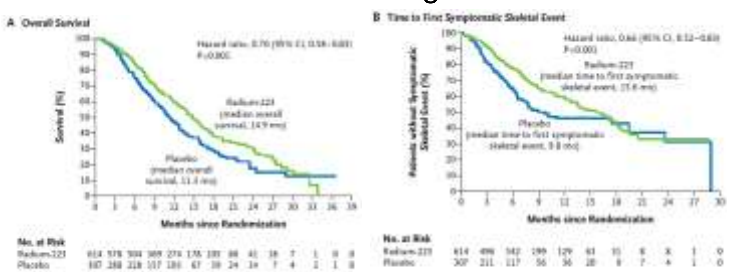


Diffusion and release measurements to develop new beams
e.g. *P. Hoff et al., NIM 221 (1984) 313.*

Isotopes for targeted alpha therapy



^{223}Ra: Xofigo

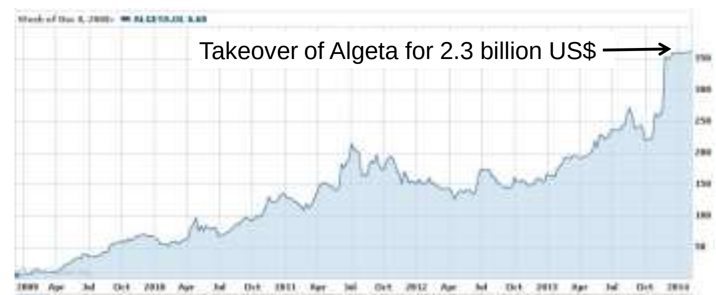


C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang,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

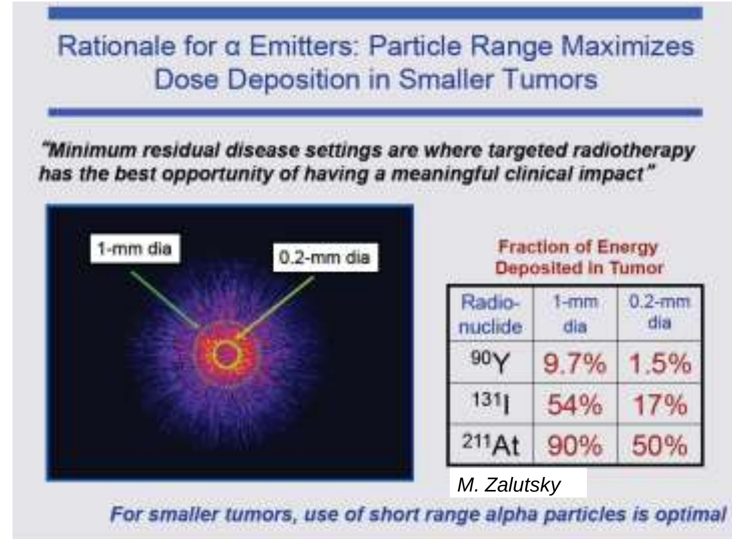
The NEW ENGLAND JOURNAL of MEDICINE

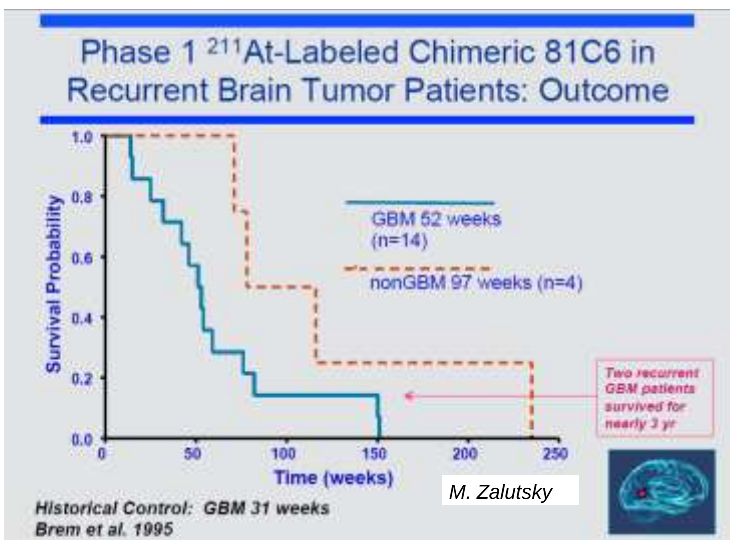
ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Prospects of targeted alpha therapies ?

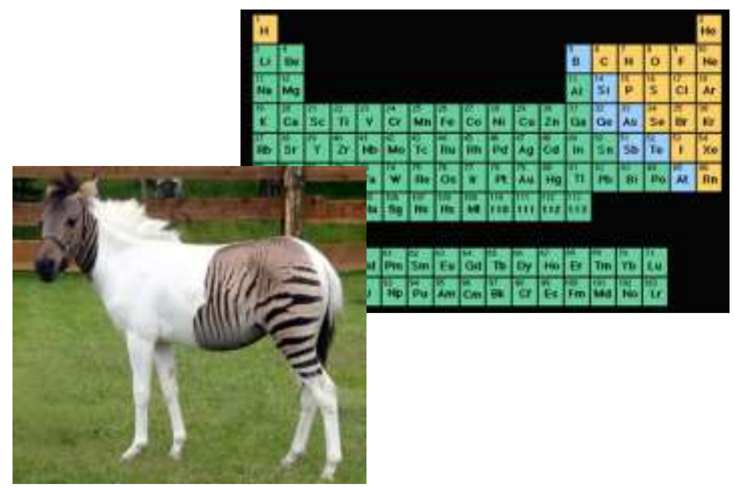


Bayer HealthCare SANOFI AREVA Med Roche

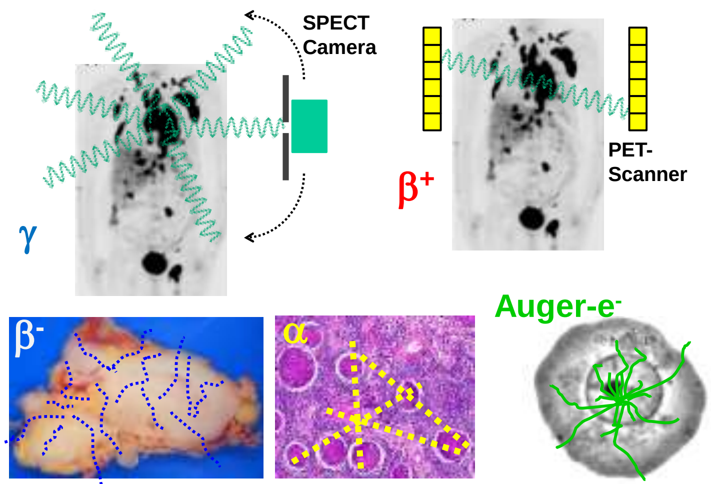




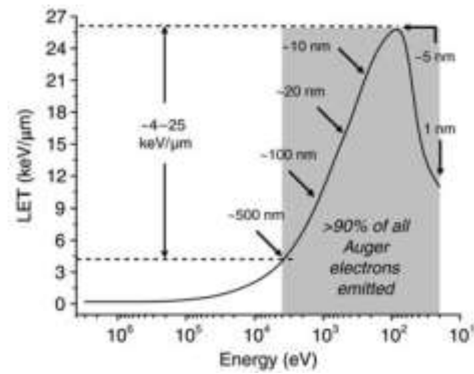
Astatine: a chemical hybrid – halogen/metalloid

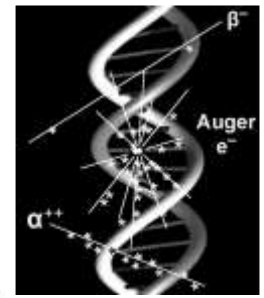


The Nuclear Medicine Alphabet



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.*

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

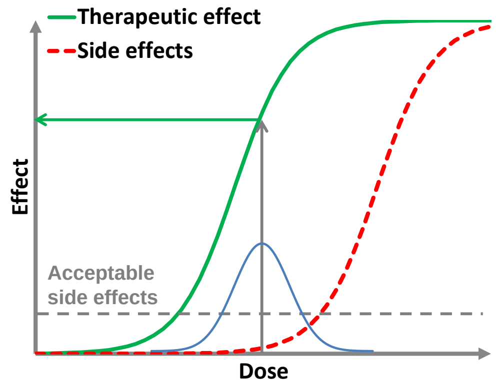
Established isotopes

Emerging isotopes

R&D isotopes: supply-limited!

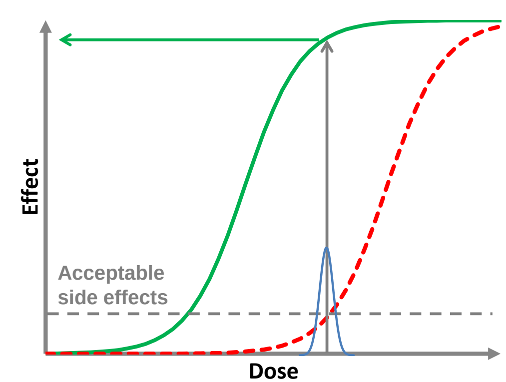
Modern, better targeted bioconjugates require shorter-range radiation ⇒ need for adequate (R&D) radioisotope supply.

Theranostics



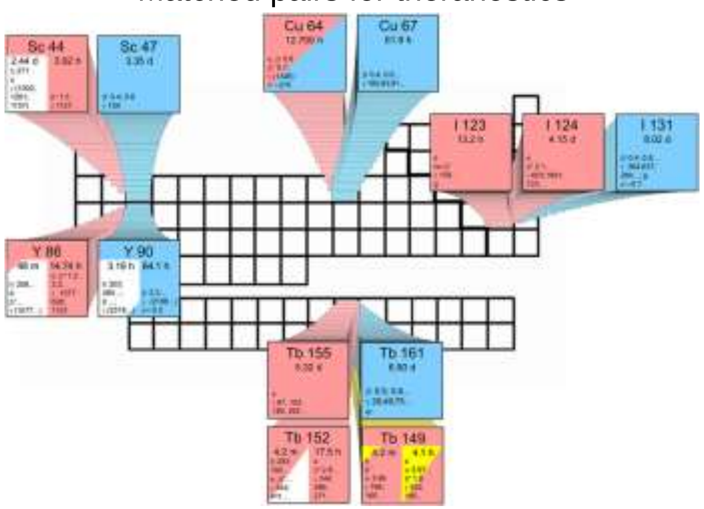
Accurate dosimetry is essential for optimum use of the therapeutic window.

Theranostics



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

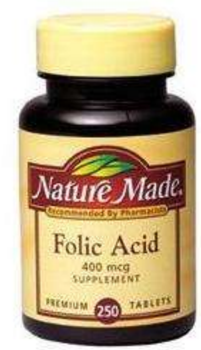
Matched pairs for theranostics



Folate-receptor positive cancers

Frequent overexpression of folate receptor in cancer of:

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



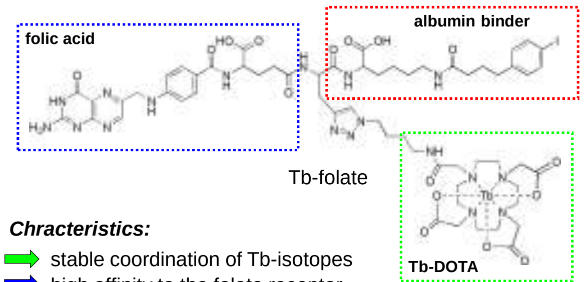
folic acid = vitamine B9

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

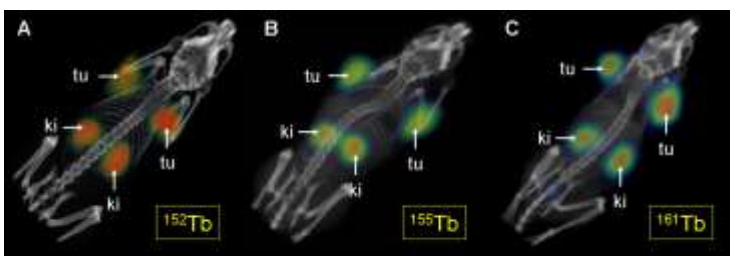


Chracteristics:

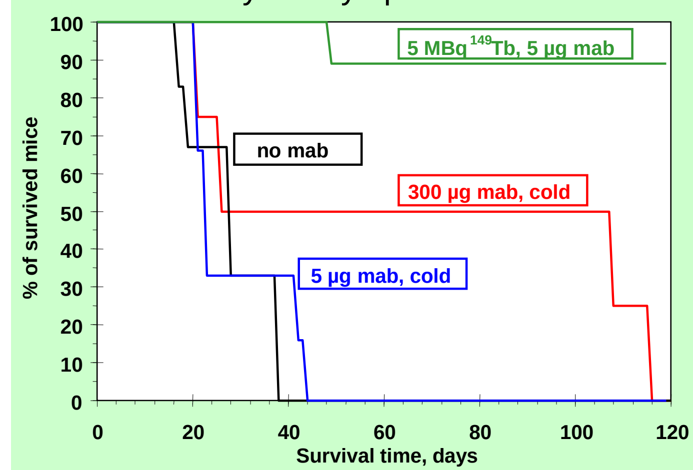
- stable coordination of Tb-isotopes
- high affinity to the folate receptor
- prolonged blood circulation time

Theranostics with terbium isotopes

PET *SPECT* *SPECT*

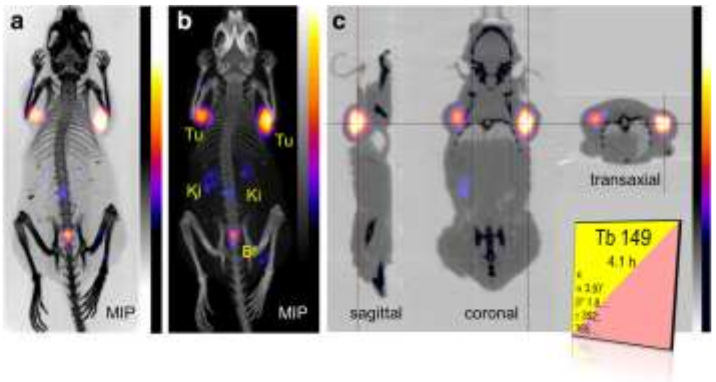


IS528 Collaboration: C. Müller et al., J. Nucl. Med. 2012;53:1951.



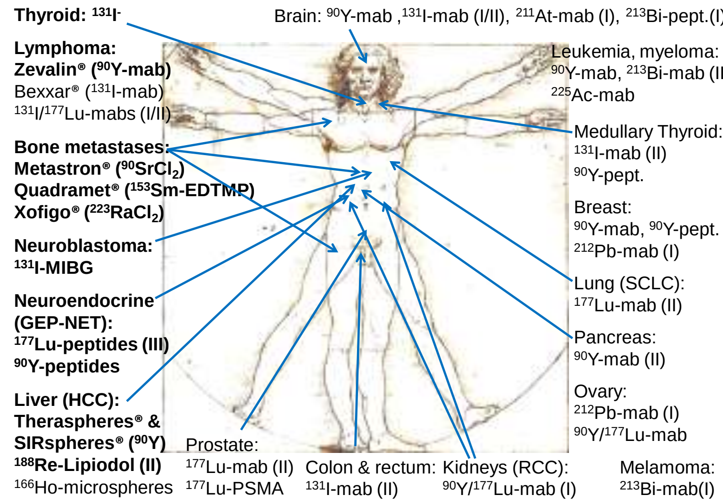
G.J. Beyer et al., Eur J Nucl Med Molec Imaging 2004:31;547.

Alpha-PET with ^{149}Tb

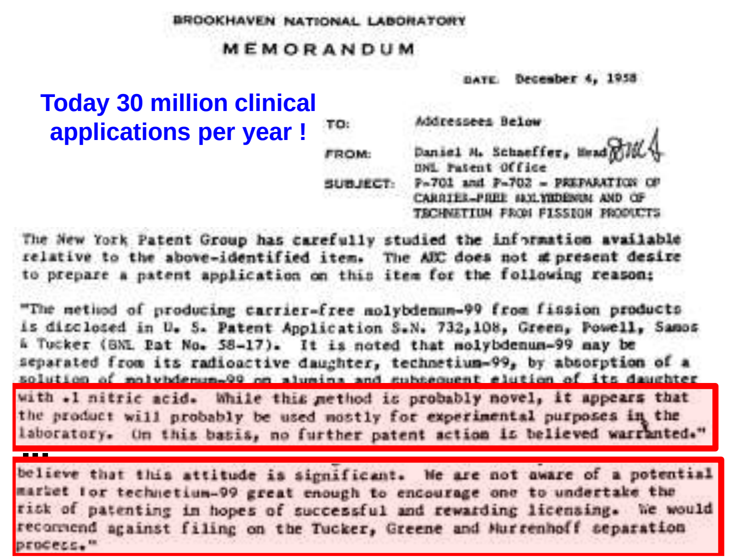


C. Müller et al. EJNMMI Radiopharm Chem 2016;1:5.

Targeted radionuclide therapies in the clinic



Today 30 million clinical applications per year !



BROOKHAVEN NATIONAL LABORATORY

MEMORANDUM

DATE: December 4, 1958

TO: Addressees Below

FROM: Daniel H. 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."

...

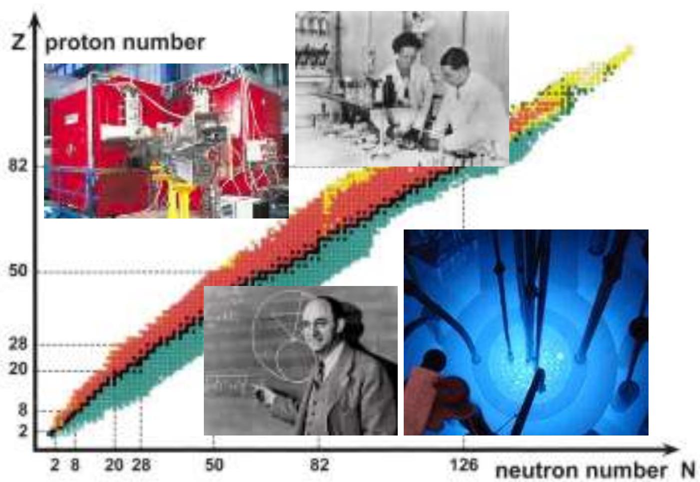
believe that this attitude is significant. We are not aware of a potential market for technetium-99 great enough to encourage one to undertake the risk of patenting in hopes of successful and rewarding licensing. We would recommend against filing on the Tucker, Greene and Murrenhoff separation process."

Which radionuclides will we need for medicine in 2030 ?

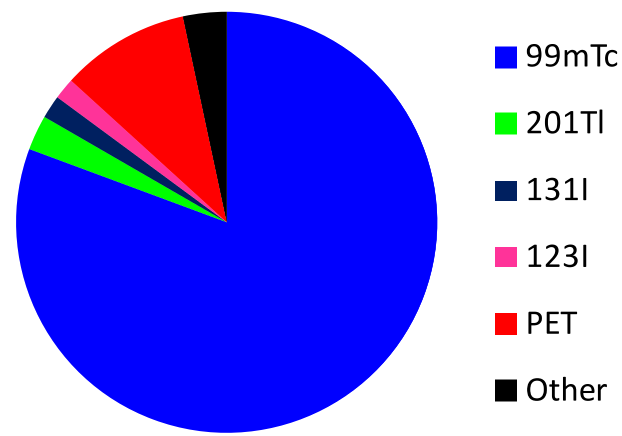
Radioisotope Production

The Tordesillas meridian

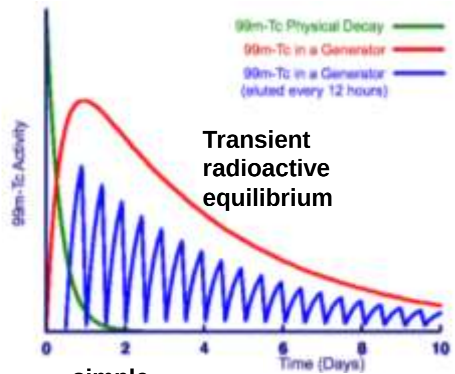
The Tordesillas meridian of radioisotope production



Cumulative use of diagnostic isotopes in Europe

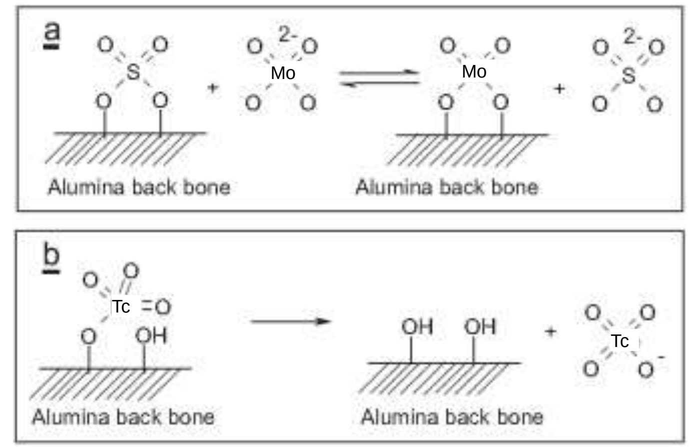


$^{99}Mo/^{99m}Tc$ generator



- simple
- reliable
- portable
- self-shielded

Principle of alumina based generator

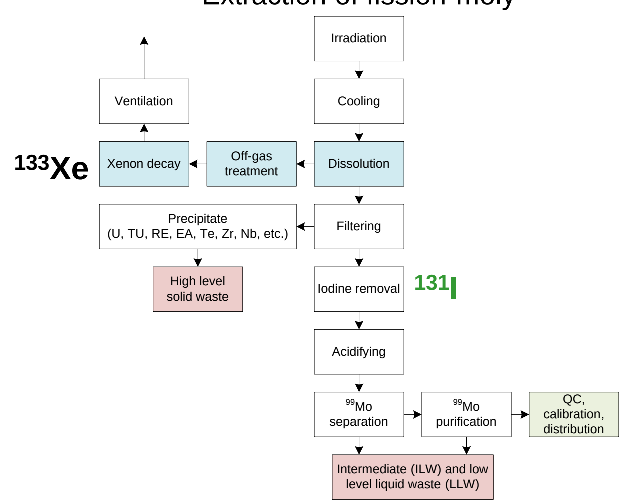


Sorption capacity about 2 mass% MoO_4^{2-} per Al_2O_3

Fission production

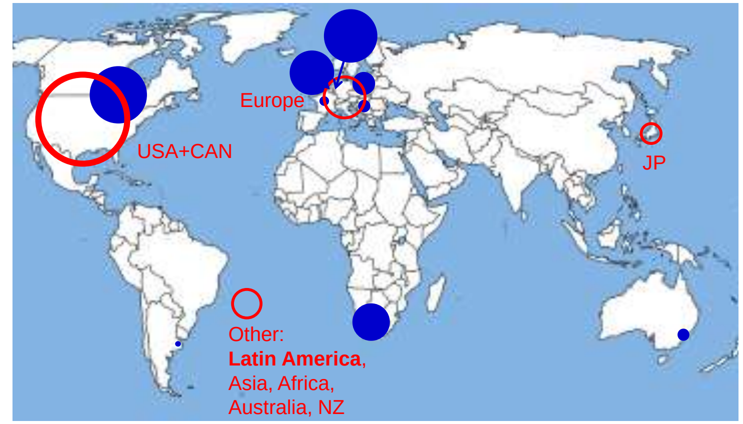
After irradiation, decay and chemical processing:
$^{99}Mo/^{all}Mo \approx 10\%$, i.e. 10% of theoretical specific activity 480 kCi/g

Extraction of fission-moly



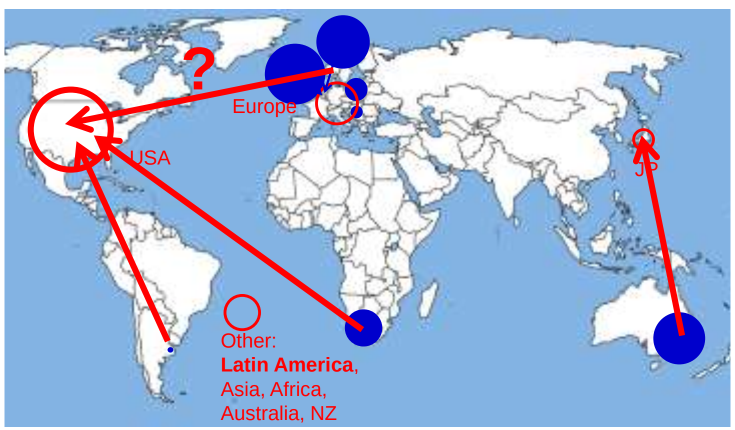
The traditional supply chain of $^{99}Mo/^{99m}Tc$

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.


Isotope shortage means a healthcare crisis
European hospitals cope with Mo-99 supply crisis
MOLYBDENUM SUPPLY
L'inquiétante pénurie d'isotopes pour l'imagerie
Engpässe in der Tumormedizin
Medical isotope shortage reaches crisis level
Krebsärzten gehen die Diagnosemittel aus
Médecine nucléaire : il faut prolonger le réacteur Osiris
We Need to Expand Medical Isotope Production!
ANALYSIS | The made-in-Canada isotope shortage facing medical scans
Desperately Seeking Moly
Isotopes médicaux - Crise mondiale à l'horizon
Aucune solution n'existe pour résoudre le problème d'approvisionnement
Isotope shortage to get worse with closing of more reactors
L'OCDE s'inquiète des risques de pénurie d'isotopes médicaux
Mangel an medizinisch verwendbaren Isotopen
Szintigraphien fallen aus, für Februar droht der Notstand
Mo-99 crisis


Nordion broke ground last month on a $75 million isotope production facility that looks out on the runways of Capital Region International. The company expects to move in by the end of the year, to make its first medical isotopes early next year, to be producing them commercially by early 2016. It expects to add 90 jobs to its 70-member staff in the process.

UBC SCIENTISTS HELP AVERT A NUCLEAR MEDICINE MELTDOWN

Moly 99 reactor using Sandia design could lead to U.S. supply of isotope to track disease

Canada seeks to avoid medical isotope shortage, extends nuclear reactor

Isotope breakthrough may stave off shortage concerns

Coqui Pharma completes design of medical isotope facility

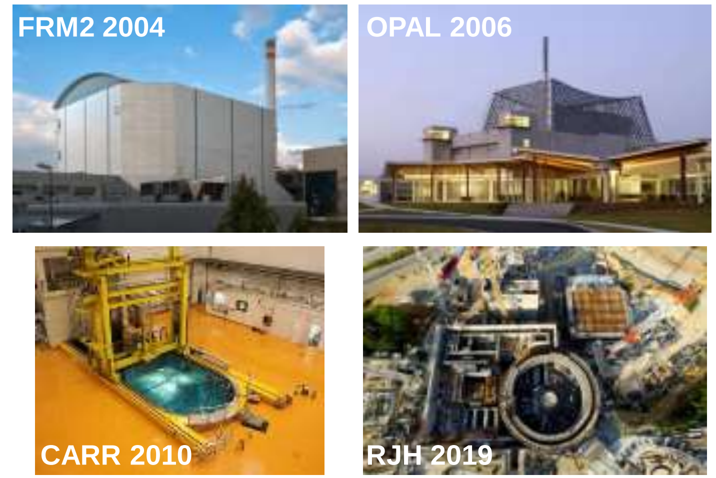
Lab confirms new commercial method for producing medical isotope (Argonne)

NorthStar Medical Radioisotopes ready to begin Mo-99 production

It Takes Two: GE Healthcare and SHINE team up to solve longstanding radiopharmaceutical supply concerns in medical imaging

Successful generation of Tc-99m is a supply chain advancement that can help ensure patient access to critical medical imaging scans.

New research reactors



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

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

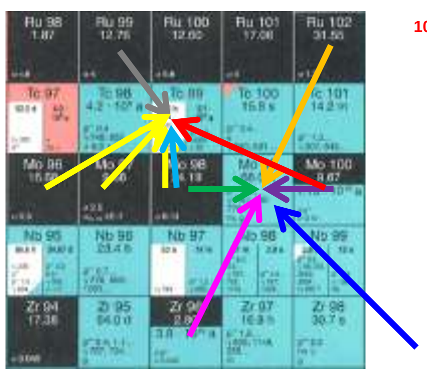
^{235}U(n_{th},f)
^{238}U(n_{fast},f)
^{238}U(γ,f)
^{238}U(p,f)

^{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)

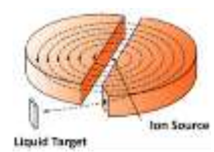
^{nat}Mo(α,x)

^{98}Mo(d,n)

^{99}Ru(n,p)

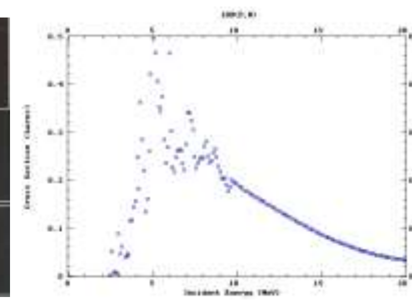
^{18}F production via ^{18}O(p,n)

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

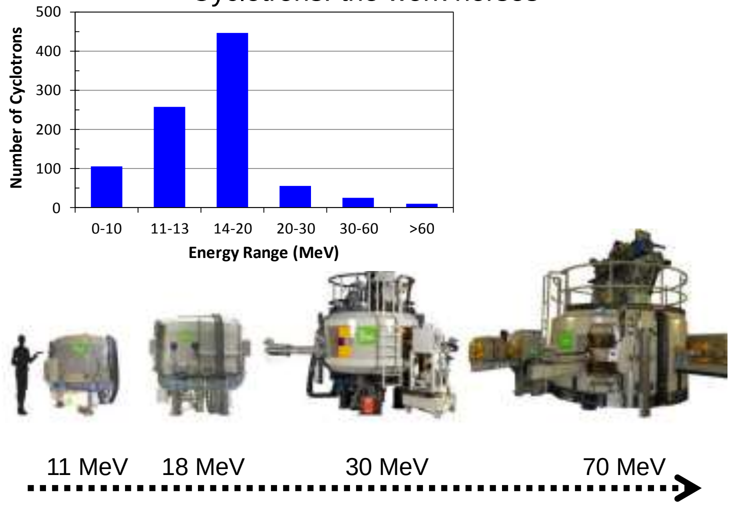


Cyclotron irradiation

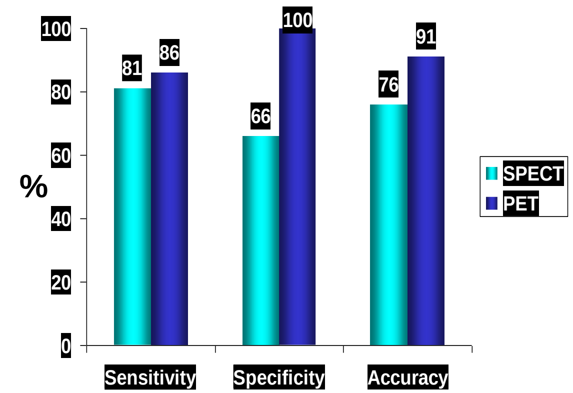
Transformation into FDG



Cyclotrons: the work horses

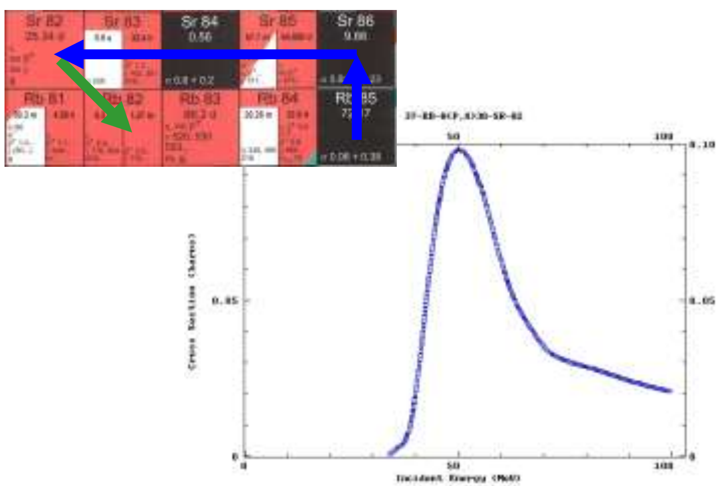


Diagnostic Accuracy: ^{82}Rb PET vs ^{99m}Tc SPECT



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

^{82}Sr production



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

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.

"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)

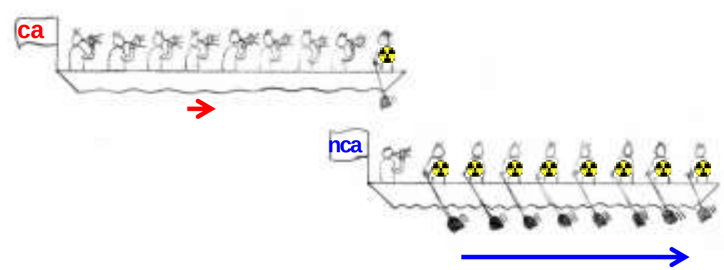
2007 Rapid large-scale separation
of n.c.a. ^{177}Lu from irradiated Yb
by ITG Garching

Specific activity

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).

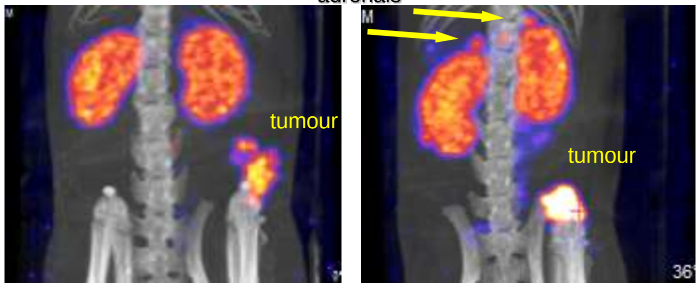
Carrier added vs. non-carrier added



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

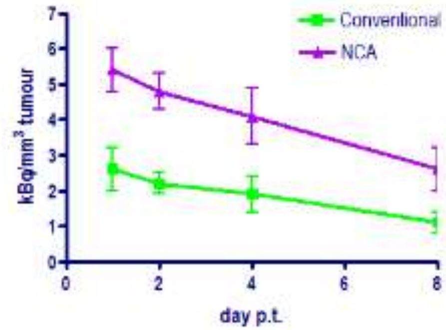
Conv. ^{177}Lu-octreotate, 11 µg NCA ^{177}Lu-octreotate, 2 µg

adrenals



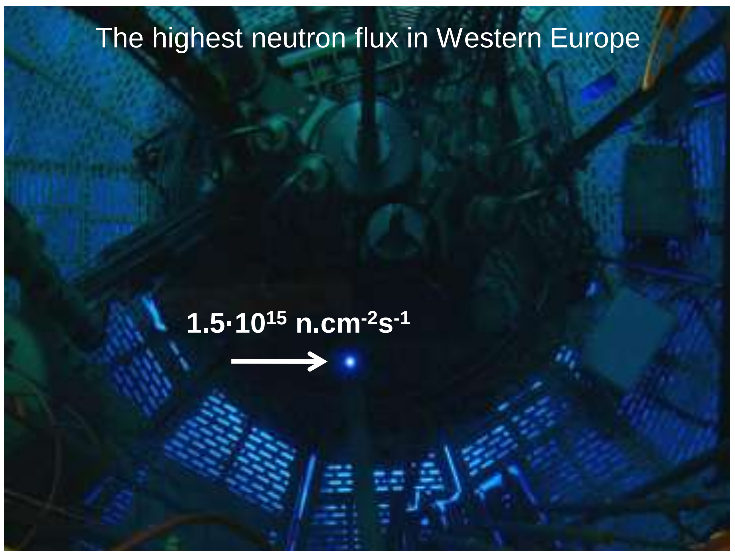
M. de Jong, Erasmus MC, Rotterdam

Tumor uptake, based on SPECT quantification



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

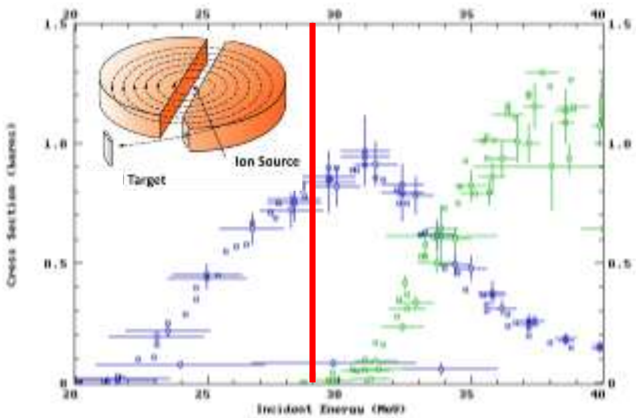
M. de Jong, Erasmus MC, Rotterdam



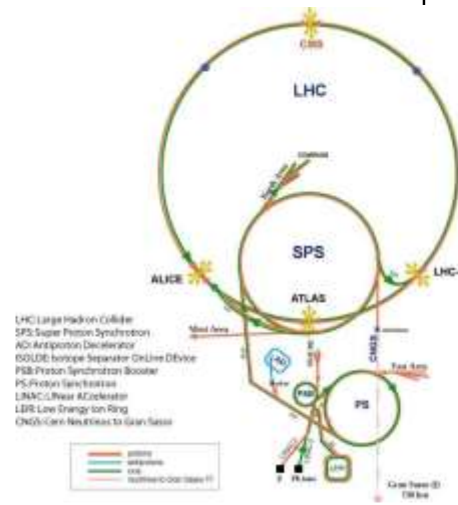
^{188}W/^{188}Re generator

^{211}At production

^{209}Bi(α,2n)^{211}At ^{209}Bi(α,3n)^{210}At > ^{210}Po

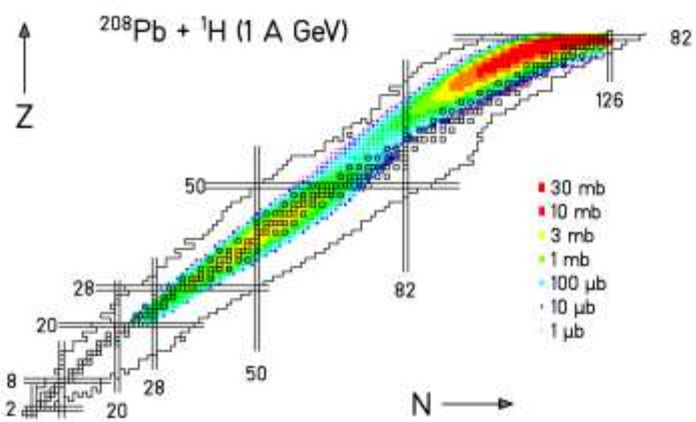


The accelerator complex of CERN



Ion source	90 keV
LINAC2	50 MeV
PSB	1.4 GeV
PS	25 GeV
SPS	450 GeV
LHC	6500 GeV

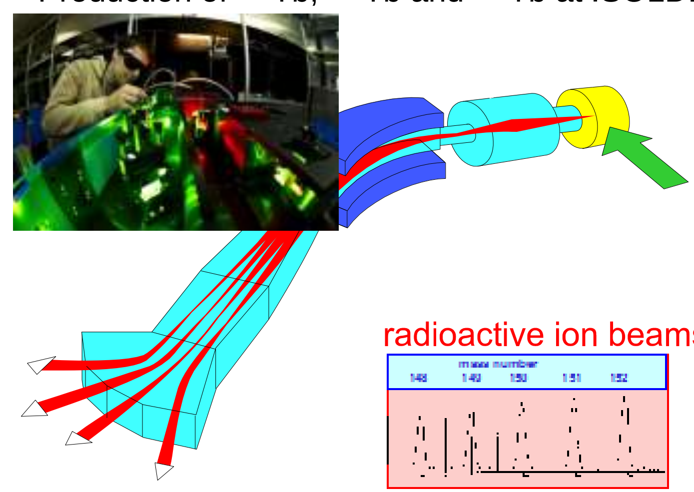
Spallation + Fragmentation + Fission



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

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

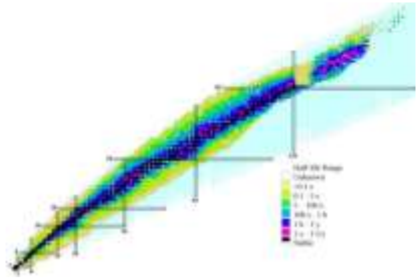
Production of ^{149}Tb, ^{152}Tb and ^{155}Tb at ISOLDE



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