Overview

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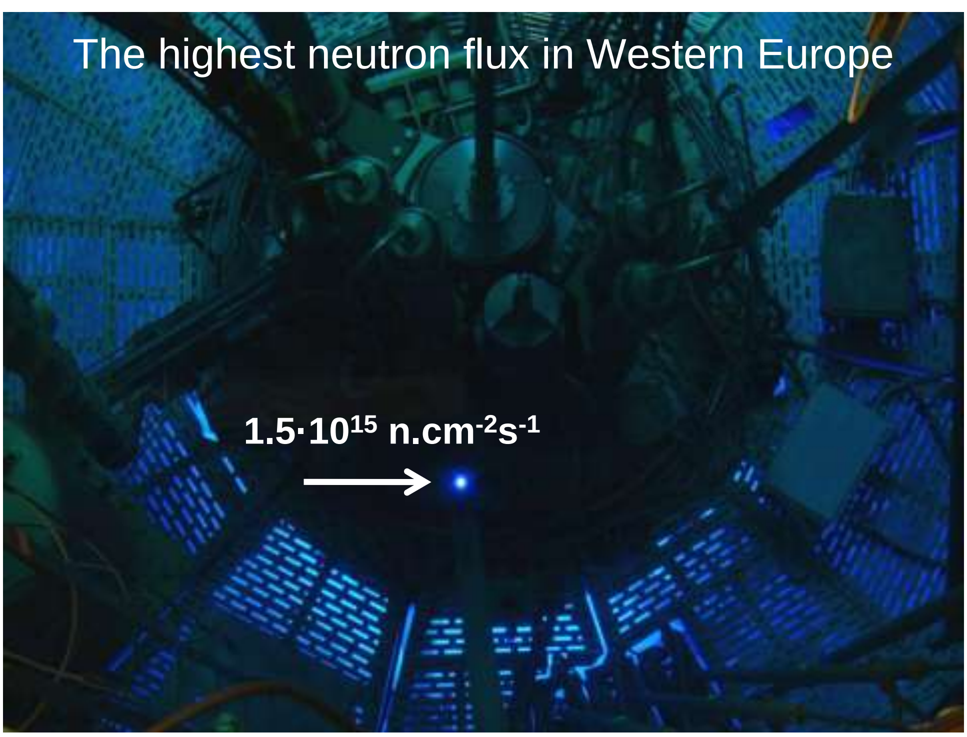
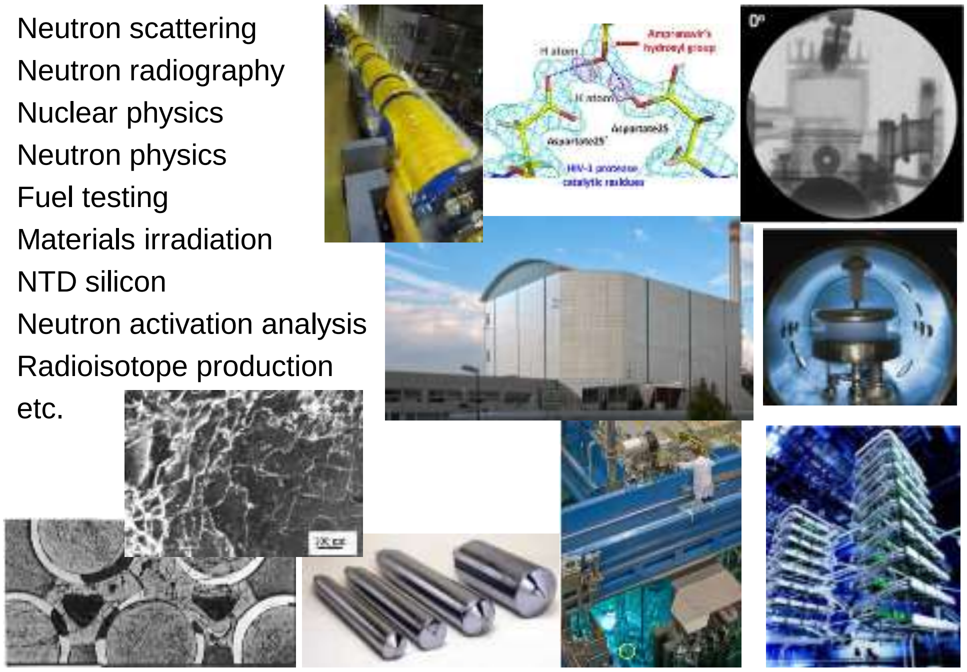
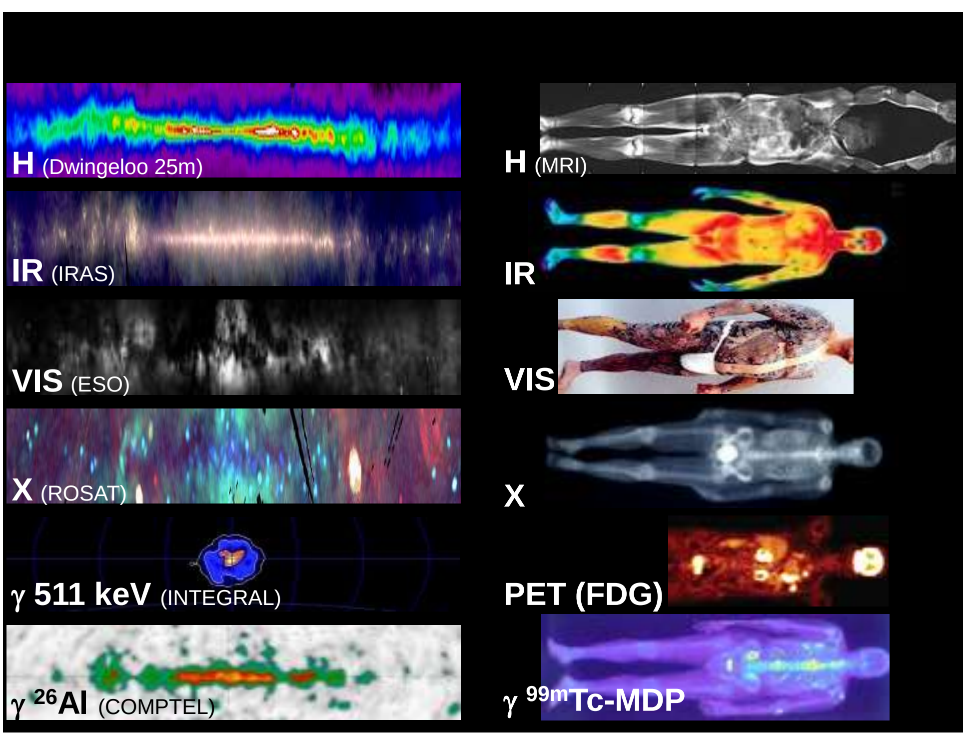
MEDICIS-PROMED
9 February 2016



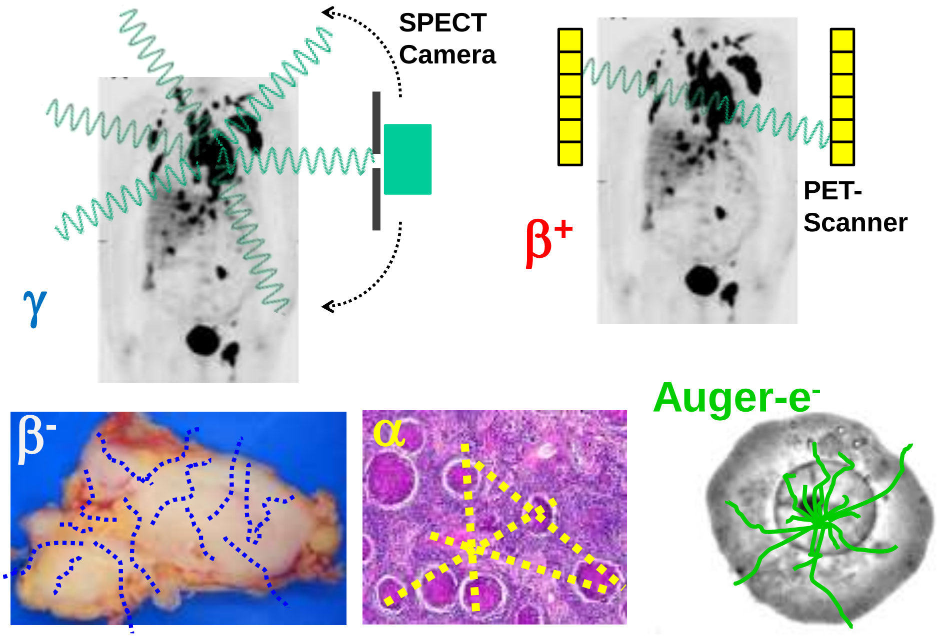
Research reactors are multi-use facilities

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

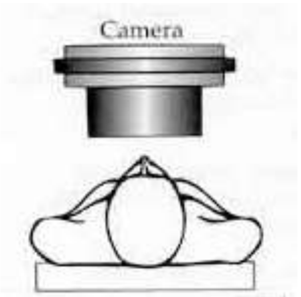




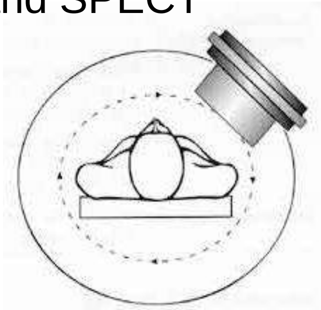
The Nuclear Medicine Alphabet



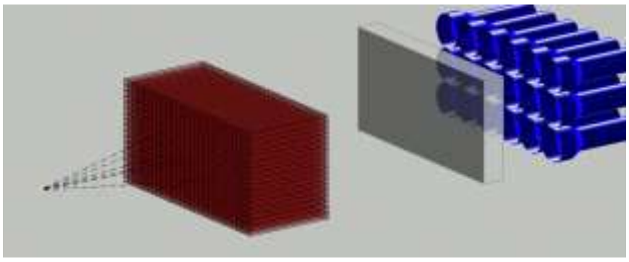
Scintigraphy and SPECT



2D: planar scan
(Gamma camera)

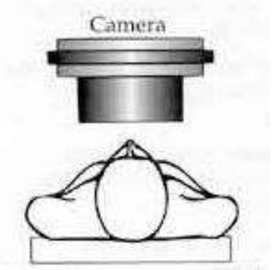


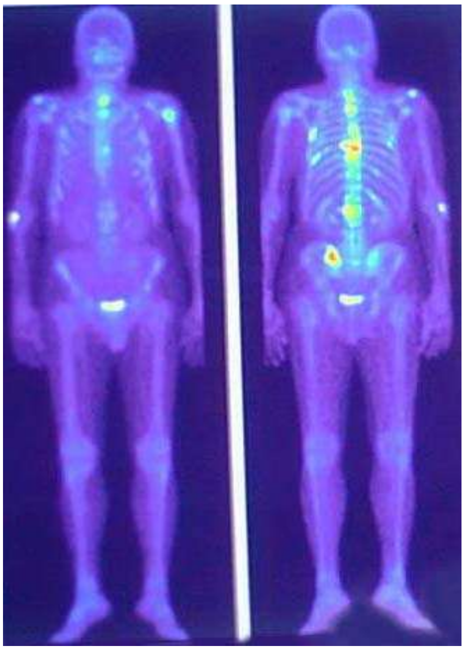
3D: SPECT: Single Photon Emission Computer Tomography



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

Bone metastases

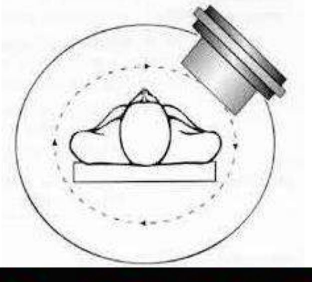


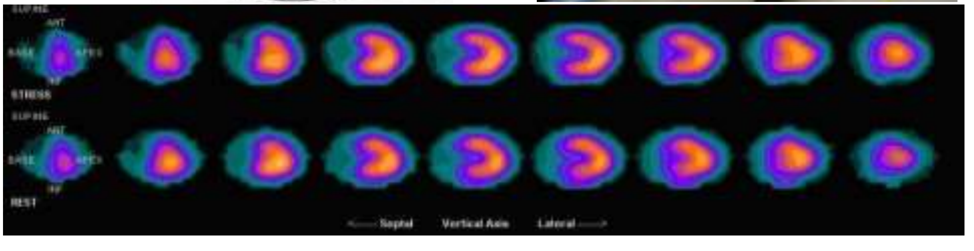


- planar or SPECT scan for bone metastases
- differentiate between local and generalized disease
- decide on treatment options: surgery or radiation therapy versus systemic therapy
- Bone: 35% of NM procedures in Europe

Ischemic heart disease

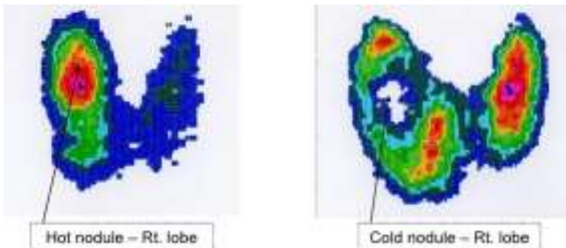
- diagnose by ECG, quantify by cardiac stress test with SPECT
- treatment by medication, angioplasty or bypass surgery
- 26% of NM procedures in Europe

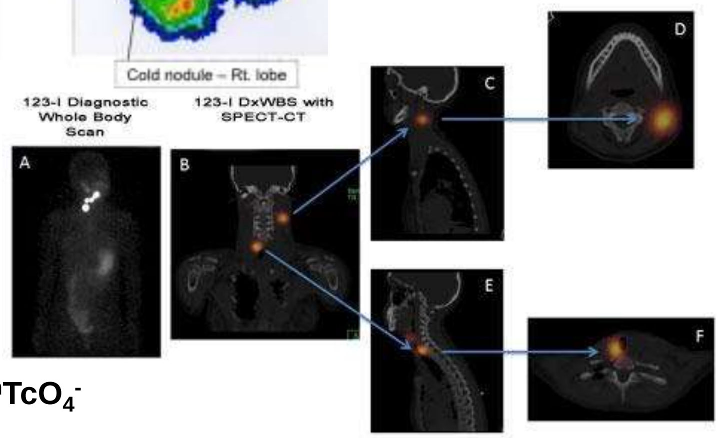




Thyroid scintigraphy

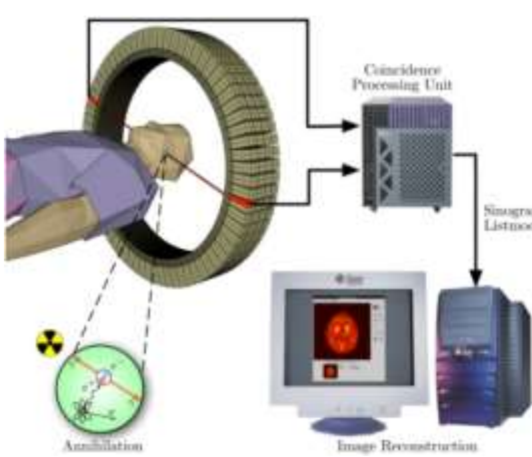
Thyroid: 12% of NM procedures in Europe

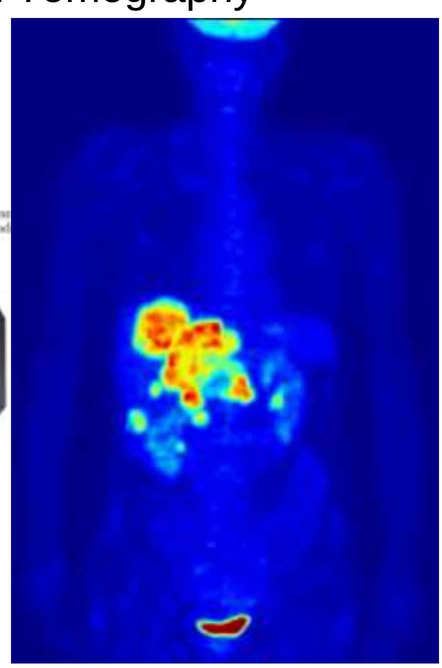


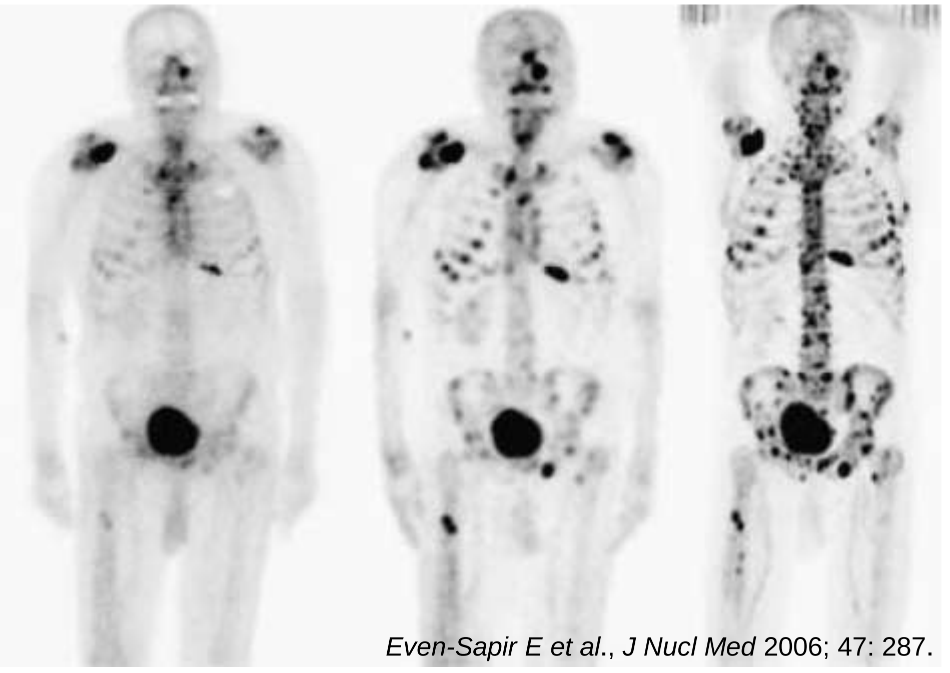


$^{123}I^-$, $^{131}I^-$ or $^{99m}TcO_4^-$

Positron Emission Tomography

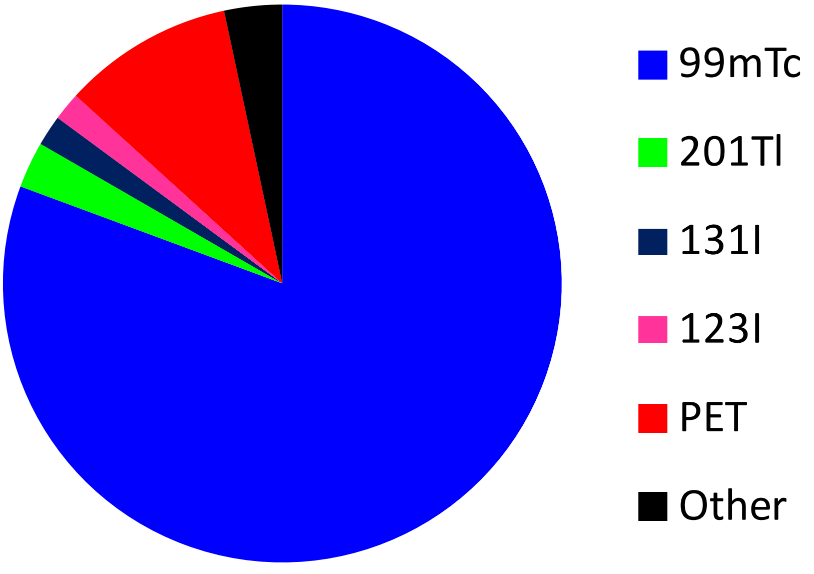






^{99m}Tc-MDP planar **^{99m}Tc-MDP SPECT** **$^{18}F^{-}$ PET**

Cumulative use of diagnostic isotopes in Europe

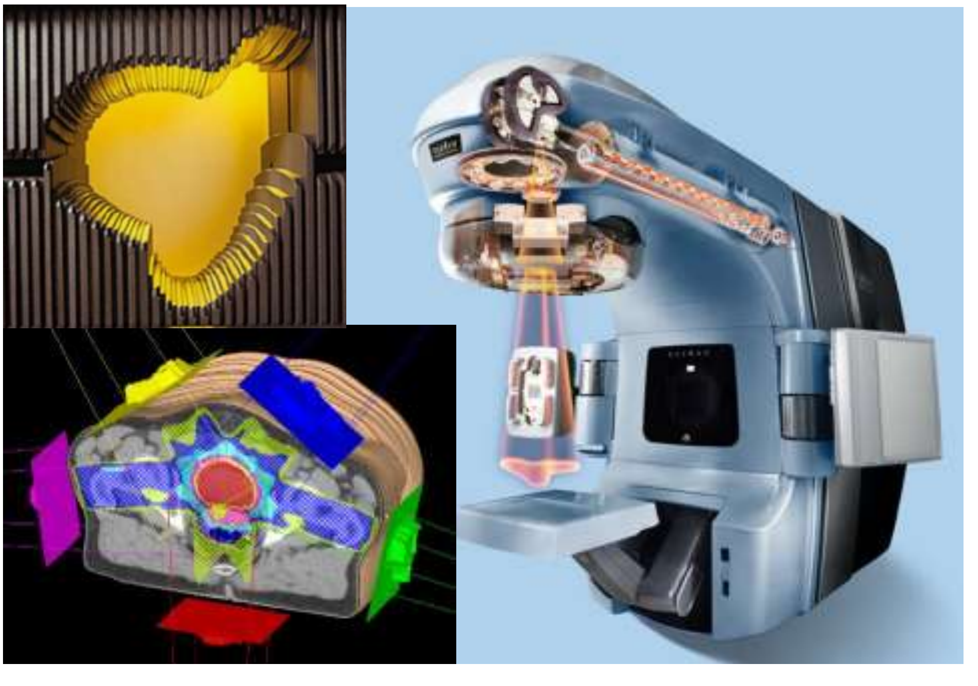


http://www.nupecc.org/npmed/npmed2014.pdf

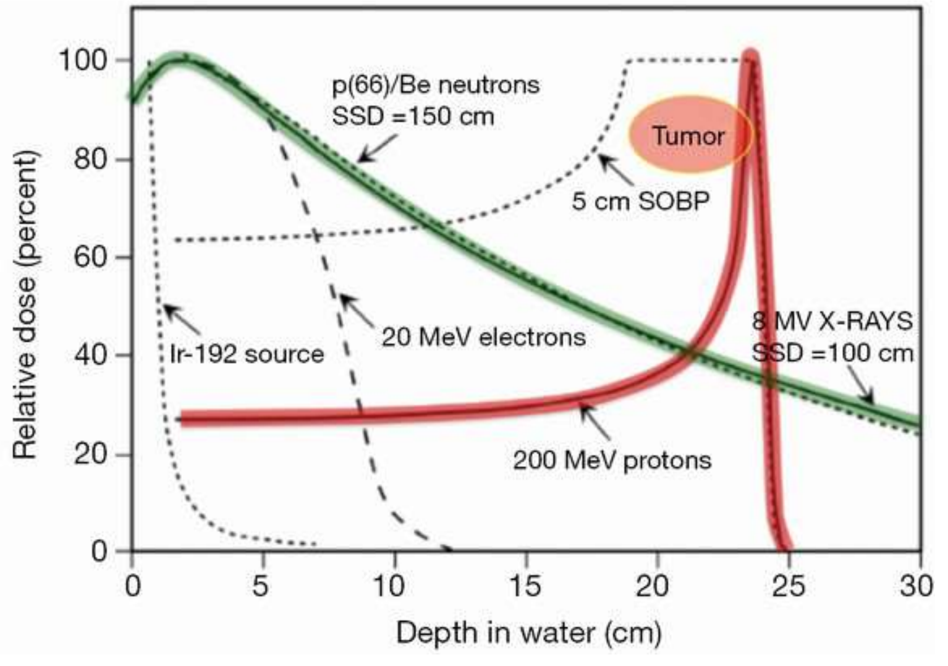
From diagnostics

to therapy

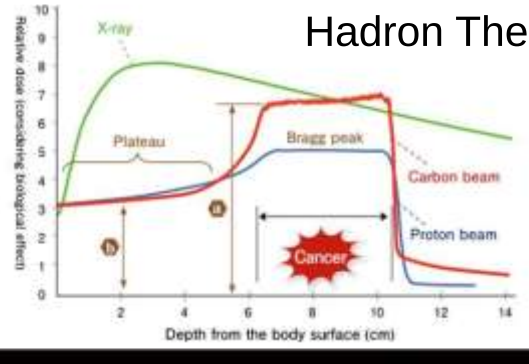
EBRT (External Beam Radiation Therapy)

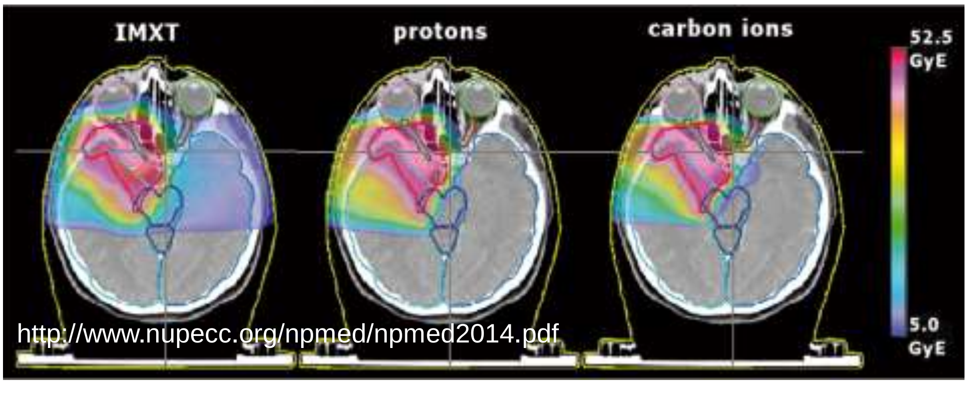


EBRT (External Beam Radiation Therapy)



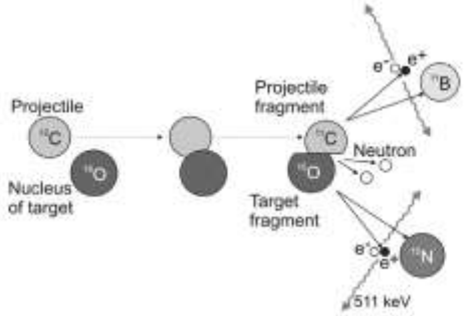
Hadron Therapy

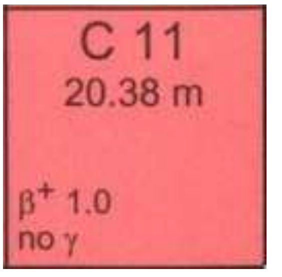


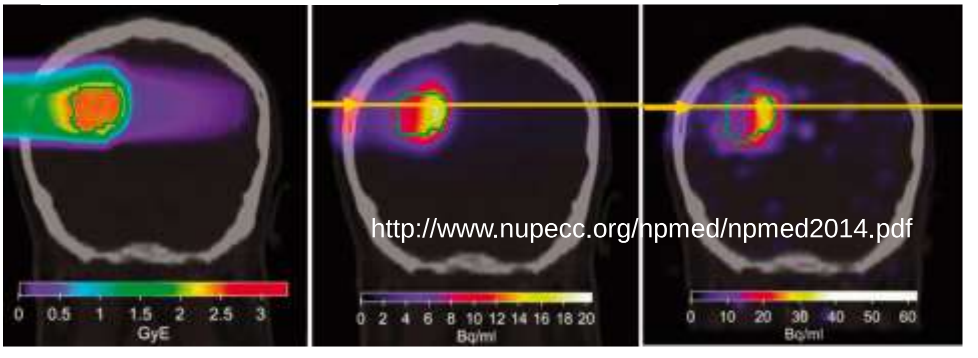


http://www.nupecc.org/npmed/npmed2014.pdf

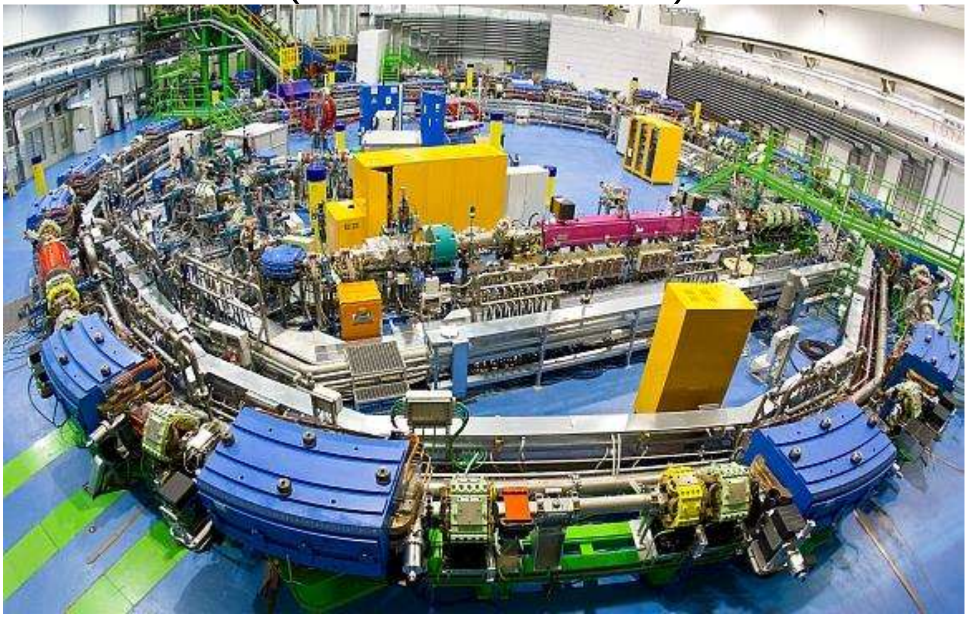
PET for Quality Control in Hadron Therapy



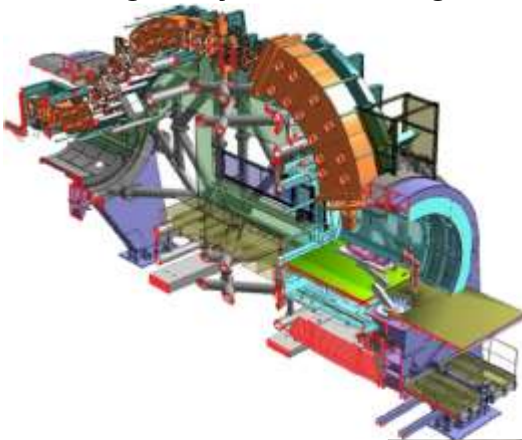




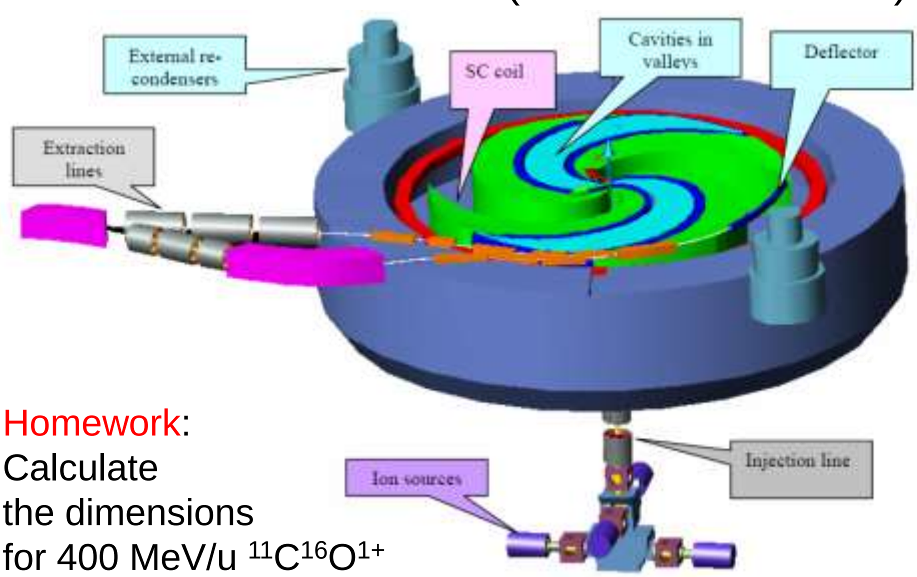
CNAO synchrotron: 78 m long, 25 m diameter (for 400 MeV/u $^{12}C^{6+}$)



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

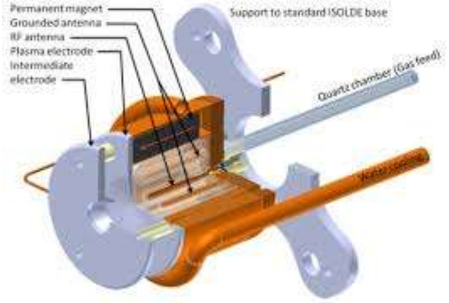


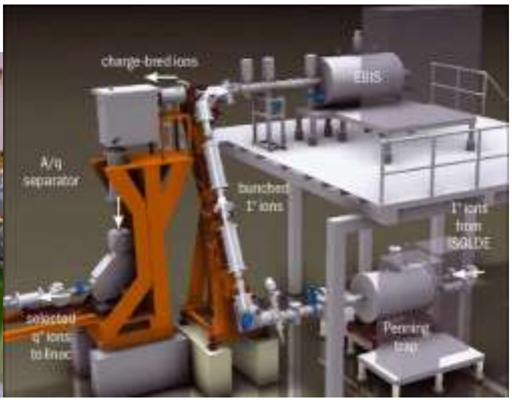
IBA C400 cyclotron: 6.6 m diameter, 700 tons
(for 400 MeV/u $^{12}C^{6+}$)



Homework:
Calculate
the dimensions
for 400 MeV/u $^{11}C^{16}O^{1+}$

Molecular beams and charge breeding

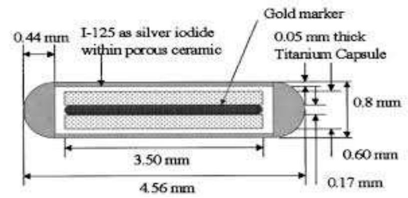




Brachytherapy

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")



Cancer and efficiency of treatments

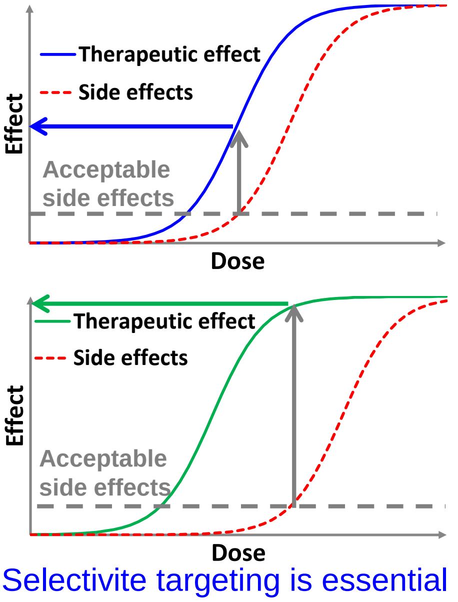
At time of diagnosis	Primary tumor	With metastases	Total
Diagnosed	58%	42%	100%
Cured by:			
Surgery	22%		
Radiation therapy	12%		
Surgery+radiation therapy	6%		
All other treatments and combinations incl. chemotherapy		5%	
Fraction cured	69%	12%	45%

Over one million deaths per year from cancer in EU.

⇒ improve early diagnosis
⇒ improve systemic treatments

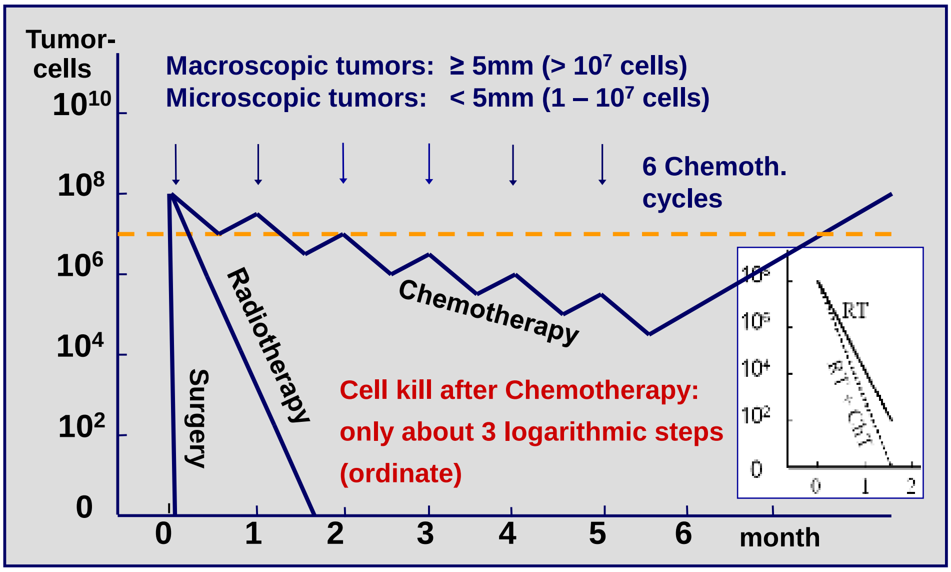
Targeted therapies

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!

Comparison of Therapies

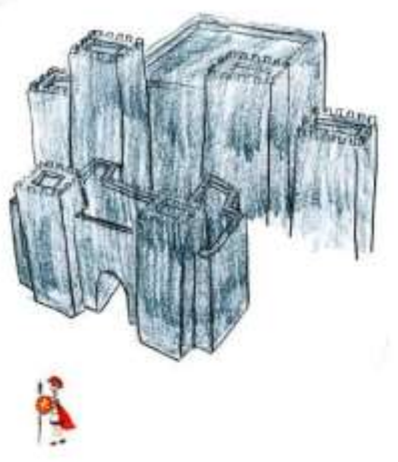


(Molls, TU München; according to Tannock: Lancet 1998, Nature 2006)

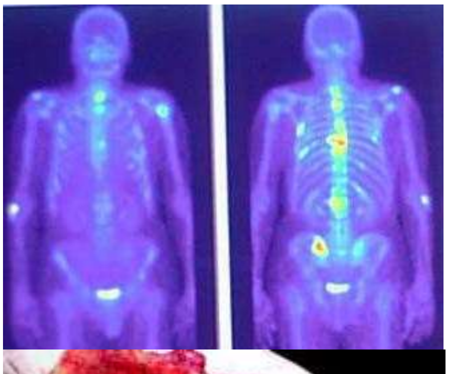
Learning from history

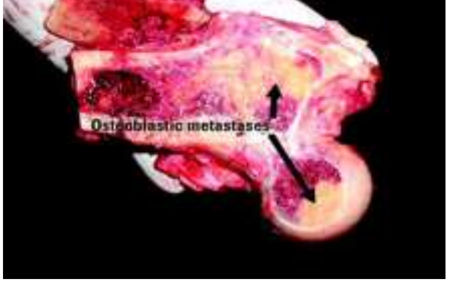
The principle of targeted therapies

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



Metabolic targeting





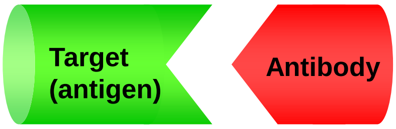
Thyroid cancer
$^{123}I^-$ for imaging
$^{131}I^-$ for therapy

Bone metastases
1.5 million patients world-wide

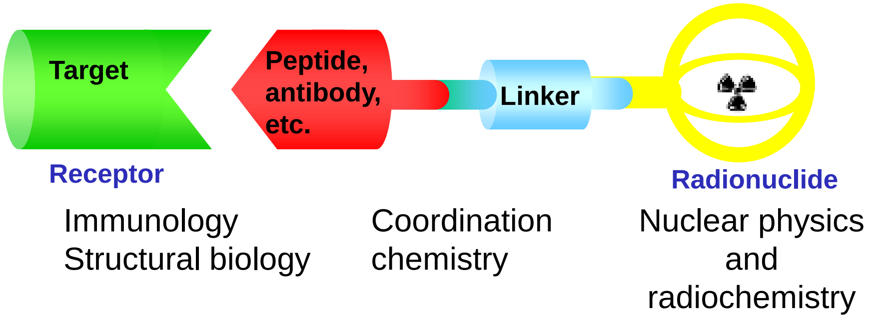
^{99m}Tc-MDP for SPECT imaging
$^{18}F^-$ for PET imaging

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

Immunology approach

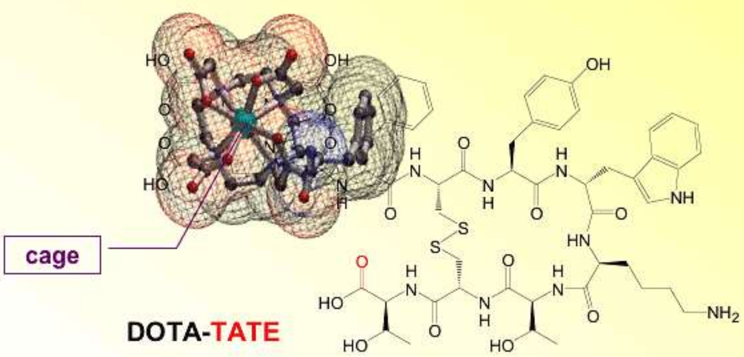


Multidisciplinary collaboration
to fight cancer



Nuclear medicine and medical physics

Structural Formula of DOTA-TOC/TATE



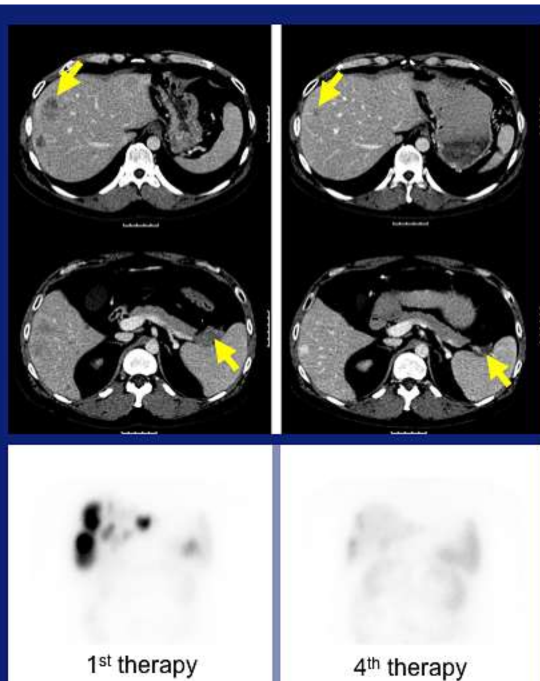
1,4,7,10-tetraazacyclododecantetraacetate

^{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

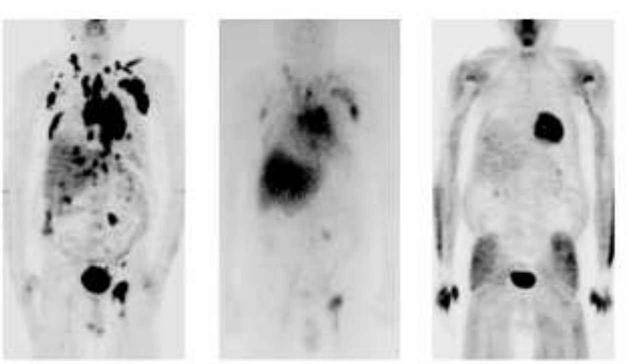
Roelf Valkema, EANM-2008.

Erasmus MC

Lymphoma therapy: RITUXIMAB+^{177}Lu

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

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



1.9.2002	13.9.2002	15.11.2002	15.9.2009

Still in CR

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

University Hospital Basel, CH

Radionuclides for targeted radionuclide therapy

Radio-nuclide	Half-life (d)	E mean (keV)	Eγ (B.R.) (keV)	Range	
Y-90	2.7	934 β	-	**12 mm**	**Established isotopes**
I-131	8.0	182 β	364 (82%)	**3 mm**	
Lu-177	6.7	134 β	208 (10%) 113 (6%)	**2 mm**	**Emerging isotope**

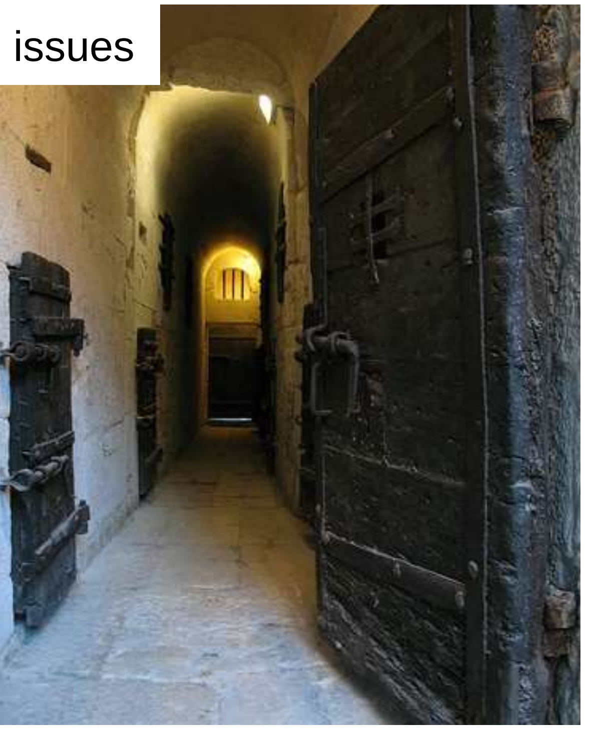
^{131}I: radioprotection issues

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

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

"hot zone" (IAEA/NRCP)

requires dedicated shielded treatment rooms

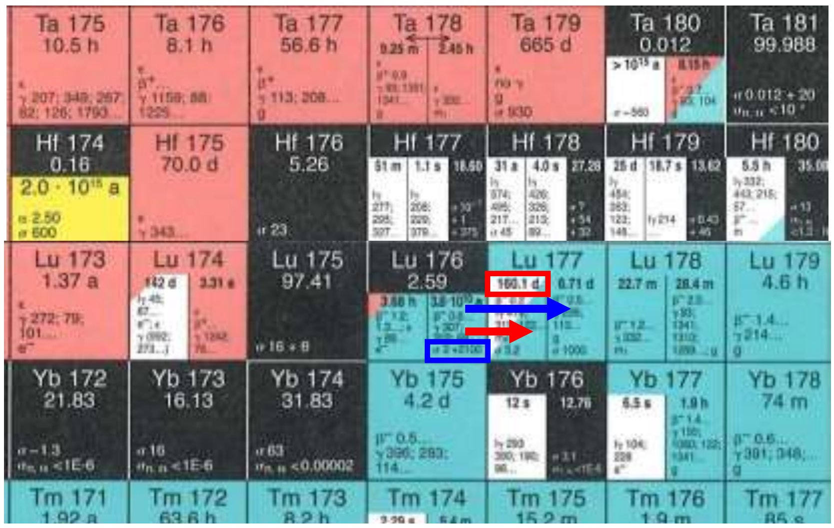


^{90}Y: collateral damage from long range betas ?

$Q_{ß-}$ = 2.28 MeV
up to 12 mm range

The rising star
for therapy

Production of ^{177}Lu

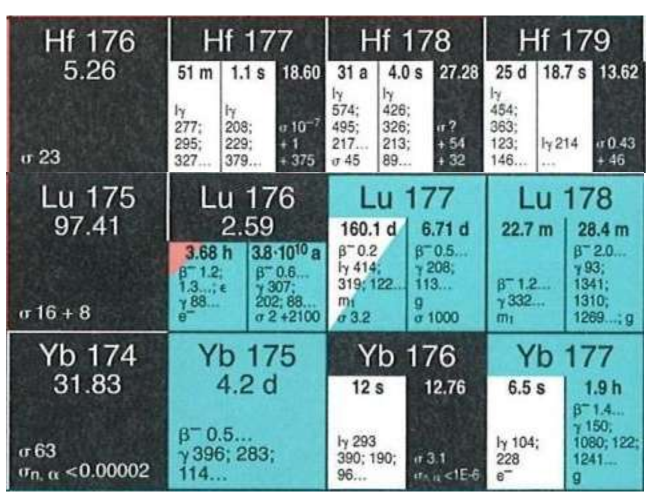


Waste problem for hospitals!

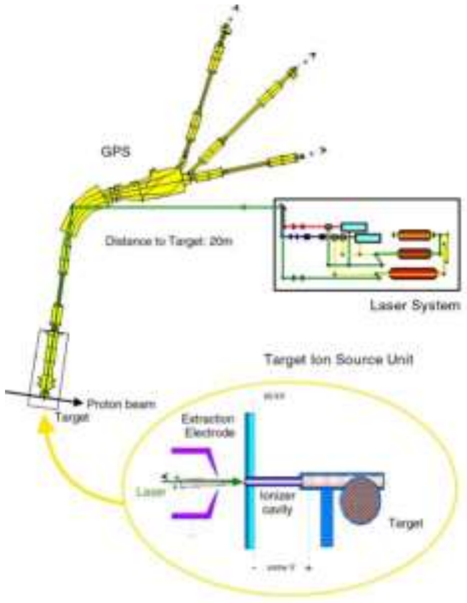
R. Henkelmann et al., Eur. J. Nucl. Med. Mol. Imag. 36 (2009) S260.

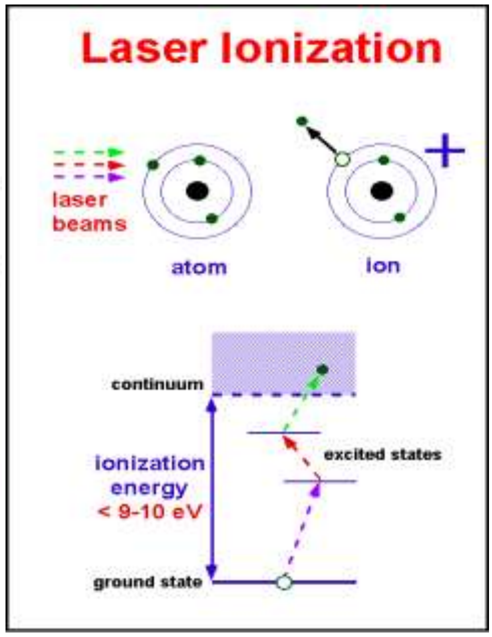
Question

How to get ^{177g}Lu without ^{177m}Lu contamination ?

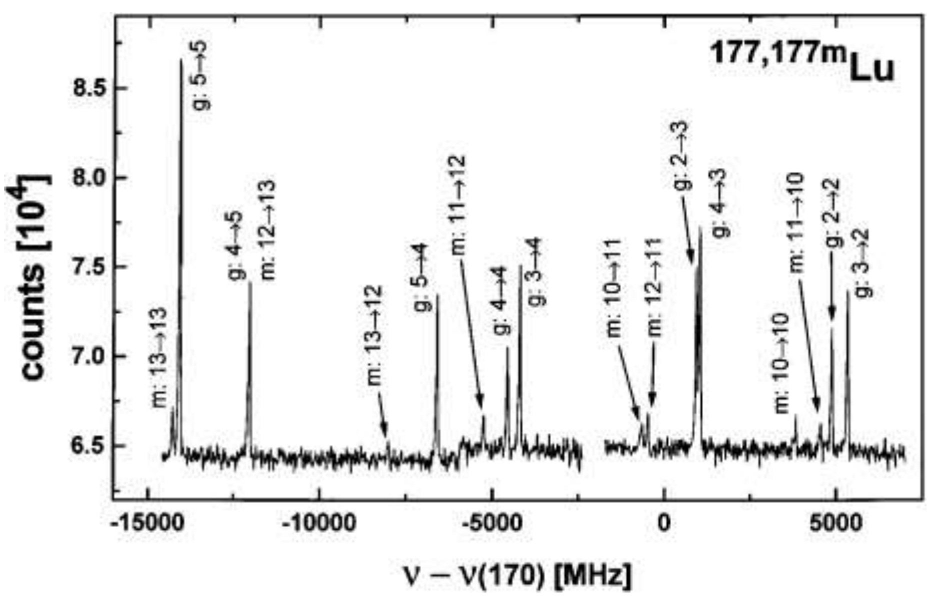


Resonance Ionization Laser Ion Source





Hyperfine Structure of $^{177g/m}$Lu



U. Georg et al. Eur. Phys. J. A 3 (1998) 225.

“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

“Clean” production route to ^{177}Lu

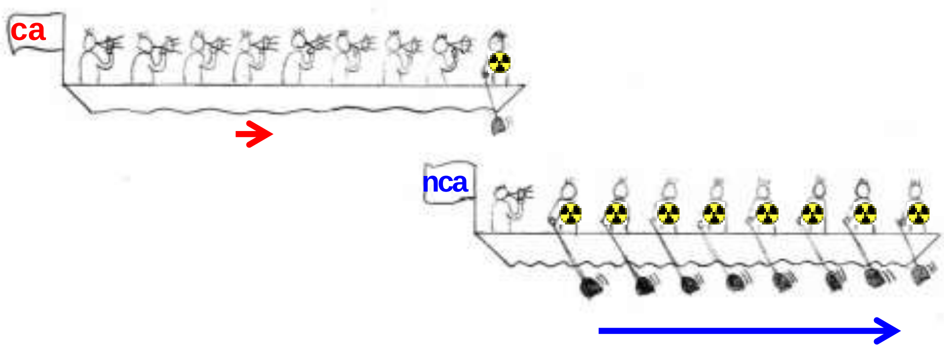
- **Free of long-lived isomer**
- **Non-carrier-added quality**
- **Requires high-flux reactor and advanced radiochemistry**

Specific activity

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

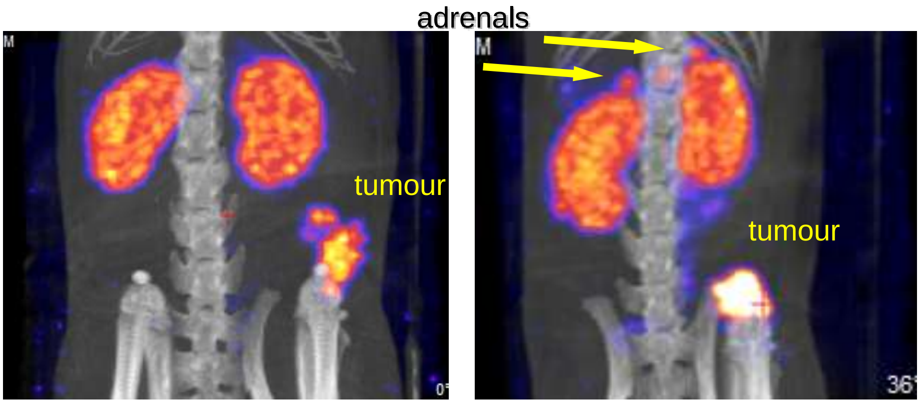
basically the ratio of radioactive atoms to all atoms (including stable ones).

Carrier added vs. non-carrier added



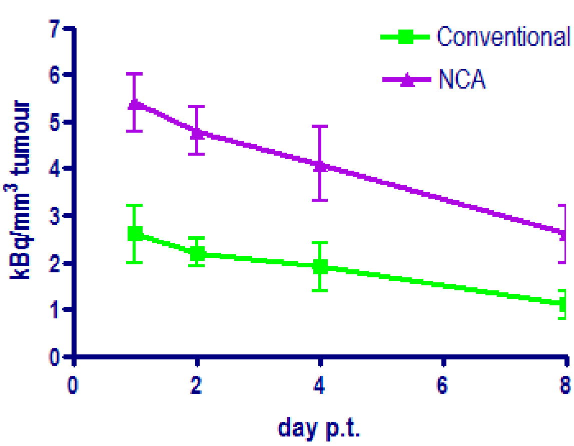
SPECT/CT day 1 p.t. Lu-octreotate

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



M. de Jong, ICTR-PHE 2012

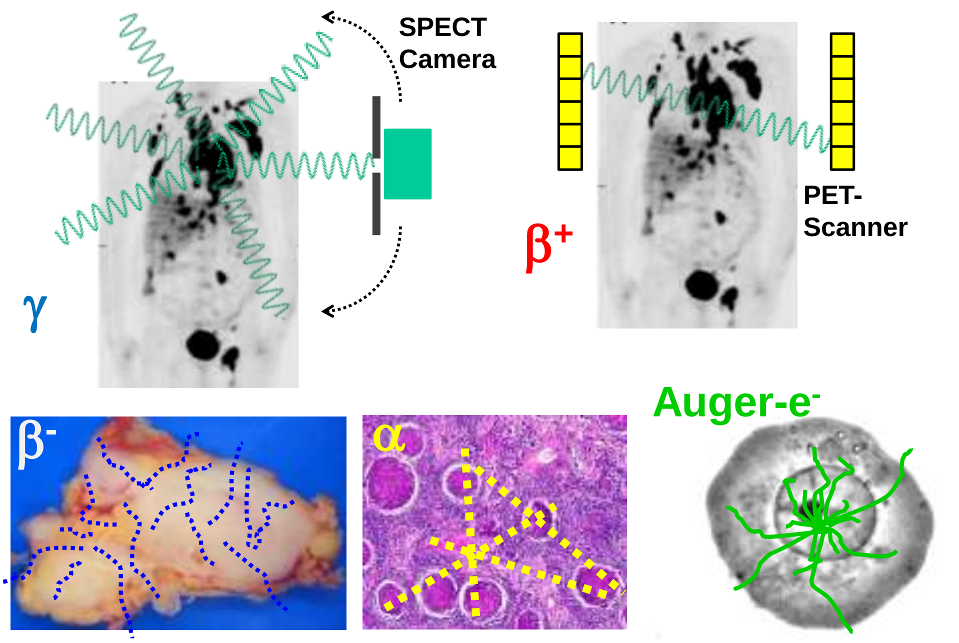
Tumour uptake, based on SPECT quantification



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

M. de Jong, ICTR-PHE 2012

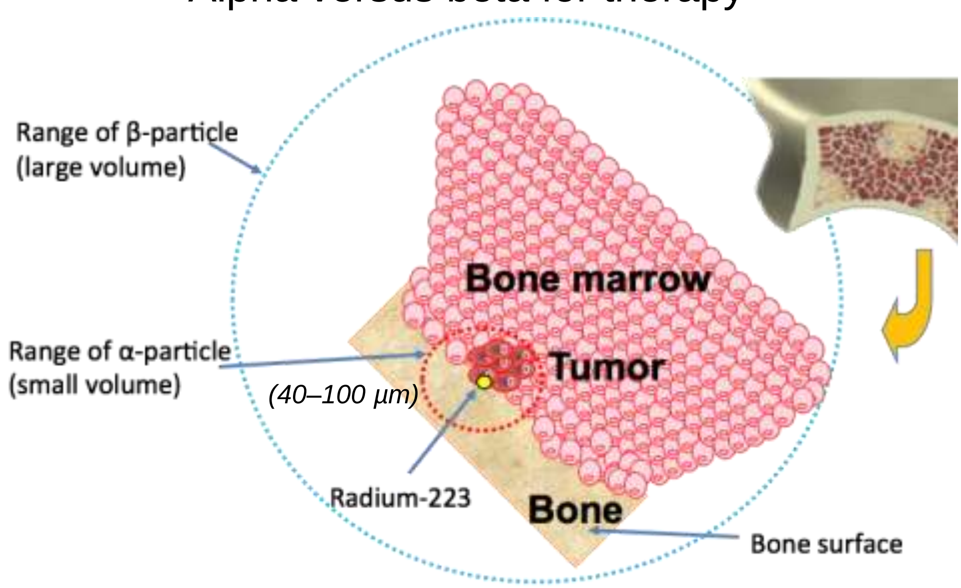
The Nuclear Medicine Alphabet



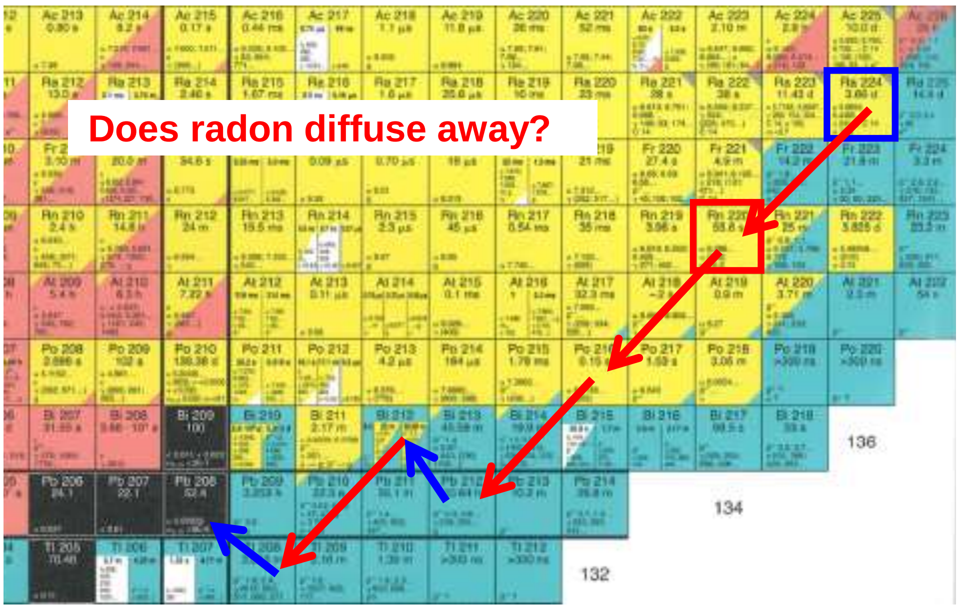
Radio-nuclide	Half-life	Daugh-ters	Half-life	Cumulative α/decay	E_α mean (MeV)	Range (μm)
Tb-149	4.1 h			0.17	3.97	25
Pb-212	*10.6 h*	Bi-212 Po-212	1.01 h 0.3 μs	1	7.74	65
Bi-212	1.01 h	Po-212	0.3 μs	1	7.74	65
Bi-213	*0.76 h*	Po-213	4 μs	1	8.34	75
At-211	7.2 h	Po-211	0.5 s	1	6.78	55
Ra-223	11.4 d	Rn-219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

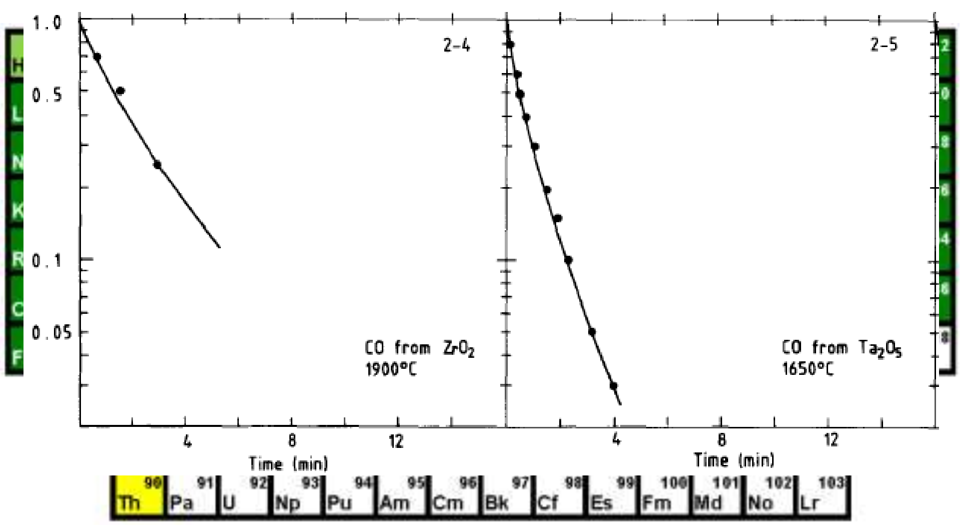
Alpha versus beta for therapy



Isotopes for targeted alpha therapy

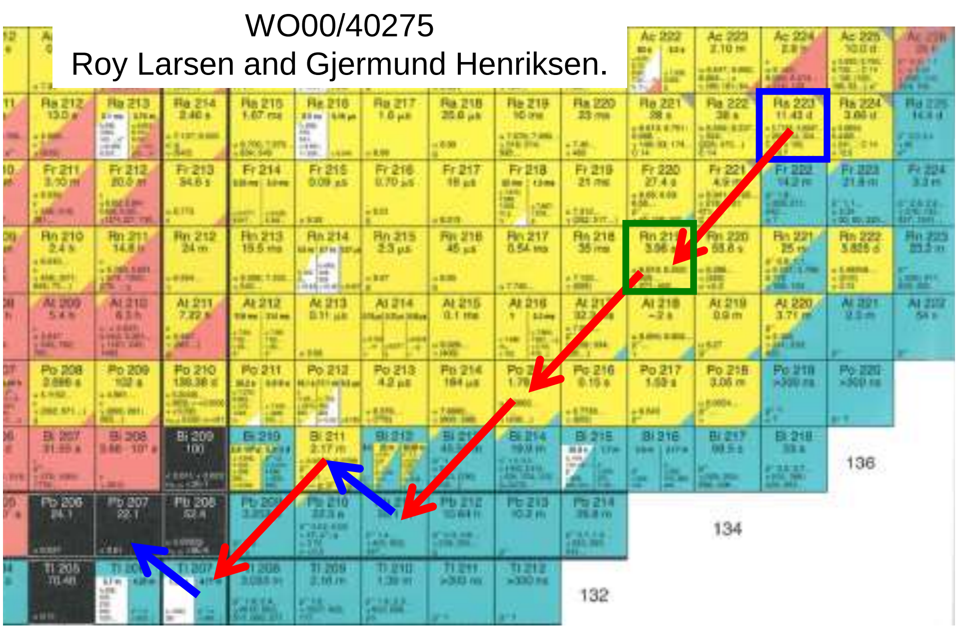


Radioisotopes available at ISOLDE-CERN

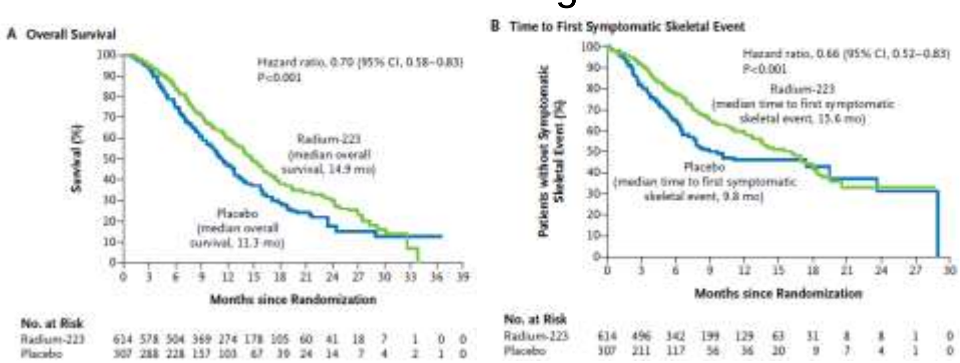


Diffusion and release measurements to develop new beams
e.g. ***P. Hoff et al., NIM 221 (1984) 313.***

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*

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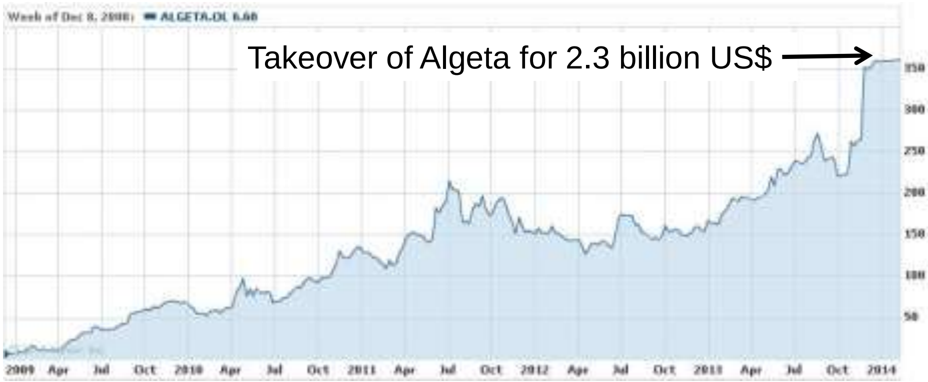
Prospects of targeted alpha therapies ?



Bayer HealthCare SANOFI AREVA Med 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

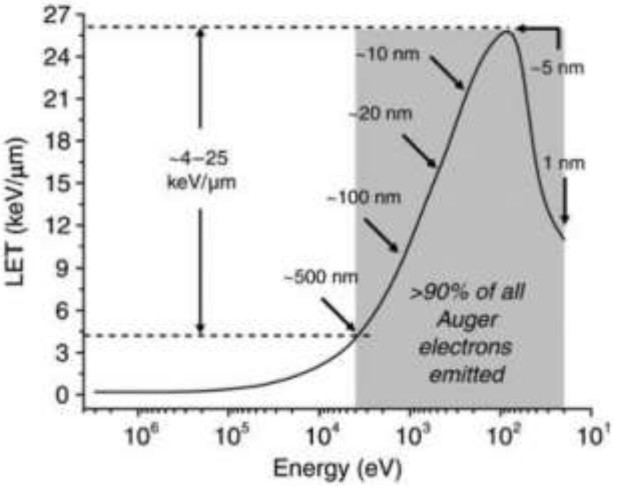
Established isotopes (Y-90, I-131)

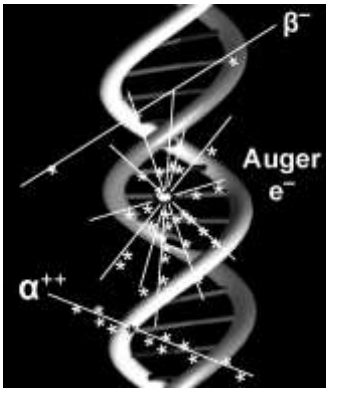
Emerging isotopes (Lu-177)

R&D isotopes: supply-limited! (Tb-161, Tb-149, Ge-71, Er-165)

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

Radiobiological effectiveness of Auger electrons





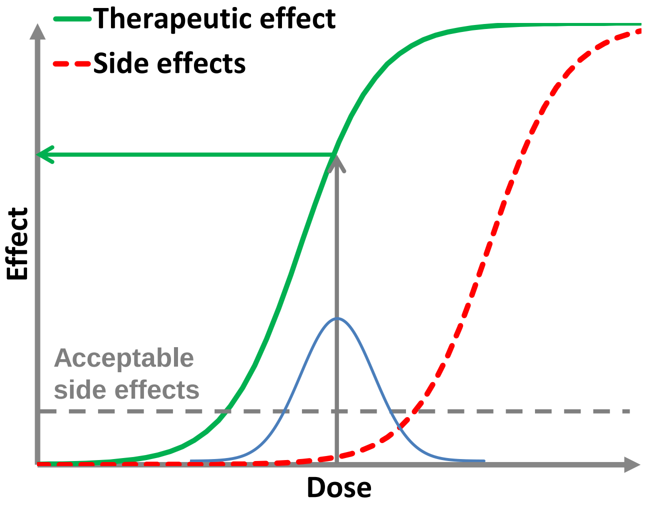
A.I. Kassis, Rad. Prot. Dosimetry 2011;143:241.

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.

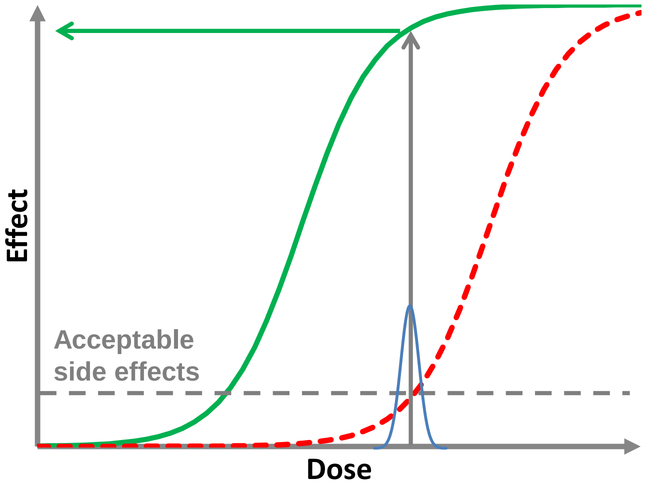
*C. Regaud, A. Lacassagne, Radiophysiologie et Radiotherapie **1927**;1:95.*

Theranostics



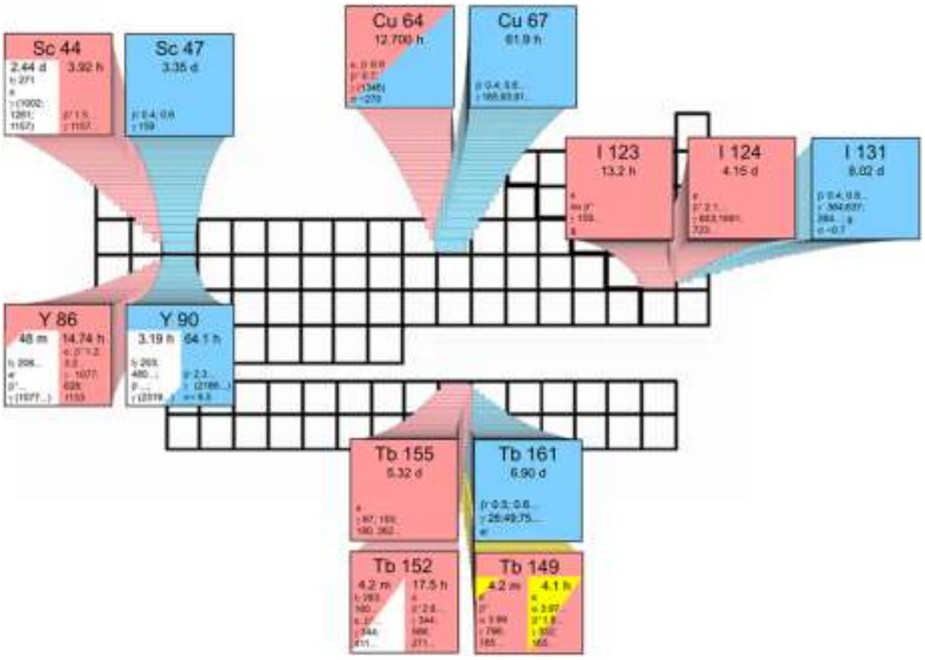
Accurate dosimetry is essential for optimum use of the therapeutic window.

Theranostics



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

Matched pairs for theranostics

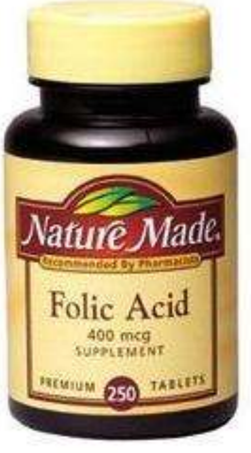


Terbium: a unique element for nuclear medicine

Folate-receptor positive cancers

Frequent overexpression of folate receptor in cancer of:

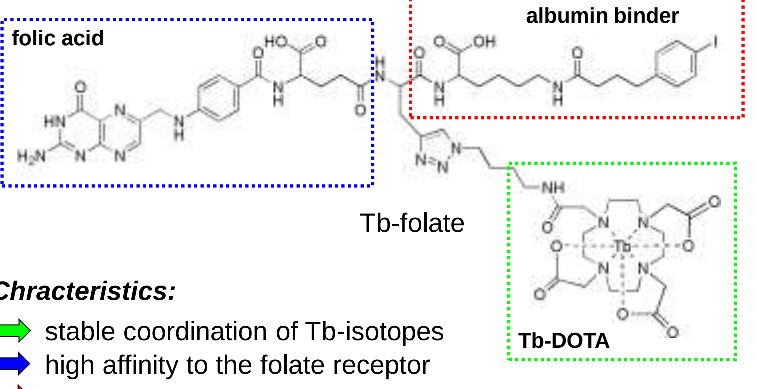
- ovaries
- cervix uteri
- lung
- kidney
- brain
- colon
- breast
- leukemia



folic acid = vitamine B9

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

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

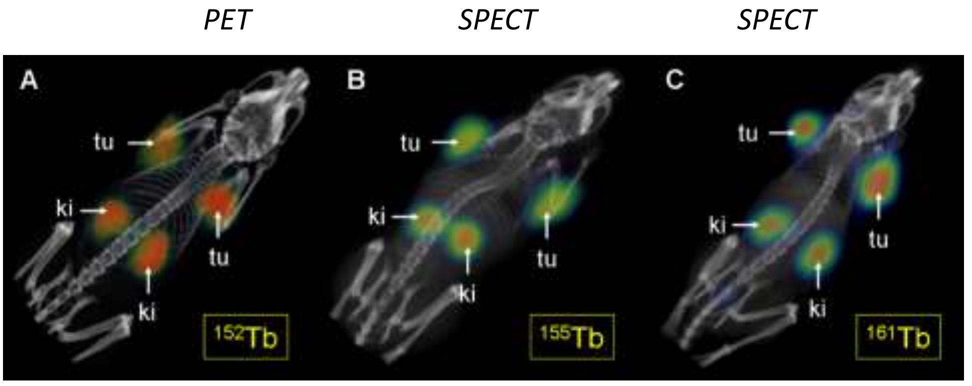


Tb-folate

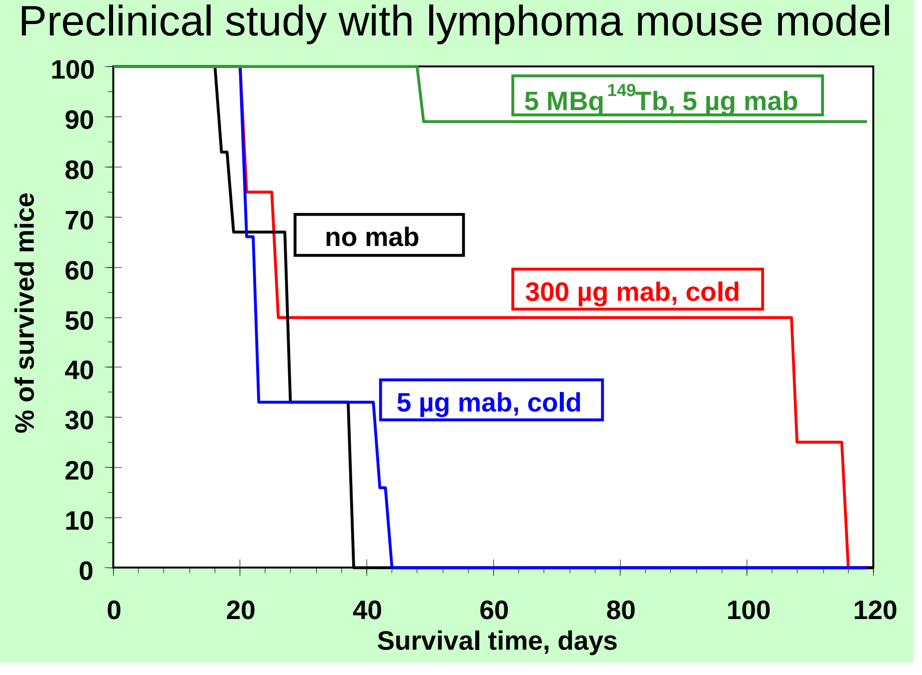
Chracteristics:

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

Theranostics with terbium isotopes



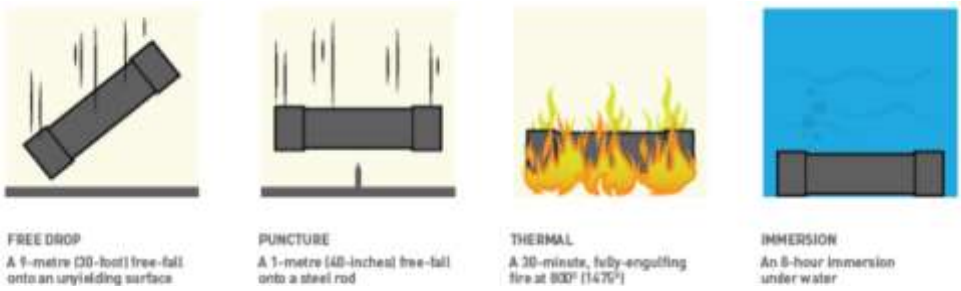
IS528 Collaboration: C. Müller et al., J. Nucl. Med. 2012;53:1951.



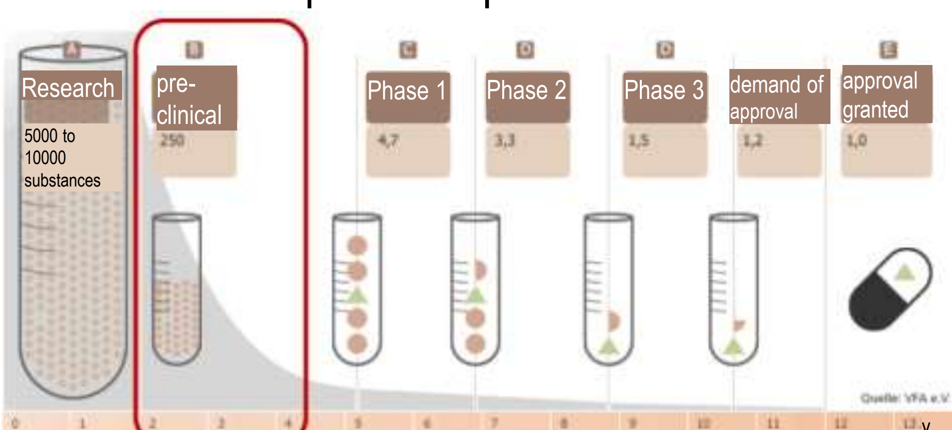
G.J. Beyer et al., Eur J Nucl Med Molec Imaging 2004:31;547.

Radioactive transport

Isotope	A2 (GBq)
^{18}F	600
^{99m}Tc	4000
^{131}I	700
^{177}Lu	700
^{211}At	500
^{161}Tb (βγ)	20
^{149}Tb (α)	0.09



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

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?

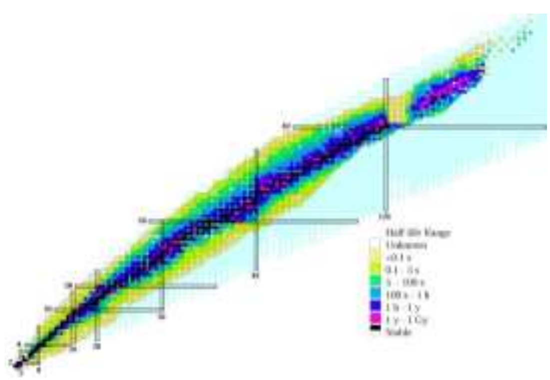
*"**A single infusion of ZEVALIN matched roughly 16 infusions of rituximab in terms of achieving the same increase in progression free survival.** I leave it up to the audience to draw conclusions about cost effectiveness. Thus, in conclusion, RIT represents the most effective single drug in the treatment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

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

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."

ESR	
1	Molecule (CO, CO2, CHx) breakup in RFQ
2	Facility development and safety (149/152Tb)
3	Charge breeding REX
4	Graphene coating of UCx target
5	RILIS installation at HUG (Lu, Tb, Er)
6	Mass separation of cyclotron produced radioisotopes (47Sc..)
7	U nanofiber target
8	Radiopharmaceuticals for Auger therapy (161Tb)
9	Tracers to follow tumour response in hadron therapy
10	Container for radioisotope shipping
11	Molecular beams (CO+, etc.)
CH1	Ovarian cancer bimodal imaging
CH2	RIT and imaging of ovarian cancer (translation preclinical>clinical)
CH3	Robotic placement of brachytherapy (brain, ovarian, pancreatic)
CH4	Radiopharmaceutical synthesis for ovarian cancer (fluorescent & PET)

"Main lines" of MEDICIS-PROMED

1. Mass separated isotopes, e.g. Tb
   (ESR2, 4, 5, 7, 10)

2. ^{11}C ("tracer ammunition" for hadron therapy)
   (ESR3, 9, 11, ESRCH1, 4)

3. Targeted therapies for ovarian cancer
   (ESR1, 6, 8, ESRCH2, 3)