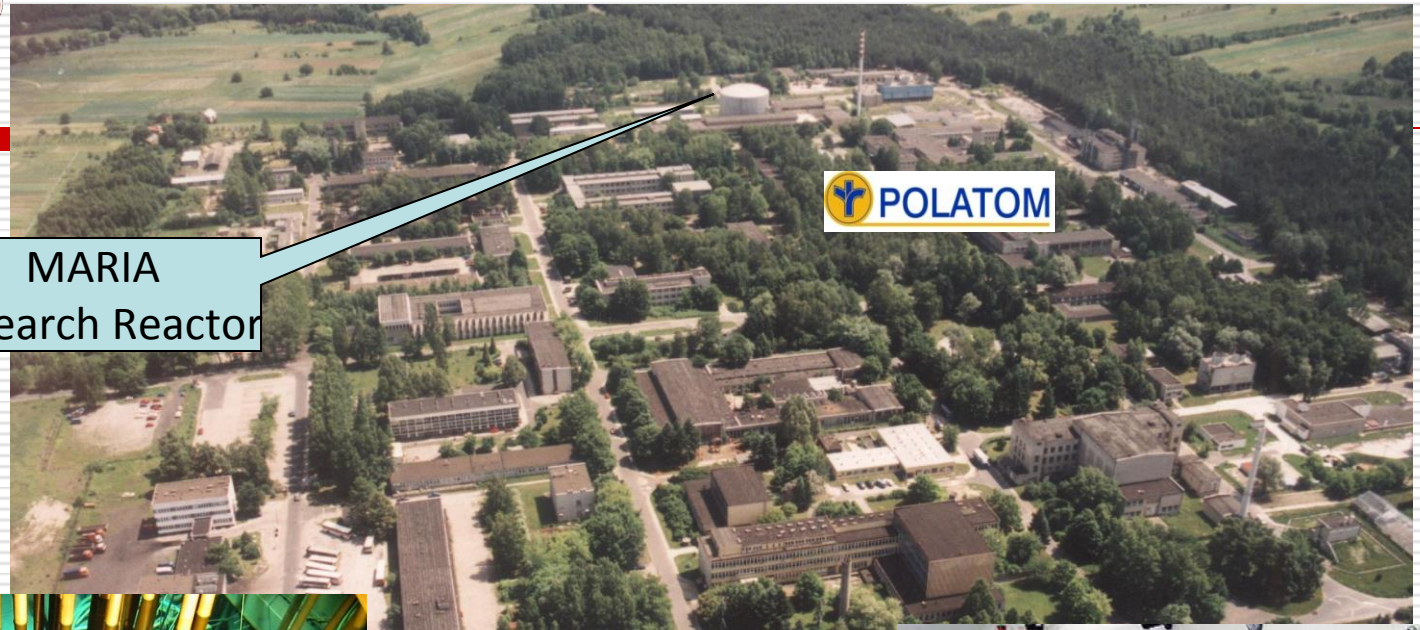
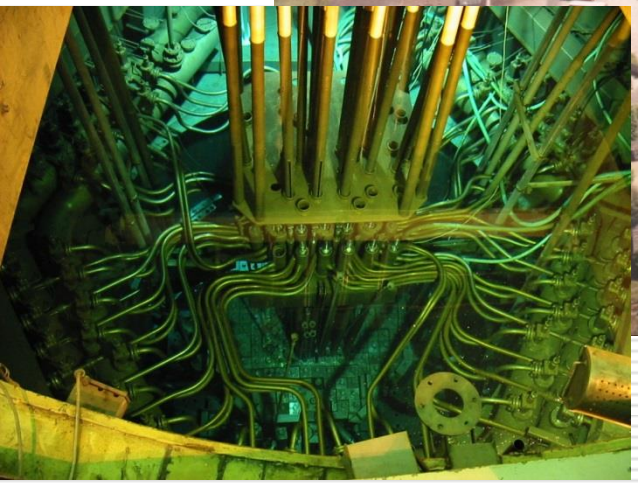
ELA-MAT PODKARPACKIE

Radionuclides and radiopharmaceuticals for therapy

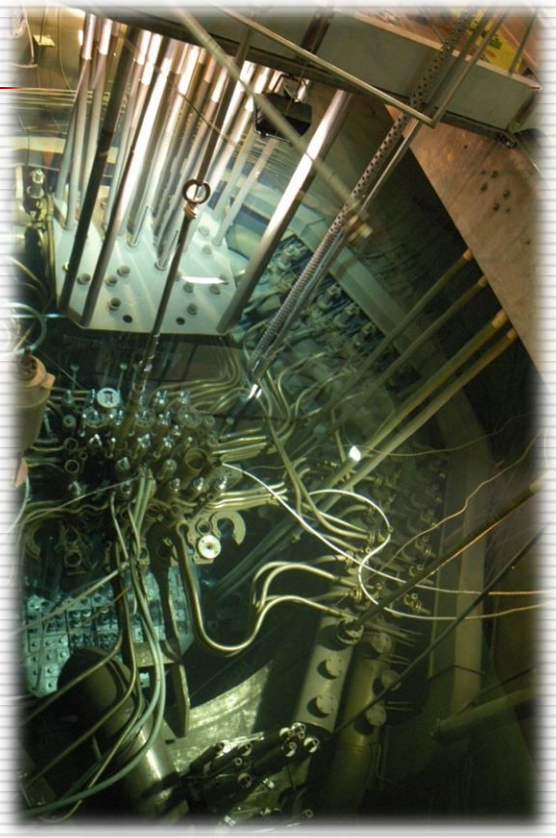
Renata Mikolajczak
NCBJ Radioisotope Centre POLATOM
05-400 Otwock, Poland

National Centre for Nuclear Research





Maria Research Reactor



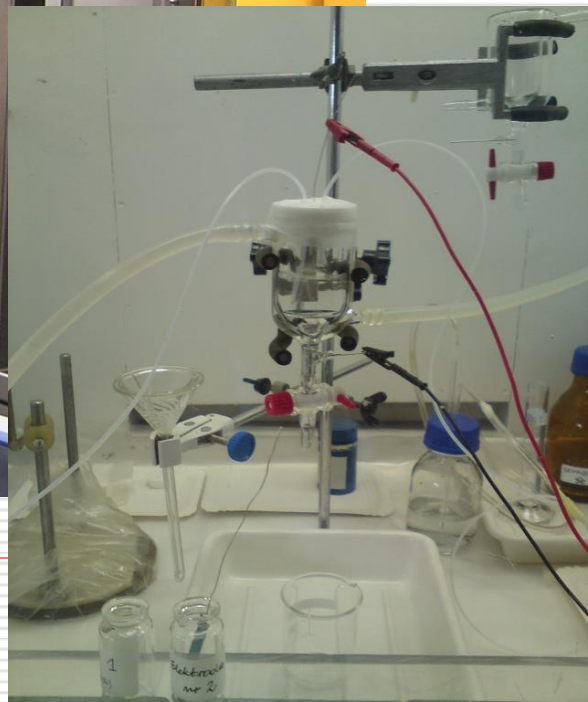
- The high flux research reactor MARIA is a water and beryllium moderated reactor of 30 MW power level;
- Pool type reactor with pressurized fuel channels containing concentric tube assemblies of fuel elements;
- Fuel channels are situated in matrix containing beryllium blocks surrounded by graphite reflector:
  - nominal power — 30 MW
  - thermal neutron flux density — 2.5×10^{14} n/cm^{2}s
  - moderator — H_2O, beryllium
  - reflector — graphite in Al
  - cooling system — channel type
- Operated since Dec. 16, 1974
- Expected operation time of reactor: 2030

MARIA RR started with fuel conversion program according to RERTR Initiative (Reduce Enrichment for Research and Test Reactors) is in progress *19.75% / 485 g U-235 per FE / density of 4.8 g/cm^3*
The first LEU type FE made by CERCA was loaded to the core on Sep'12

Radioisotope Centre POLATOM

- Division in the National Centre for Nuclear Research
- Research programs on the development of novel radiopharmaceuticals
- Results of our research programs and innovation activities can be directly implemented in the GMP certified production and QC facilities.

Hot-cells for production of ^{90}Y and ^{177}Lu

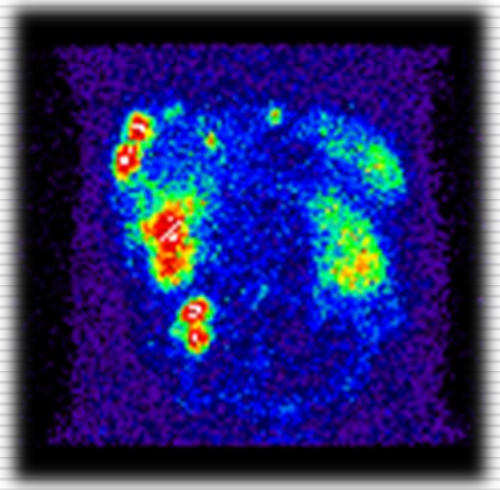


POLATOM

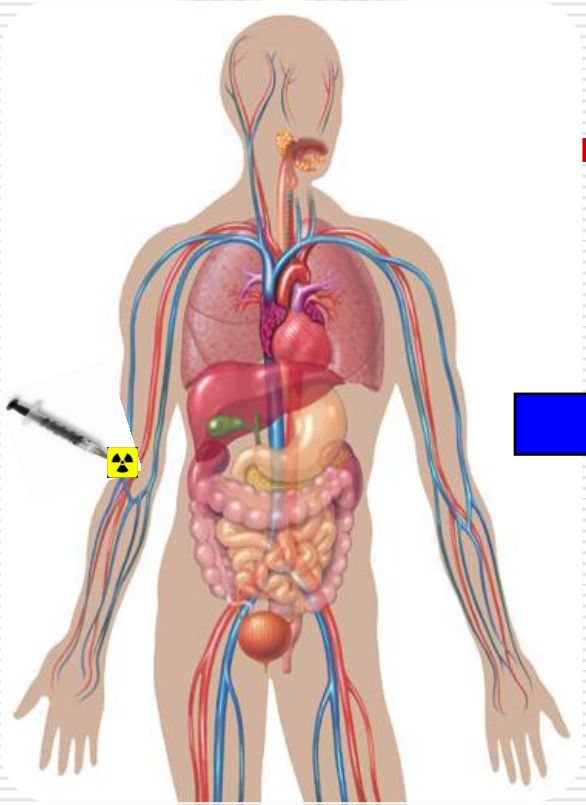
Hot cells for Iodine-131

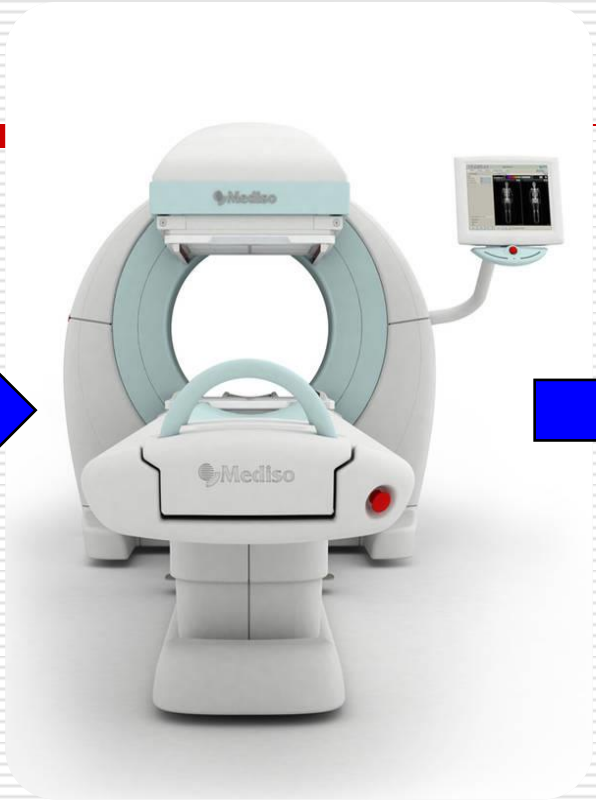
- ✓ dry distillation of TeO_2
- ✓ 1000 Ci of ^{131}I / week

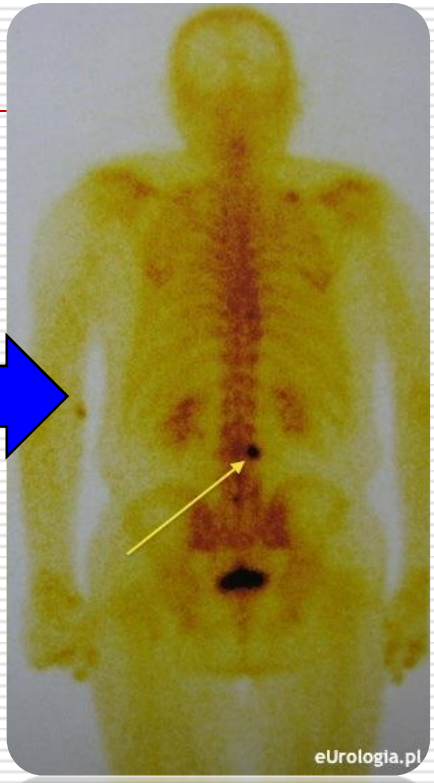
Nuclear Medicine



Radiopharmaceuticals







Radiopharmaceutical is administered to the patient, enters the blood stream and is then taken up selectively in targeted organ or tissue

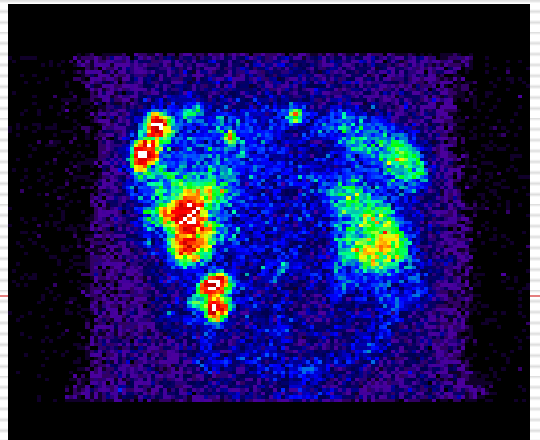
The emitted radiation, depending on its physical characteristics, is either used for visualization or for destroying the pathological tissue.

Radiopharmaceuticals

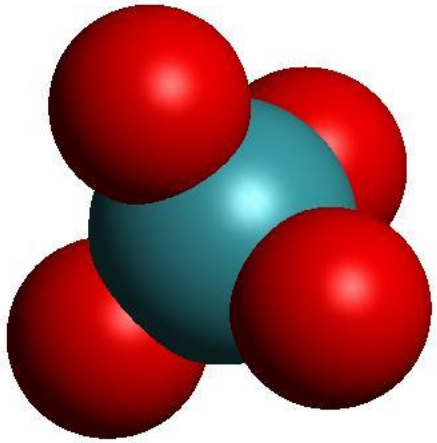
Radiopharmaceutical is a substance formed in a chemical combination of two components:

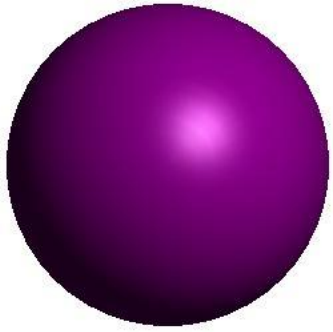
- **radionuclide**, radioactive isotope of certain element – radiation emitted by this isotope is either registered and allows imaging of tracer distribution in the patient's body or it can destroy the target tissue.

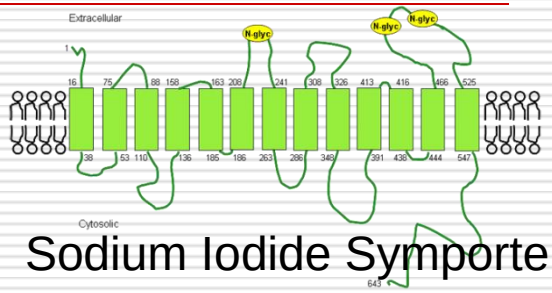
- **ligand**, chemical compound, molecule or cell which is selectively taken up, metabolized or actively taking part in the physiological process in the selected organ or tissue.



Tracer Concepts and Design



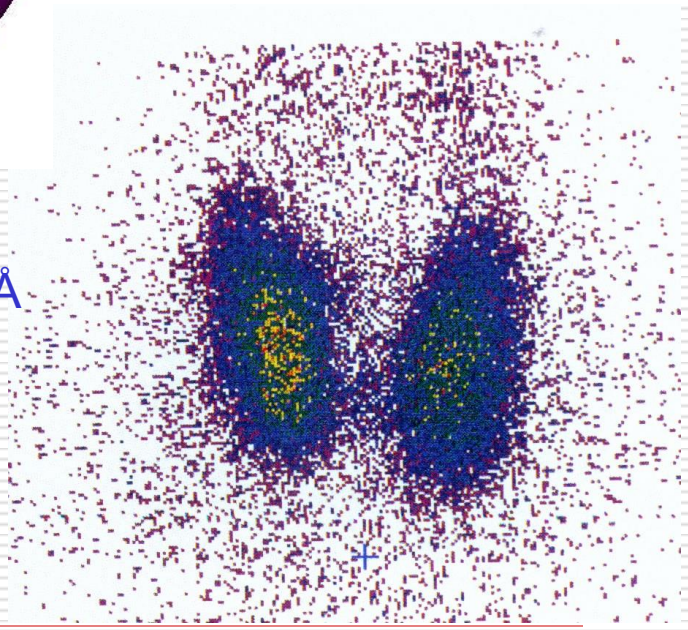




Sodium Iodide Symporter

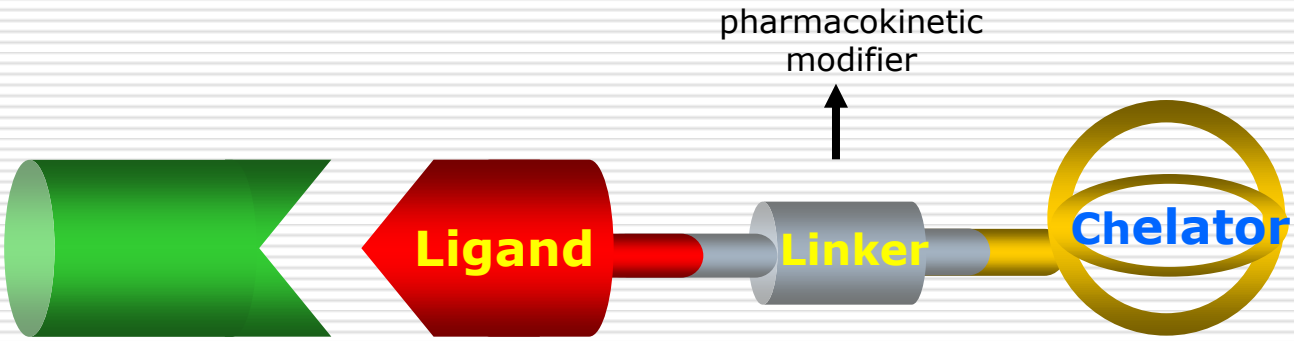
TcO_4^- vs. I^-

r = 2.52 Å 2.20 Å



Credit to B. Johannsen

Schematic Representation of a Drug for Imaging and Targeted Therapy



Target

- Antigens (CD20, HER2)
- GPCRs
- Transporters

Molecular Address

- Antibodies, their fragments and modifications
- Regulatory peptides and analogs thereof
- Amino Acids

Reporting Unit

- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{68}Ga
- Gd^{3+}

Cytotoxic Unit

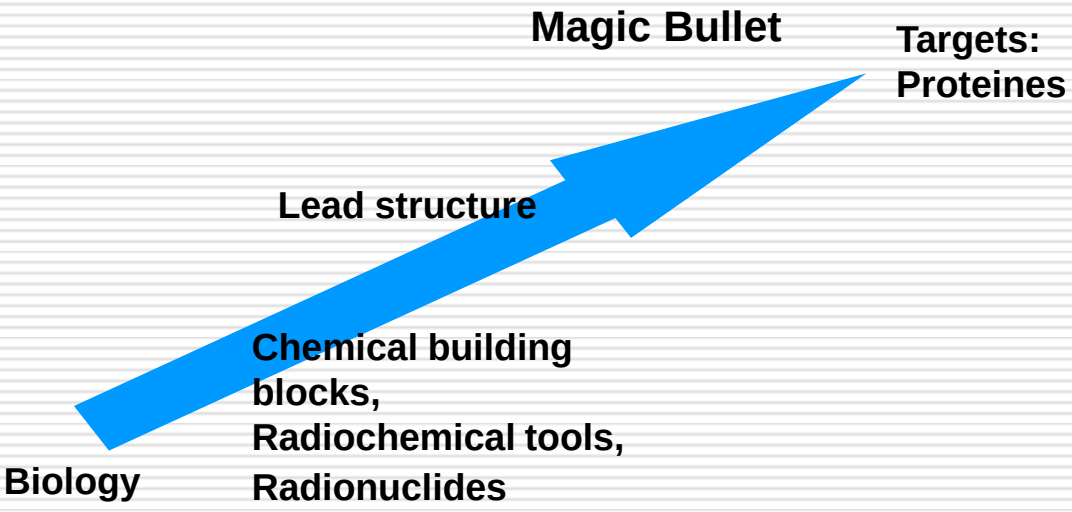
- ^{90}Y, ^{177}Lu, ^{213}Bi
- ^{105}Rh, ^{67}Cu, $^{186,188}Re$

Credit to H.R. Maecke

Theranostics: combination of diagnosis and therapy

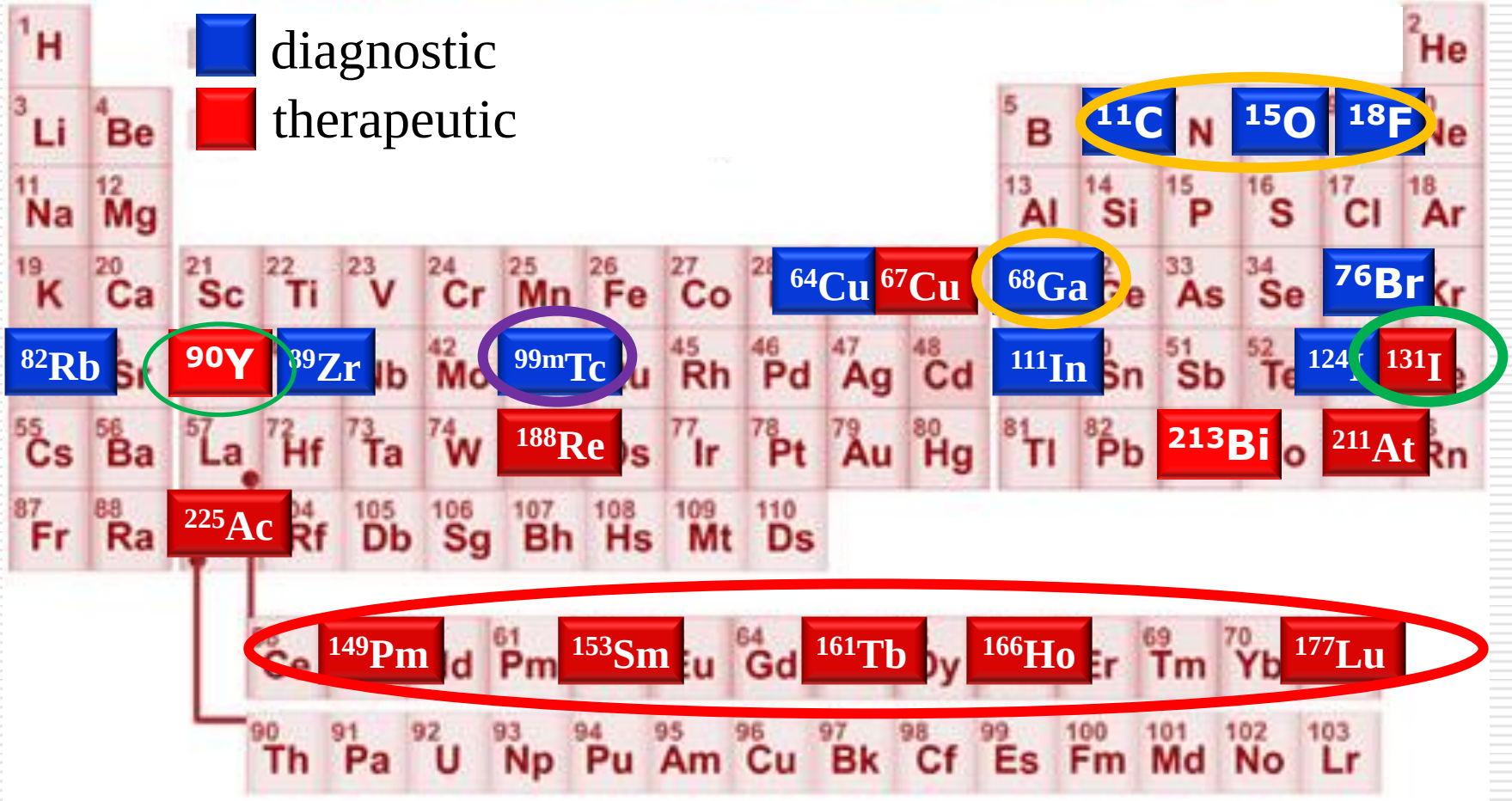
Personalized medicine/tailored medicine/

Matching the right drug for the right patient



Radionuclides

Suitable Radionuclides for Diagnosis and Therapy



Credit to B. Johannsen

Diagnostic Radionuclides

Gamma-Emitters

^{99m}Tc, ^{111}In, ^{67}Ga, ^{201}Tl, ^{123}I

Positron-Emitters

^{89}Zr, ^{68}Ga, ^{64}Cu, ^{11}C, ^{13}N, ^{15}O, ^{18}F

Therapeutic Radionuclides

Beta-Emitters

^{90}Y, $^{186/188}Re$, ^{177}Lu, ^{131}I, ^{165}Dy, ^{166}Ho, ^{105}Rh, ^{111}Ag

Alpha-Emitters

^{212}Bi, ^{213}Bi, ^{211}At, ^{255}Fm, ^{225}Ac

Theranostic pairs (matched pairs)

^{99m}Tc/ $^{186/188}Re$

^{111}In/ lanthanides, ^{90}Y

^{64}Cu/ ^{67}Cu

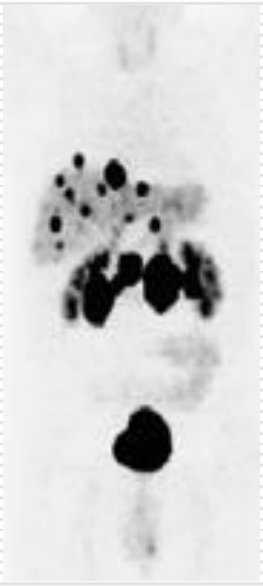
$^{123/124}I$/^{131}I

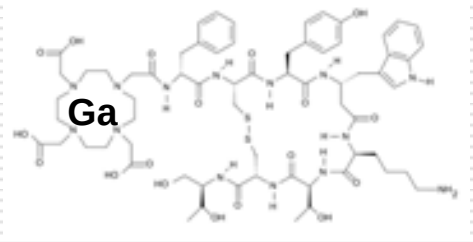
^{68}Ga/^{67}Ga (Auger)

^{43}Sc/^{44}Sc/^{47}Sc

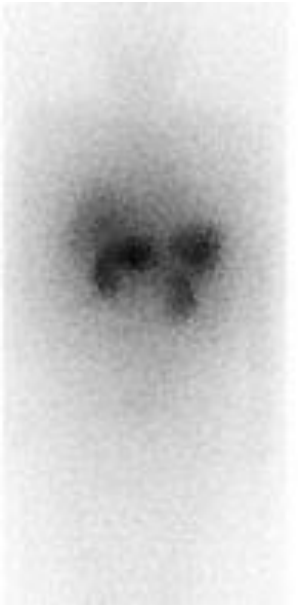
Radiopeptide Therapy in Neuroendocrine Tumors

^{68}Gallium – DOTATATE





^{90}Yttrium – DOTATATE



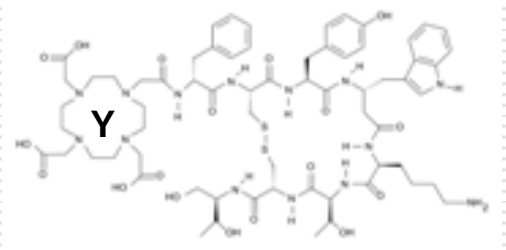


Image → **Treat**

Credit to H.R. Maecke

β^- radionuclides suitable for labelling molecules for targeted radiotherapy of tumors (produced in nuclear reactor)

Radioisotope	Half-life	Eβ- (max) meV	Eγ (%) keV	Production method	Approx. max range in tissue [mm]
^{186}Re	3.7 d	1.07	137 (9)	^{185}Re(n,γ)^{186}Re	3
^{188}Re	17 hr	2.11	155 (15)	^{187}Re(n, γ) ^{188}Re, ^{188}W/^{188}Re generator	8
^{177}Lu	6.7 d	0.5	113 (6.4), 208 (11)	^{176}Lu (n, γ)^{177}Lu, ^{176}Yb (n,γ) ^{177}Yb→^{177}Lu	2
^{90}Y	2.7 d	2.27	-	^{90}Sr/^{90}Y generator	12
^{105}Rh	1.4 d	0.57, 0.25	319 (19), 306 (5)	^{104}Rn(n,γ)^{105}Rn→^{105}Rh	2
^{149}Pm	2.2 d	1.07	286 (3)	^{148}Nd (n,γ)^{149}Nd→^{149}Pm	3
^{153}Sm	1.95 d	0.69, 0.64	103 (30), 70 (5)	^{152}Sm(n, γ)^{153}Sm	2
^{166}Ho	1.1 d	1.85, 1.77	80 (6), 1379 (1)	^{164}Dy (n, γ)^{165}Dy (n,γ)^{166}Dy→^{166}Ho	9
^{32}P	14.3 d	1.71	-	^{32}S(n,p) ^{32}P	8.2
^{169}Er	9.6 d	0.34	-	^{168}Er(n,γ)^{169}Er	2
^{131}I	8.0 d	0.6	364 (81), 637 (7)	^{130}Te (n, γ)^{131}Te→^{131}I	2
^{111}Ag	7.5 d	0.81	342 (6)	^{110}Pd (n, γ) ^{111}Pd→^{111}Ag	2
^{67}Cu	2.4 d	0.57	184 (48), 92 (23)	^{67}Zn(n,p)^{67}Cu	2
^{47}Sc	3.35d	0.6, 0.44	159 (68)	^{47}Ti(n,p)^{47}Sc, ^{46}Ca(n,γ)^{47}Ca→^{47}Sc	2
^{199}Au	3.2 d	0.46	158 (37), 208 (8)	^{198}Pt(n,γ)^{199}Pt→^{199}Au	2

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^{177}Lu	6.7 d	0.5	113 (6.4), 208 (11)	^{176}Lu (n, γ)^{177}Lu, ^{176}Yb (n,γ) ^{177}Yb→^{177}Lu	**2**
^{90}Y	2.7 d	2.27	-	^{90}Sr/^{90}Y generator	**12**
^{105}Rh	1.4 d	0.57, 0.25	319 (19), 306 (5)	^{104}Rn(n,γ)^{105}Rn→^{105}Rh	2
^{149}Pm	2.2 d	1.07	286 (3)	^{148}Nd (n,γ)^{149}Nd→^{149}Pm	3
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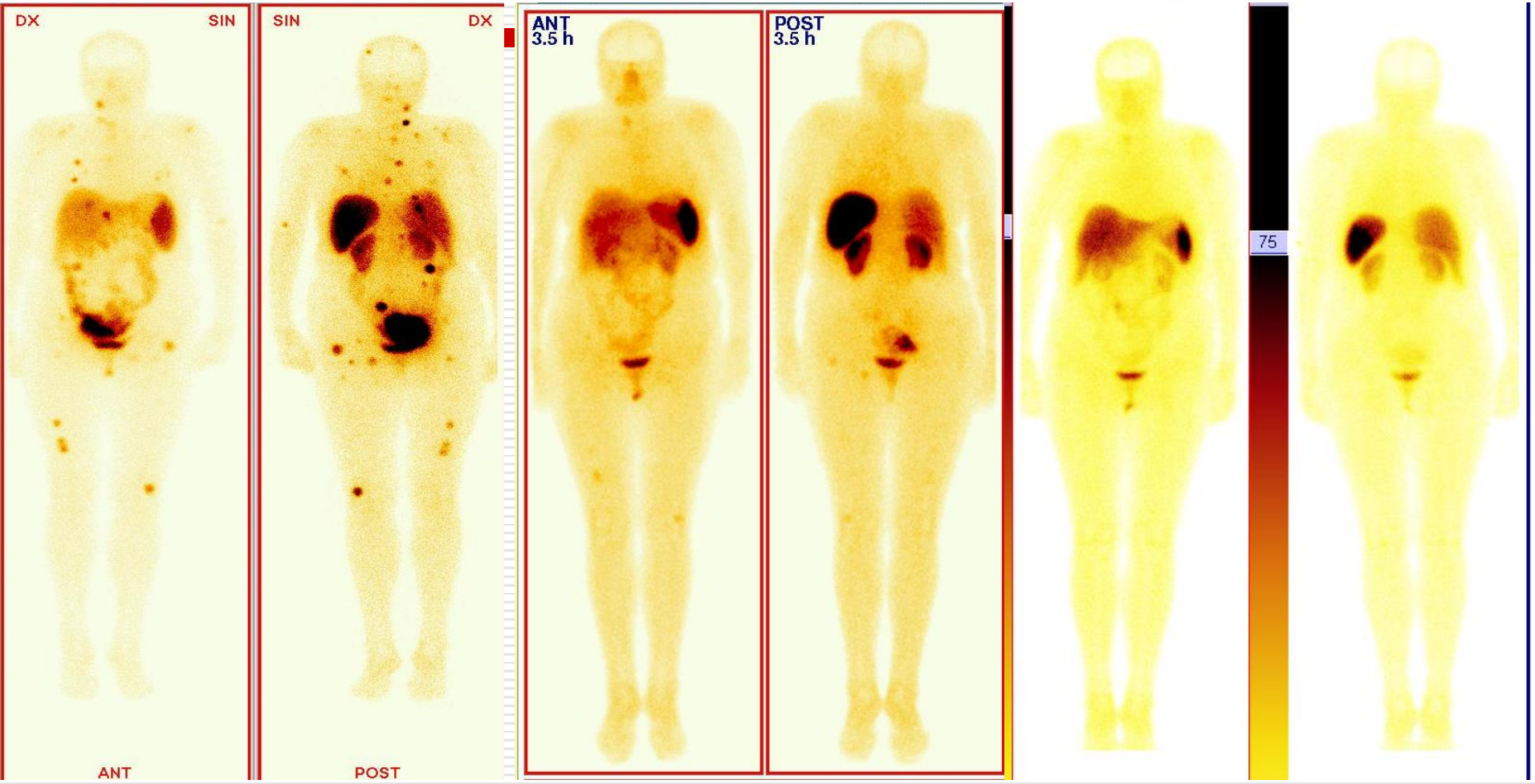
^{67}Cu	2.4 d	0.57	184 (48), 92 (23)	^{67}Zn(n,p)^{67}Cu	2
^{47}Sc	3.35d	0.6, 0.44	159 (68)	^{47}Ti(n,p)^{47}Sc, ^{46}Ca(n,γ)^{47}Ca→^{47}Sc	2

Comparison between clinical results of PRRT with ^{90}Y-DOTATATE and ^{90}Y/^{177}Lu-DOTATATE

J.Kunikowska, et al. Clinical results of radionuclide therapy of neuroendocrine tumors with ^{90}Y-DOTATATE and tandem ^{90}Y/^{177}Lu-DOTATATE cocktail – which is a better therapy option? *Eur J Nucl Med. Mol Imaging 2011*

Effect of treatment with $^{90}Y/^{177}Lu$ DOTA-TATE



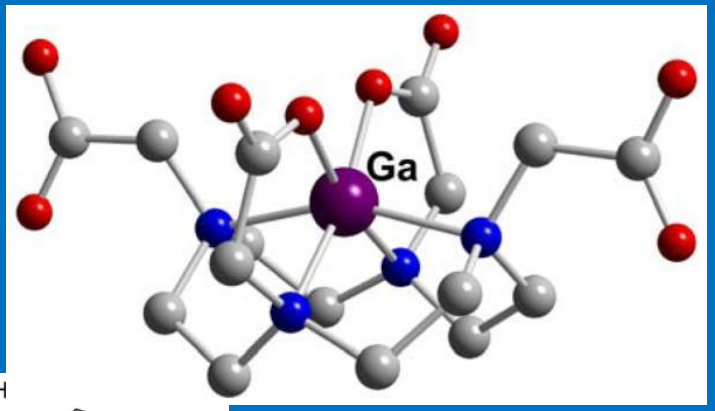
Before therapy

12 months follow-up

24months follow-up

DOTA-TATE

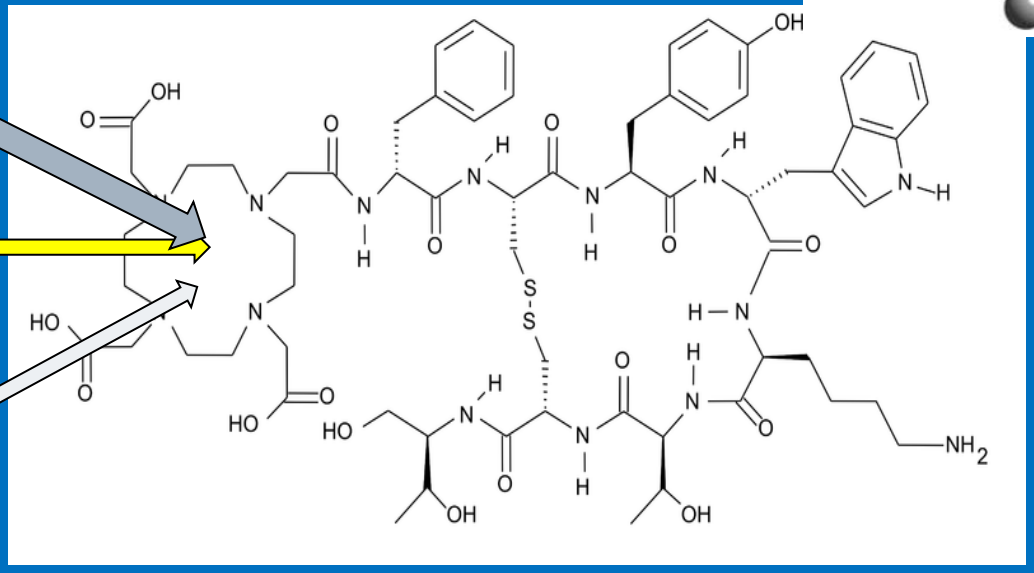
DOTA-somatostatin analogue



^{68}Ga

$^{177}Lu^{3+}$

^{90}Y



^{44}Sc and ^{47}Sc

^{44}Sc is a positron emitter (Eβ^+ 1475.4 keV with 94.27% positron branching) and gamma radiation component of 1157 keV(99.9%).

^{47}Sc ($T_{1/2}$ = 3.35 d) is emitting β^- radiation with max. energy 0.600 MeV (31.6%) and 0.439 MeV (68.4%) γ radiation of 159.4 keV (63.3%) suitable for imaging.

Matched β^+/β^- pairs

- $^{44}Sc/^{47}Sc$
- $^{64}Cu/^{67}Cu$
- $^{86}Y/^{90}Y$
- $^{124}I/^{123/131}I$

^{47}Sc and ^{67}Cu can be produced in nuclear reactor and in cyclotron

The „twin" isotope of the same element can be used for diagnostic imaging or therapy follow up, while the other is used for therapy using the same carrier molecules.

Matched Radionuclide Pairs for Imaging and Therapy (edited by A. Bockish)
Eur J Nucl Med Mol Imaging, Vol 38, Suppl 1, June 2011

β^- radionuclides suitable for labelling molecules for targeted radiotherapy of tumors (produced in nuclear reactor)

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^{105}Rh	1.4 d	0.57, 0.25	319 (19), 306 (5)	^{104}Rn(n,γ)^{105}Rn→^{105}Rh	2
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^{67}Cu	2.4 d	0.57	184 (48), 92 (23)	^{67}Zn(n,p)^{67}Cu	2
^{47}Sc	3.35d	0.6, 0.44	159 (68)	^{47}Ti(n,p)^{47}Sc, ^{46}Ca(n,γ)^{47}Ca→^{47}Sc	2
^{199}Au	3.2 d	0.46	158 (37), 208 (8)	^{198}Pt(n,γ)^{199}Pt→^{199}Au	2

^{44}Sc and ^{47}Sc as matched pair for molecular imaging

^{44}Sc

Due to the half life ($T_{1/2}$ = 3.92h) almost 4 times as long as the half life of ^{68}Ga ($T_{1/2}$ = 67.71 min) it is an attractive candidate for development of novel PET-radiopharmaceuticals.

^{47}Sc

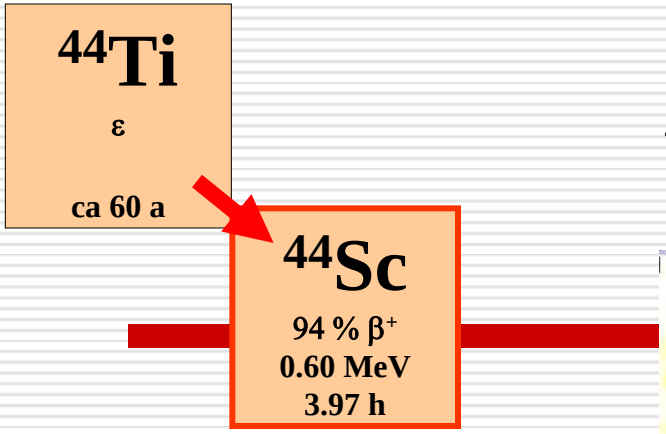
can be utilized in radiotherapy using the same vector molecules

Mean range in tissue	**^{47}Sc -**	**810 µm**
	^{177}Lu –	**670 µm**
	^{90}Y –	**3900 µm**

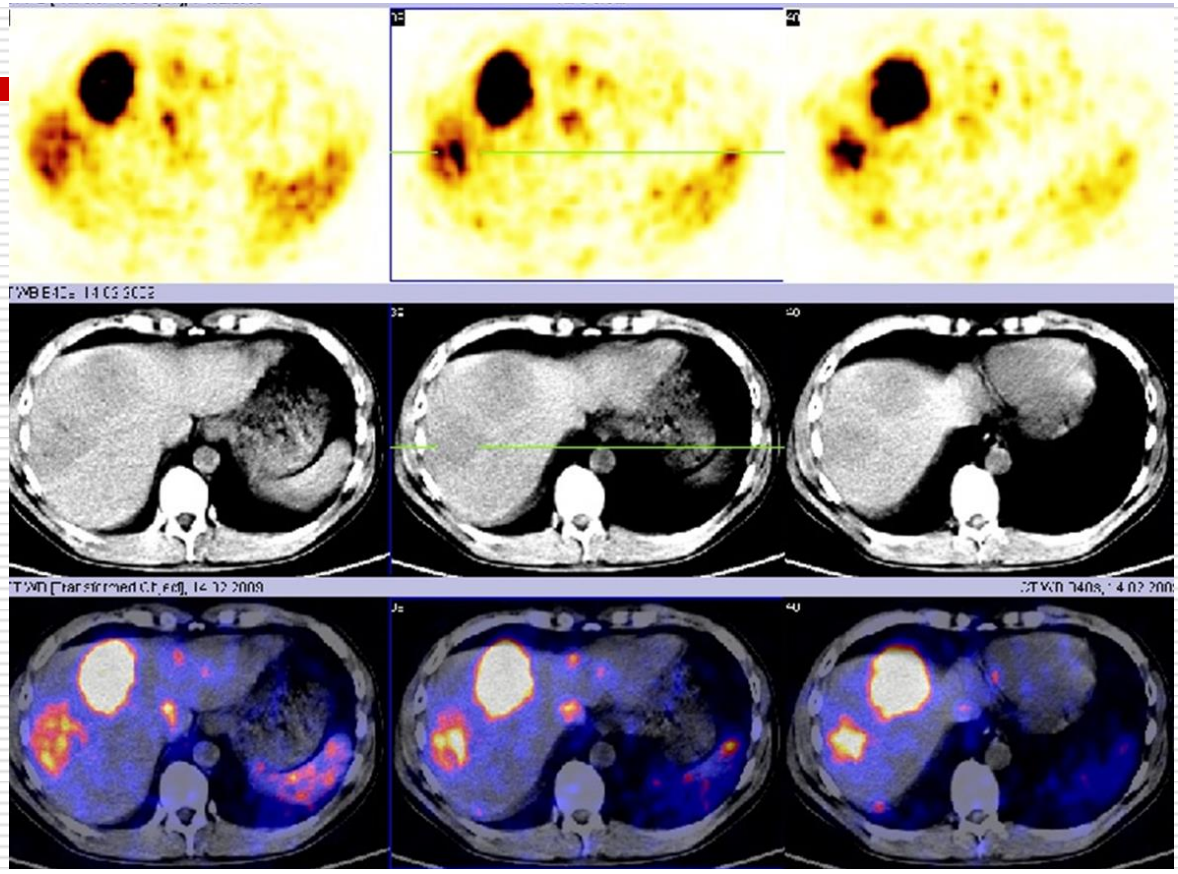
Both radionuclides can create a **matched pair** and their clinical application may bring additional value, particularly in combination with ligands requiring longer observation time than in case of ^{18}F or ^{68}Ga labeled molecules.

Matched Radionuclide Pairs for Imaging and Therapy (edited by A. Bockish)
Eur J Nucl Med Mol Imaging, Vol 38, Suppl 1, June 2011

^{44}Sc: development of PET-tracers



^{44}Sc-DOTA-TOC PET/CT: 18 h p.i.



^{44}Sc-DOTA-TOC
for dosimetric interest
and long-term imaging

Pruszyński M, Majkowska-Pilip M, Loktionova NS, Rösch F
Radiolabeling of DOTATOC with the longer-lived, generator-derived positron emitter ^{44}Sc

Pruszyynski M, Loktionova NS, Filosofov DV, Rösch F,
Post-elution processing of ^{44}Ti/^{44}Sc generator-derived ^{44}Sc for clinical application
Appl Radiat Isot 68 (2010) 1636-1641

Dept. of Nuclear Medicine/P.E.T. Center, Zentralklinik Bad Berka

JG|U
JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Radioisotopes of Sc with medical potential

Radionuclide	Reaction	Half-life	β energies	γ energies
^{47}Sc	^{48}Ti(p,2p)^{47}Sc ^{50}Ti(p,2p2n)^{47}Sc ^{47}Ti(n,p)^{47}Sc ^{46}Ca(n,γ)^{47}Sc	3.35 d	0.6 (32%) 0.44 (68%)	159 keV (68%)
$^{44/44m}$Sc	^{44}Ca(d,2n)^{44}Sc	3.97 h / 58.6 h	0.632 MeV	511 keV (94.72%) / 511 keV (100%)
^{44}Sc/^{44}Ti	Generator available	3.97 h	0.632 MeV	511 keV (94.72%)
^{43}Sc	^{nat}Ti(p,x) ^{47}Ti(p,nα) ^{48}Ti(p,2nα)	3.89 h	0.825 (17.2%) 1.198 (70.9%)	511 keV (100%)

Collaborative project carried out by Institute of Nuclear Chemistry and Technology, Heavy Ion Laboratory, UW, NCBJ POLATOM

Scandium-47

The n.c.a. **^{47}Sc** can be produced by proton irradiation in accelerators and in a nuclear reactor.

In neutron irradiation there are 2 ways possible:

$^{47}Ti(n,p)^{47}Sc$

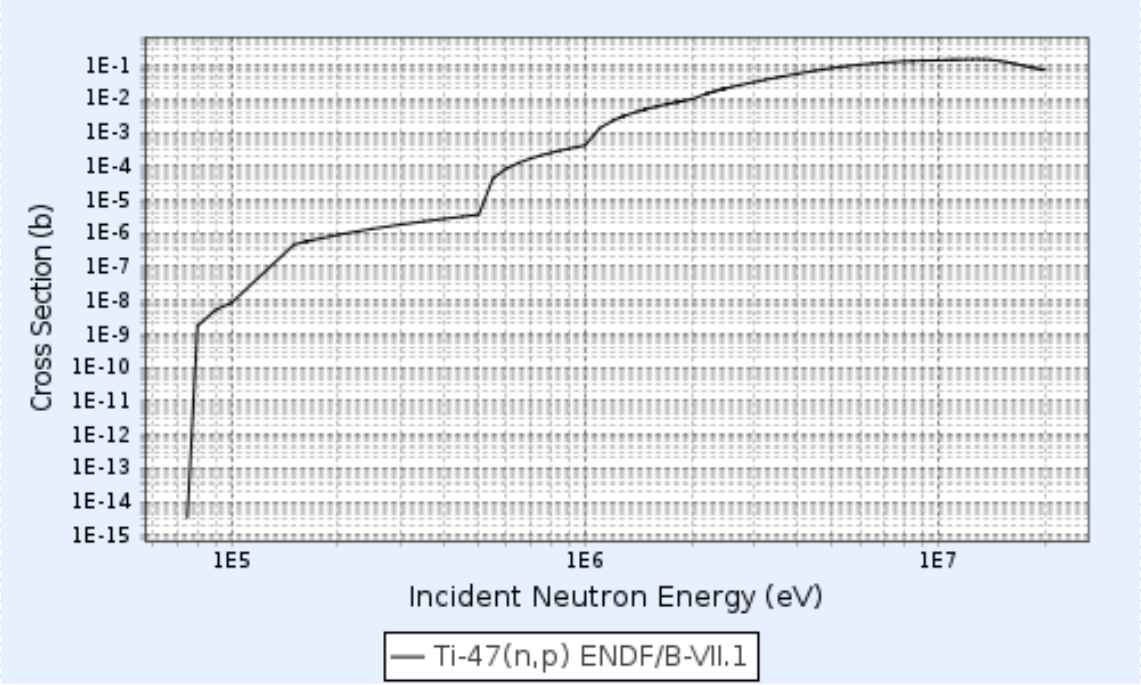
$^{46}Ca(n,\gamma)^{47}Ca$ and consecutive β-decay of ^{47}Ca

both routes require further chemical separation

L.F. Mausner, K.L. Kolsky, V.Joshi and S.C.Srivastava.Radionuclide development at BNL for nuclear medicine therapy. Appl Radiat Isot (1998) 49; 285-294

K. L. Kolsky, V. Joshi, L. F. Mausner and S. C. Srivastava. Radiochemical purification of no-carrier-added scandium-47 for radioimmunotherapy Appl Radiat Isot (1998) 49; 1541-1549

Neutron-induced cross sections for ^{47}Ti (n,p) reaction



http://atom.kaeri.re.kr/nuchart/#

Estimations for ^{47}Sc production by neutron activation

Target material , activation site	^{46}Sc [Bq]	^{47}Sc [Bq]	^{48}Sc[Bq]
Ti nat Maria	$6.0*10^3$	**$1.6*10^5$**	$2.0*10^4$
Ti nat ELAMAT	$6.9*10^4$	**$1.8*10^6$**	$2.1*10^5$
^{47}Ti 92% Maria	$8.5*10^2$	**$2.2*10^6$**	$2.3*10^4$
^{47}Ti 92% ELAMAT	$8.4*10^3$	**$2.0*10^7$**	$2.2*10^4$

Irradiation time – 7 days, mass of target Ti – 1 mg, target enrichment ^{47}Ti 92%
Fast neutron flux [$n \times cm^{-2}s^{-1}$]: Maria $1*10^{13}$ ELAMAT $1*10^{14}$

Constraints for neutron irradiation of targets for production of medical isotopes

- enriched target materials
- neutron flux /neutron cross sections
- facilities for tagret irradiation
- transport of irradiated materials
- processing of irradiated target metrial
- pharmaceutical development

Multidisciplinary approach, collaboration between groups of various expertise – international programs

Acknowledgements

Helmut R Maecke, Basel
Marion de Jong, Rotterdam
W.A.P. Breeman, Rotterdam
Richard Baum, Bad Berka

Alicja Hubalewska-Dydejczyk, Krakow
Katarzyna Fröss, Krakow
Anna Staszczak, Krakow
Jaroslaw B. Cwikla, Warsaw
Jolanta Kunikowska, Warsaw
Leszek Krolicki, Warsaw
Clemens Decristoforo
and Radiopharmacy Committee

D. Pawlak, B. Janota, W. Wojdowska, P. Garnuszek
E. Koumarianou Radioisotope Centre POLATOM

COST TD1004 – Theragnostics Imaging and Therapy: An Action to Develop Novel Nanosized Systems for Imaging-Guided Drug Delivery (2011-2015), leader of WG1 Imaging reporters for theranostic agents and in
COST CM1105 - Functional metal complexes that bind to biomolecules (2012–2016)