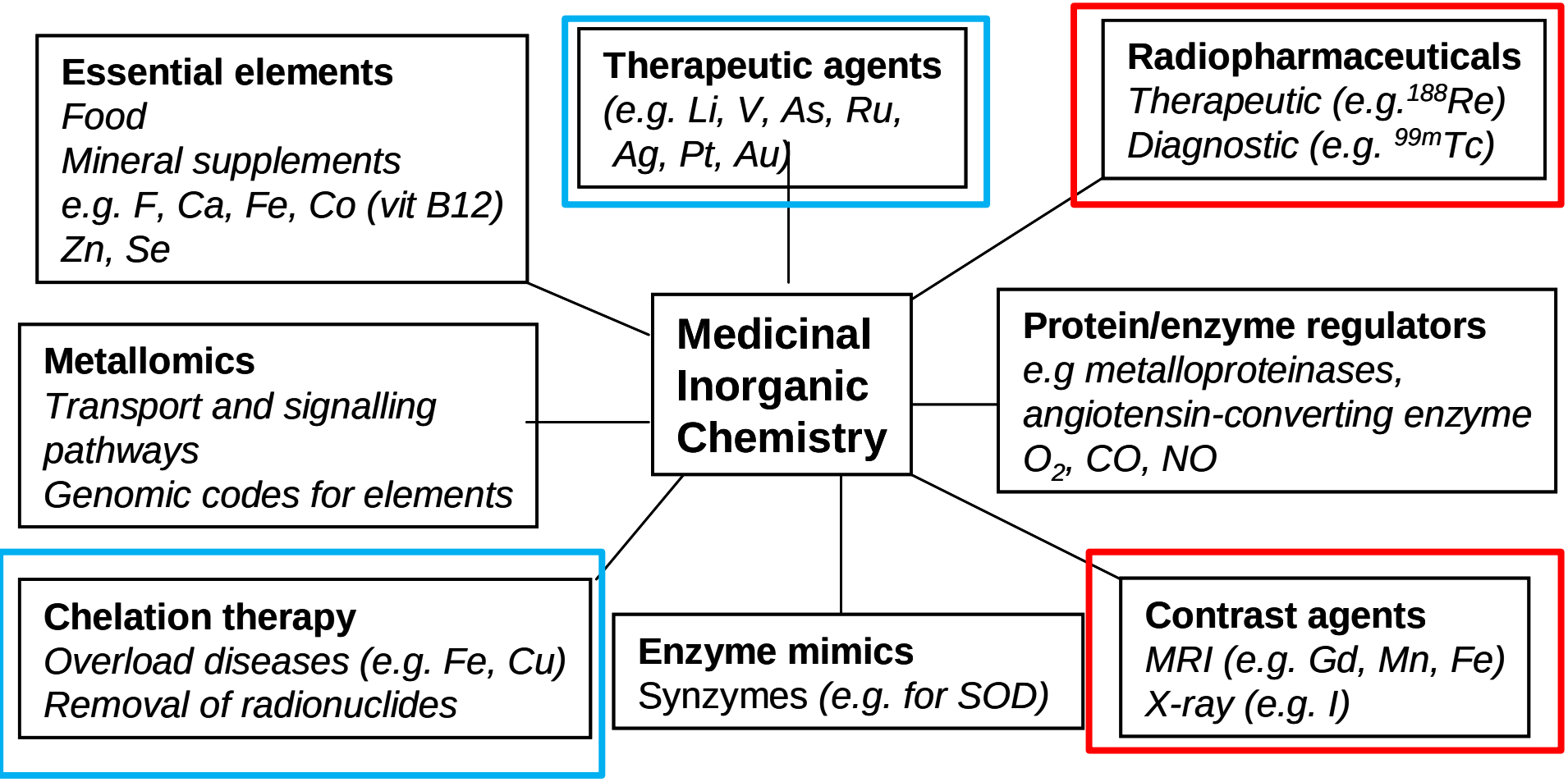
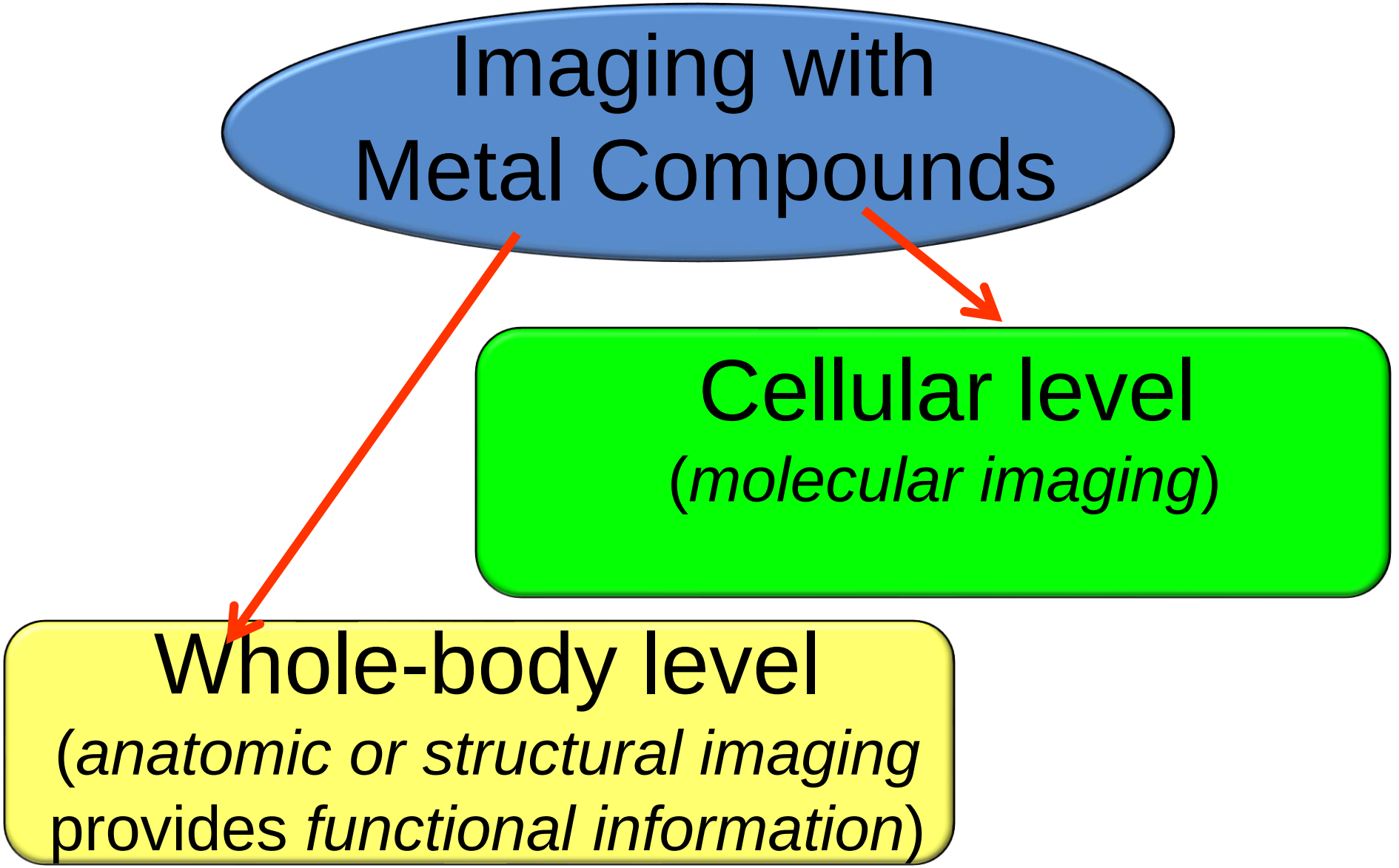
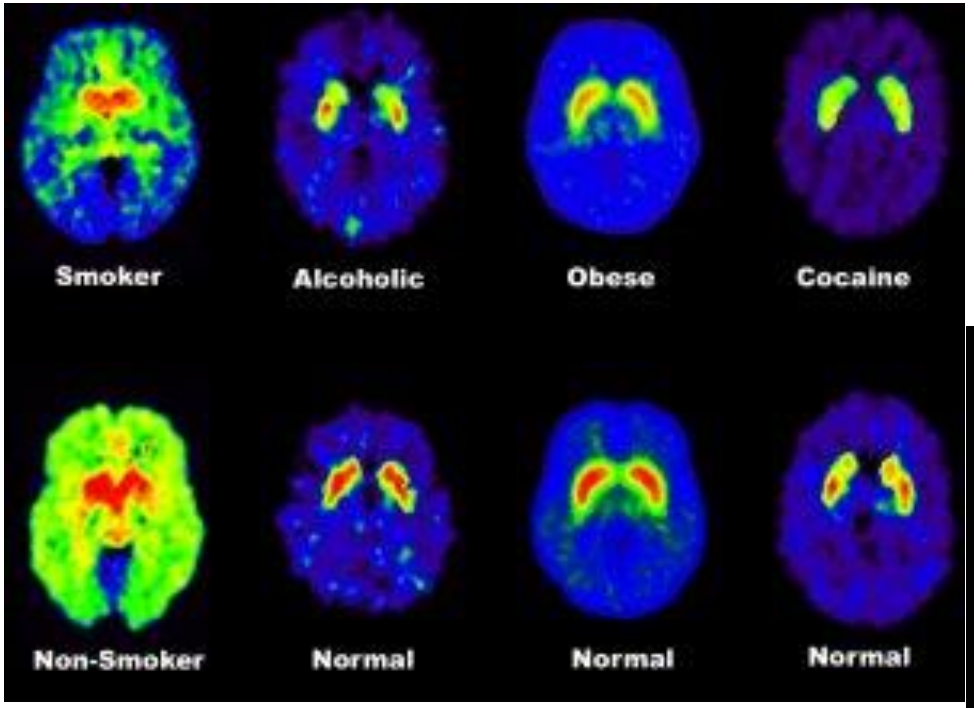
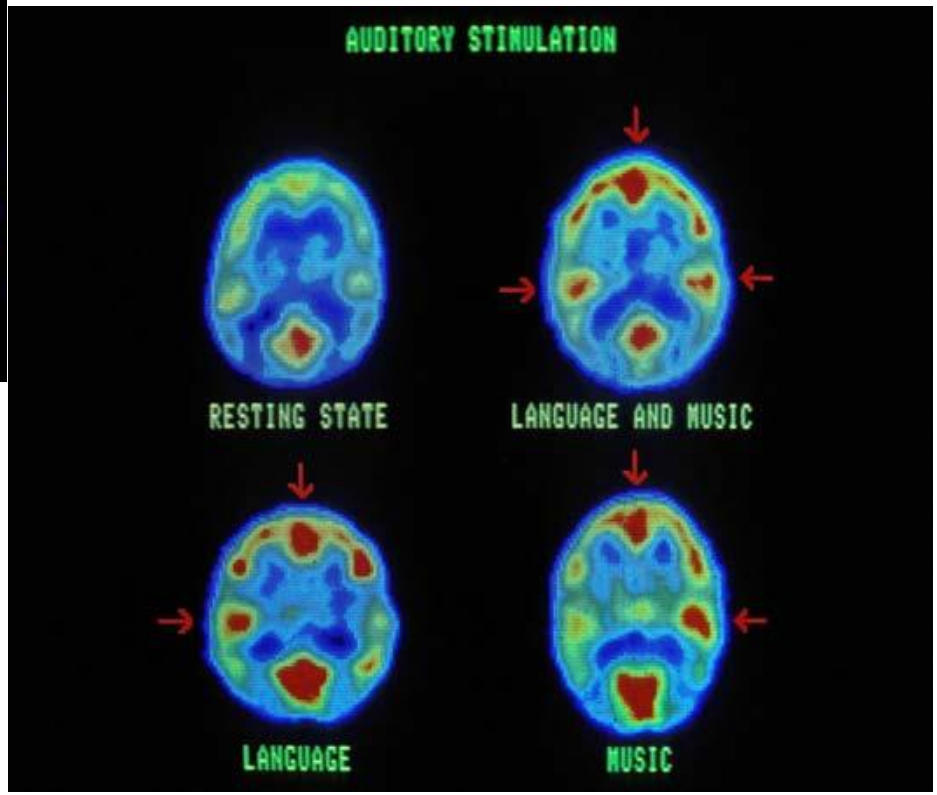

Essential elements
Food
Mineral supplements
e.g. F, Ca, Fe, Co (vit B12)
Zn, Se
Therapeutic agents
(e.g. Li, V, As, Ru,
Ag, Pt, Au)
Radiopharmaceuticals
Therapeutic (e.g. 188Re)
Diagnostic (e.g. 99mTc)
Medicinal Inorganic Chemistry
Metallomics
Transport and signalling pathways
Genomic codes for elements
Protein/enzyme regulators
e.g metalloproteinases, angiotensin-converting enzyme
O2, CO, NO
Chelation therapy
Overload diseases (e.g. Fe, Cu)
Removal of radionuclides
Enzyme mimics
Synzymes (e.g. for SOD)
Contrast agents
MRI (e.g. Gd, Mn, Fe)
X-ray (e.g. I)


Imaging with
Metal Compounds
Cellular level
(*molecular imaging*)
Whole-body level
(*anatomic or structural imaging*
provides *functional information*)

Definition of molecular imaging (2007): *molecular imaging concerns the visualization, characterization, and measurement of biological processes at the molecular or cellular level in humans or other living organisms*.

Molecular Imaging





Spontaneous processes in radioactive nuclei

- Emission of particles (α, β-, β+)
- Electron capture (EC or ε)
- Emission of radiation (X, γ ray)

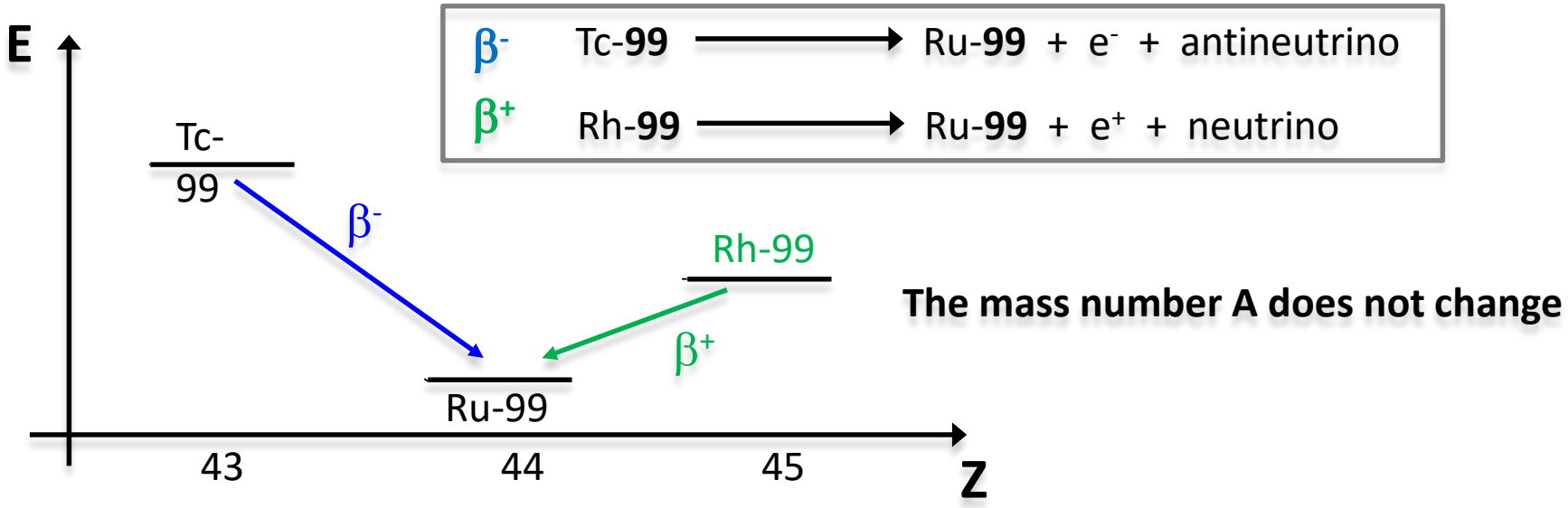
Both β+ emission and electron capture formally transform a proton into a neutron.

β+ emission occurs when $\Delta E_{pf} > 1.022$ MeV

Electron capture occurs when $\Delta E_{pf} < 1.022$ MeV

Radioactivity: Why are nuclei unstable?

a chemical **energy scheme**



β^-	Tc-**99**	⟶	Ru-**99** + e^- + antineutrino
β^+	Rh-**99**	⟶	Ru-**99** + e^+ + neutrino

The mass number A does not change

➡ Isobars have the **same number** of internucleon interactions

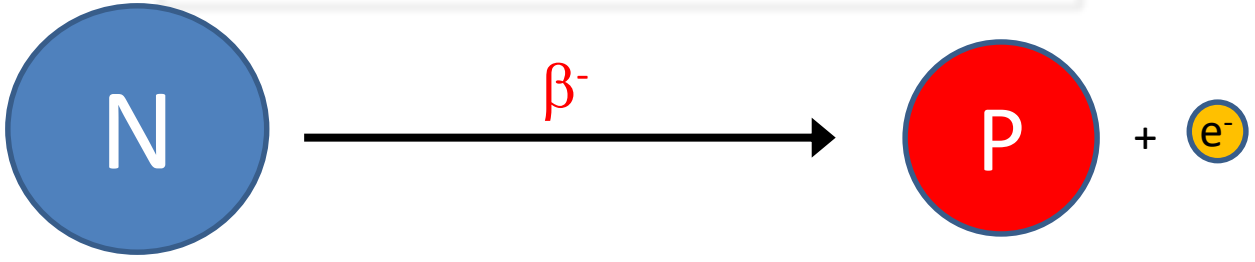
➡ One combination n-p ; p-p ; n-n must be **the most favorable one**, hence the most stable nucleus

➡ All other combinations n/p are higher in energy, **hence unstable**

Radioactivity: Decay modes

stability on the atomic nucleus scale **means MASS**, hence, **the lighter the more stable**

Neutron:	m_n	= 1.0086647 a.u.
Proton:	m_p	= 1.007276 a.u.
(Electron):	m_e	= $5.485799 \cdot 10^{-4}$ a.u.



the proton is by 0.0013887 amu **lighter than a neutron**

the mass of an electron is 0.0005485799 amu

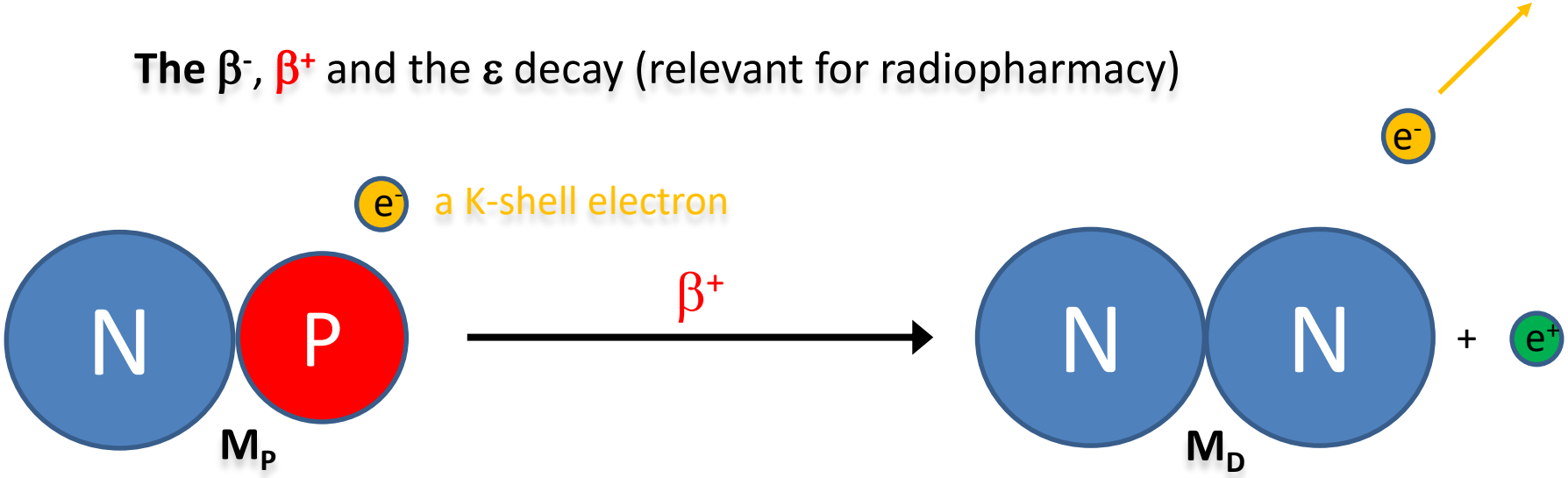
The mass difference $\Delta m = m_n - (m_p + m_e)$ is thus 0.000840121 amu corresponds to 0.78MeV energy

Thus, a **free neutron** **decays** into a proton and an electron (and an antineutrino)

is exactly what is **experimentally found** $n \rightarrow p^+ + e^- + (^0_0\bar{\nu})$ ($t_{½}$ = 10.4 min, β^- = 0.78MeV)

A model decay

The β^-, β^+ and the ε decay (relevant for radiopharmacy)



the new nucleus looses a shell electron with m_e = 0.0005485 amu

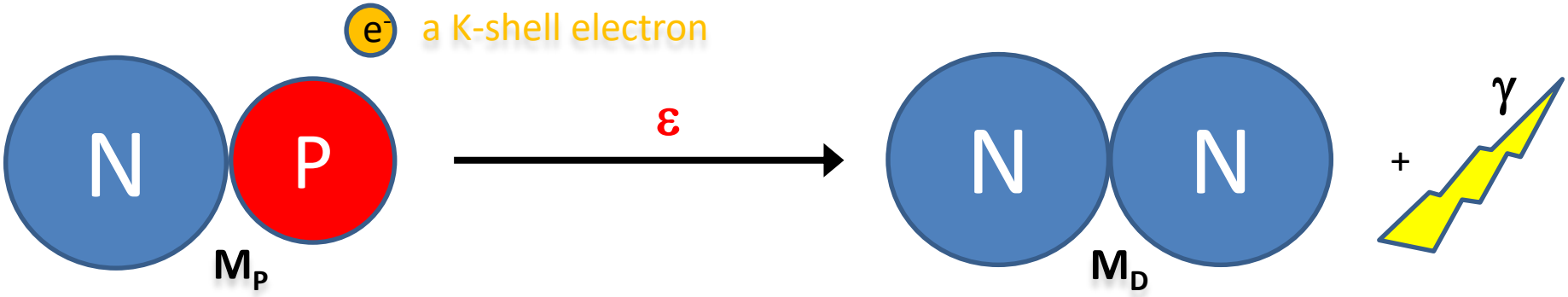
in addition, **we generate a β^+** particle with m = 0.0005485 amu

in total, **we generate a mass** = 0.001097 amu = 1.022MeV

Thus, if the new nucleus has **less than 1.022MeV additional binding energy,** the β^+ decay is uphill and **will not happen**

Radioactivity: Decay modes

The β^-, β^+ and the ε decay (relevant for radiopharmacy)



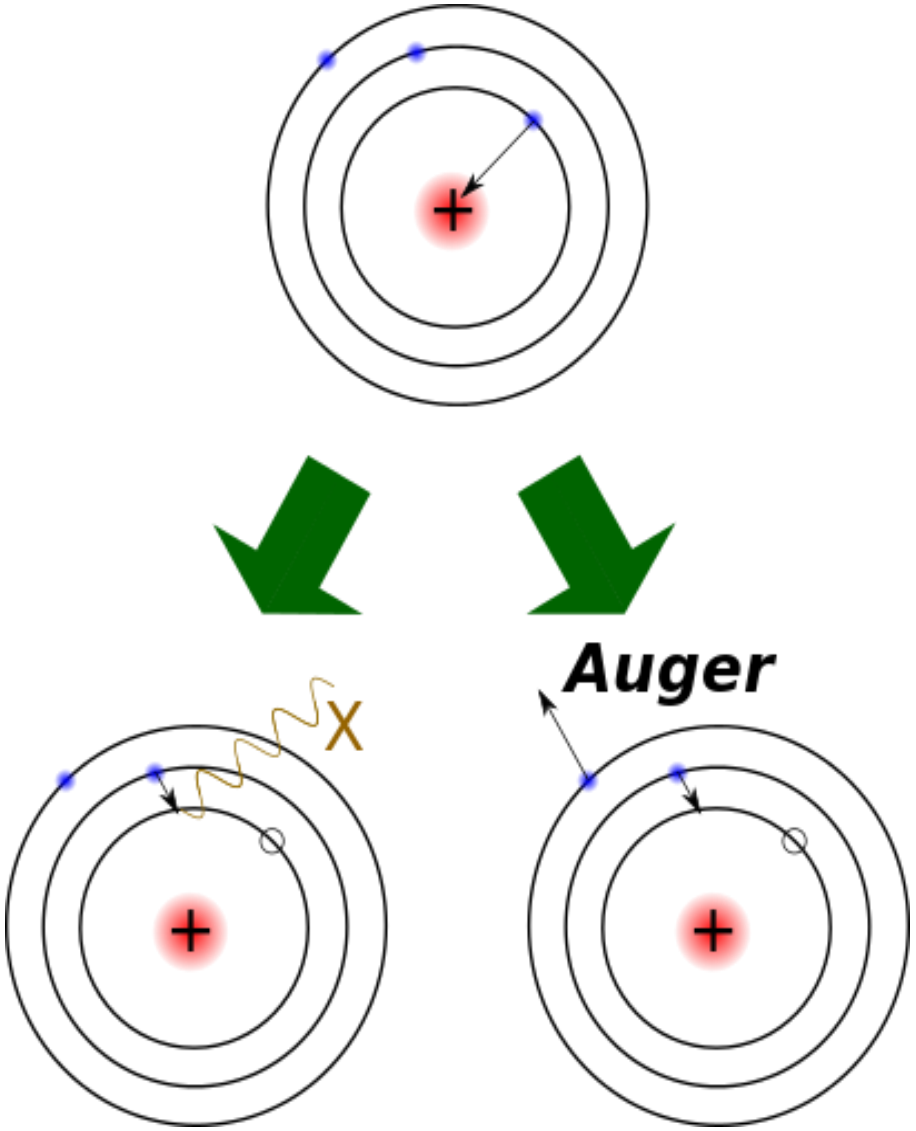
an electron from the K-shell **is trapped** by a proton **inside the nucleus**

Thus neither a positron nor an electron are lost

The decay energy Q is equivalent to M_P-M_D in form of a **γ-quant**

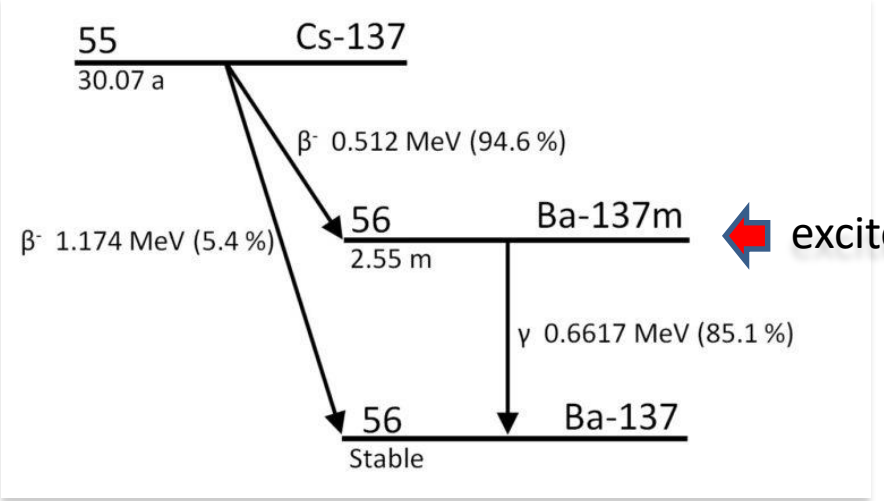
if Q < 1.022MeV, **exclusively ε-decay,** if larger, both β^+ and ε-decays may **occur in parallel**

Electron capture (EC) can produce Auger electrons



Phenomena following up the decay

After the β (and α) decay, the daughter nucleus is generally **in an excited state**



excited state

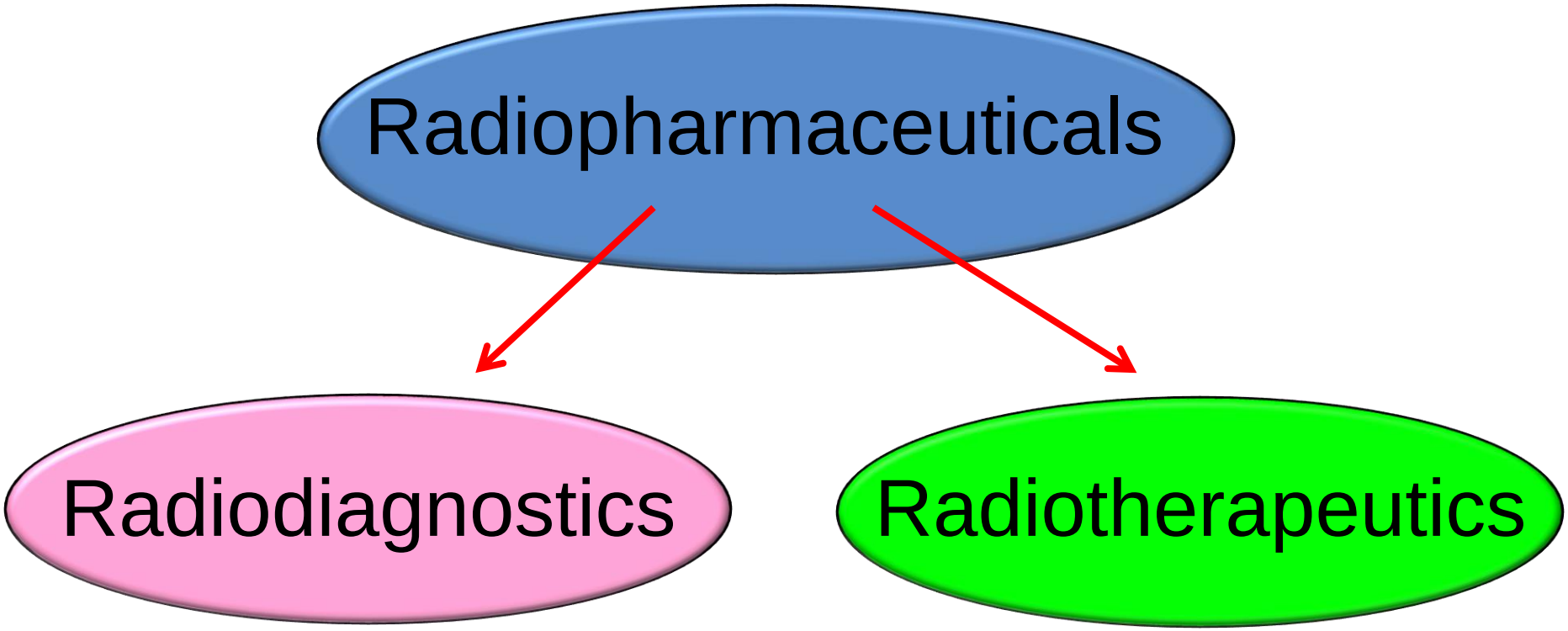
the excited state goes into the ground state by

emitting one (or more) γ-quants

or

by emitting electrons from the shell

Auger electrons



γ-emitters (SPECT)
positron-emitters (β^+) (PET)
10^{-6} – 10^{-8} M

α or β^- emitters

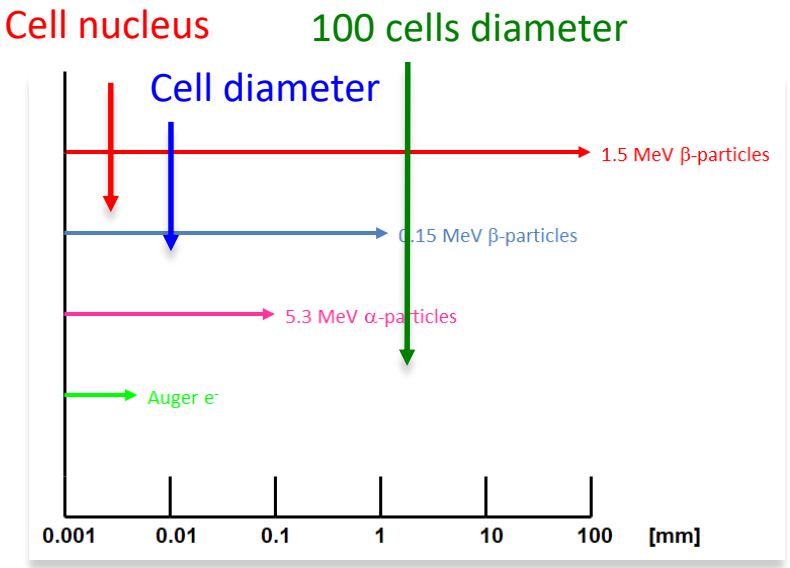
Selection of **appropriate** radionuclides

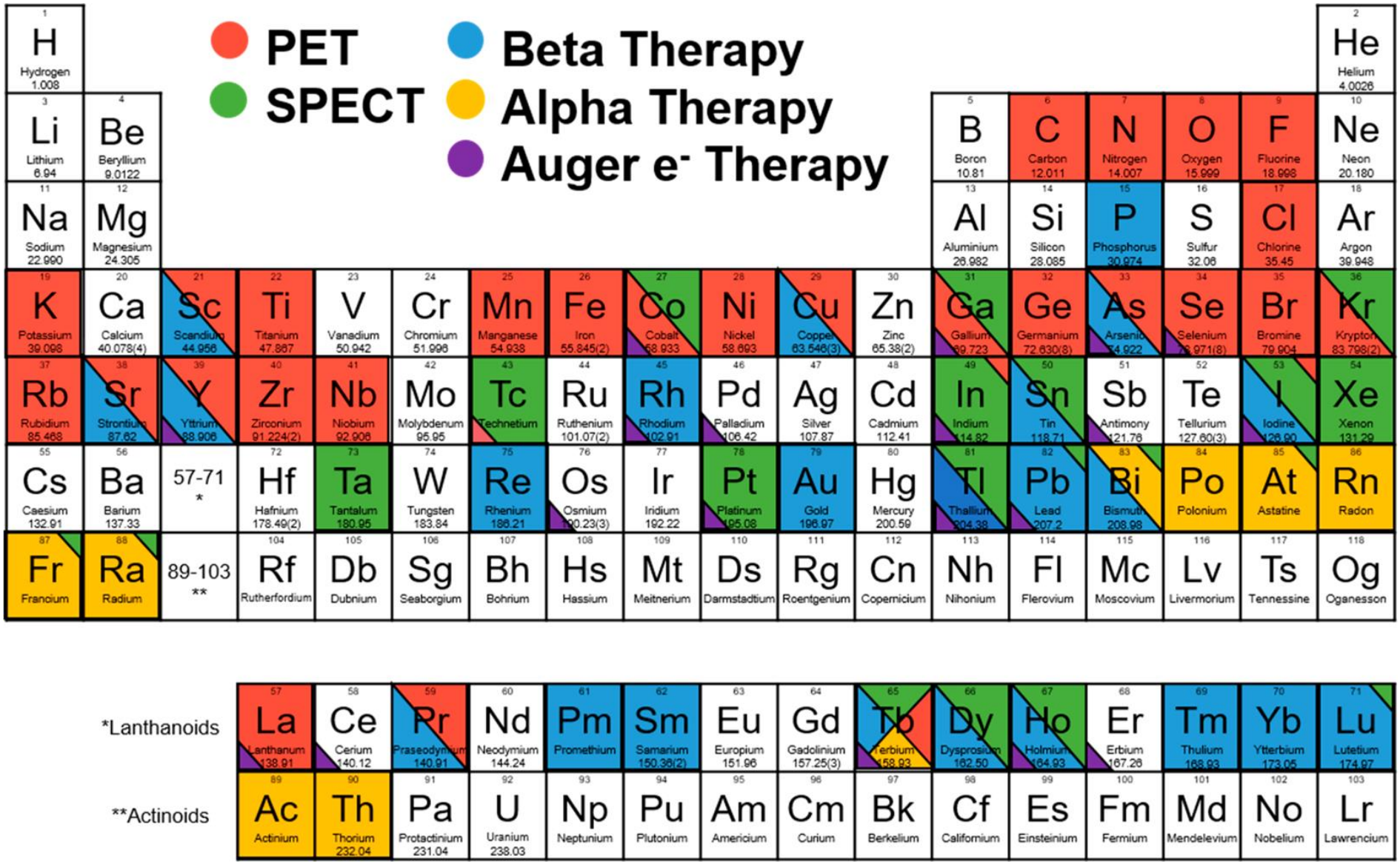
Diagnosis / Imaging ➡ **pure γ- emitting** nuclides are preferred since …

particulate radiations (such as α or β) **increase the dose** to the patient

but are non-penetrating and therefore do not contribute to the image.

Therapy ➡ particulate radiation **and** γ-emitters are preferred




PET
SPECT
Beta Therapy
Alpha Therapy
Auger e- Therapy
1 H Hydrogen 1.008
2 He Helium 4.0026
3 Li Lithium 6.94
4 Be Beryllium 9.0122
5 B Boron 10.81
6 C Carbon 12.011
7 N Nitrogen 14.007
8 O Oxygen 15.999
9 F Fluorine 18.998
10 Ne Neon 20.180
11 Na Sodium 22.990
12 Mg Magnesium 24.305
13 Al Aluminium 26.982
14 Si Silicon 28.085
15 P Phosphorus 30.974
16 S Sulfur 32.06
17 Cl Chlorine 35.45
18 Ar Argon 39.948
19 K Potassium 39.098
20 Ca Calcium 40.078(4)
21 Sc Scandium 44.956
22 Ti Titanium 47.867
23 V Vanadium 50.942
24 Cr Chromium 51.996
25 Mn Manganese 54.938
26 Fe Iron 55.845(2)
27 Co Cobalt 58.933
28 Ni Nickel 58.693
29 Cu Copper 63.546(3)
30 Zn Zinc 65.38(2)
31 Ga Gallium 69.723
32 Ge Germanium 72.630(8)
33 As Arsenic 74.922
34 Se Selenium 78.971(8)
35 Br Bromine 79.904
36 Kr Krypton 83.798(2)
37 Rb Rubidium 85.468
38 Sr Strontium 87.62
39 Y Yttrium 88.906
40 Zr Zirconium 91.224(2)
41 Nb Niobium 92.906
42 Mo Molybdenum 95.95
43 Tc Technetium
44 Ru Ruthenium 101.07(2)
45 Rh Rhodium 102.91
46 Pd Palladium 106.42
47 Ag Silver 107.87
48 Cd Cadmium 112.41
49 In Indium 114.82
50 Sn Tin 118.71
51 Sb Antimony 121.76
52 Te Tellurium 127.60(3)
53 I Iodine 126.90
54 Xe Xenon 131.29
55 Cs Caesium 132.91
56 Ba Barium 137.33
57-71 *
72 Hf Hafnium 178.49(2)
73 Ta Tantalum 180.95
74 W Tungsten 183.84
75 Re Rhenium 186.21
76 Os Osmium 190.23(3)
77 Ir Iridium 192.22
78 Pt Platinum 195.08
79 Au Gold 196.97
80 Hg Mercury 200.59
81 Tl Thallium 204.38
82 Pb Lead 207.2
83 Bi Bismuth 208.98
84 Po Polonium
85 At Astatine
86 Rn Radon
87 Fr Francium
88 Ra Radium
89-103 **
104 Rf Rutherfordium
105 Db Dubnium
106 Sg Seaborgium
107 Bh Bohrium
108 Hs Hassium
109 Mt Meitnerium
110 Ds Darmstadtium
111 Rg Roentgenium
112 Cn Copernicium
113 Nh Nihonium
114 Fl Flerovium
115 Mc Moscovium
116 Lv Livermorium
117 Ts Tennessine
118 Og Oganesson
*Lanthanoids
57 La Lanthanum 138.91
58 Ce Cerium 140.12
59 Pr Praseodymium 140.91
60 Nd Neodymium 144.24
61 Pm Promethium
62 Sm Samarium 150.36(2)
63 Eu Europium 151.96
64 Gd Gadolinium 157.25(3)
65 Tb Terbium 158.93
66 Dy Dysprosium 162.50
67 Ho Holmium 164.93
68 Er Erbium 167.26
69 Tm Thulium 168.93
70 Yb Ytterbium 173.05
71 Lu Lutetium 174.97
**Actinoids
89 Ac Actinium
90 Th Thorium 232.04
91 Pa Protactinium 231.04
92 U Uranium 238.03
93 Np Neptunium
94 Pu Plutonium
95 Am Americium
96 Cm Curium
97 Bk Berkelium
98 Cf Californium
99 Es Einsteinium
100 Fm Fermium
101 Md Mendelevium
102 No Nobelium
103 Lr Lawrencium

Preparation of a radiopharmaceutical, step 1: the radionuclide

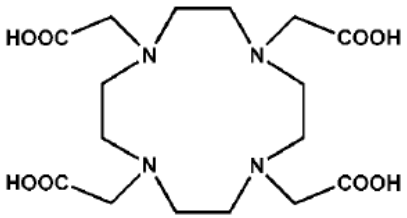
Radio-isotopes can be obtained:

- By decay of longer half-life radionuclides in a **generator**
- Via a **cyclotron** by bombarding an appropriate element or its compound with accelerated charged particles, typically protons or deuterium nuclei
- By nuclear bombardment with neutrons in a **nuclear reactor**
- Purification from parent isotope and by-products (also depends on isotopic purity of target nucleus)
- Incorporation into a compound, often via a polydentate chelator

Most-common chelators

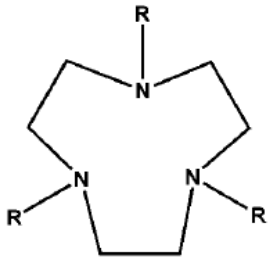
Diethylenetriamino-pentaaceticacid

a)



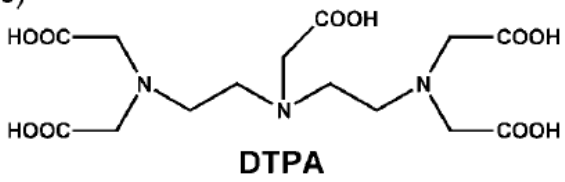
DOTA

b)



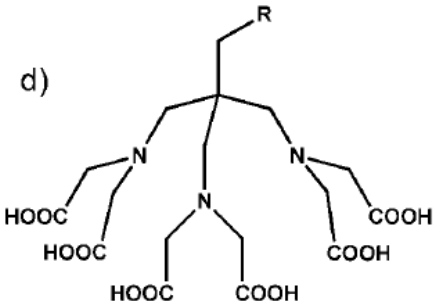
NOTA	R = CH_2COOH
TACN-TM	R = CH_2CH_2SH
NOTP	R = $CH_2PO_3H_2$
NOTPME	R = $CH_2PO_2(OCH_2CH_3)$

c)



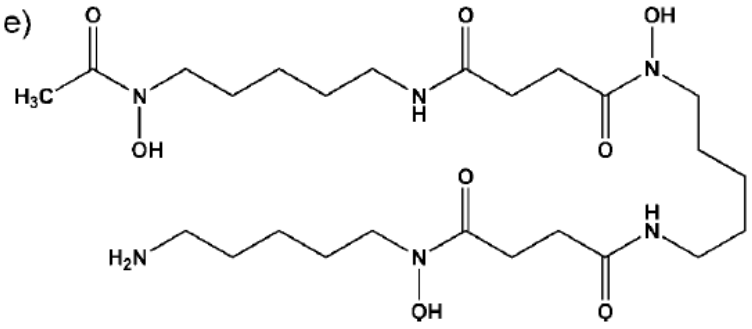
DTPA

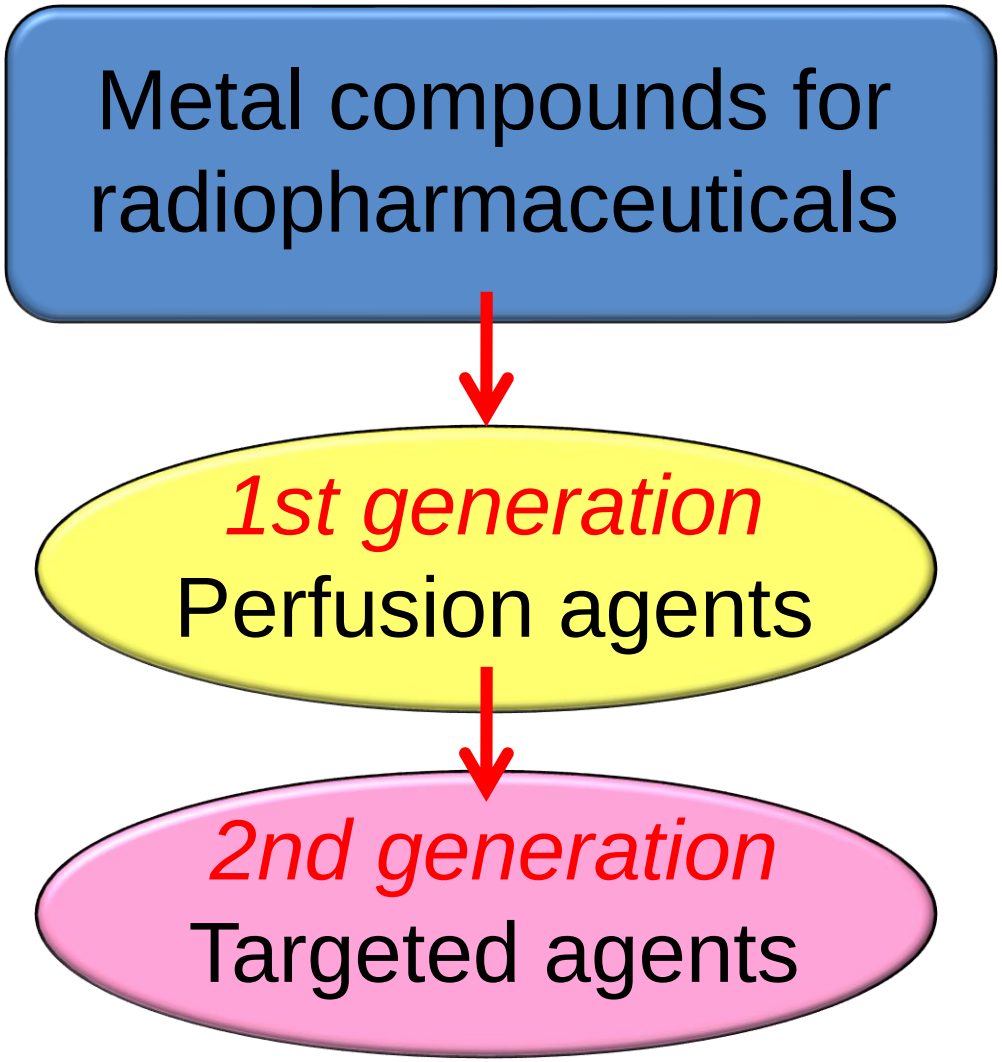
d)



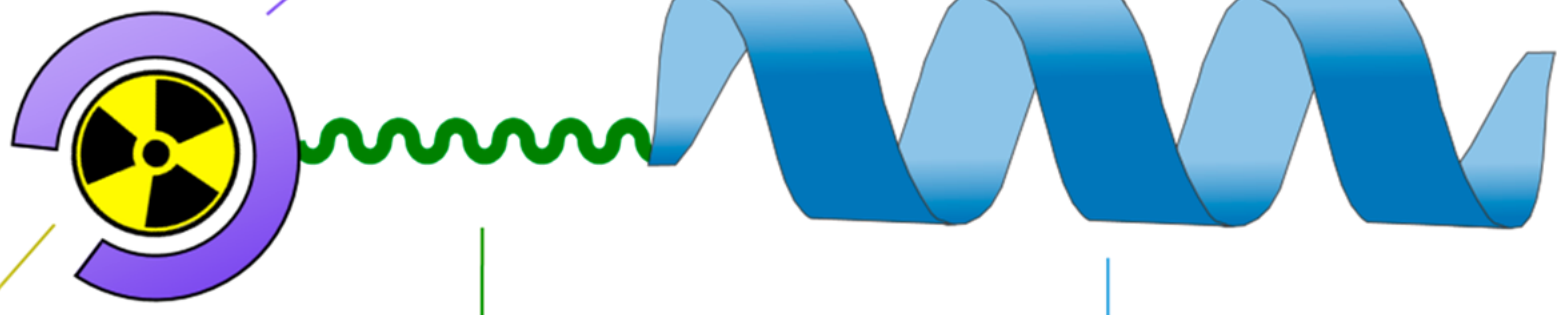
TAME Hex

e)




Metal compounds for radiopharmaceuticals
1st generation
Perfusion agents
2nd generation
Targeted agents

Targeted Approach
(*Trojan horse*)



Bifunctional Chelator

Secures metal for safe biological transport

Radiometal

Source of desired radiation

Linker

Joins radioactive and targeting moieties

Bioconjugate

Ensures drug accumulates at target

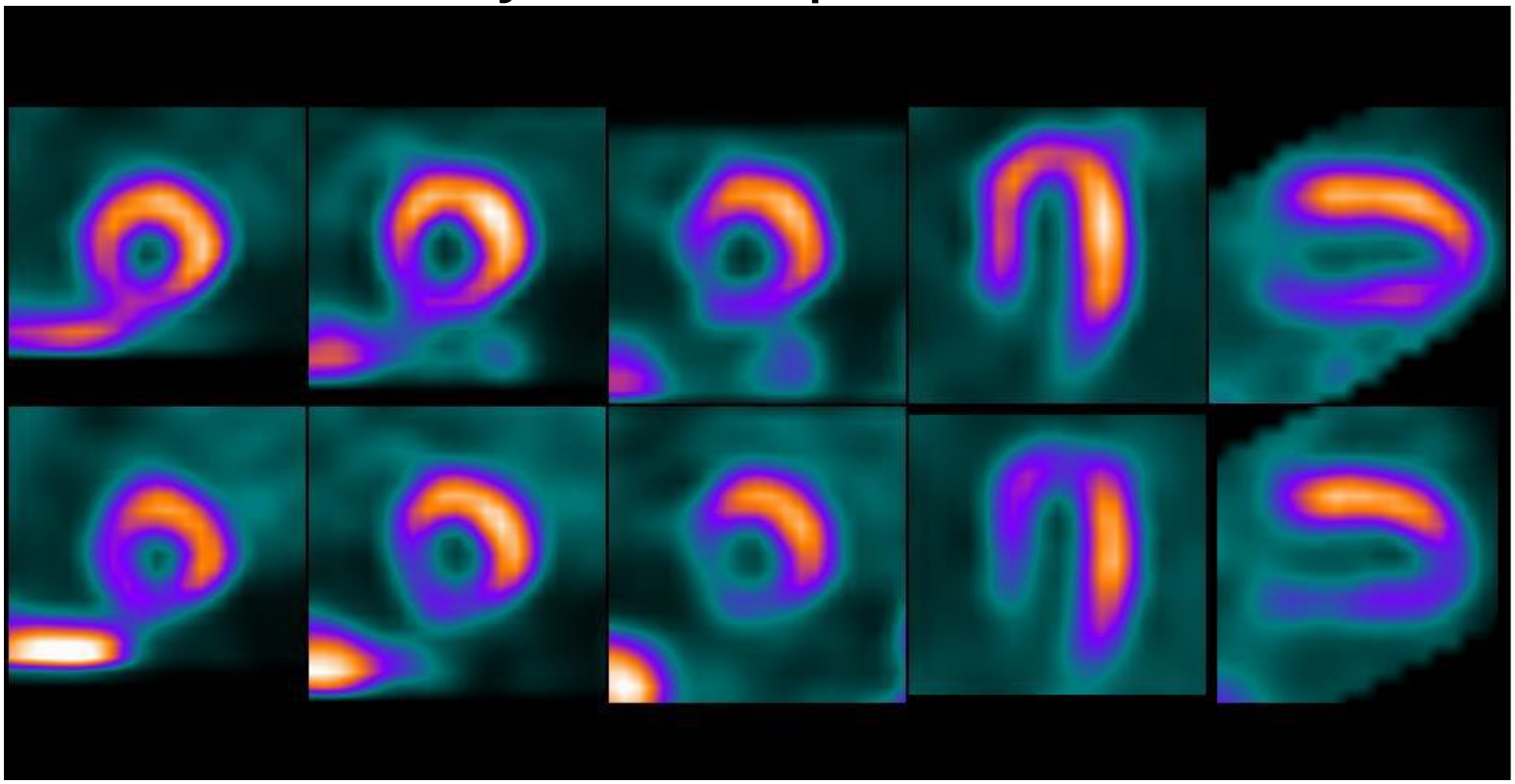
(targeting vector)

Targeting molecules: monoclonal antibodies, peptides, vitamins, carbohydrates,..

SPECT: Single Photon Emission Computed Tomography

γ emitters, 100 – 250 keV

Myocardial perfusion



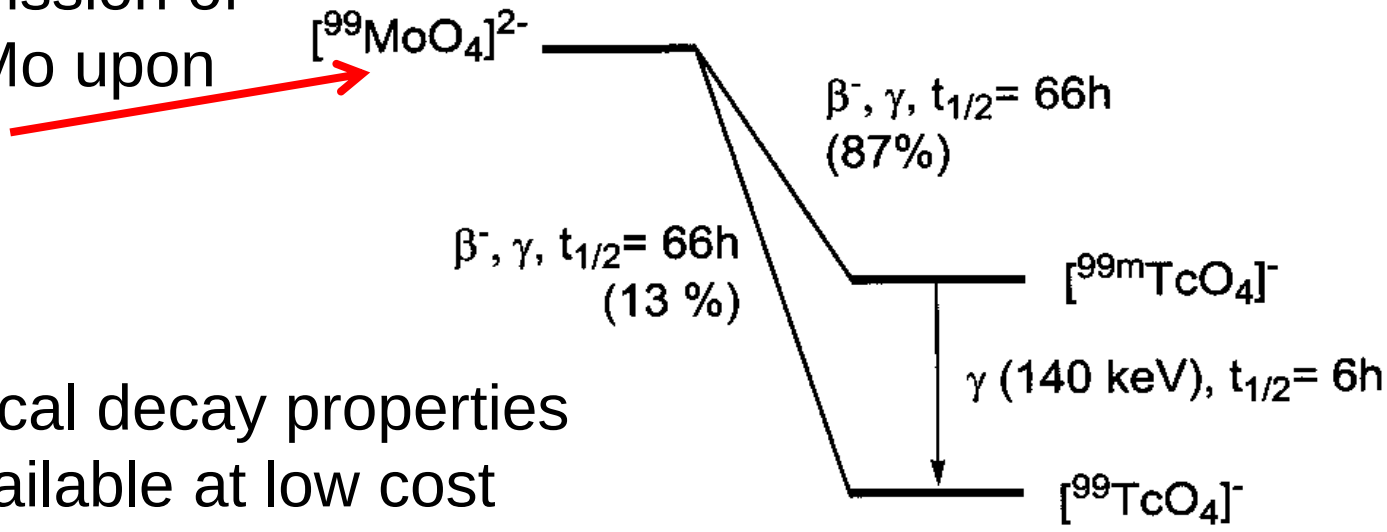
Main radionuclides for SPECT

Radionuclide	**Half life**	**Energy of main γ emission (keV)**
^{67}Ga (γ)	78 h	93, 185, 300
^{99m}Tc (γ)	6 h	140
^{111}In (γ)	67 h	171, 245
^{131}I (β, γ)	8 d	364

^{99m}Tc: the *workhorse* of radioimaging

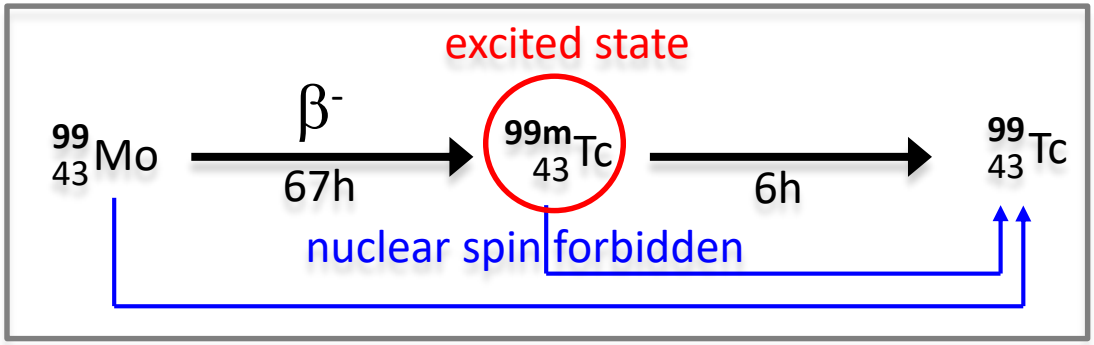
(used in >80% of diagnostic scans, more than 25 M in 2007)

Obtained from fission of ^{235}U or from ^{98}Mo upon (n, γ) reaction



Pure β-emitter

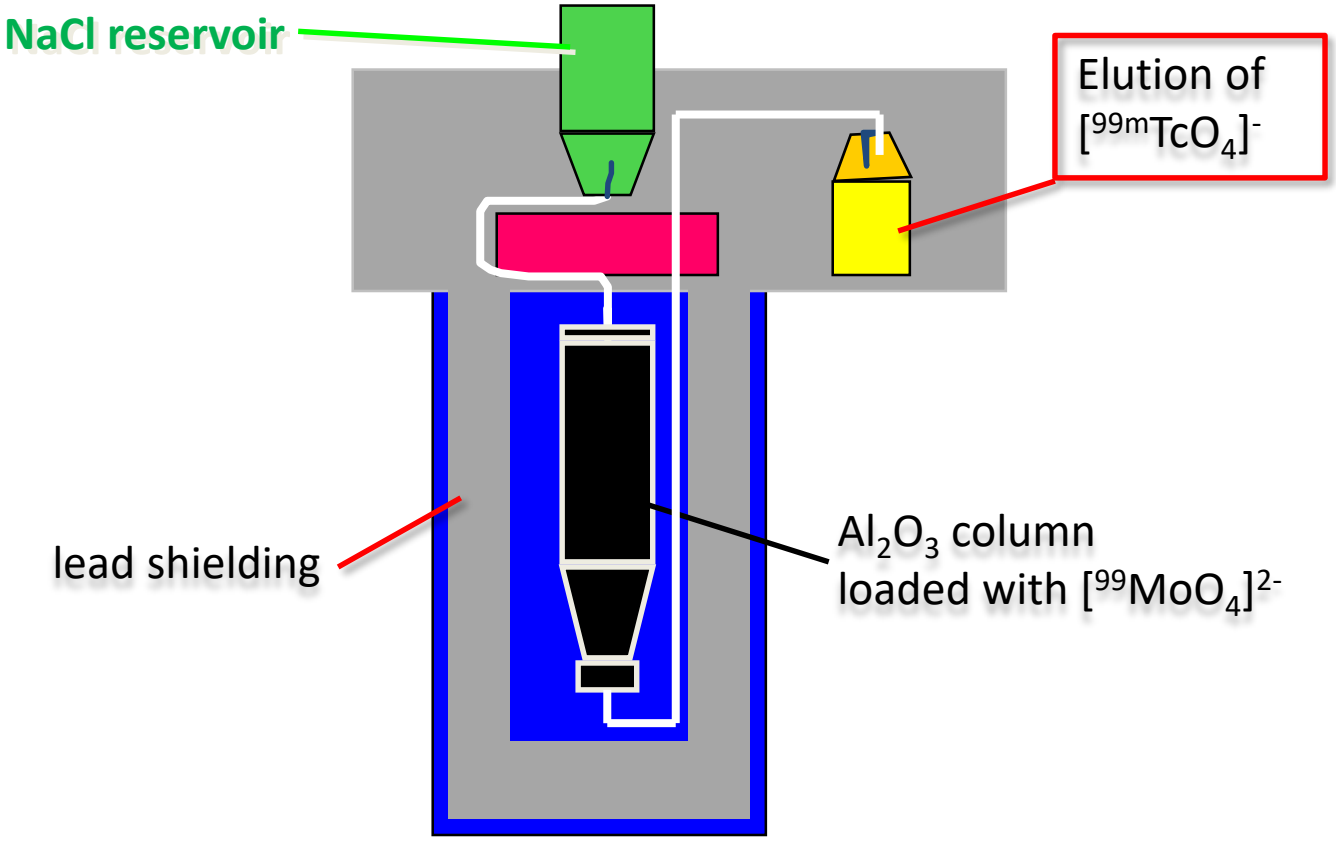
- Ideal physical decay properties
- Readily available at low cost
- Many oxidation states (+7 – -1)
- Various coordination geometries (4 – 9)
- *Cold* Re for characterization (matched-pair approach)



nuclear spin forbidden: compare to **spin forbidden transitions** in the electron shell ➡ **phosphorescence**

$^{99m}TcO_4^-$ generator

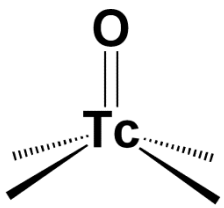
^{99}Mo (parent) $\xrightarrow{k_1}$ **^{99m}Tc** (desired nuclide) $\xrightarrow{k_2}$ **^{99}Tc** (final product)



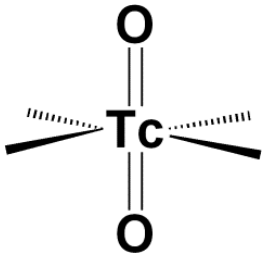
Preparation of radiopharmaceuticals: "*Shake and bake*" principle

- Preparation has to be done "on site" in clinics (kits)
- Yields must be > 98% (even at very low metal ion concentration)
- Compound must be ready for administration
- No lenghty purification or separation
- Saline aqueous solutions
- Non-toxic reagents (e.g. Sn(II) componds as reducing agents) and byproducts

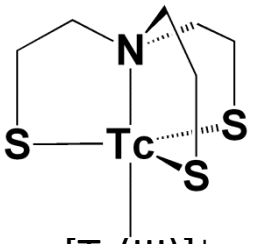
Most relevant oxidation states and core structures



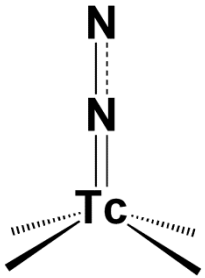
$[Tc(V)]^{3+}$



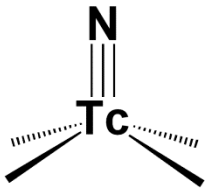
$[Tc(V)]^{+}$



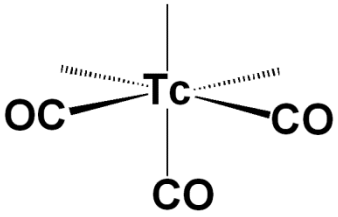
$[Tc(III)]^{+}$



$[Tc(V)]$



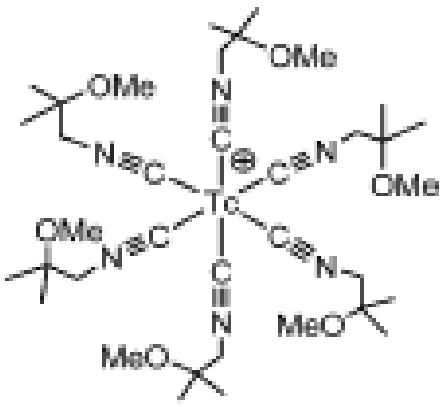
$[Tc(V)]^{2+}$



$[Tc(I)]^{+}$

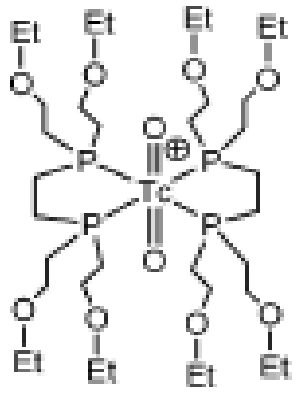
- "vacant sites must be occupied by **stable / inert** ligands
- synthesis from $[^{99m}TcO_4]^-$ **in 0.9% NaCl solution**

First generations ^{99m}Tc agents



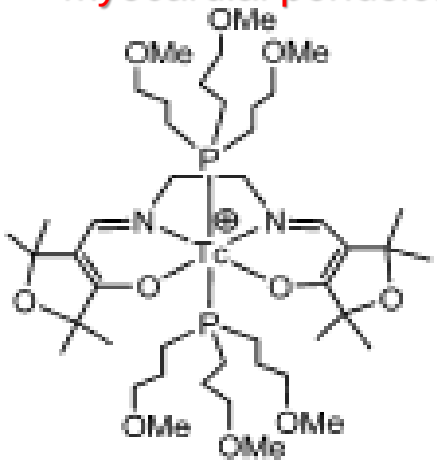
^{99m}Tc-Sestamibi

cardiac imaging



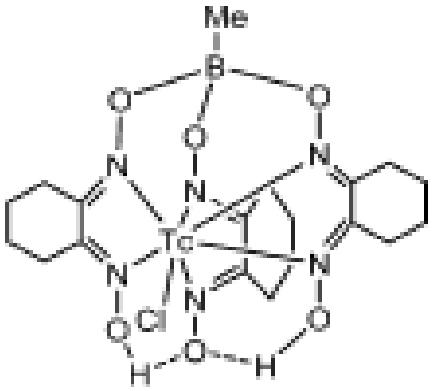
^{99m}Tc-Tetrofosmin

myocardial perfusion

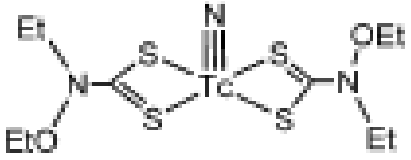


Q12

cardiac imaging

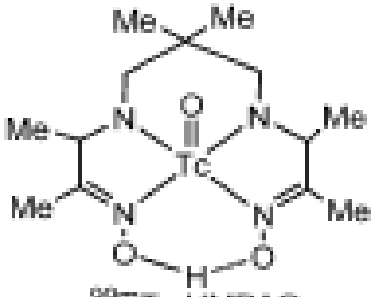


^{99m}Tc-Teboroxime



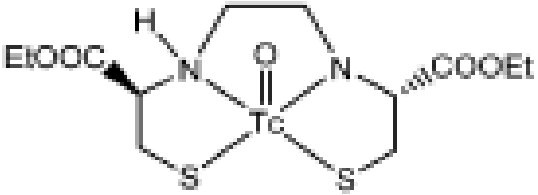
^{99m}TcN-NOET

myocardial perfusion



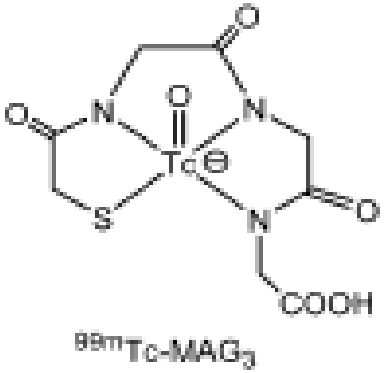
^{99m}Tc-HMPAO

cereberal perfusion



^{99m}Tc-Bicisate

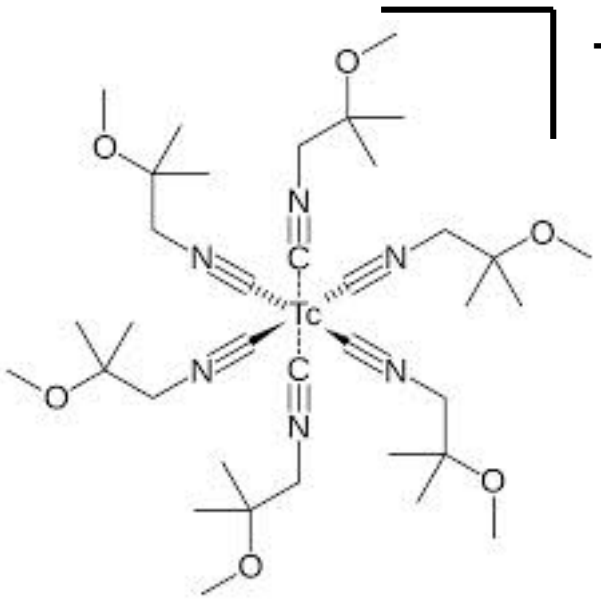
brain imaging



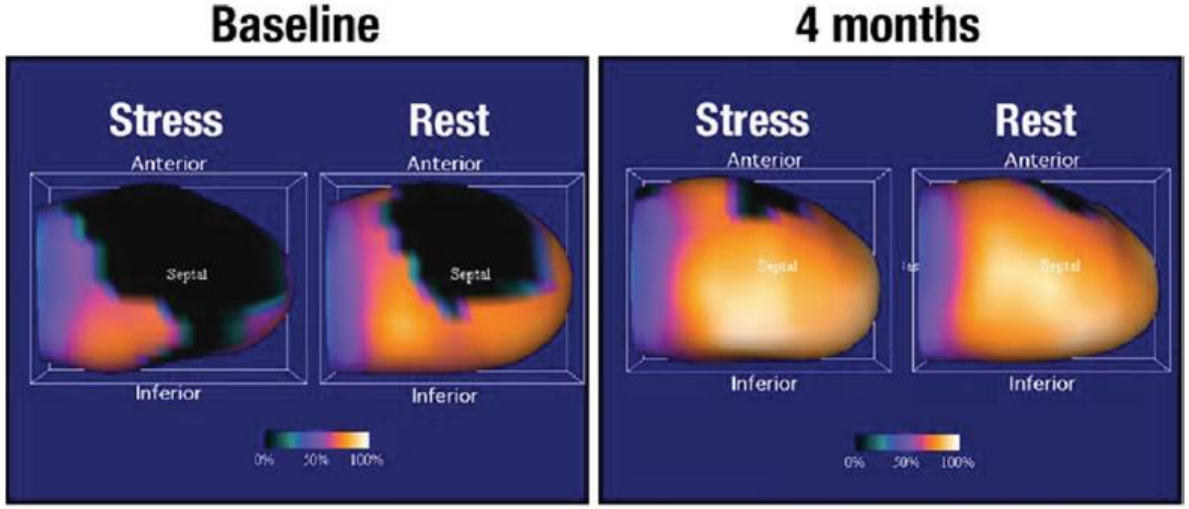
^{99m}Tc-MAG$_3$

renal imaging

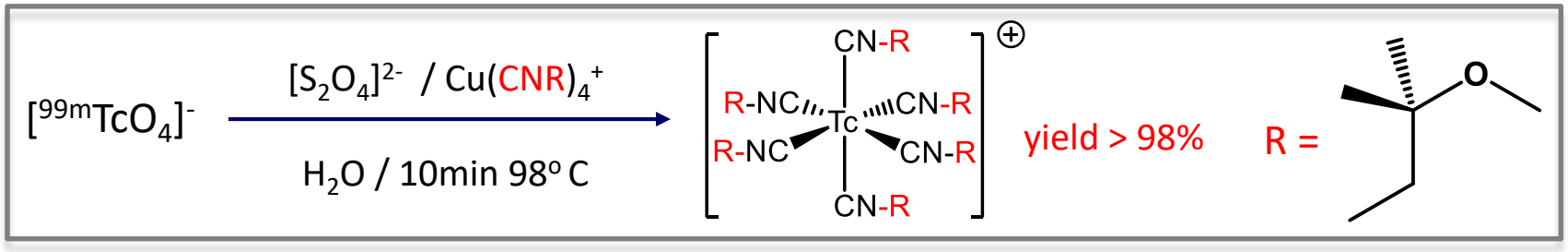
^{99m}Tc-sestamibi



Localizes in mithocondria



- Cardiac imaging (uptake proportional to blood flux)
- Cancer diagnosis (breast cancer)
- Thyroid imaging (adenoma)

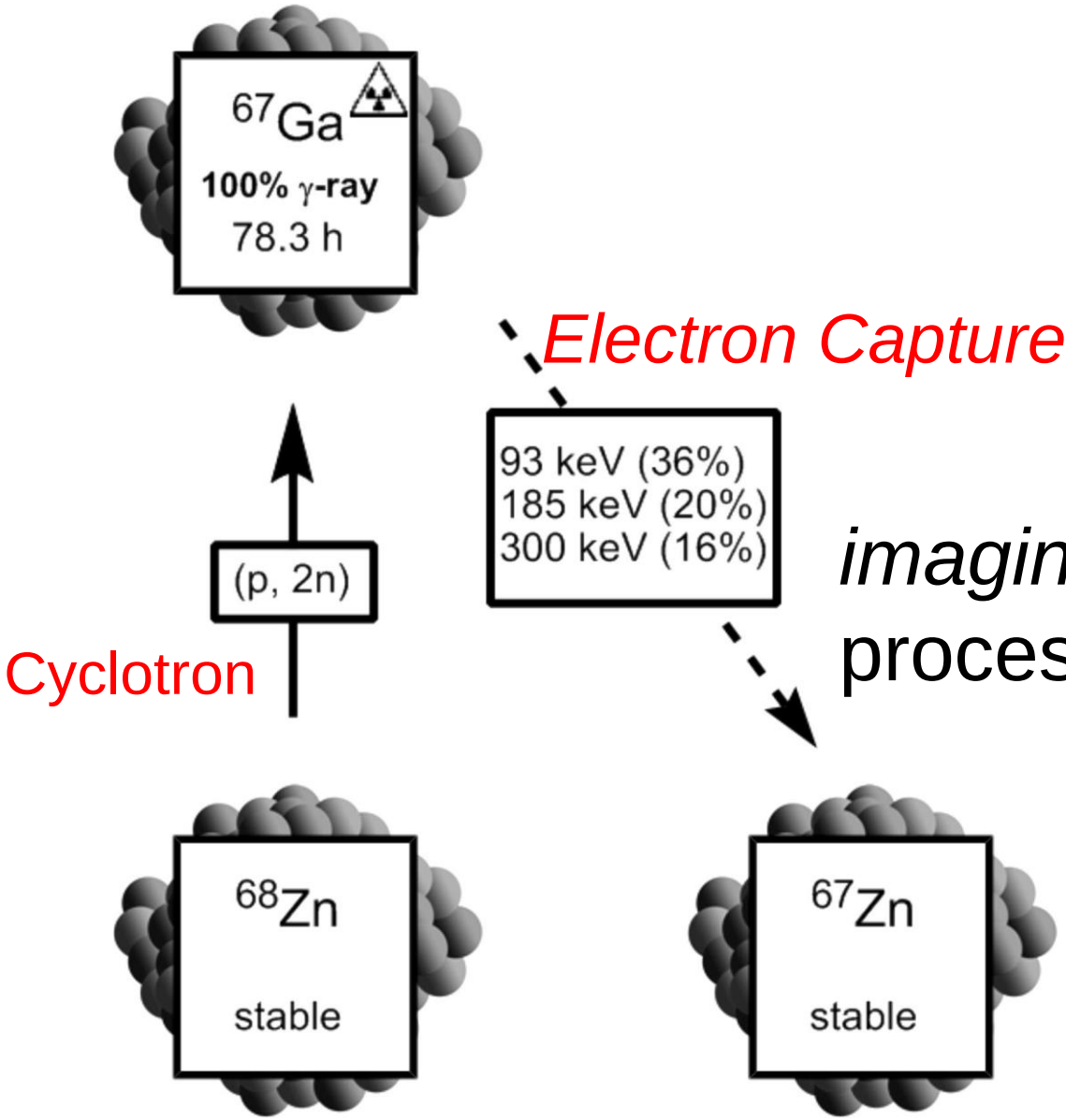


Chemistry is difficult, **redox chemistry** involved

$[^{99m}TcO_4]^-$ **Tc^{VII}** → **Tc^{I}** $[^{99m}Tc(CNR)_6]^+$ **6 electrons**

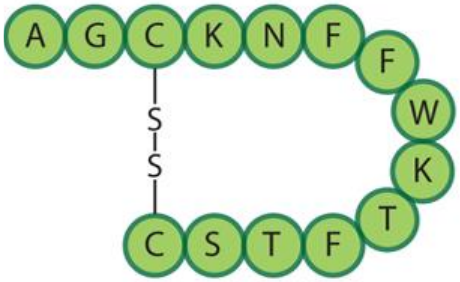
- quantitative yield (**> 98%**)
- water as solvent, **boiling**
- high dilution, **kinetic** reaction **control**

>500 M$ per year

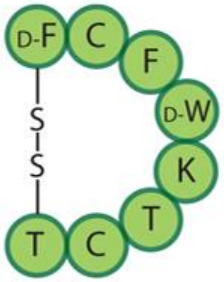


imaging of inflammatory processes and tumors

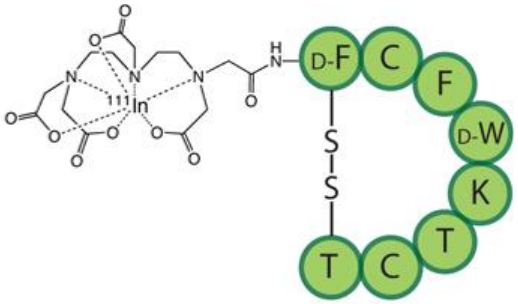
Radio-immuno-scintigraphy



Somatostatin

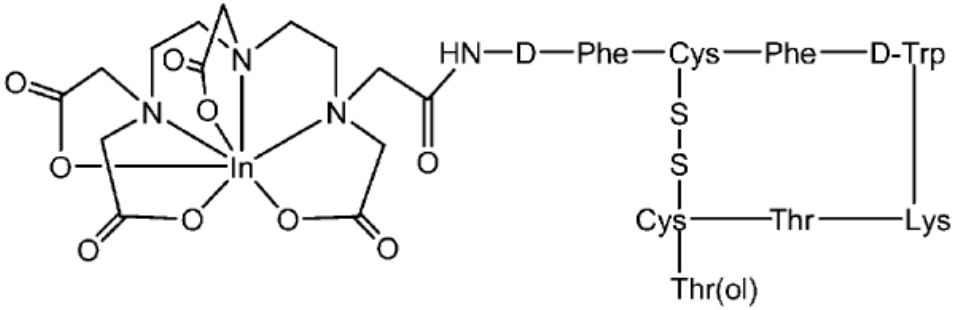


Octreotide



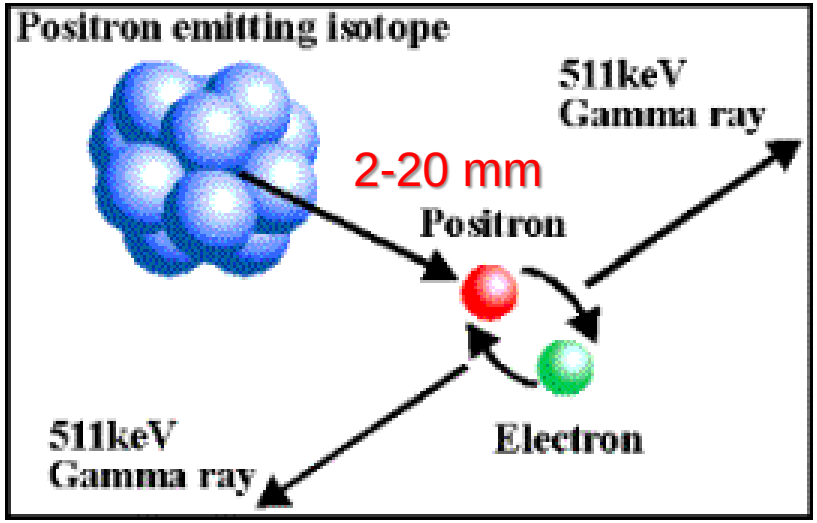
^{111}In-DTPA-Octreotide

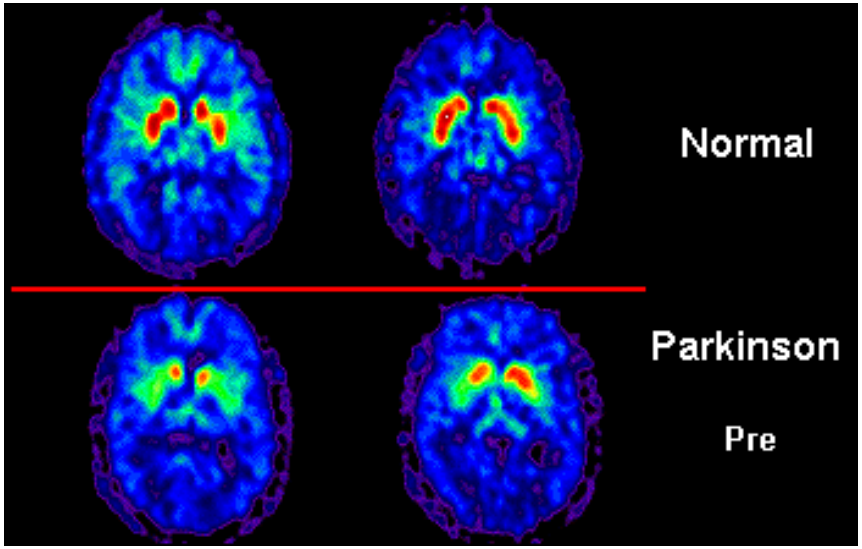
Somatostatin is a polypeptide hormone that regulates the endocrine system and cell growth and proliferation. Somatostatin receptors are trans-membrane proteins that are overexpressed in many types of **neuroendocrine tumors**. Octreotide is similar to somatostatin.

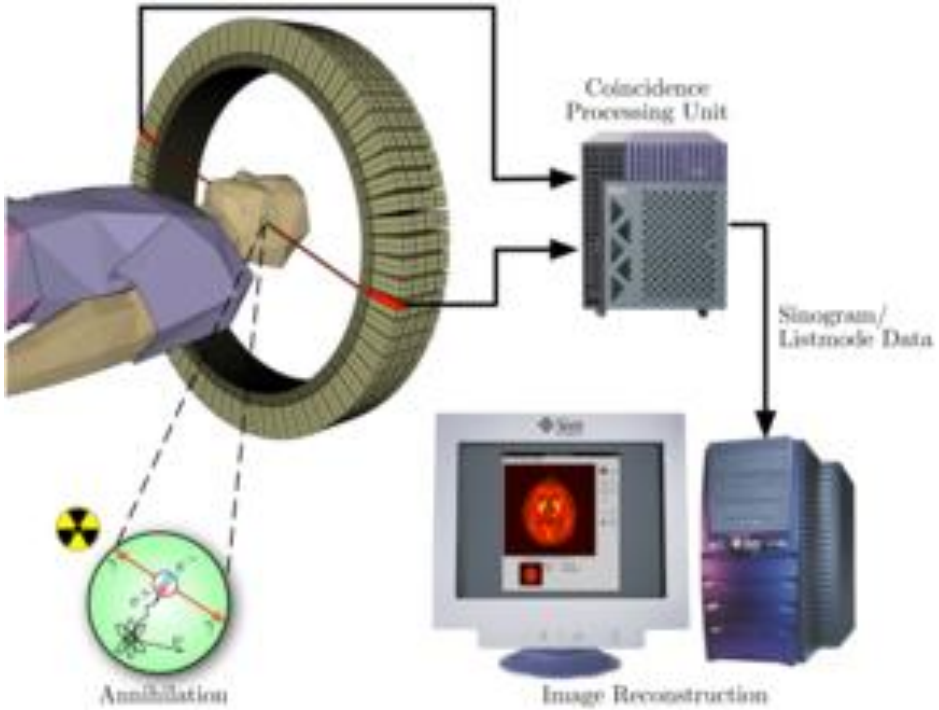


^{111}In-DTPA-Octreotide (OctreoScan®)

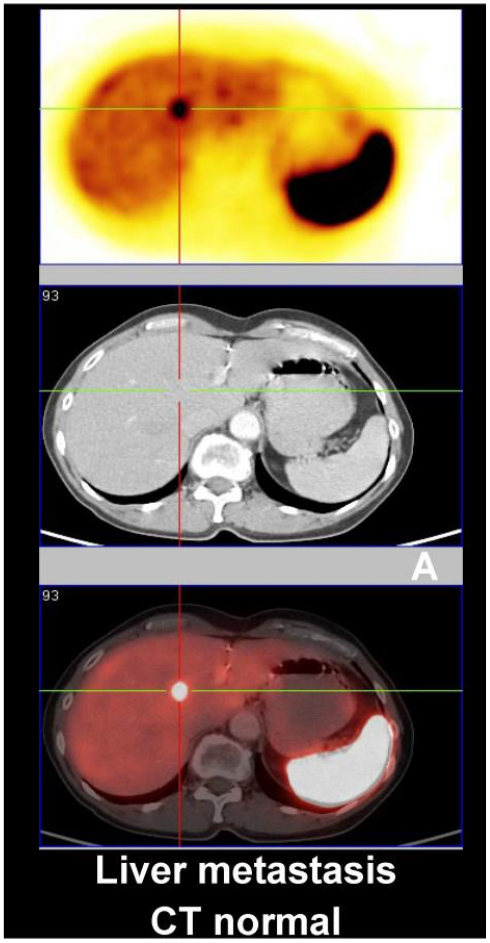
PET: Positron Emission Tomography







PET/CT: combination of imaging techniques (structural and functional)



PET

CT

PET + CT

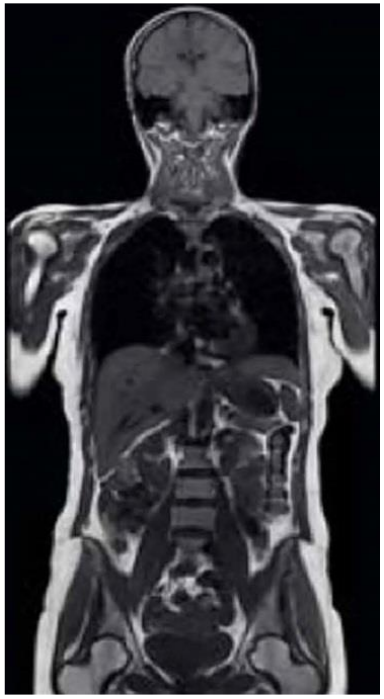
PET imaging and hybrid modalities

PET

Functional imaging

High sensitivity - Target specific

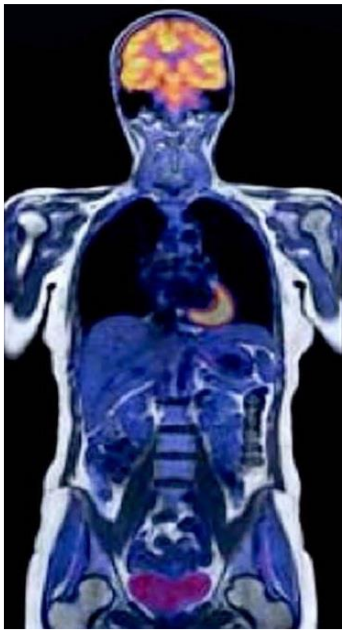
MRI



Anatomic / physiologic imaging

High resolution - Soft tissue contrast

PET/MRI



Improved clinical accuracy

Reduced radiation dose

Broader pathologic scope

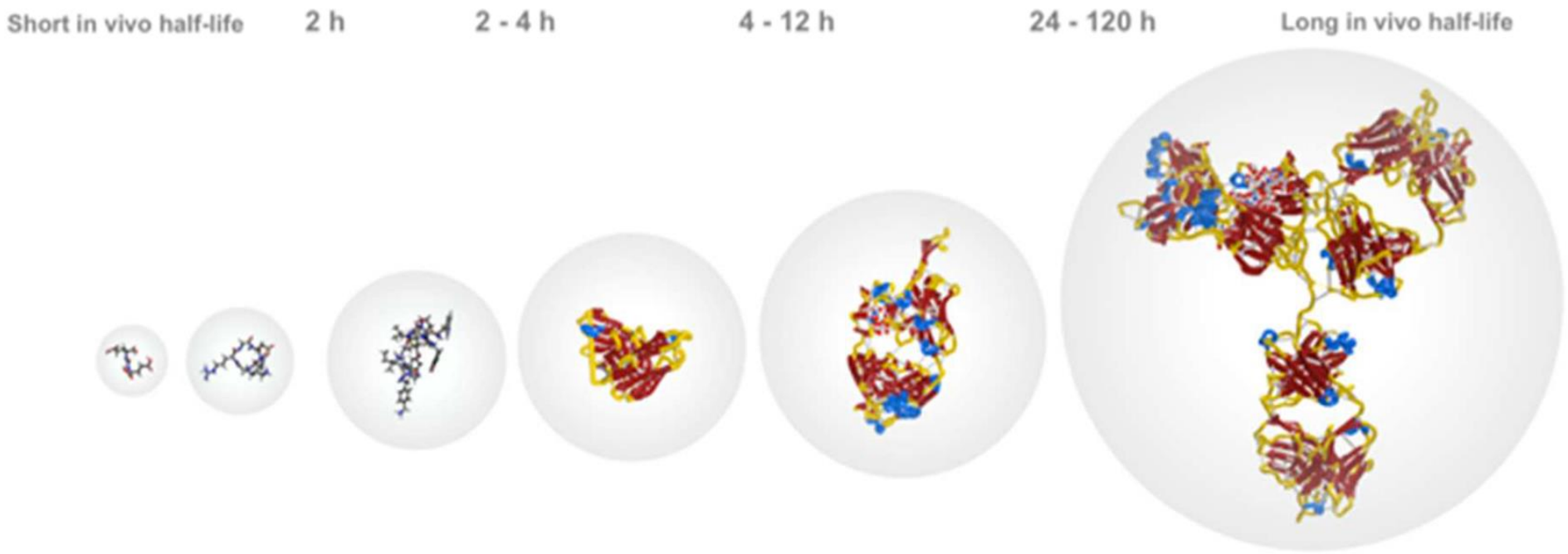
Most relevant radionuclides for PET

Table 1. Physical Properties of Commonly Used Positron-Emitting Radionuclides

nuclide	half-life (min)	maximum energy (MeV)	mode of decay (%)	theoretical specific activity (GBq/μmol)
^{18}F	110	0.64	β+ (97%) EC[a] (3%)	6.3×10^4
^{11}C	20.3	0.97	β+ (99%)	3.4×10^5
^{13}N	10	1.20	β+ (100%)	7.0×10^5
^{15}O	2	1.74	β+ (100%)	3.4×10^6
^{76}Br	972	4.0	β+ (57%) EC (43%)	7.2×10^3
^{124}I	60 192	2.14	β+ (25%) EC (75%)	1.15×10^3
^{68}Ga	68.1	1.90	β+ (89%) EC (11%)	1.02×10^5
^{64}Cu	762	0.655	β+ (19%) EC (41%) β+ (40%)	9.13×10^3

[a] EC: electron capture.

Radionuclide half-life and biodistribution half-life

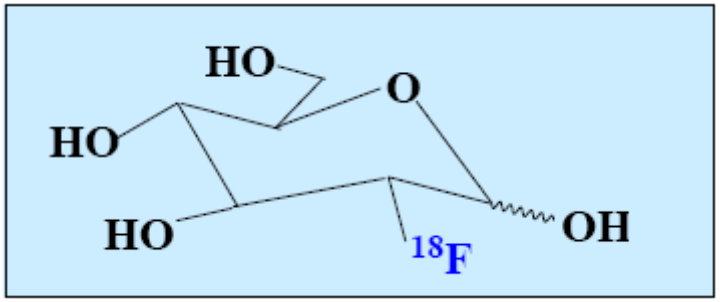


Short radionuclide half-life

Long radionuclide half-life

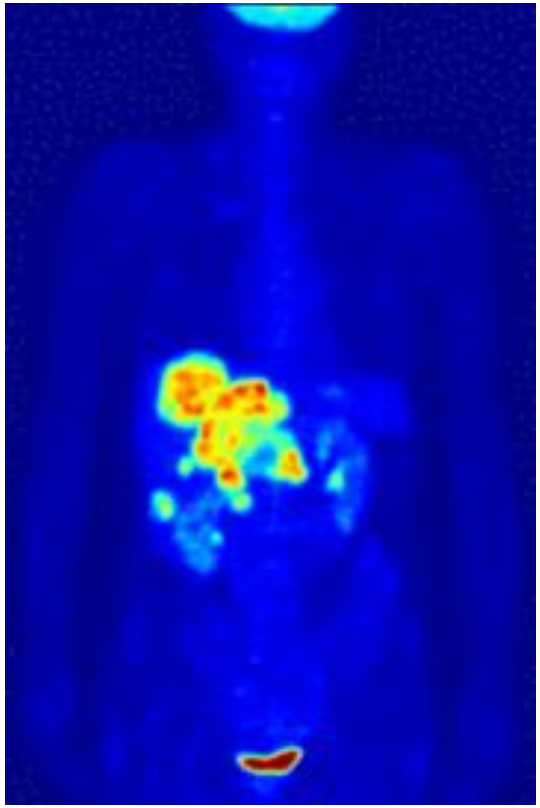
^{63}Zn $t_{1/2}$= 0.6 h	^{94m}Tc $t_{1/2}$= 0.9 h	^{45}Ti $t_{1/2}$= 3.1 h	^{99m}Tc $t_{1/2}$= 6 h	^{64}Cu $t_{1/2}$= 12.6 h	^{90}Nb $t_{1/2}$= 14.6 h	^{55}Co $t_{1/2}$= 17.5 h	^{89}Zr $t_{1/2}$= 78 h	^{52}Mn $t_{1/2}$= 134 h
					^{188}Re (359 keV) $t_{1/2}$ = 17 h	^{104}Rh (566 keV) $t_{1/2}$ = 35 h	^{67}Cu (580 keV) $t_{1/2}$ = 62 h	^{186}Re (791 keV) $t_{1/2}$ = 89 h

PET SPECT β^-

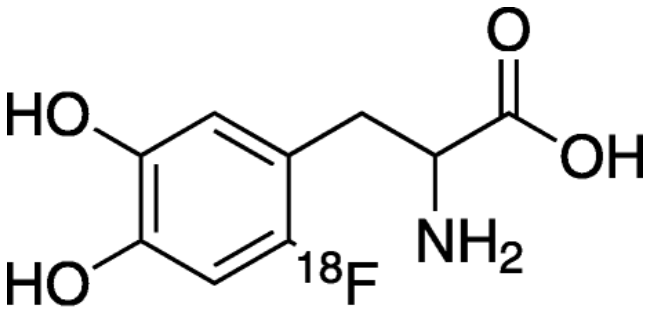


Fluorodeoxyglucose ([^{18}F] FDG)

bio-isosteric substitution

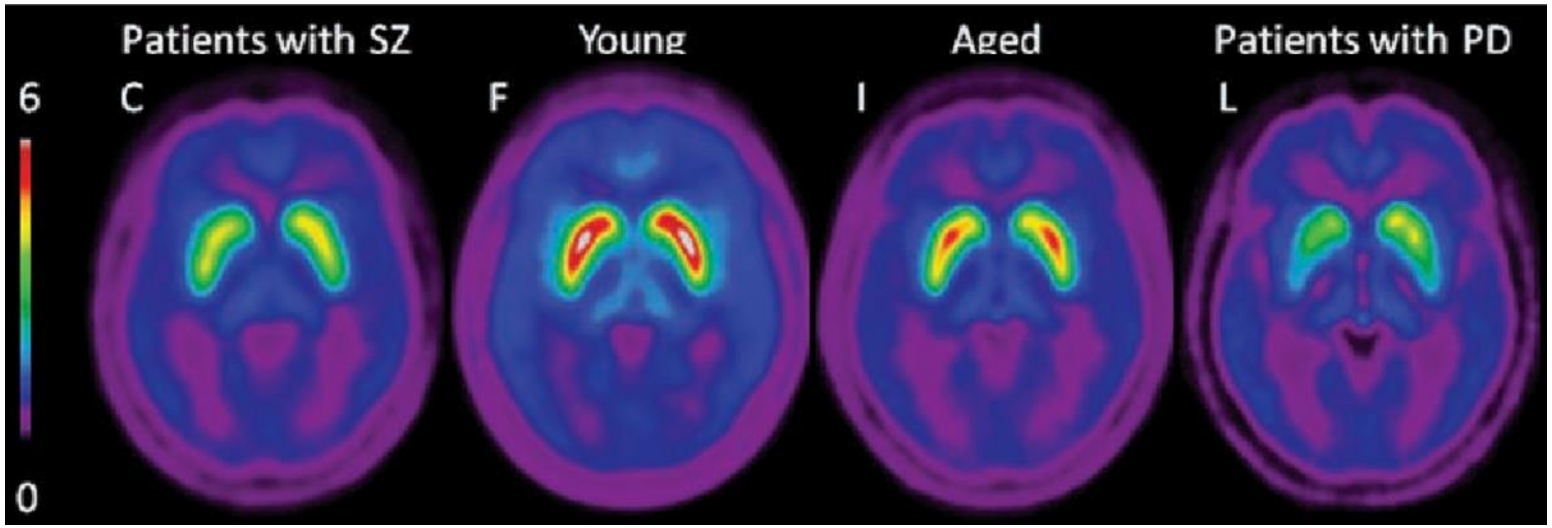


glucose metabolism
tumor localization



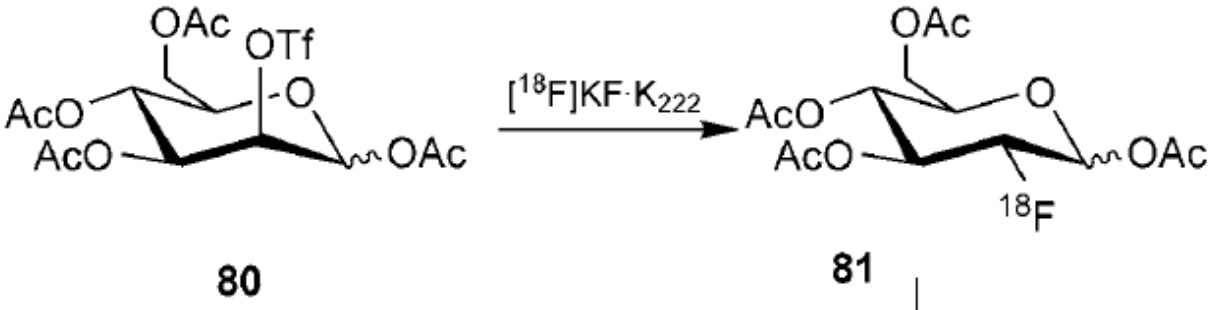
6-[18F]FDOPA,

DOPA is the precursor of the neurotransmitter dopamine.
The neurotracer 6-[18F]FDOPA is a powerful tool in PET imaging of neuropsychiatric diseases, movement disorders and brain malignancies. More recently, it also demonstrated good results in the diagnosis of other malignancies



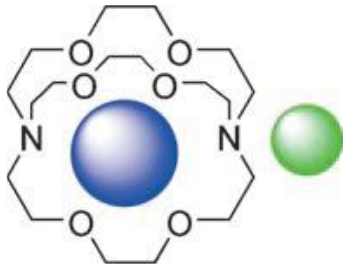
Example of nucleophilic direct fluorination ($^{18}F^-$)

$^{18}O_{(\text{from } H_2O)}(p, n)^{18}F$

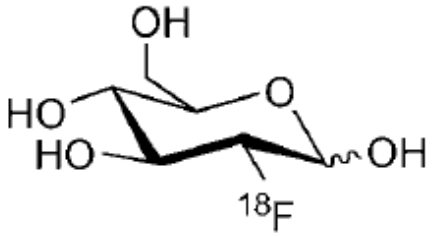


80

81

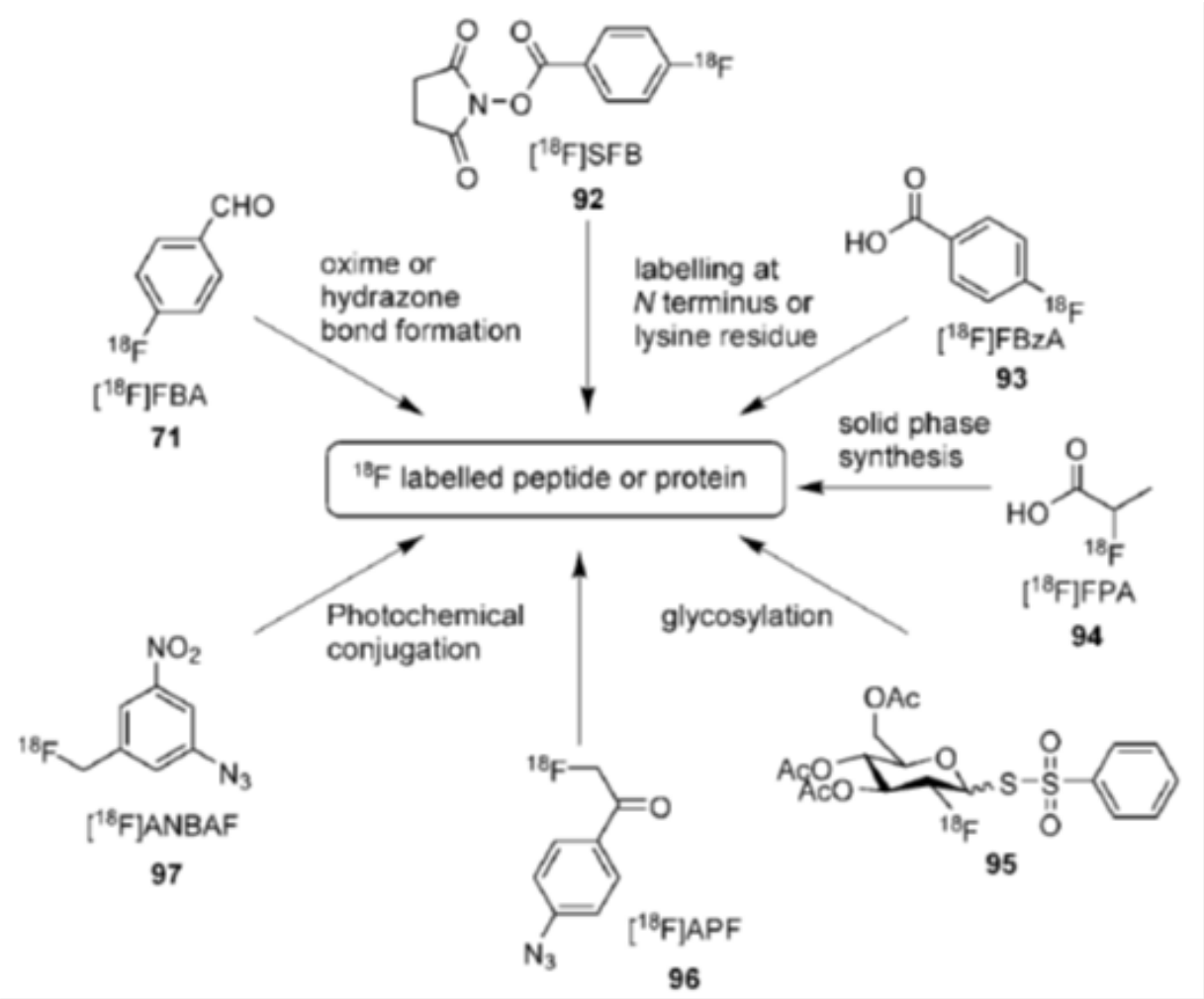


deprotection NaOH



Fluorination performed in absolute absence of water

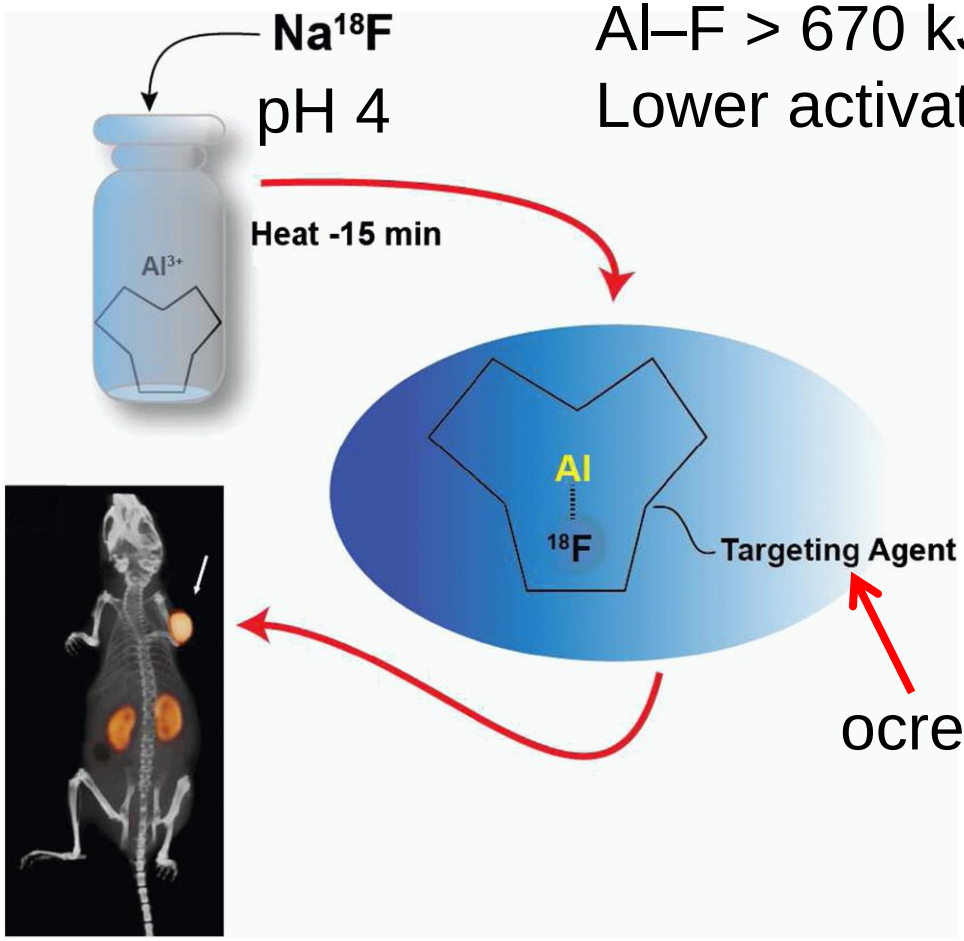
Prostetic groups for ^{18}F labeling of biomolecules



Inorganic fluoruration (B, Si, Al…)

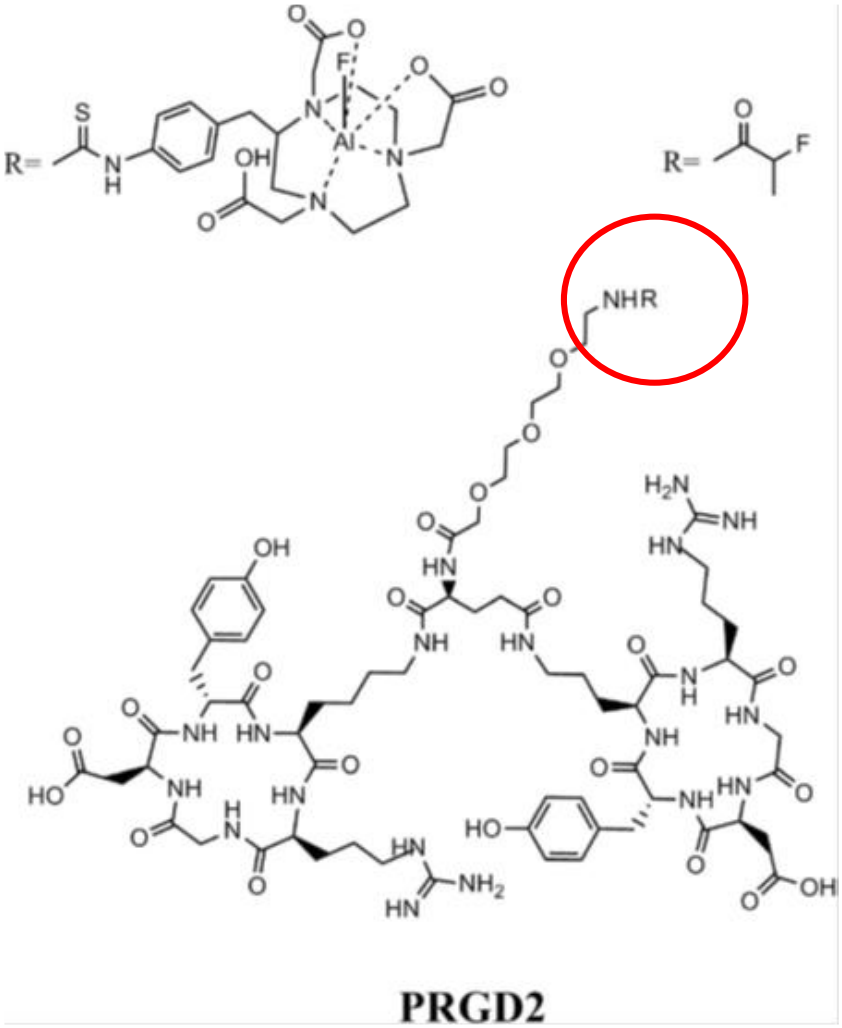
Al–F > 670 kJ mol^{-1} vs 480 kJ mol^{-1} for C–F

Lower activation energy



ocreotide

Clinical study for PET imaging a lung cancer



PRGD2

Cyclic RGD peptides have high affinity and selectivity for the integrin receptor $\alpha_v\beta_3$

Visualizing and quantifying this integrin makes it possible to assess the neo-vascularization of a tumor and determine whether it is likely to respond to anti-angiogenic therapy

Metal radionuclides for PET

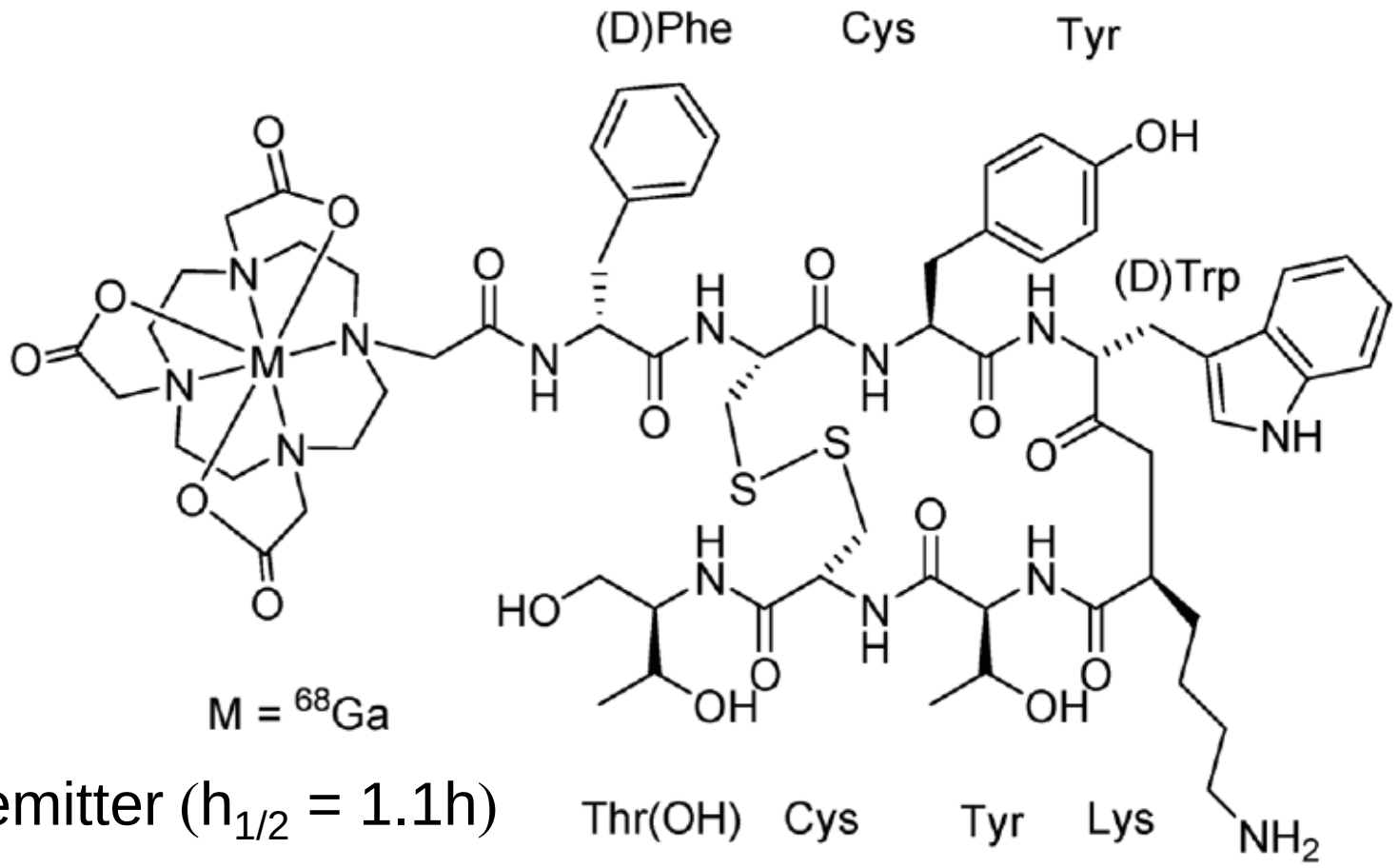
Table 1. Physical Properties of Some Common PET Radiometals[a]

isotope	half-life/h	source	production reaction	decay mode (% branching ratio)	E_{β^+}/keV	abundance, $I_{\beta+}$/%	E_γ/keV (intensity, I_γ/%)	relevant oxidation states	common coordination numbers
^{64}Cu	12.7	cyclotron	^{64}Ni(p,n)^{64}Cu	$\varepsilon + \beta^+$ (61.5) β^+ (17.6) β^- (38.5)	278.2(9)	17.60(22)	511.0 (35.2)	1+, 2+	4, 5, 6
^{68}Ga	1.1	generator	^{68}Ge/^{68}Ga	$\varepsilon + \beta^+$ (100) β^+ (89.1)	836.02(56)	87.94(12)	511.0 (178.3)	3+	4, 5, 6
^{86}Y	14.7	cyclotron	^{86}Sr(p,n)^{86}Y	$\varepsilon + \beta^+$ (100) β^+ (31.9)	535(7)	11.9(5)	443.1 (16.9) 511.0 (64) 627.7 (36.2) 703.3 (15) 777.4 (22.4) 1076.6 (82.5) 1153.0 (30.5) 1854.4 (17.2) 1920.7 (20.8)	3+	8, 9
^{89}Zr	78.4	cyclotron	^{89}Y(p,n)^{89}Zr	$\varepsilon + \beta^+$ (100) β^+ (22.7)	395.5(11)	22.74(24)	511.0 (45.5) 909.2 (99.0)	4+	8

^{68}Ga-DOTA-tyr3-Octreotide

(^{68}Ga-DOTATOC, FDA-approved 2016)

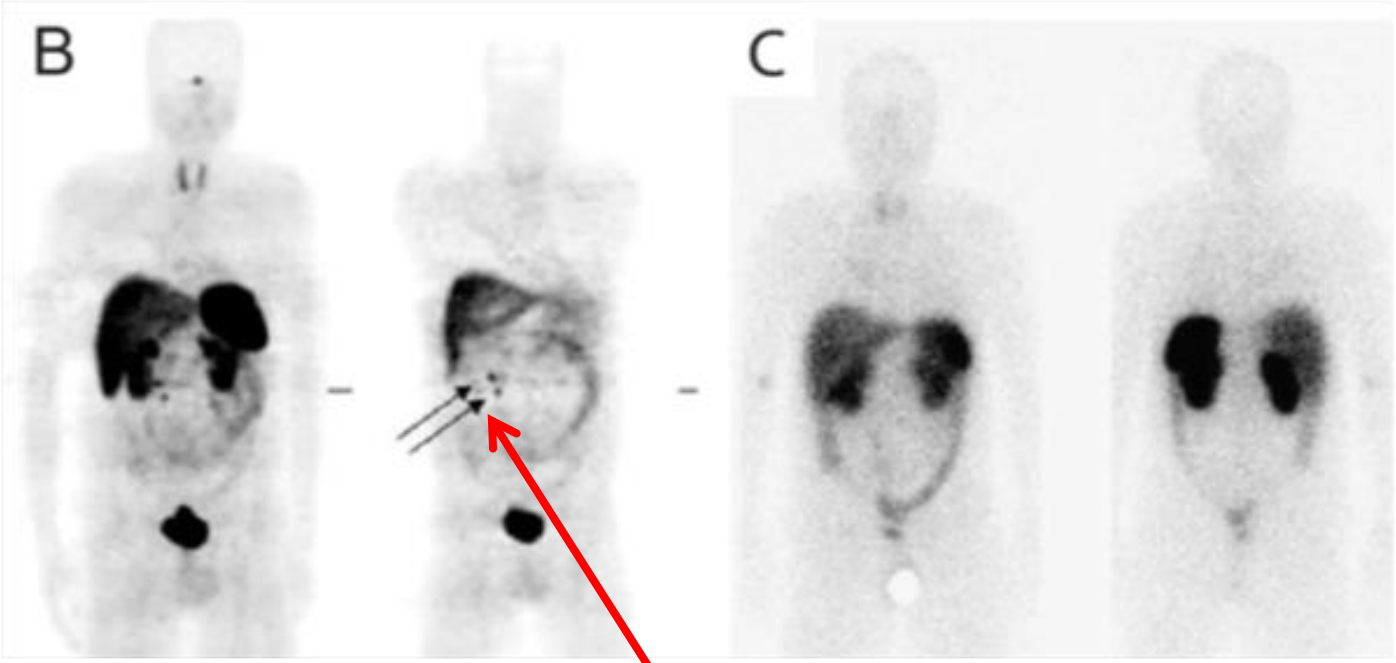
High resolution PET imaging of neuroendocrine tumors



β^+ emitter ($h_{1/2}$ = 1.1h)

^{68}Ga is obtained in a generator from ^{68}Ge through EC.

PET vs SPECT imaging of an endocrinous tumor



^{68}Ga-DOTATOC
(PET)

^{111}In-DPTA-ocreotide
(SPECT)

abdominal lymphnodes

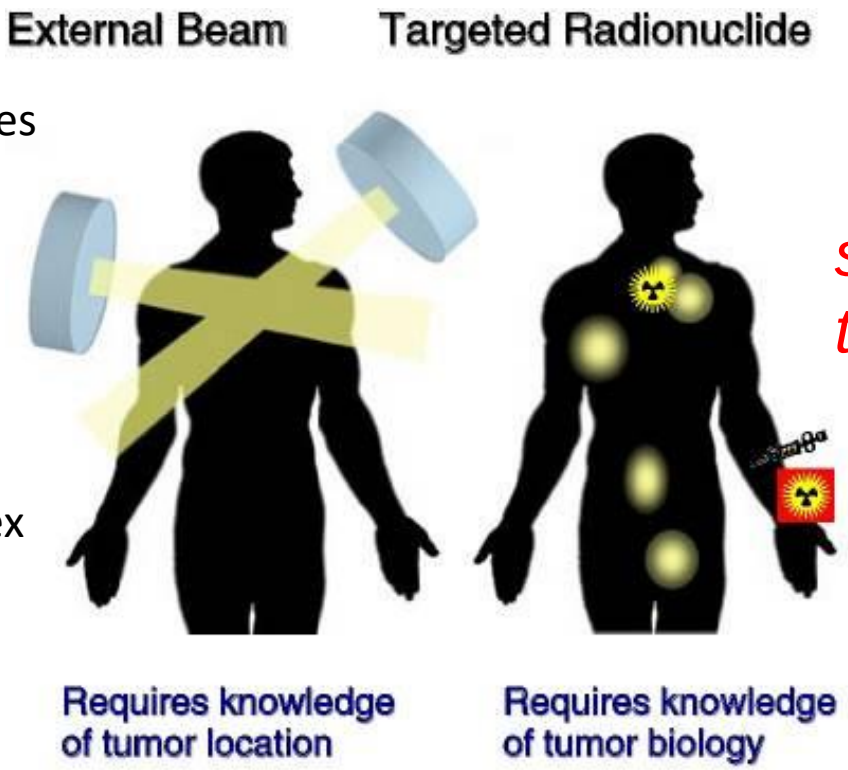
Targeted Radiotherapy (*Radio(immuno)therapy*)

Required radiation dosages

- lymphomas: 1500–2000 cGy
- solid tumors: 3500–10000 cGy

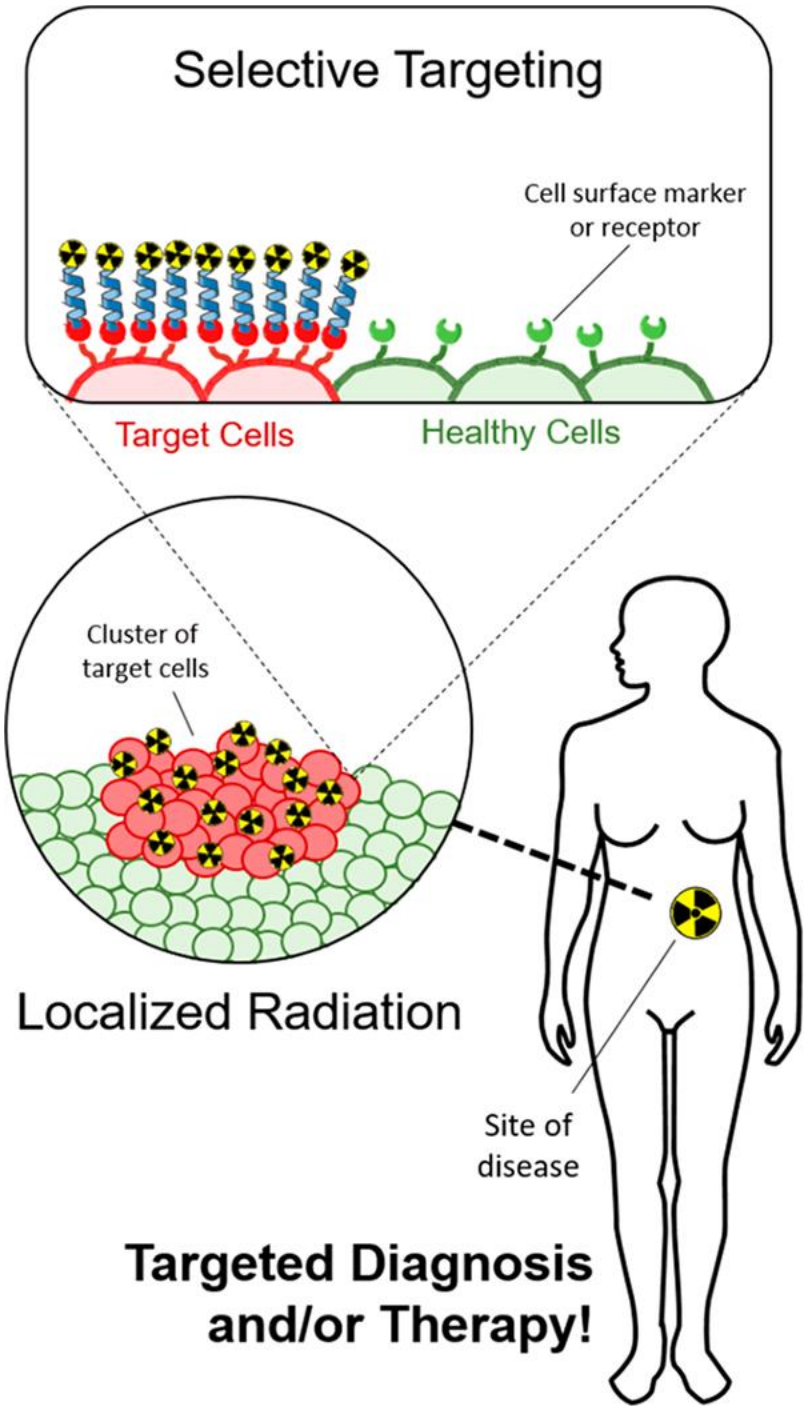
Required Therapeutic Index

- TI > 10 for kidney and lung
- TI > 50 for spinal cord

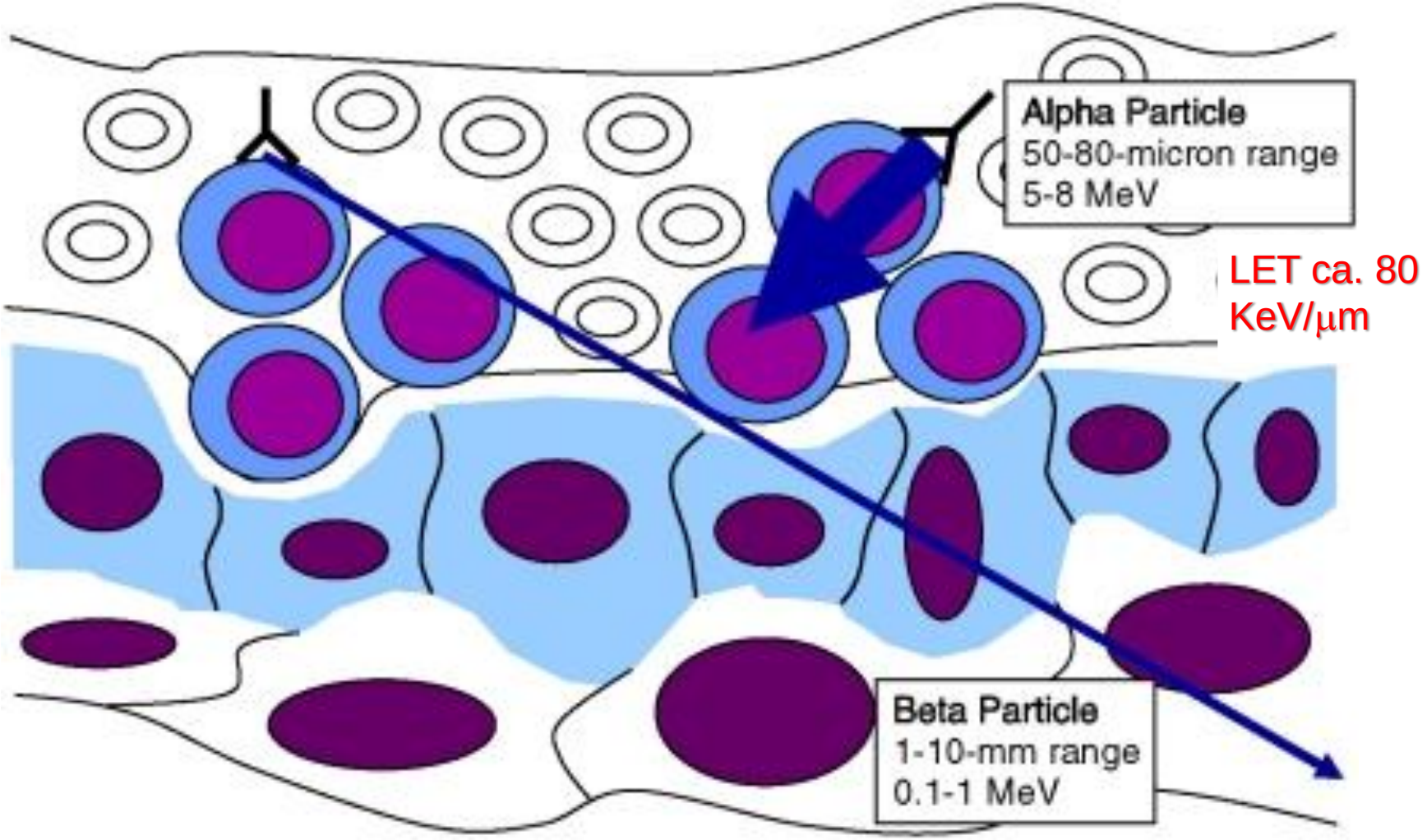


systemic treatment

TI = therapeutic index


Selective Targeting
Cell surface marker or receptor
Target Cells
Healthy Cells
Cluster of target cells
Localized Radiation
Site of disease
Targeted Diagnosis and/or Therapy!

Penetrating power of α and β particles



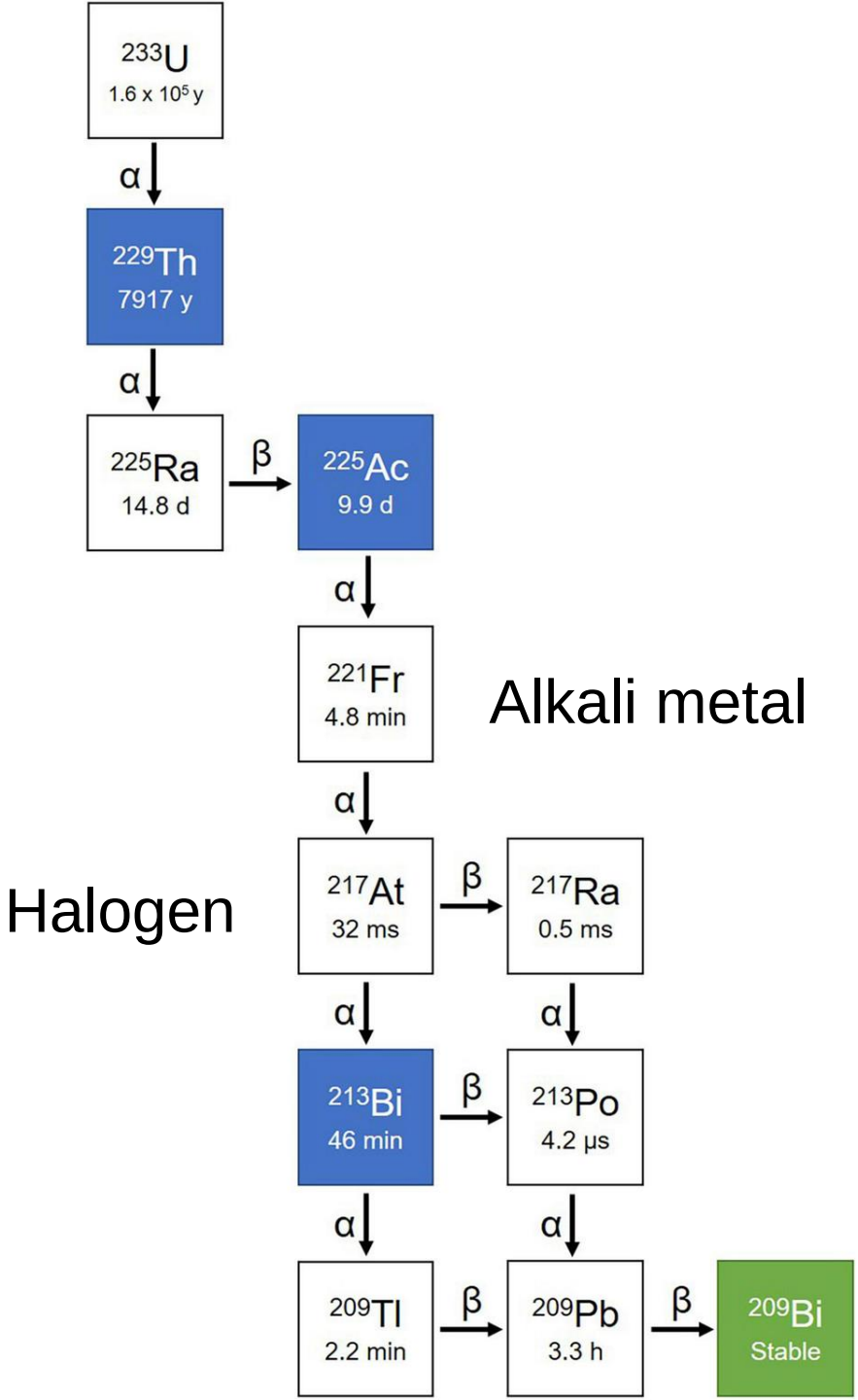
linear energy transfer (LET, KeV/μm)

Linear Energy Transfer (LET) refers to the amount of energy transferred by an ionizing particle to the material it passes through per unit distance traveled. It essentially quantifies the energy deposited by radiation into matter, with **higher LET generally leading to more damage in biological systems**

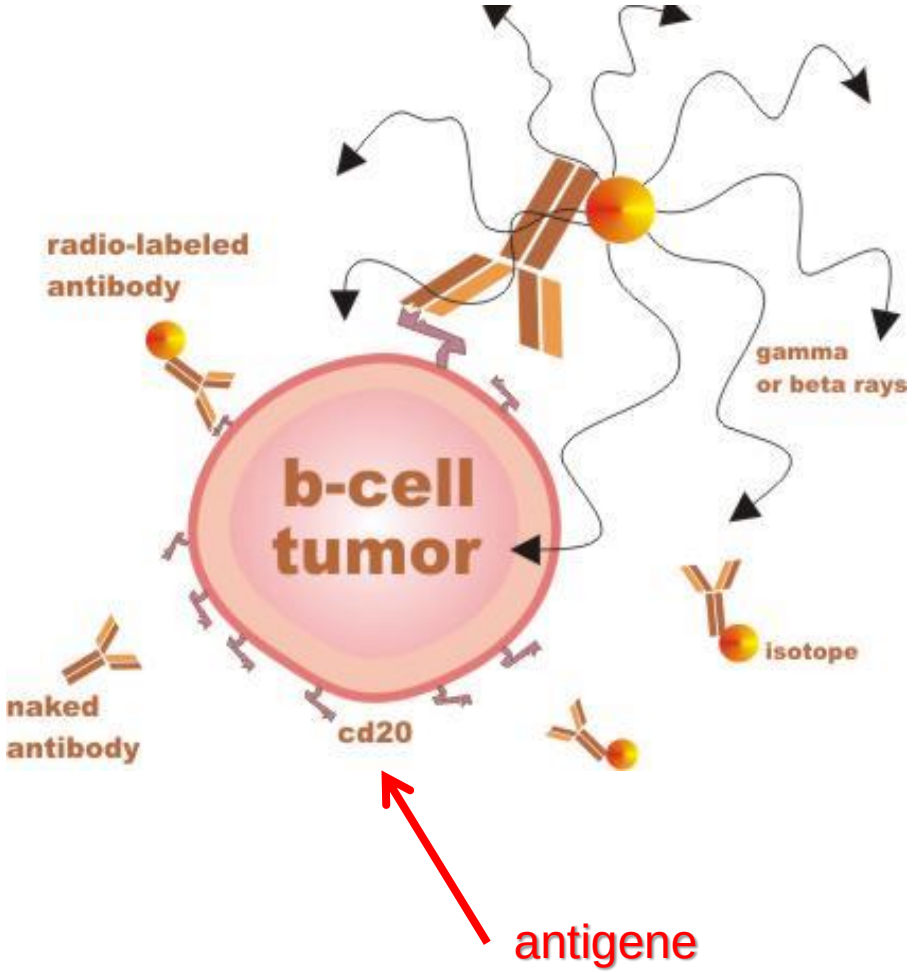
Main radionuclides for Targeted Radiotherapy

Radionuclide	**Half life**	**Average energy of decay particle (KeV)**
^{67}Cu (β, γ)	62 h	
^{90}Y (β)	64 h	934
^{153}Sm (β, γ)	46 h	
^{131}I (β, γ)	8 d	
^{177}Lu(β, γ)	6.6 d	134
^{188}Re (β, γ)	17 h	
^{213}Bi (α, β, γ)	1 h	
^{225}Ac ($5\alpha + 3\beta$)	10 d	5800 - 8400

Due to the different energy, the average tissue penetration of β particles is ca. 2 mm for ^{177}Lu *vs* 11 mm for ^{90}Y


233U
1.6 x 10^5 y
α
229Th
7917 y
α
225Ra
14.8 d
β
225Ac
9.9 d
α
221Fr
4.8 min
α
217At
32 ms
β
217Ra
0.5 ms
α
α
213Bi
46 min
β
213Po
4.2 µs
α
α
209Tl
2.2 min
β
209Pb
3.3 h
β
209Bi
Stable
Alkali metal
Halogen

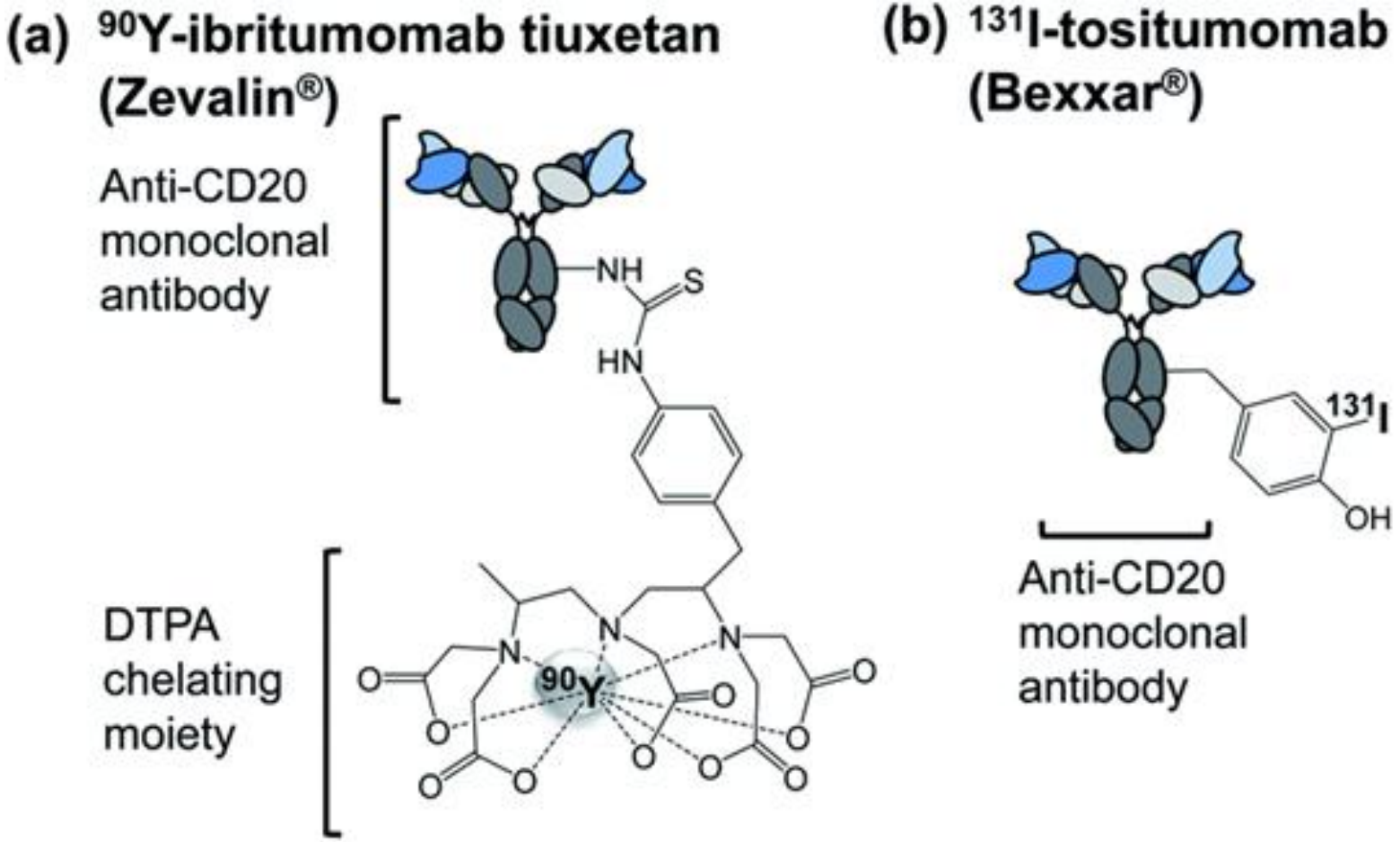
Treatment of B-cell non-Hodgkin's limphoma



ideal antigen:

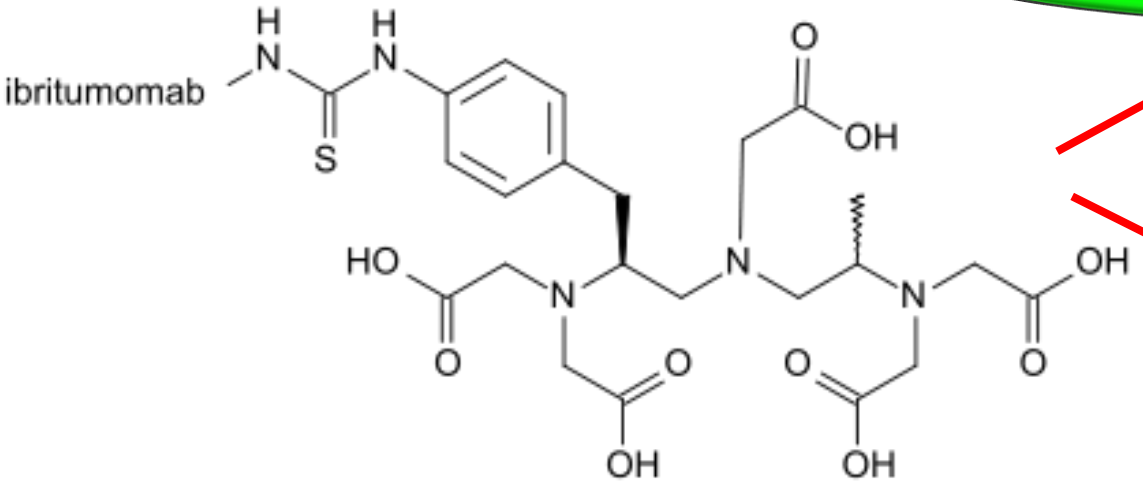
- highly expressed with uniform density on the surface of all tumor cells (> 10^5 sites per cell),
- not to be expressed (or much less) in healthy cells,
- antigen-antibody affinity in the nanomolar order
- internalization

FDA approved



Zevalin®

Ibritumomab (MC antibody) covalently conjugated to the ^{90}Y chelator tiuxetan



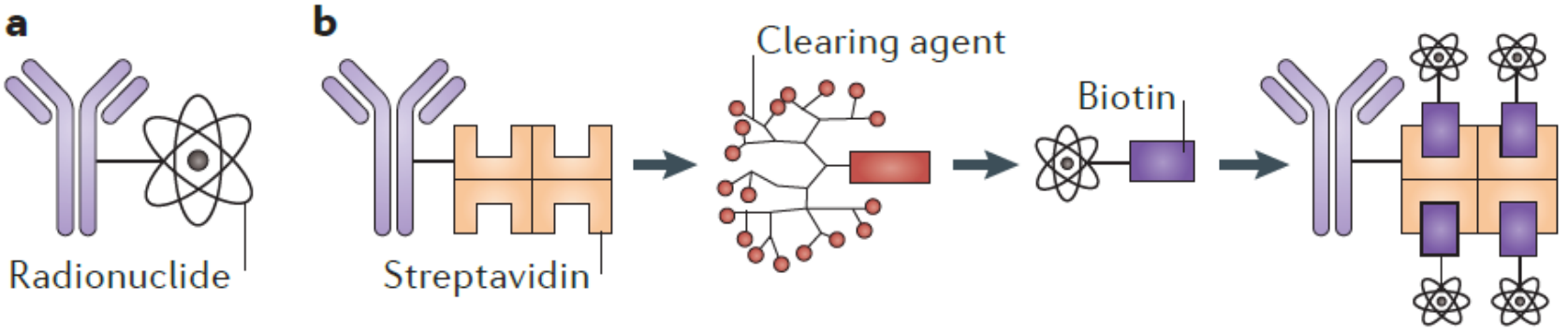
$^{111}In^{3+}$ or – better – $^{86}Y^{3+}$ for imaging

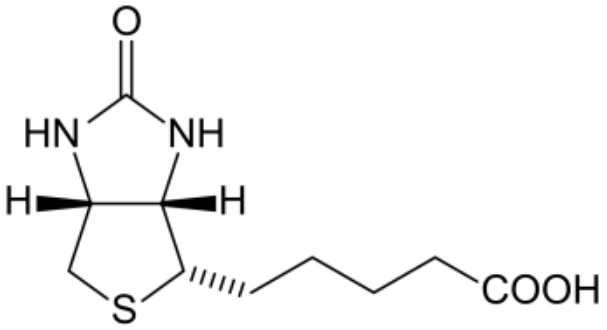
^{90}Y is a pure β^- emitter

$^{90}Y^{3+}$ for therapy

Example of the matched-pair approach

multi-step pre-targeted radio-immunotherapy (PRIT)

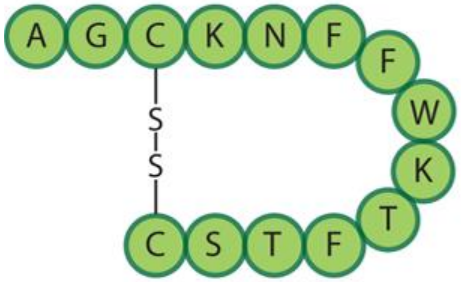




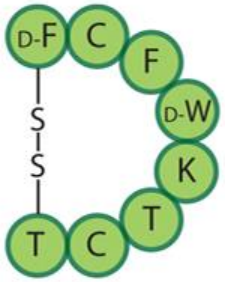
Biotin

The **streptavidin-biotin** binding constant is in the order of 10^{14} mol L^{-1}

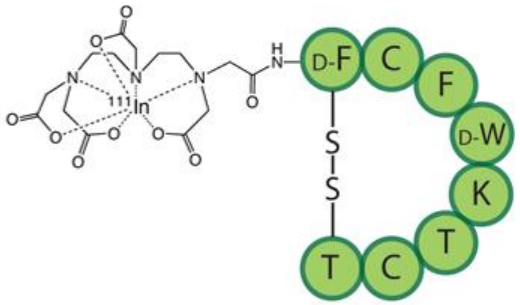
Radio-immunotherapy of neuroendocrine tumors



Somatostatin



Octreotide



^{111}In-DTPA-Octreotide

SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTATOC for PET imaging

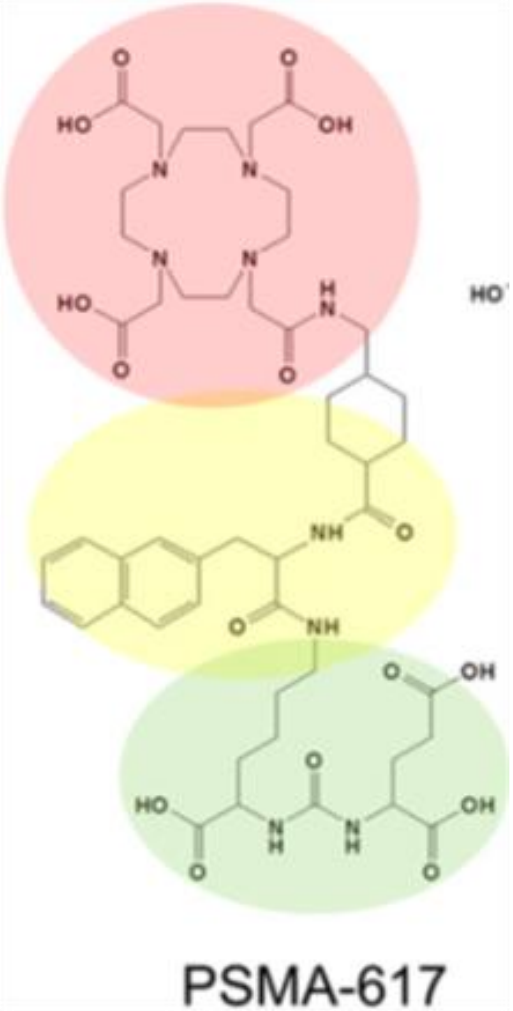
^{90}Y-DOTATOC and ^{177}Lu-DOTATATE for radiotherapy

^{177}Lu-DOTATATE (*Lutathera*) FDA approved in 2018 for treatment of neuroendocrine pancreatic tumors

^{177}Lu-PSMA-167

Linker

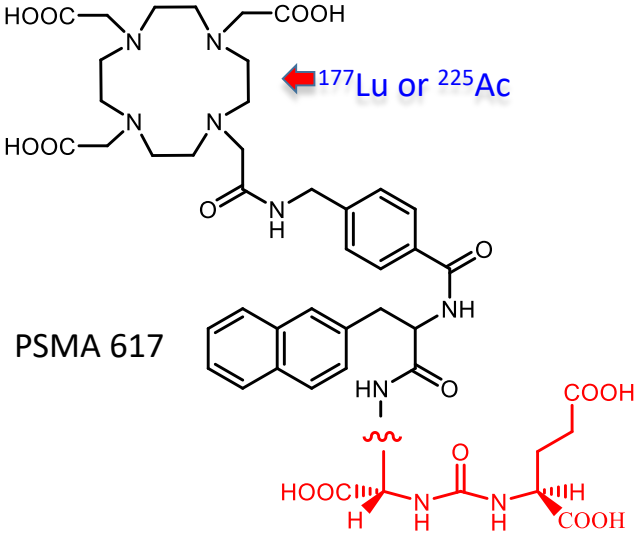
Peptidomimetic

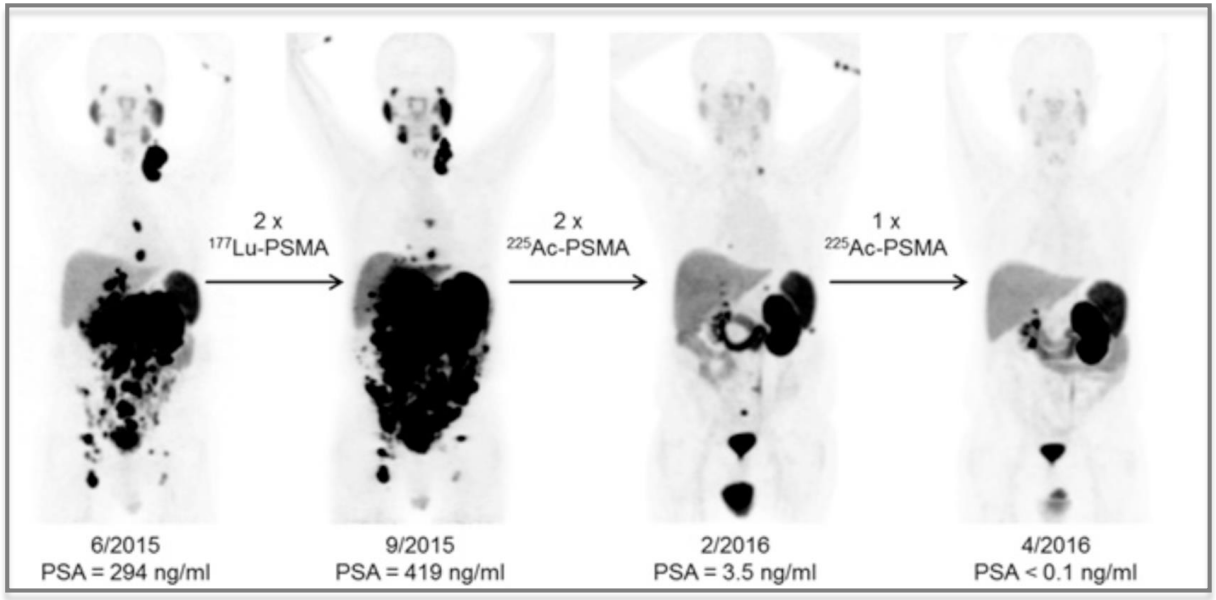


PSMA = *prostate-specific membrane antigen*

The Concept of Radiopharmaceutical Production: α-emitters

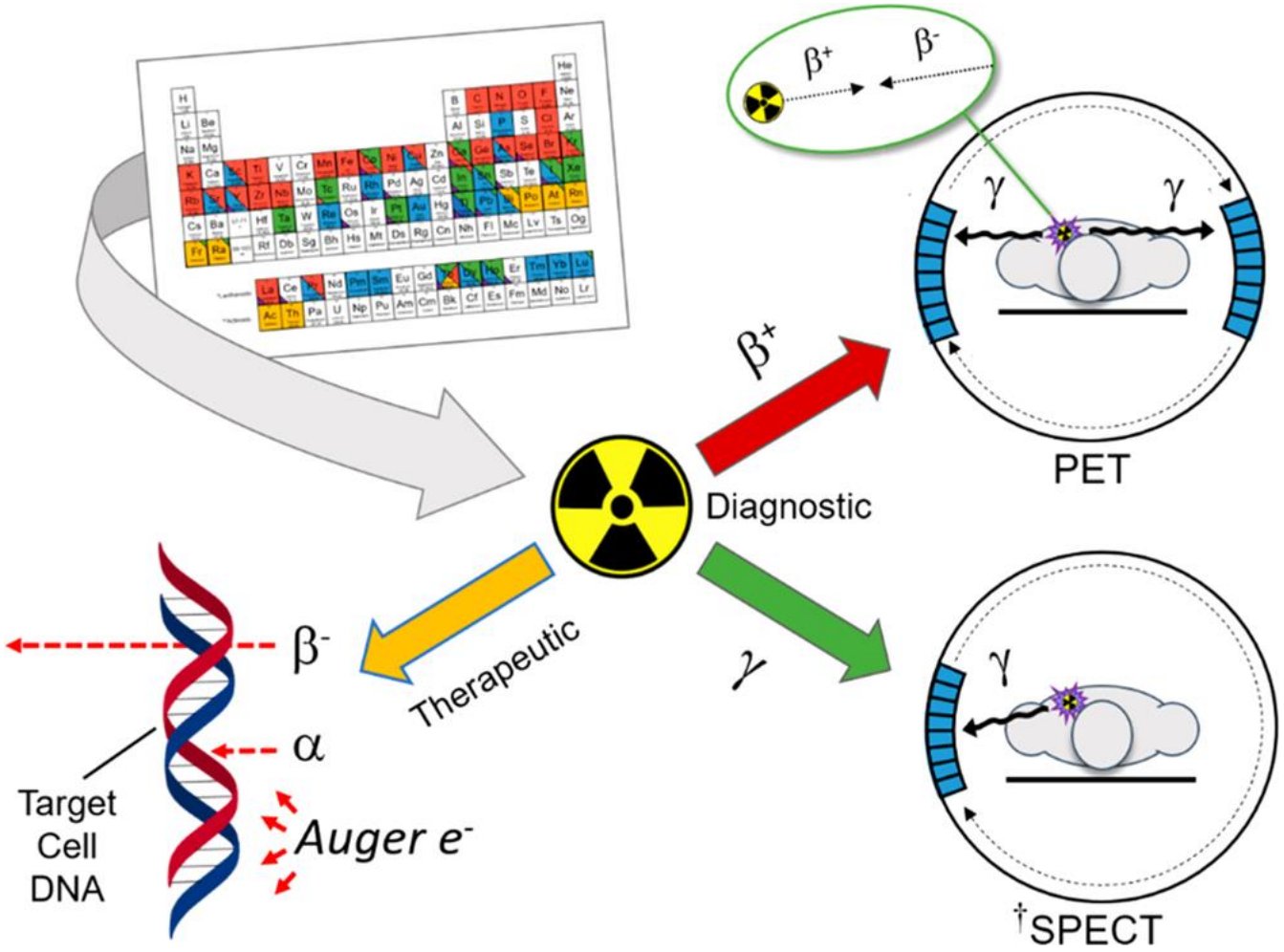
An example for ^{225}Ac PSMA617 α-emitters in radiotherapy





- Patient **did not respond** to [^{177}Lu]LUPSMA-617 radionuclide treatment
- PCa showed continued **progression** after two rounds of ^{177}Lu
- Three cycles of [^{225}Ac]AcPSMA-617 treatment led to **complete response**

Kratochwil *et al.*, *J. Nucl. Med.*, **2016**, *57*, 1170


β+
β-
γ
γ
PET
β+
Diagnostic
Therapeutic
γ
γ
†SPECT
β-
α
Auger e-
Target
Cell
DNA