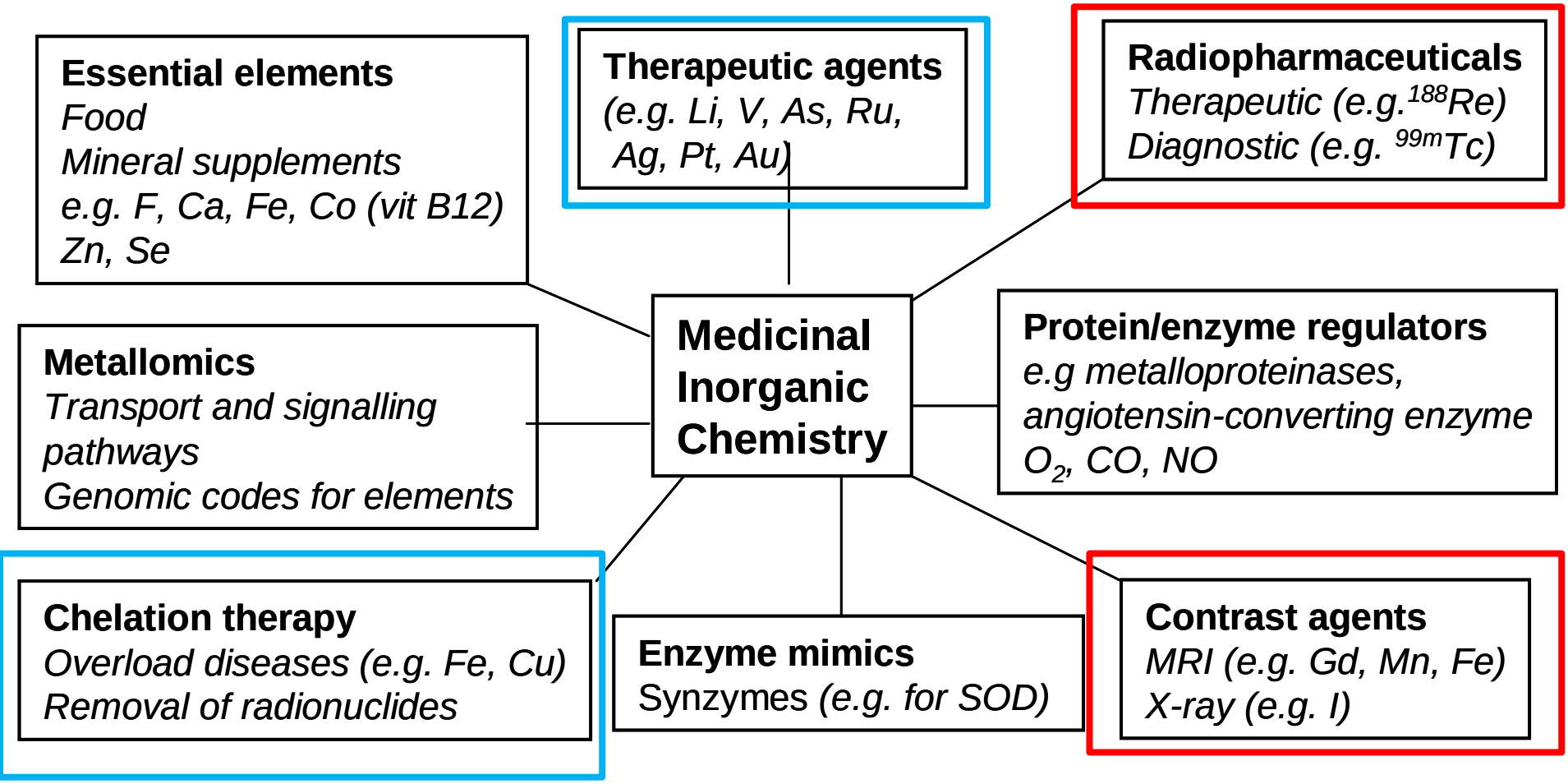
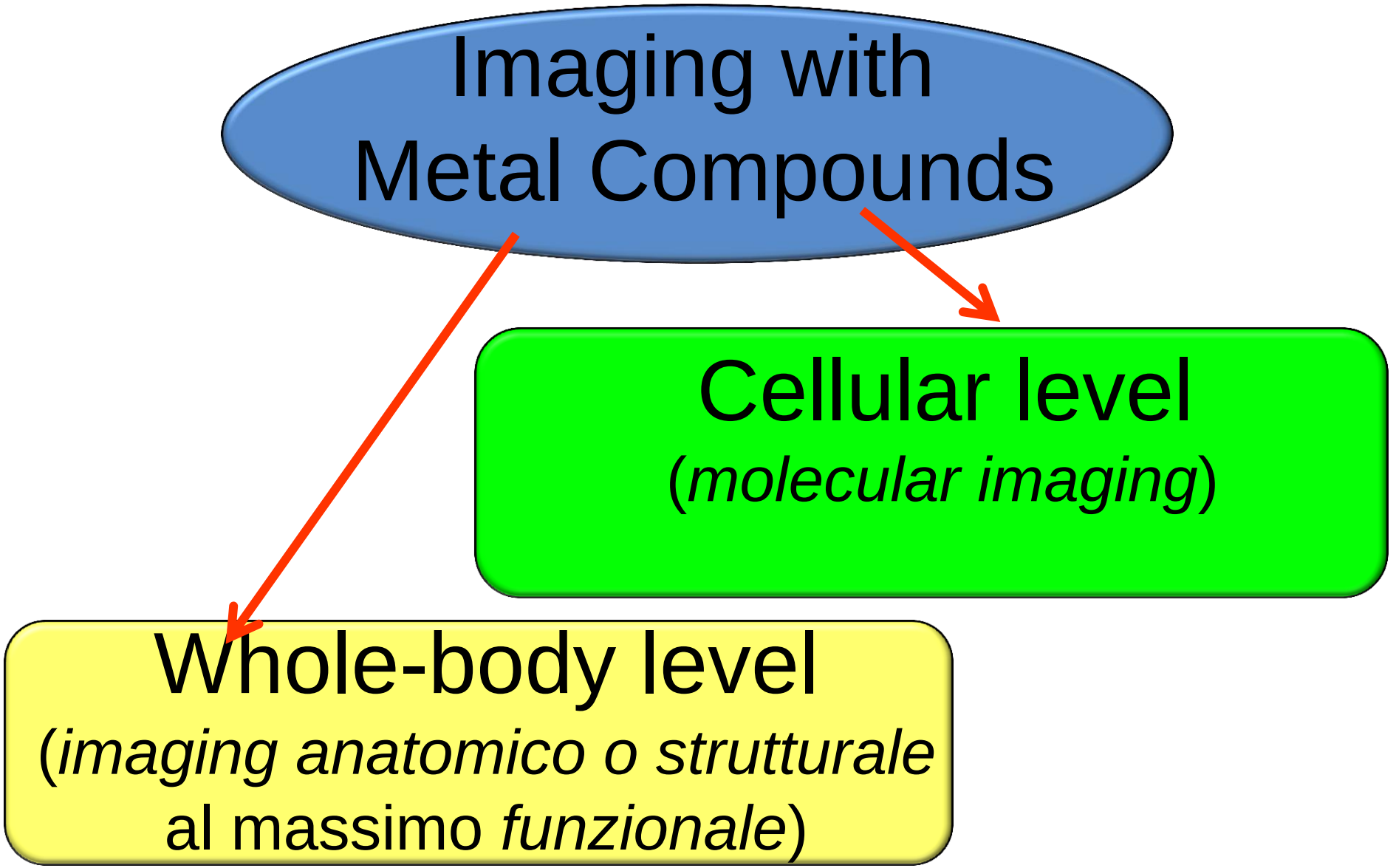
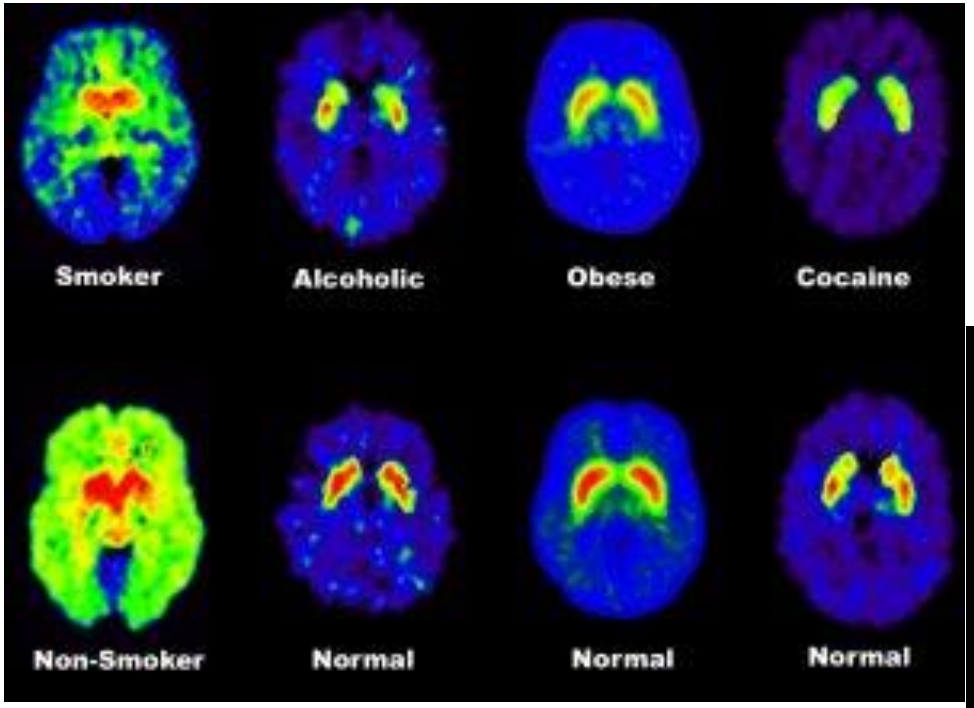
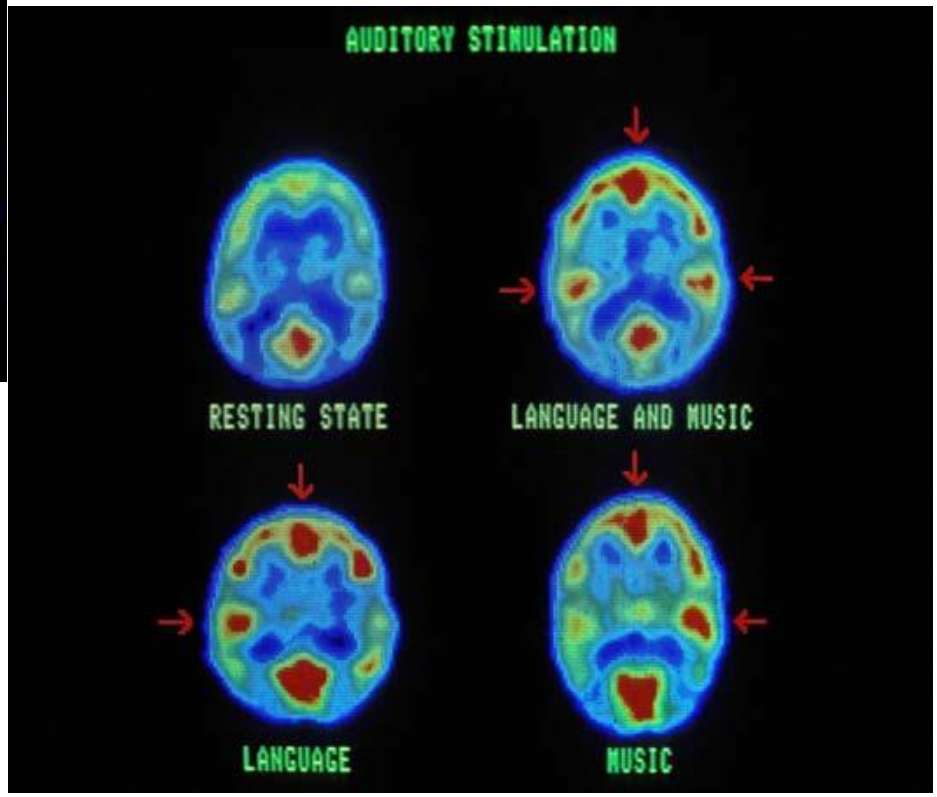

Essential elements
Food
Mineral supplements
e.g. F, Ca, Fe, Co (vit B12)
Zn, Se
Therapeutic agents
(e.g. Li, V, As, Ru,
Ag, Pt, Au)
Radiopharmaceuticals
Therapeutic (e.g. 188Re)
Diagnostic (e.g. 99mTc)
Medicinal Inorganic Chemistry
Metallomics
Transport and signalling pathways
Genomic codes for elements
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
(*imaging anatomico o strutturale*
al massimo *funzionale*)

Definizione di *molecular imaging* (2007): il *molecular imaging* riguarda la visualizzazione, caratterizzazione e misurazione di processi biologici a livello molecolare o cellulare nell'uomo o in altri organismi viventi.

Molecular Imaging

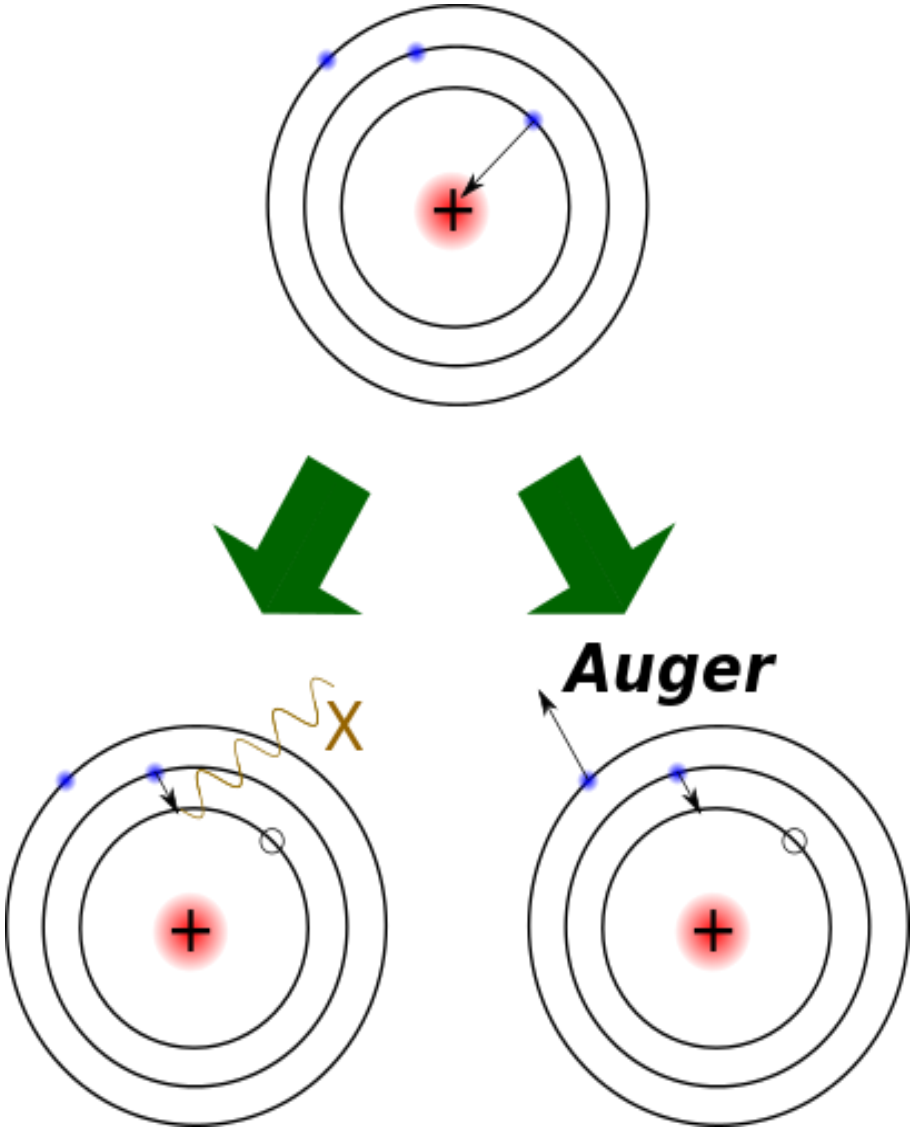


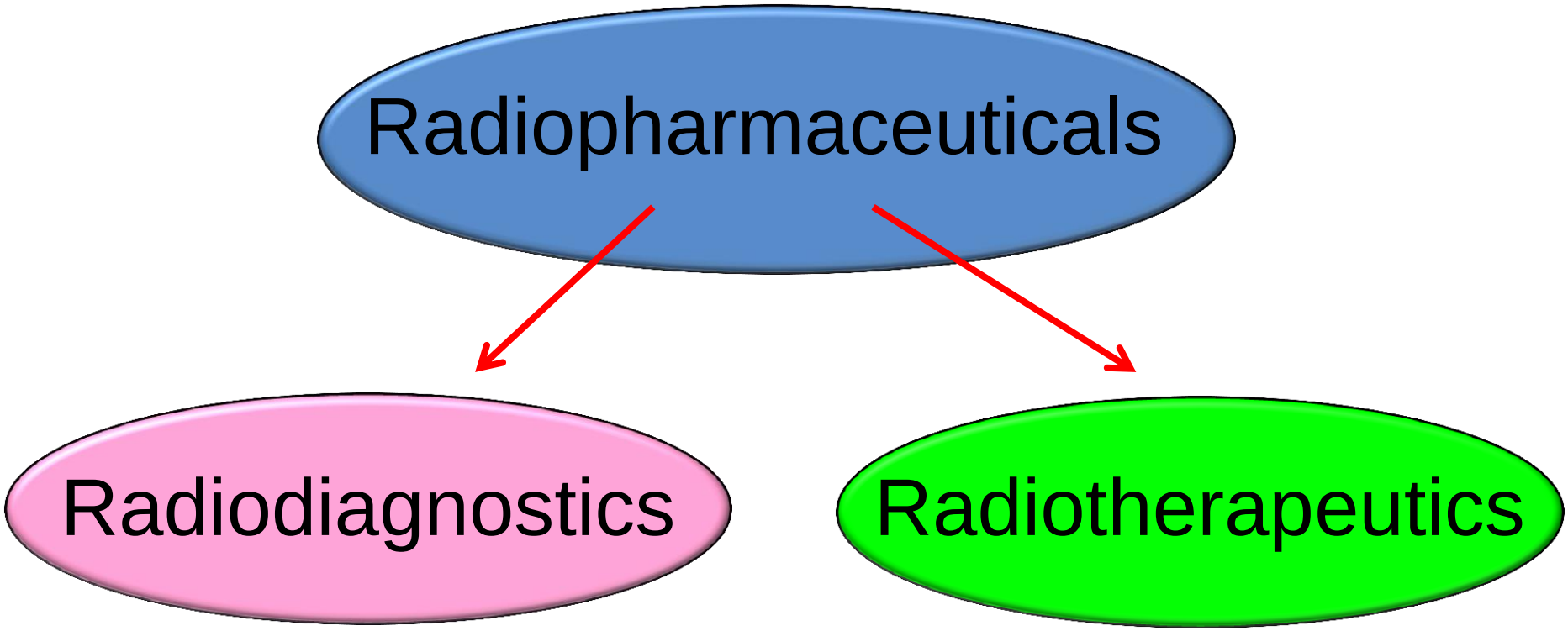


Processi spontanei nei nuclei radioattivi

- Emissione di particelle (α, β-, β+)
- Cattura di elettroni
- Emissione di radiazioni (raggi X, γ)

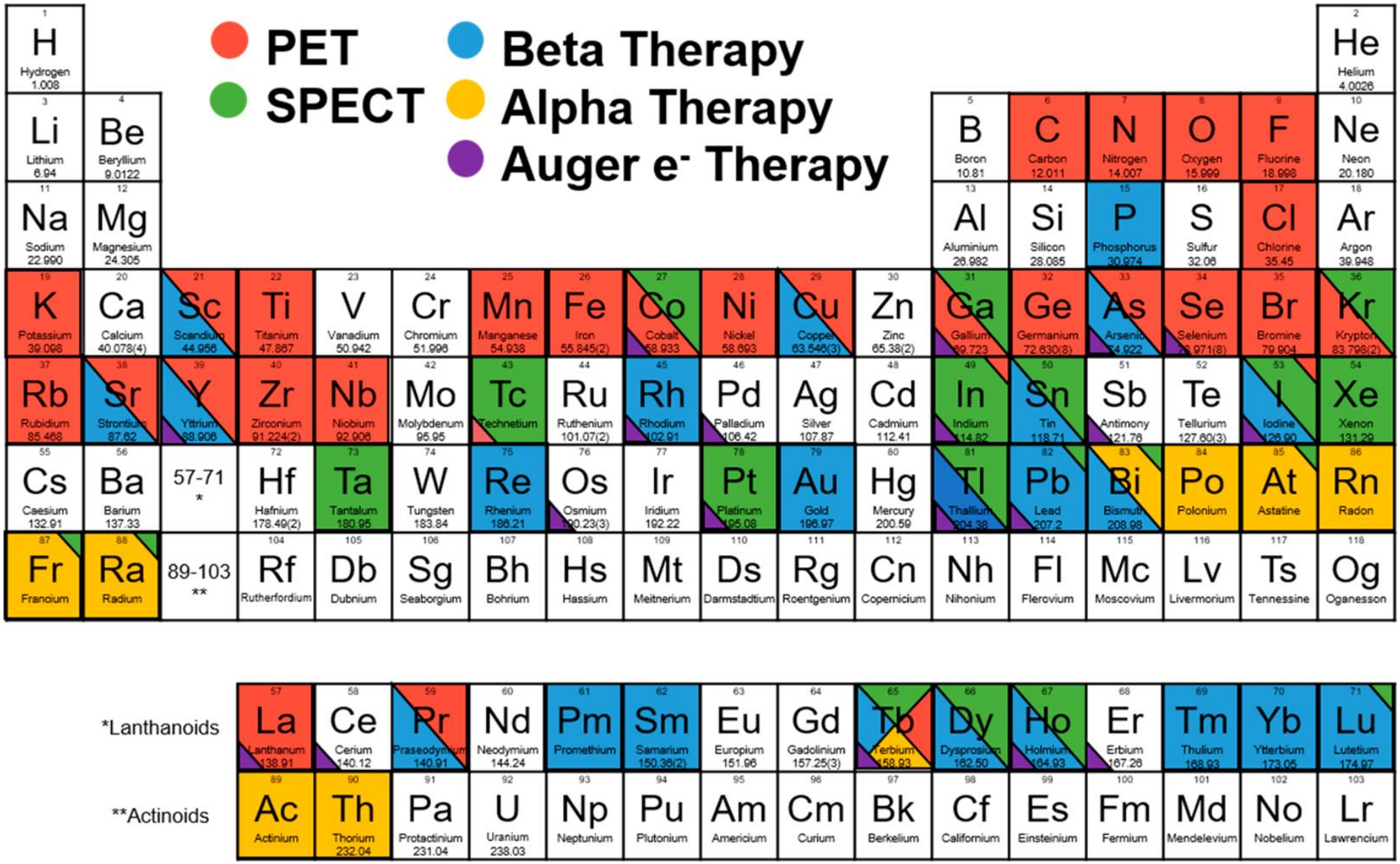
Electron capture (EC)





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

α or β^- emitters


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

Preparazione di un radio-farmaco

I radio-isotopi si possono ottenere:

- per decadimento di radionuclidi a tempo di semi-vita più lungo in un generatore
- tramite un ciclotrone, bombardando un opportuno elemento o suo composto con particelle cariche accelerate, tipicamente protoni o nuclei di deuterio;
- tramite bombardamento nucleare con neutroni in un reattore nucleare

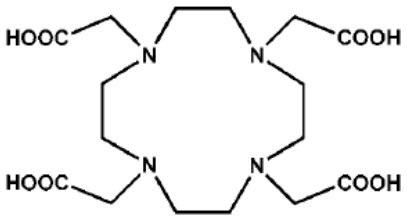
- Purificazione da isotopo padre e sottoprodotti

- Incorporazione in un composto, spesso tramite un chelante polidentato

Chelanti più comuni

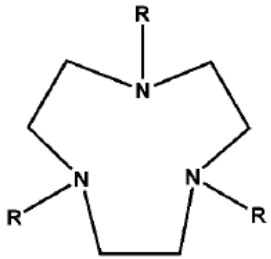
Diethylenetriamino-pentaaceticacid

a)



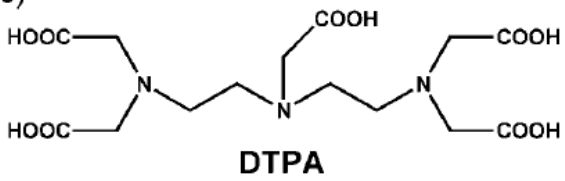
DOTA

b)



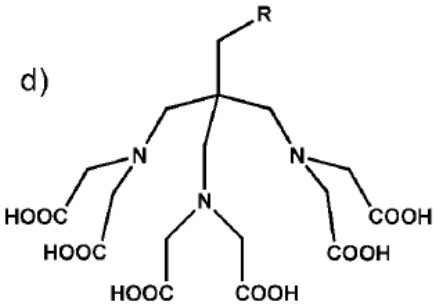
NOTA	R = CH_2COOH
TACN-TM	R = CH_2CH_2SH
NOTP	R = $CH_2PO_3H_2$
NOTPME	R = $CH_2PO_2(OCH_2CH_3)$

c)



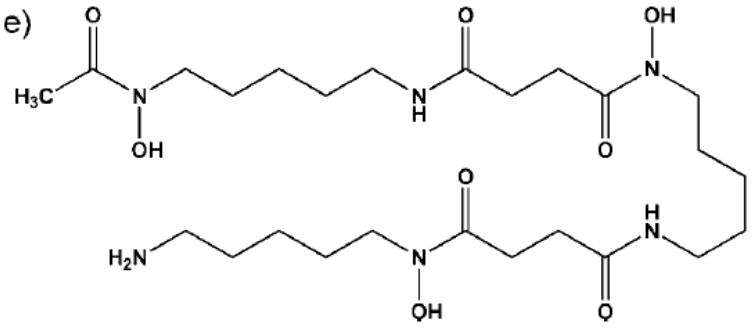
DTPA

d)

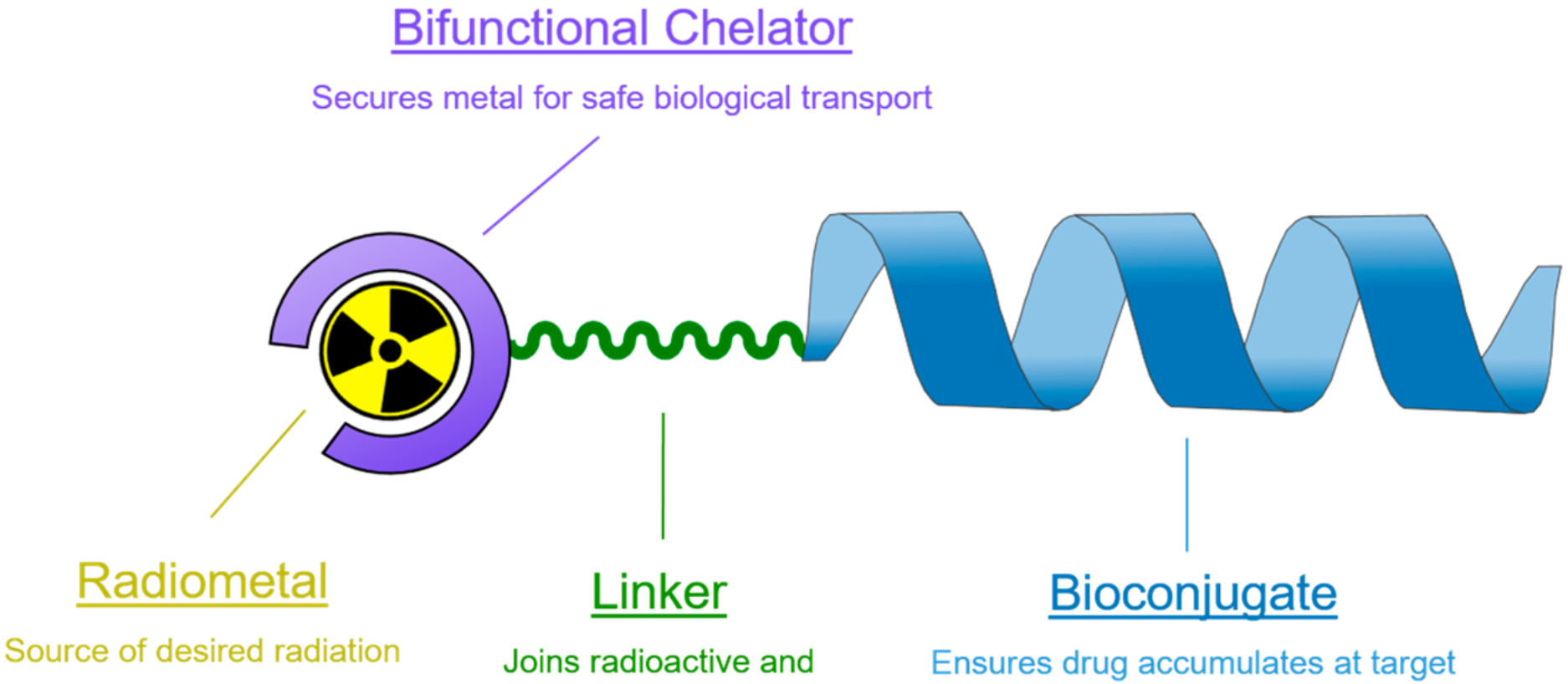


TAME Hex

e)



Targeted Approach
(*Trojan horse*)



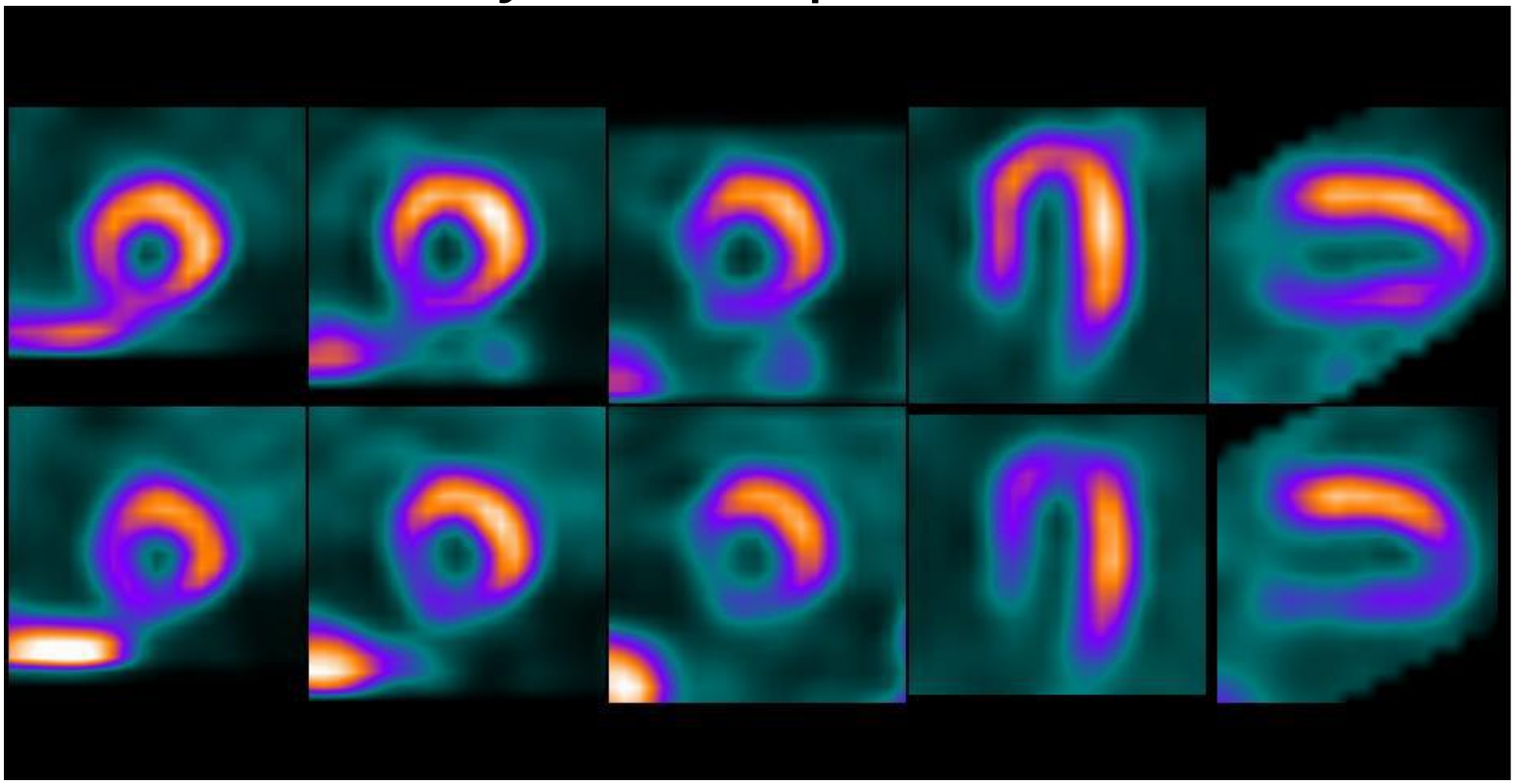
(targeting vector)

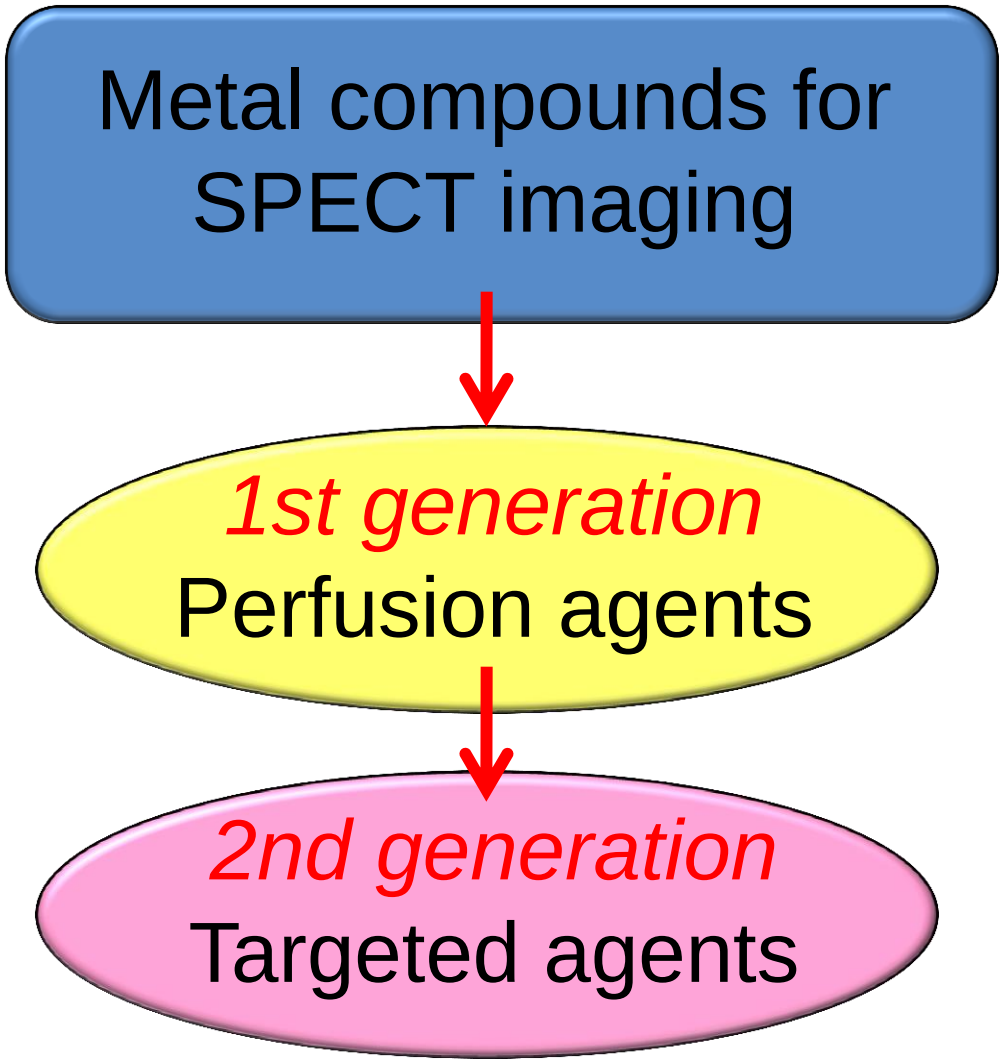
Targeting molecules: monoclonal antibodies, peptides, vitamins, carbohydrates,..

SPECT: Single Photon Emission Computed Tomography

γ emitters, 100 – 250 keV

Myocardial perfusion




Metal compounds for SPECT imaging
1st generation
Perfusion agents
2nd generation
Targeted agents

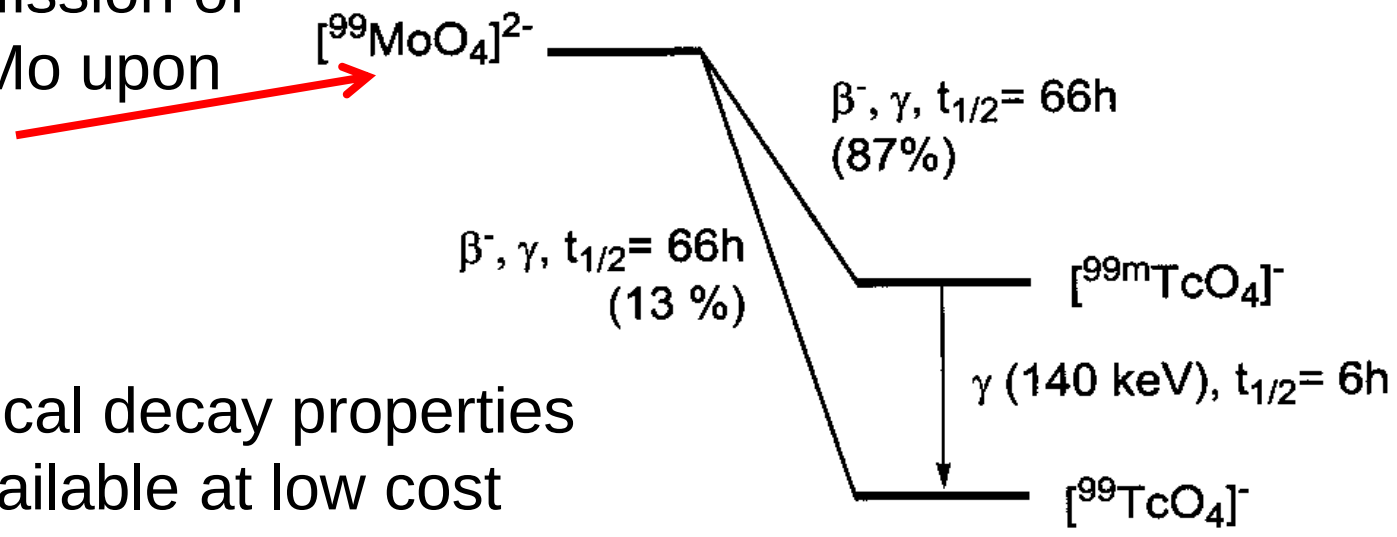
Main radionuclides for SPECT

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)

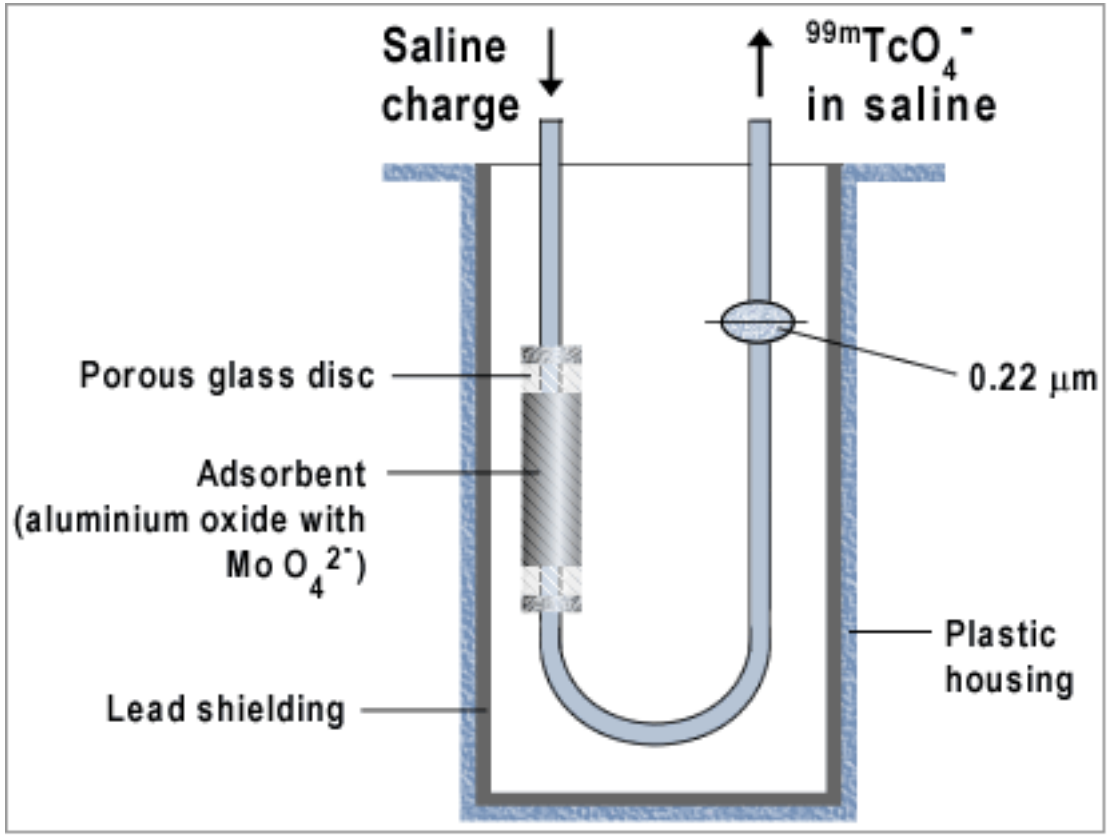
Obtained from fission of ^{235}U or from ^{98}Mo upon (n, γ) reaction



- 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)

Pure β-emitter

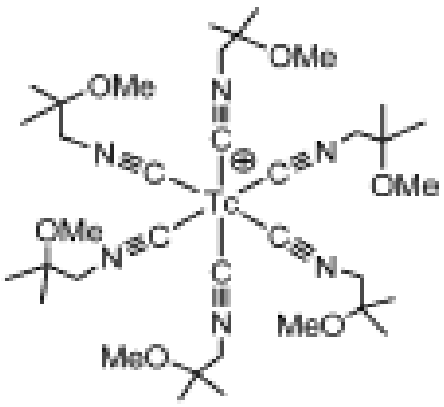
Generatore di $^{99m}TcO_4^-$



‘*Shake and bake*’ principle

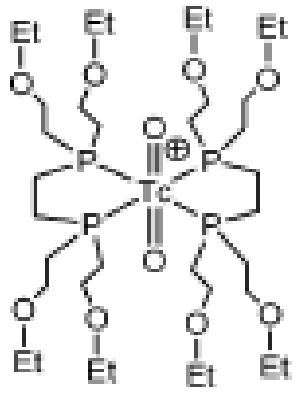
- Preparations must be performed in kits
- Yields must be > 98% (even at very low metal ion concentration)
- Compound must be ready for administration
- No lenghty purification or separation
- Aqueous solutions
- Non-toxic reagents and byproducts

Radiofarmaci di tecnezio di prima generazione



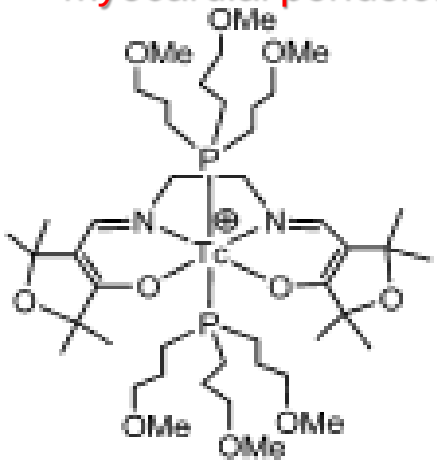
^{99m}Tc-Sestamibi

cardiac imaging



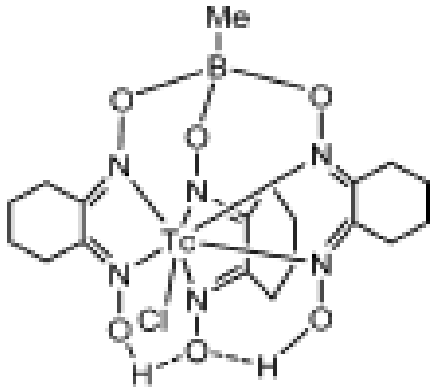
^{99m}Tc-Tetrofosmin

myocardial perfusion

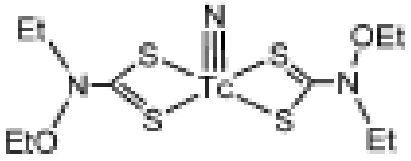


Q12

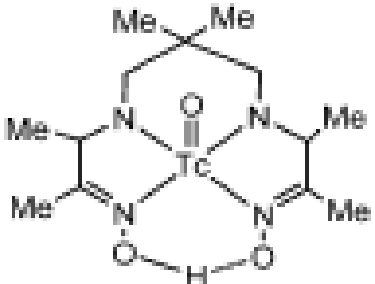
cardiac imaging



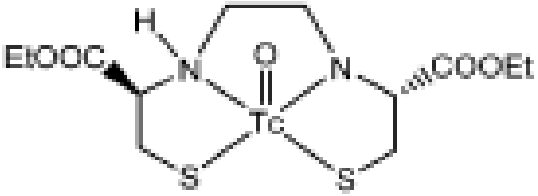
^{99m}Tc-Teboroxime



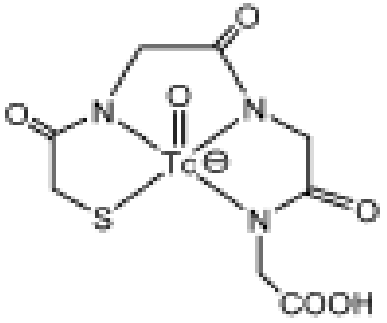
^{99m}TcN-NOET



^{99m}Tc-HMPAO



^{99m}Tc-Bicisate



^{99m}Tc-MAG$_3$

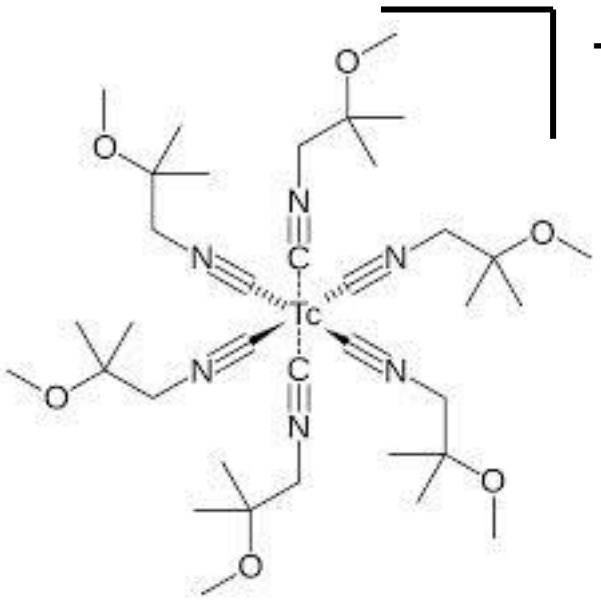
myocardial perfusion

cereberal perfusion

brain imaging

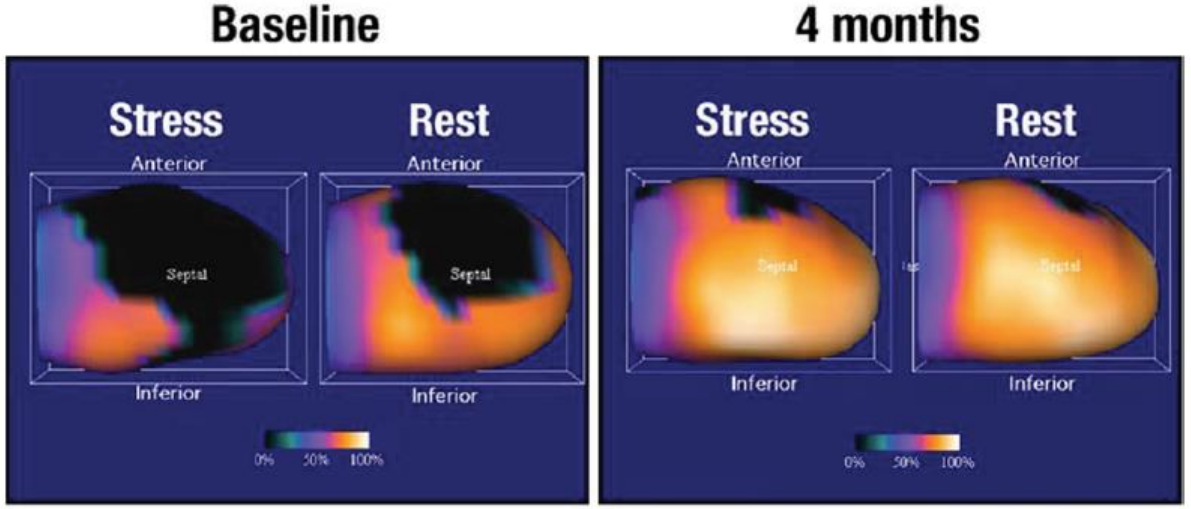
renal imaging

^{99m}Tc-sestamibi

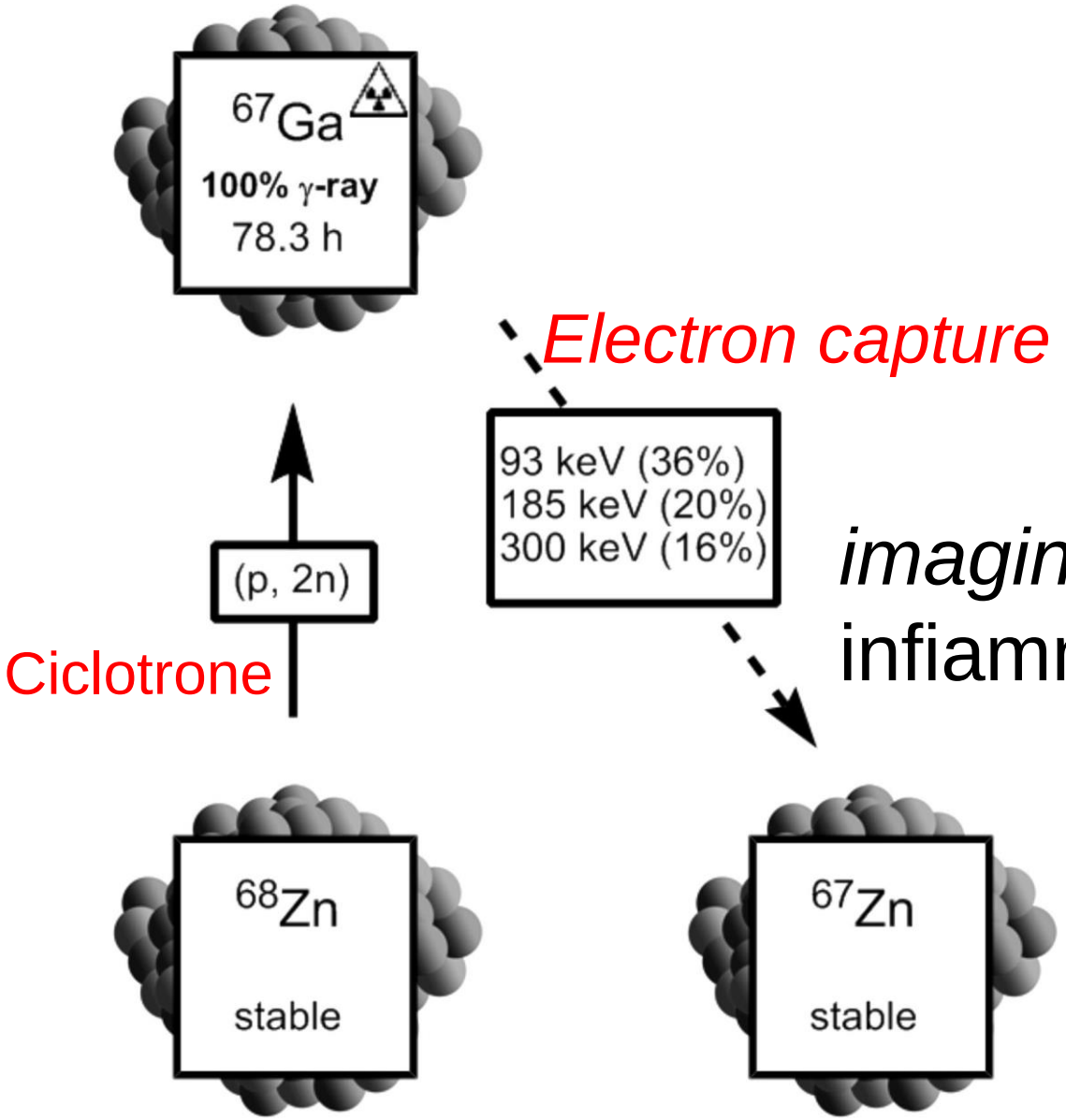


+

Localizzazione nei mitocondri



- Imaging cardiaco
- Diagnosi dei tumori (seno)
- Imaging della tiroide (adenomi)



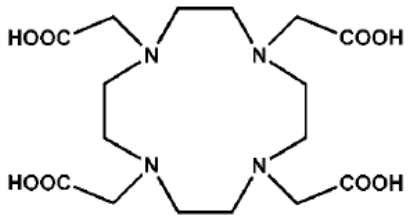
imaging di processi infiammatori e di tumori

Chelators for the "3^+ family": Ga, In, Y and Lanthanides

(e.g. ^{67}Ga, ^{68}Ga, ^{111}In, ^{90}Y, ^{153}Sm, ^{177}Lu)

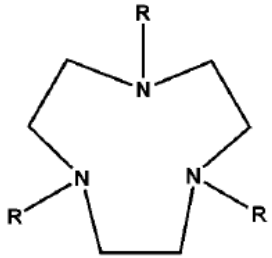
Diethylenetriamino-pentaaceticacid

a)



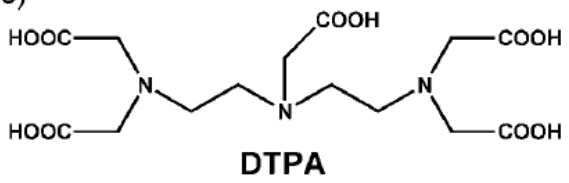
DOTA

b)



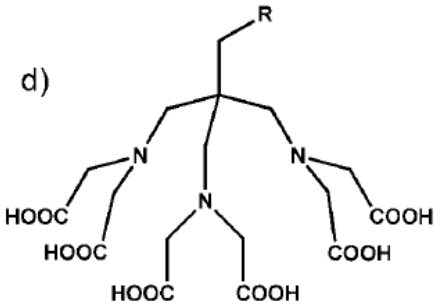
NOTA	R = CH_2COOH
TACN-TM	R = CH_2CH_2SH
NOTP	R = $CH_2PO_3H_2$
NOTPME	R = $CH_2PO_2(OCH_2CH_3)$

c)



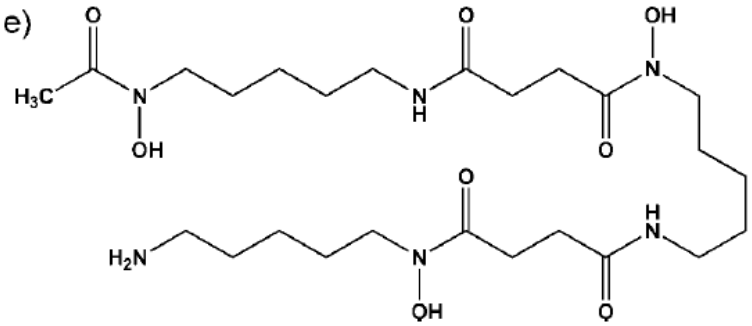
DTPA

d)

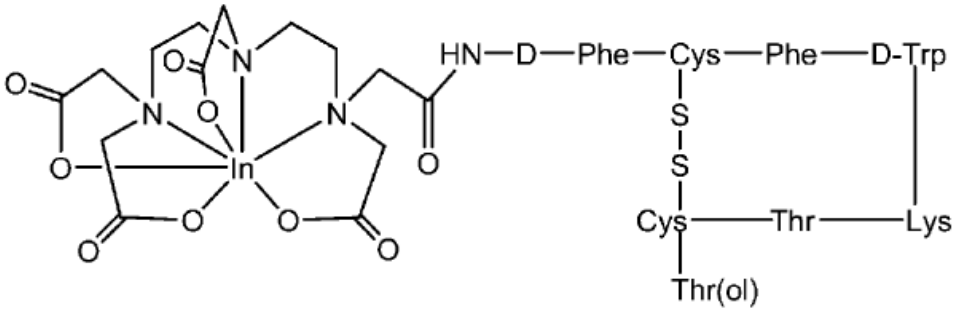


TAME Hex

e)

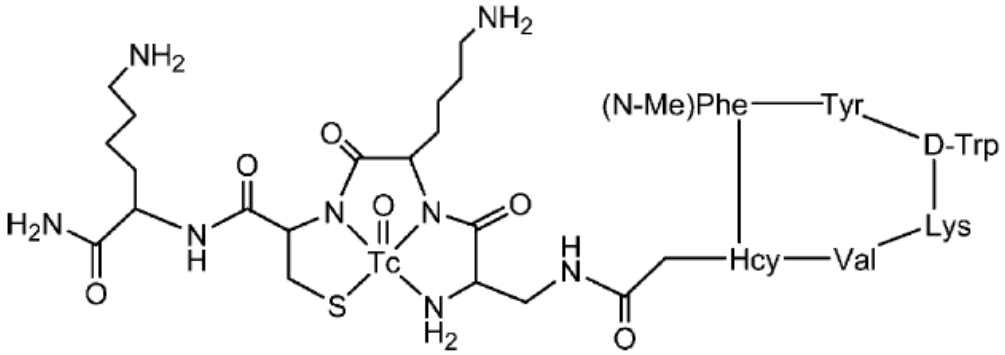


Octreotide e Depreotide
peptidi specifici per i recettori della somatostatina



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

SPECT imaging of neuroendocrine tumors

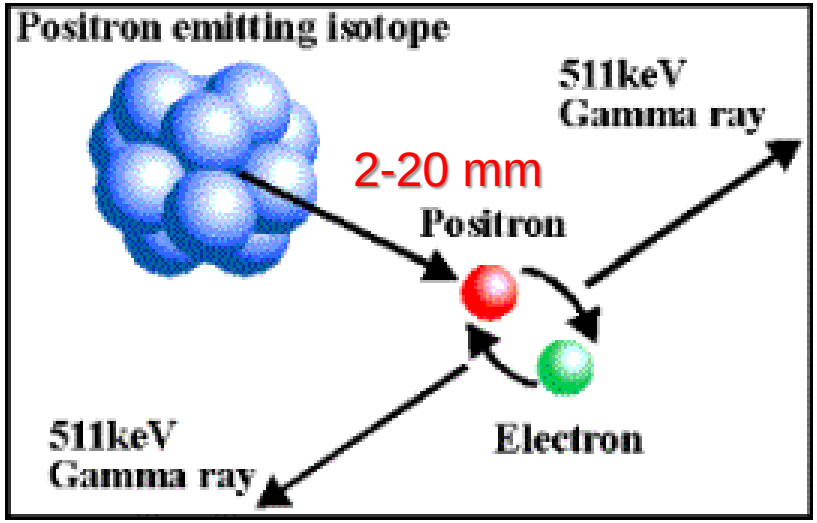


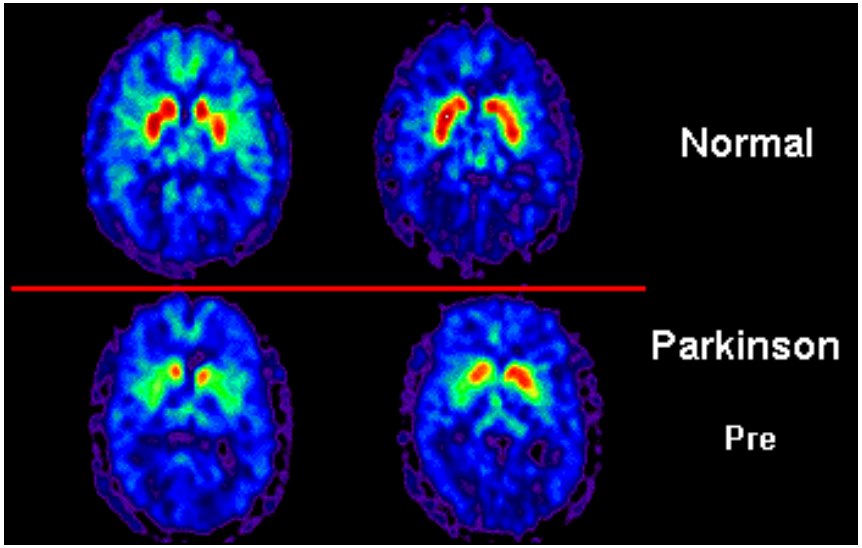
^{99m}Tc-P829 (NeoTect®)

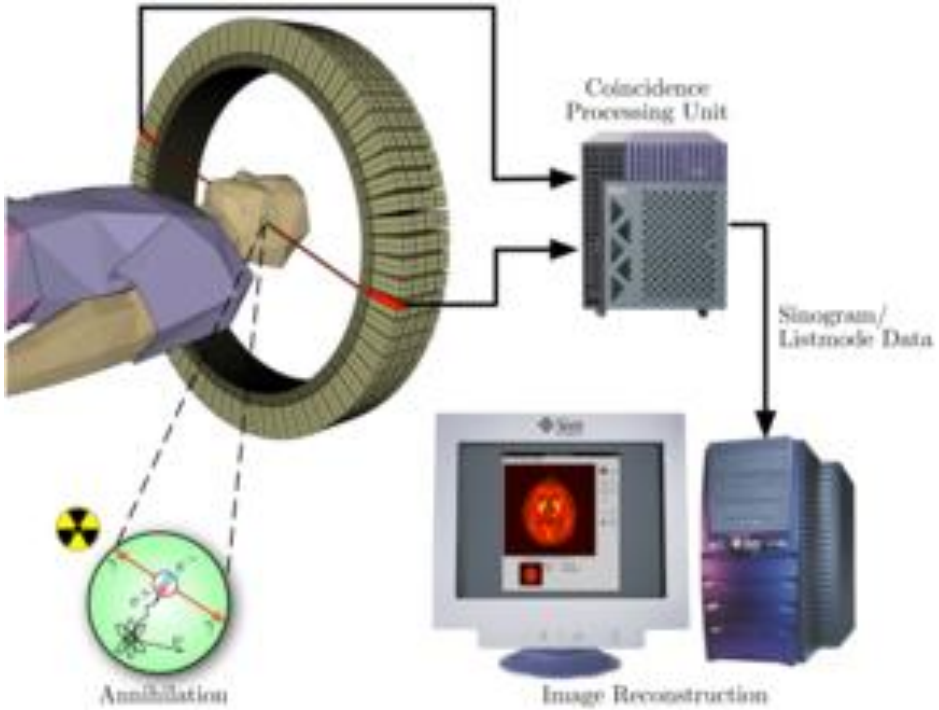
SPECT imaging of lung tumors

La somatostatina è un ormone polipeptidico che regola il sistema endocrino, la crescita e la proliferazione cellulare. I recettori della somatostatina sono proteine trans-membrana, sovra-espressi in molti tipi di tumori. L'octreotide è simile alla somatostatina

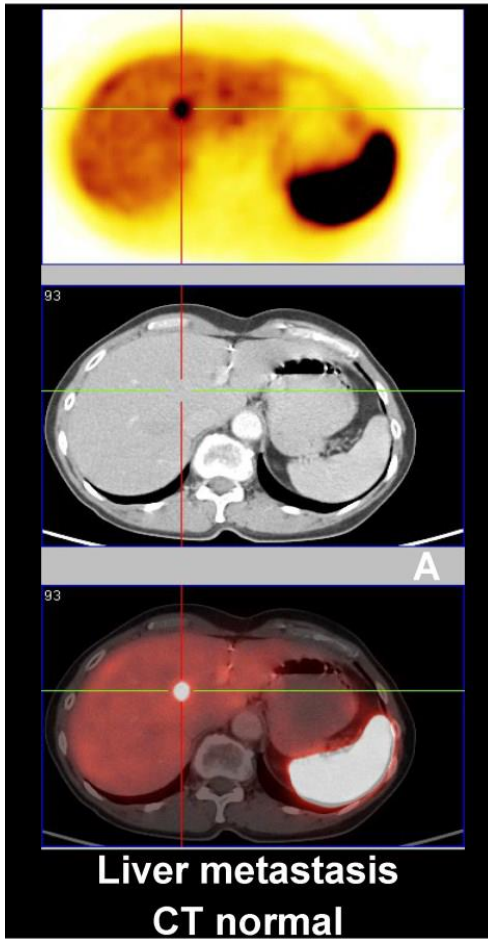
PET: Positron Emission Tomography







PET/CT: combinazione di imaging strutturale e funzionale



PET

CT

PET + CT

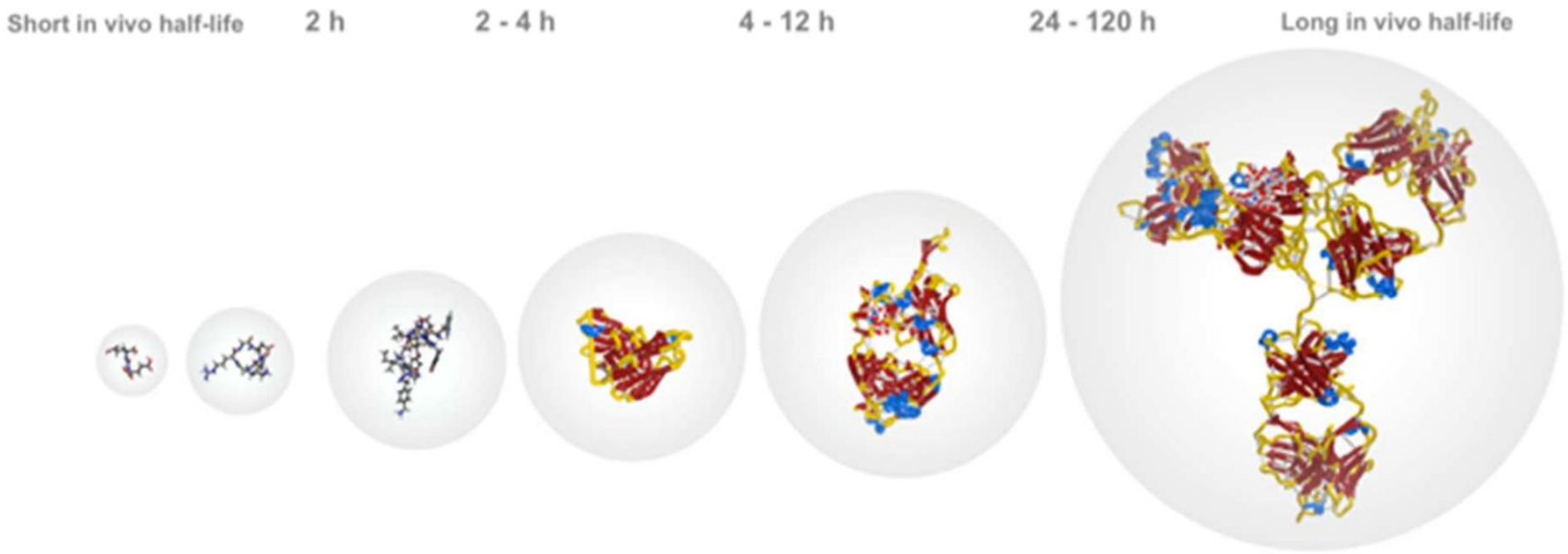
Principali radionuclidi per PET

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.

Tempo di semi-vita e tempo di biodistribuzione

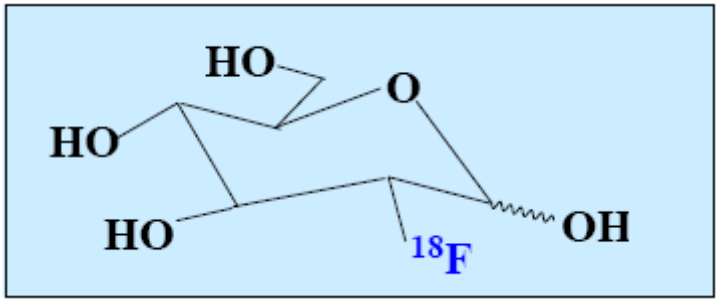


Short radionuclide half-life

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

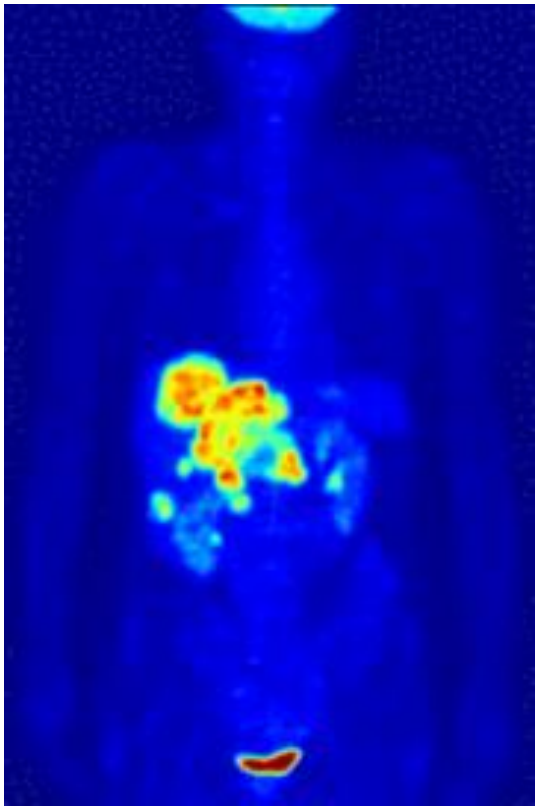
PET SPECT β^-



Fluorodeoxyglucose ([^{18}F] FDG)

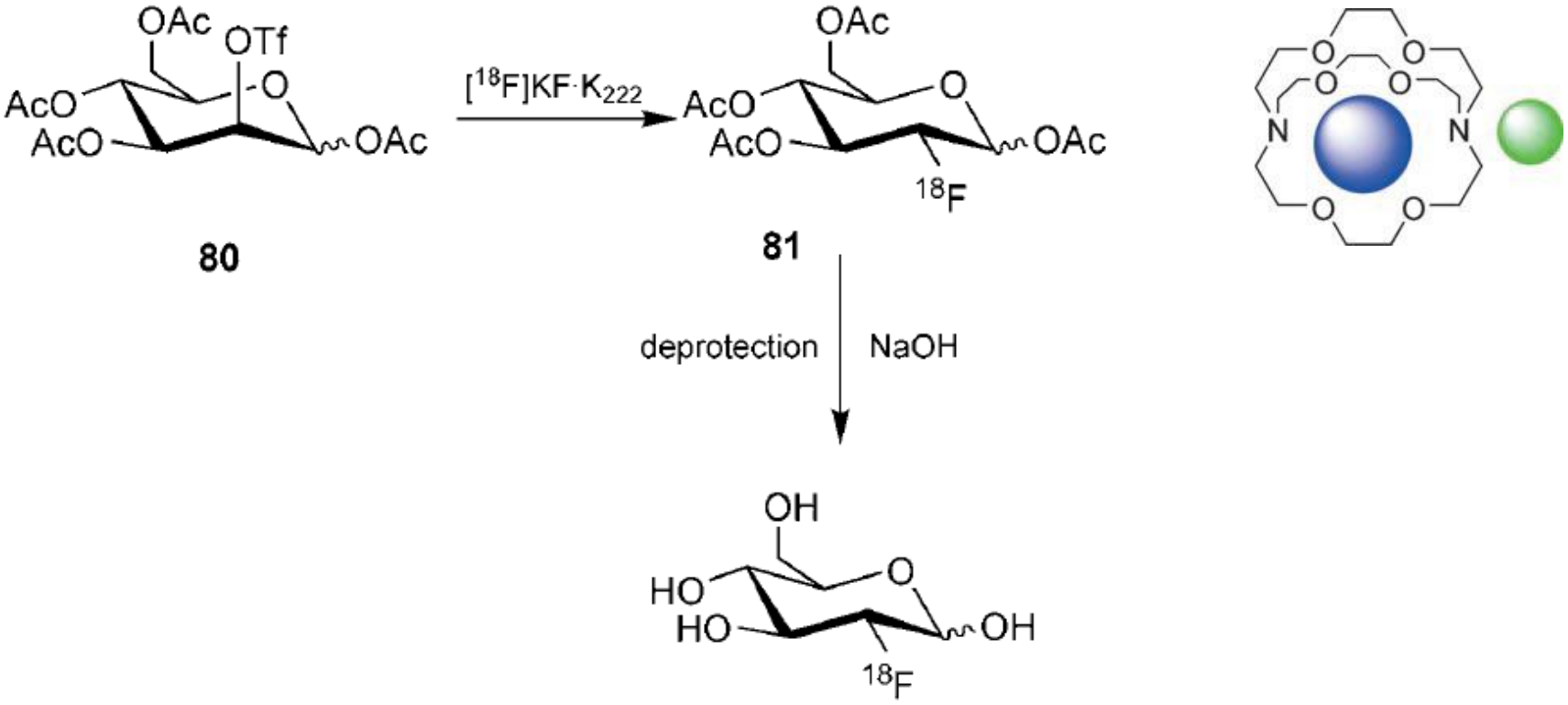
Sostituzione bio-isosterica

metabolismo del glucosio
localizzazione di tumori

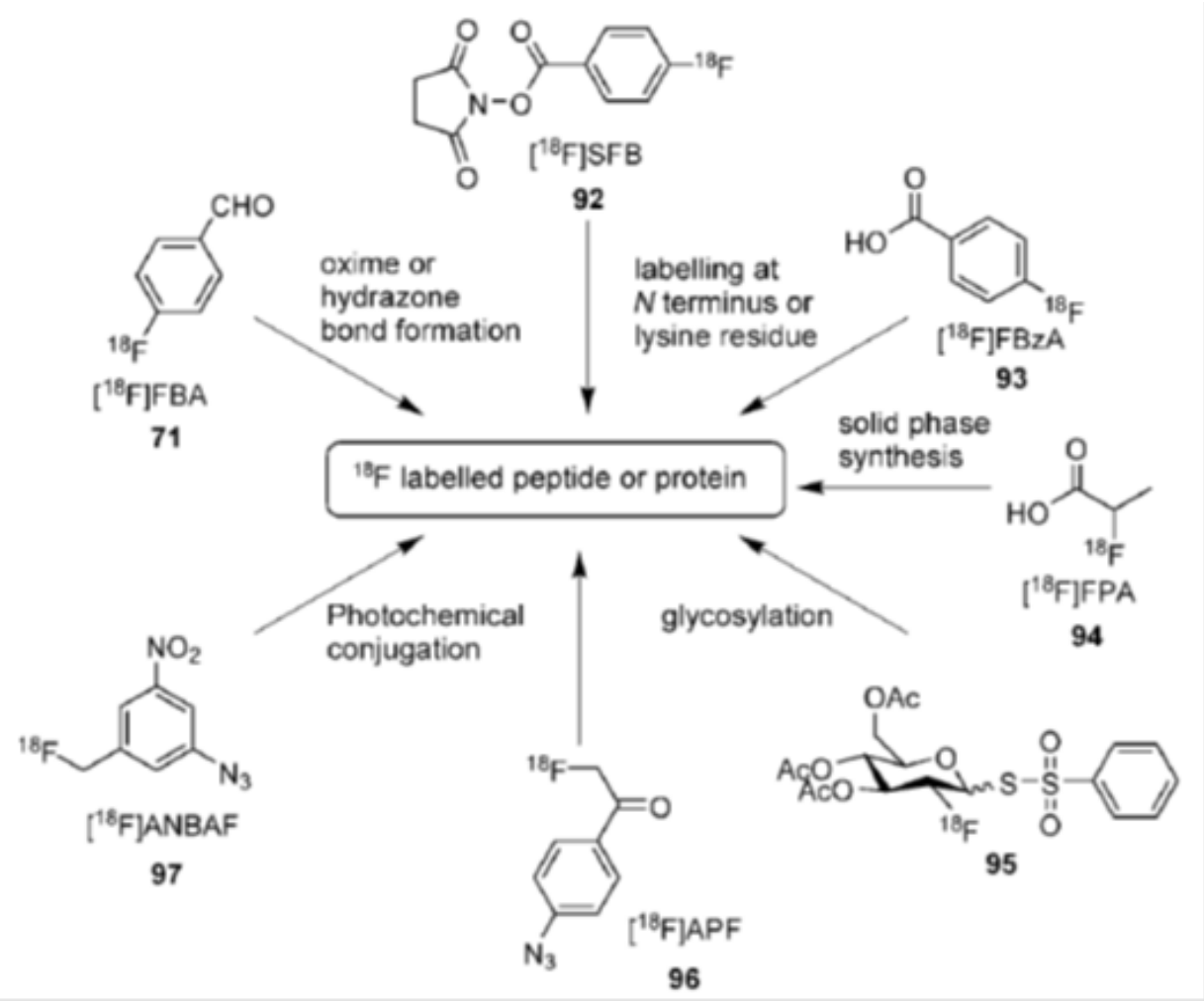


Esempio di fluorurazione diretta (nucleofila)

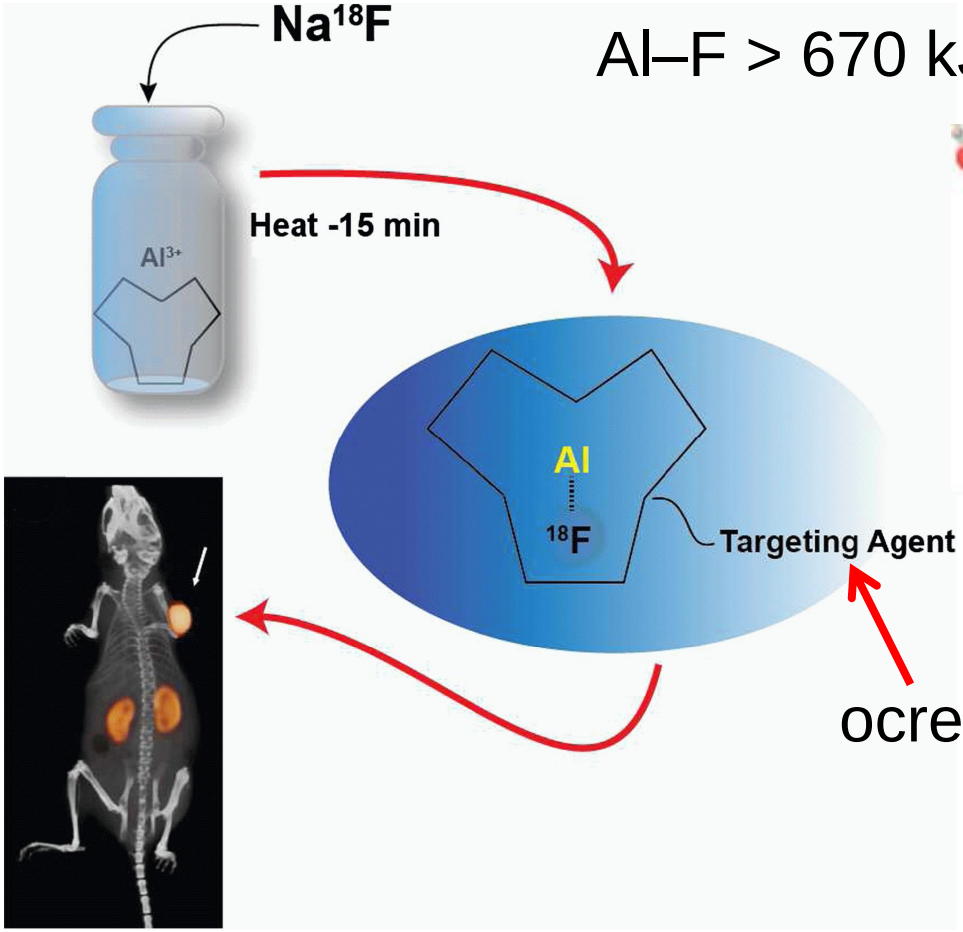
$^{18}O_{(da\ H_2O)}(p, n)^{18}F$



Gruppi prostetici per marcare biomolecole con ^{19}F

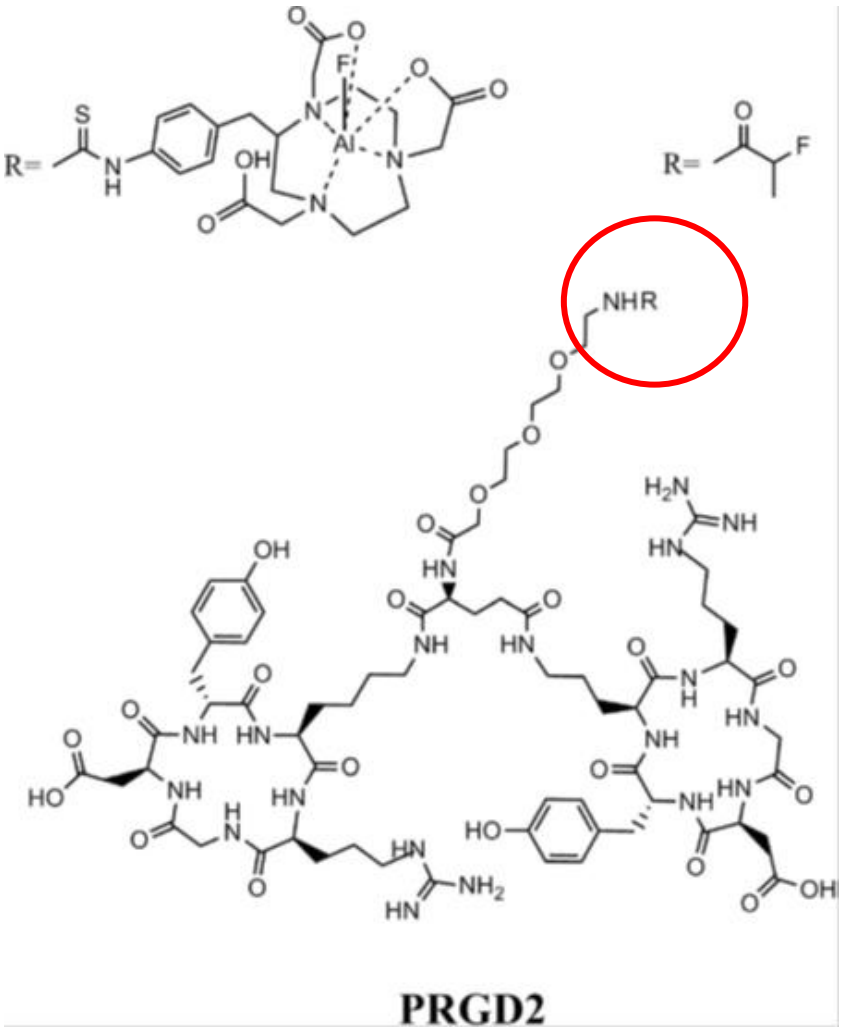


Fluorurazione inorganica (B, Si, Al…)



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

ocreotide



I peptidi RGD ciclici hanno un'alta affinità e selettività per il recettore dell'integrina $\alpha_v\beta_3$

Visualizzare e quantificare questa integrina permette di valutare la neo-vascolarizzazione di un tumore e stabilire se ha probabilità di rispondere a una terapia anti-angiogenica

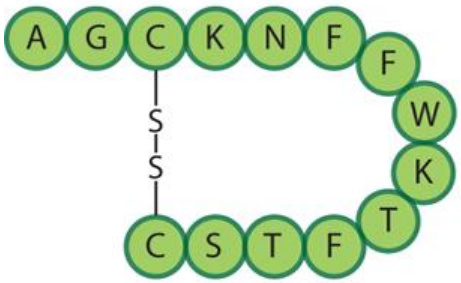
studio clinico nell'uomo per l'*imaging* di un tumore al polmone

Radionuclidi metallici per PET

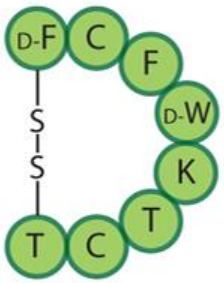
Table 1. Physical Properties of Some Common PET Radiometals[a]

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

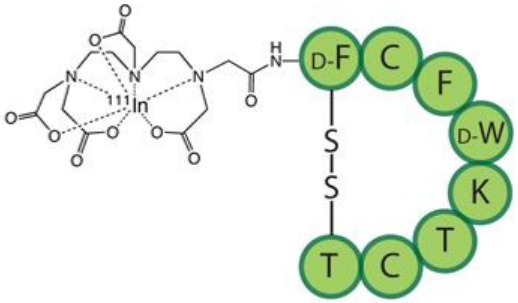
I tumori neuroendocrini sovra-esprimono i recettori per la somatostatina



Somatostatin



Octreotide



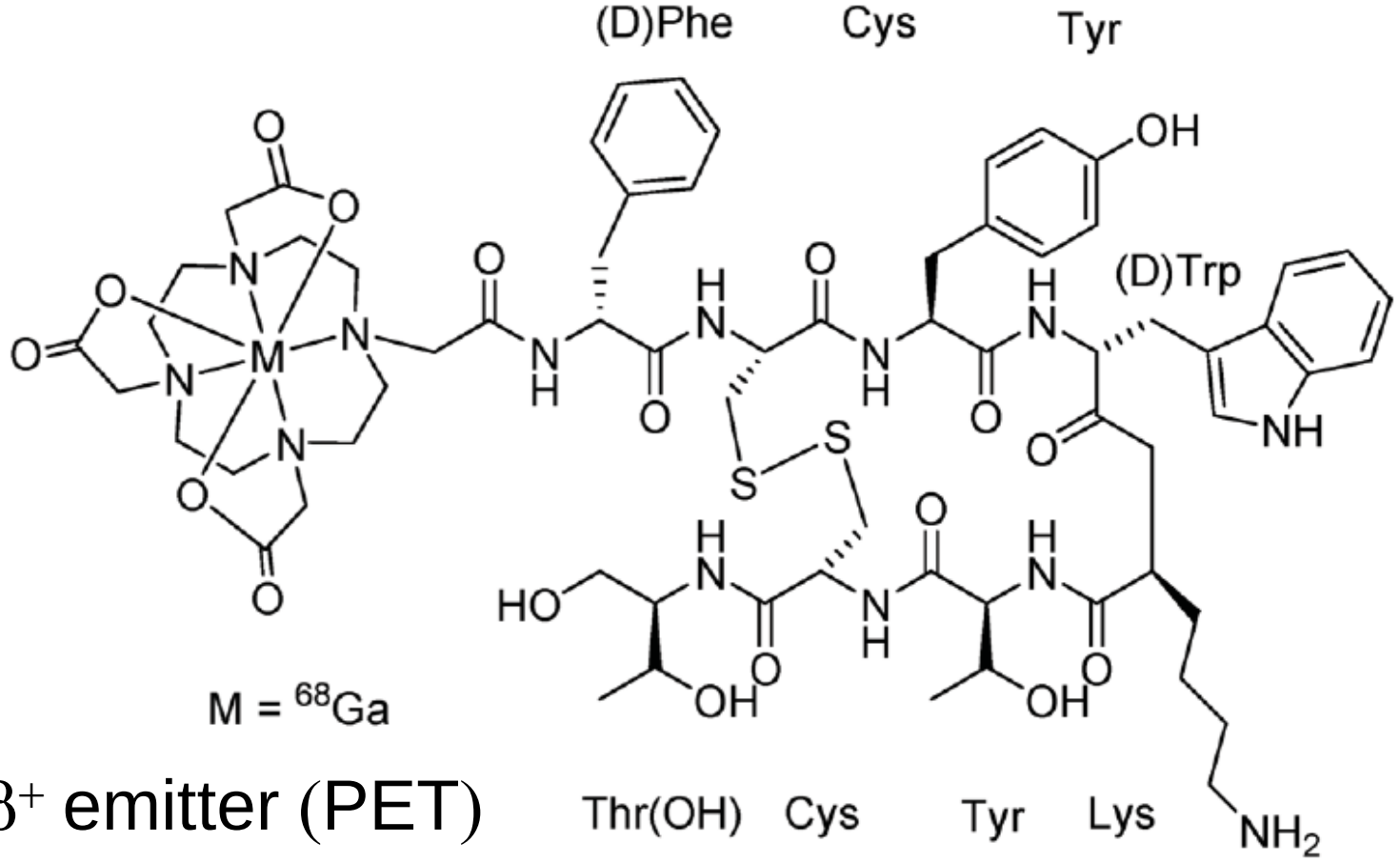
^{111}In-DTPA-Octreotide

SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTA-tyr3-Octreotide

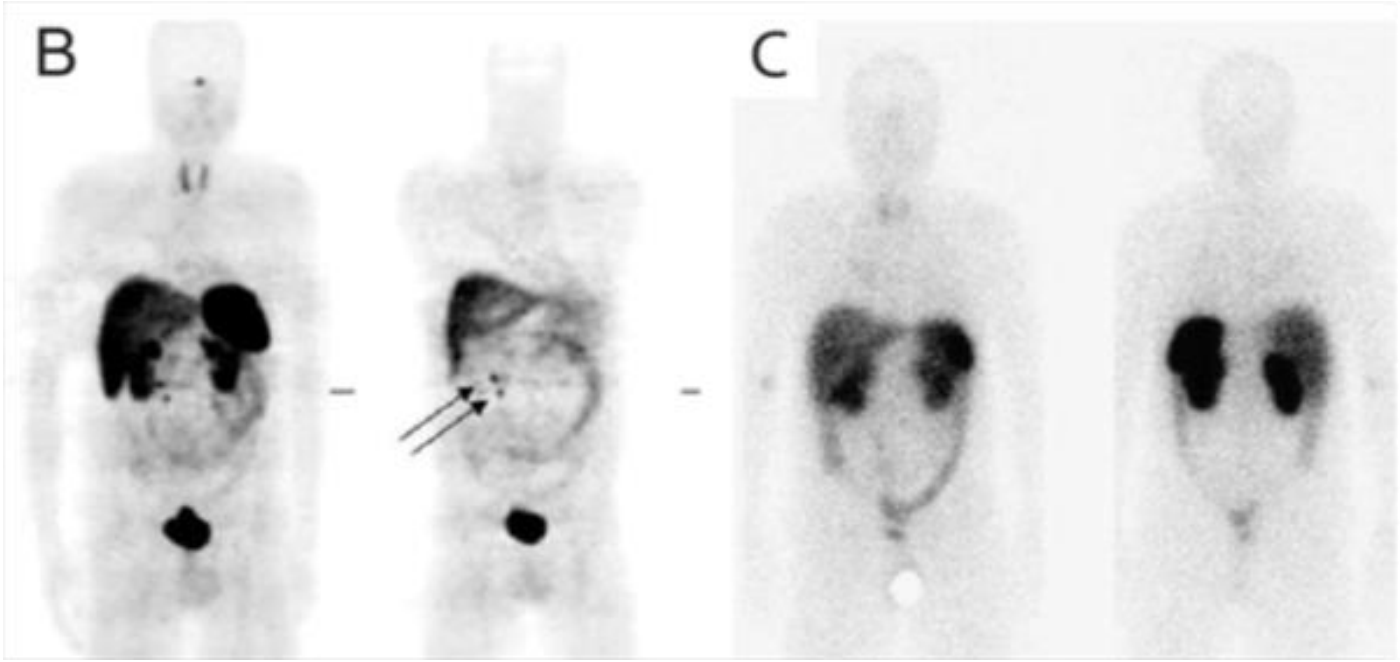
(^{68}Ga-DOTATOC, FDA-approved 2016)

High resolution PET imaging of neuroendocrine tumors



β^+ emitter (PET)

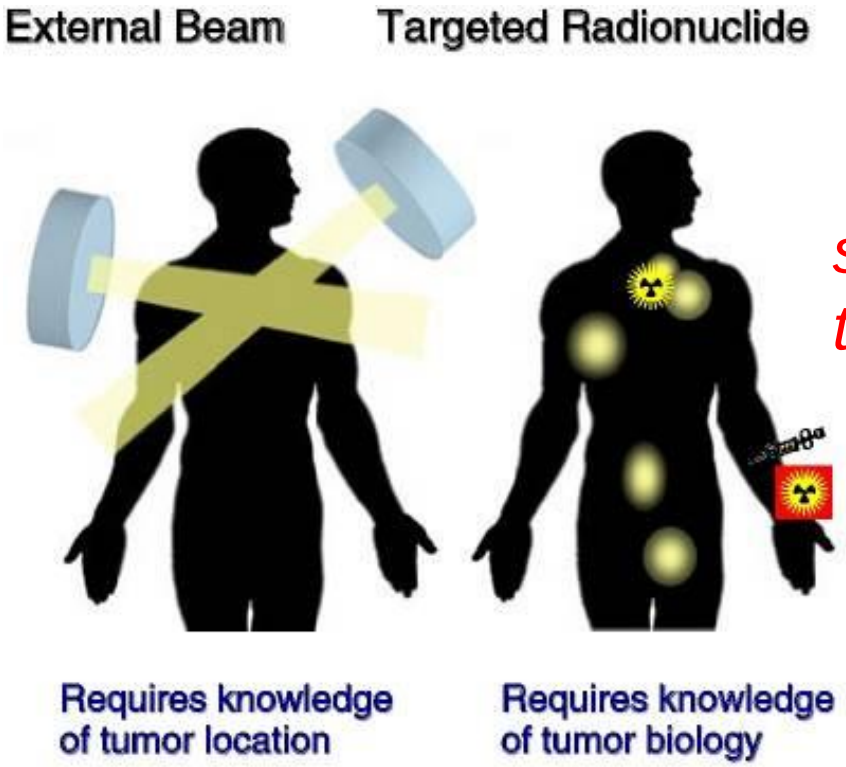
imaging di un tumore endocrino



^{68}Ga-DOTATOC
(PET)

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

Targeted Radiotherapy (*Radio(immuno)therapy*)

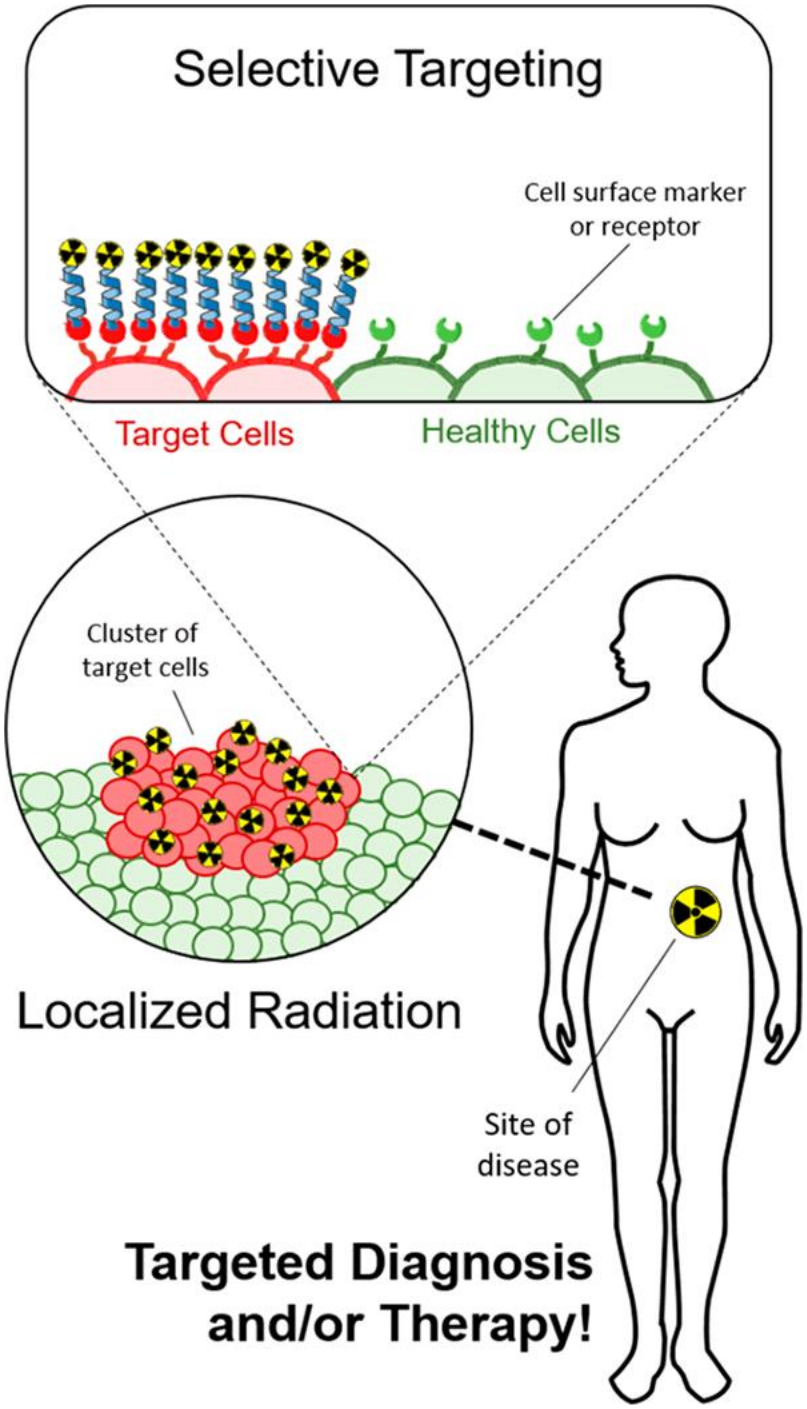


- Linfomi: 1500–2000 cGy
- Tumori solidi: 3500–10000 cGy

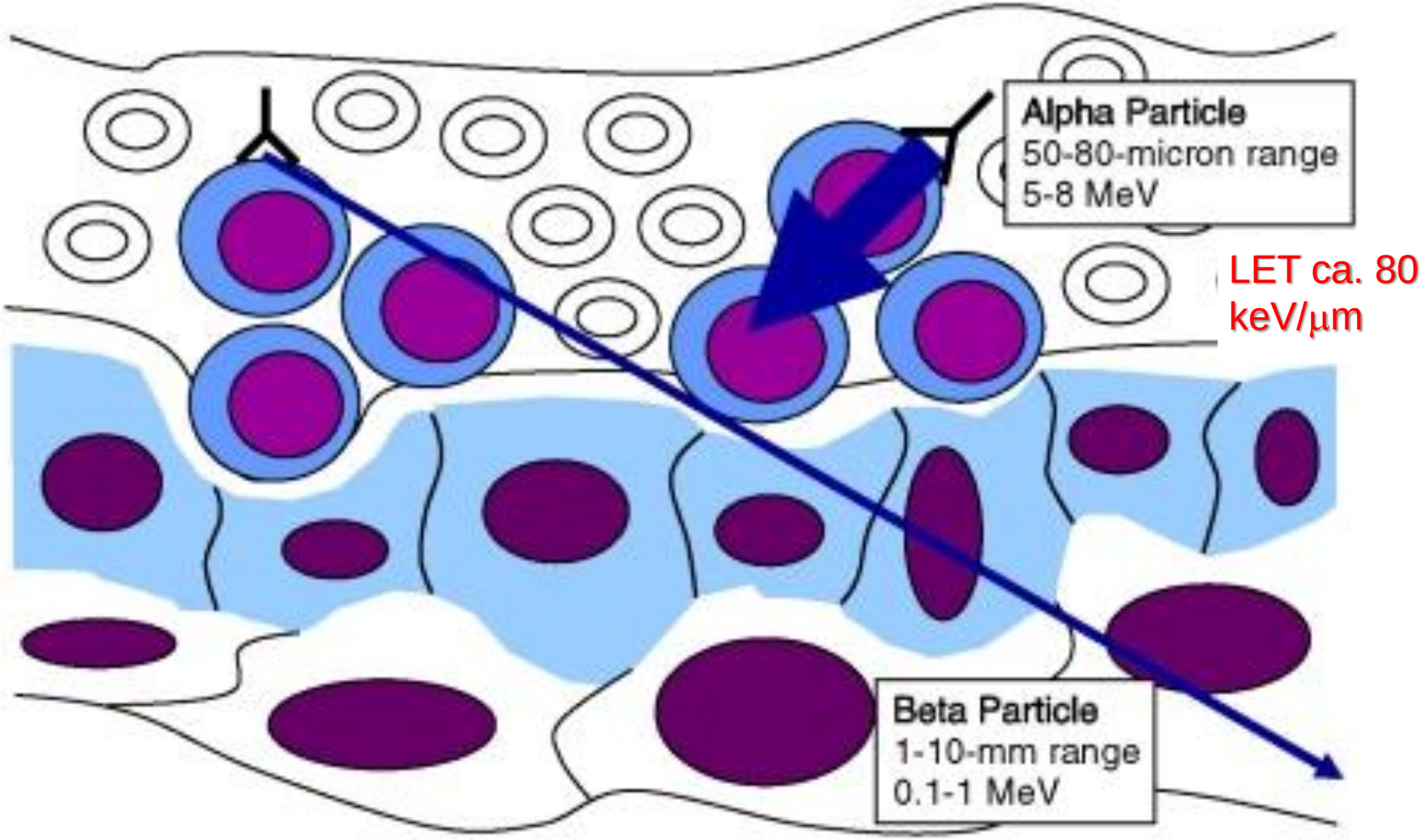
systemic treatment

- TI > 10 per reni e polmoni
- TI > 50 per midollo spinale

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

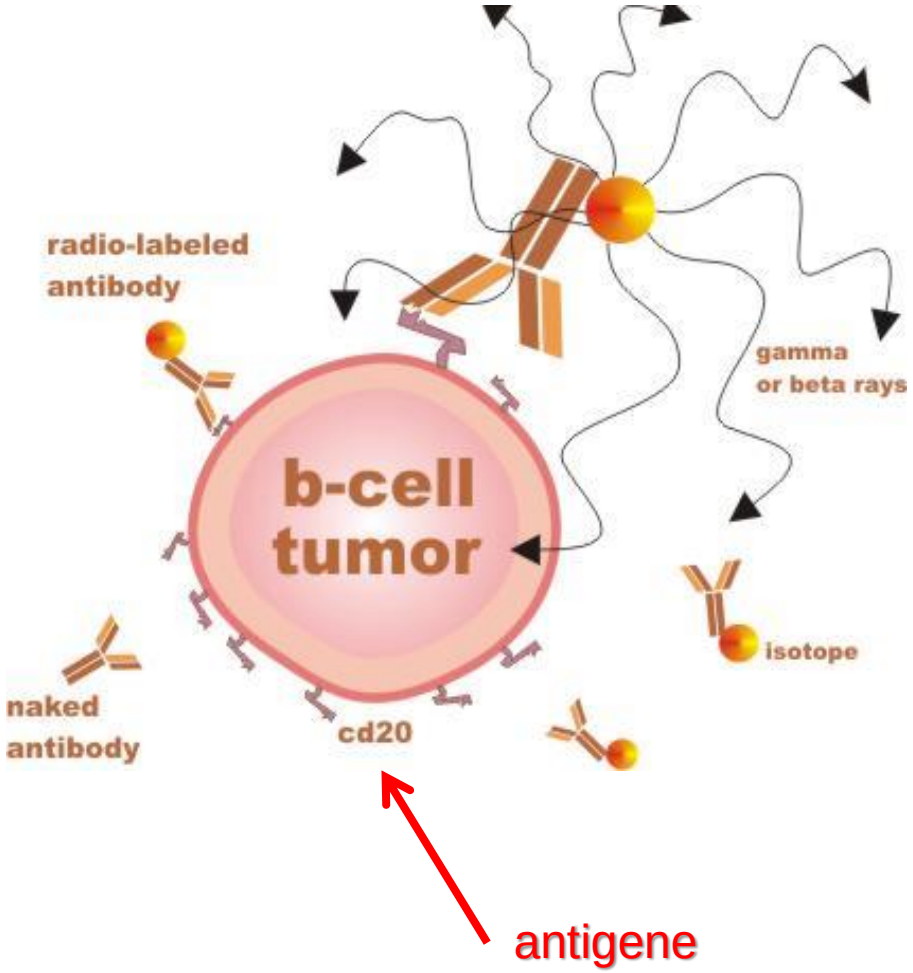


linear energy transfer (LET, keV/μm)

Main radionuclides for Targeted Radiotherapy

Radionuclide	**Half life**	**Energy of main γ emission (keV)**
^{67}Cu (β, γ)	62 h	93, 185
^{90}Y (β)	64 h	
^{153}Sm (β, γ)	46 h	103
^{131}I (β, γ)	8 d	364
^{177}Lu(β, γ)	6.6 d	497
^{188}Re (β, γ)	17 h	155
^{213}Bi (α, β, γ)	1 h	727
^{225}Ac (5α, 3β)	10 d	5800 - 8400

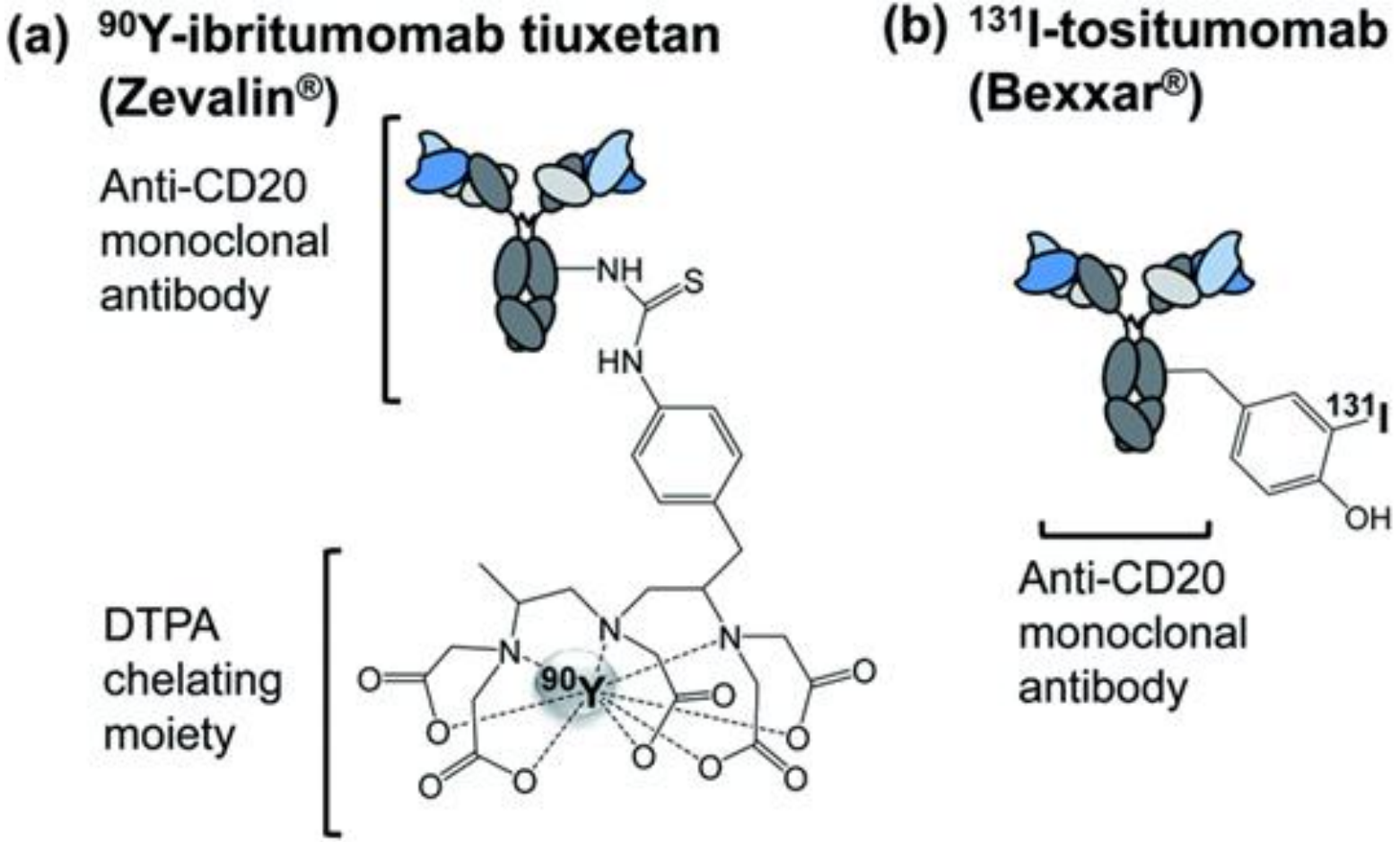
Treatment of B-cell non-Hodgkin's limphoma



Antigene ideale:

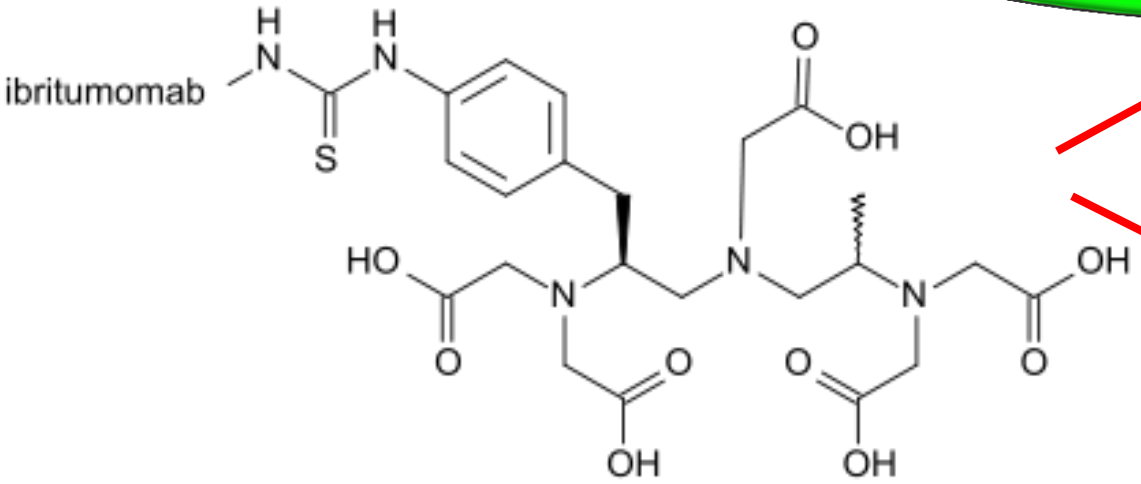
- altamente espresso con densità uniforme sulla superficie di tutte le cellule del tumore (> 10^5 siti per cellula),
- non deve essere espresso (o molto meno) nelle cellule sane,
- affinità antigene-anticorpo dell'ordine nanomolare
- internalizzazione

FDA approved



Zevalin®

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



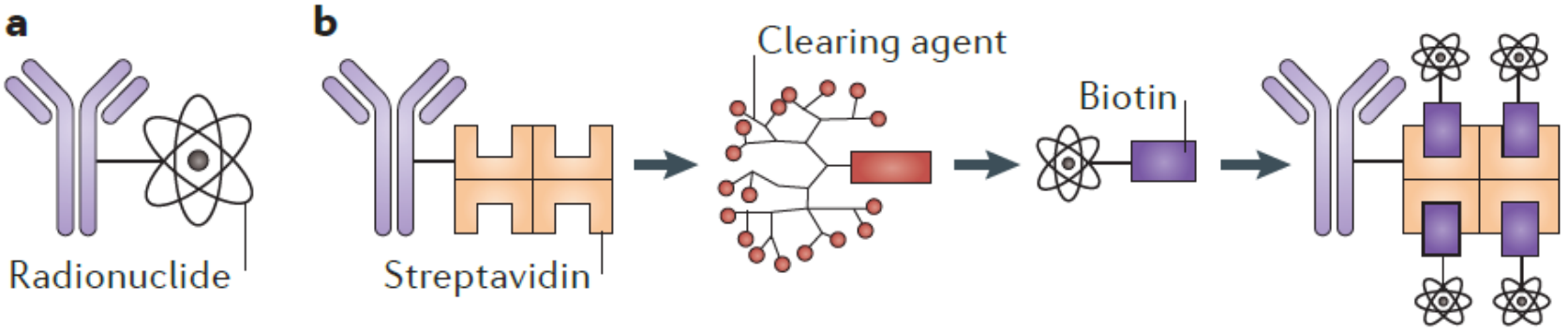
$^{111}In^{3+}$ or – better – $^{86}Y^{3+}$ for imaging

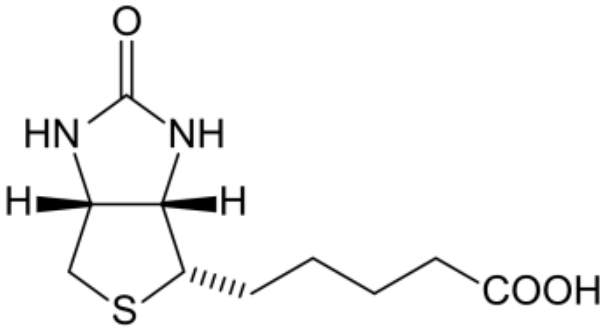
^{90}Y is a pure β^+ emitter

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

Example of the matched-pair approach

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

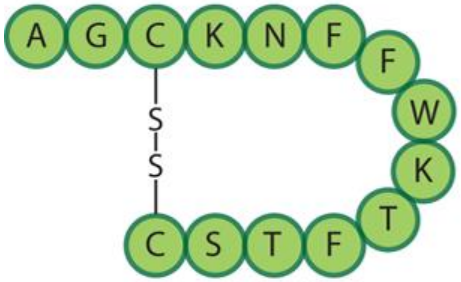




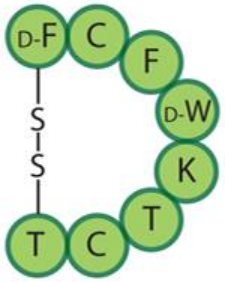
Biotina

la costante di binding **streptavidina-biotina** è dell'ordine di 10^{14} mol L^{-1}

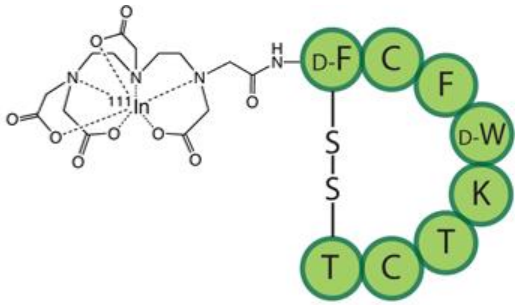
Radio-immunotherapy of neuroendocrine tumors



Somatostatin



Octreotide



^{111}In-DTPA-Octreotide

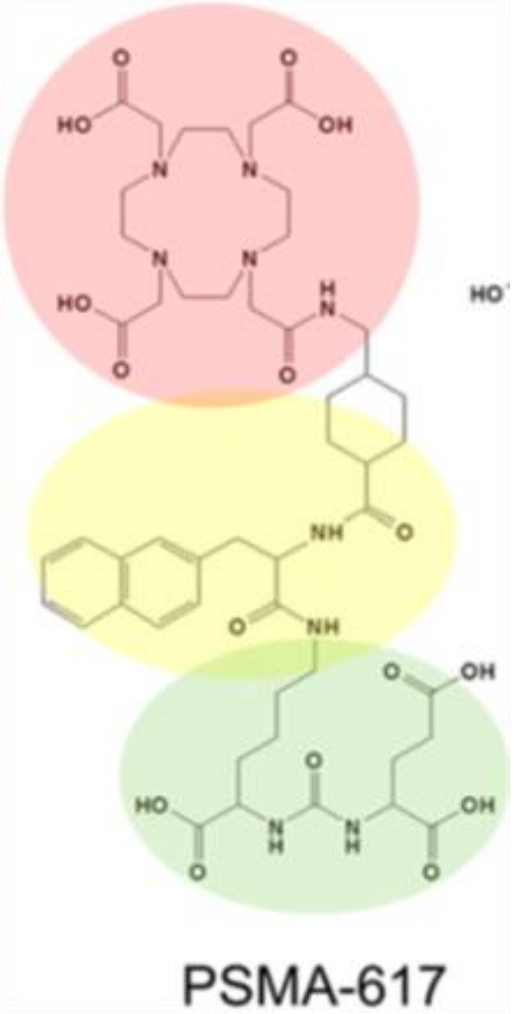
SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTATOC for PET imaging

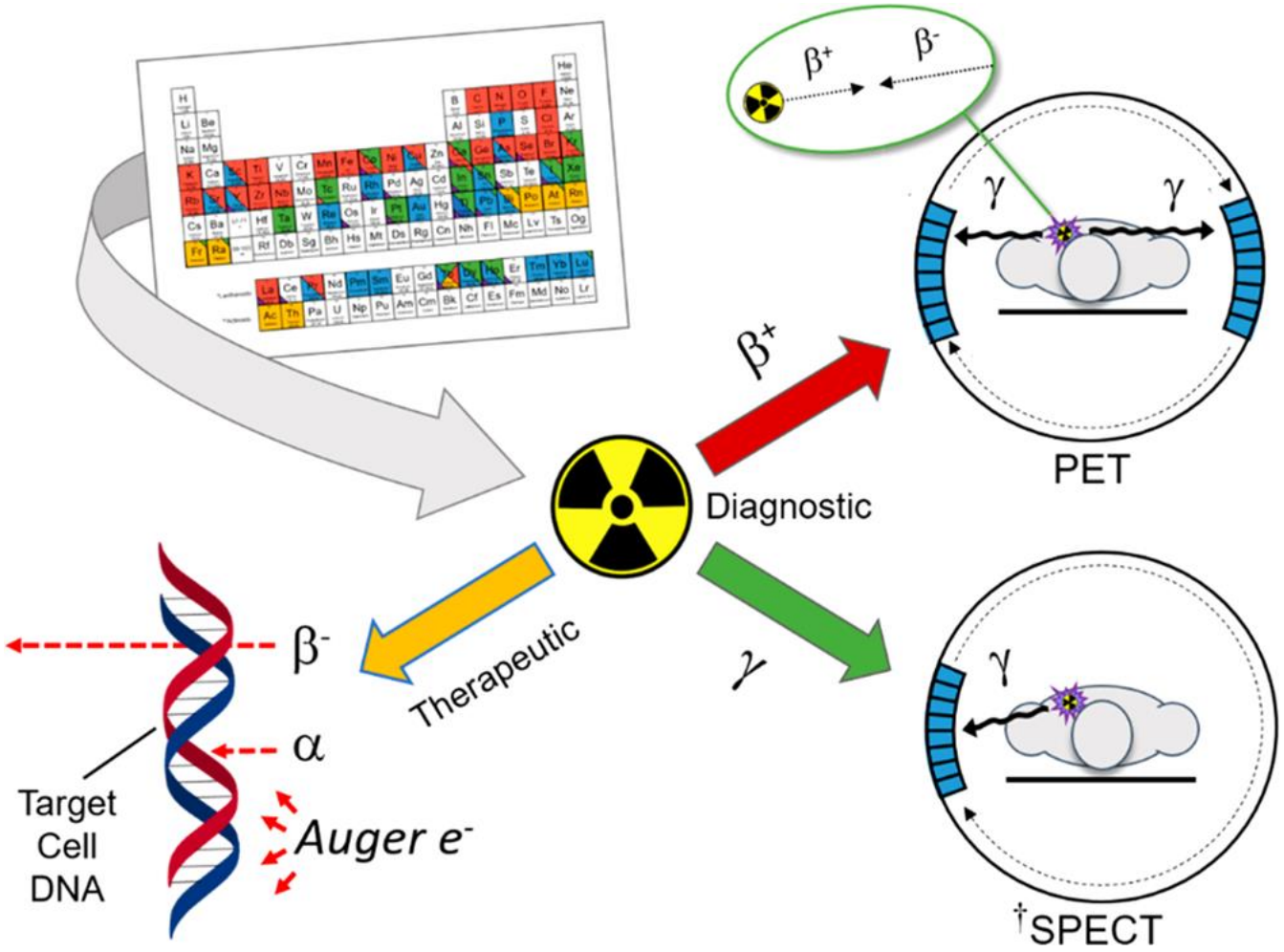
^{90}Y-DOTATOC and ^{177}Lu-DOTATATE for radiotherapy

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

^{177}Lu-PSMA-167



PSMA = *prostate-specific membrane antigen*


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

The $^{99m}Tc/^{188}Re$ *matched-pair*