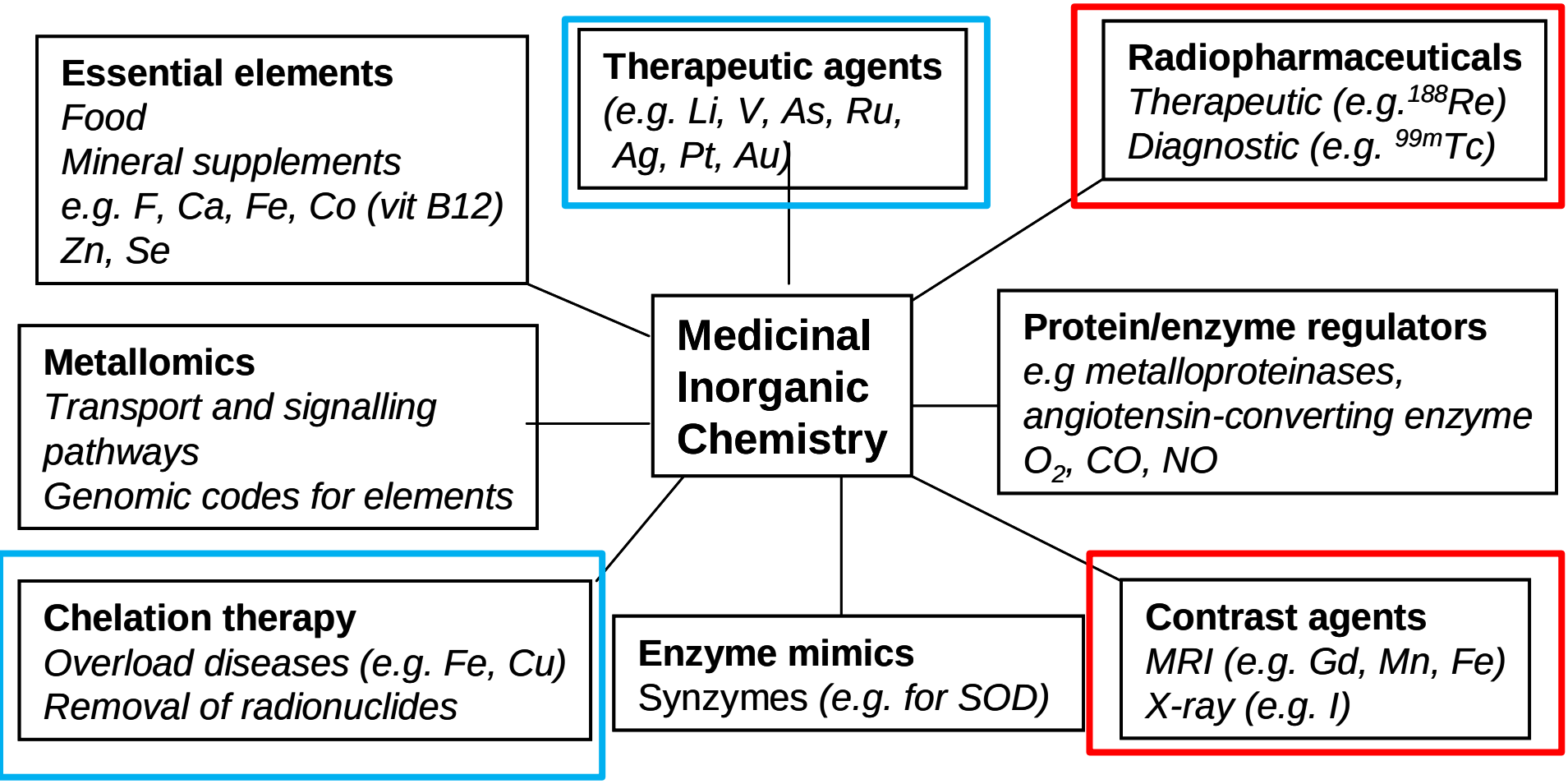
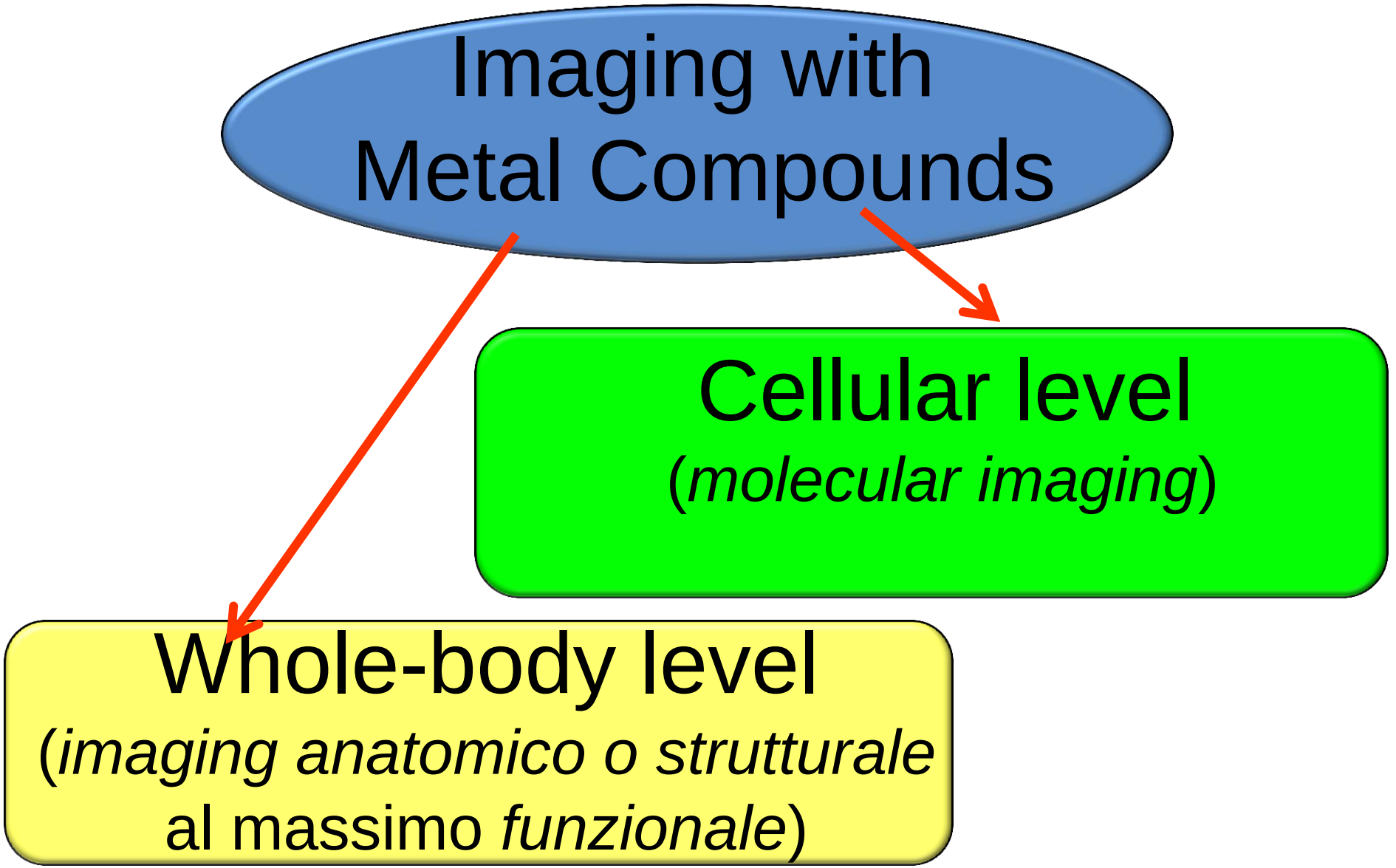
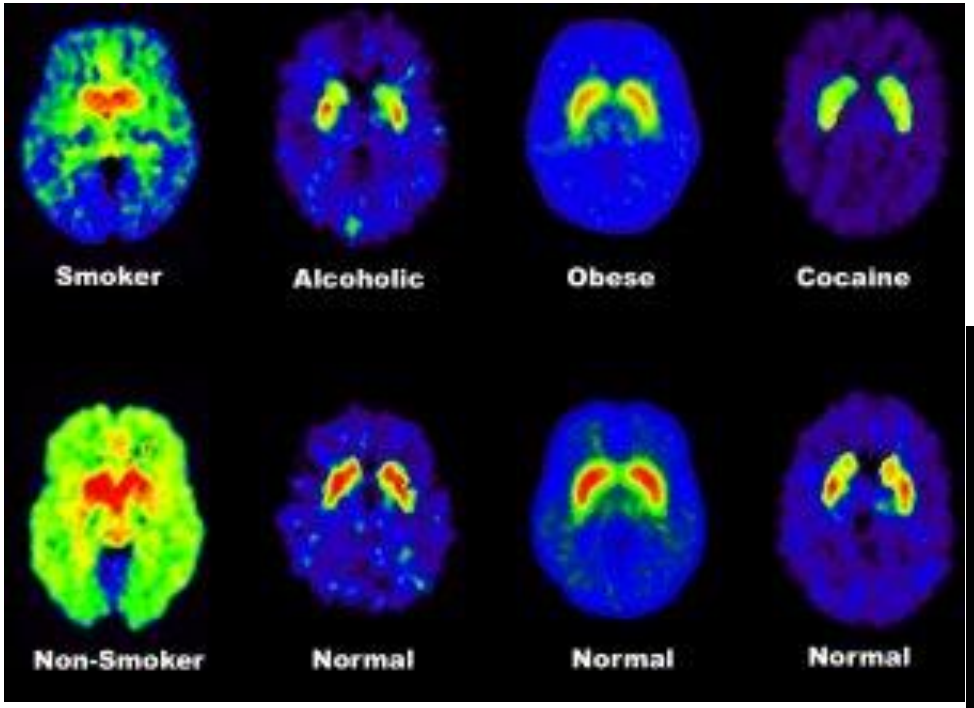
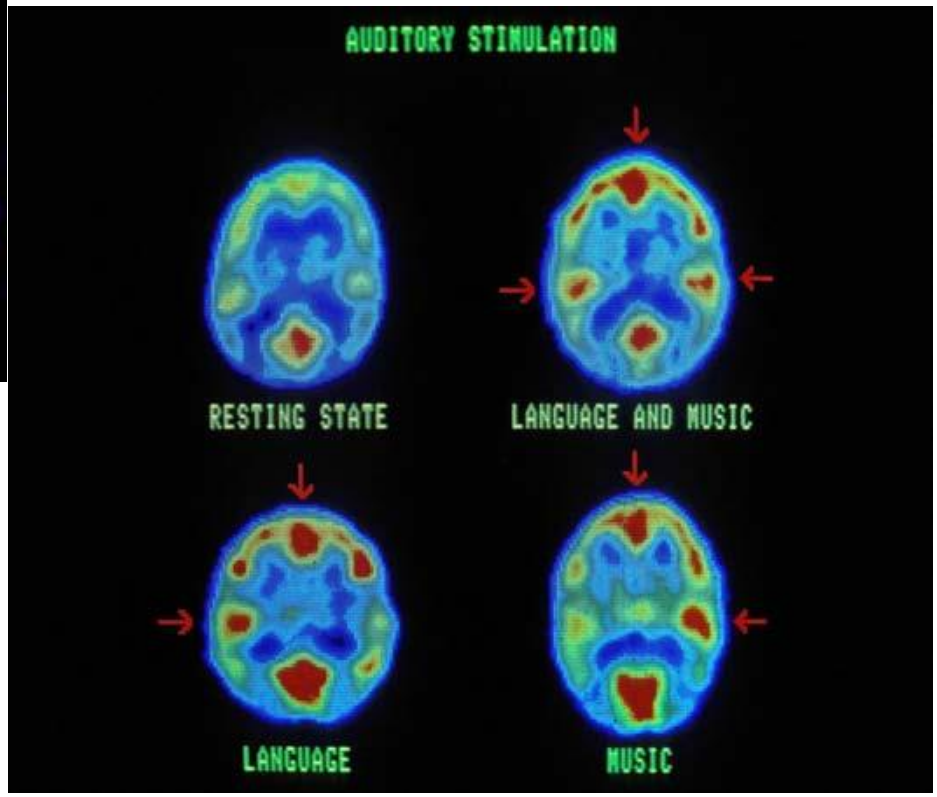

Essential elements
Food
Mineral supplements
e.g. F, Ca, Fe, Co (vit B12)
Zn, Se
Therapeutic agents
(e.g. Li, V, As, Ru,
Ag, Pt, Au)
Radiopharmaceuticals
Therapeutic (e.g. 188Re)
Diagnostic (e.g. 99mTc)
Medicinal Inorganic Chemistry
Metallomics
Transport and signalling pathways
Genomic codes for elements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

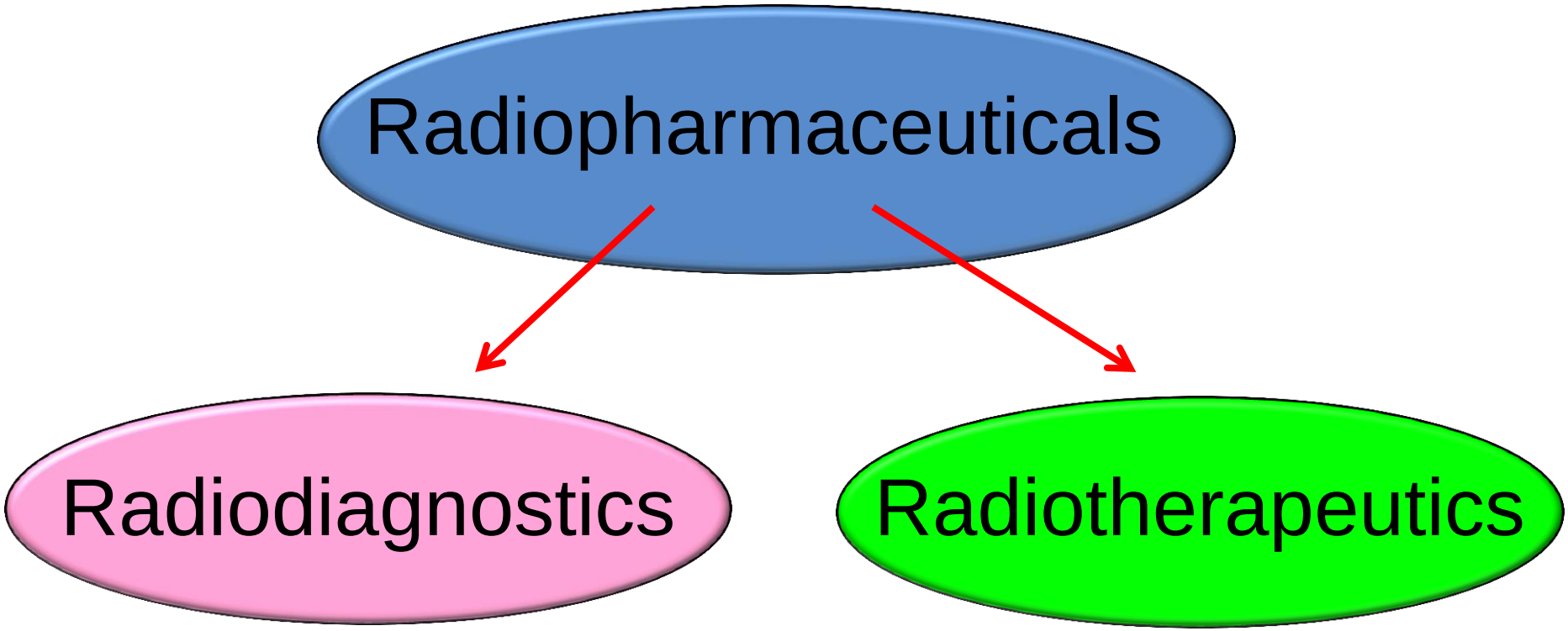
Molecular Imaging





Processi spontanei nei nuclei radioattivi

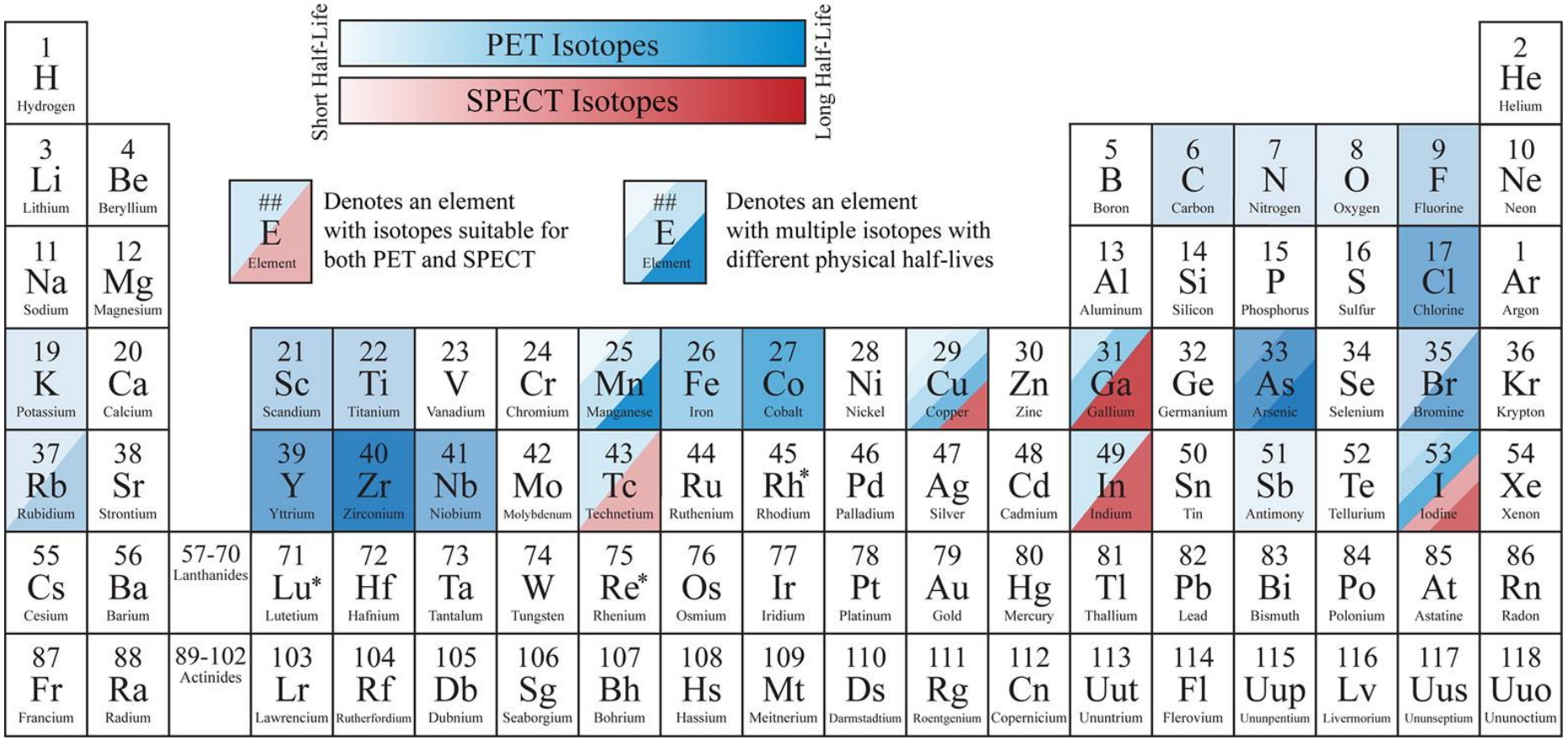
- Emissione di particelle (α, β-, β+)
- Cattura di elettroni
- Emissione di radiazioni (raggi X, γ)



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

α or β^- emitters

Isotopes suitable for nuclear imaging



*Isotopes typically used for radiotherapy with which SPECT is also possible but not common — *e.g.*, ^{177}Lu, ^{105}Rh, ^{186}Re, etc. — have been omitted.

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

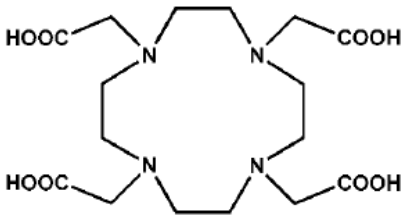
- Purificazione da isotopo padre e sottoprodotti

- Incorporazione in un composto, spesso tramite un chelante polidentato

Chelanti più comuni

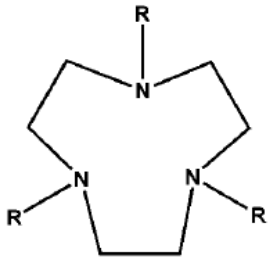
Diethylenetriamino-pentaaceticacid

a)



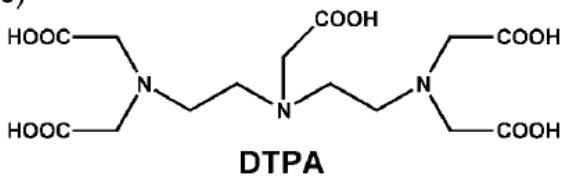
DOTA

b)



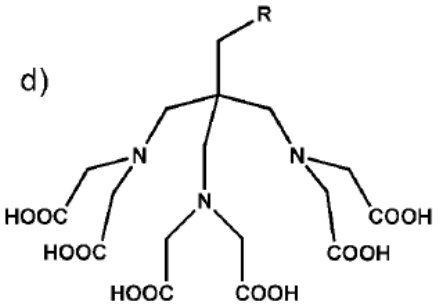
NOTA	R = CH_2COOH
TACN-TM	R = CH_2CH_2SH
NOTP	R = $CH_2PO_3H_2$
NOTPME	R = $CH_2PO_2(OCH_2CH_3)$

c)



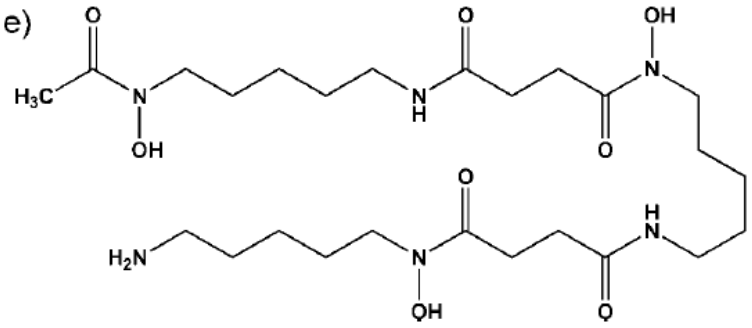
DTPA

d)

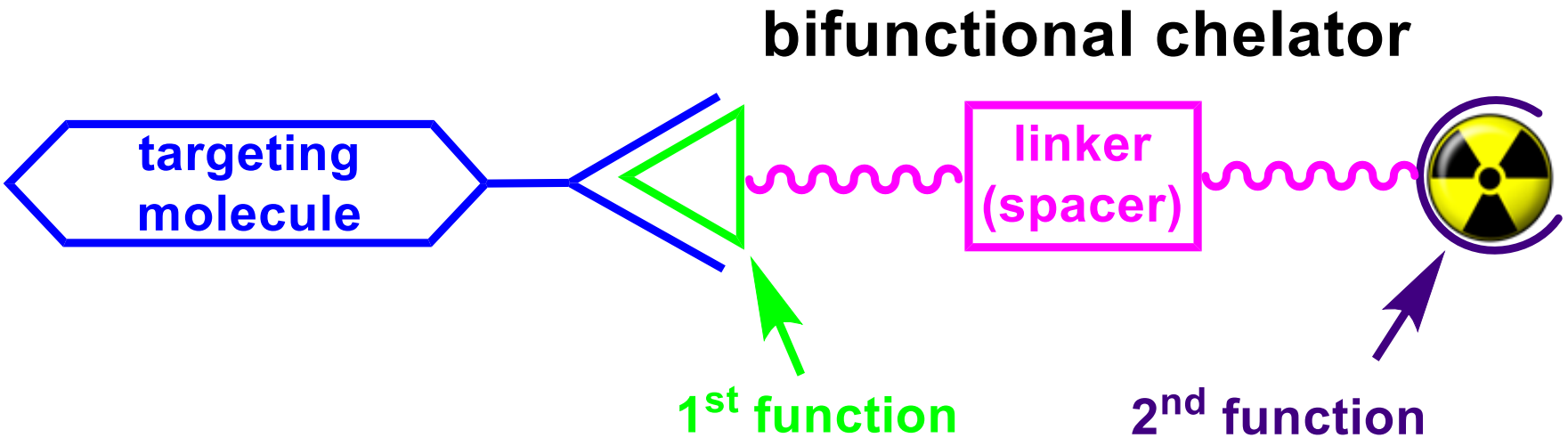


TAME Hex

e)



Targeted Approach
(*Trojan horse*)



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

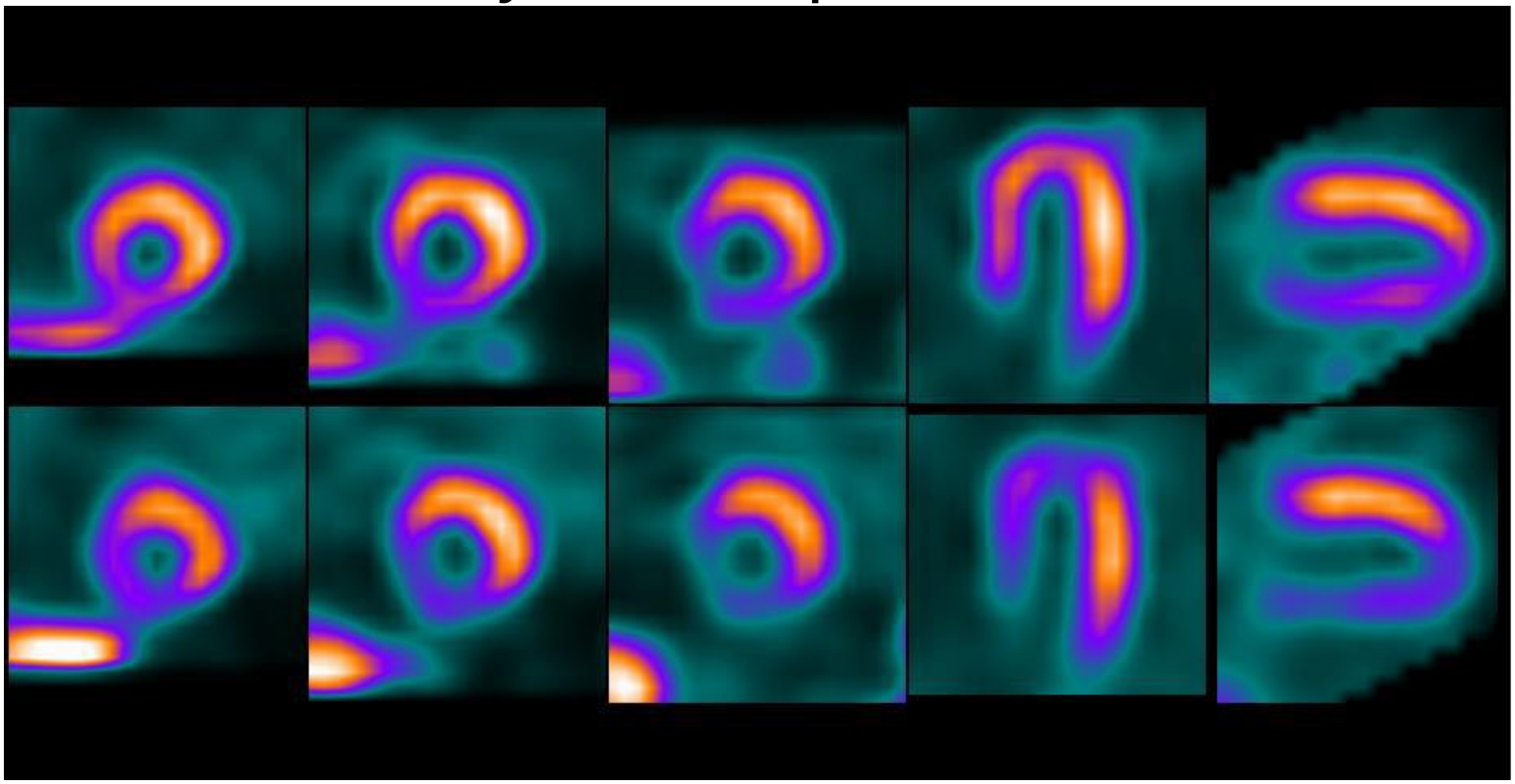
‘*Shake and bake*’ principle

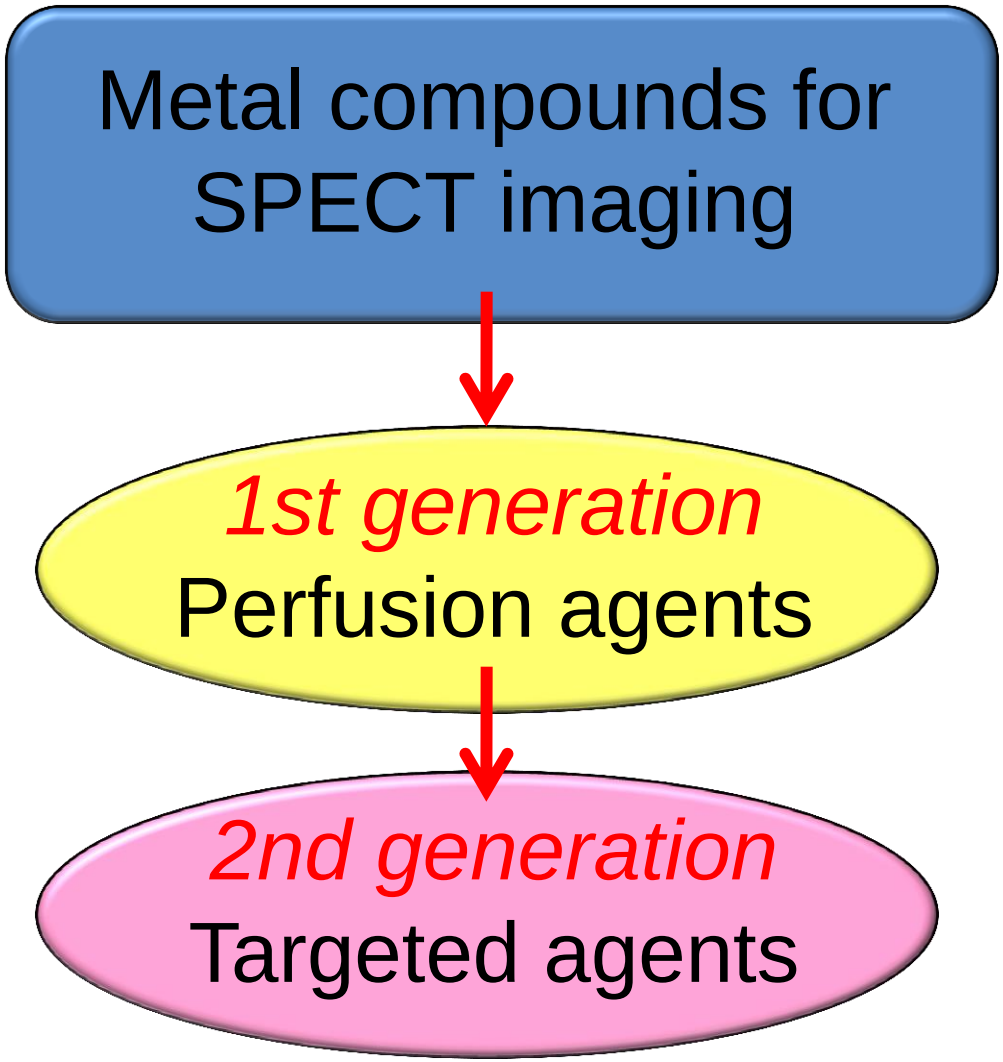
- Preparations must be performed in kits
- Yields must be > 98% (even at very low metal ion concentration)
- Compound must be ready for administration
- No lenghty purification or separation
- Aqueous solutions
- Non-toxic reagents and byproducts

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

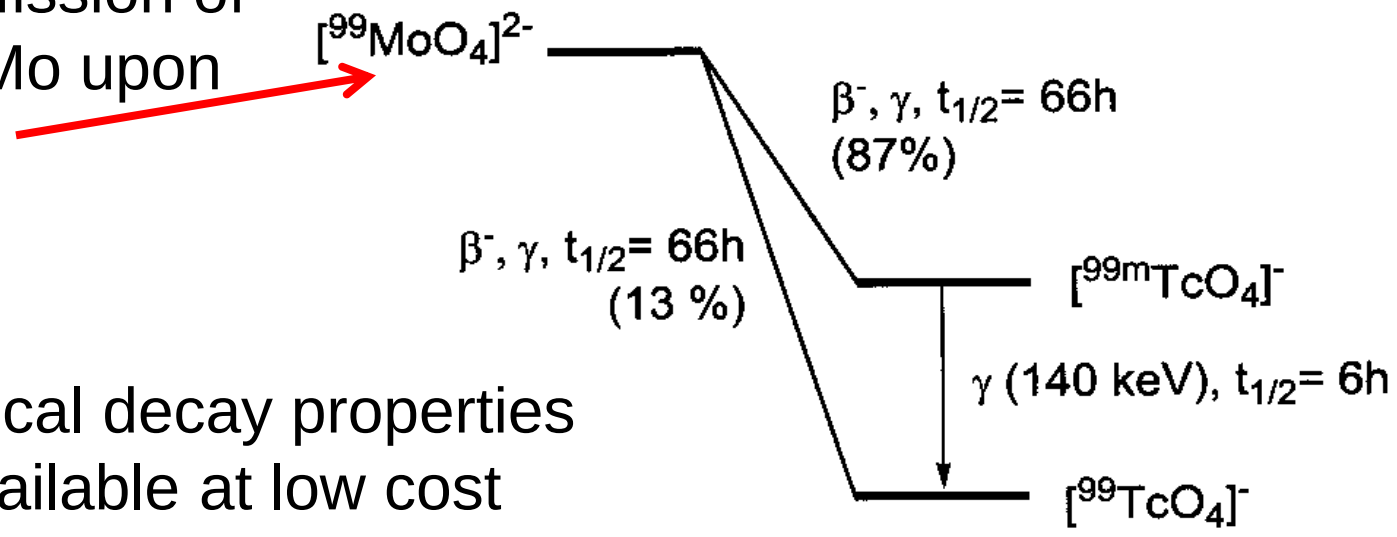
Main radionuclides for SPECT

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)

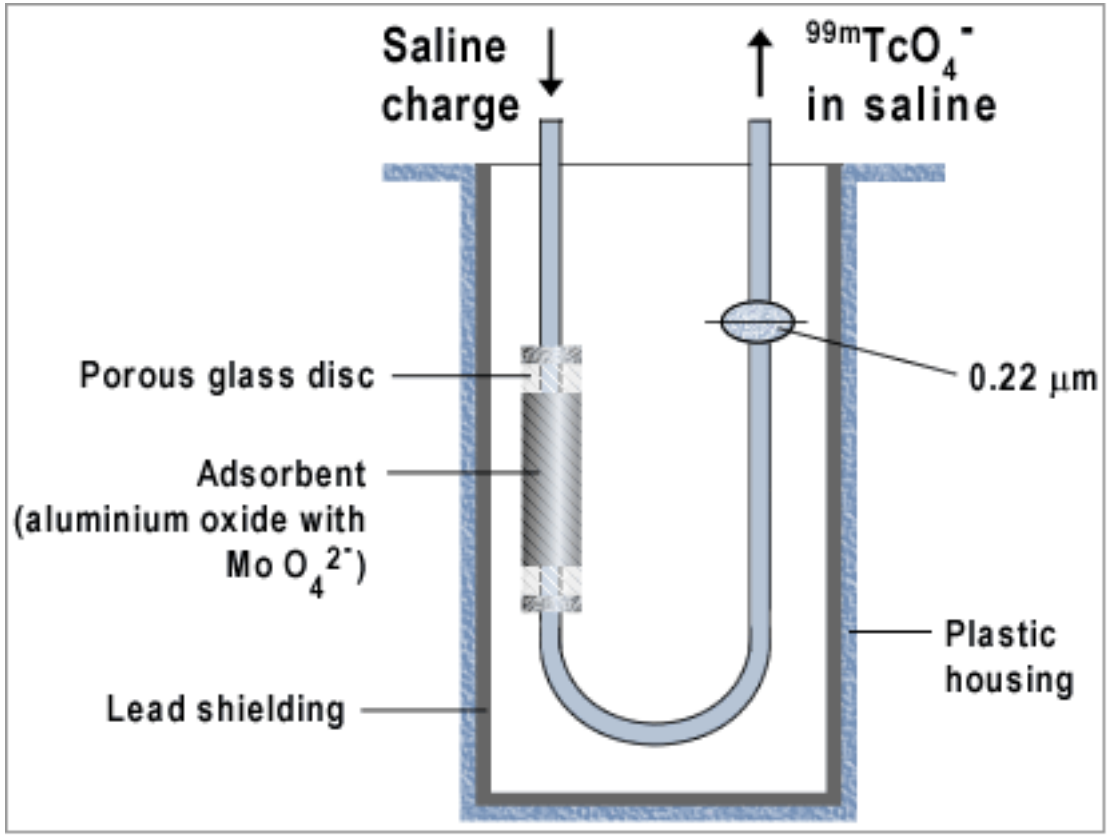
Obtained from fission of ^{235}U or from ^{98}Mo upon (n, γ) reaction



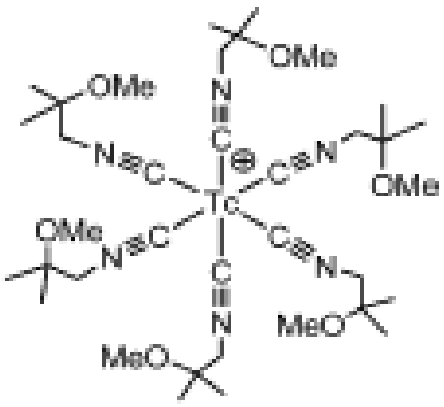
- Ideal physical decay properties
- Readily available at low cost
- Many oxidation states (+7 – -1)
- Various coordination geometries (4 – 9)
- *Cold* Re for characterization (matched-pair approach)

Pure β-emitter

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

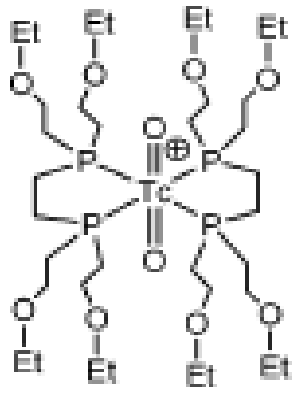


Radiofarmaci di tecnezio di prima generazione



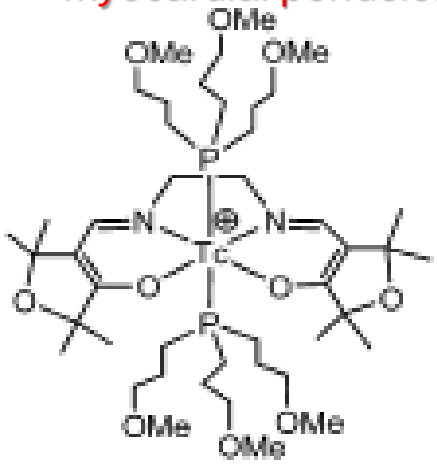
^{99m}Tc-Sestamibi

cardiac imaging



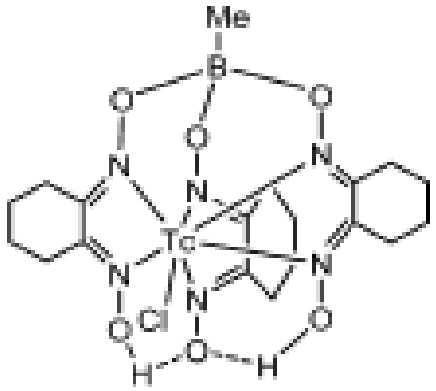
^{99m}Tc-Tetrofosmin

myocardial perfusion

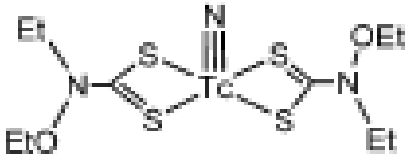


Q12

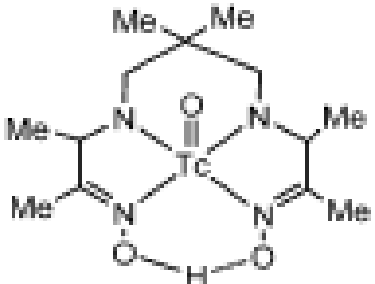
cardiac imaging



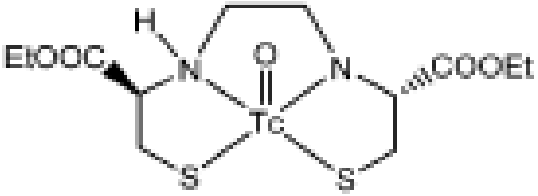
^{99m}Tc-Teboroxime



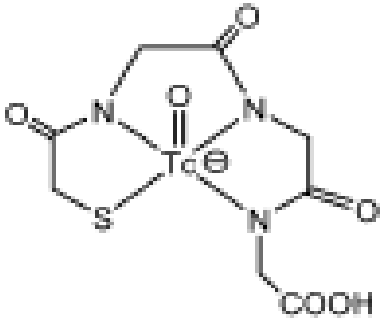
^{99m}TcN-NOET



^{99m}Tc-HMPAO



^{99m}Tc-Bicisate



^{99m}Tc-MAG$_3$

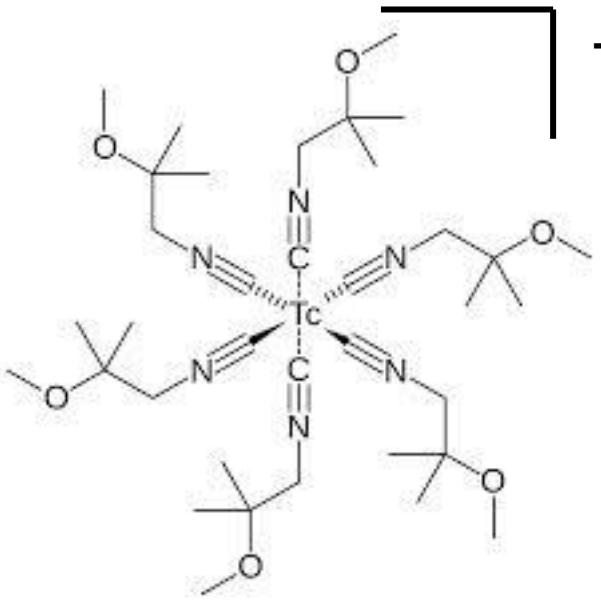
myocardial perfusion

cereberal perfusion

brain imaging

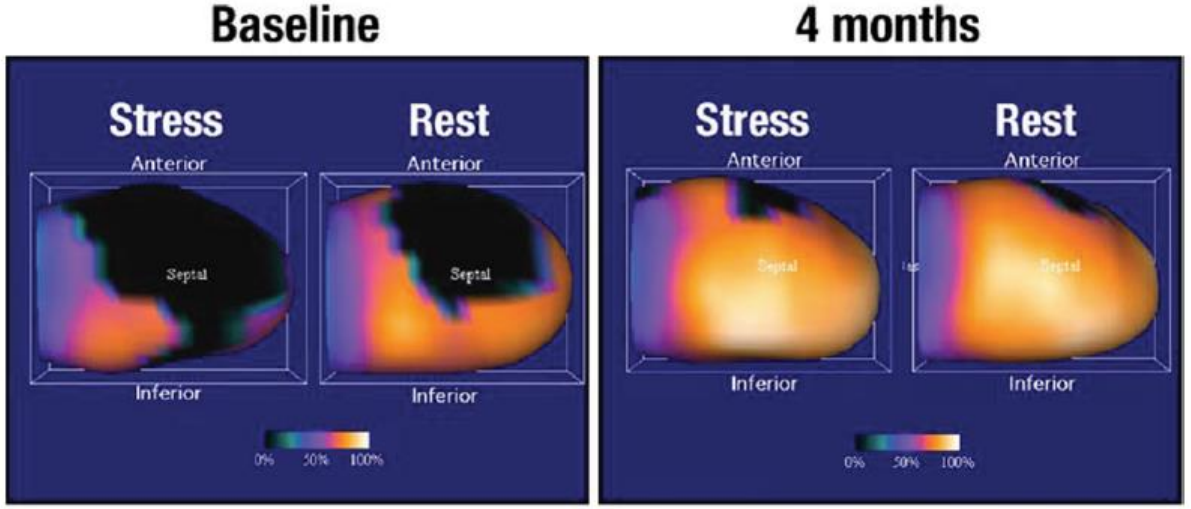
renal imaging

^{99m}Tc-sestamibi

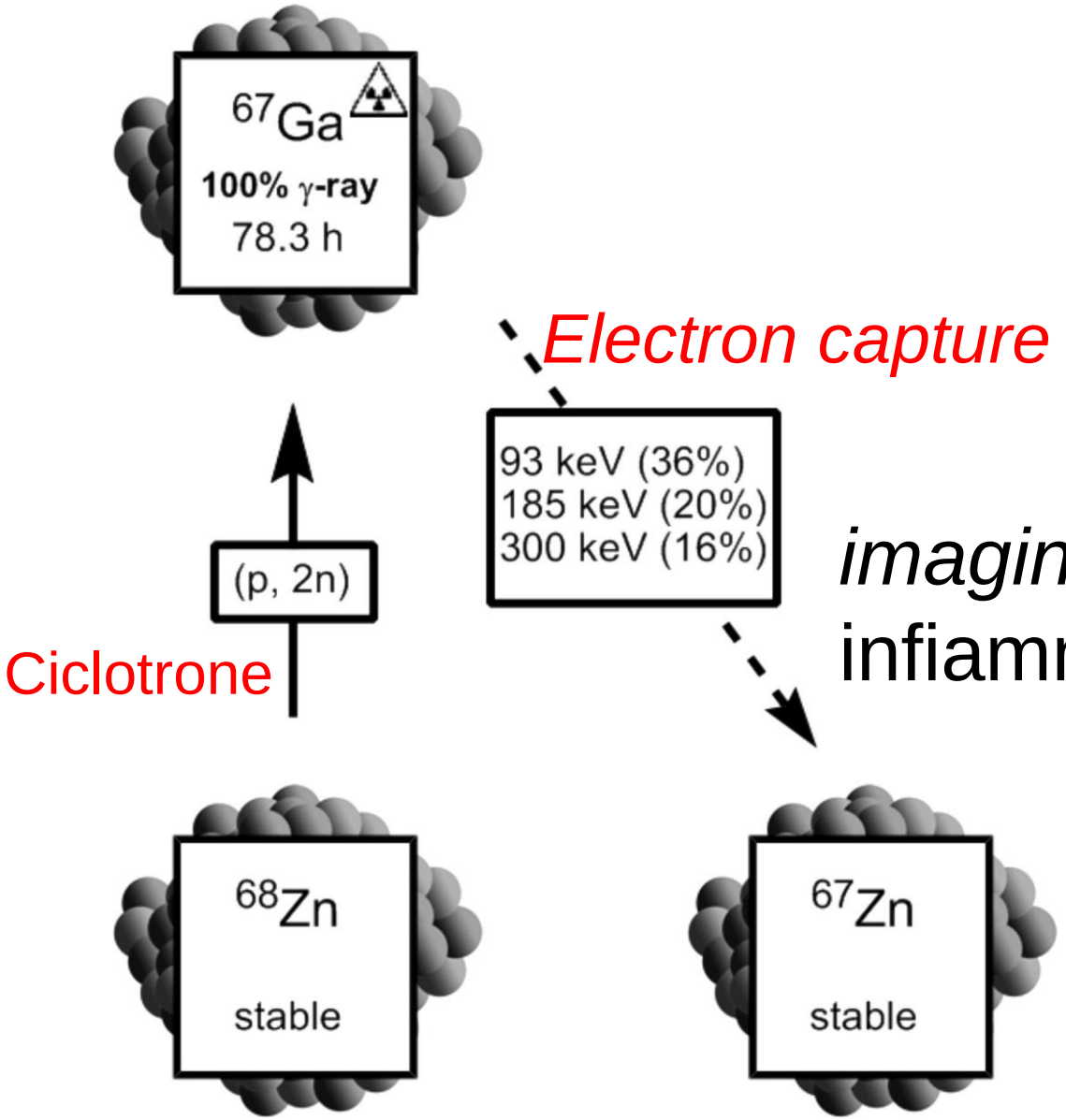


+

Localizzazione nei mitocondri



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



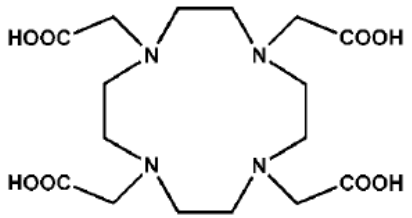
imaging di processi infiammatori e di tumori

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

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

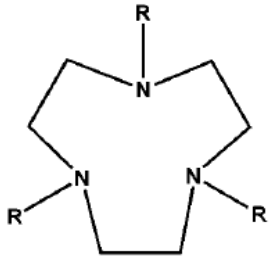
Diethylenetriamino-pentaaceticacid

a)



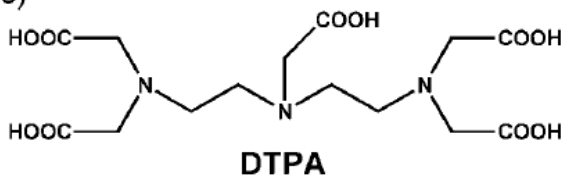
DOTA

b)



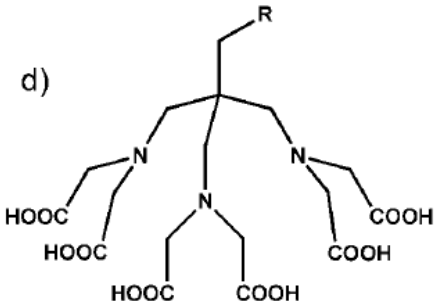
NOTA	R = CH_2COOH
TACN-TM	R = CH_2CH_2SH
NOTP	R = $CH_2PO_3H_2$
NOTPME	R = $CH_2PO_2(OCH_2CH_3)$

c)



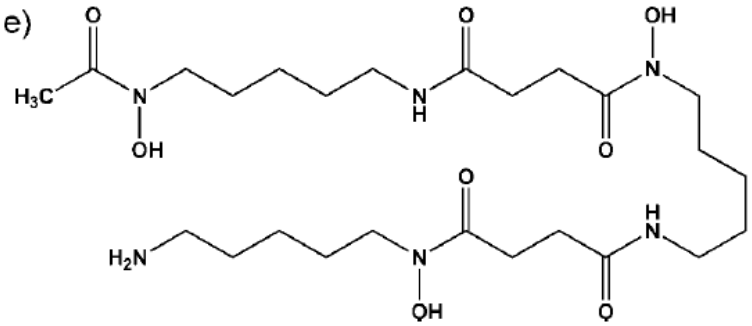
DTPA

d)

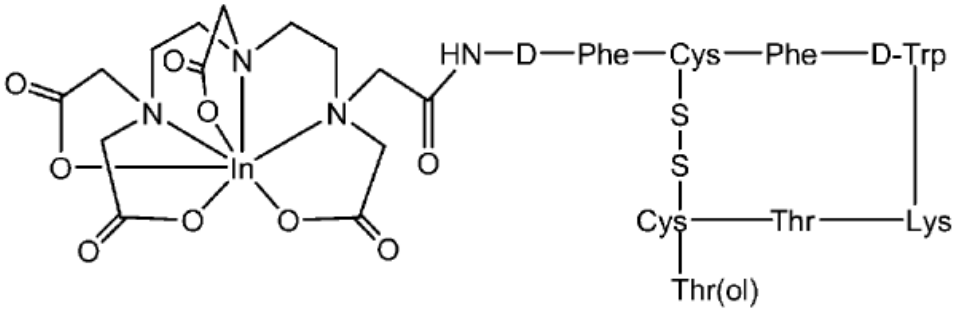


TAME Hex

e)

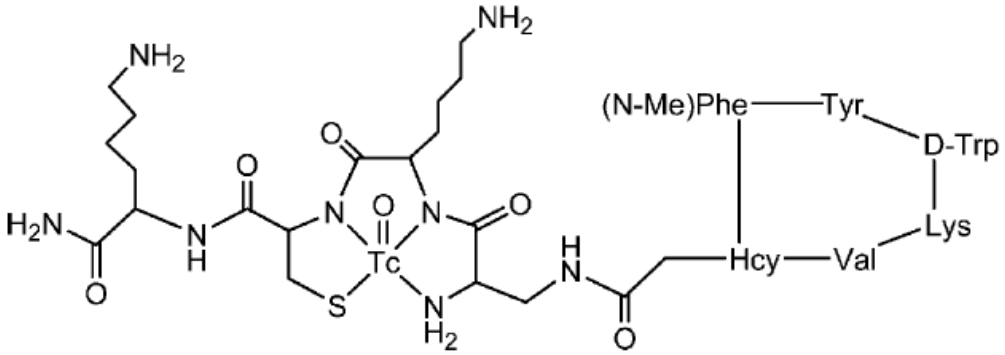


Octreotide e Depreotide
peptidi specifici per i recettori della somatostatina



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

SPECT imaging of neuroendocrine tumors

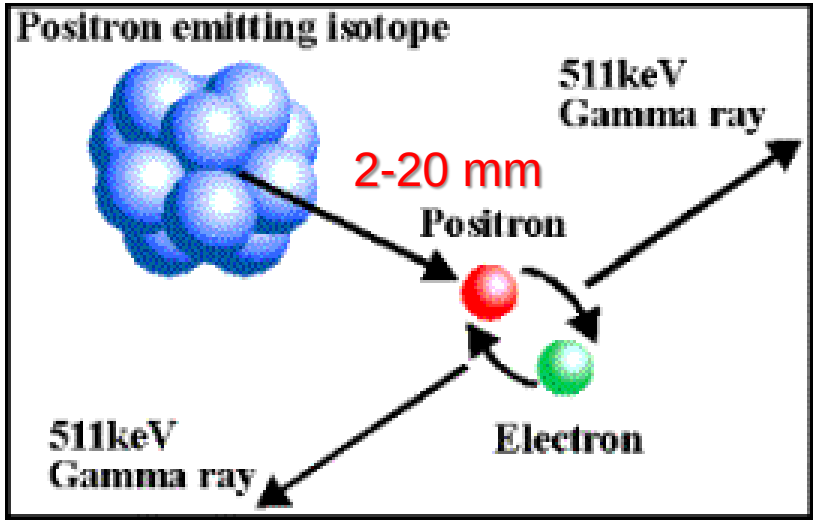


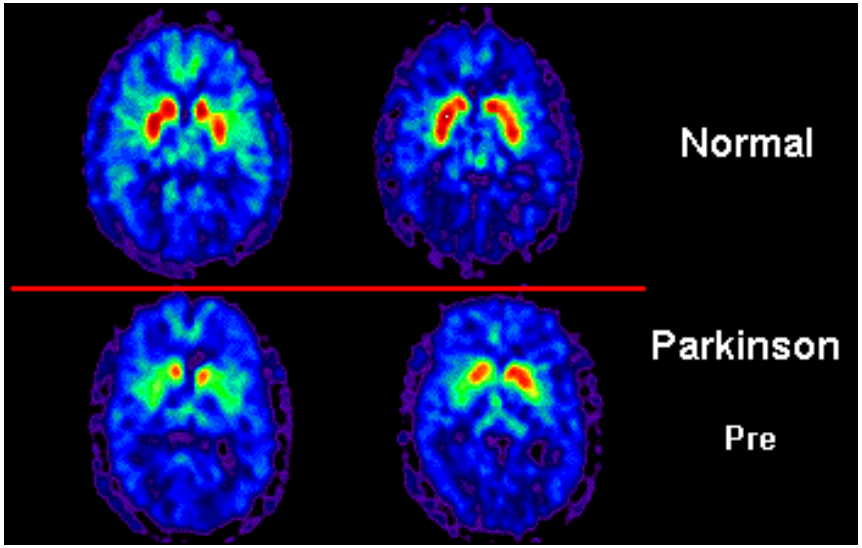
^{99m}Tc-P829 (NeoTect®)

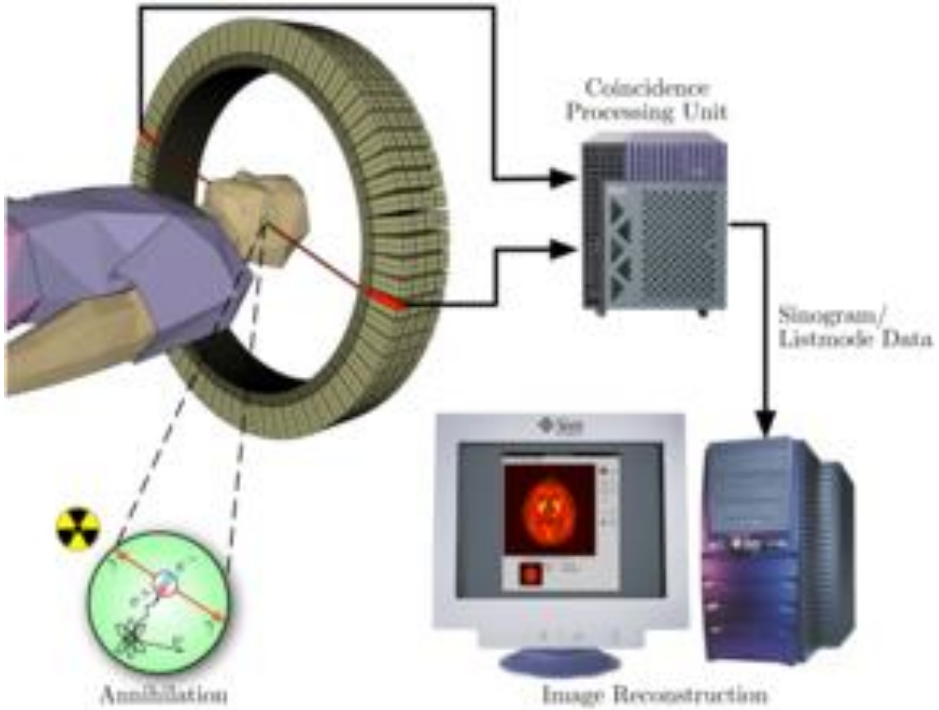
SPECT imaging of lung tumors

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

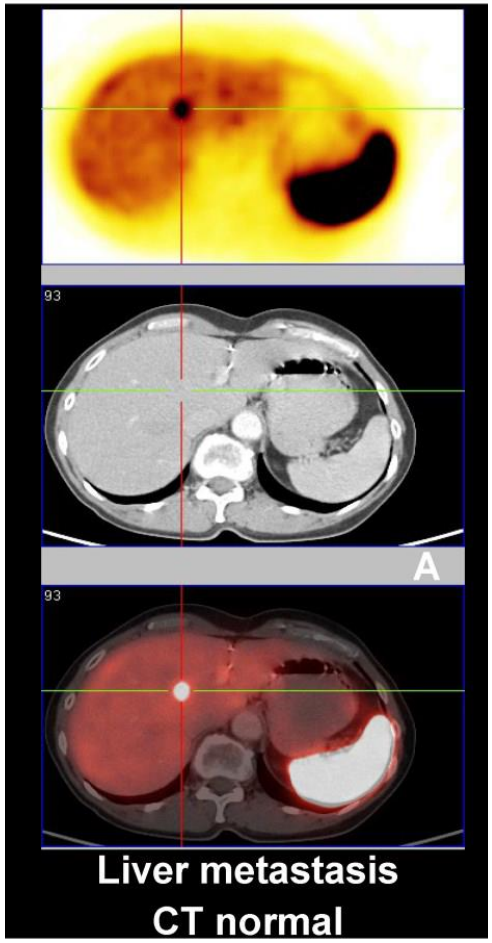
PET: Positron Emission Tomography







PET/CT: combinazione di imaging strutturale e funzionale



PET

CT

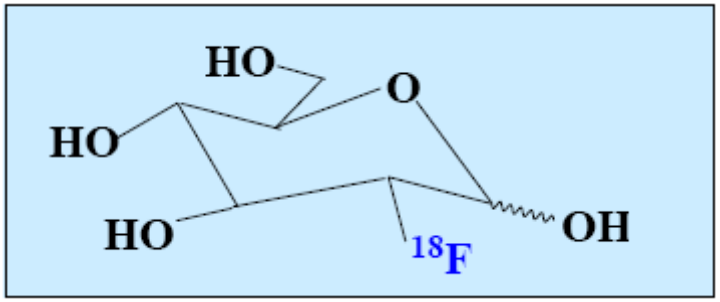
PET + CT

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

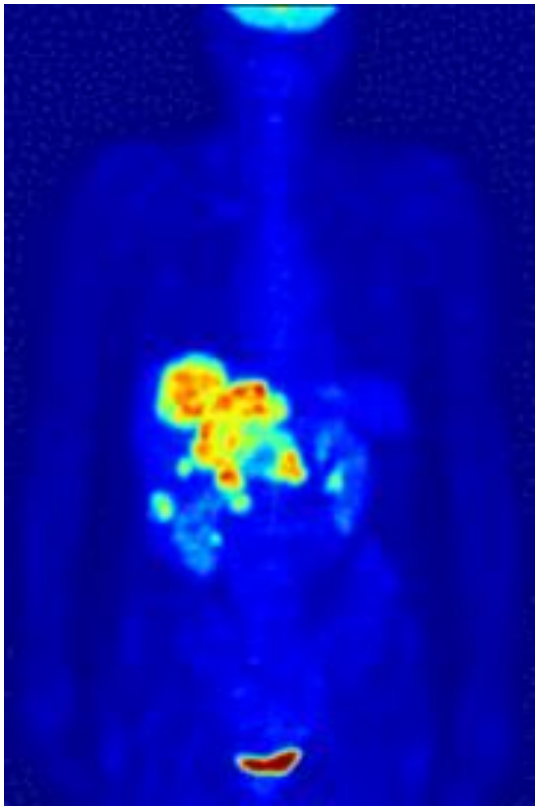
[a] EC: electron capture.



Fluorodeoxyglucose ([^{18}F] FDG)

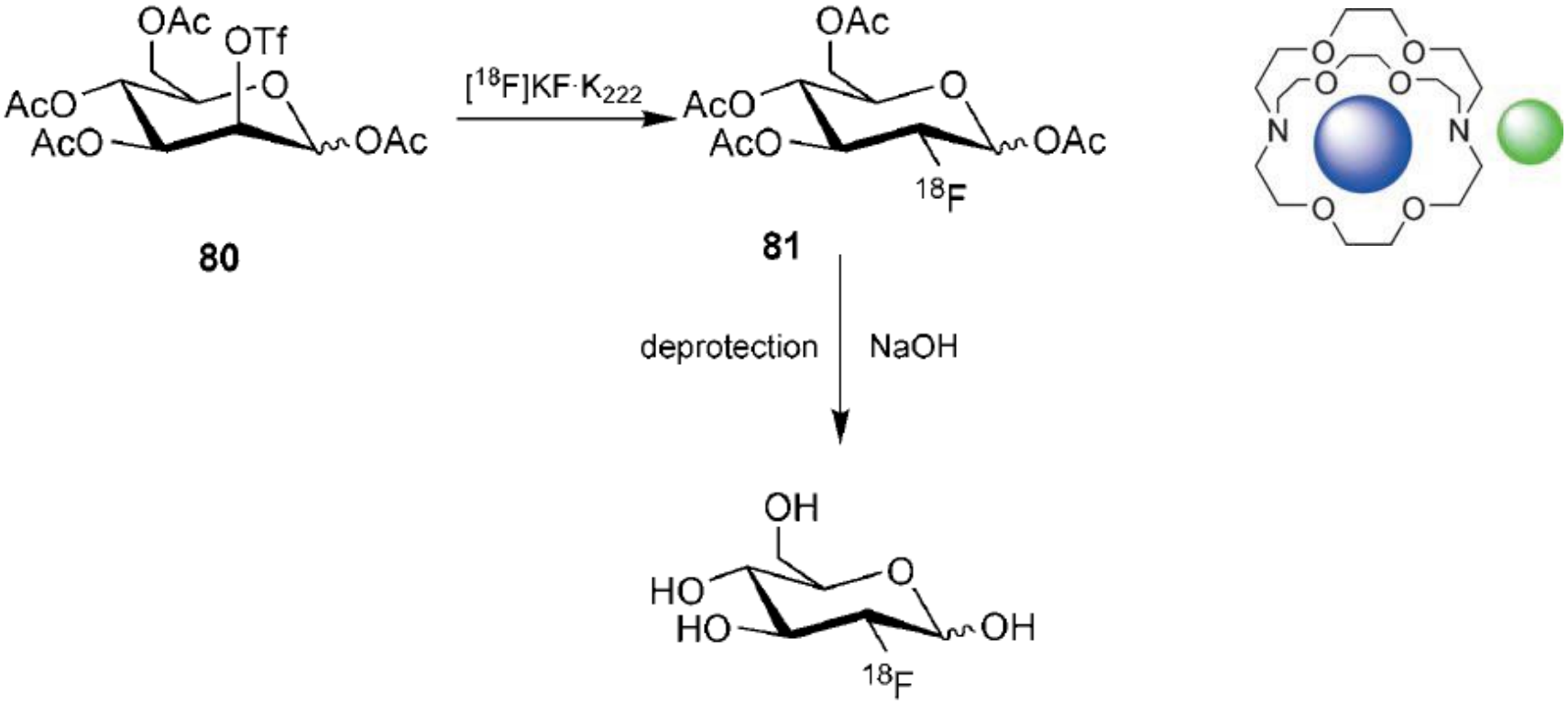
Sostituzione bio-isosterica

metabolismo del glucosio
localizzazione di tumori

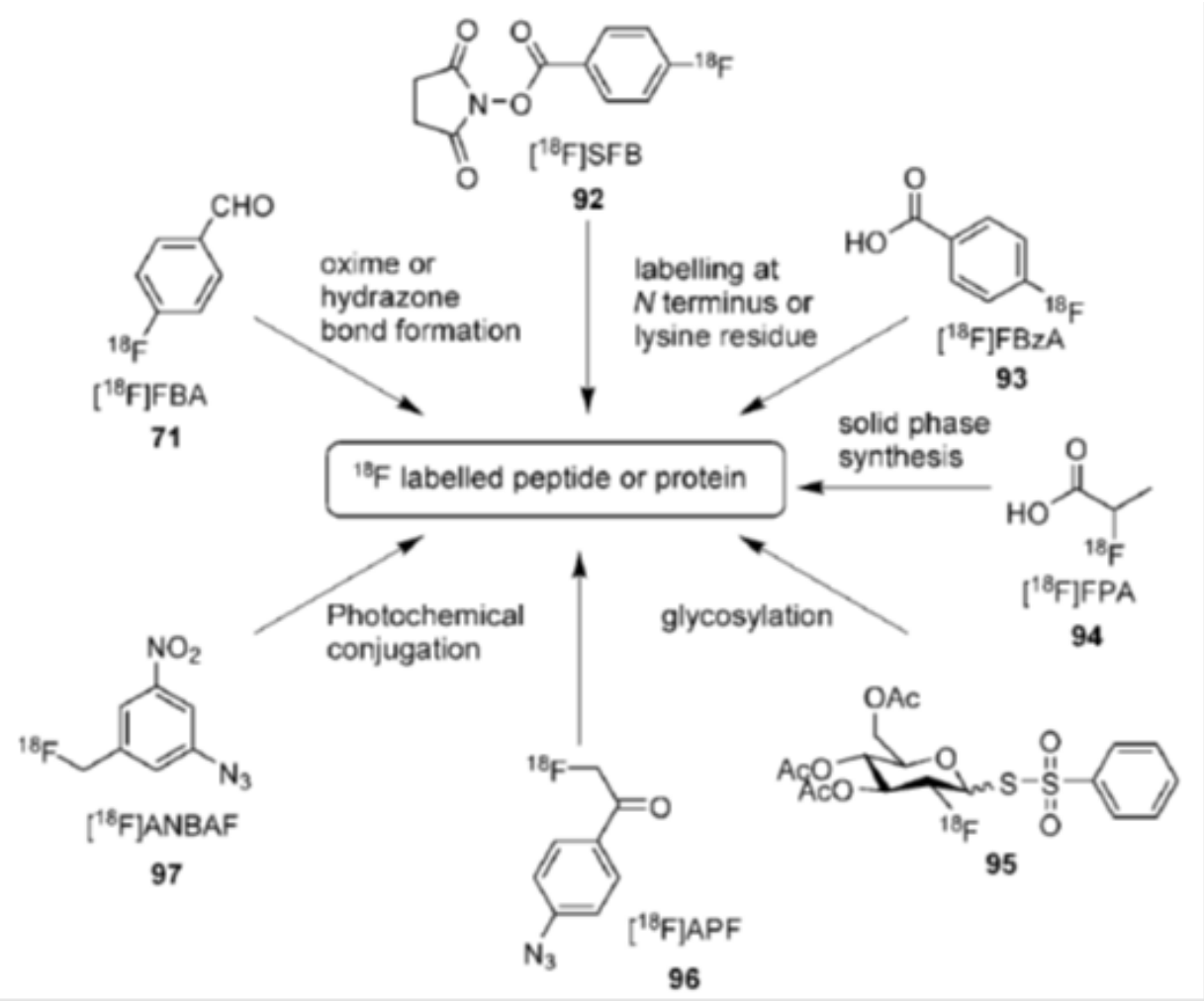


Esempio di fluorurazione diretta (nucleofila)

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

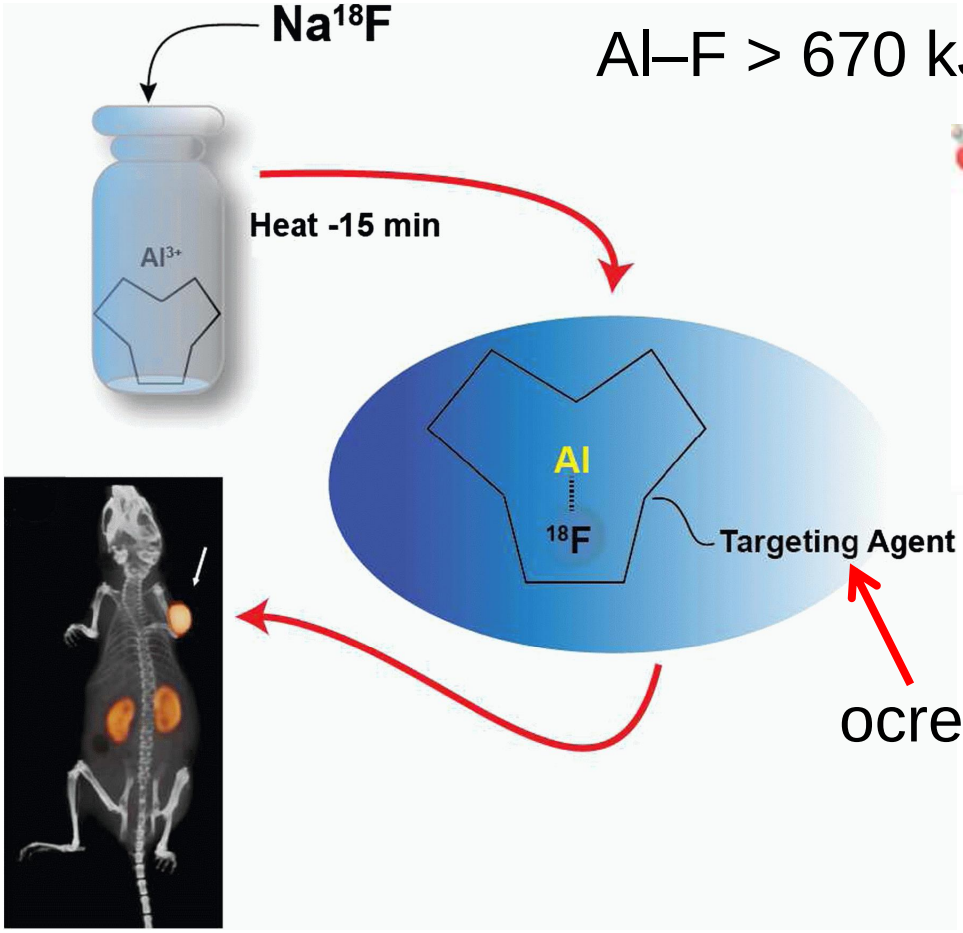


Gruppi prostetici per marcare biomolecole con ^{19}F

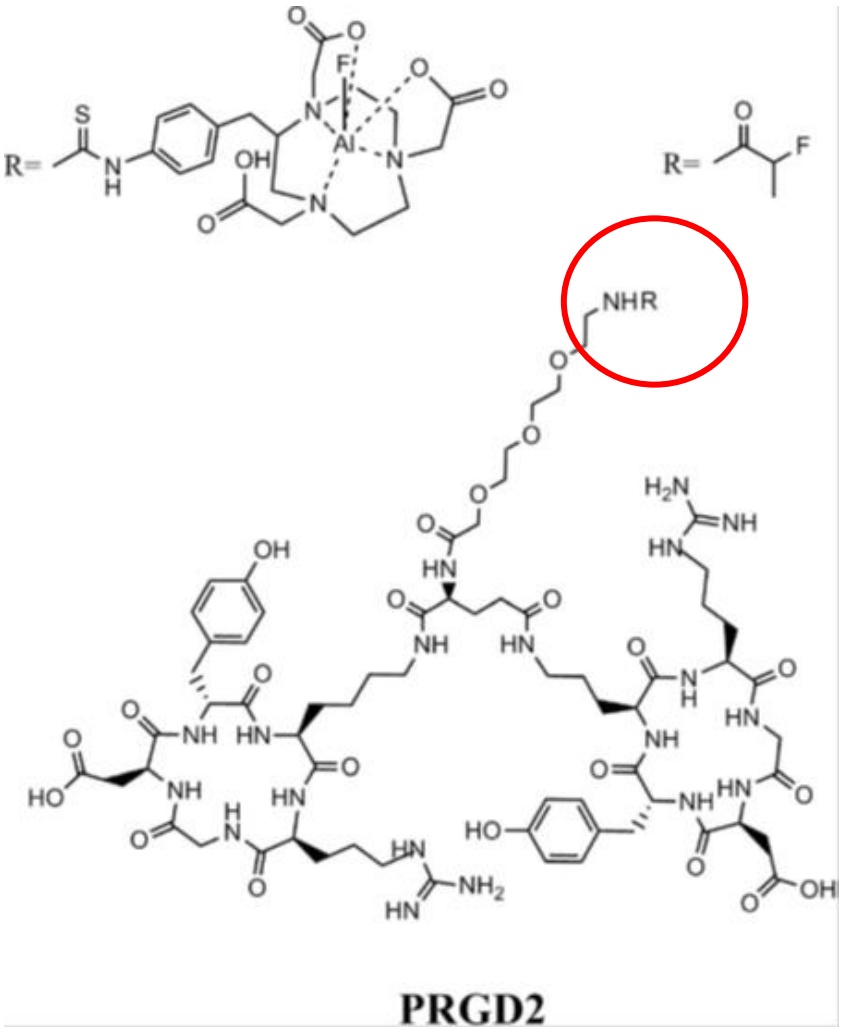


Fluorurazione inorganica

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

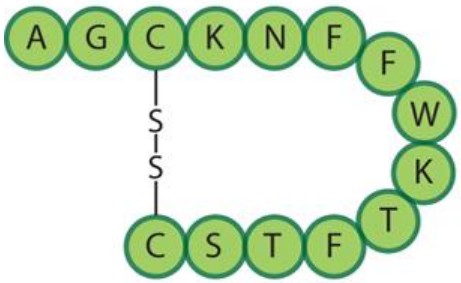
studio clinico nell'uomo per l'*imaging* di un tumore al polmone

Radionuclidi metallici per PET

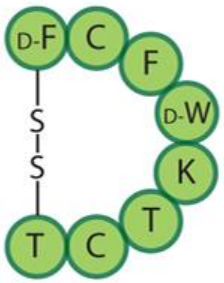
Table 1. Physical Properties of Some Common PET Radiometals[a]

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

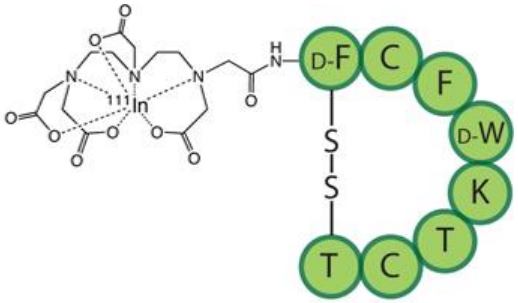
I tumori neuroendocrini sovra-esprimono i recettori per la somatostatina



Somatostatin



Octreotide



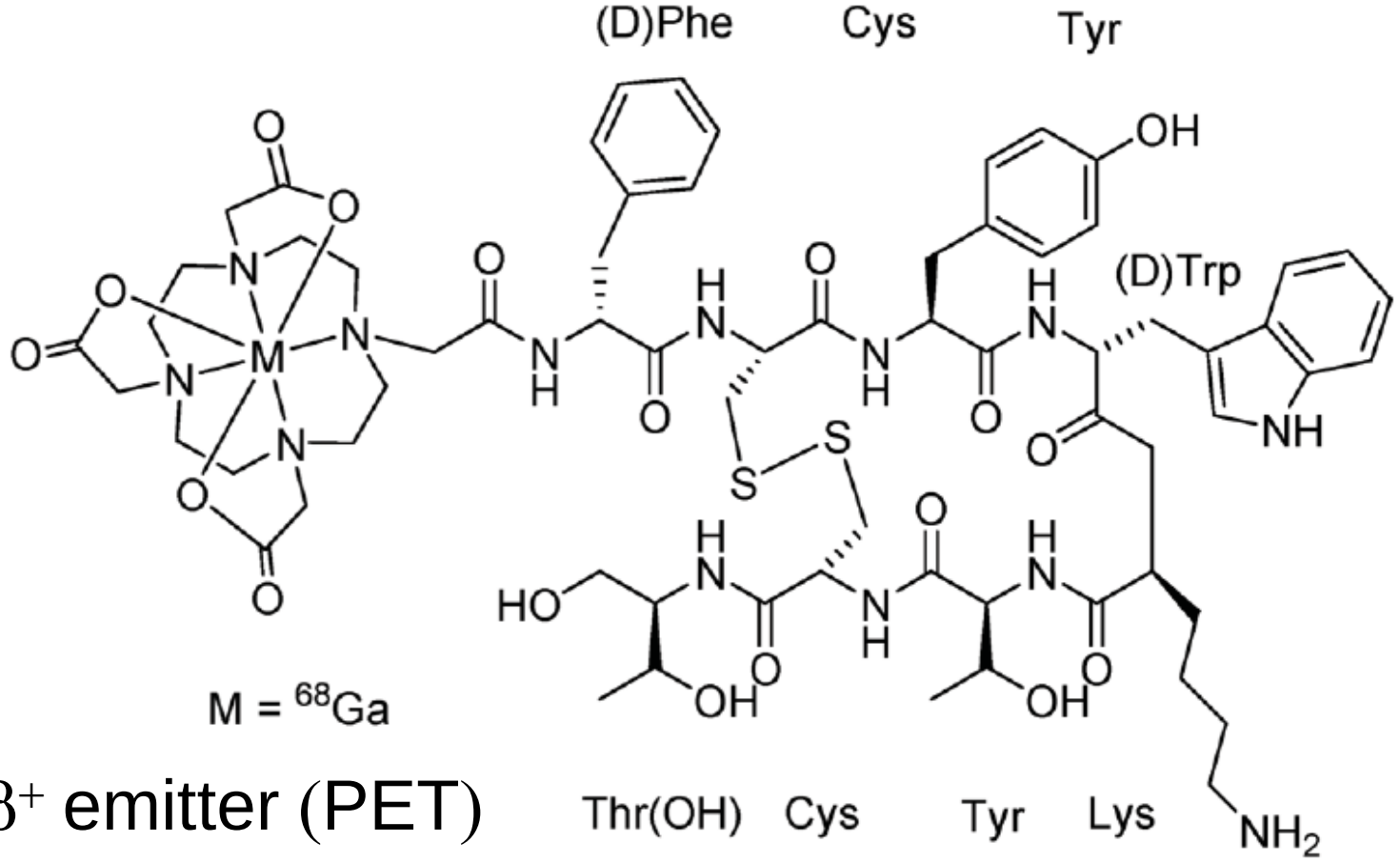
^{111}In-DTPA-Octreotide

SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTA-tyr3-Octreotide

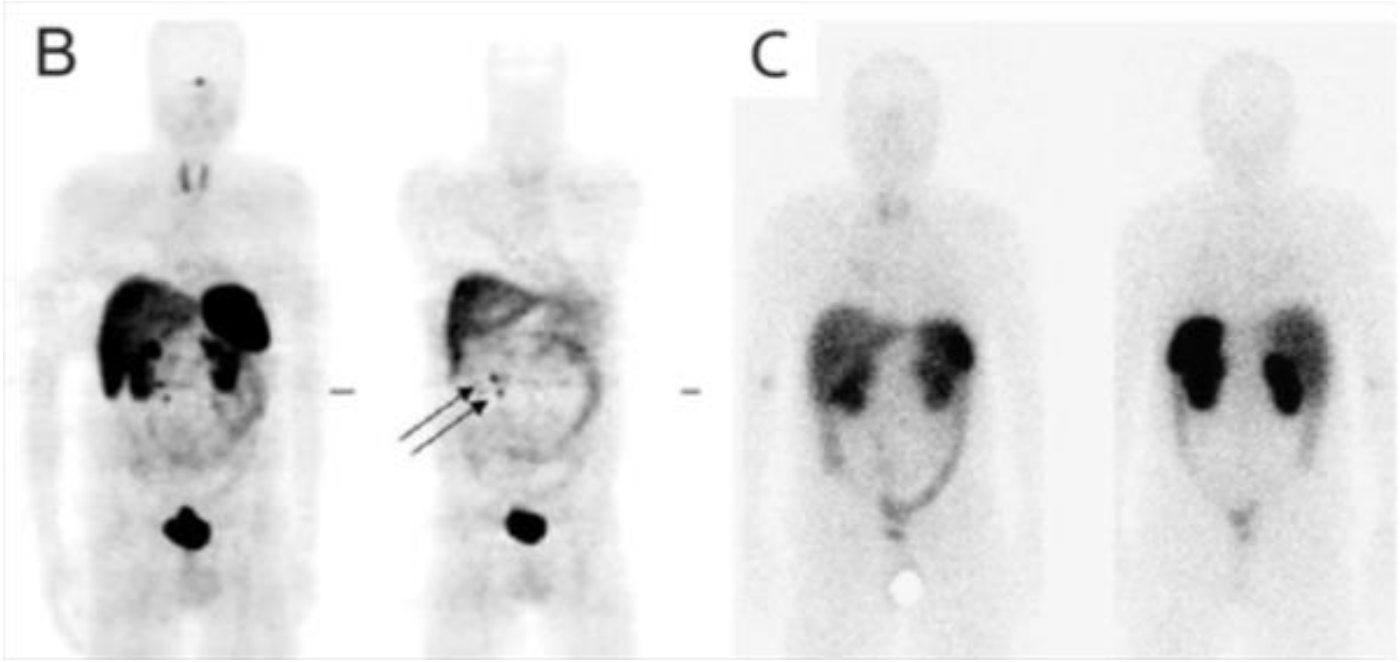
(^{68}Ga-DOTATOC)

High resolution PET imaging of neuroendocrine tumors



β^+ emitter (PET)

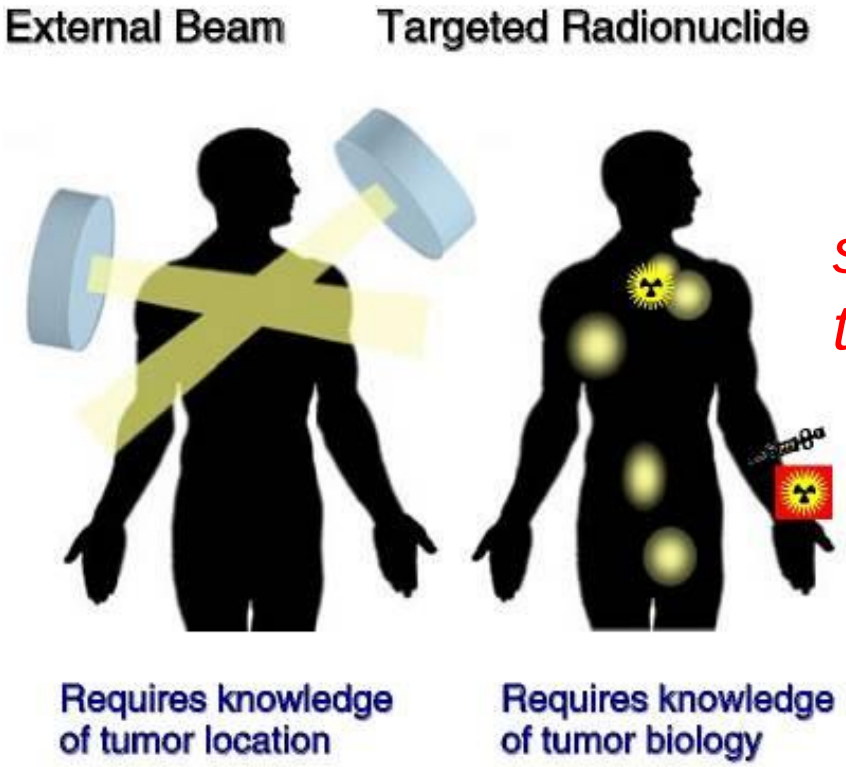
imaging di un tumore endocrino



^{68}Ga-DOTATOC
(PET)

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

Targeted Radiotherapy (*Radio(immuno)therapy*)



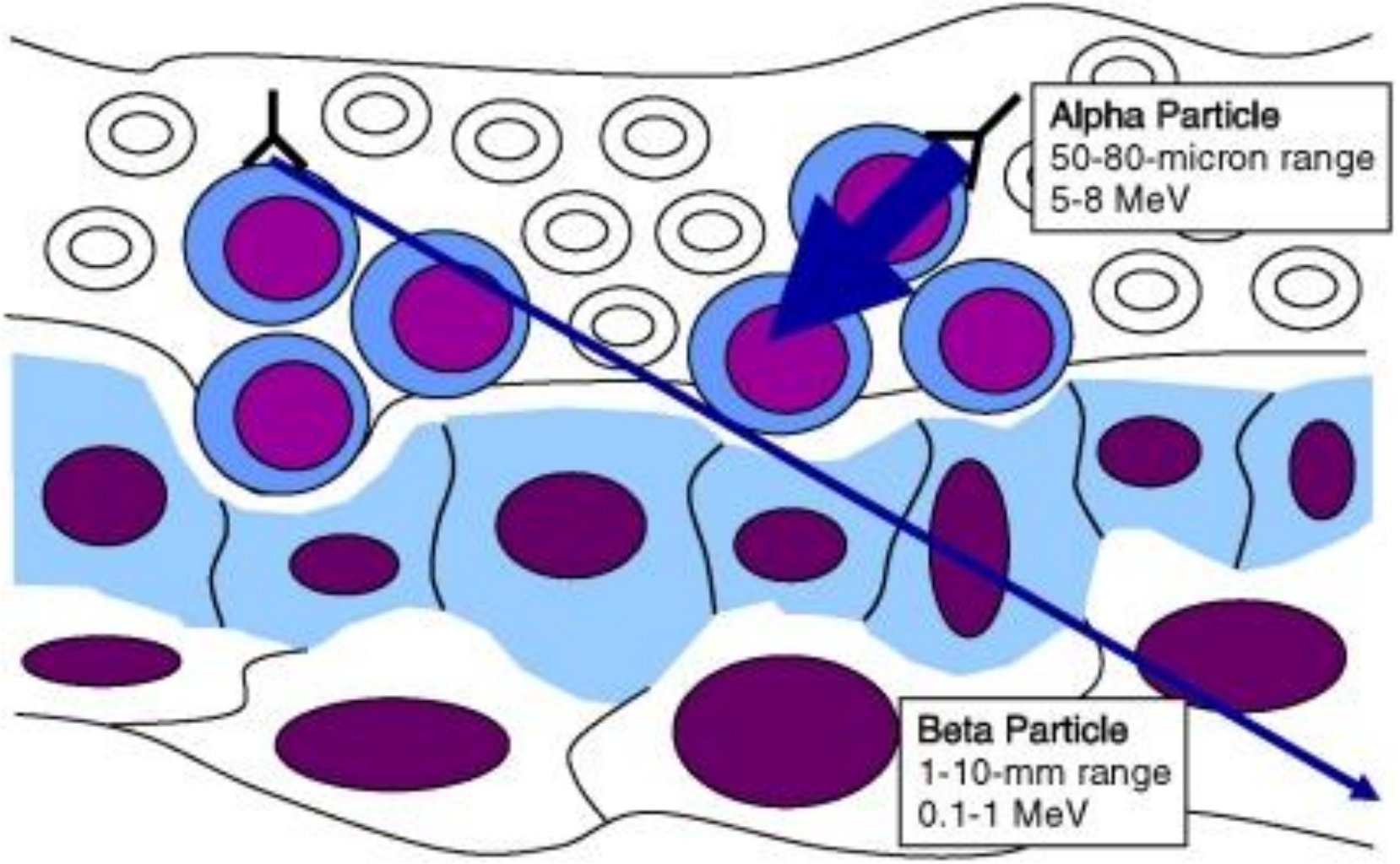
- Linfomi: 1500–2000 cGy
- Tumori solidi: 3500–10000 cGy

systemic treatment

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

TI = therapeutic index

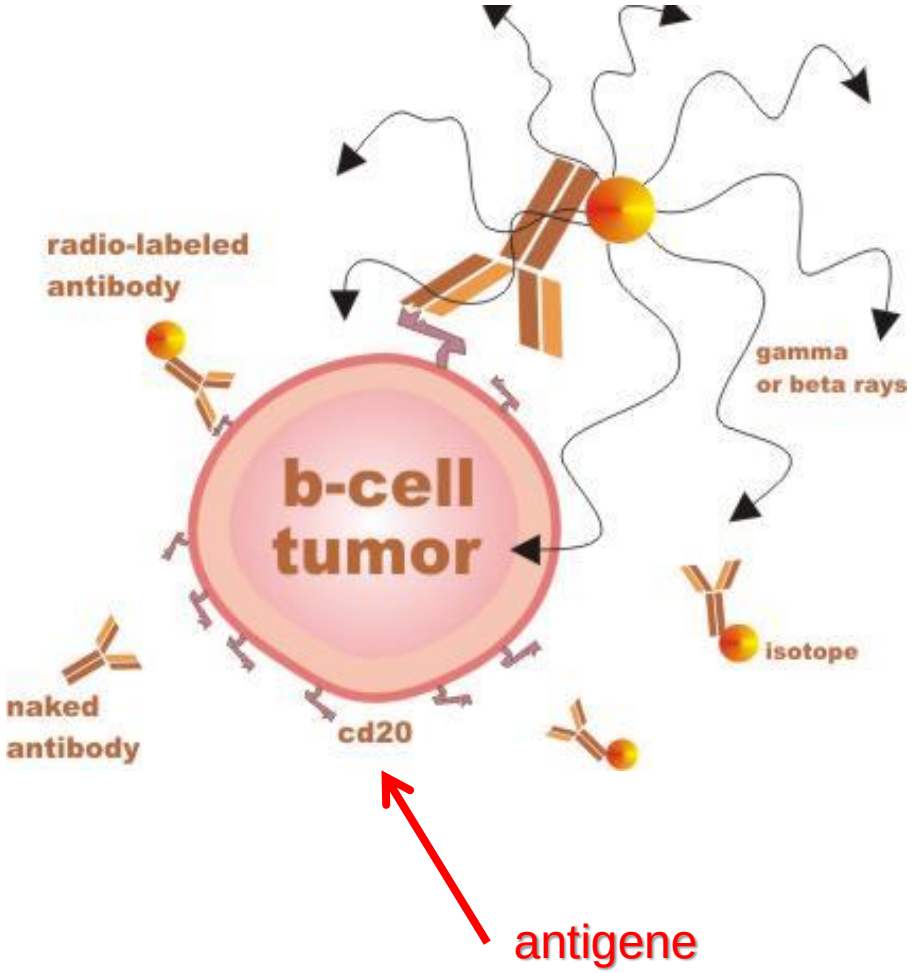
Penetrating power of α and β particles



Main radionuclides for Targeted Radiotherapy

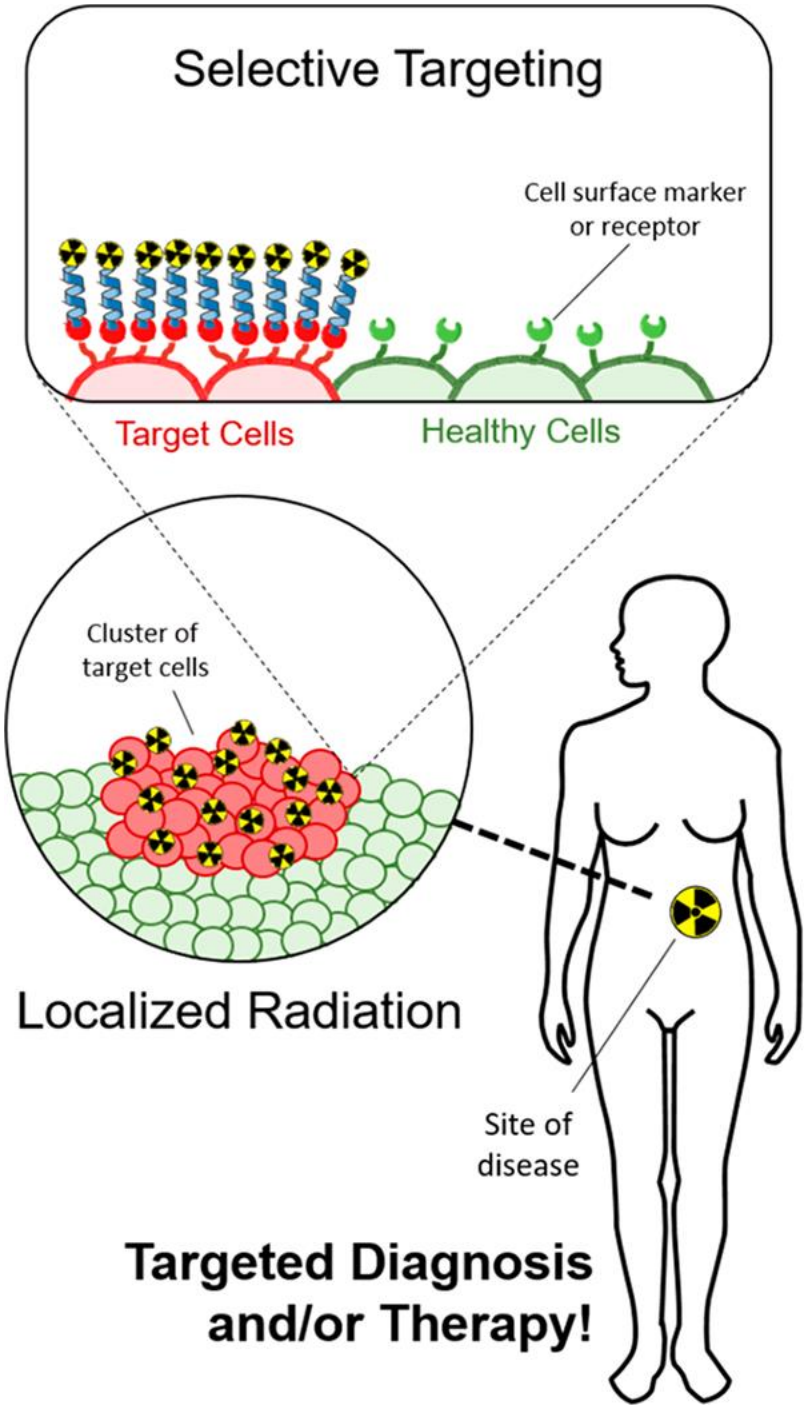
Radionuclide	**Half life**	**Energy of main γ emission (keV)**
^{67}Cu (β, γ)	62 h	93, 185
^{90}Y (β)	64 h	
^{153}Sm (β, γ)	46 h	103
^{131}I (β, γ)	8 d	364
^{177}Lu(β, γ)	6.6 d	497
^{188}Re (β, γ)	17 h	155
^{213}Bi (α, β, γ)	1 h	727
^{225}Ac (5α, 3β)	10 d	5800 - 8400

Treatment of B-cell non-Hodgkin's limphoma

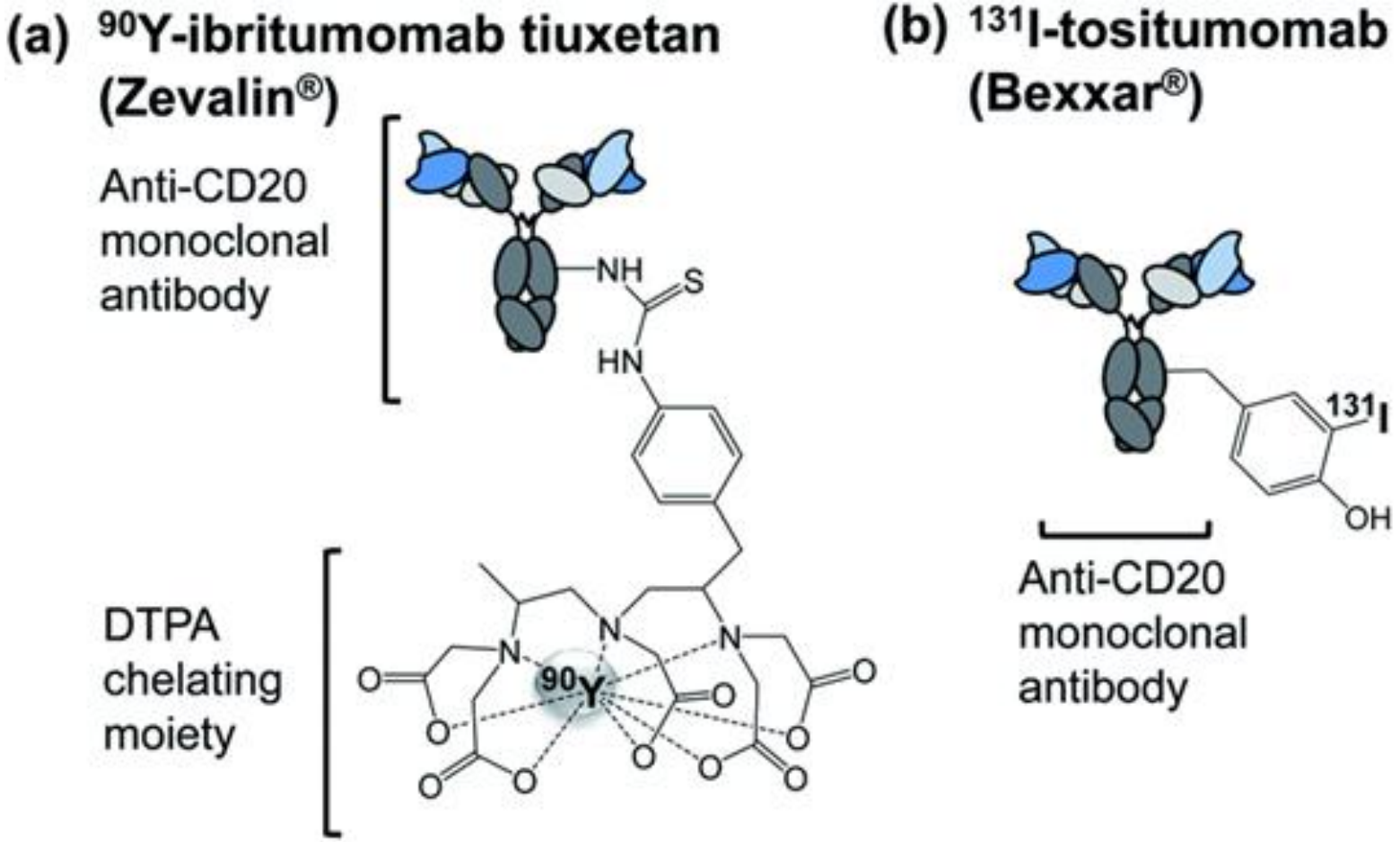


Antigene ideale:

- 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

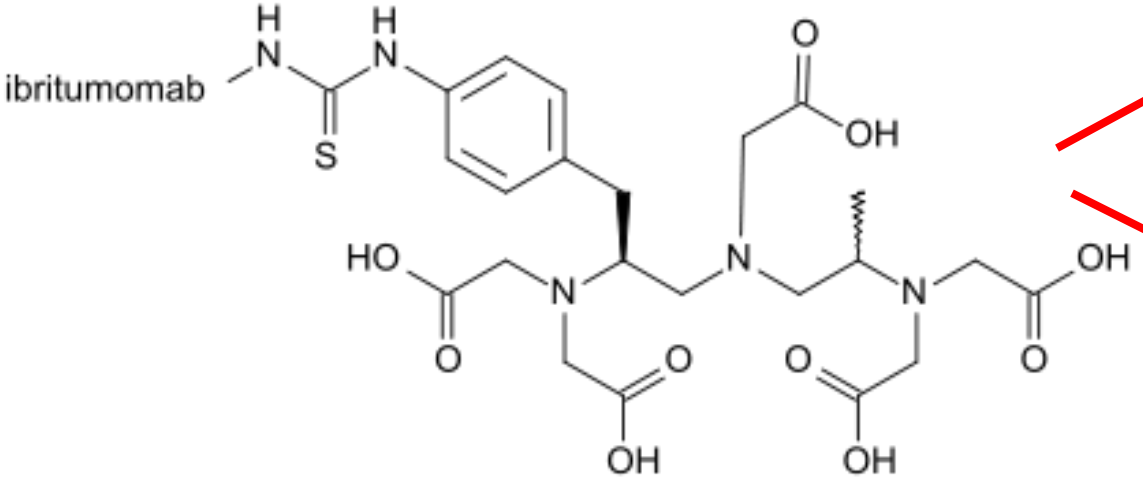

Selective Targeting
Cell surface marker or receptor
Target Cells
Healthy Cells
Cluster of target cells
Localized Radiation
Site of disease
Targeted Diagnosis and/or Therapy!

FDA approved



Zevalin®

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



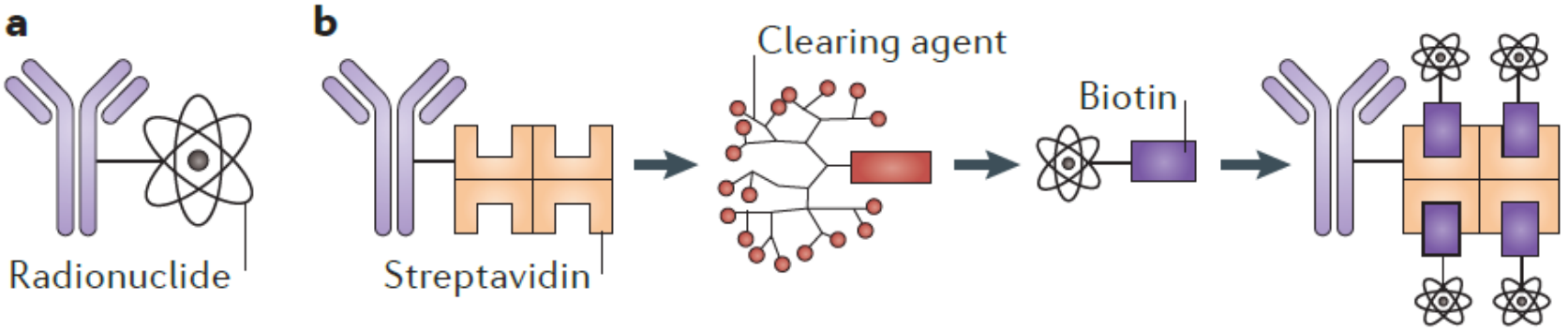
$^{111}In^{3+}$ for imaging

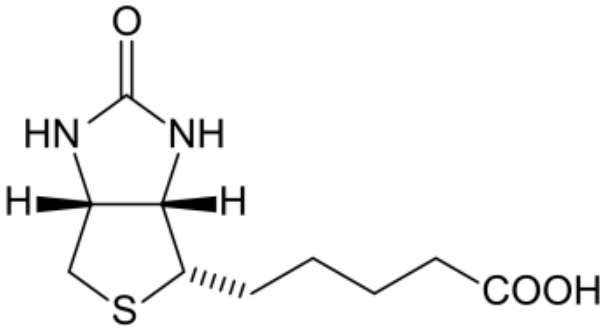
^{90}Y is a pure β^+ emitter

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

Example of the matched-pair approach

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

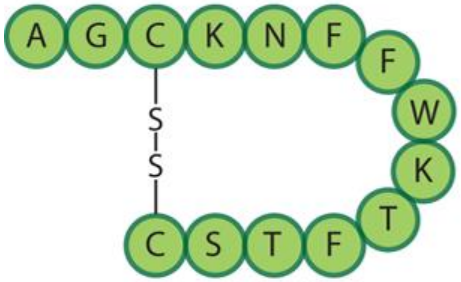




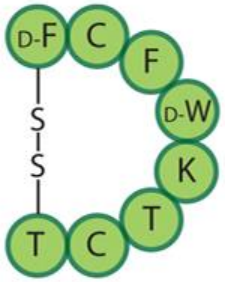
Biotina

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

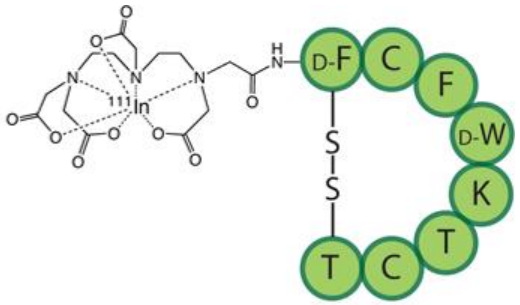
Radio-immunotherapy of neuroendocrine tumors



Somatostatin



Octreotide



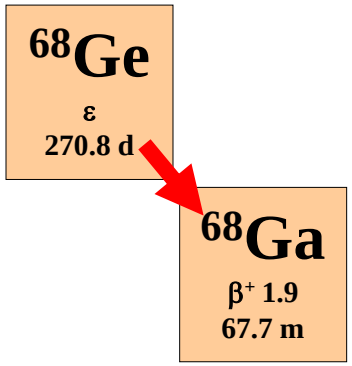
^{111}In-DTPA-Octreotide

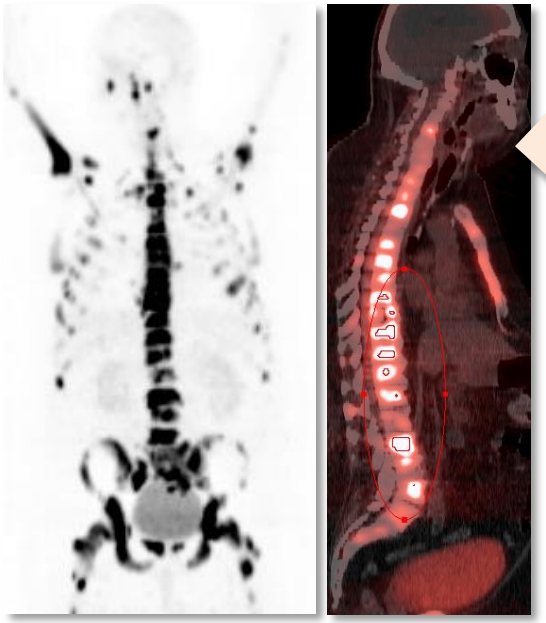
SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTATOC for PET imaging

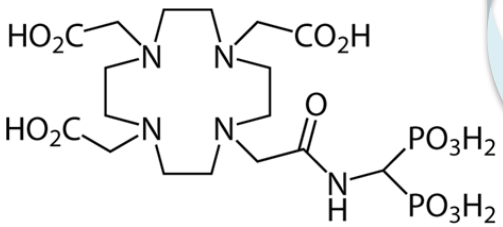
^{90}Y-DOTATOC and ^{177}Lu-DOTATATE for radiotherapy

Radiometal-based *theranostics*: the *matched-pair* strategy

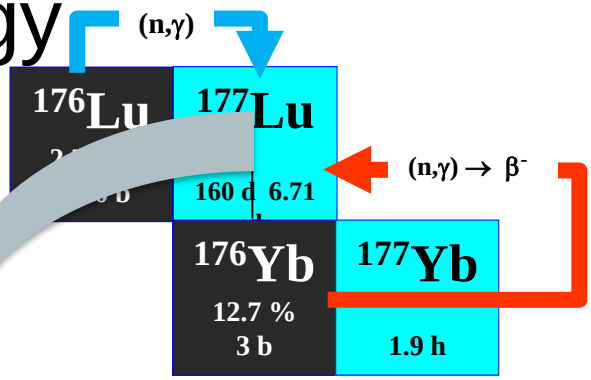




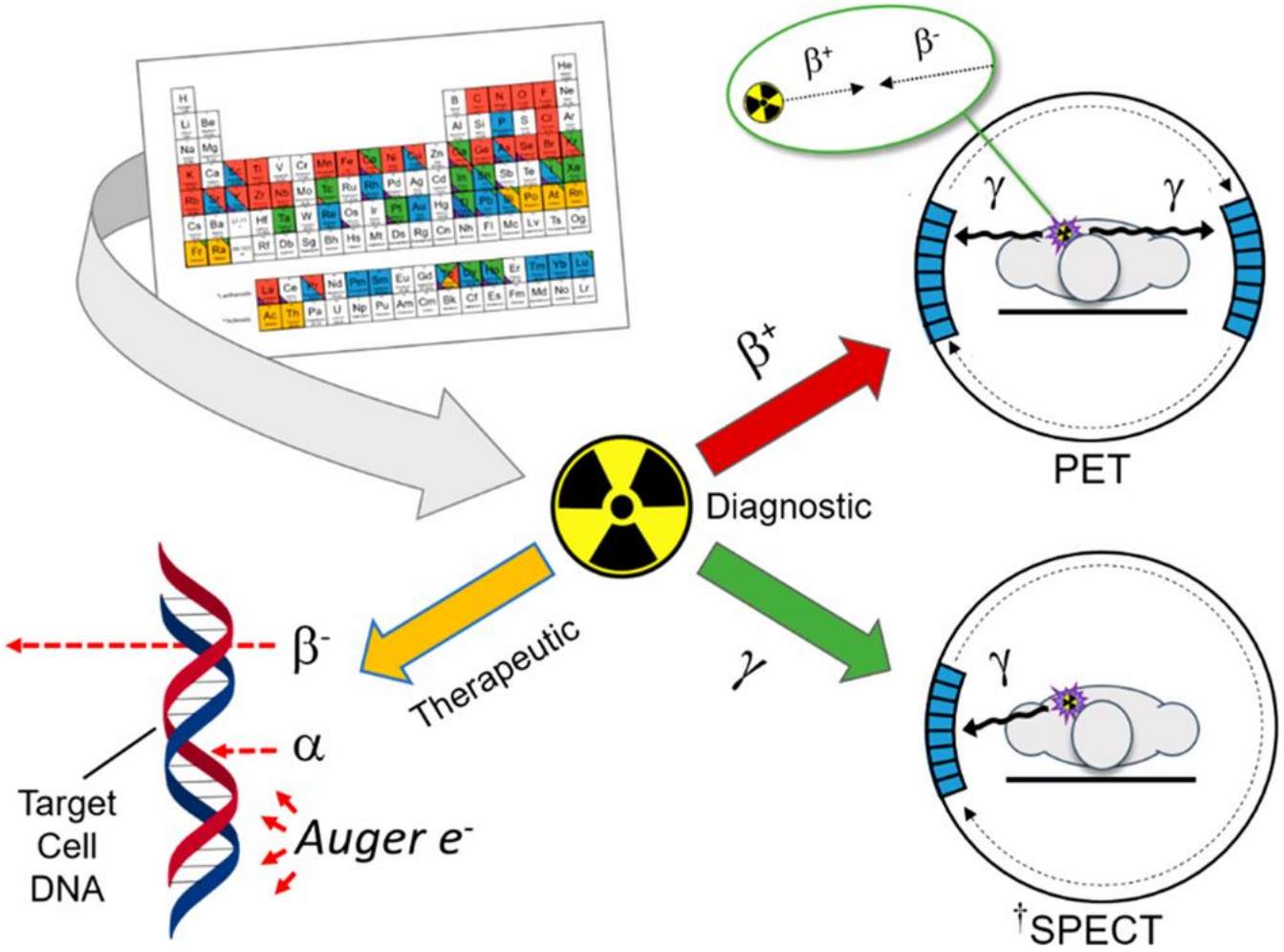
DOTA-bisphsophantae amide
„BPAMD“



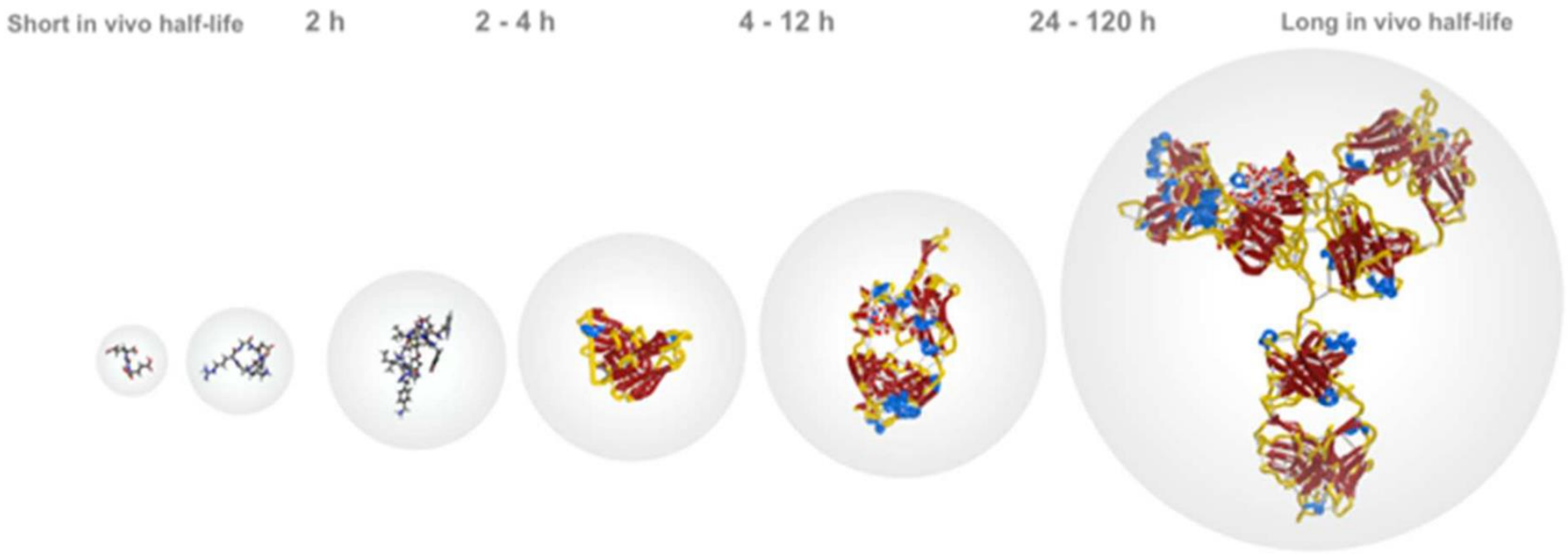
^{68}Ga-BPAMD
Diagnosis (PET/CT)



^{177}Lu-BPAMD
Therapy


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

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^-

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