METALLI IN MEDICINA

A.A. 2016-2017

PARTE 5

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DEGLI STUDI DI TRIESTE

METALLI IN MEDICINA 2016-2017
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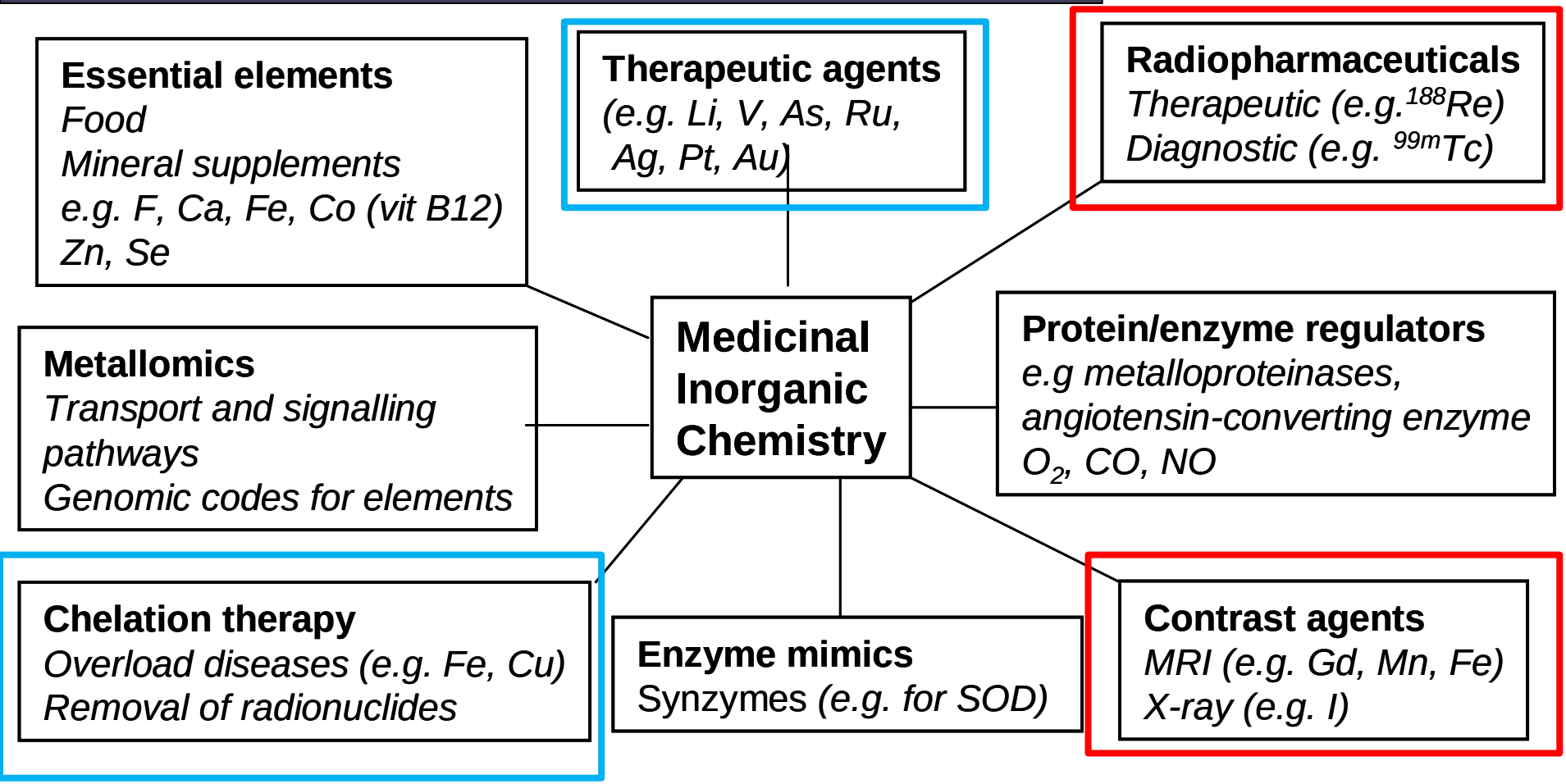

Imaging with Metal Compounds

Cellular level

(*molecular imaging o imaging funzionale*)

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.

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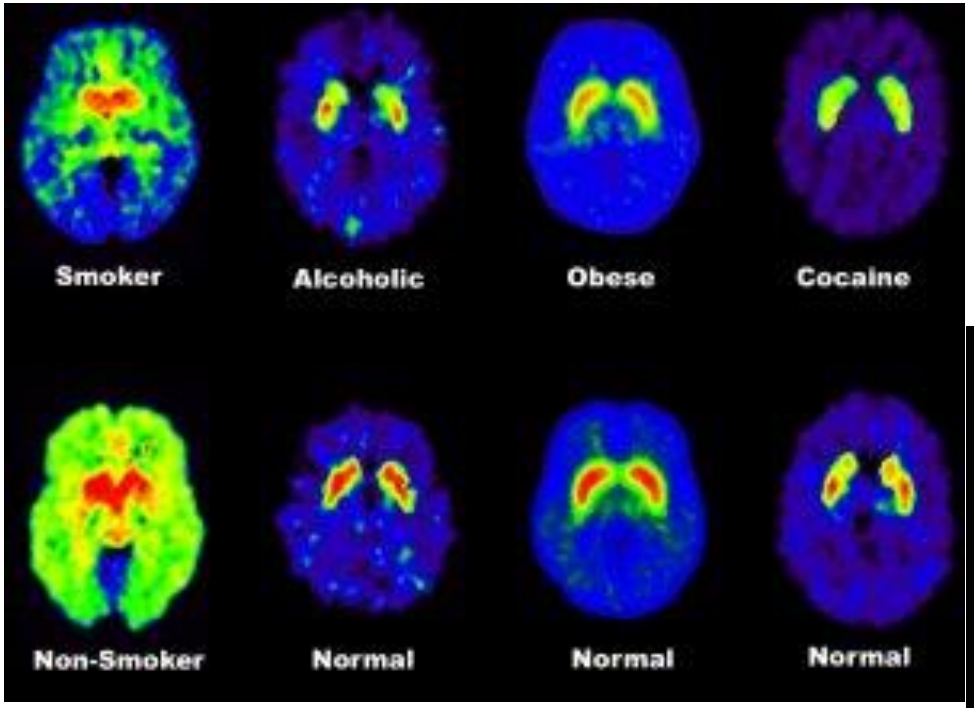

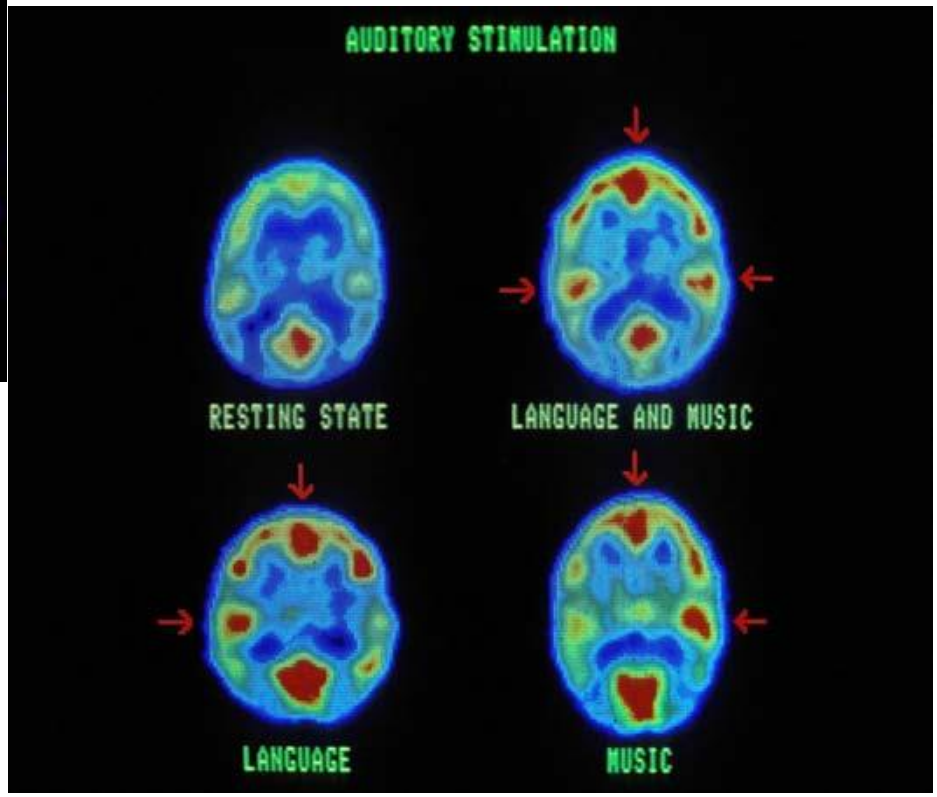

Radiopharmaceuticals

Radiodiagnostics

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

Radiotherapeutics

α or β^- emitters

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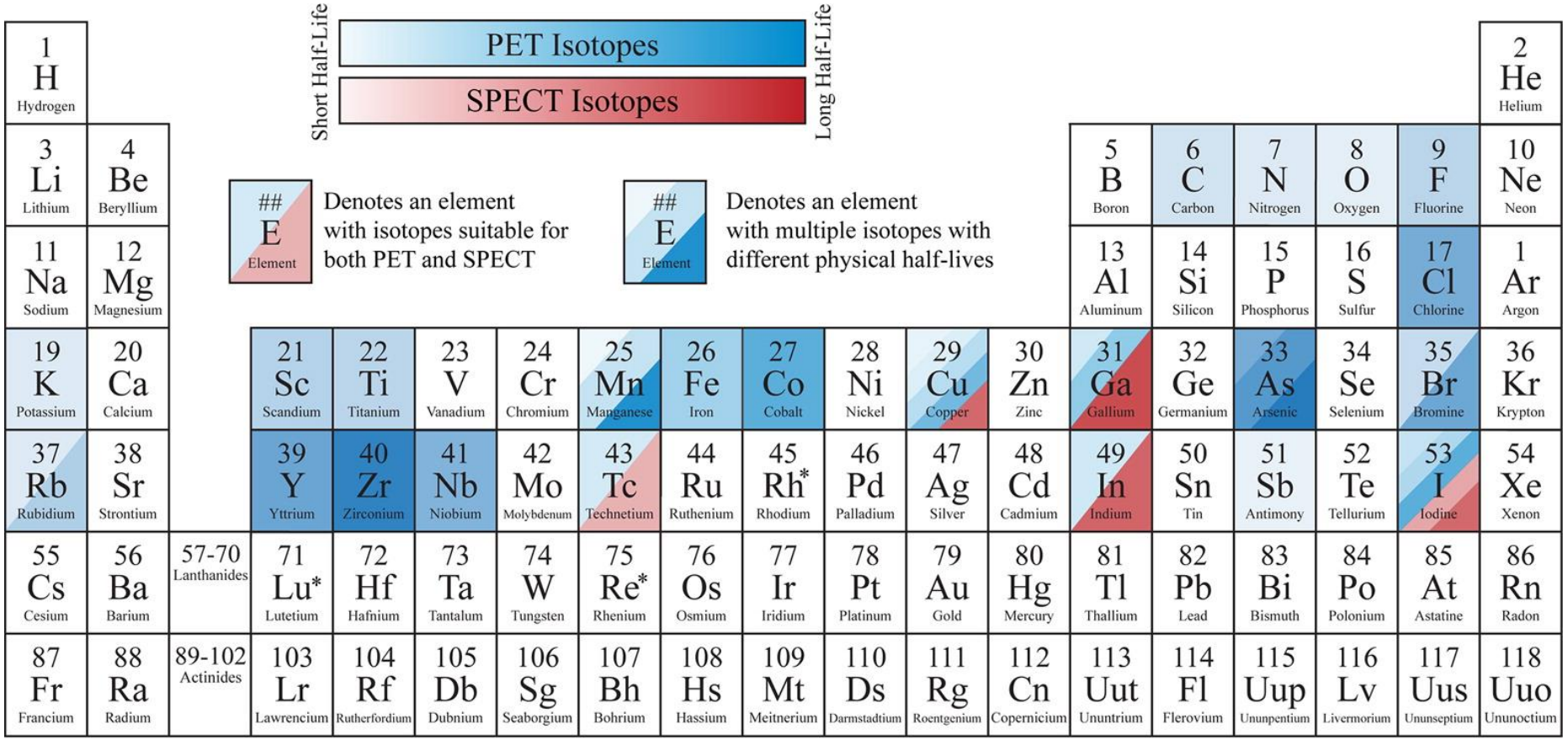
Isotopes suitable for nuclear imaging

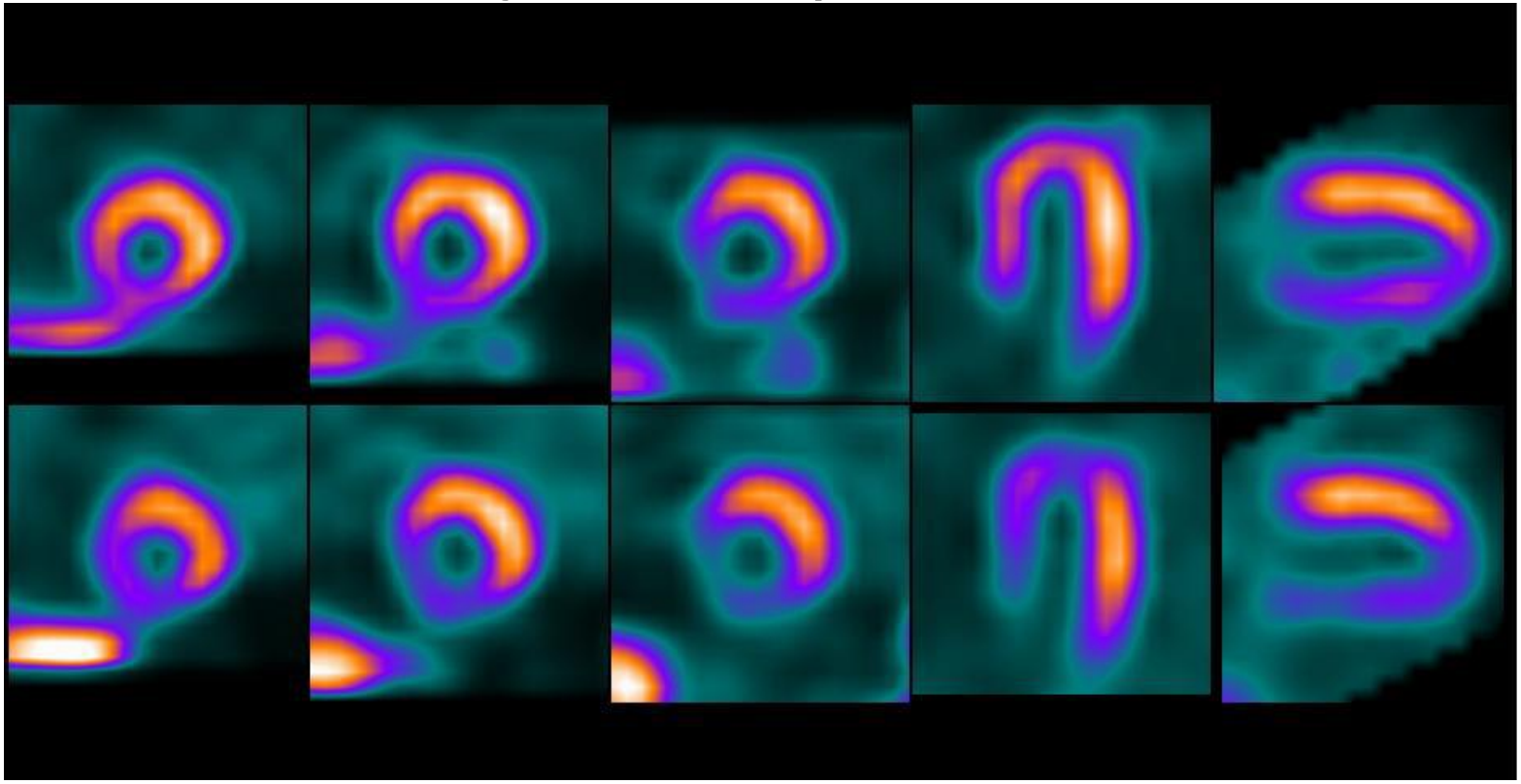


*Isotopes typically used for radiotherapy with which SPECT is also possible but not common — *e.g.*, ^{177}Lu, ^{105}Rh, ^{186}Re, etc. — have been omitted.

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

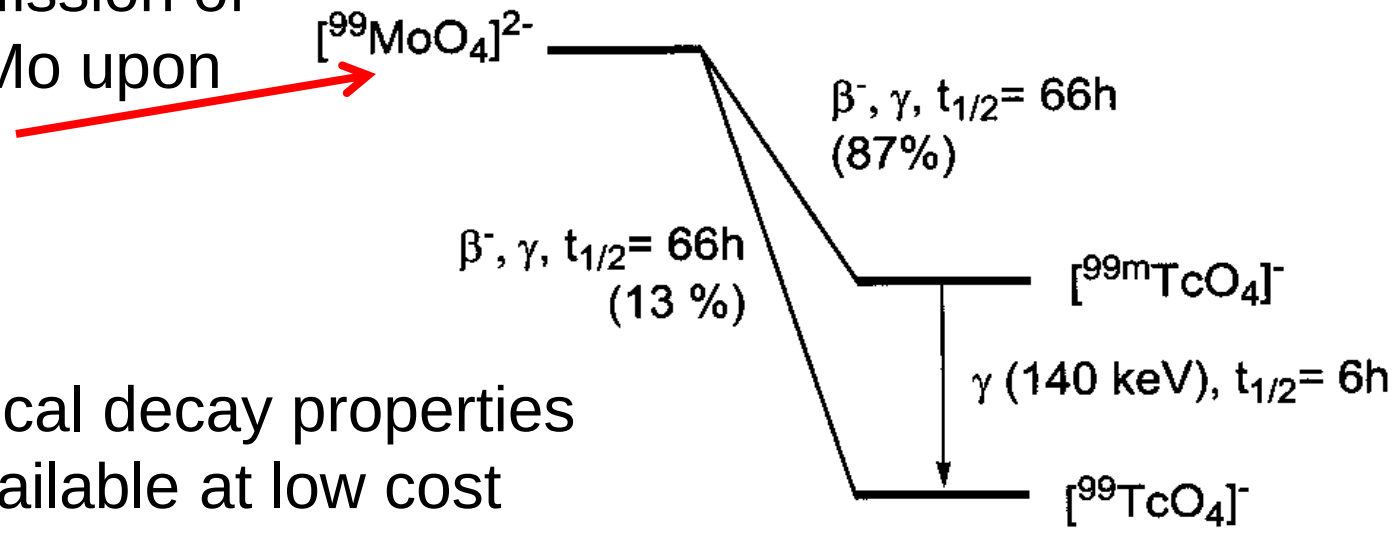
Main radionuclides for SPECT

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

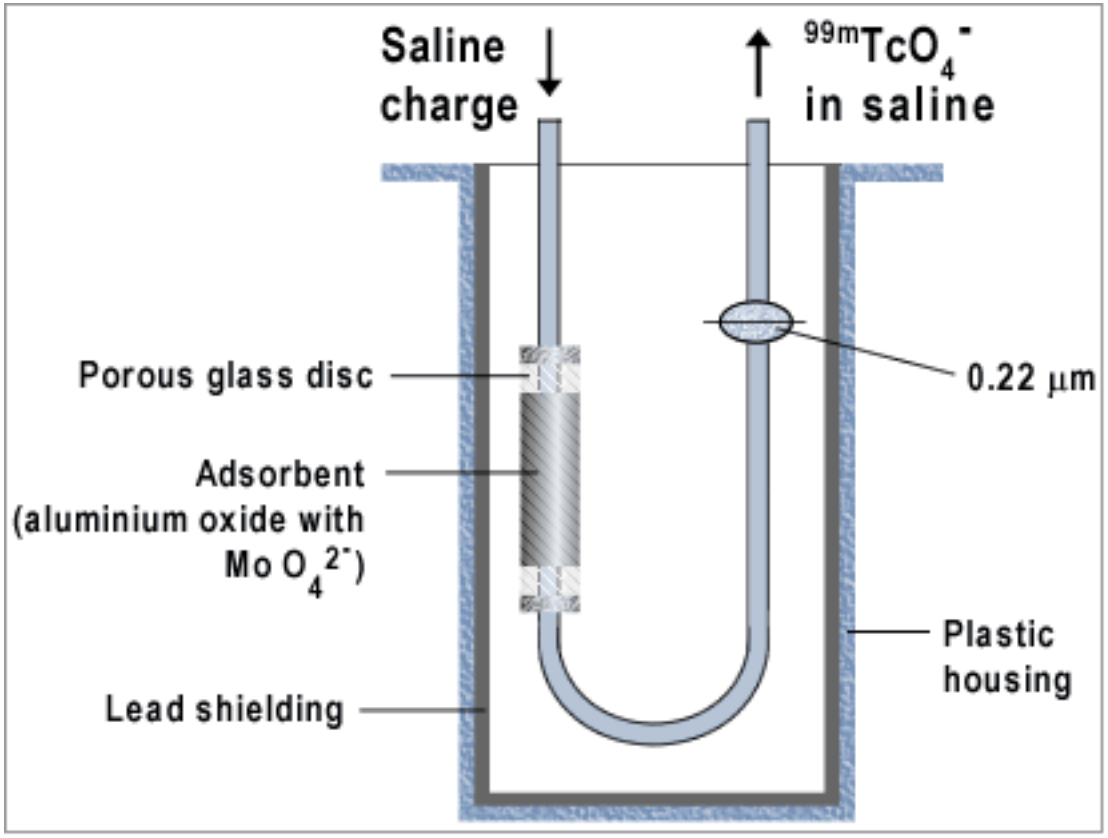
(used in >80% of diagnostic scans, more than 25 M in 2007)

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


Saline charge
$^{99m}TcO_4^-$ in saline
Porous glass disc
Adsorbent (aluminium oxide with MoO_4^{2-})
Lead shielding
0.22 μm
Plastic housing

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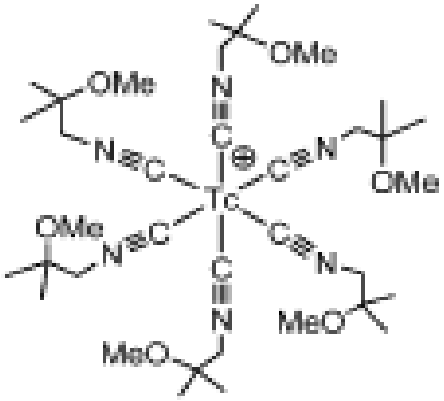
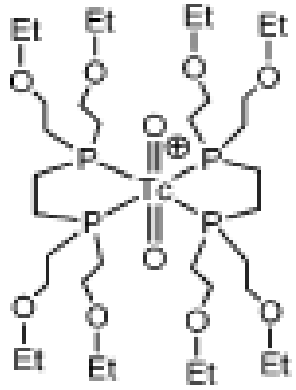
cardiac imaging

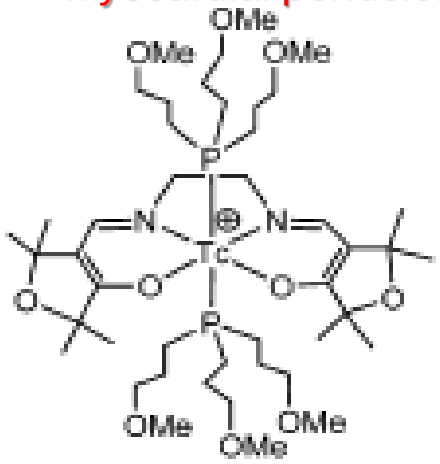


^{99m}Tc-Sestamibi



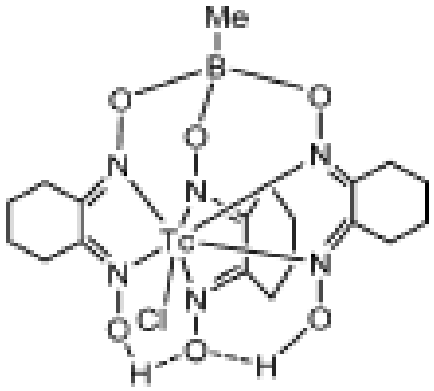
^{99m}Tc-Tetrofosmin

myocardial perfusion

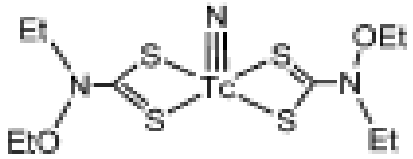


Q12

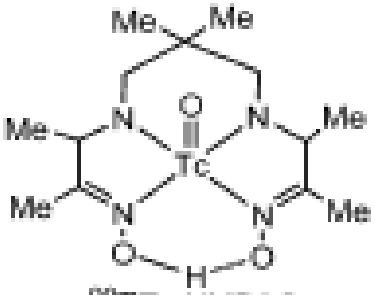
cardiac imaging



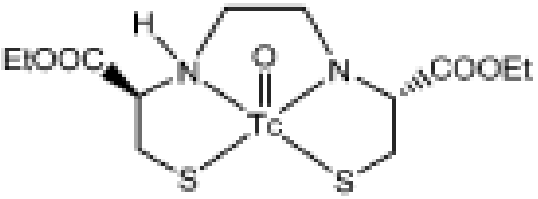
^{99m}Tc-Teboroxime



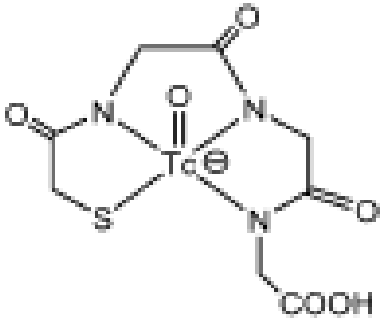
^{99m}TcN-NOET



^{99m}Tc-HMPAO



^{99m}Tc-Bicisate



^{99m}Tc-MAG$_3$

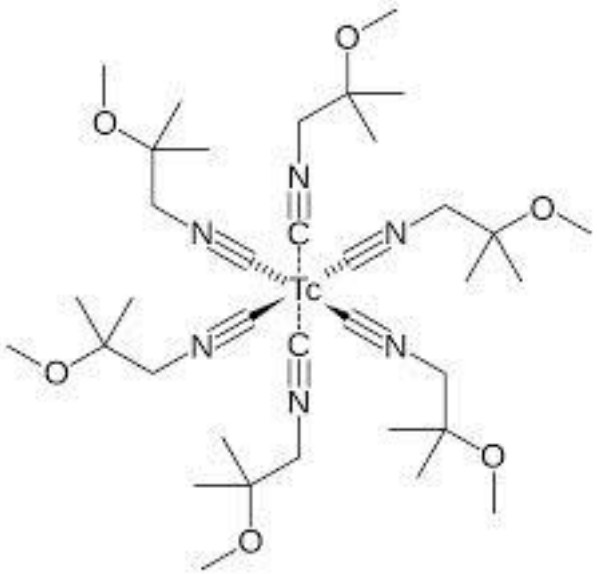
myocardial perfusion

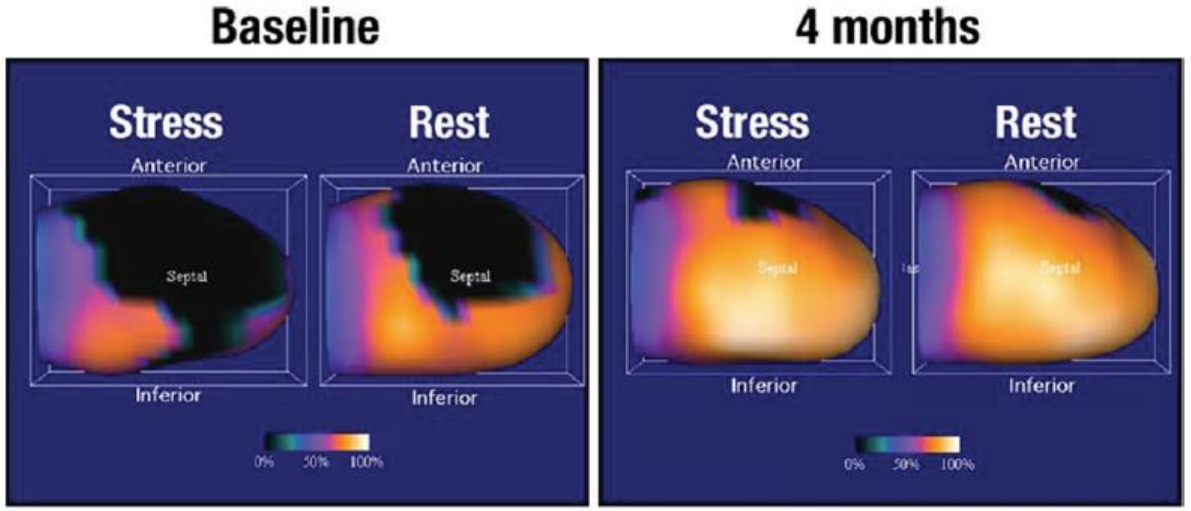
cereberal perfusion

brain imaging

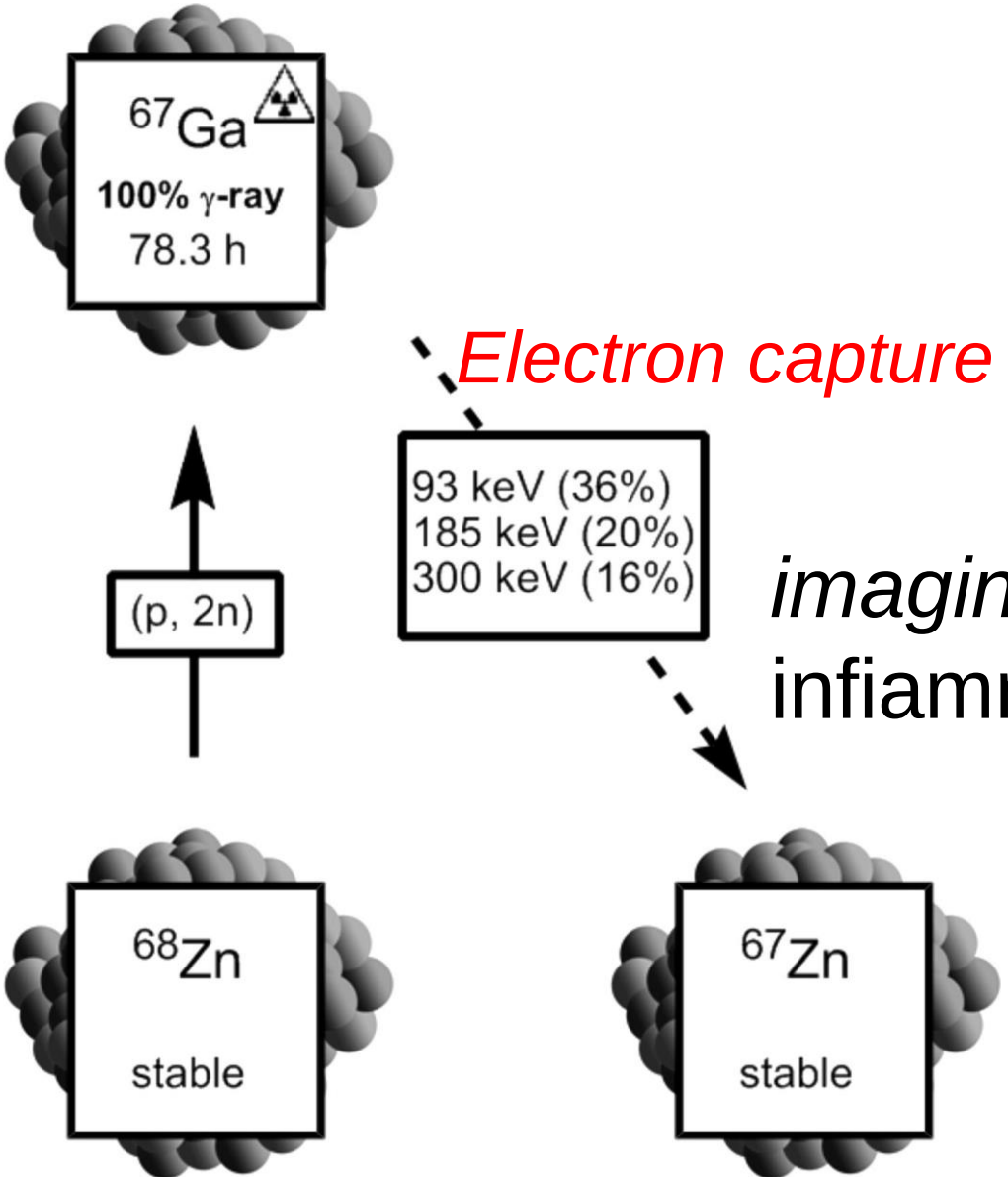
renal imaging

^{99m}Tc-sestamibi





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

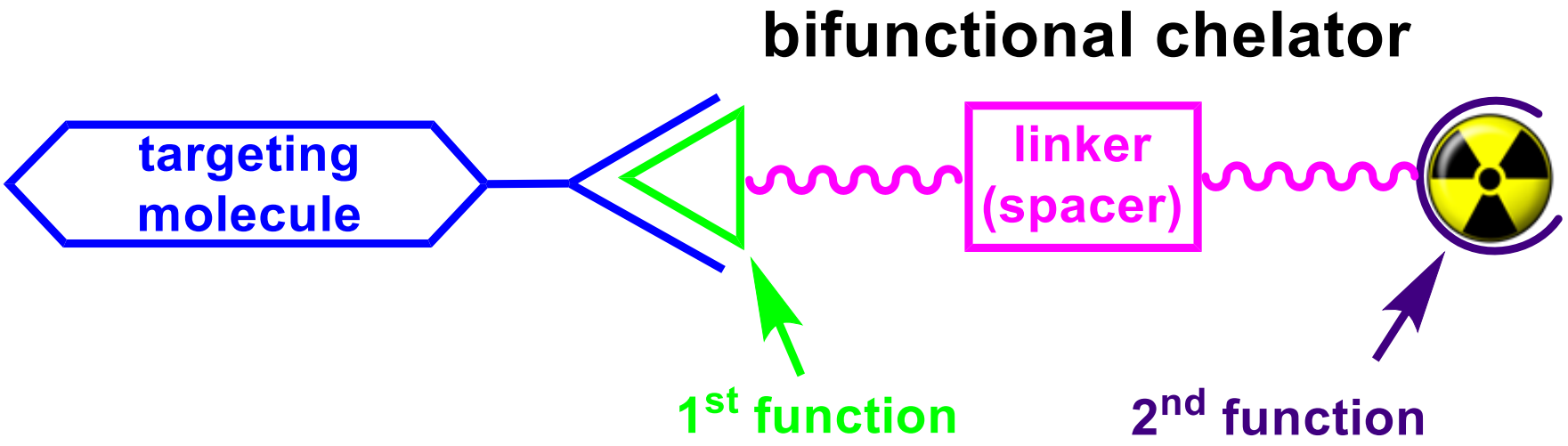


imaging di processi infiammatori e di tumori

'*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

Targeted Approach (*Trojan horse*)



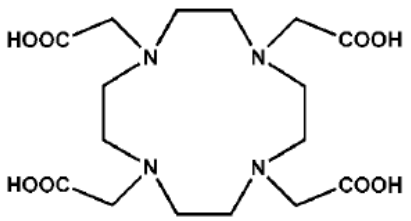
Targeting molecules: monoclonal antibodies, peptides, vitamins, carbohydrates,..

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

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

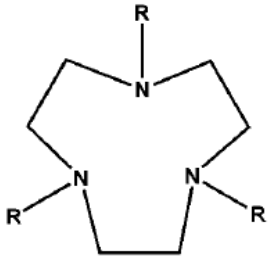
Diethylenetriamino-pentaaceticacid

a)



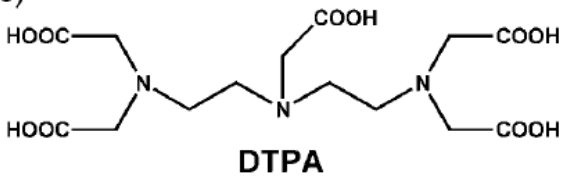
DOTA

b)



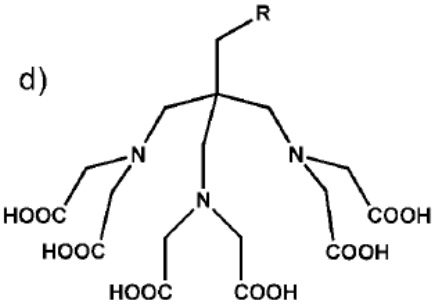
NOTA	R = CH_2COOH
TACN-TM	R = CH_2CH_2SH
NOTP	R = $CH_2PO_3H_2$
NOTPME	R = $CH_2PO_2(OCH_2CH_3)$

c)



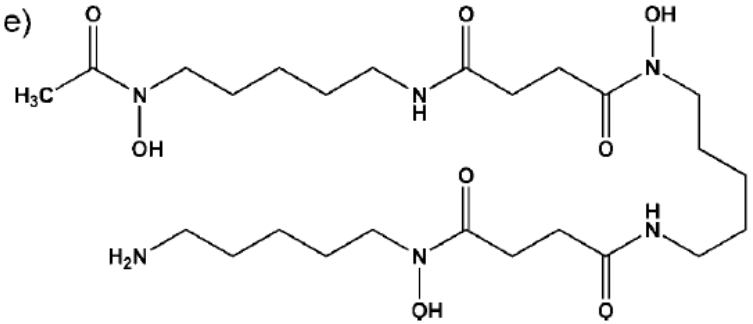
DTPA

d)

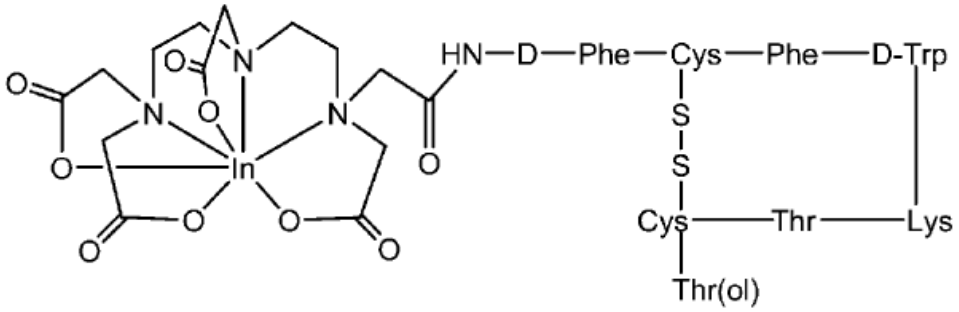


TAME Hex

e)

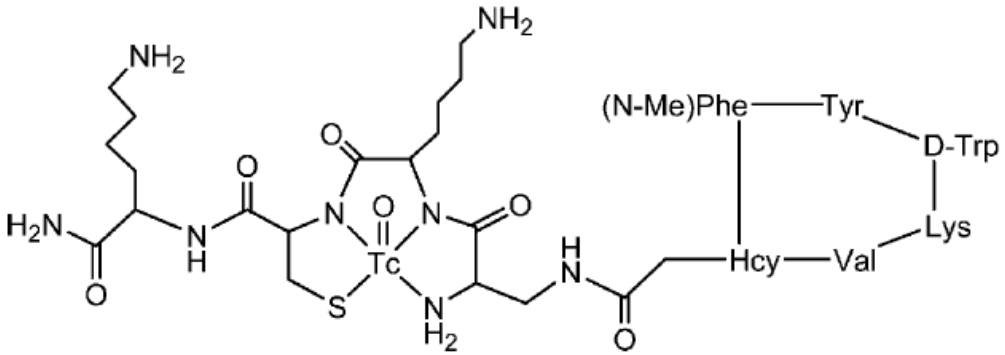


Octreotide and Depreotide peptides that target somatostatin receptors



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

SPECT imaging of neuroendocrine tumors

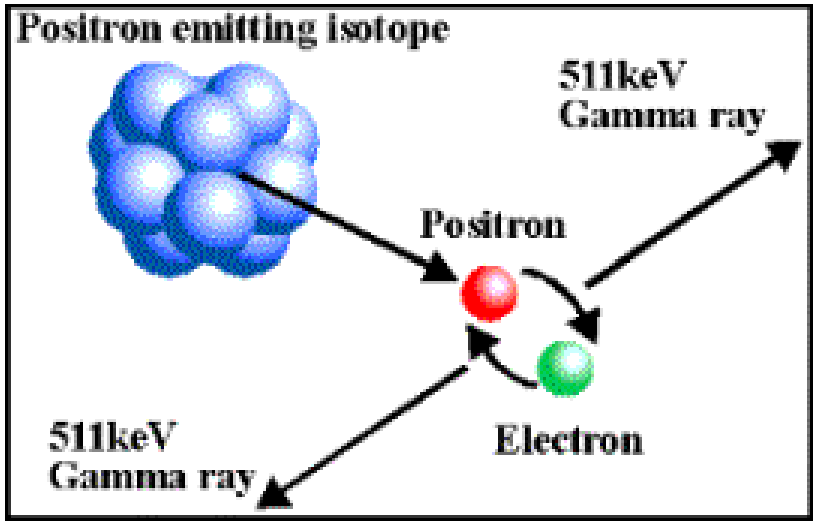


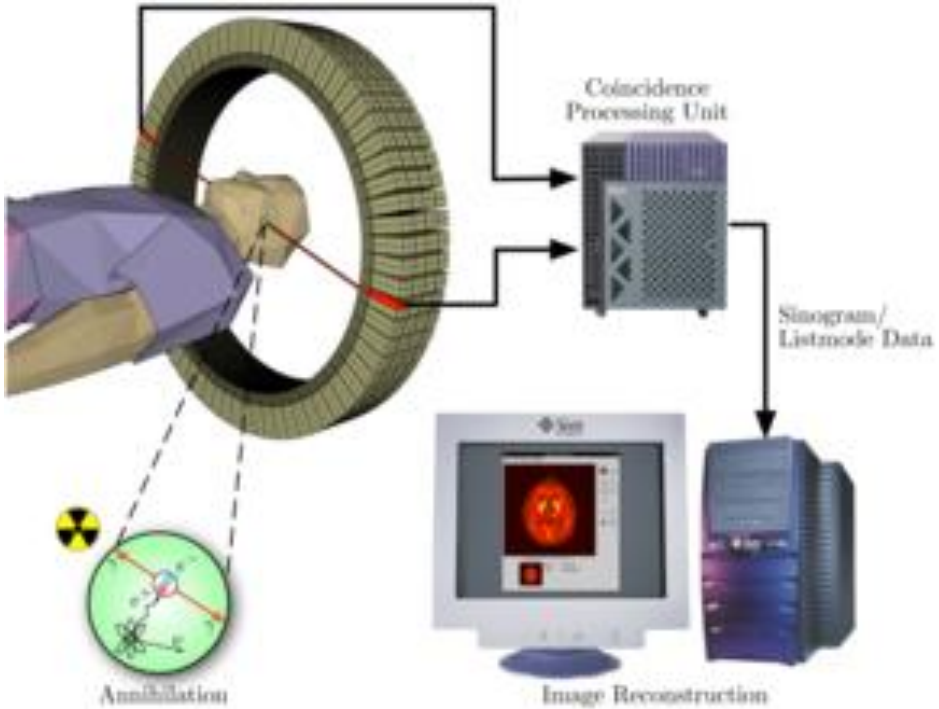
^{99m}Tc-P829 (NeoTect®)

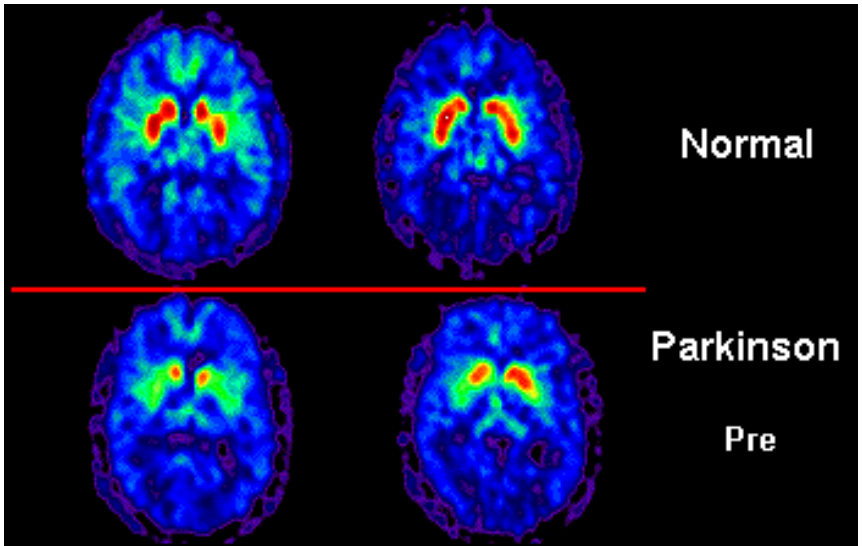
SPECT imaging of lung tumors

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, sovraespressi in molti tipi di tumori. L'octreotide è simile alla somatostatina

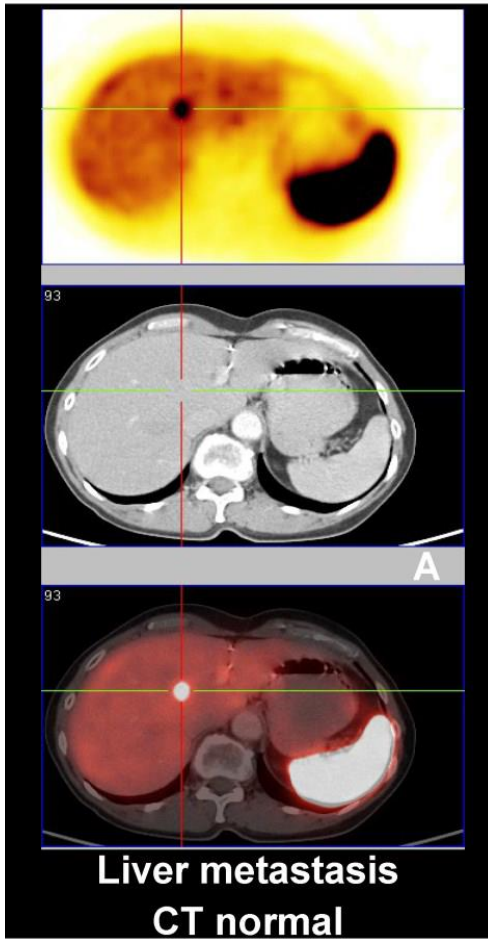
PET: Positron Emission Tomography







PET/CT: combinazione di imaging strutturale e funzionale



PET

CT

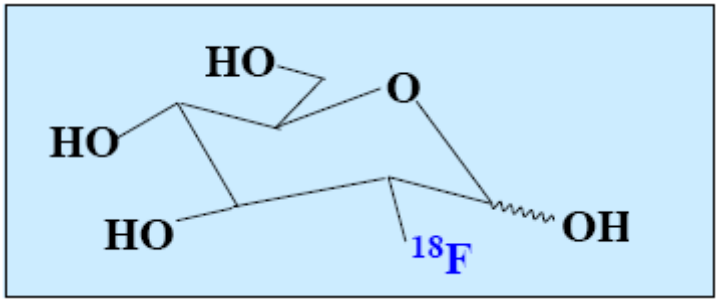
PET + CT

Main radionuclides for PET

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

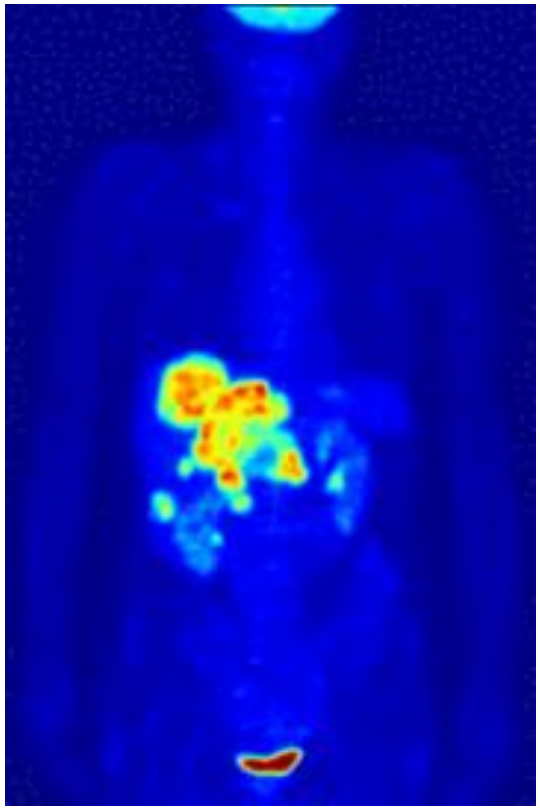
nuclide	half-life (min)	maximum energy (MeV)	mode of decay (%)	theoretical specific activity (GBq/μmol)
^{18}F	110	0.64	β+ (97%) EC[a] (3%)	6.3×10^4
^{11}C	20.3	0.97	β+ (99%)	3.4×10^5
^{13}N	10	1.20	β+ (100%)	7.0×10^5
^{15}O	2	1.74	β+ (100%)	3.4×10^6
^{76}Br	972	4.0	β+ (57%) EC (43%)	7.2×10^3
^{124}I	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.



Fluorodeoxyglucose ([^{18}F] FDG)

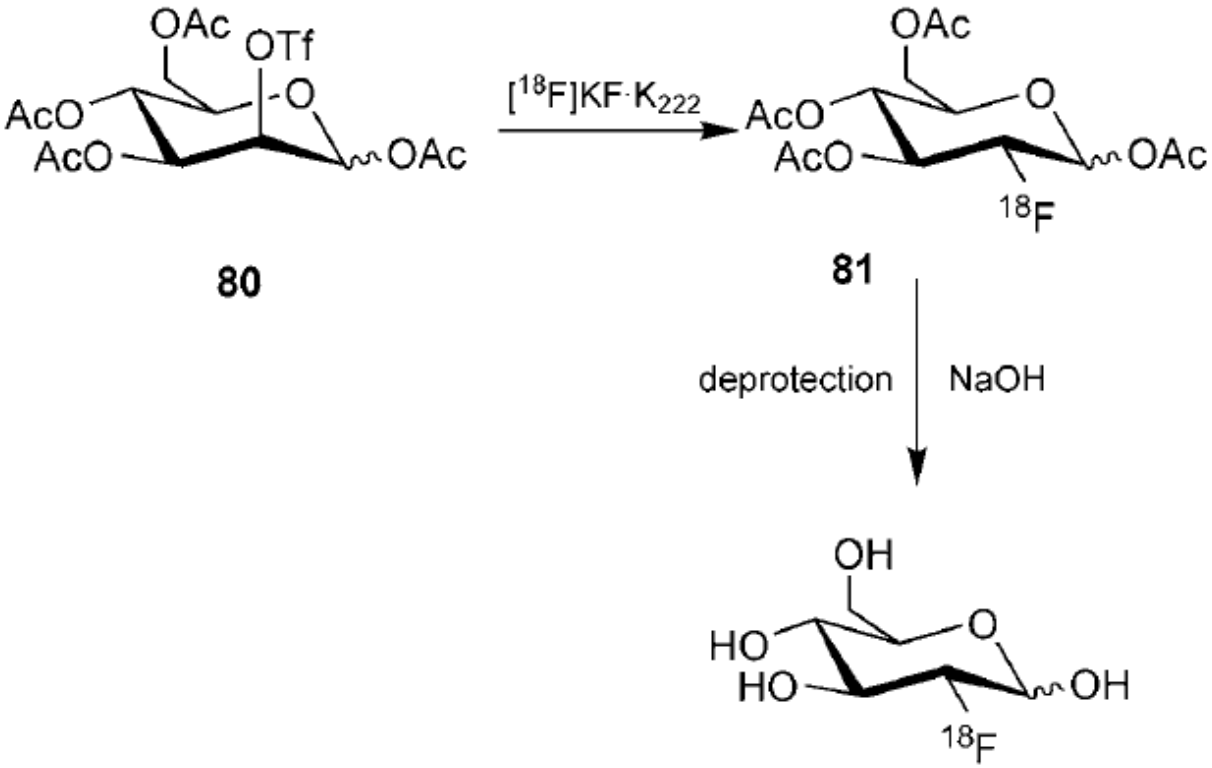
Bio-isosteric replacement

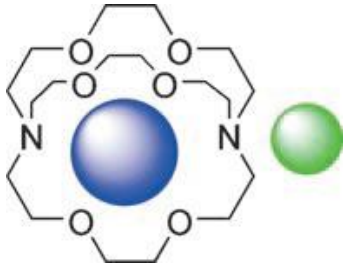


assessment of glucose metabolism

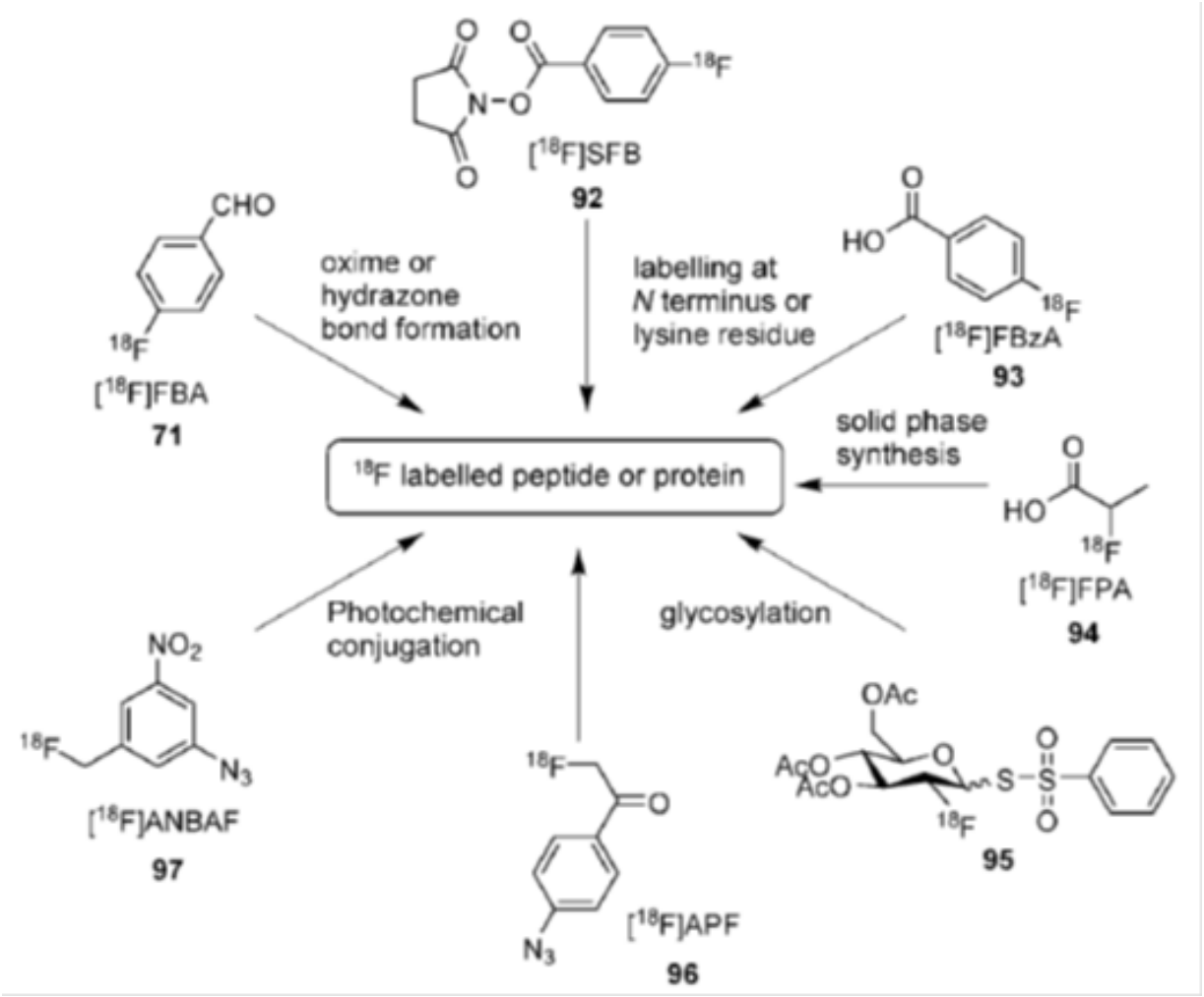
Esempio di fluorurazione nucleofila

$^{18}O(p, n)^{18}F$

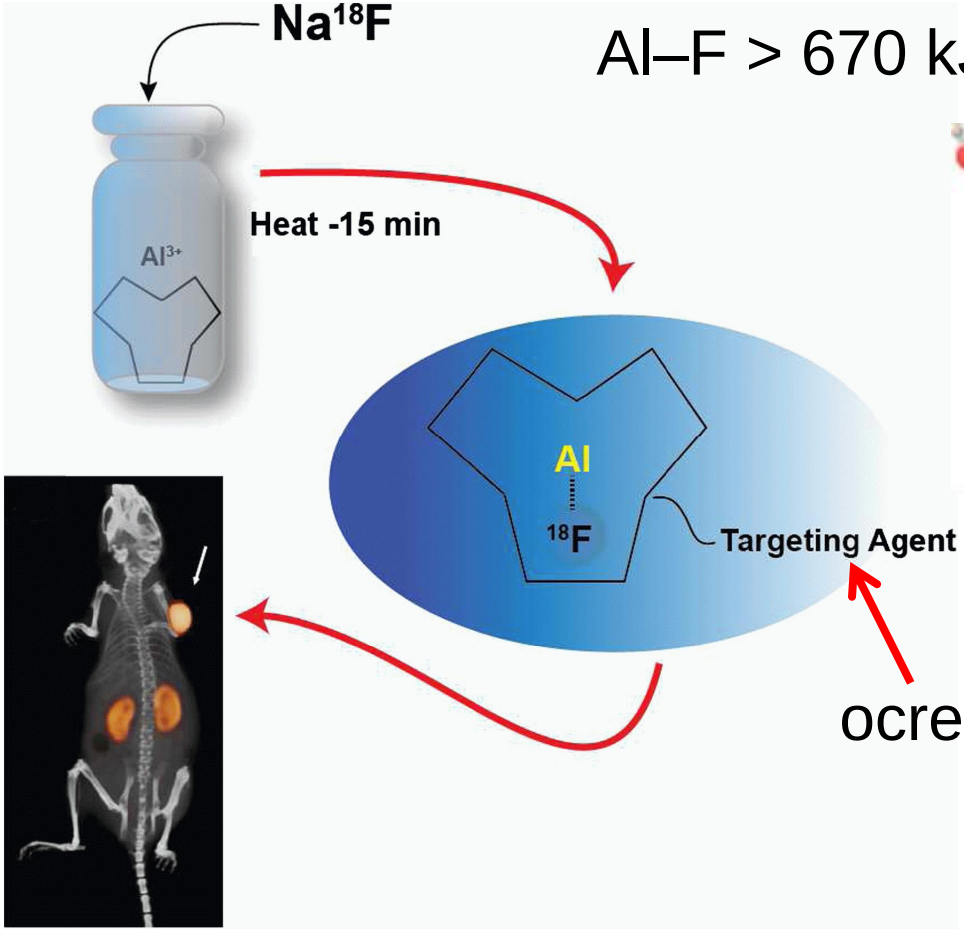




Gruppi prostetici per ^{19}F PET

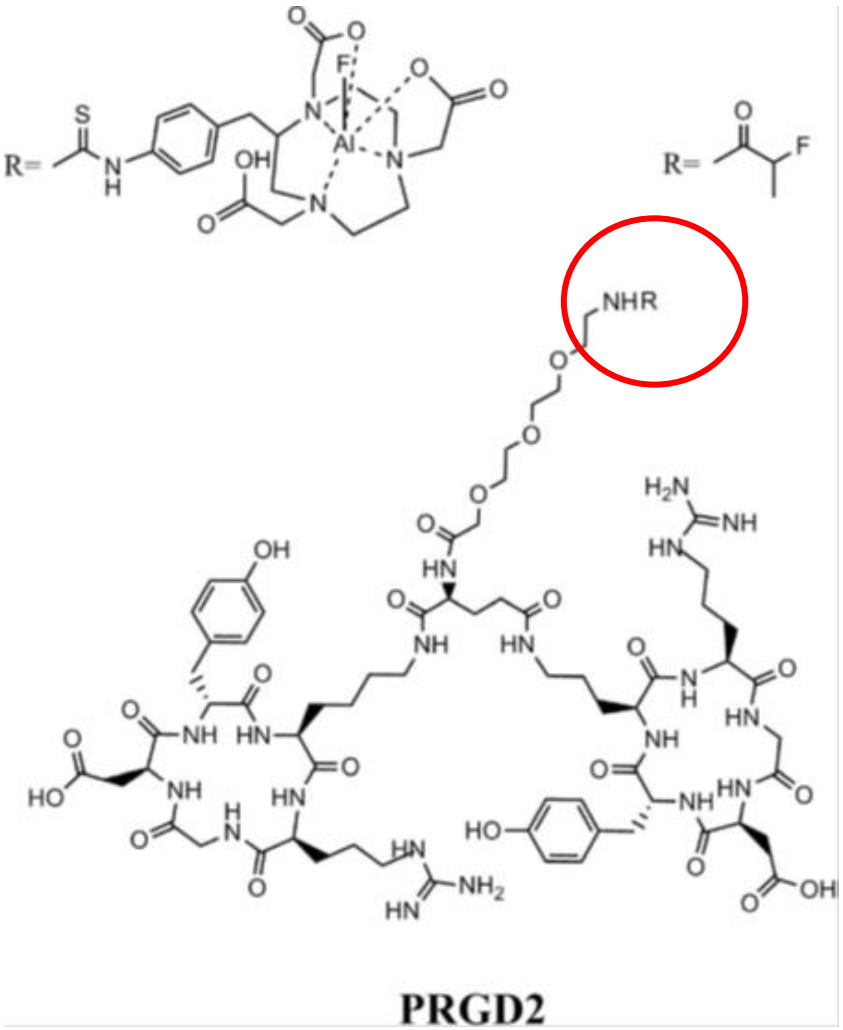


Fluorurazione inorganica



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

ocreotide



PRGD2

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

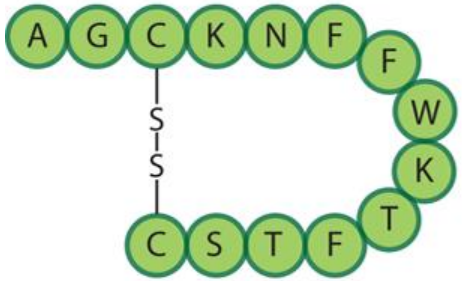
studio clinico nell'uomo per l'*imaging* di un tumore al polmone

Radionuclidi metallici per PET

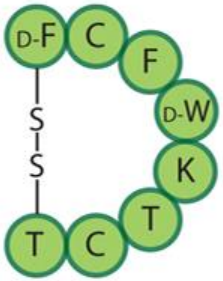
Table 1. Physical Properties of Some Common PET Radiometals[a]

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

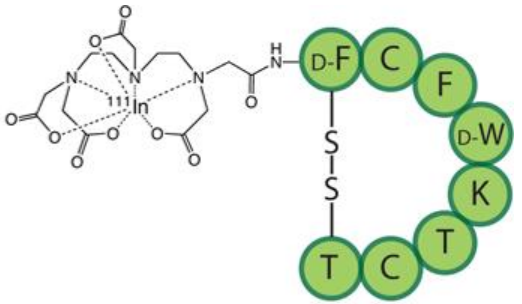
I tumori neuroendocrini sovra-esprimono i recettori per la somatostatina



Somatostatin



Octreotide



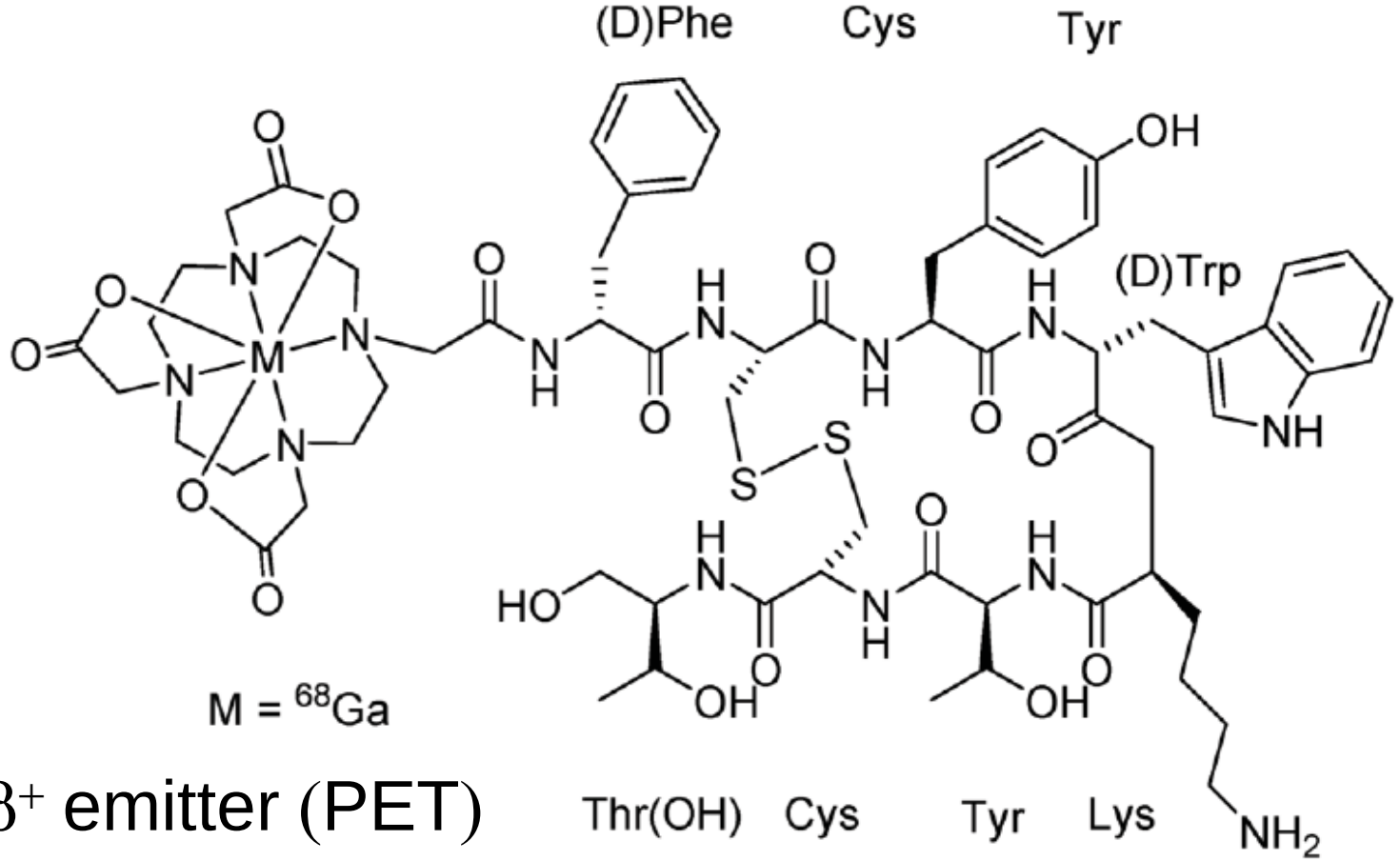
^{111}In-DTPA-Octreotide

SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTA-tyr3-Octreotide

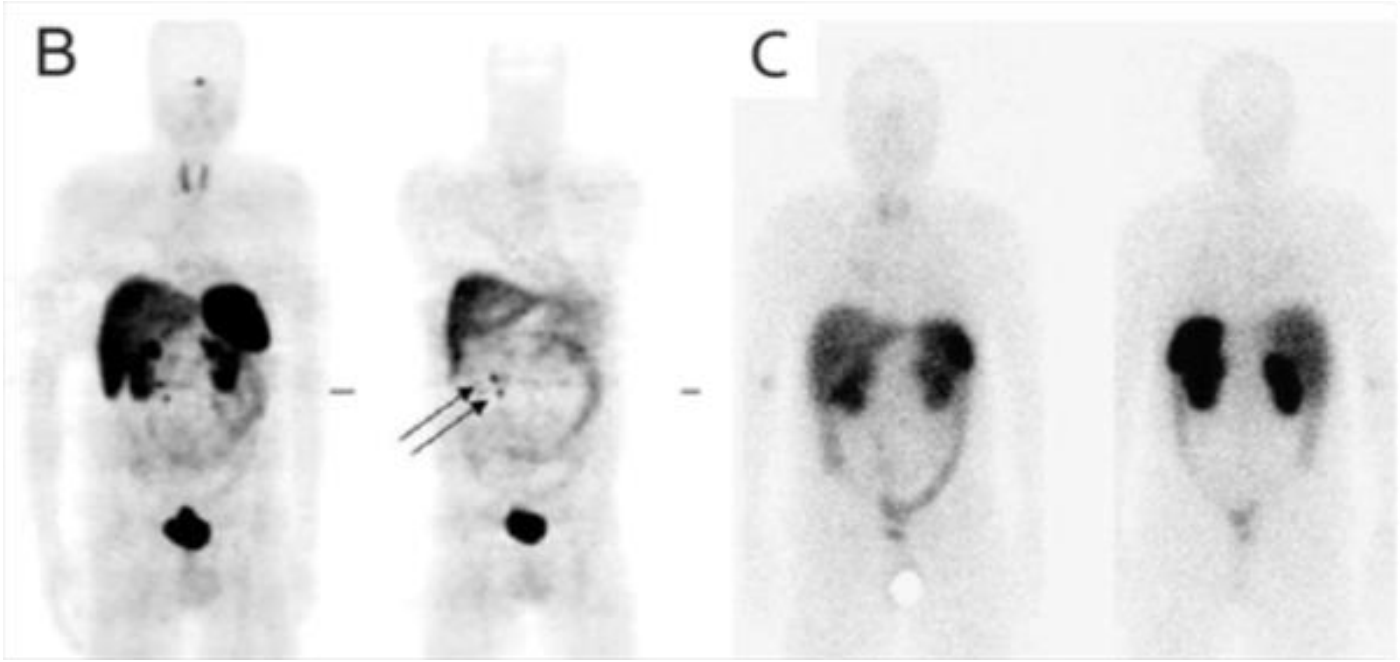
(^{68}Ga-DOTATOC)

High resolution PET imaging of neuroendocrine tumors



β^+ emitter (PET)

imaging di un tumore endocrino

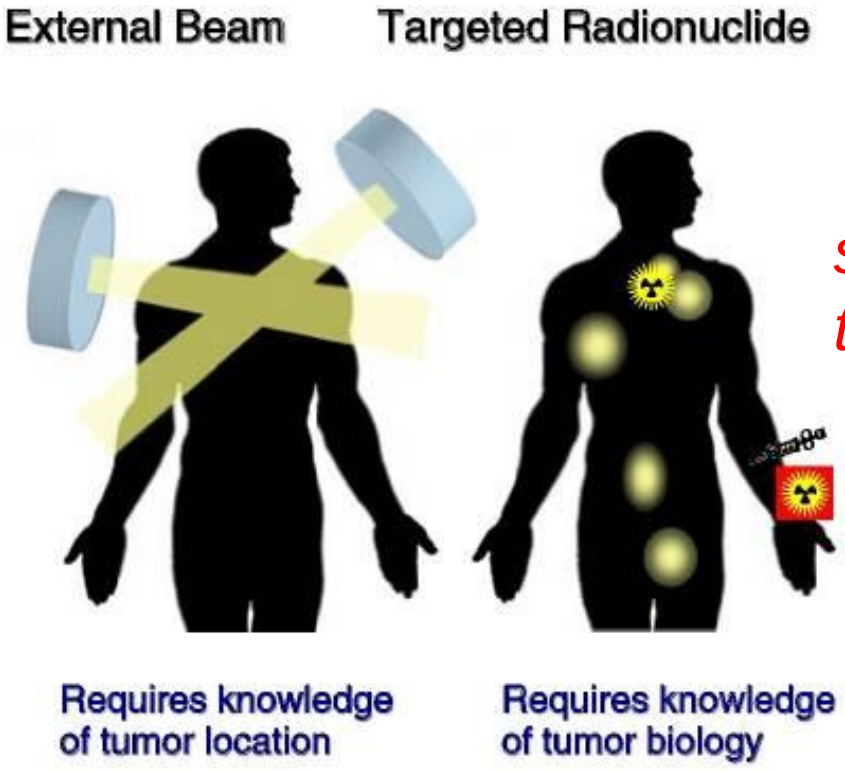


^{68}Ga-DOTATOC
(PET)

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

Targeted Radiotherapy (*Radio(immuno)therapy*)

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

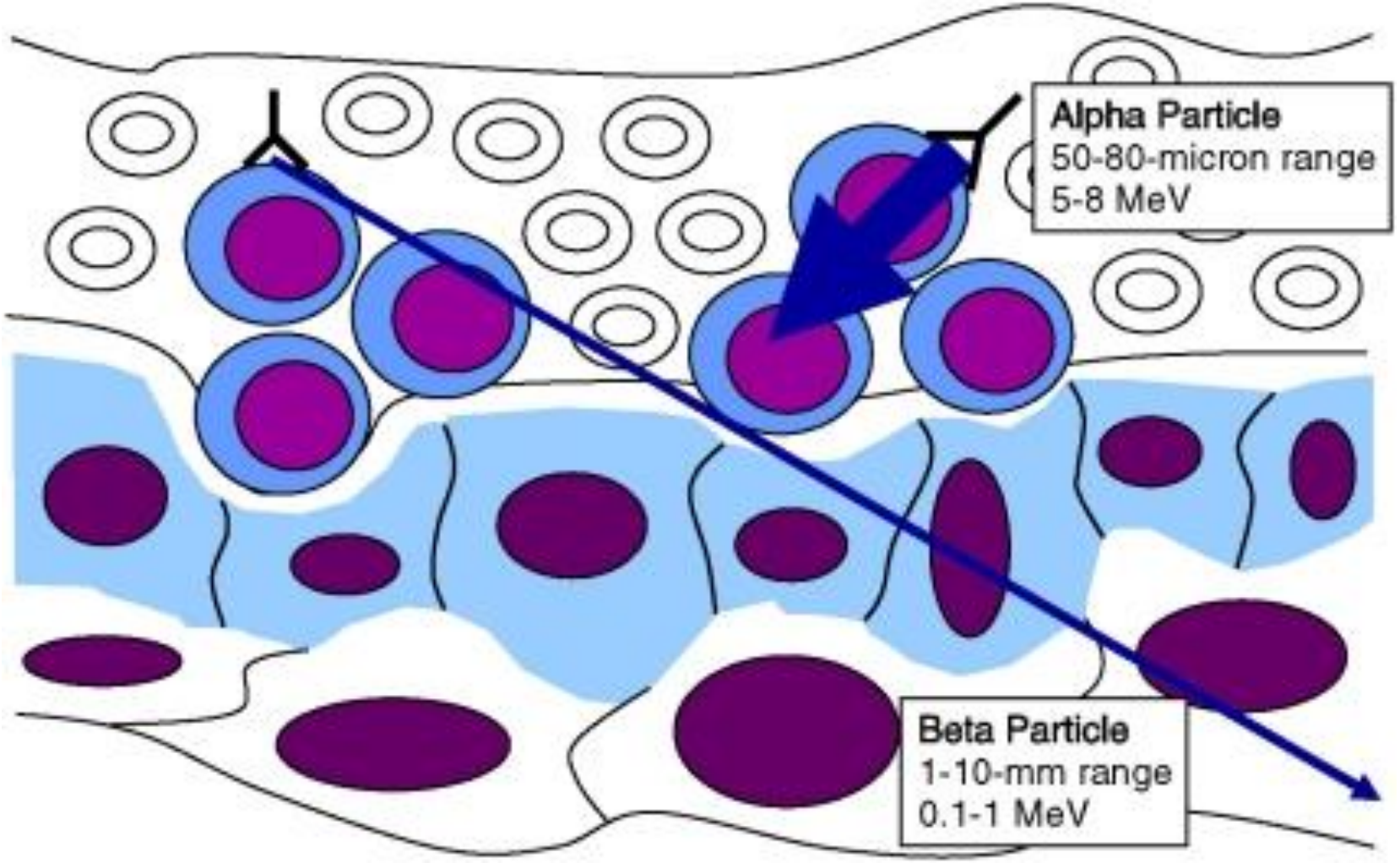


systemic treatment

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

TI = therapeutic index

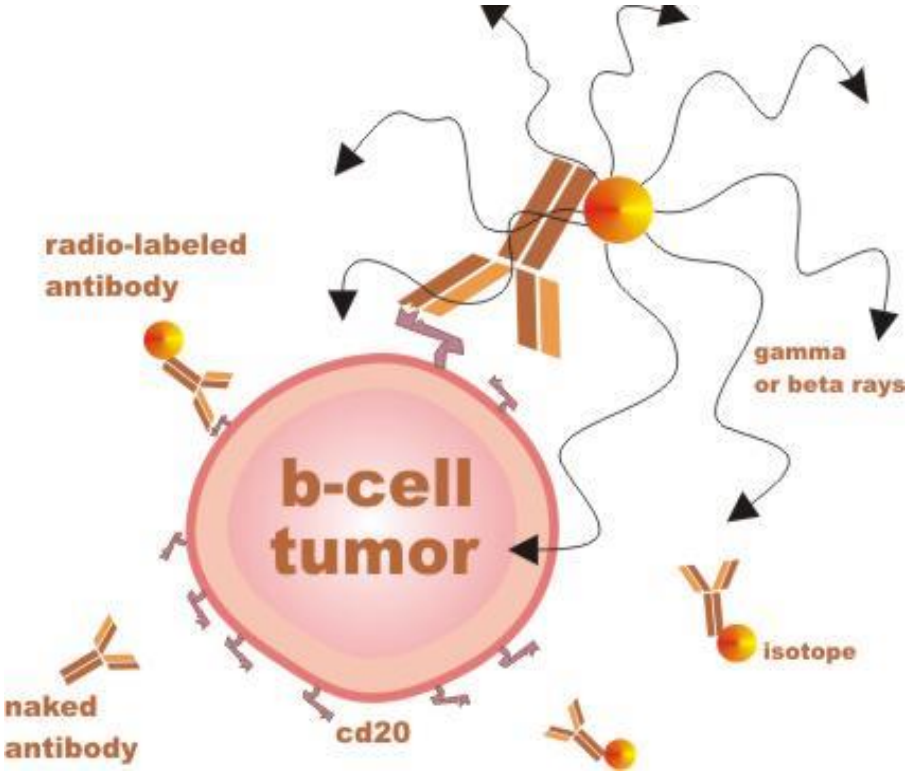
Penetrating power of α and β particles



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	556
^{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

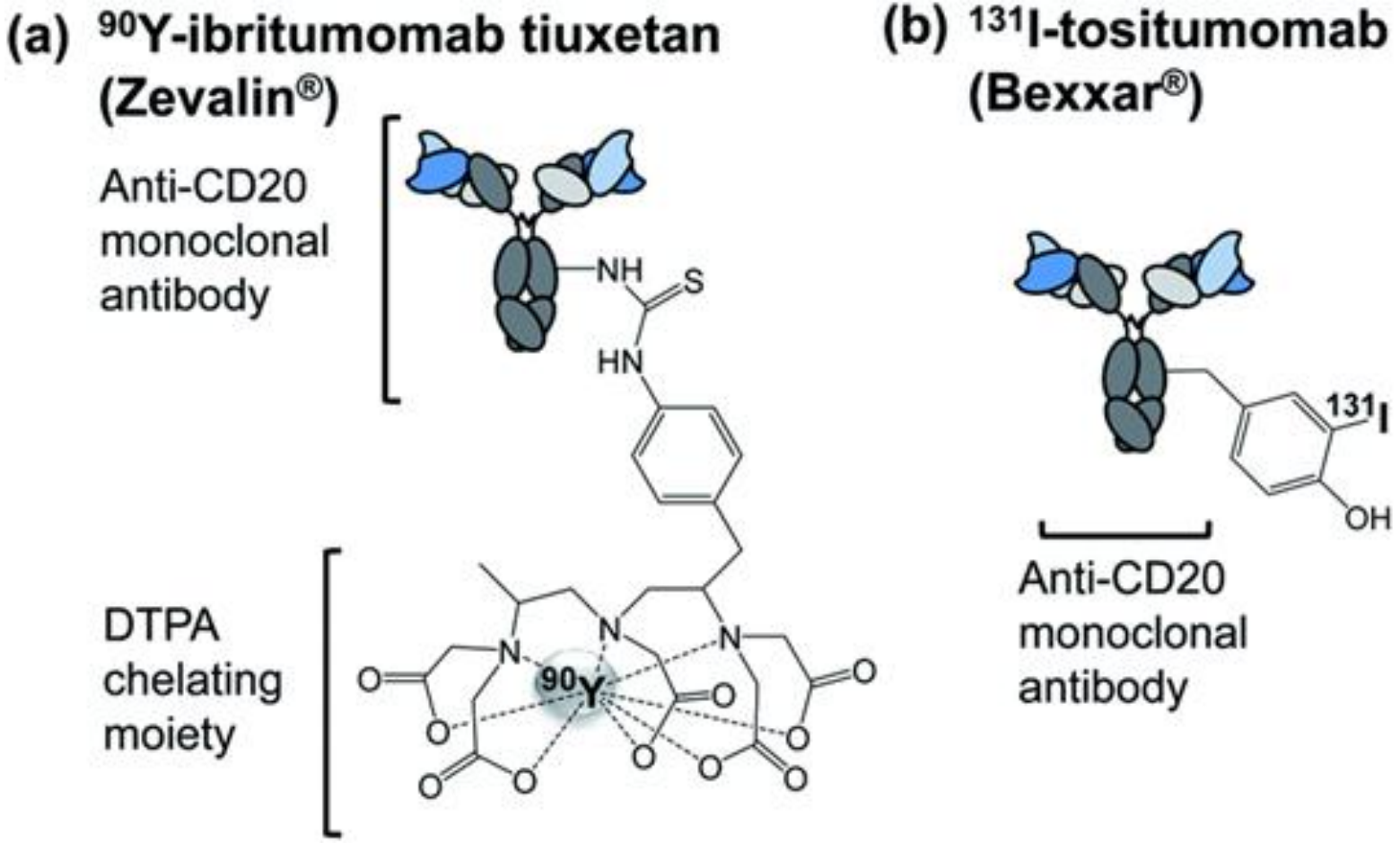
Treatment of B-cell non-Hodgkin's limphoma



Antigene ideale:

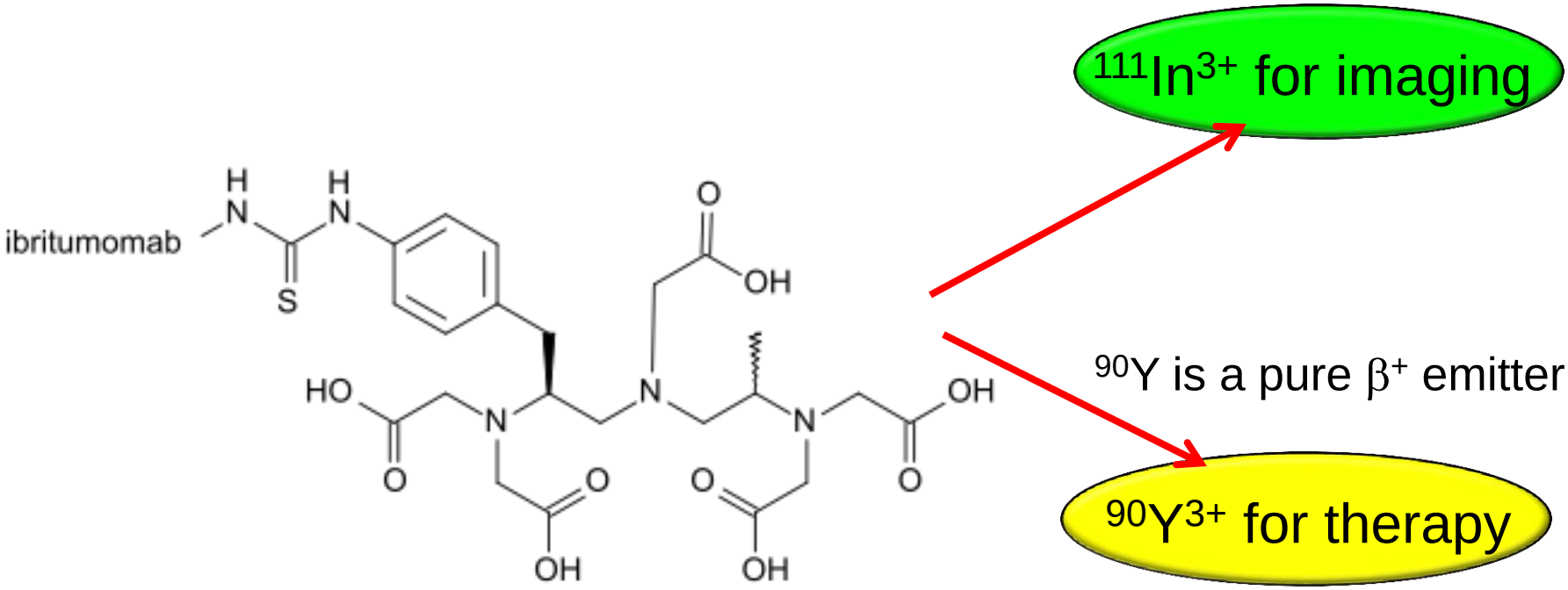
- altamente espresso con densità uniforme sulla superficie di tutte le cellule del tumore (> 10^5 siti per cellula),
- non deve essere espresso (o molto meno) nelle cellule sane,
- affinità antigene-anticorpo dell'ordine nanomolare
- internalizzazione

FDA approved



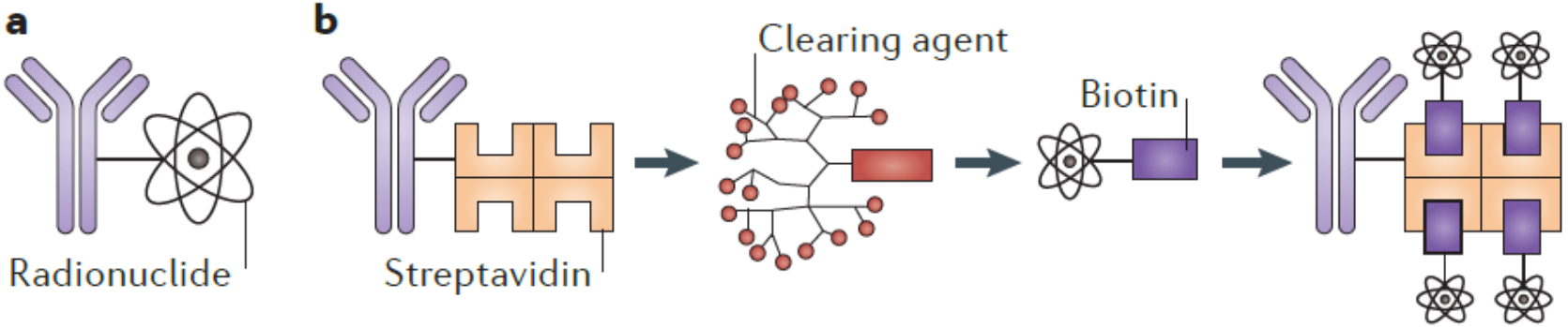
Zevalin®

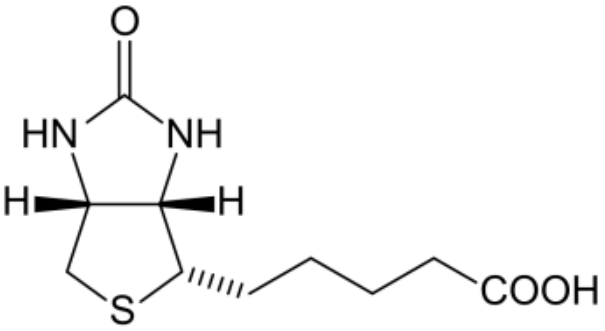
Ibritumomab (MC antibody) covalently conjugated to the ^{90}Y chelator tiuxetan



Example of the matched-pair approach

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

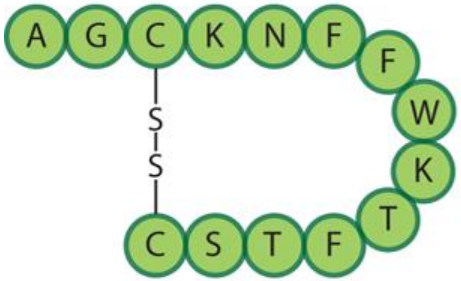




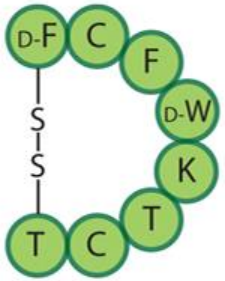
Biotina

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

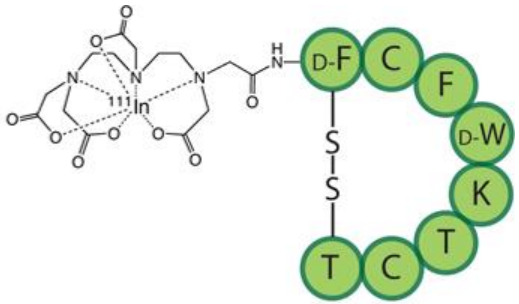
Radio-immunotherapy of neuroendocrine tumors



Somatostatin



Octreotide



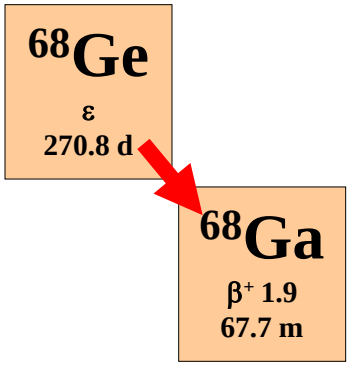
^{111}In-DTPA-Octreotide

SPECT imaging of neuroendocrine tumors

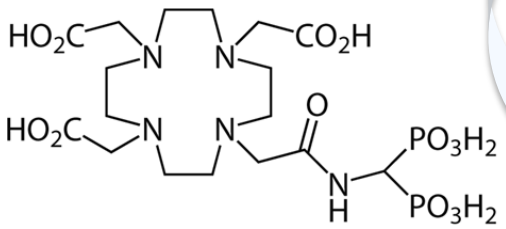
^{68}Ga-DOTATOC for PET imaging

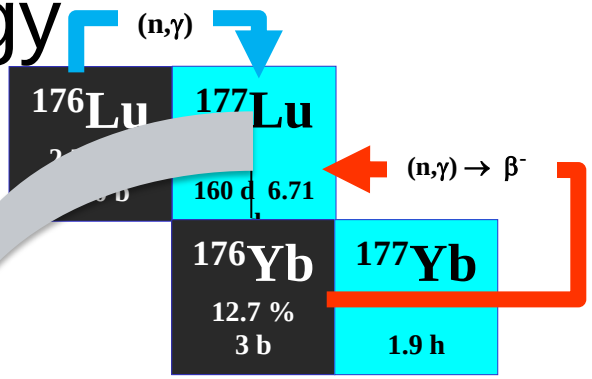
^{90}Y-DOTATOC and ^{177}Lu-DOTATATE for radiotherapy

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

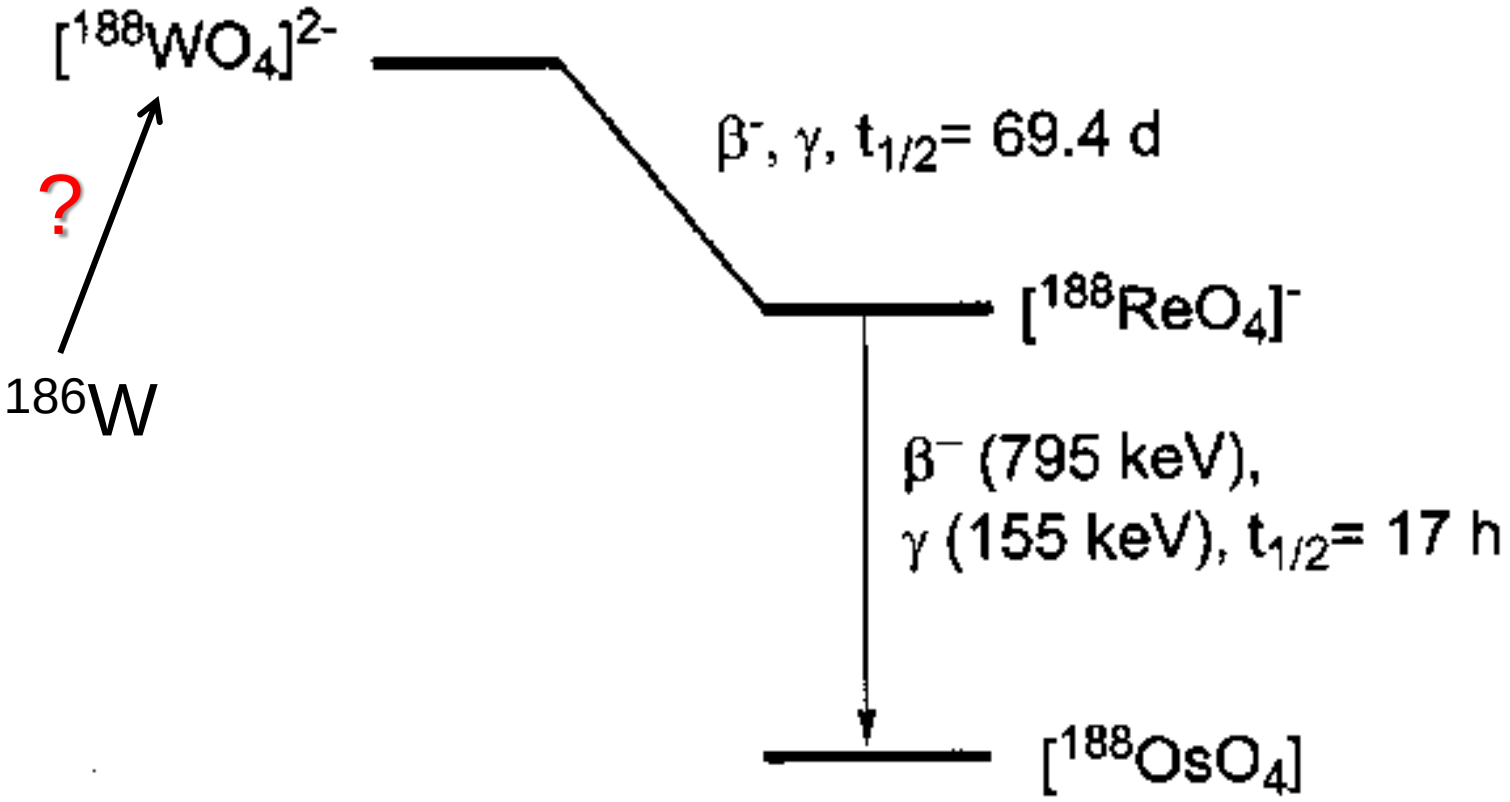


DOTA-bisphsophantae amide
„BPAMD“





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

^{177}Lu-BPAMD
Therapy

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