

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. ^{99m}Tc)

Metallomics

Transport and signalling
pathways
Genomic codes for elements

Medicinal Inorganic Chemistry

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)

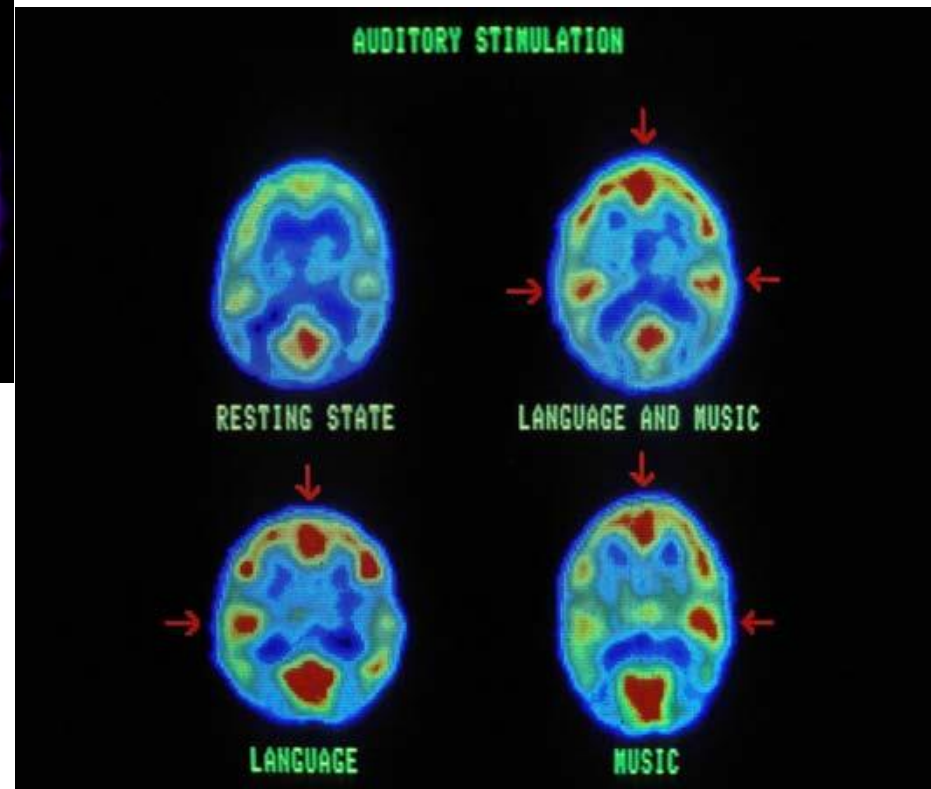
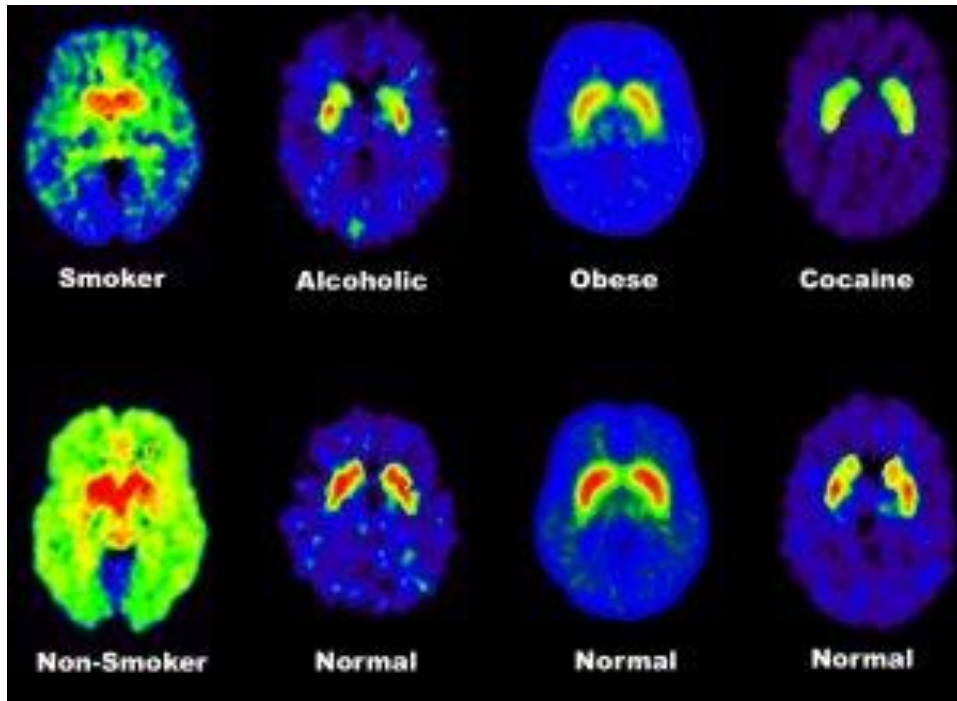
Imaging with Metal Compounds

Cellular level
*(molecular imaging 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.

Molecular Imaging



Processi spontanei nei nuclei radioattivi

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

Radiopharmaceuticals

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graph TD; A([Radiopharmaceuticals]) --> B([Radiodiagnosics]); A --> C([Radiotherapeutics]);
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Radiodiagnosics

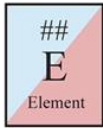
γ -emitters (SPECT)
positron-emitters (β^+) (PET)
 $10^{-6} - 10^{-8}$ M

Radiotherapeutics

α or β^- emitters

Isotopes suitable for nuclear imaging

1 H Hydrogen		<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>Short Half-Life</p> <div style="background-color: #0070C0; color: white; padding: 5px; border: 1px solid black;">PET Isotopes</div> <div style="background-color: #C00000; color: white; padding: 5px; border: 1px solid black;">SPECT Isotopes</div> <p>Long Half-Life</p> </div> </div>																2 He Helium								
3 Li Lithium		4 Be Beryllium																		5 B Boron		6 C Carbon	7 N Nitrogen	8 O Oxygen	9 F Fluorine	10 Ne Neon
11 Na Sodium		12 Mg Magnesium																		13 Al Aluminum	14 Si Silicon	15 P Phosphorus	16 S Sulfur	17 Cl Chlorine	1 Ar Argon	
19 K Potassium		20 Ca Calcium		21 Sc Scandium	22 Ti Titanium	23 V Vanadium	24 Cr Chromium	25 Mn Manganese	26 Fe Iron	27 Co Cobalt	28 Ni Nickel	29 Cu Copper	30 Zn Zinc	31 Ga Gallium	32 Ge Germanium	33 As Arsenic	34 Se Selenium	35 Br Bromine	36 Kr Krypton							
37 Rb Rubidium		38 Sr Strontium		39 Y Yttrium	40 Zr Zirconium	41 Nb Niobium	42 Mo Molybdenum	43 Tc Technetium	44 Ru Ruthenium	45 Rh* Rhodium	46 Pd Palladium	47 Ag Silver	48 Cd Cadmium	49 In Indium	50 Sn Tin	51 Sb Antimony	52 Te Tellurium	53 I Iodine	54 Xe Xenon							
55 Cs Cesium		56 Ba Barium	57-70 Lanthanides				71 Lu* Lutetium	72 Hf Hafnium	73 Ta Tantalum	74 W Tungsten	75 Re* Rhenium	76 Os Osmium	77 Ir Iridium	78 Pt Platinum	79 Au Gold	80 Hg Mercury	81 Tl Thallium	82 Pb Lead	83 Bi Bismuth	84 Po Polonium	85 At Astatine	86 Rn Radon				
87 Fr Francium		88 Ra Radium	89-102 Actinides				103 Lr Lawrencium	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 Uut Ununtrium	114 Fl Flerovium	115 Uup Ununpentium	116 Lv Livermorium	117 Uus Ununseptium	118 Uuo Ununoctium				



Denotes an element with isotopes suitable for both PET and SPECT



Denotes an element with multiple isotopes with different physical half-lives

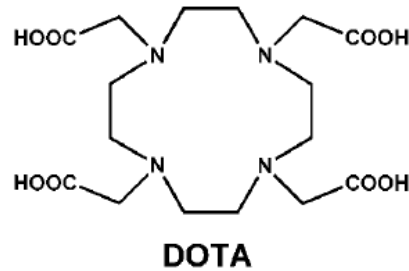
*Isotopes typically used for radiotherapy with which SPECT is also possible but not common — e.g., ¹⁷⁷Lu, ¹⁰⁵Rh, ¹⁸⁶Re, etc. — have been omitted.

I radio-isotopi si possono ottenere:

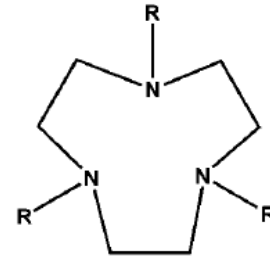
- per decadimento di radionuclidi a tempo di semi-vita più lungo in un generatore
- tramite un ciclotrone, bombardando un opportuno elemento o suo composto con particelle cariche accelerate, tipicamente protoni o nuclei di deuterio;
- tramite bombardamento nucleare con neutroni in un reattore nucleare
- Purificazione da isotopo padre e sottoprodotti
- Incorporazione in un composto, spesso tramite un chelante polidentato

Chelanti più comuni

a)



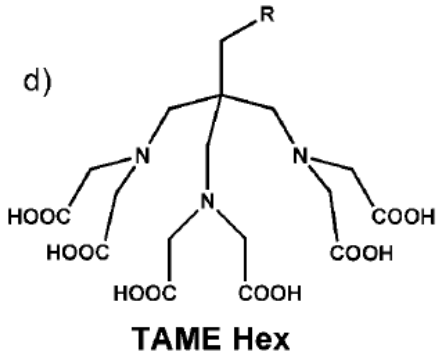
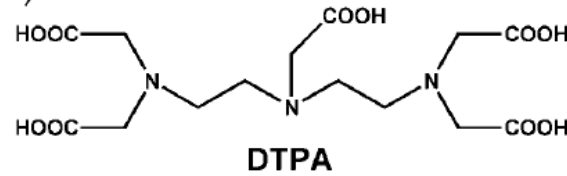
b)



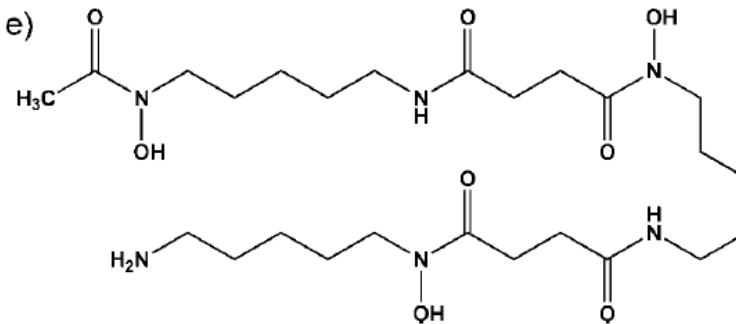
NOTA	R = CH ₂ COOH
TACN-TM	R = CH ₂ CH ₂ SH
NOTP	R = CH ₂ PO ₃ H ₂
NOTPME	R = CH ₂ PO ₂ (OCH ₂ CH ₃)

Diethylenetriamino-
pentaacetic acid

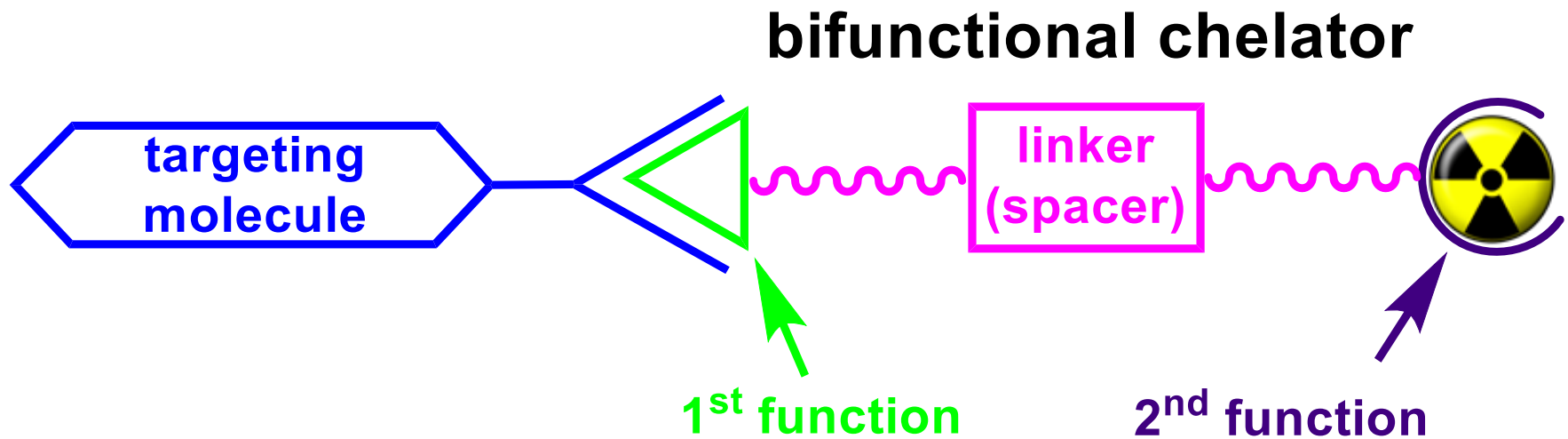
c)



e)



Targeted Approach (*Trojan horse*)



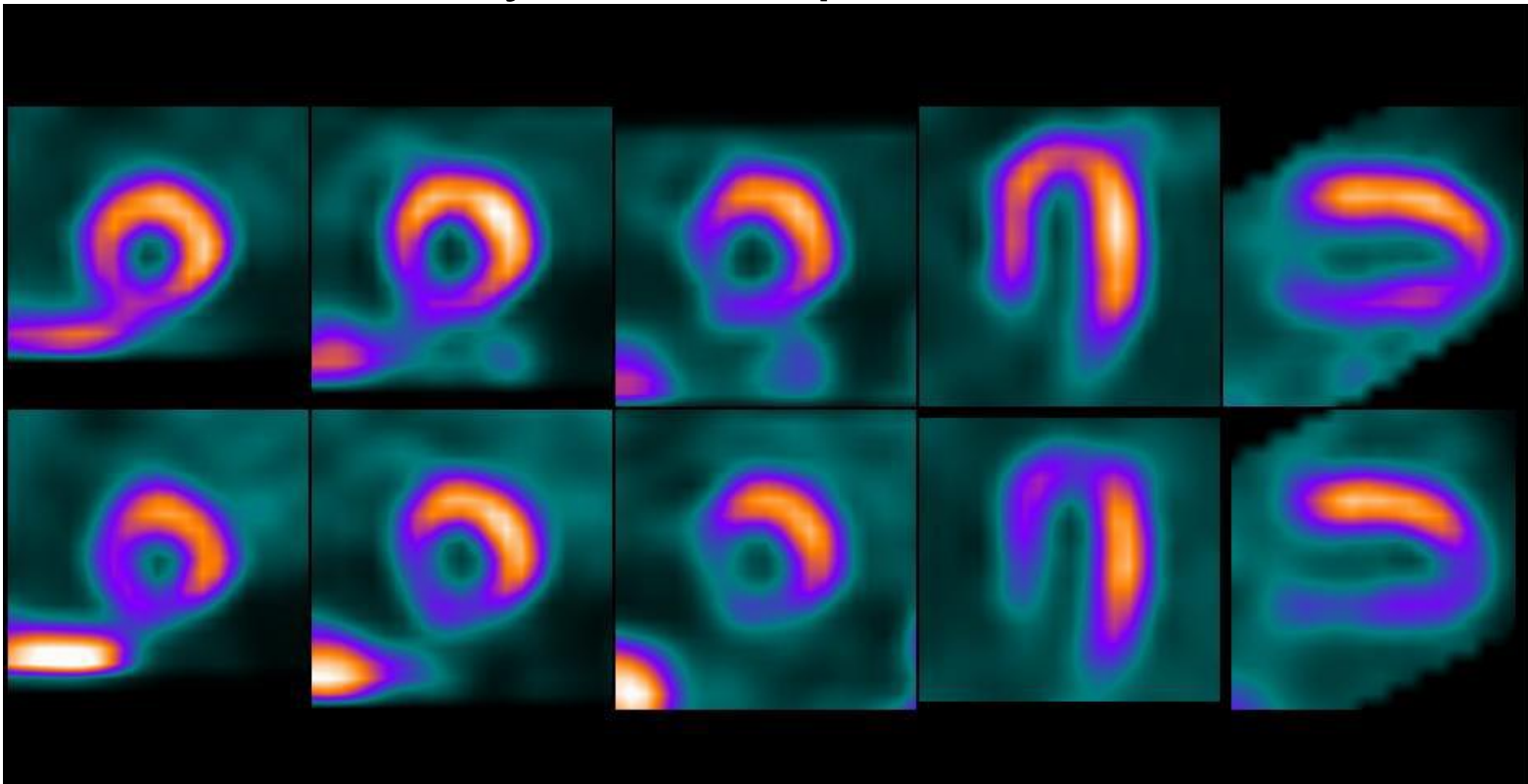
Targeting molecules: monoclonal antibodies, peptides, vitamins, carbohydrates,...

'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 lengthy 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

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graph TD; A[Metal compounds for SPECT imaging] --> B["1st generation  
Perfusion agents"]; B --> C["2nd generation  
Targeted agents"];
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1st generation

Perfusion agents

2nd generation

Targeted agents

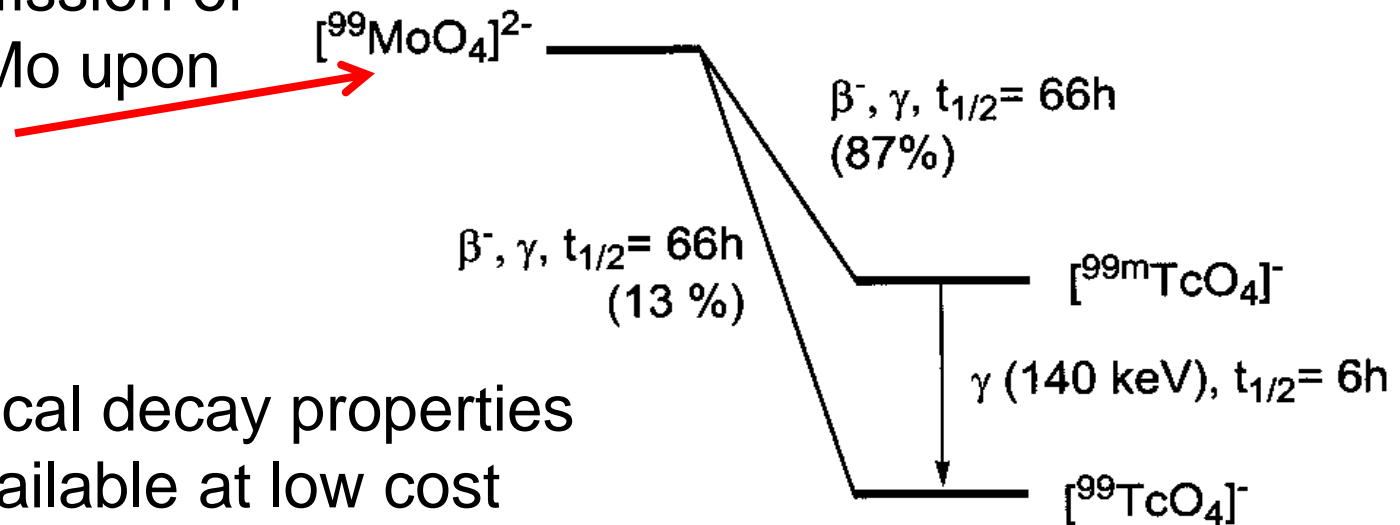
Main radionuclides for SPECT

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

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

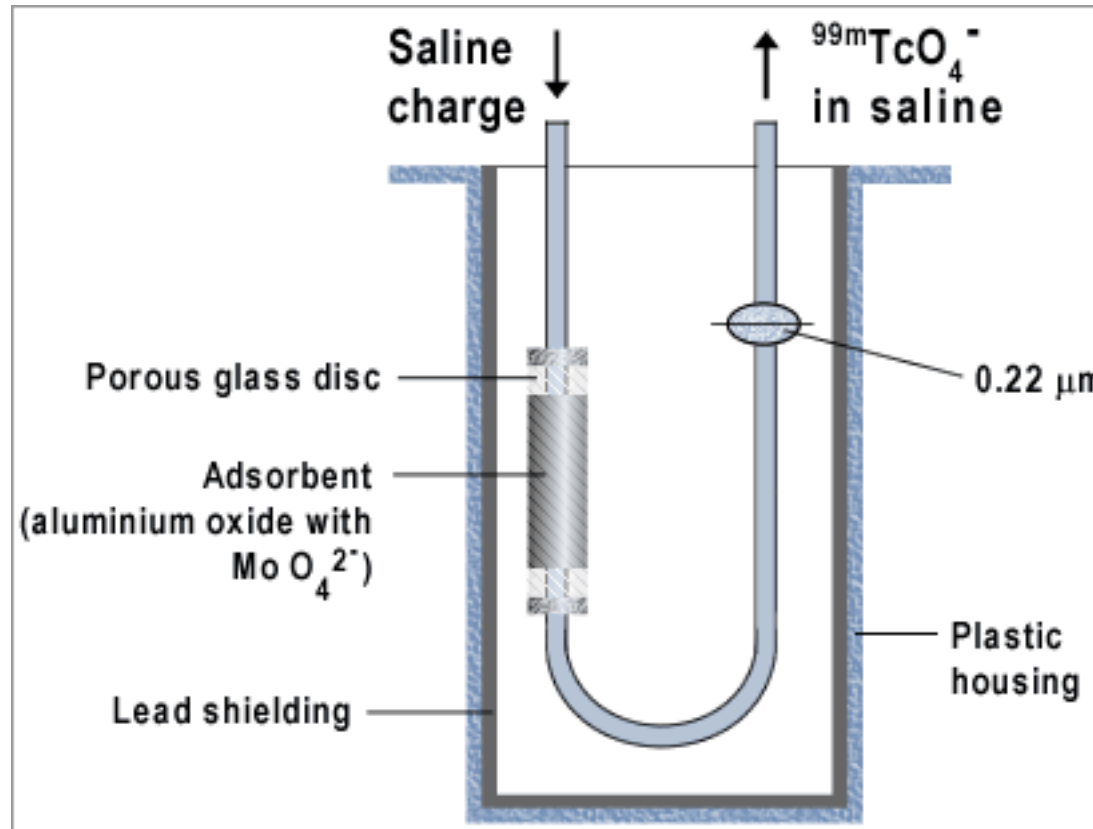
(used in >80% of diagnostic scans, more than 25 M in 2007)

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

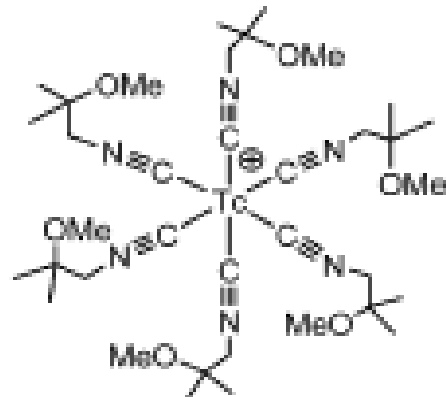


- Ideal physical decay properties
 - Readily available at low cost
 - Many oxidation states (+7 – -1)
 - Various coordination geometries (4 – 9)
 - *Cold* Re for characterization (**matched-pair approach**)
- Pure β -emitter

Generatore di $^{99m}\text{TcO}_4^-$

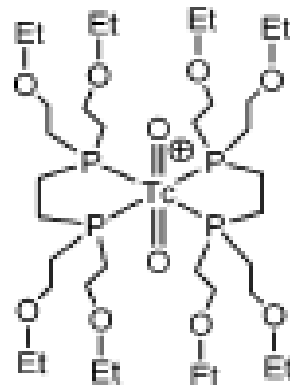


Radiofarmaci di tecnezio di prima generazione



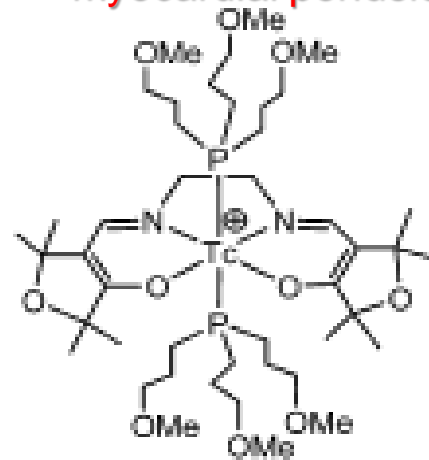
^{99m}Tc -Sestamibi

cardiac imaging



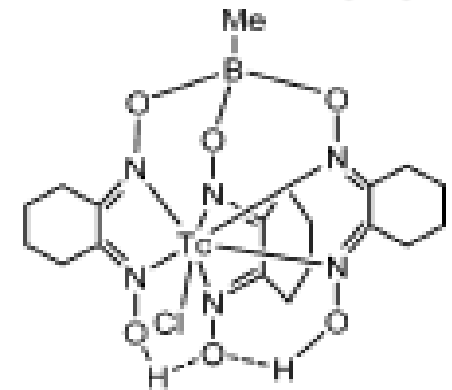
^{99m}Tc -Tetrofosmin

myocardial perfusion

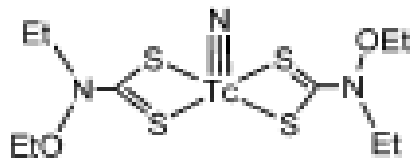


Q12

cardiac imaging

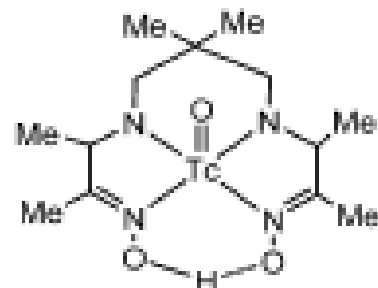


^{99m}Tc -Teboroxime



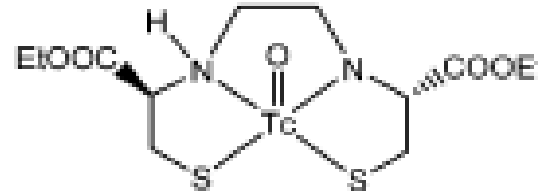
^{99m}TcN -NOET

myocardial perfusion



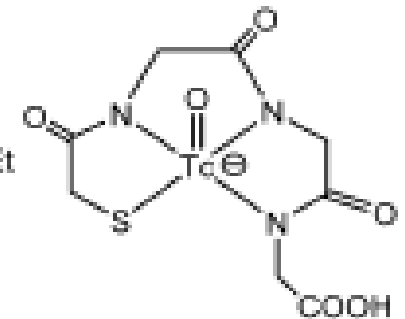
^{99m}Tc -HMPAO

cerebral perfusion



^{99m}Tc -Bicisate

brain imaging

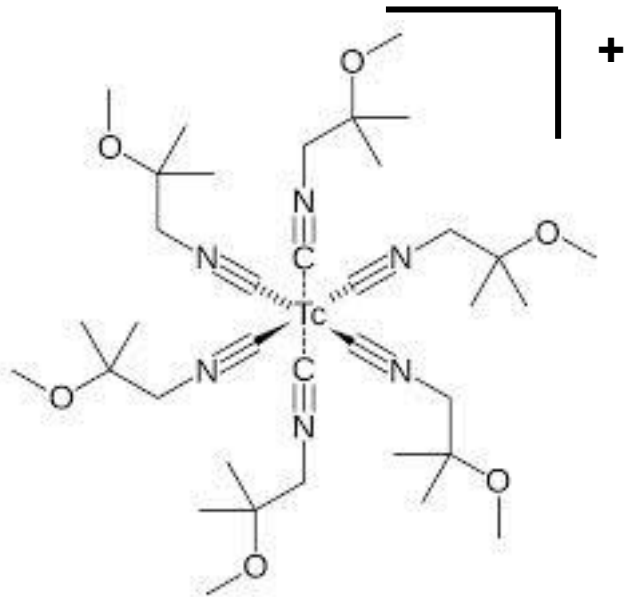


^{99m}Tc -MAG₃

renal imaging

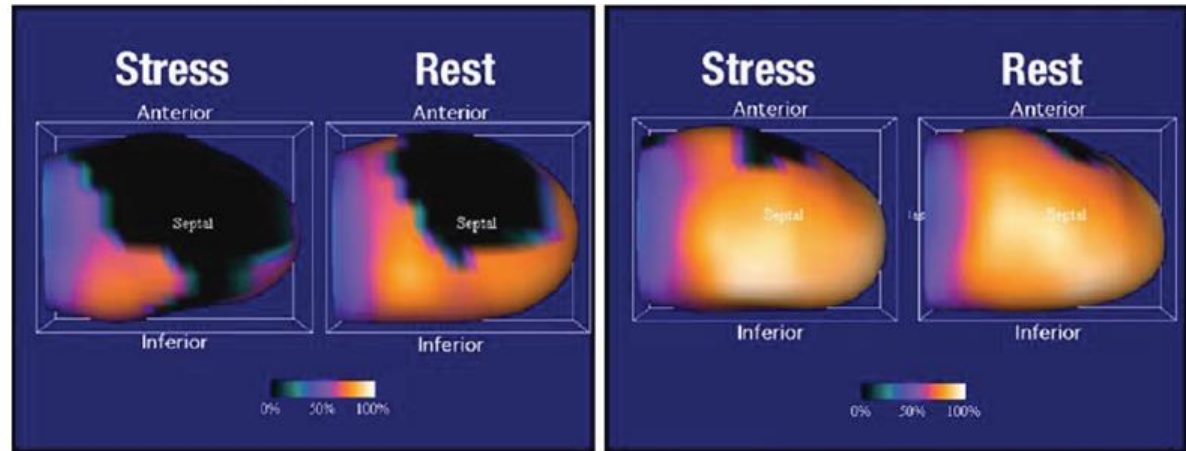
^{99m}Tc -sestamibi

Localizzazione nei mitocondri

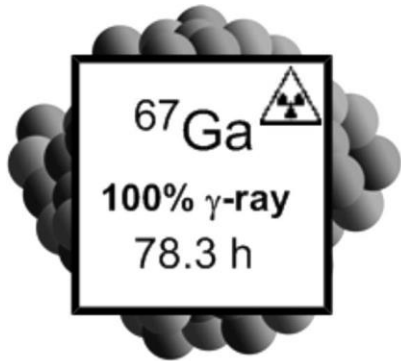


Baseline

4 months



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

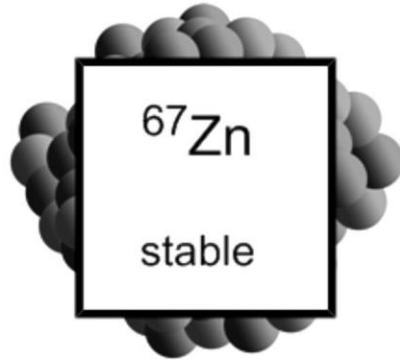
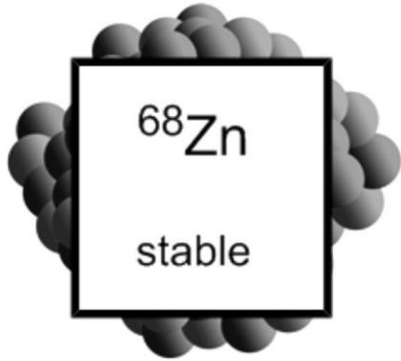
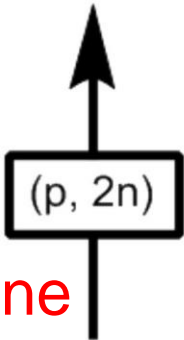


Electron capture

93 keV (36%)
185 keV (20%)
300 keV (16%)

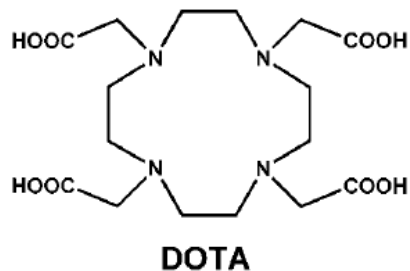
imaging di processi
infiammatori e di tumori

Ciclotrone

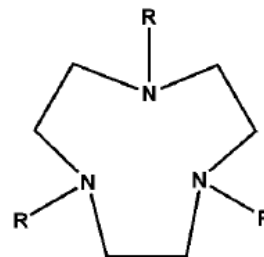


Chelators for the “**3⁺ family**”: Ga, In, Y and Lanthanides (e.g. ⁶⁷Ga, ⁶⁸Ga, ¹¹¹In, ⁹⁰Y, ¹⁵³Sm, ¹⁷⁷Lu)

a)



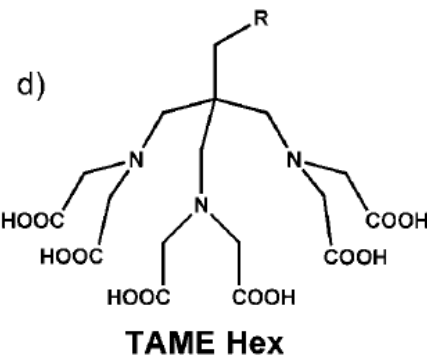
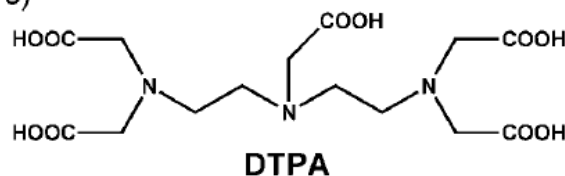
b)



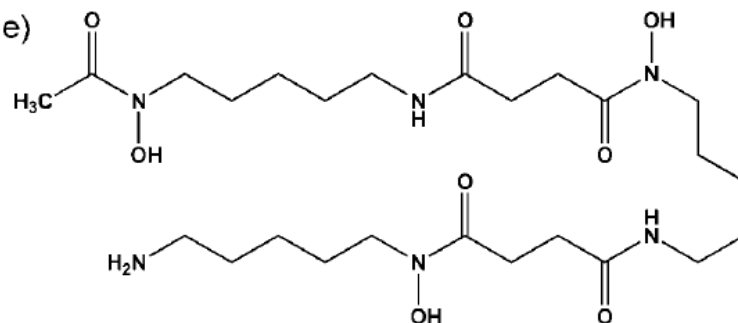
NOTA	R = CH ₂ COOH
TACN-TM	R = CH ₂ CH ₂ SH
NOTP	R = CH ₂ PO ₃ H ₂
NOTPME	R = CH ₂ PO ₂ (OCH ₂ CH ₃)

Diethylenetriamino-
pentaacetic acid

c)

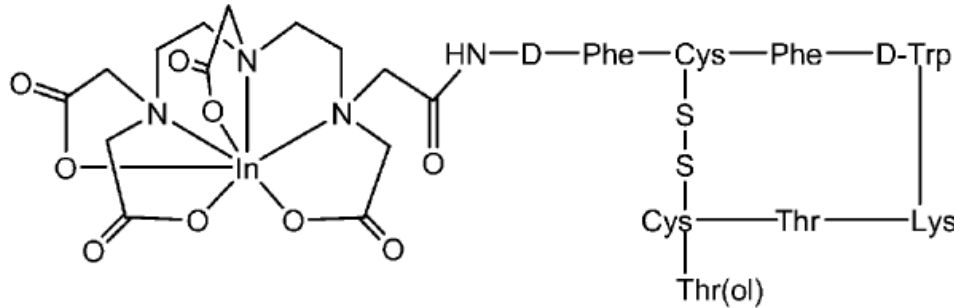


e)



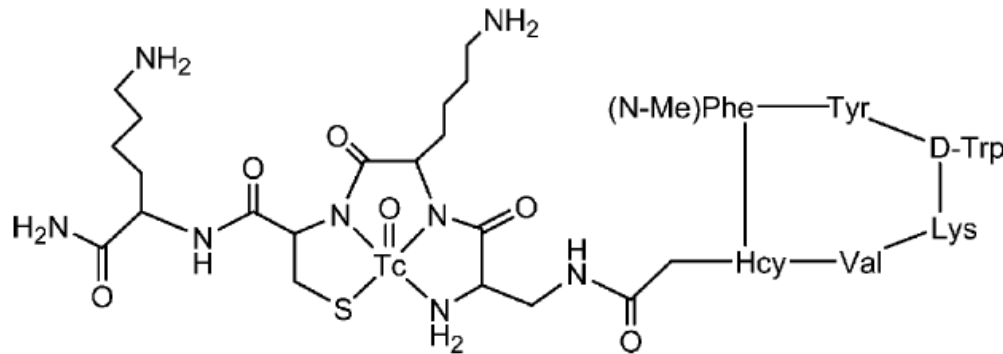
Octreotide e Depreotide

peptidi specifici per i recettori della somatostatina



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

SPECT imaging
of neuroendocrine
tumors

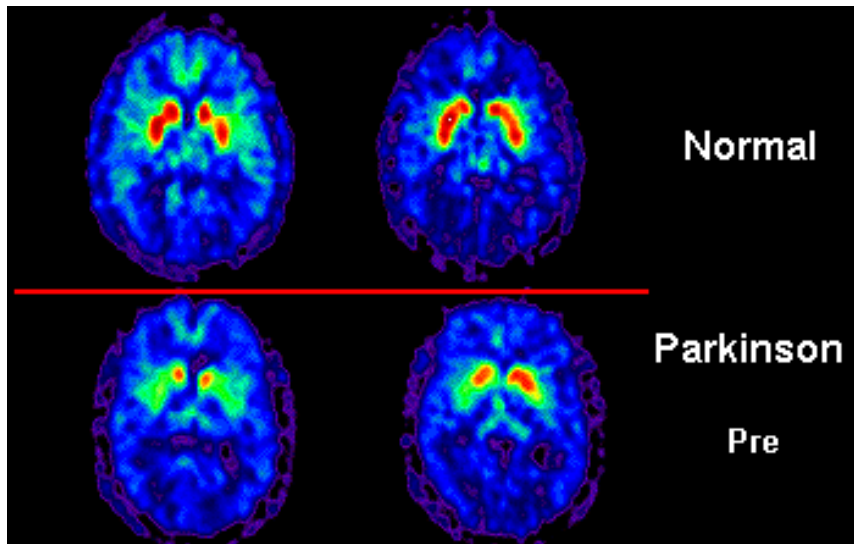
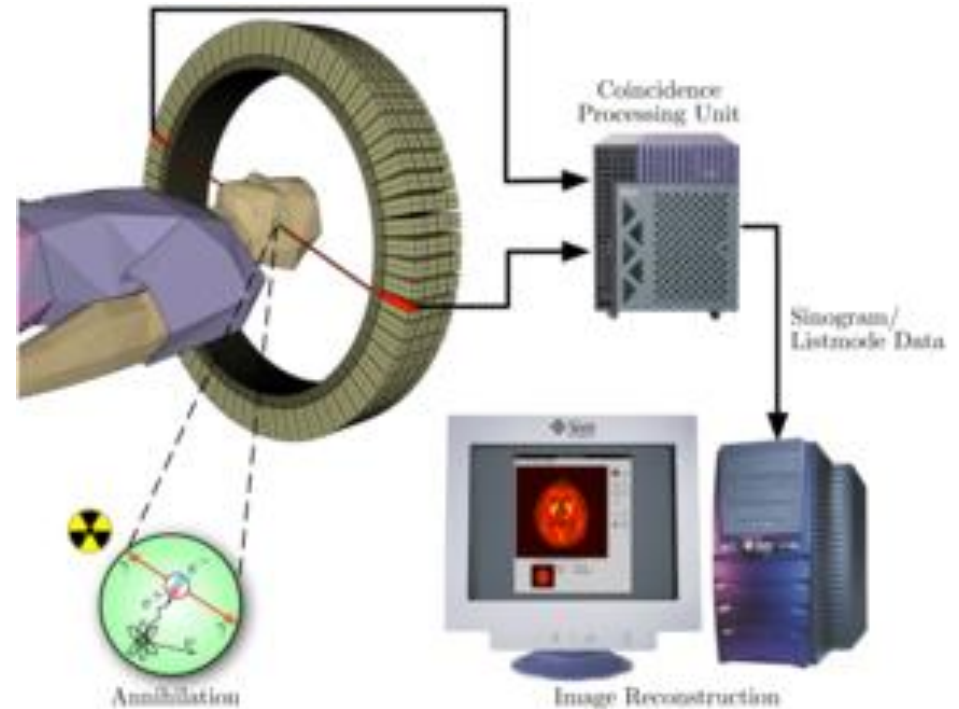
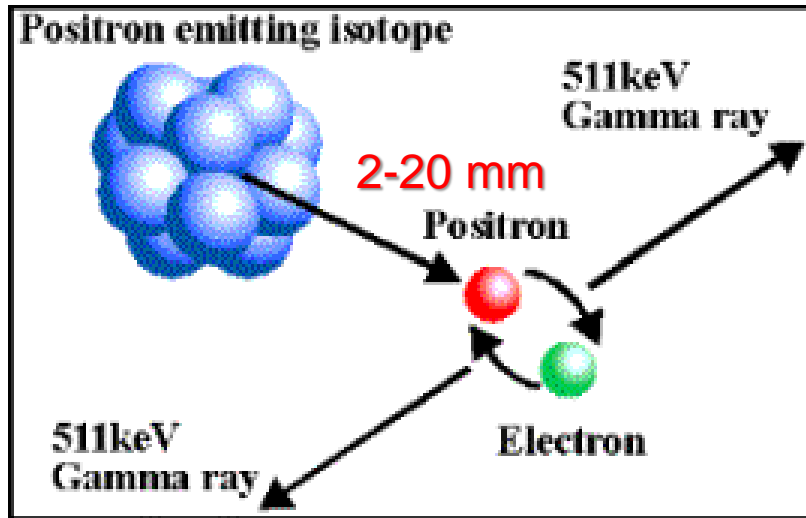


$^{99\text{m}}\text{Tc}$ -P829 (NeoTect[®])

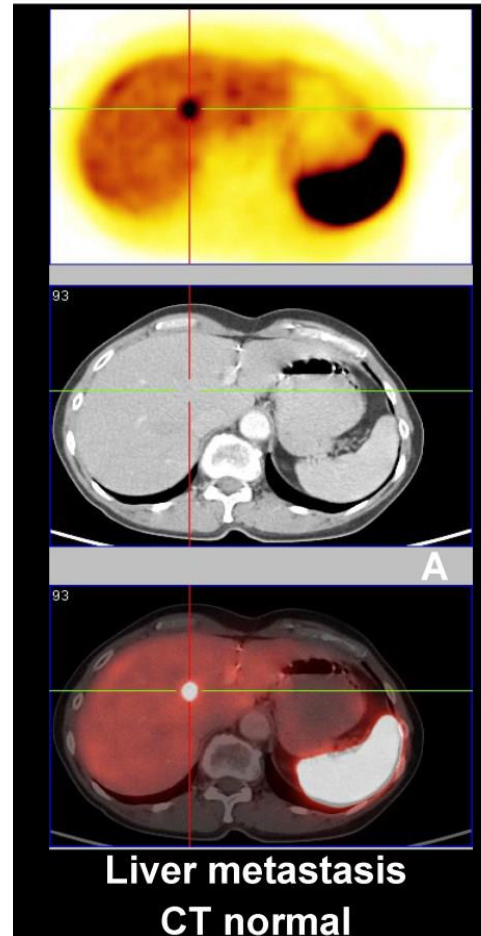
SPECT imaging
of lung tumors

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

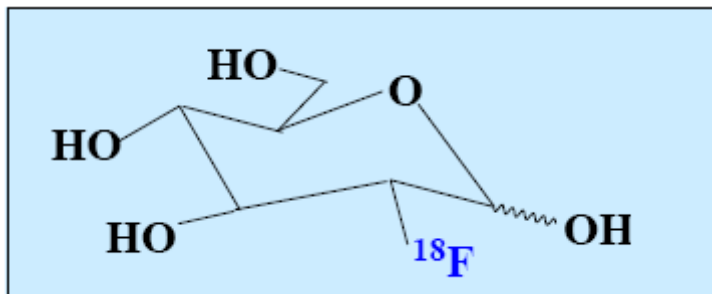
PET + CT

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/ μ mol)
^{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

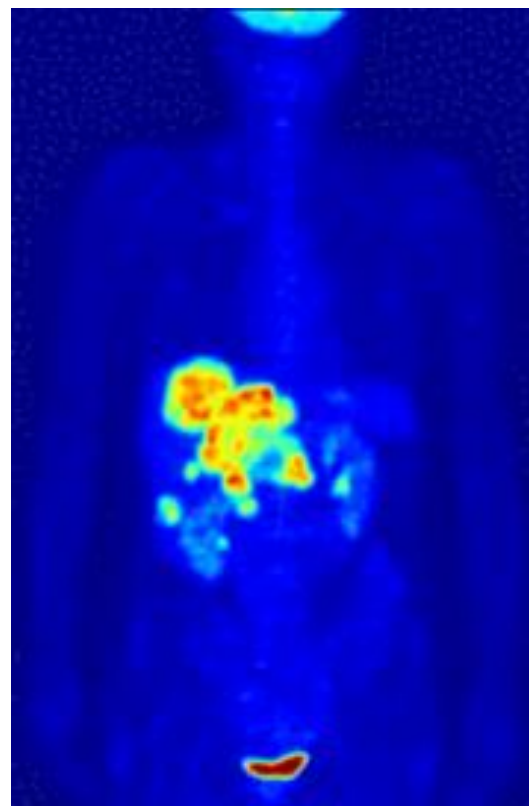
^a EC: electron capture.



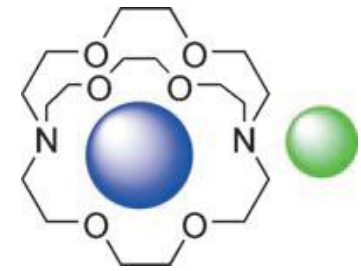
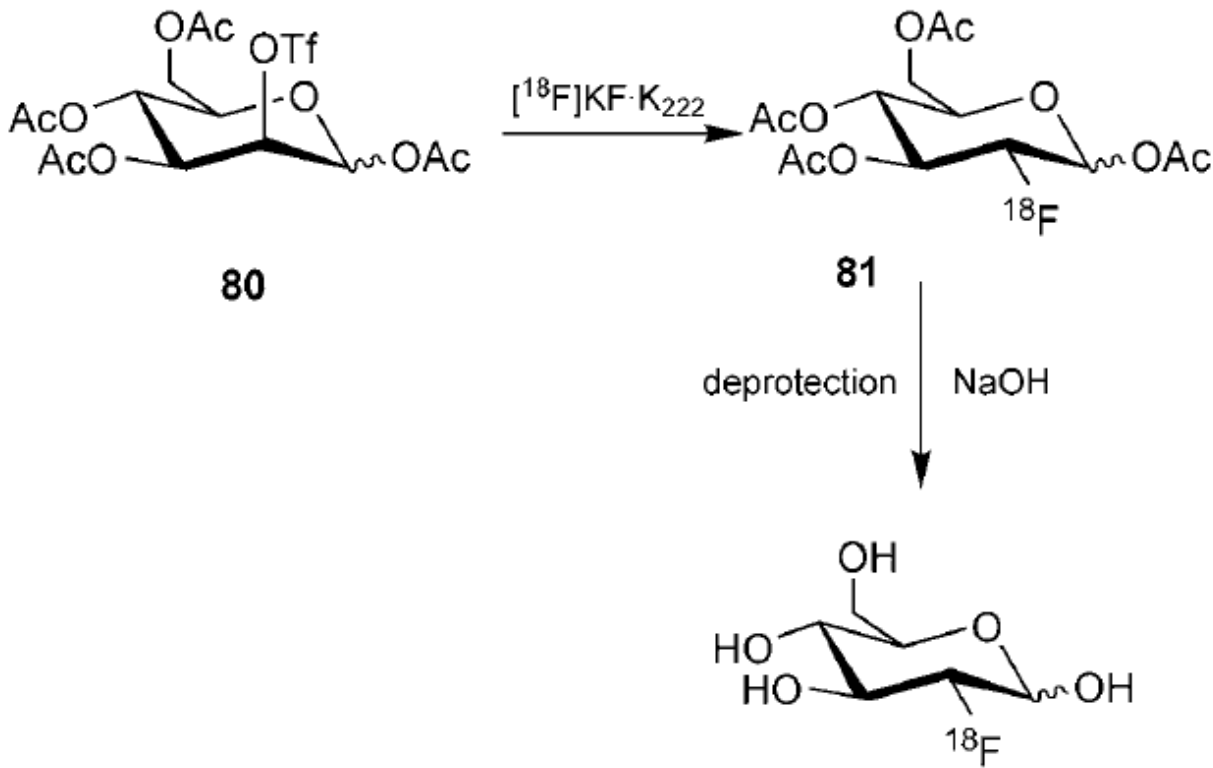
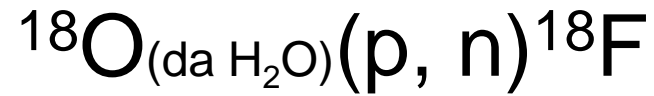
Fluorodeoxyglucose ($[^{18}\text{F}]$ FDG)

Sostituzione bio-isosterica

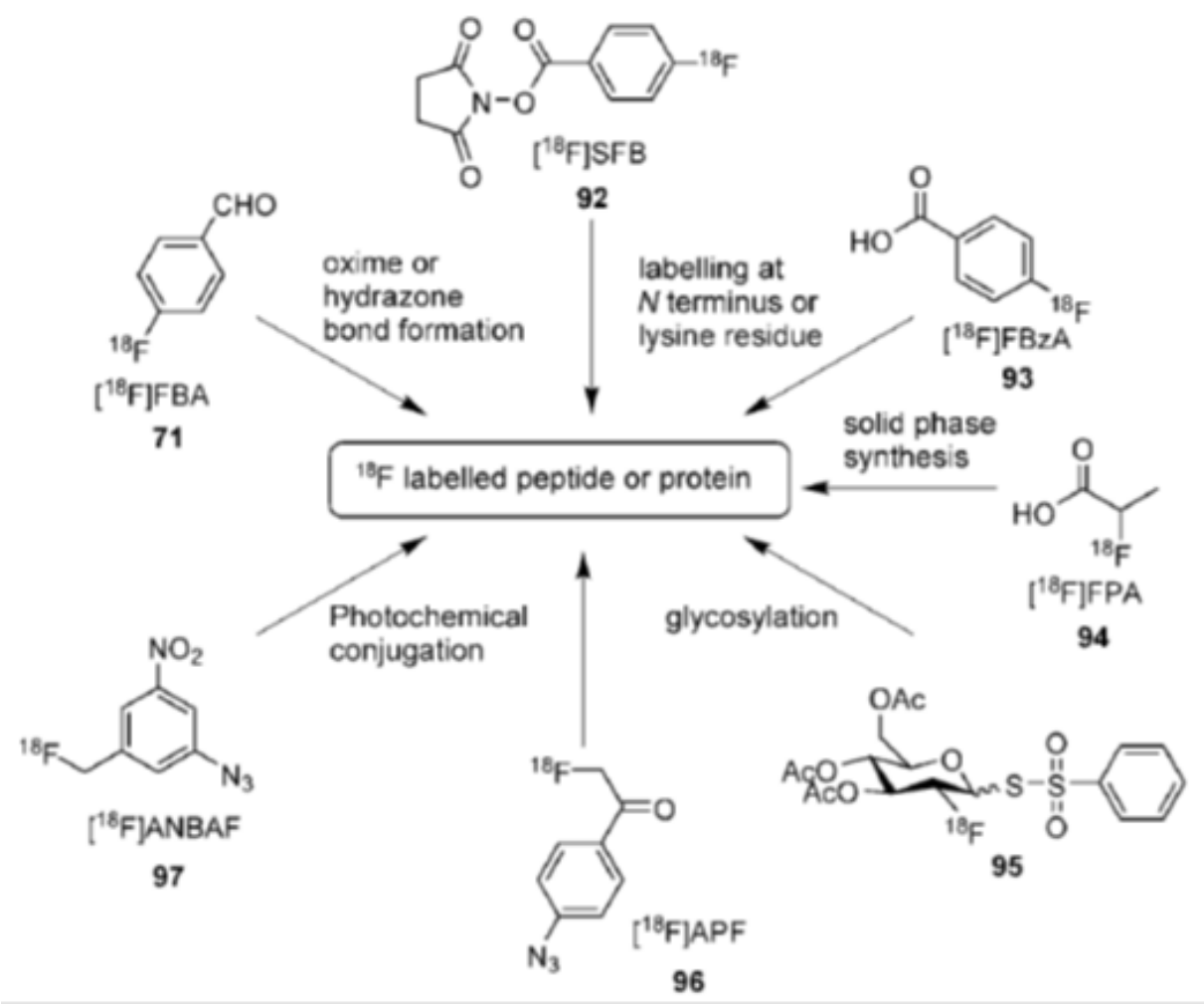
metabolismo del glucosio
localizzazione di tumori



Esempio di fluorurazione diretta (nucleofila)



Gruppi prostetici per marcare biomolecole con ^{19}F

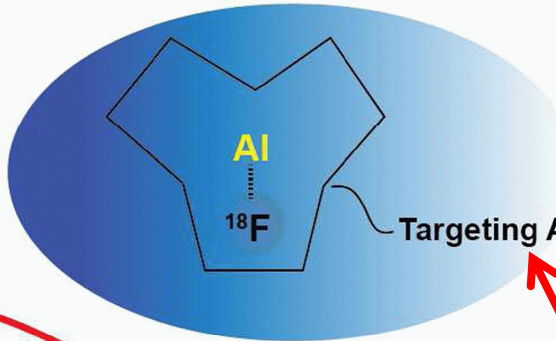


Fluorurazione inorganica

$\text{Al-F} > 670 \text{ kJ mol}^{-1}$ vs 480 kJ mol^{-1} per C-F

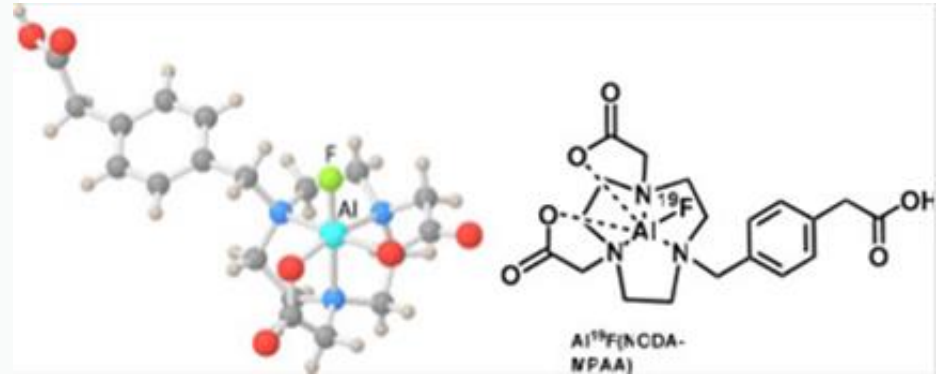
Na^{18}F

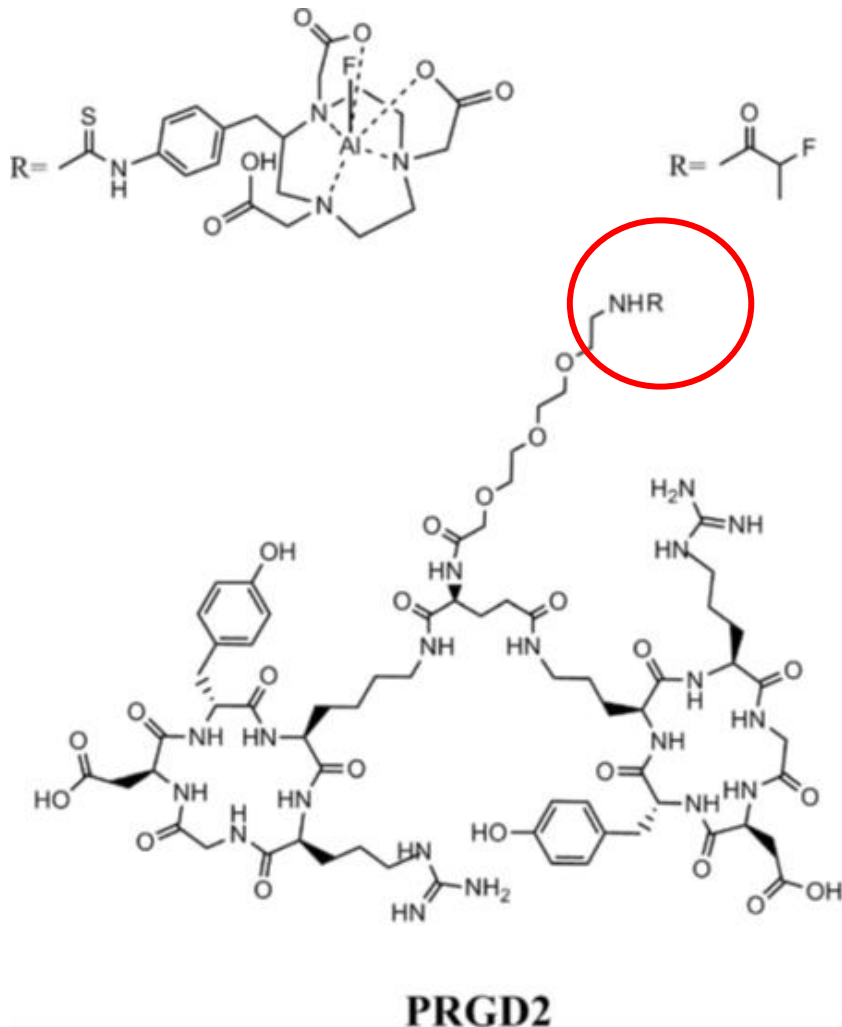
Heat -15 min



Targeting Agent

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-vascularizzazione di un tumore e stabilire se ha probabilità di rispondere a una terapia anti-angiogenica

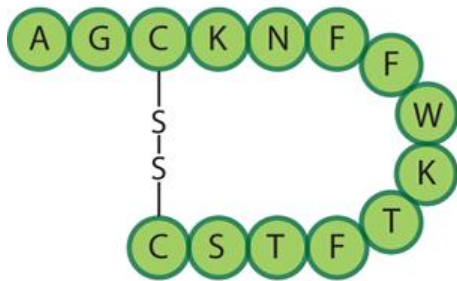
studio clinico nell'uomo per l'*imaging* di un tumore al polmone

Radionuclidi metallici per PET

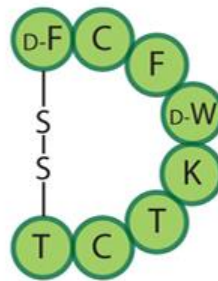
Table 1. Physical Properties of Some Common PET Radiometals^a

isotope	half-life/h	source	production reaction	decay mode (% branching ratio)	E_{β^+}/keV	abundance, $I_{\beta^+}/\%$	E_{γ}/keV (intensity, $I_{\gamma}/\%$)	relevant oxidation states	common coordination numbers
⁶⁴ Cu	12.7	cyclotron	⁶⁴ Ni(p,n) ⁶⁴ Cu	$\epsilon + \beta^+$ (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	$\epsilon + \beta^+$ (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	$\epsilon + \beta^+$ (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	$\epsilon + \beta^+$ (100) β^+ (22.7)	395.5(11)	22.74(24)	511.0 (45.5) 909.2 (99.0)	4+	8

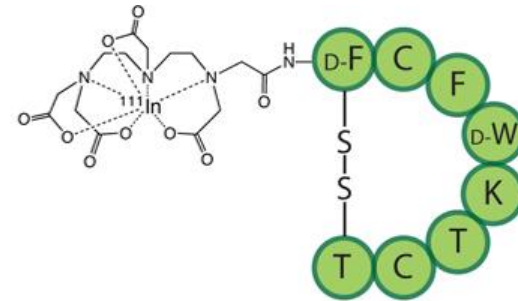
I tumori neuroendocrini sovra-esprimono i recettori per la somatostatina



Somatostatin



Octreotide



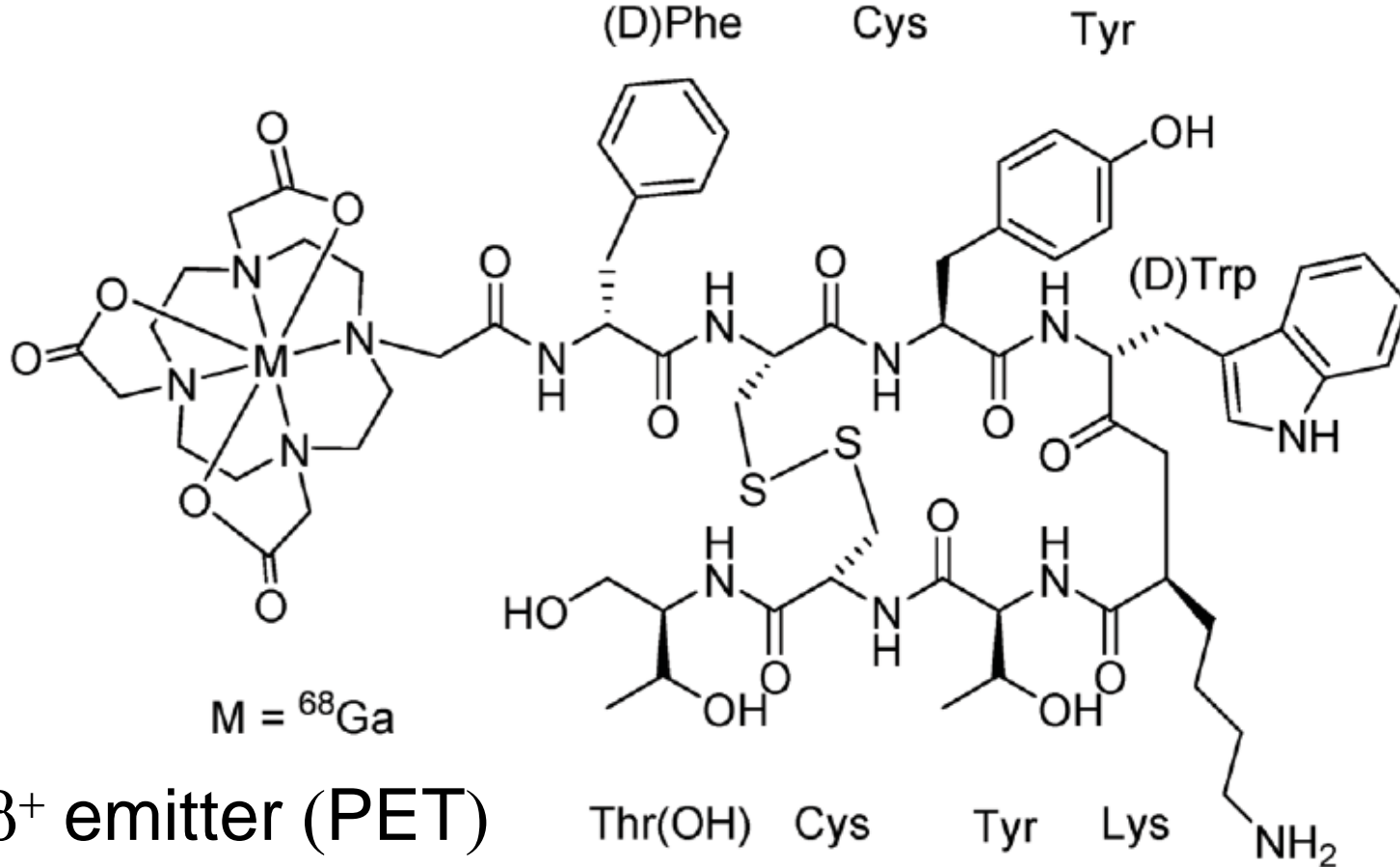
^{111}In -DTPA-Octreotide

SPECT imaging
of neuroendocrine
tumors

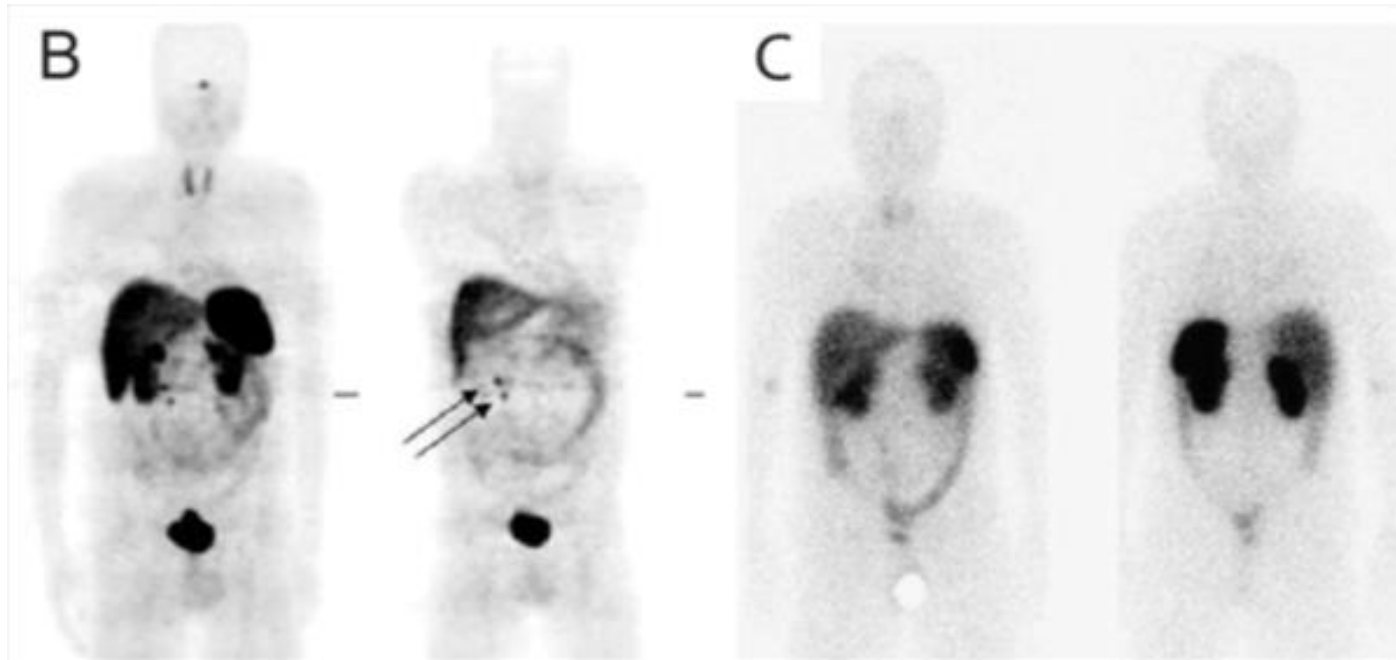
^{68}Ga -DOTA-tyr3-Octreotide

(^{68}Ga -DOTATOC)

High resolution PET imaging of neuroendocrine tumors



imaging di un tumore endocrino



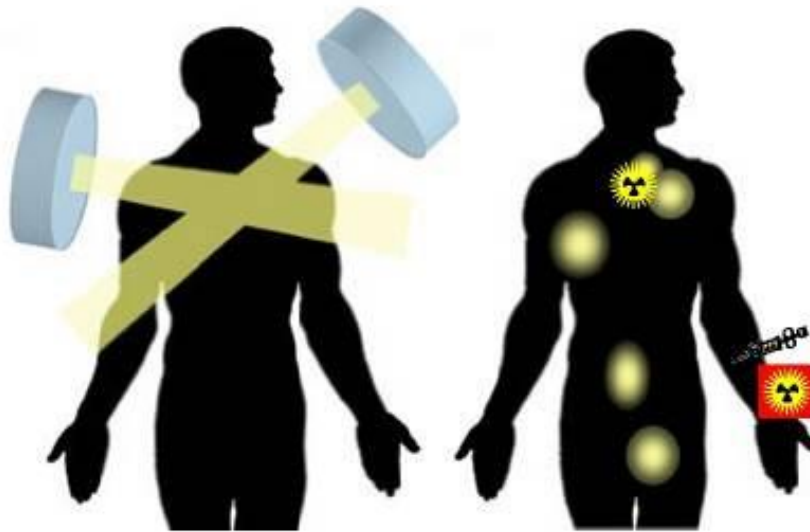
^{68}Ga -DOTATOC
(PET)

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

Targeted Radiotherapy (*Radio(immuno)therapy*)

External Beam

Targeted Radionuclide



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

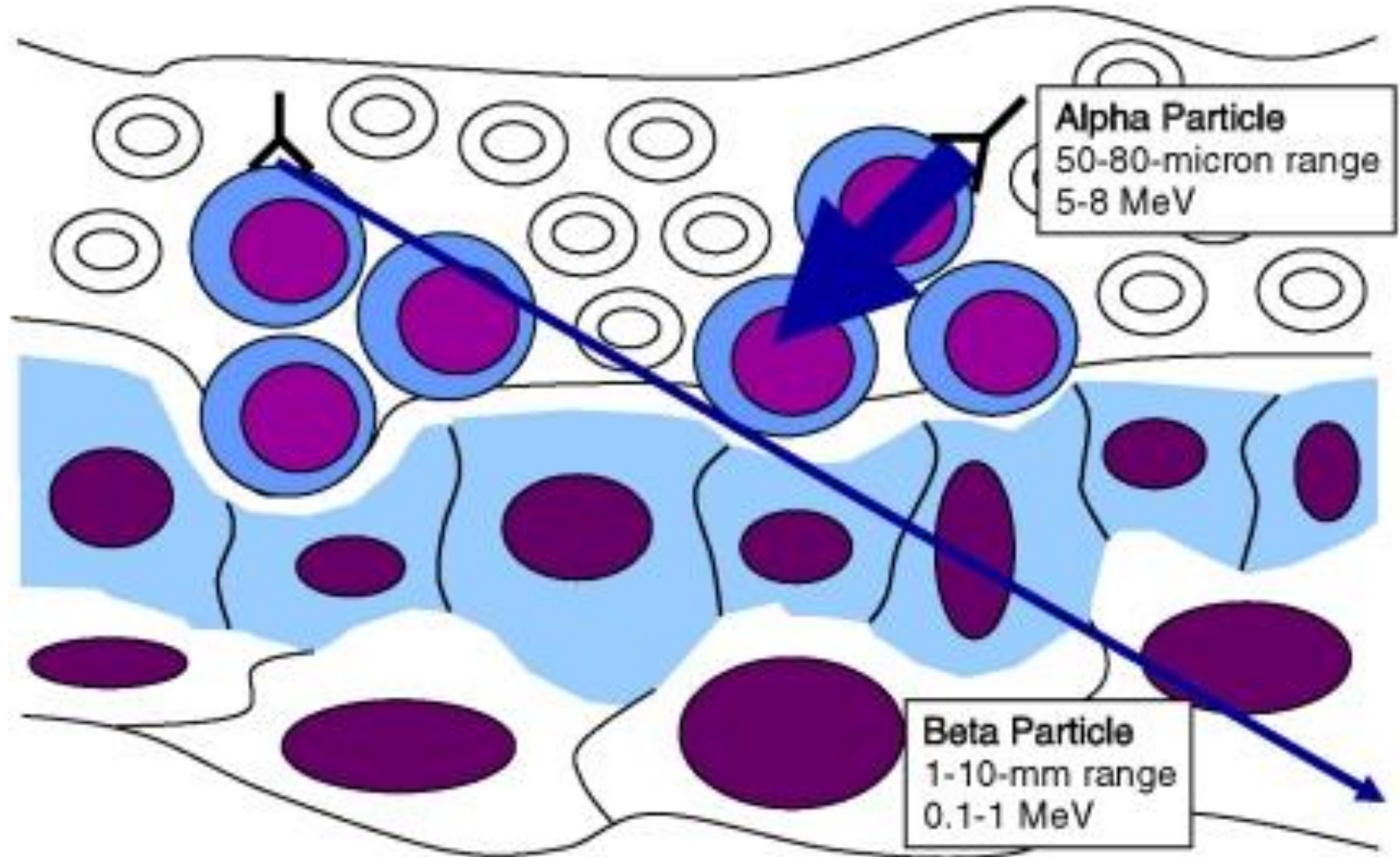
- $TI > 10$ per reni e polmoni
- $TI > 50$ per midollo spinale

Requires knowledge of tumor location

Requires knowledge of tumor biology

TI = therapeutic index

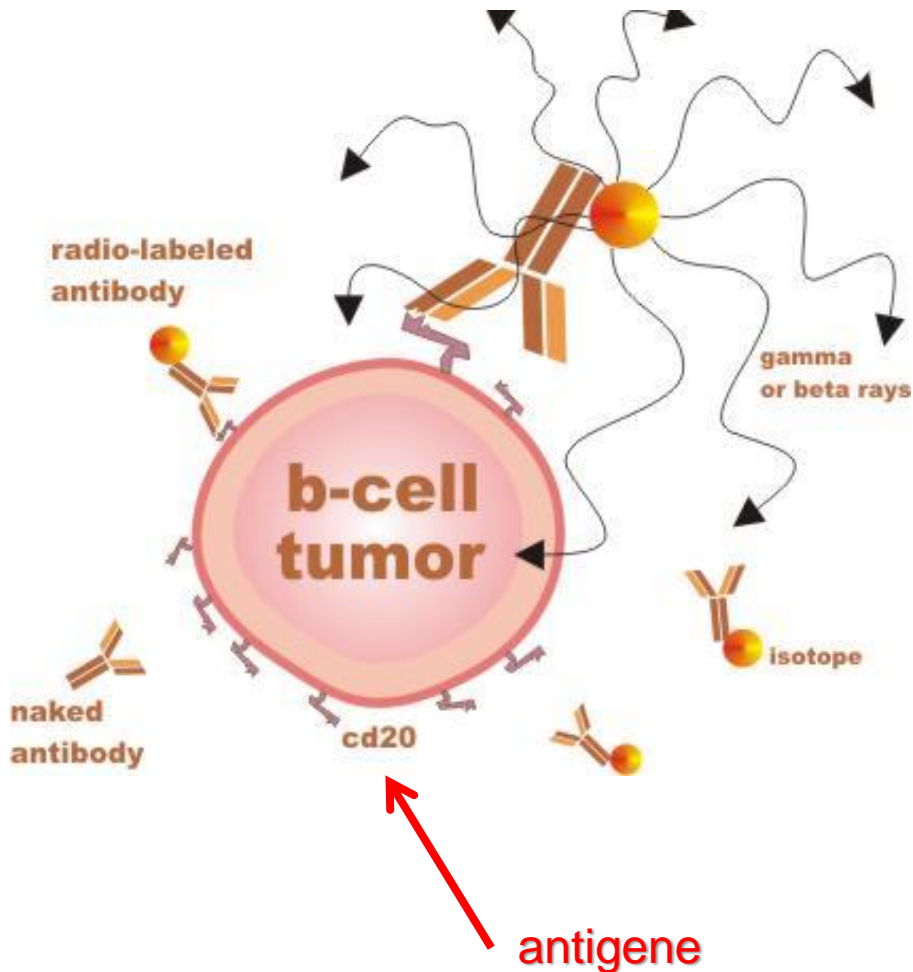
Penetrating power of α and β particles



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 lymphoma



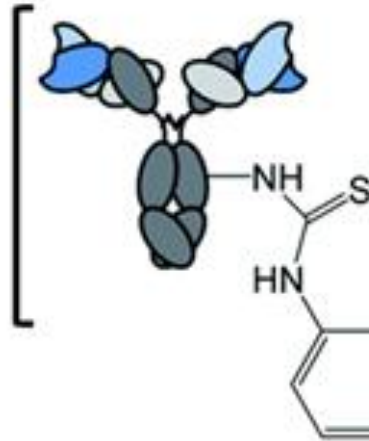
Antigene ideale:

- 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

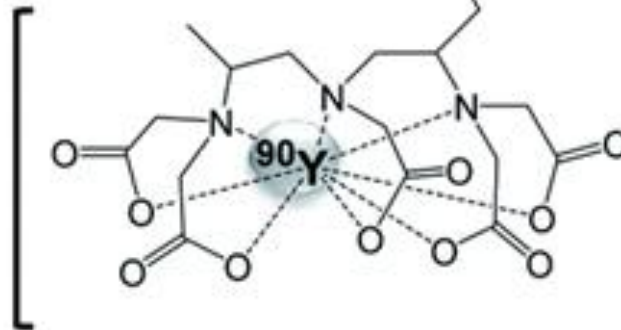
FDA approved

(a) ^{90}Y -ibritumomab tiuxetan
(Zevalin[®])

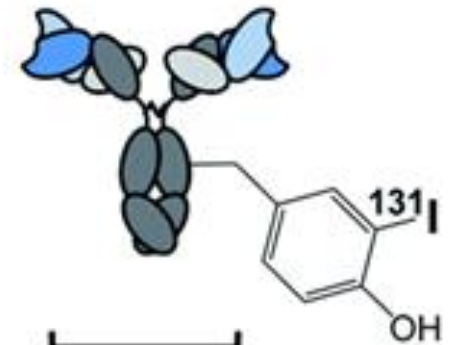
Anti-CD20
monoclonal
antibody



DTPA
chelating
moiety



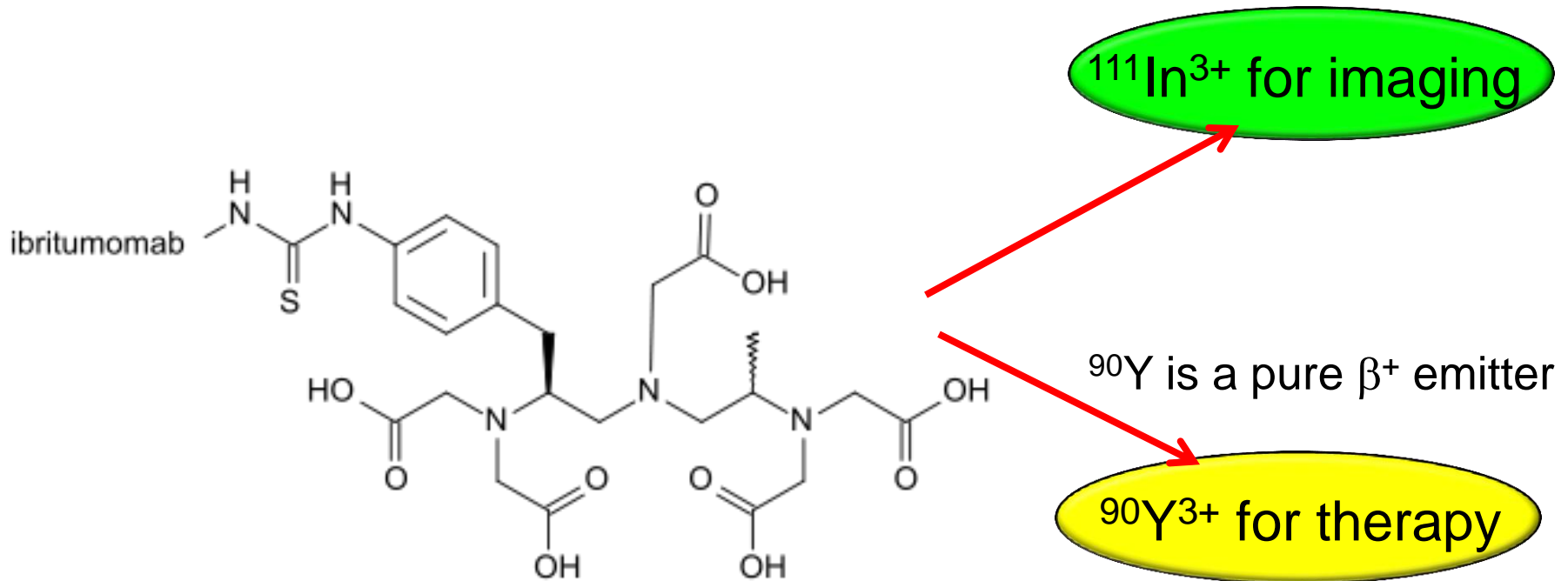
(b) ^{131}I -tositumomab
(Bexxar[®])



Anti-CD20
monoclonal
antibody

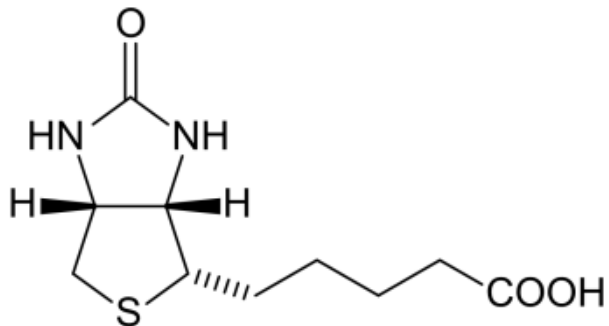
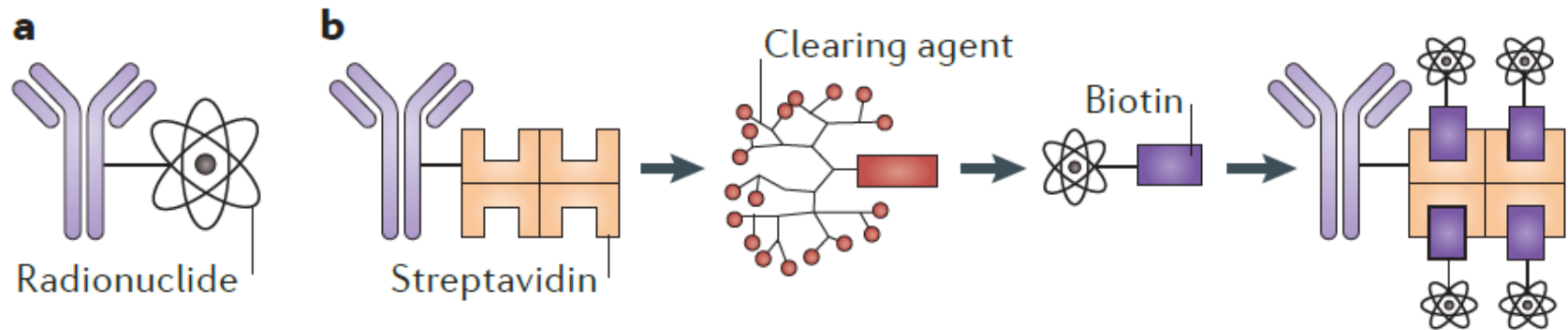
Zevalin[®]

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



Example of the **matched-pair approach**

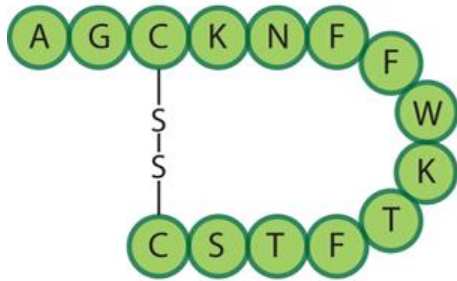
multi-step pre-targeted radio-immunotherapy (PRIT)



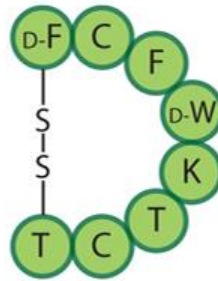
Biotina

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

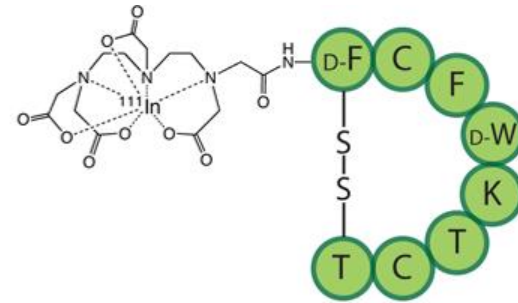
Radio-immunotherapy of neuroendocrine tumors



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

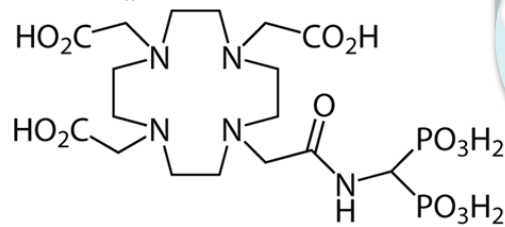
^{68}Ge
ε
270.8 d

^{68}Ga
β⁺ 1.9
67.7 m

^{176}Lu 2.98 a	^{177}Lu 160 d 6.71
^{176}Yb 12.7 % 3 b	^{177}Yb 1.9 h

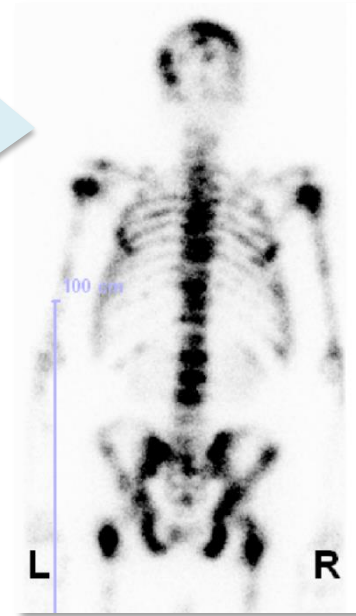
(n,γ) → β⁻

DOTA-bisphosphantae amide
„BPAMD“



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

^{177}Lu -BPAMD
Therapy



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

