

METALLI IN MEDICINA
A.A. 2016-2017
PARTE 5

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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. ^{188}Re)
Diagnostic (e.g. $^{99\text{m}}\text{Tc}$)

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



```
graph TD; A([Imaging with Metal Compounds]) --> B[Cellular level  
(molecular imaging o  
imaging funzionale)]; A --> C[Whole-body level  
(imaging anatomico o strutturale  
al massimo funzionale)];
```

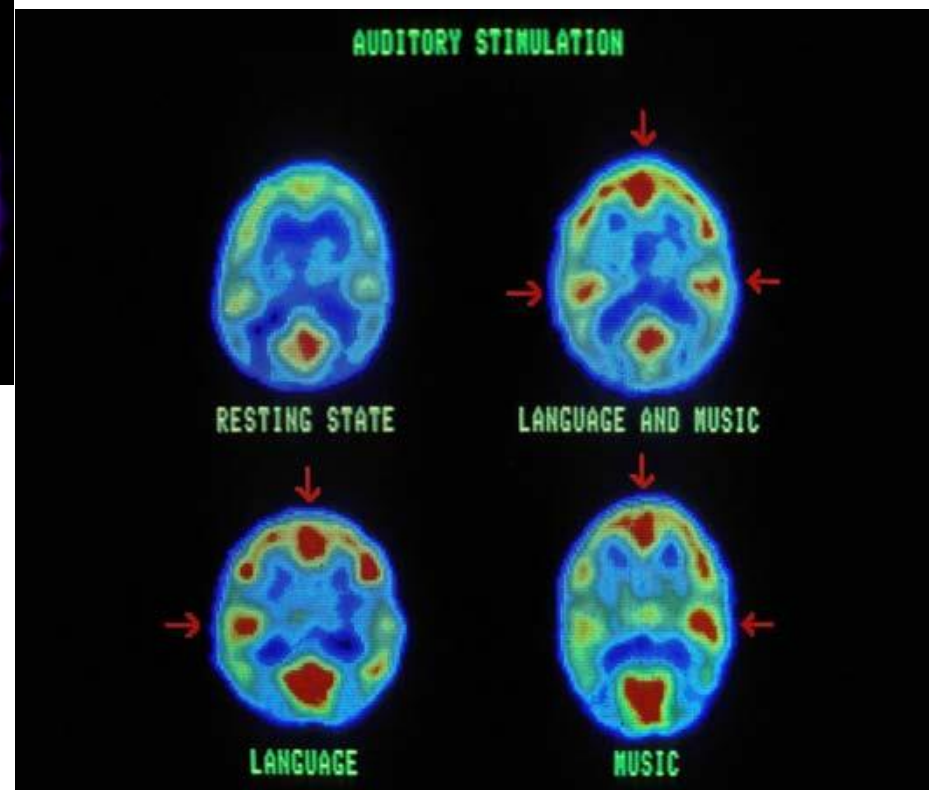
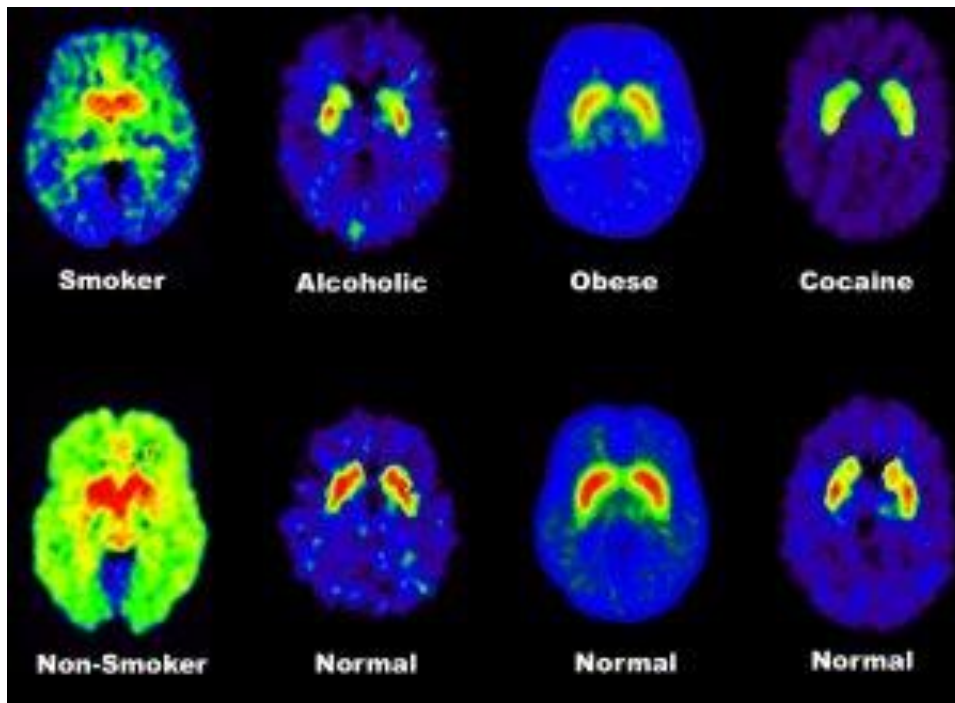
Cellular level
*(molecular imaging o
imaging funzionale)*

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



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

Radiodiagnostics

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

Radiotherapeutics

α or β^- emitters

Isotopes suitable for nuclear imaging

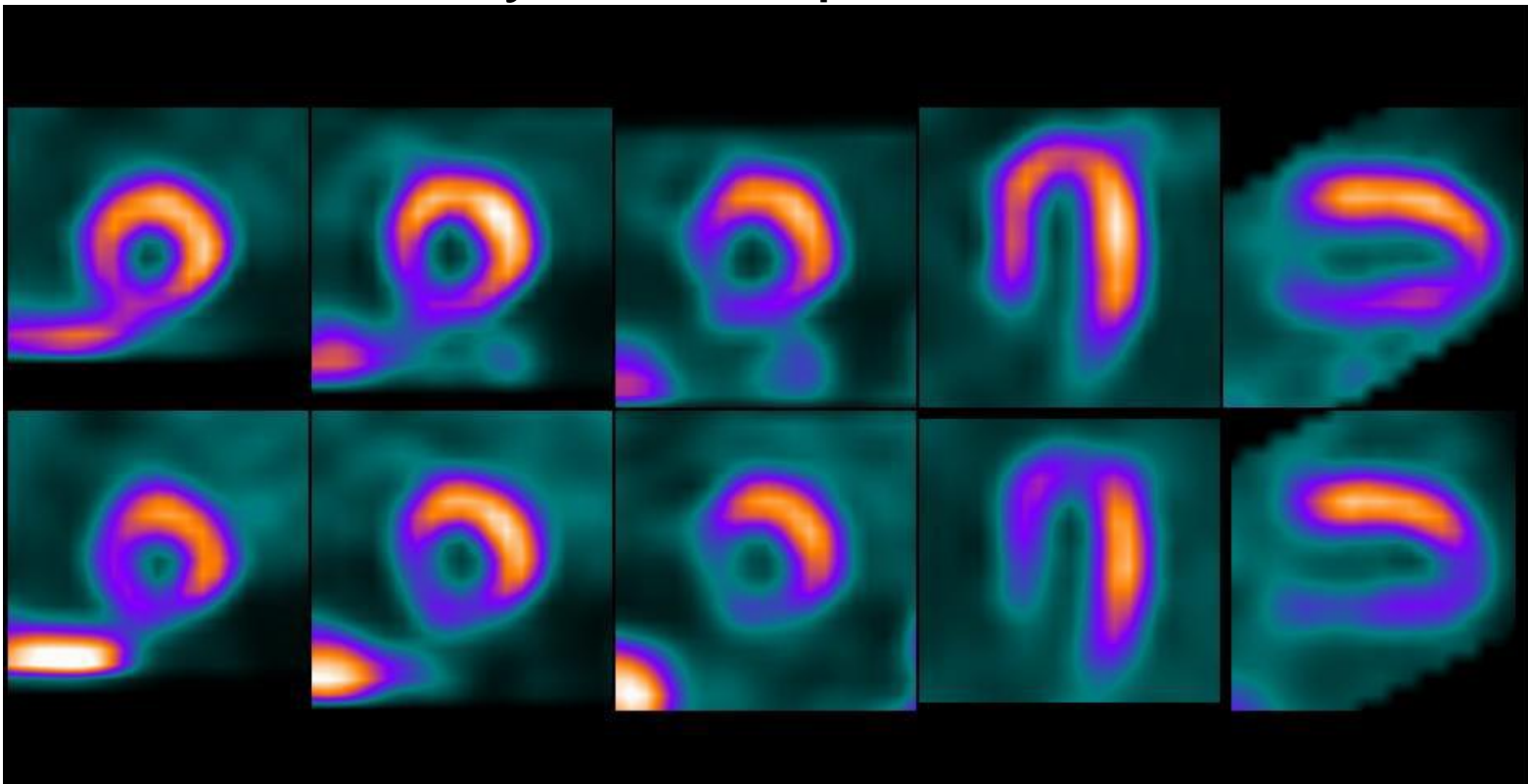
1 H Hydrogen		<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="writing-mode: vertical-rl; transform: rotate(180deg);">Short Half-Life</div> <div style="background-color: #0070C0; color: white; padding: 5px; text-align: center;">PET Isotopes</div> <div style="writing-mode: vertical-rl; transform: rotate(180deg);">Long Half-Life</div> </div> <div style="display: flex; justify-content: space-between; align-items: center; margin-top: 5px;"> <div style="background-color: #C00000; color: white; padding: 5px; text-align: center;">SPECT Isotopes</div> </div>																2 He Helium																																			
3 Li Lithium																		5 B Boron		6 C Carbon		7 N Nitrogen		8 O Oxygen		9 F Fluorine		10 Ne Neon																									
4 Be Beryllium																		13 Al Aluminum		14 Si Silicon		15 P Phosphorus		16 S Sulfur		17 Cl Chlorine		18 Ar Argon																									
11 Na Sodium																		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	
12 Mg Magnesium																		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																	

##
E
Element
Denotes an element with isotopes suitable for both PET and SPECT

##
E
Element
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.

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

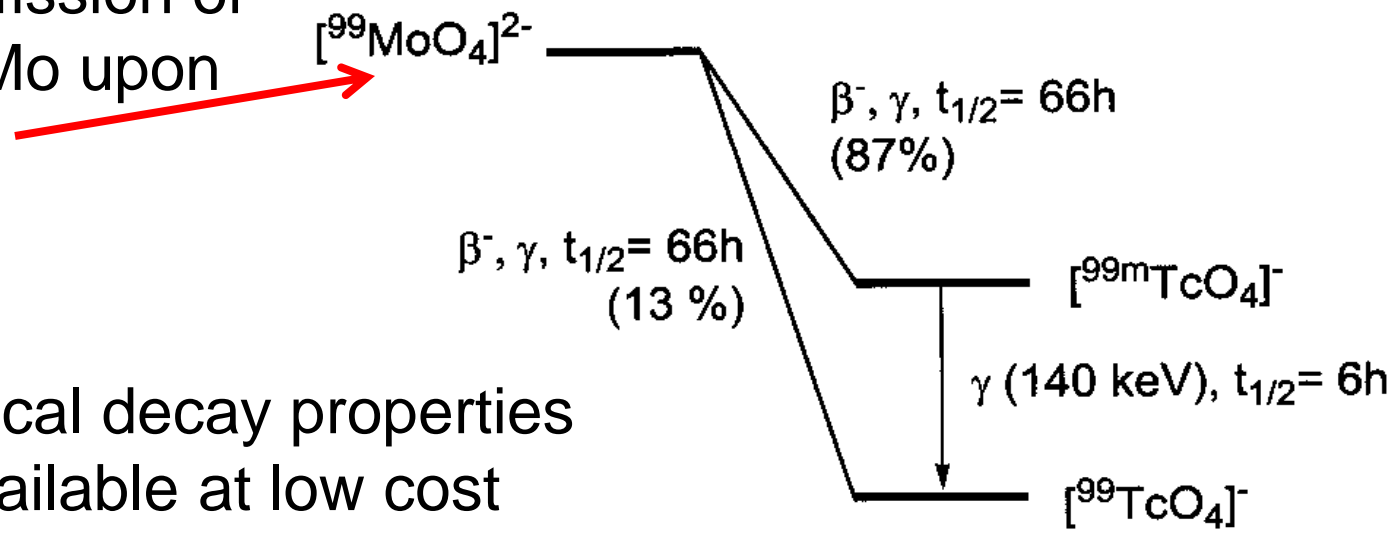
Main radionuclides for SPECT

Radionuclide	Half life	Energy of main γ emission (keV)
^{67}Ga (γ)	78 h	93, 185, 300
$^{99\text{m}}\text{Tc}$ (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)

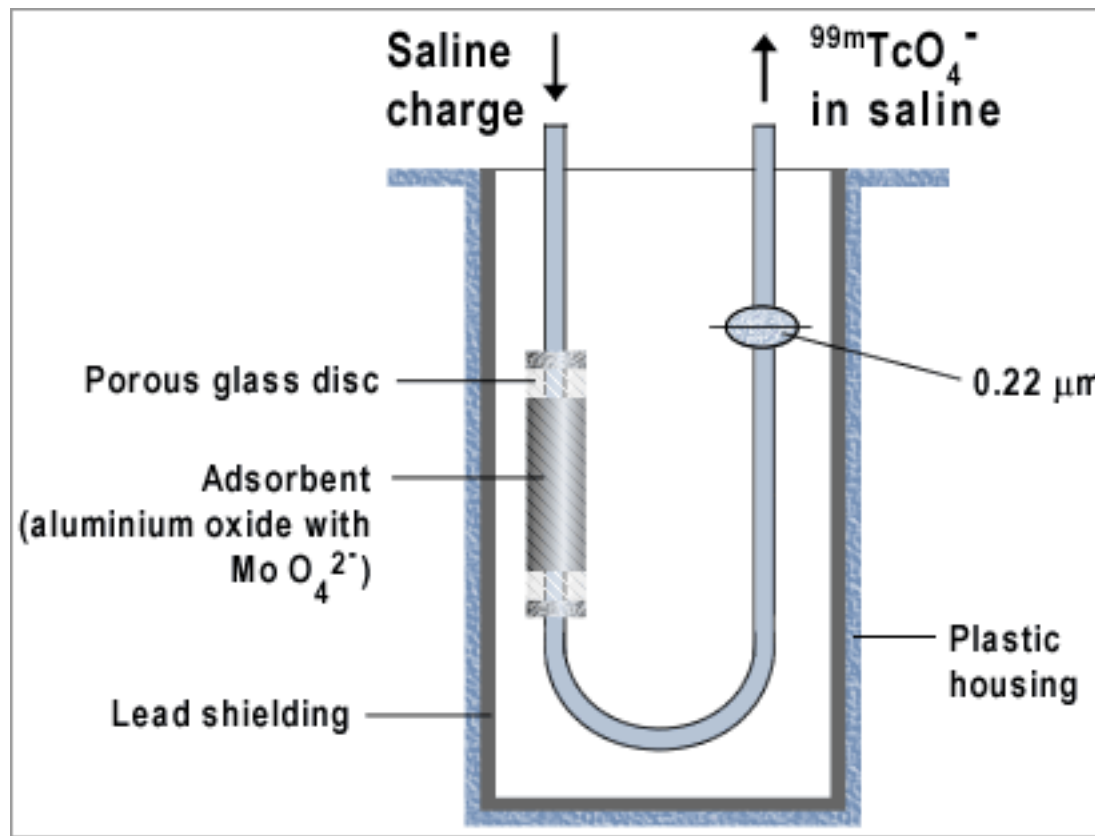
Obtained from fission of ^{235}U or from ^{98}Mo upon (n, γ) reaction



- 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

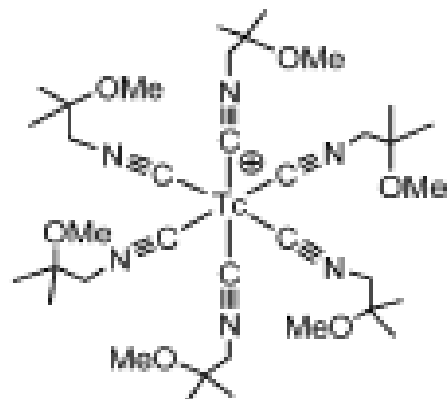
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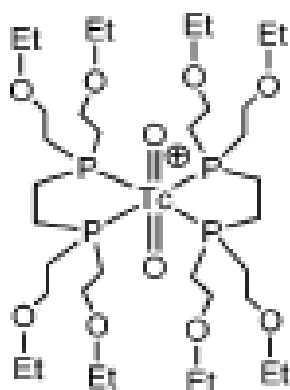
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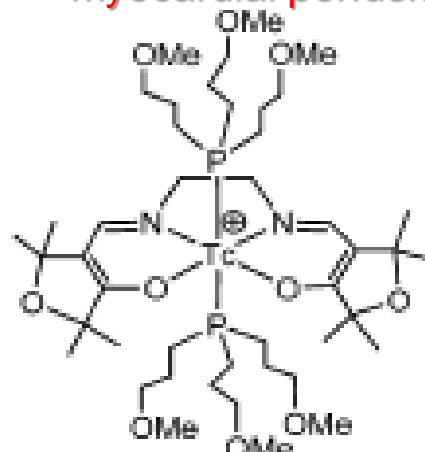
^{99m}Tc -Sestamibi

cardiac imaging



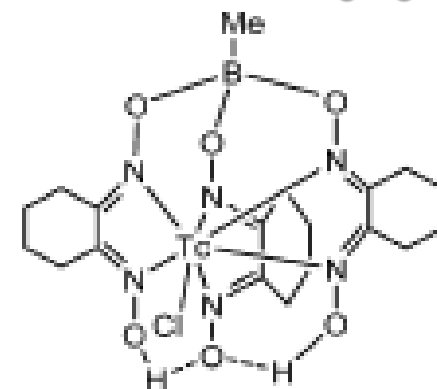
^{99m}Tc -Tetrofosmin

myocardial perfusion

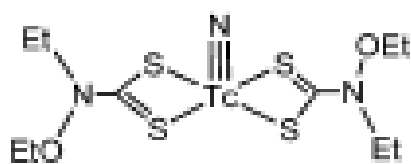


Q12

cardiac imaging

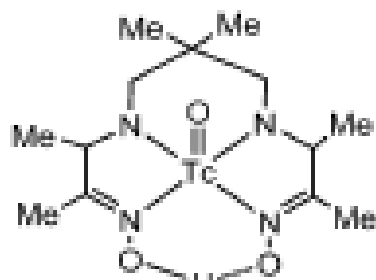


^{99m}Tc -Teboroxime



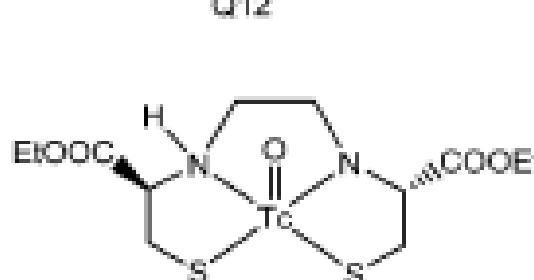
^{99m}TcN -NOET

myocardial perfusion



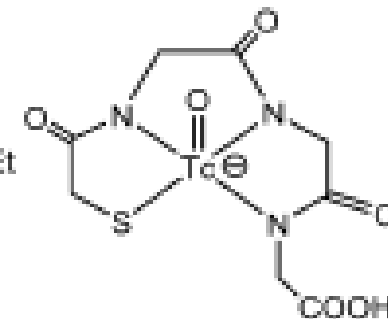
^{99m}Tc -HMPAO

cerebral perfusion



^{99m}Tc -Bicisate

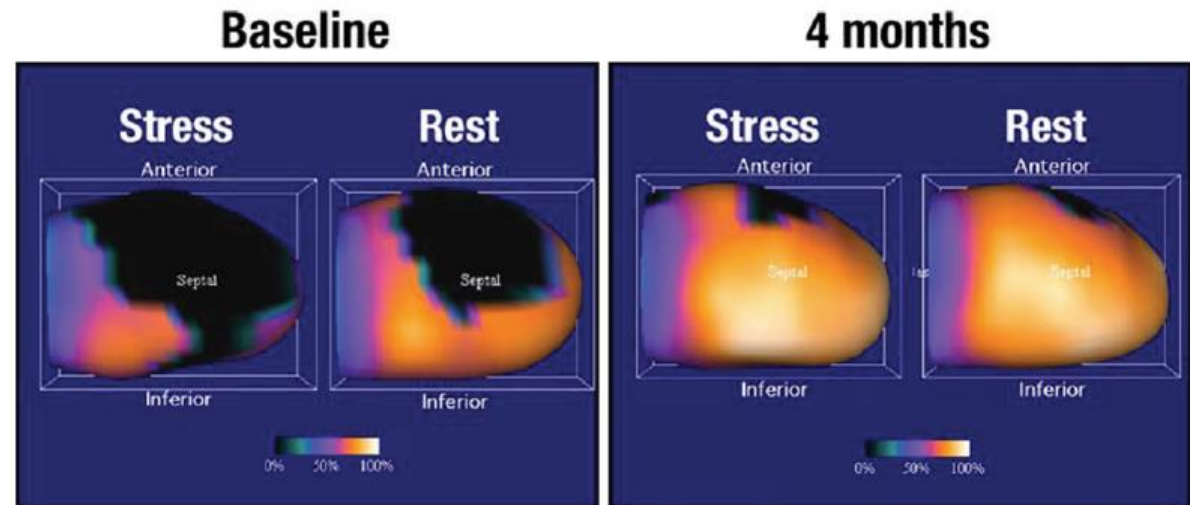
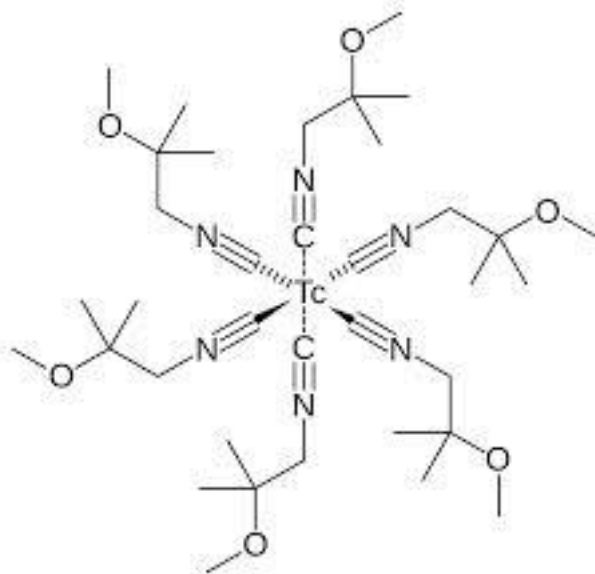
brain imaging



^{99m}Tc -MAG₃

renal imaging

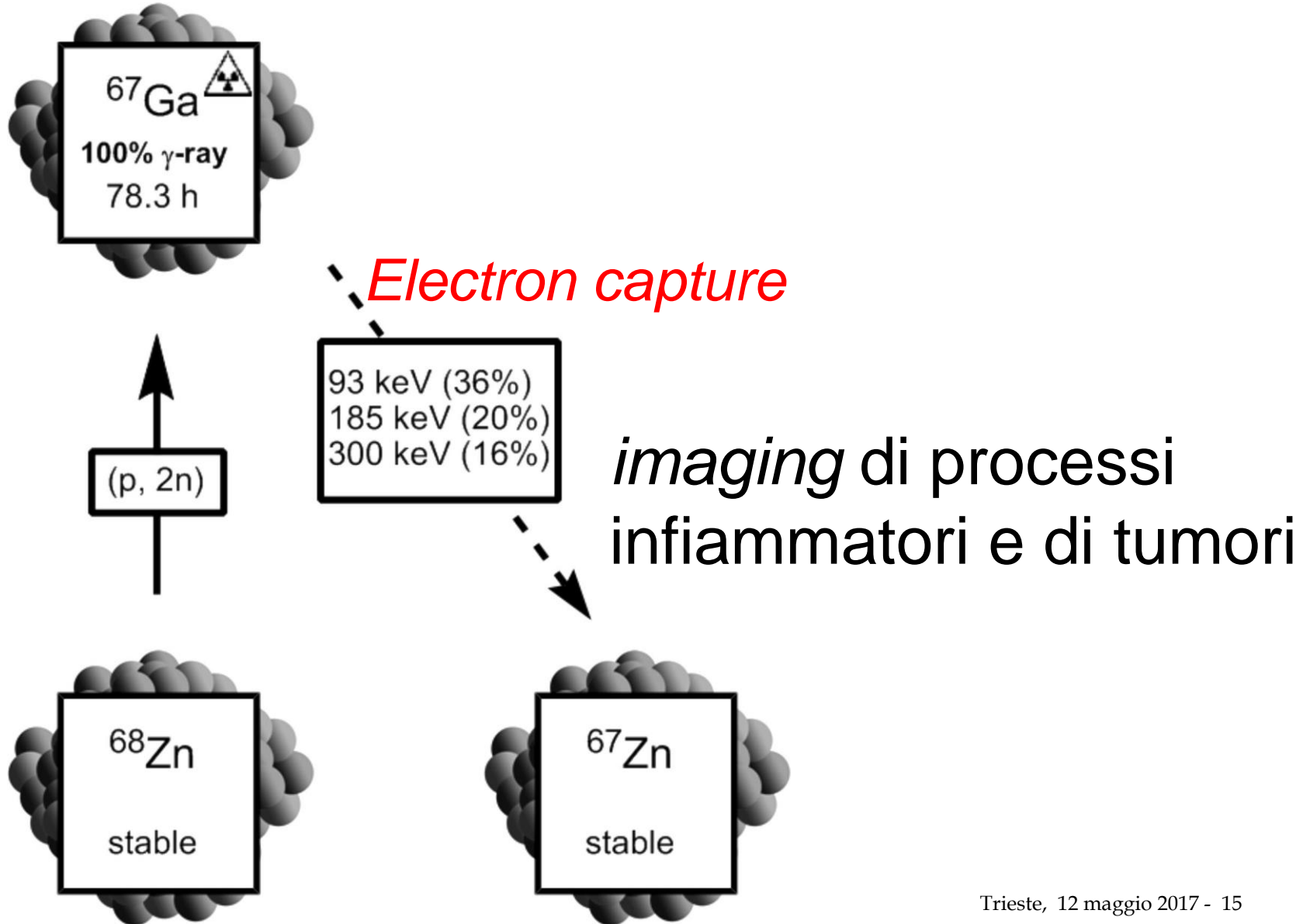
^{99m}Tc -sestamibi



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

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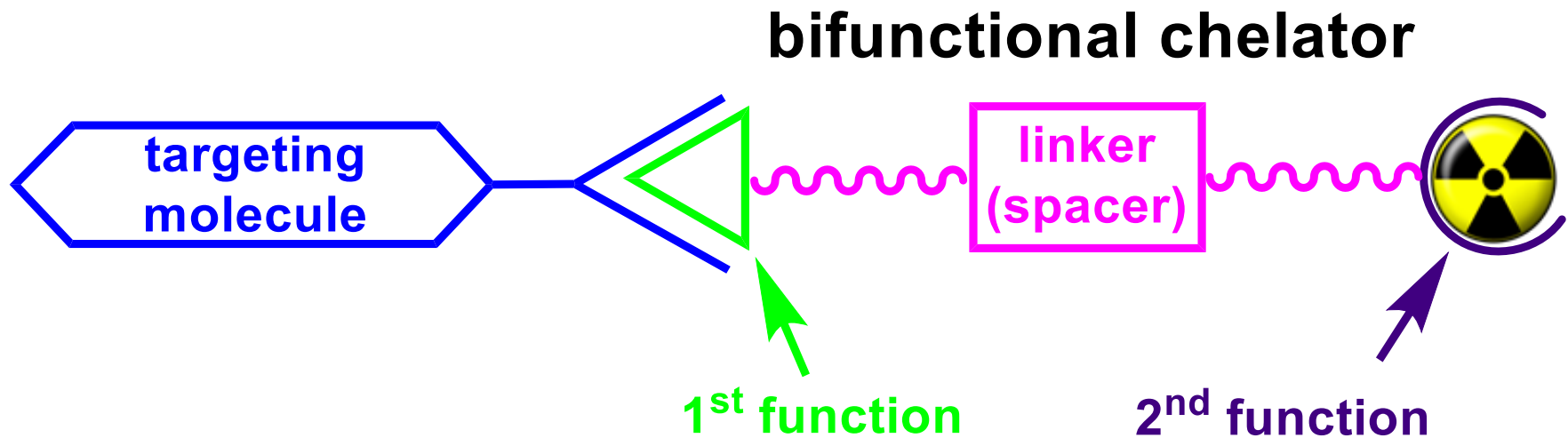
PARTE 5



'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

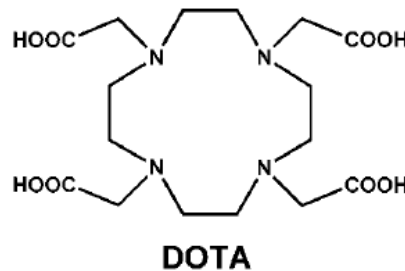
Targeted Approach (*Trojan horse*)



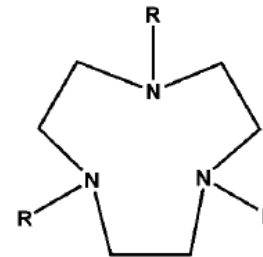
Targeting molecules: monoclonal antibodies, peptides, vitamins, carbohydrates,..

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

a)



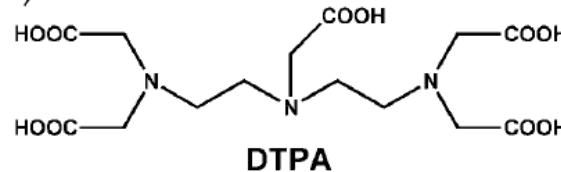
b)



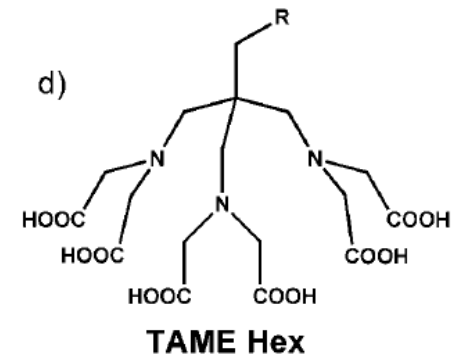
NOTA	R = CH ₂ COOH
TACN-TM	R = CH ₂ CH ₂ SH
NOTP	R = CH ₂ PO ₃ H ₂
NOTPME	R = CH ₂ PO ₂ (OCH ₂ CH ₃)

Diethylenetriamino-
pentaacetic acid

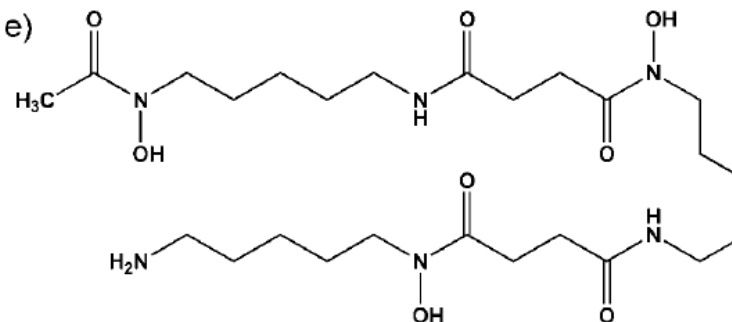
c)



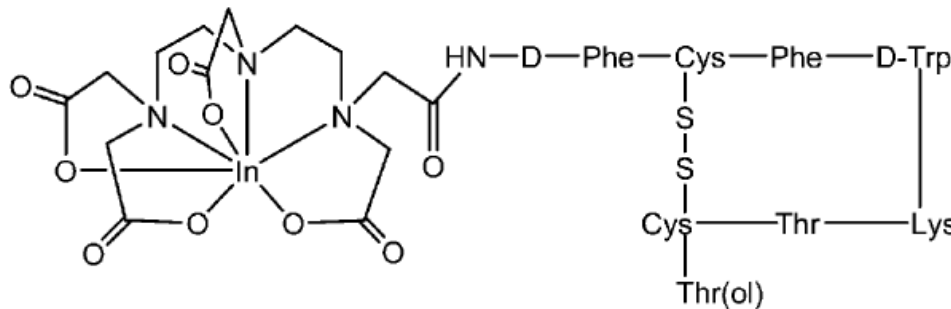
d)



e)

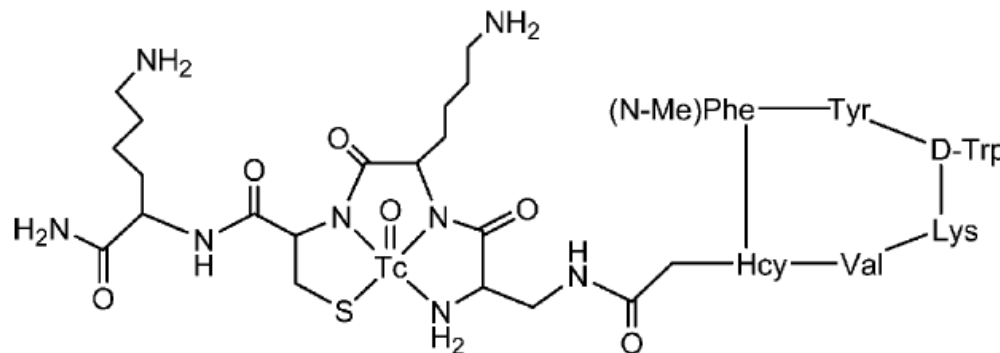


Octreotide and Depreotide peptides that target somatostatin receptors



¹¹¹In-DTPA-Octreotide (OctreoScan®)

SPECT imaging
of neuroendocrine
tumors

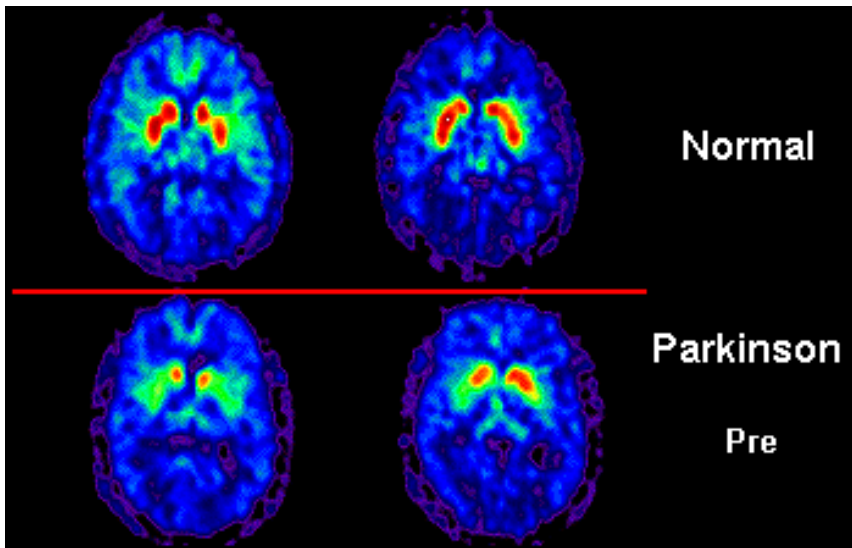
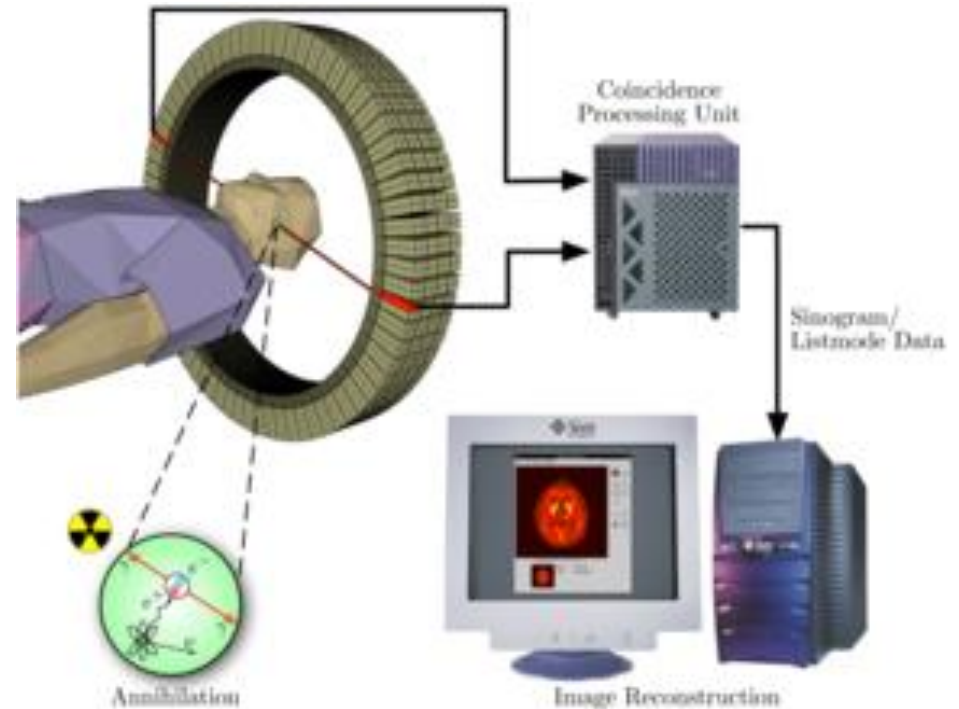
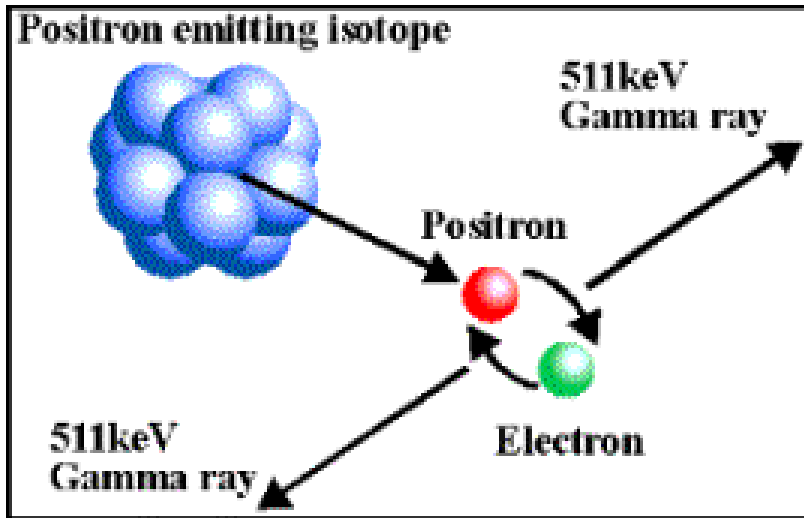


^{99m}Tc-P829 (NeoTect®)

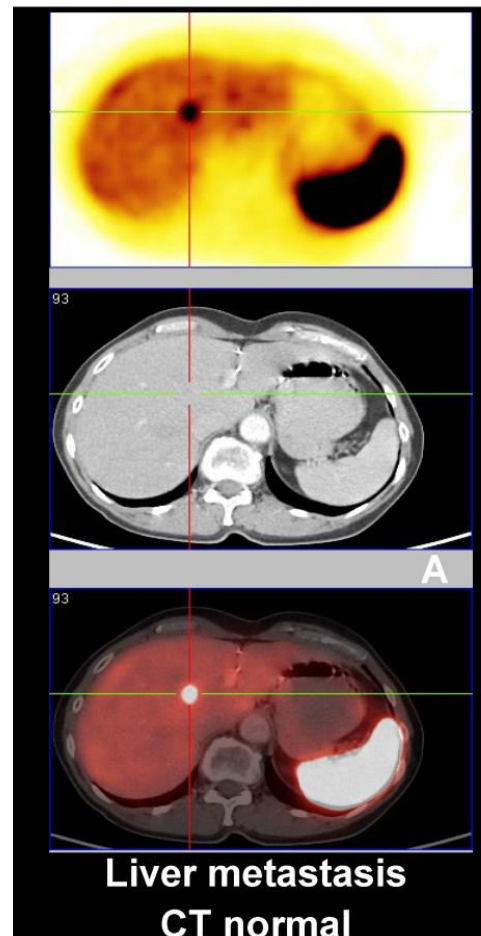
SPECT imaging
of lung tumors

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

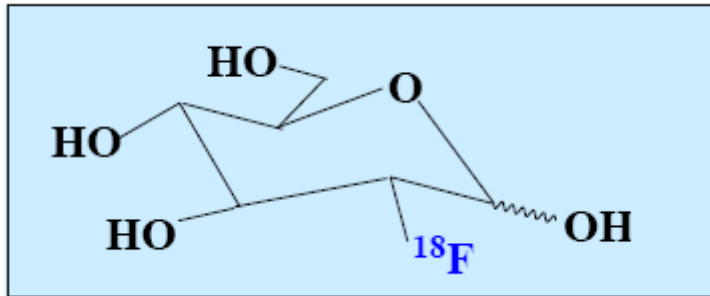
PET + CT

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/ μ mol)
^{18}F	110	0.64	$\beta+$ (97%) EC ^a (3%)	6.3×10^4
^{11}C	20.3	0.97	$\beta+$ (99%)	3.4×10^5
^{13}N	10	1.20	$\beta+$ (100%)	7.0×10^5
^{15}O	2	1.74	$\beta+$ (100%)	3.4×10^6
^{76}Br	972	4.0	$\beta+$ (57%) EC (43%)	7.2×10^3
^{124}I	60 192	2.14	$\beta+$ (25%) EC (75%)	1.15×10^3
^{68}Ga	68.1	1.90	$\beta+$ (89%) EC (11%)	1.02×10^5
^{64}Cu	762	0.655	$\beta+$ (19%) EC (41%) $\beta+$ (40%)	9.13×10^3

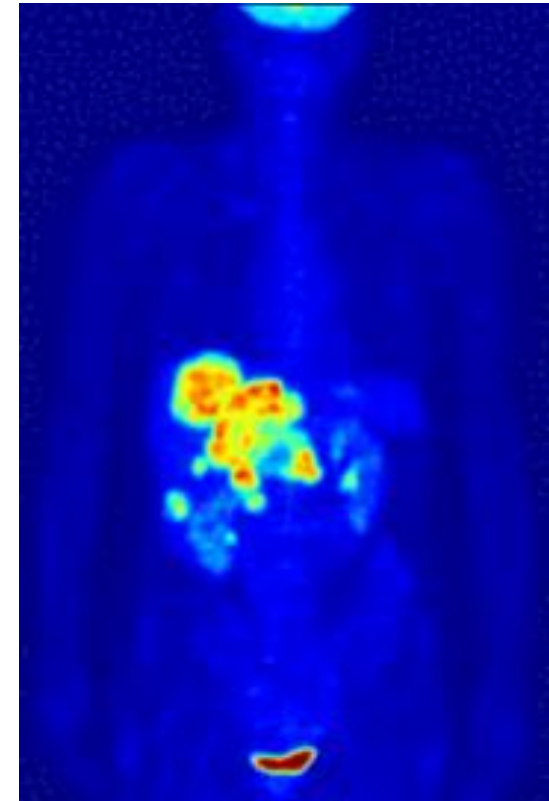
^a EC: electron capture.



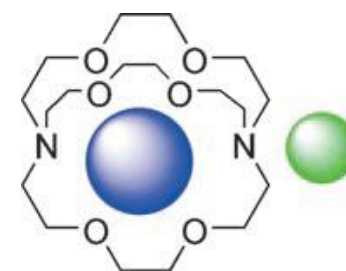
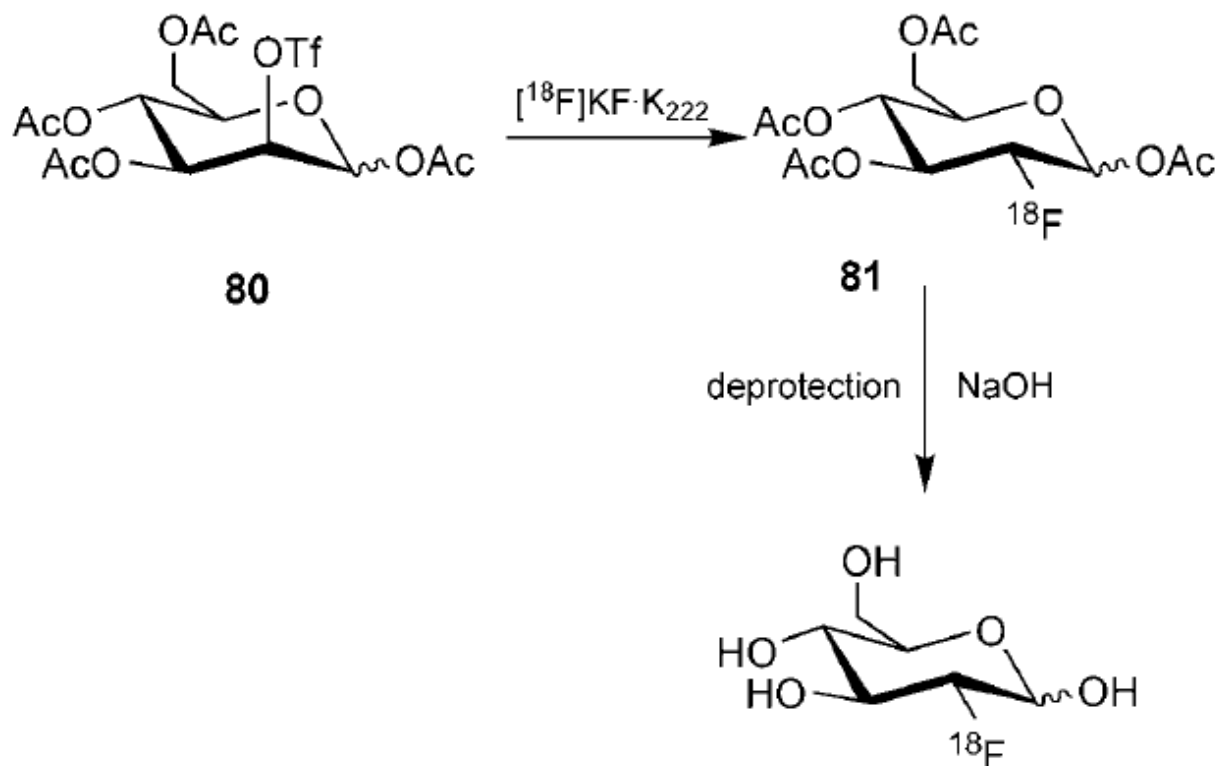
Fluorodeoxyglucose ($[^{18}\text{F}]$ FDG)

Bio-isosteric replacement

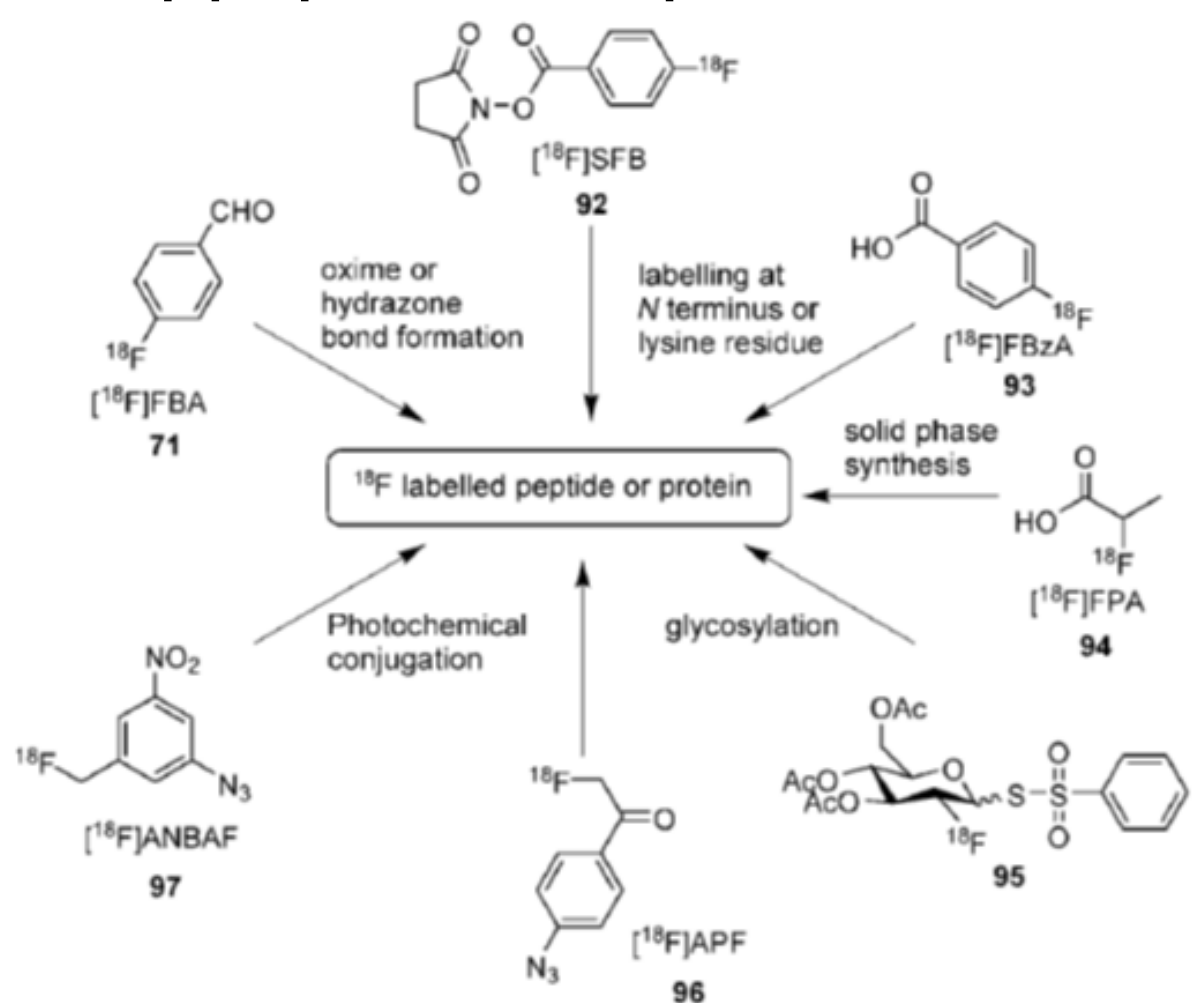
assessment of glucose metabolism



Esempio di fluorurazione nucleofila

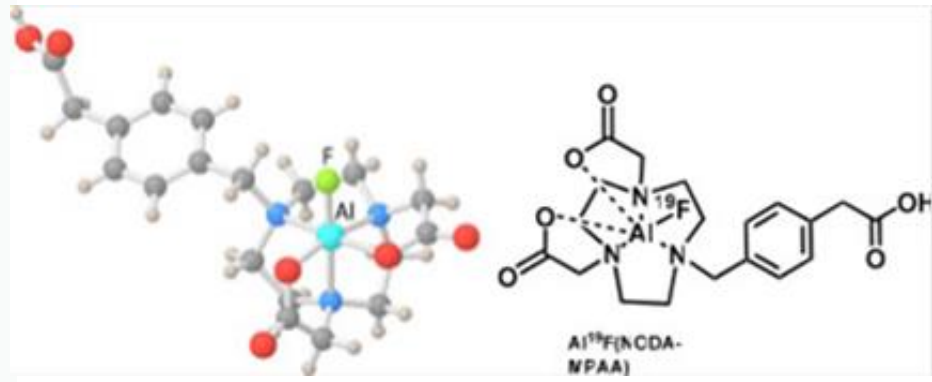
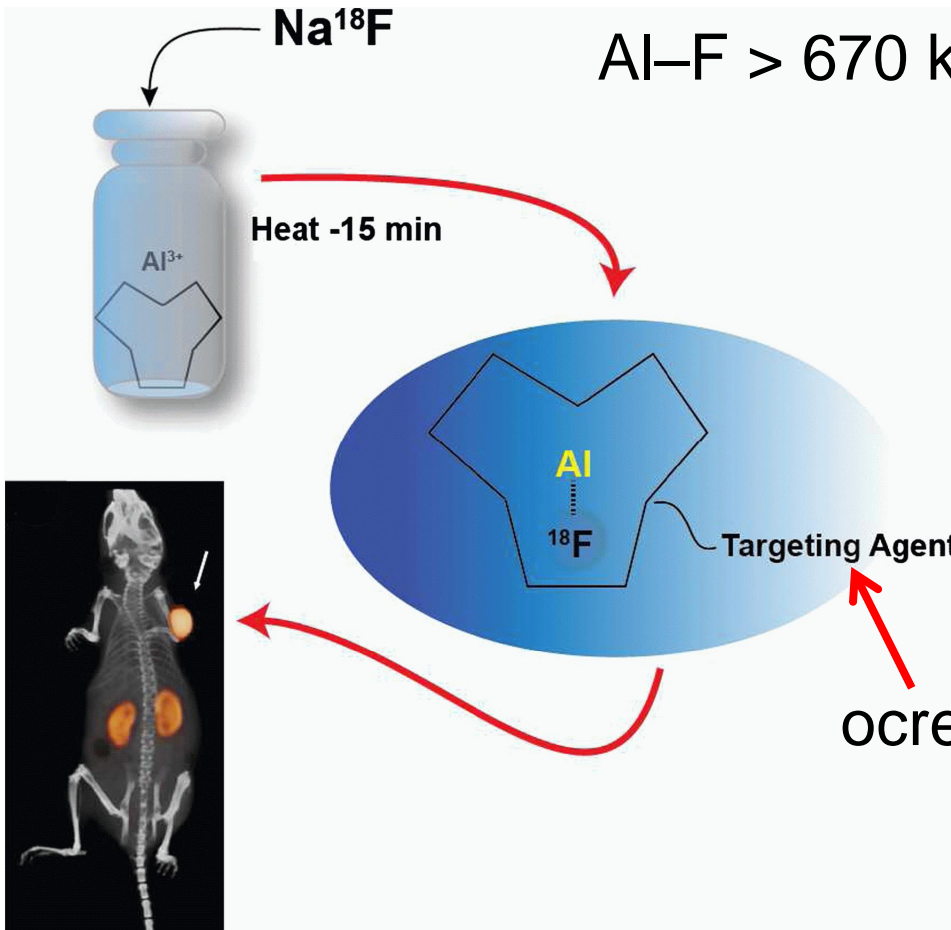


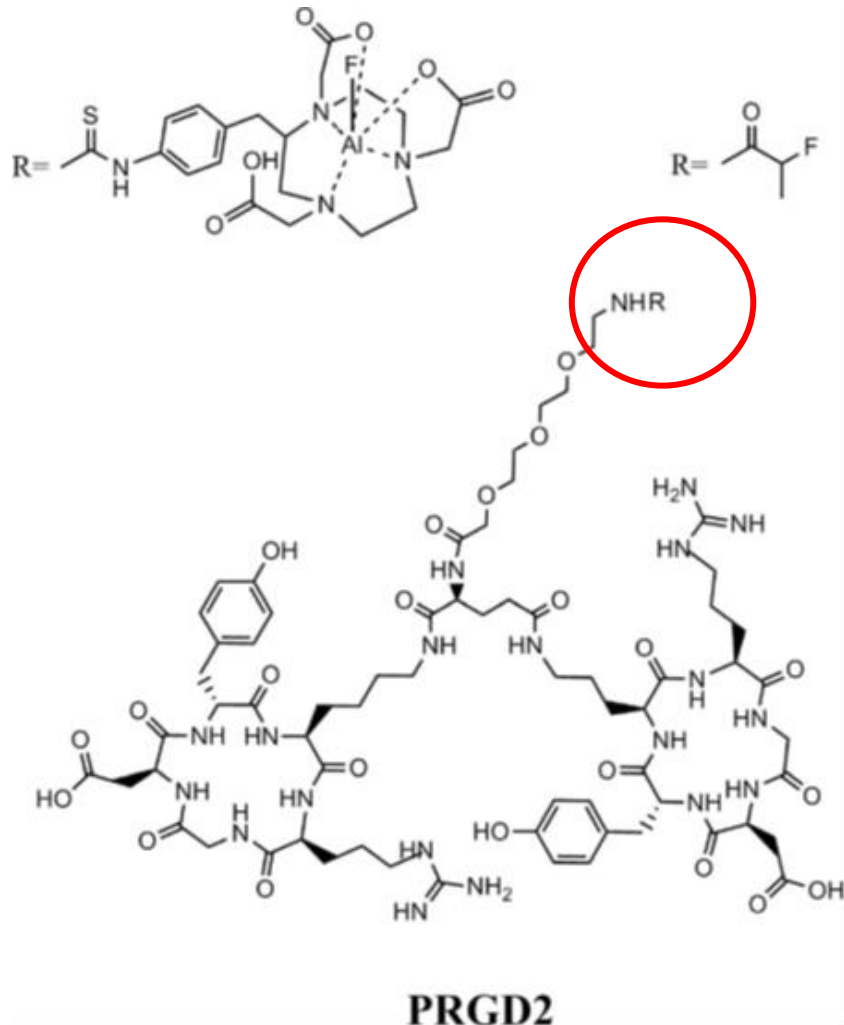
Gruppi prostetici per ^{19}F PET



Fluorurazione inorganica

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





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

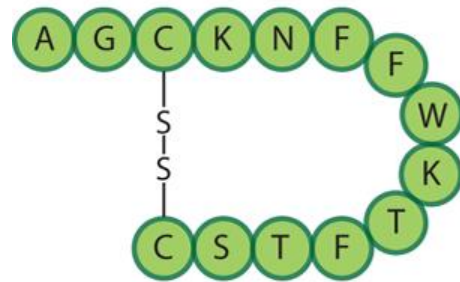
studio clinico nell'uomo per l'*imaging* di un tumore al polmone

Radionuclidi metallici per PET

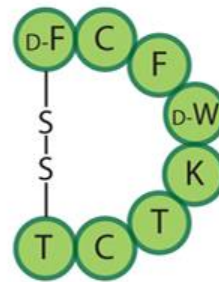
Table 1. Physical Properties of Some Common PET Radiometals^a

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

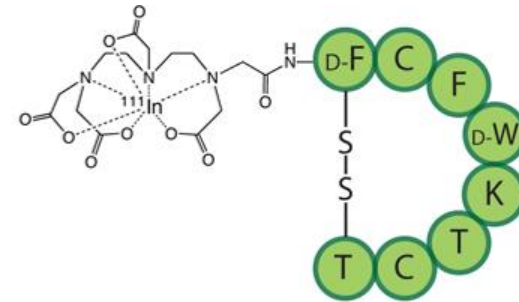
I tumori neuroendocrini sovra-esprimono i recettori per la somatostatina



Somatostatin



Octreotide

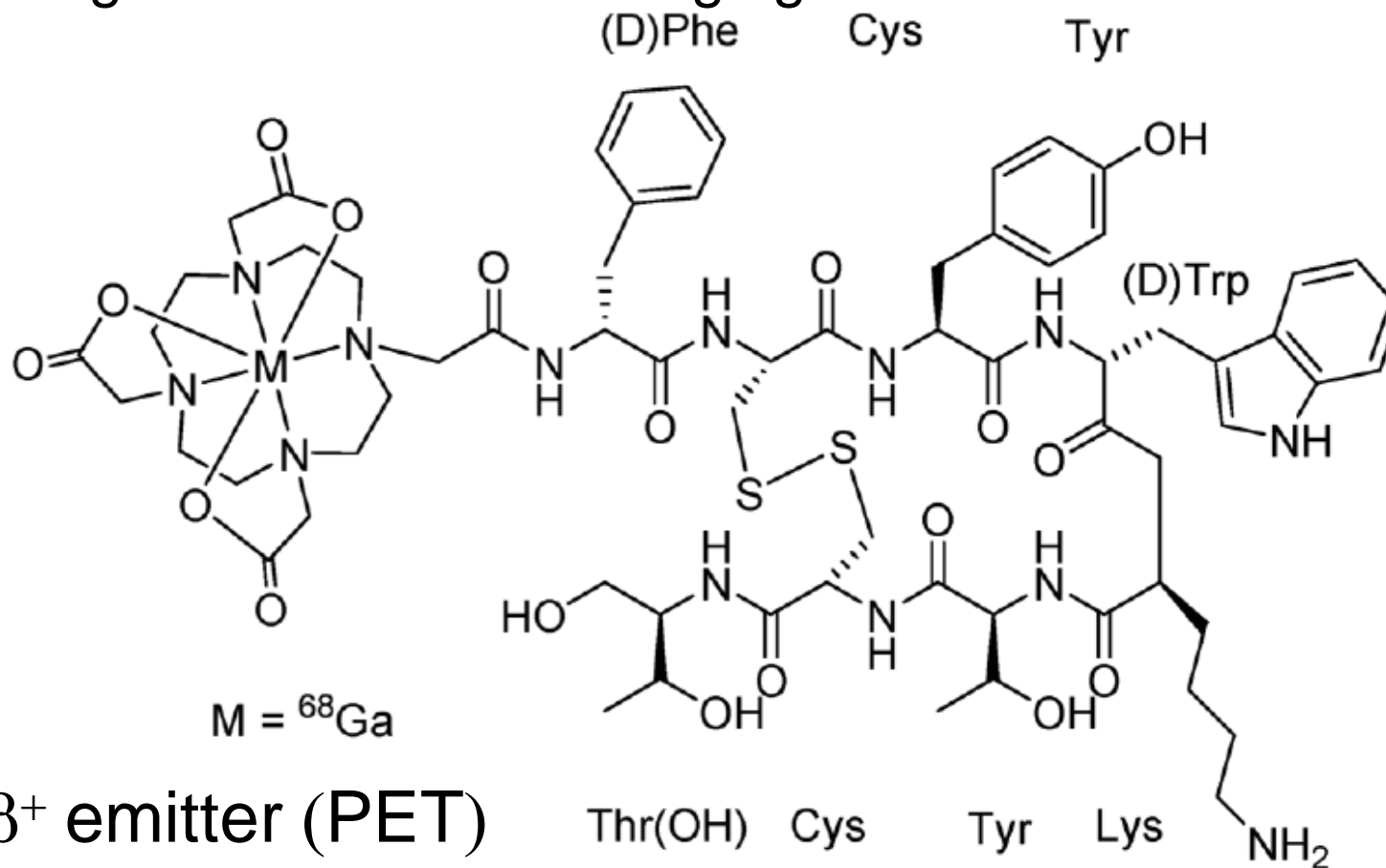


¹¹¹In-DTPA-Octreotide

SPECT imaging
of neuroendocrine
tumors

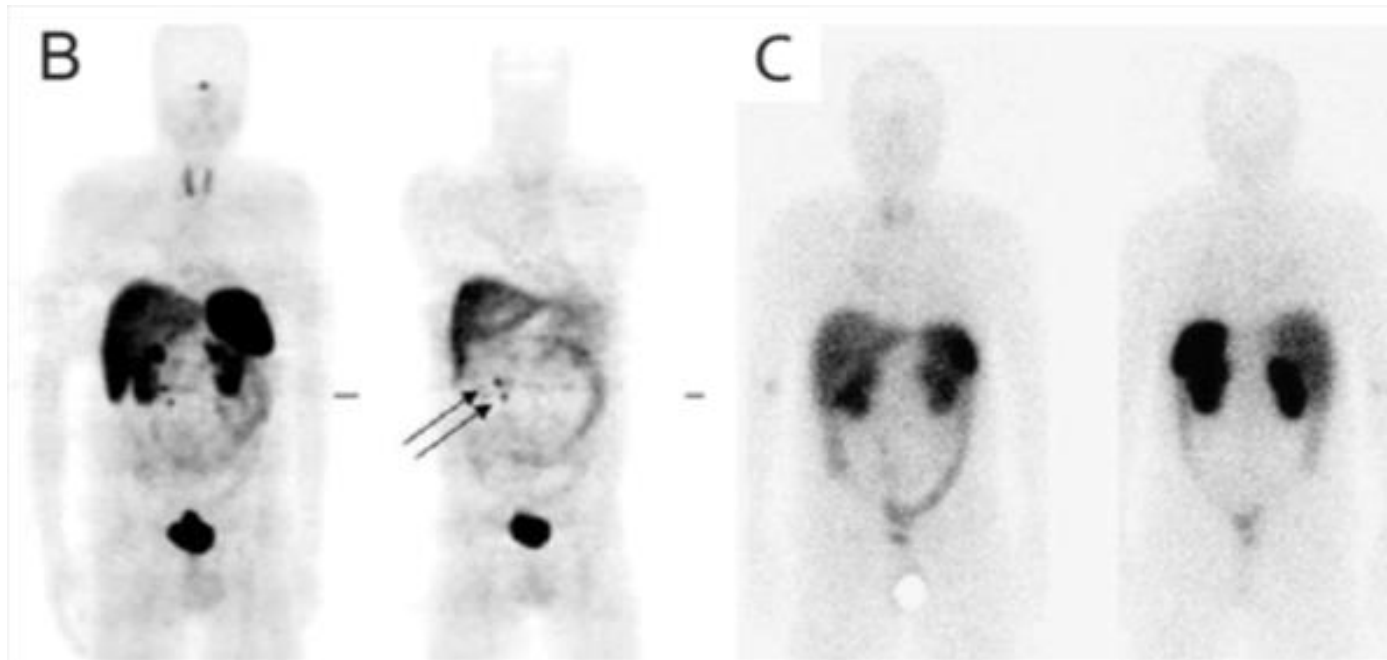
^{68}Ga -DOTA-tyr3-Octreotide (^{68}Ga -DOTATOC)

High resolution PET imaging of neuroendocrine tumors



β^+ emitter (PET)

imaging di un tumore endocrino



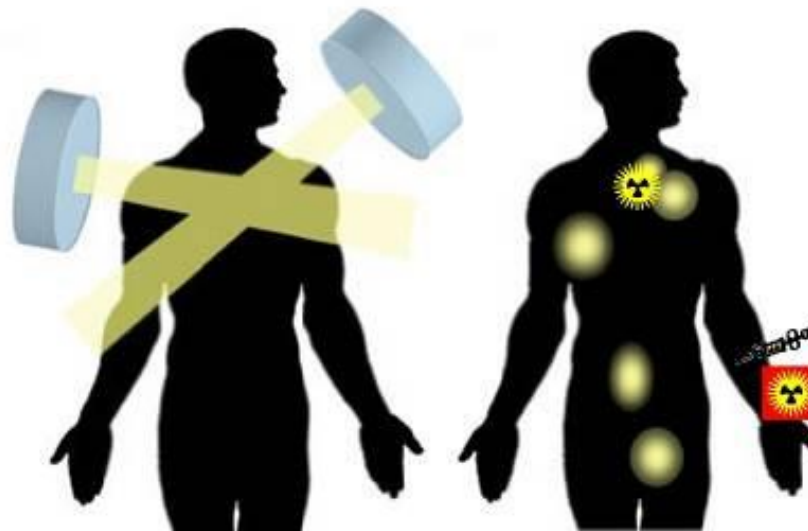
^{68}Ga -DOTATOC
(PET)

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

Targeted Radiotherapy (*Radio(immuno)therapy*)

External Beam

Targeted Radionuclide



*systemic
treatment*

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

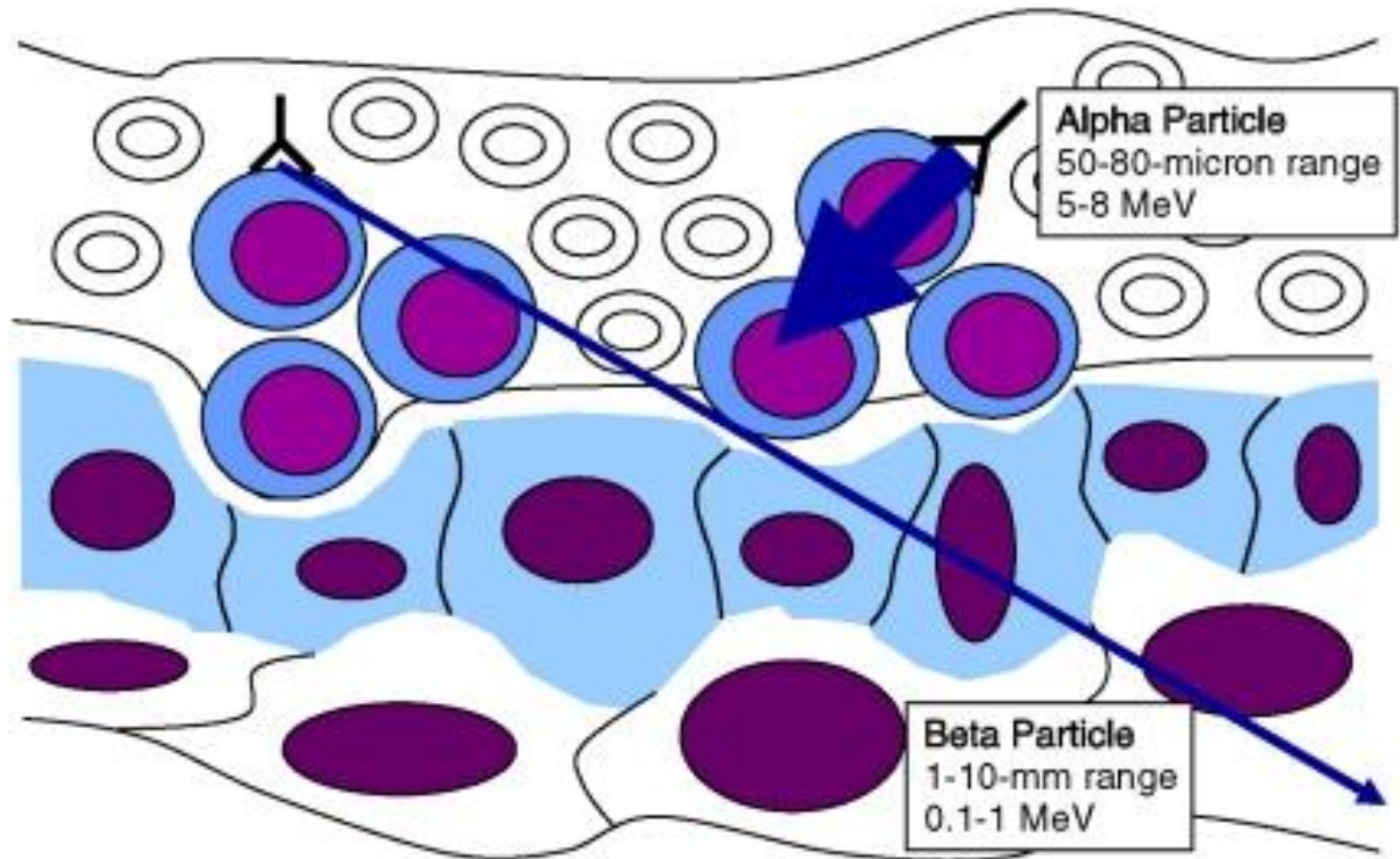
- $TI > 10$ per reni e polmoni
- $TI > 50$ per midollo spinale

Requires knowledge
of tumor location

Requires knowledge
of tumor biology

TI = therapeutic index

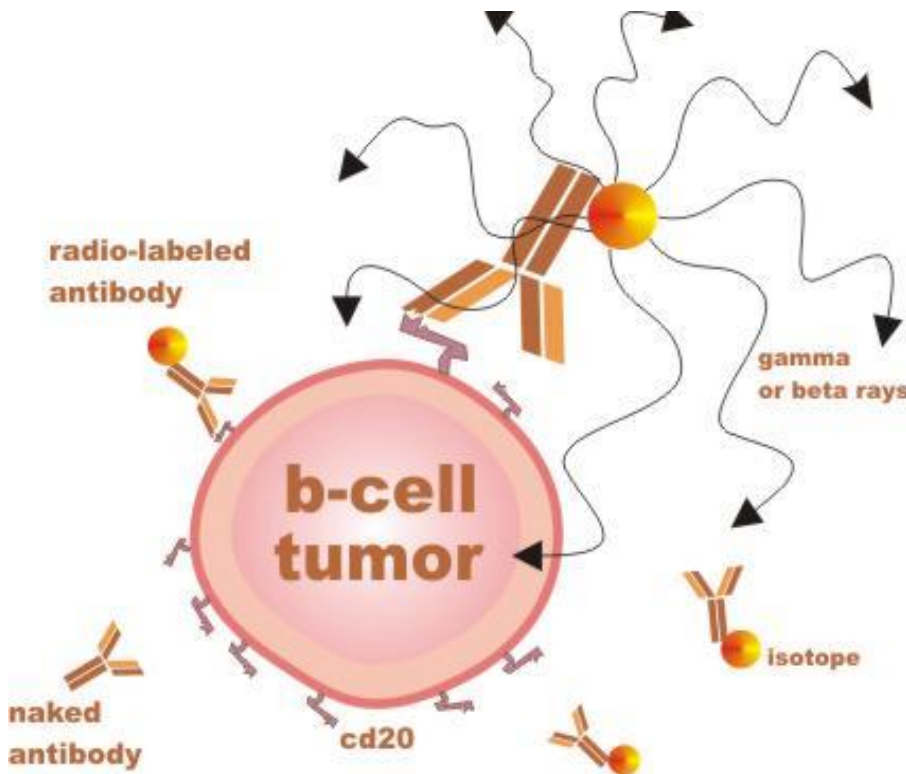
Penetrating power of α and β particles



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



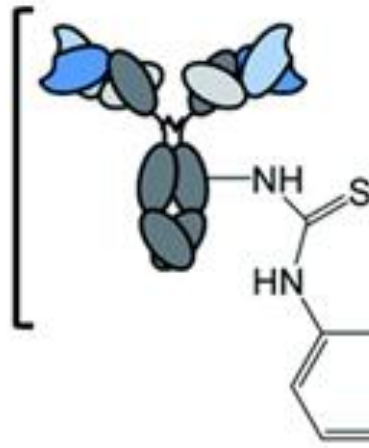
Antigene ideale:

- 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

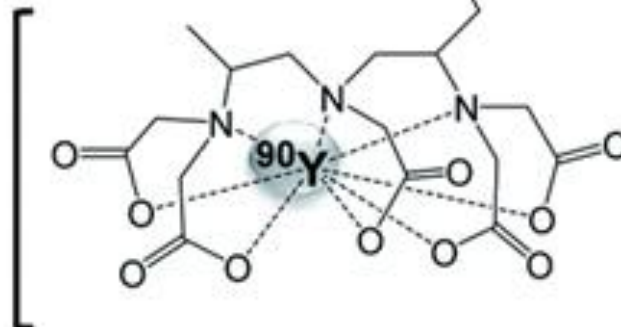
FDA approved

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

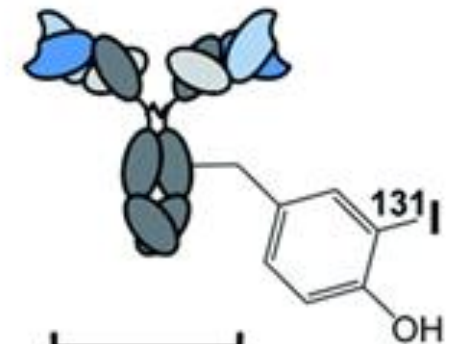
Anti-CD20
monoclonal
antibody



DTPA
chelating
moiety



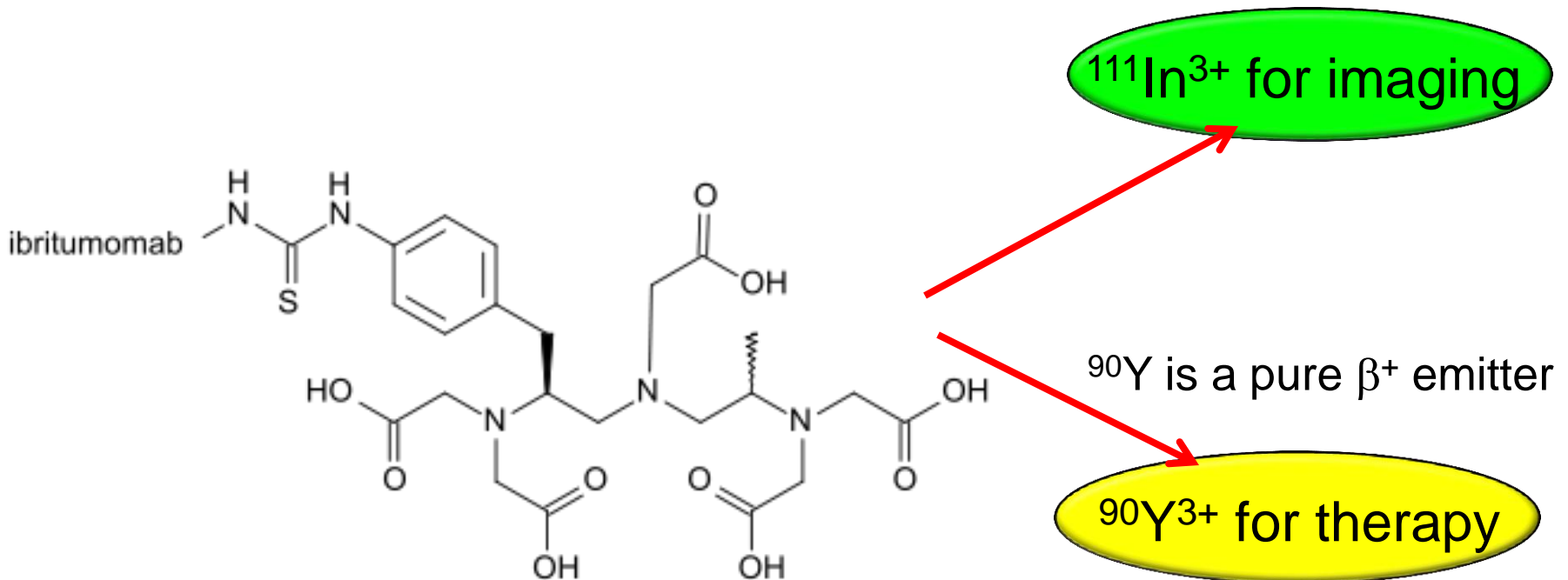
(b) ^{131}I -tositumomab
(Bexxar[®])



Anti-CD20
monoclonal
antibody

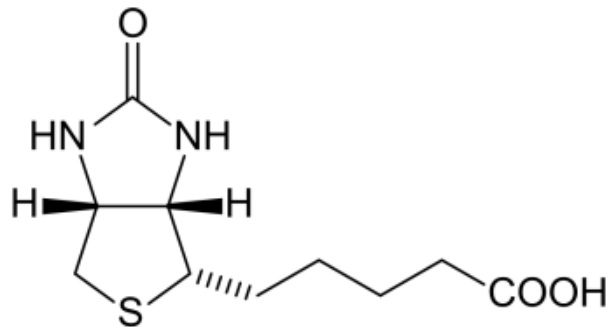
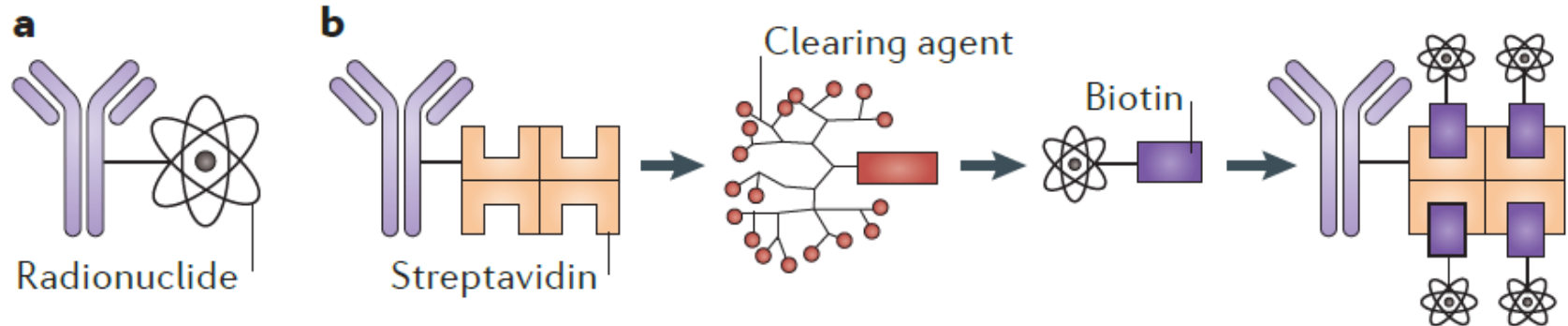
Zevalin[®]

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



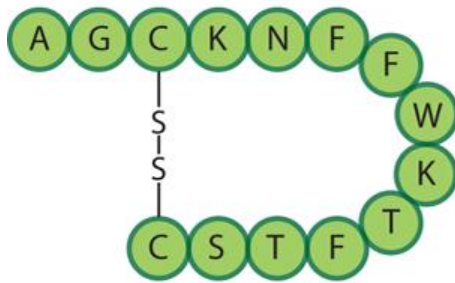
Example of the **matched-pair approach**

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

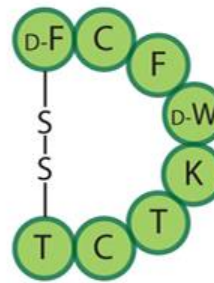


Biotina
la costante di binding
streptavidina-biotina è
dell'ordine di 10^{14} mol L⁻¹

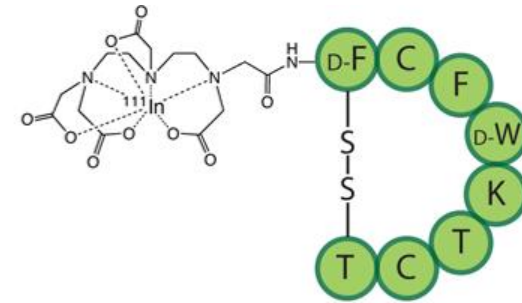
Radio-immunotherapy of neuroendocrine tumors



Somatostatin



Octreotide



¹¹¹In-DTPA-Octreotide

SPECT imaging
of neuroendocrine
tumors

⁶⁸Ga-DOTATOC for PET imaging

⁹⁰Y-DOTATOC and ¹⁷⁷Lu-DOTATATE for radiotherapy

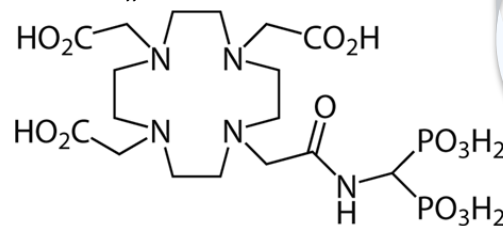
Radiometal-based *theranostics*: the *matched-pair* strategy

^{68}Ge
 ϵ
270.8 d

^{68}Ga
 β^+ 1.9
67.7 m

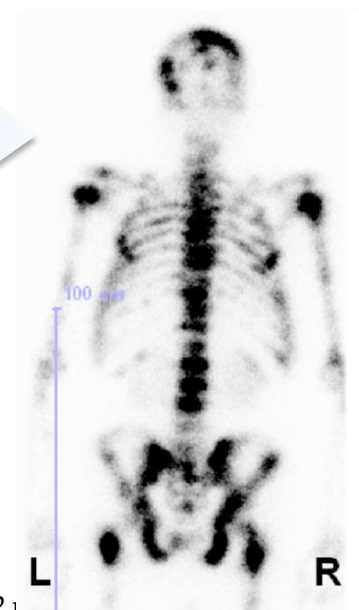
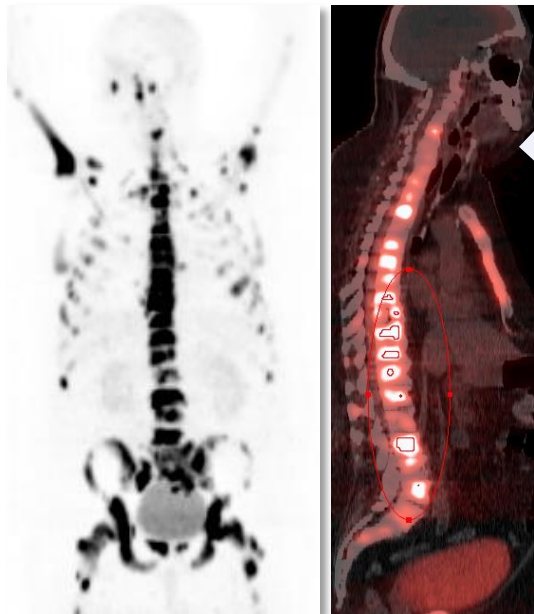
^{176}Lu	^{177}Lu
2.6 a	160 d 6.71
^{176}Yb	^{177}Yb
12.7 % 3 b	1.9 h

DOTA-bisphosphantae amide
„BPAMD“



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

^{177}Lu -BPAMD
Therapy



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

