Medicinal Inorganic Chemistry

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. ^{99m}*Tc)*

Metallomics
Transport and signalling pathways
Genomic codes for elements

Protein/enzyme regulators
e.g metalloproteinases, angiotensin-converting enzyme
O_2*, 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

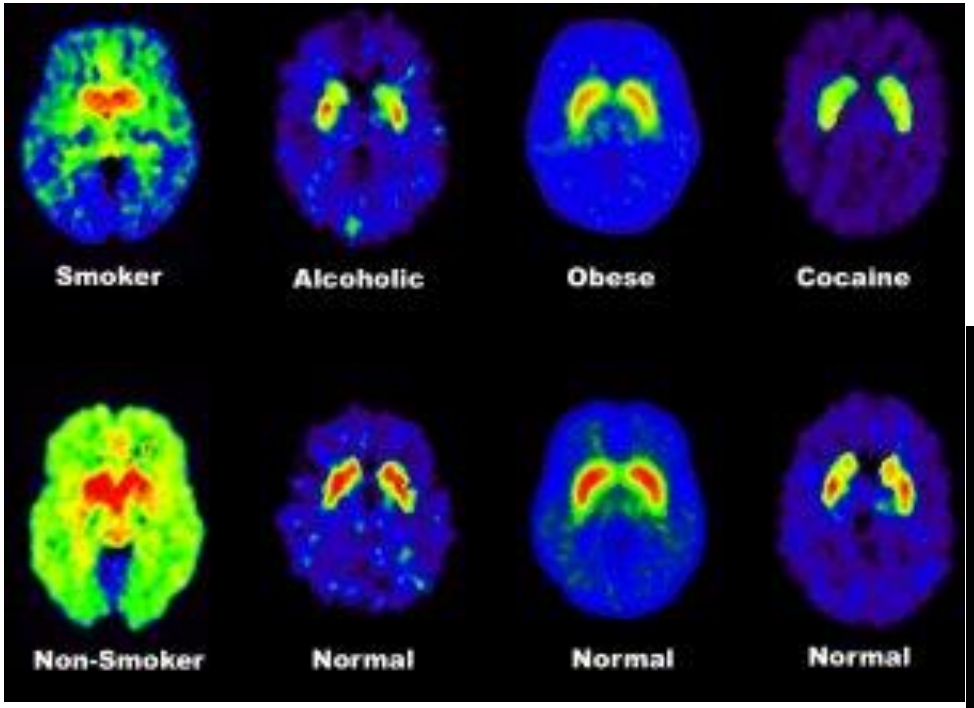
(*molecular imaging*)

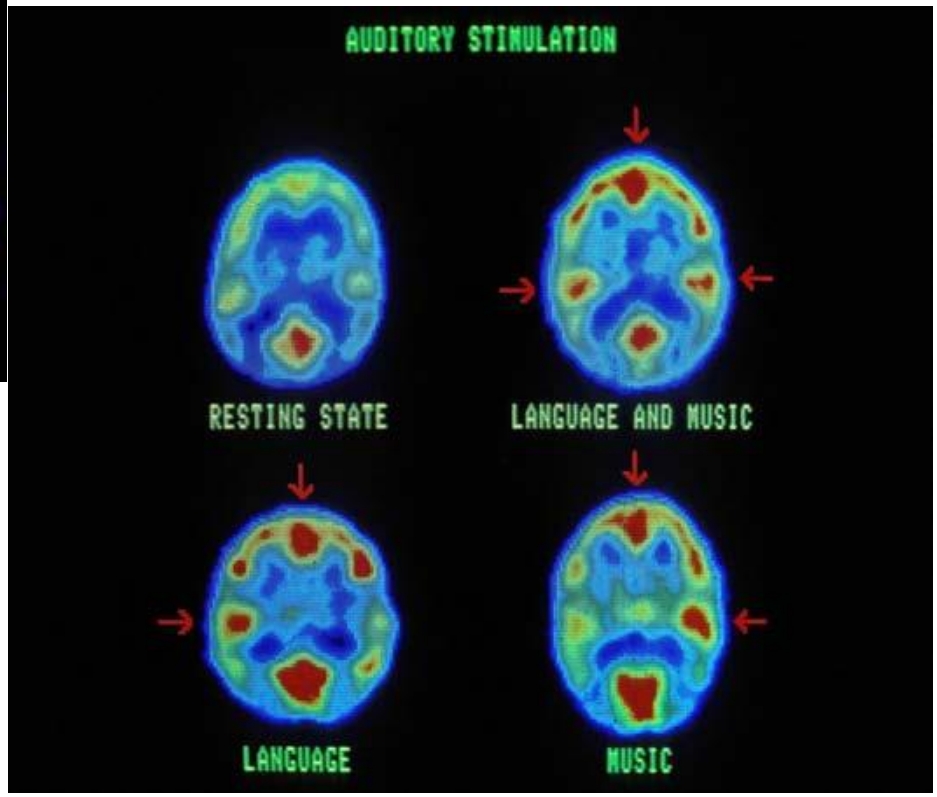
Whole-body level

(*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

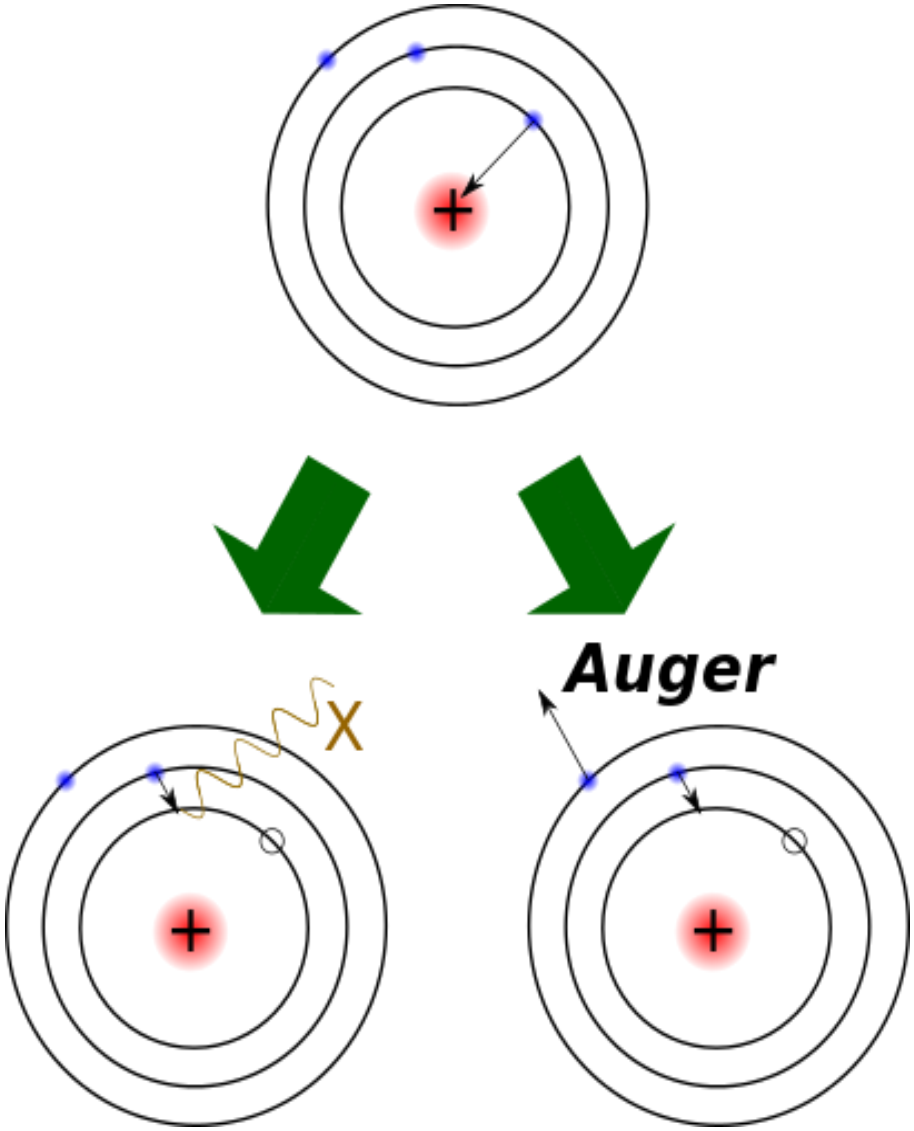




Processi <u>spontanei</u> nei nuclei radioattivi

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

Electron capture (EC)



Radiopharmaceuticals

Radiodiagnostics

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

Radiotherapeutics

α or β^- emitters

- PET
- SPECT
- Beta Therapy
- Alpha Therapy
- Auger e⁻ Therapy

1 H Hydrogen 1.008																	2 He Helium 4.0026
3 Li Lithium 6.94	4 Be Beryllium 9.0122											5 B Boron 10.81	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180
11 Na Sodium 22.990	12 Mg Magnesium 24.305											13 Al Aluminium 26.982	14 Si Silicon 28.085	15 P Phosphorus 30.974	16 S Sulfur 32.06	17 Cl Chlorine 35.45	18 Ar Argon 39.948
19 K Potassium 39.098	20 Ca Calcium 40.078(4)	21 Sc Scandium 44.956	22 Ti Titanium 47.867	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.845(2)	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546(3)	30 Zn Zinc 65.38(2)	31 Ga Gallium 69.723	32 Ge Germanium 72.630(8)	33 As Arsenic 74.922	34 Se Selenium 78.971(8)	35 Br Bromine 79.904	36 Kr Krypton 83.798(2)
37 Rb Rubidium 85.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224(2)	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium	44 Ru Ruthenium 101.07(2)	45 Rh Rhodium 102.91	46 Pd Palladium 106.42	47 Ag Silver 107.87	48 Cd Cadmium 112.41	49 In Indium 114.82	50 Sn Tin 118.71	51 Sb Antimony 121.76	52 Te Tellurium 127.60(3)	53 I Iodine 126.90	54 Xe Xenon 131.29
55 Cs Caesium 132.91	56 Ba Barium 137.33	57-71 *	72 Hf Hafnium 178.49(2)	73 Ta Tantalum 180.95	74 W Tungsten 183.84	75 Re Rhenium 186.21	76 Os Osmium 190.23(3)	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.97	80 Hg Mercury 200.59	81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 208.98	84 Po Polonium	85 At Astatine	86 Rn Radon
87 Fr Francium	88 Ra Radium	89-103 **	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Cn Copernicium	113 Nh Nihonium	114 Fl Flerovium	115 Mc Moscovium	116 Lv Livermorium	117 Ts Tennessine	118 Og Oganesson

*Lanthanoids	57 La Lanthanum 138.91	58 Ce Cerium 140.12	59 Pr Praseodymium 140.91	60 Nd Neodymium 144.24	61 Pm Promethium	62 Sm Samarium 150.36(2)	63 Eu Europium 151.96	64 Gd Gadolinium 157.25(3)	65 Tb Terbium 158.93	66 Dy Dysprosium 162.50	67 Ho Holmium 164.93	68 Er Erbium 167.26	69 Tm Thulium 168.93	70 Yb Ytterbium 173.05	71 Lu Lutetium 174.97
**Actinoids	89 Ac Actinium	90 Th Thorium 232.04	91 Pa Protactinium 231.04	92 U Uranium 238.03	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium

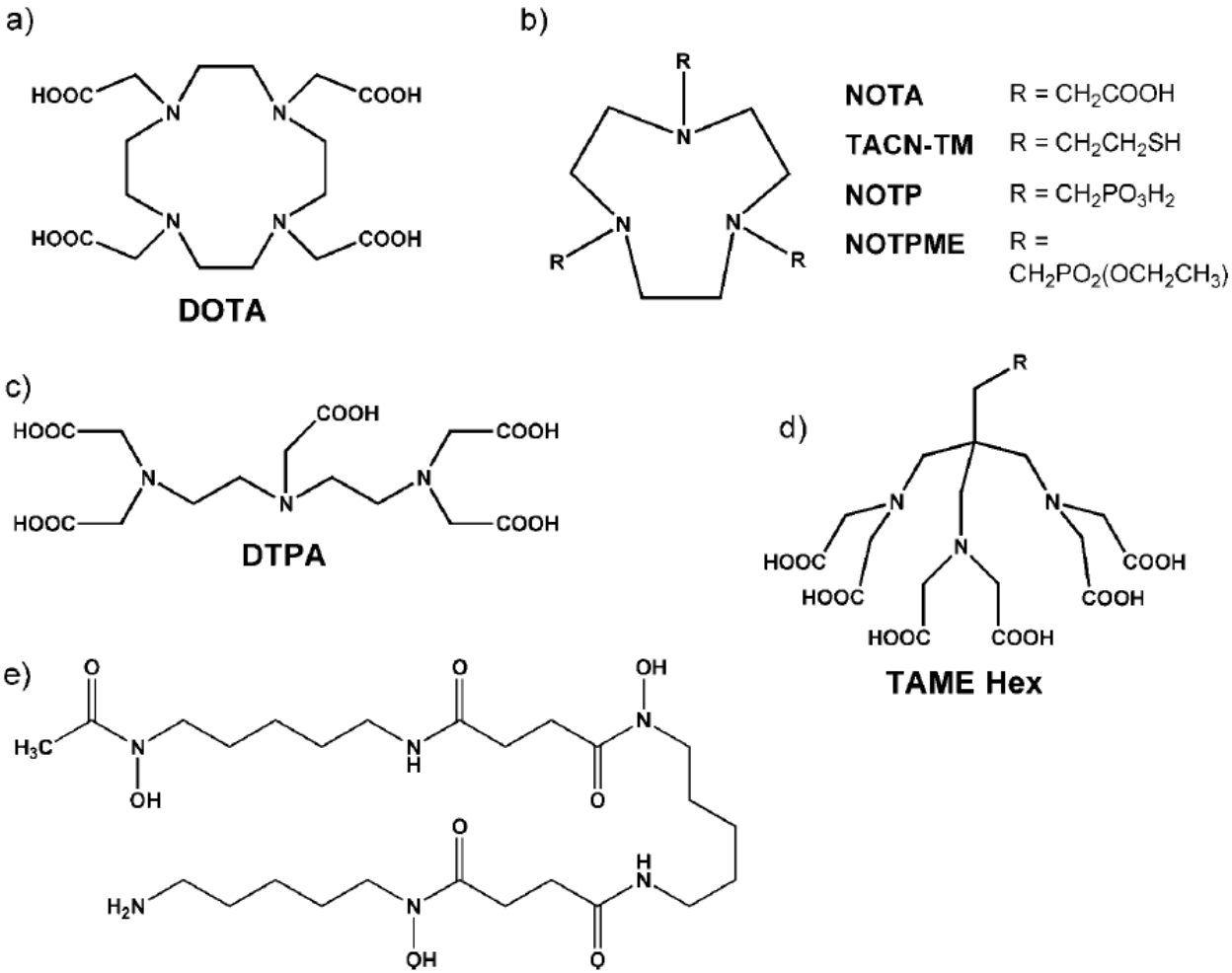
Preparazione di un radio-farmaco

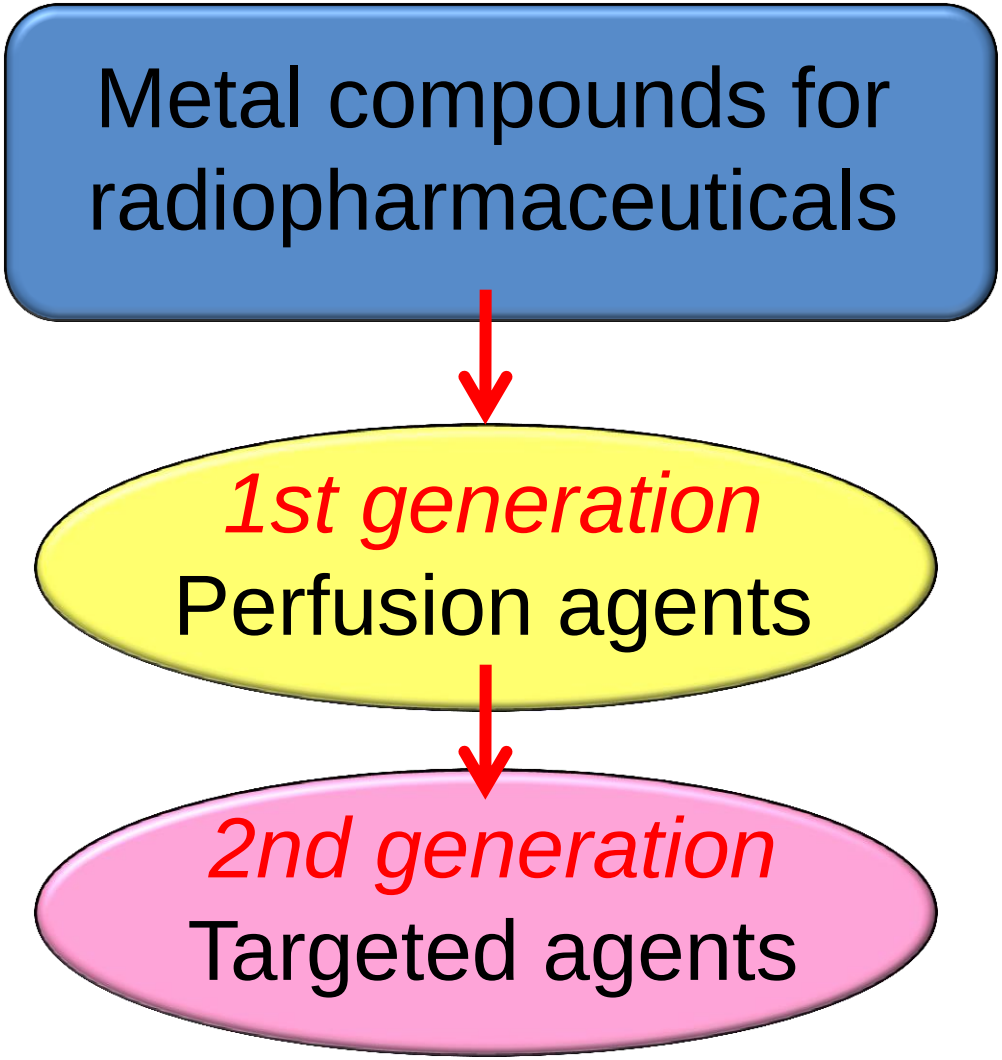
I radio-isotopi si possono ottenere:

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

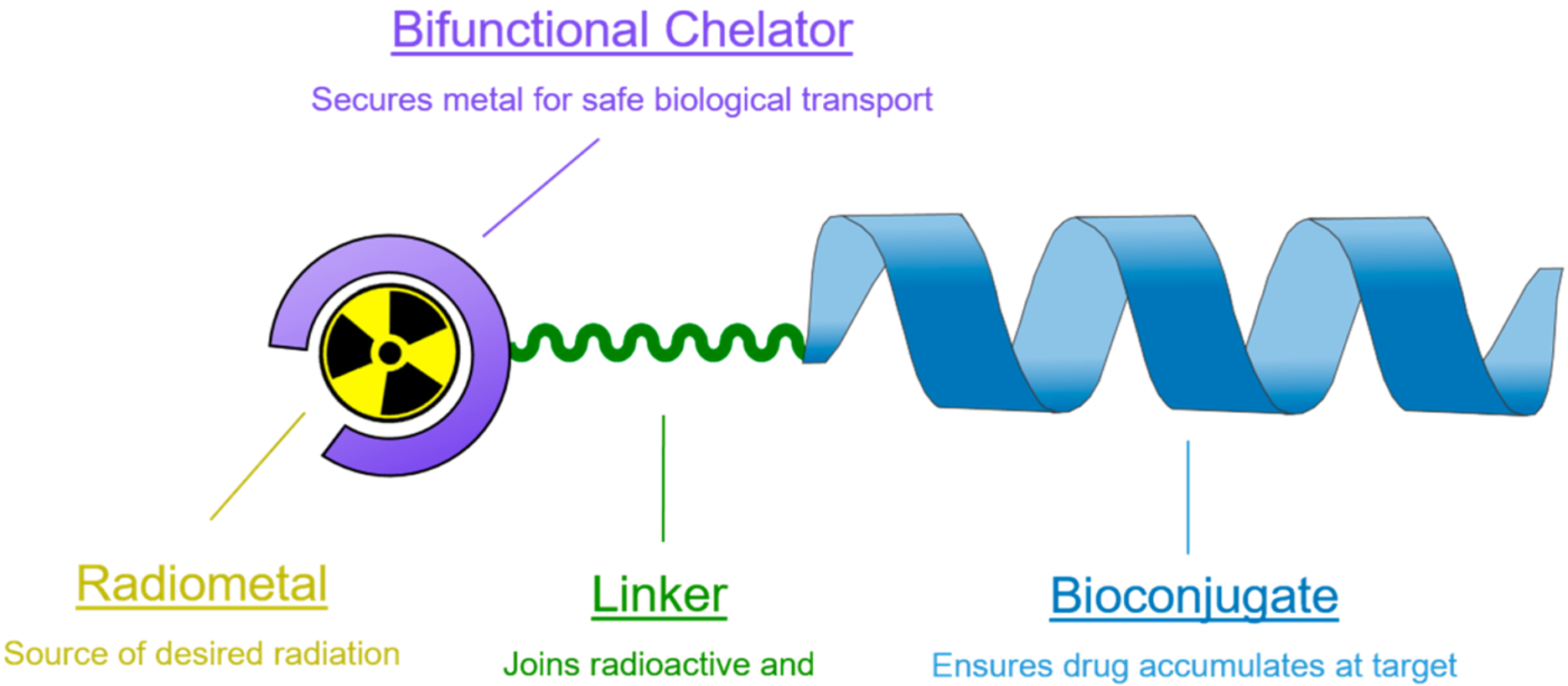
Chelanti più comuni

Diethylenetriamino-pentaaceticacid




Metal compounds for radiopharmaceuticals
1st generation
Perfusion agents
2nd generation
Targeted agents

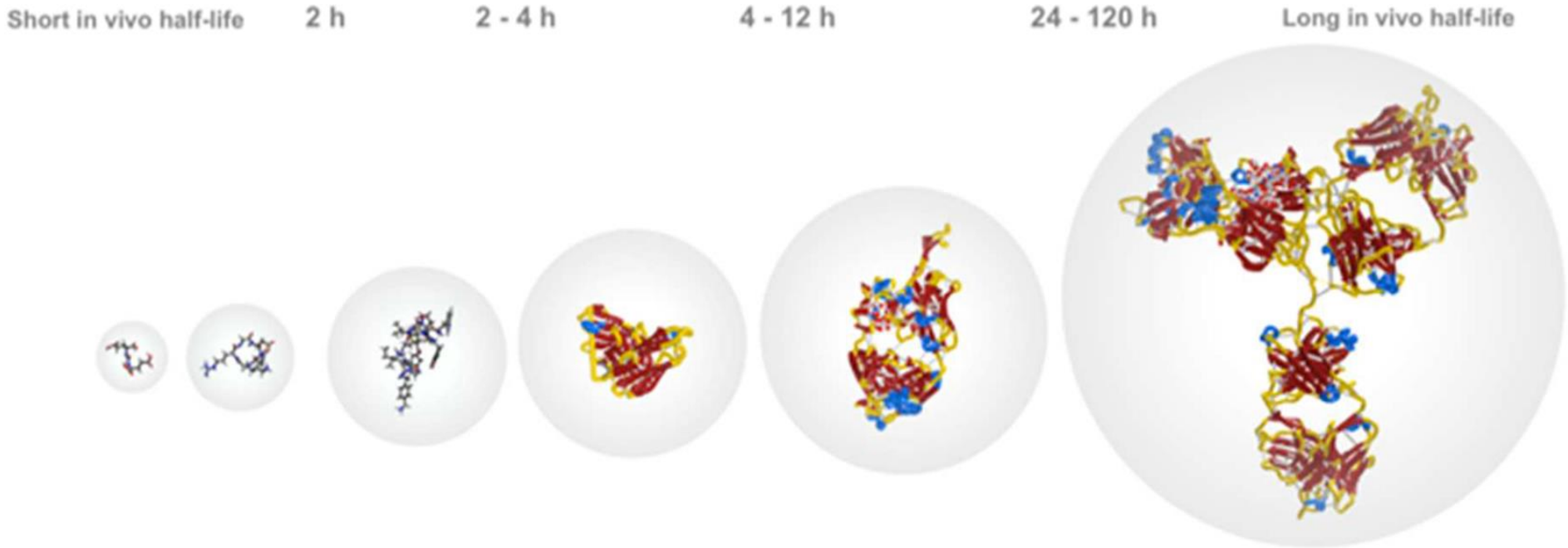
Targeted Approach
(*Trojan horse*)



(targeting vector)

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

Tempo di semi-vita e tempo di biodistribuzione



Short radionuclide half-life — Long radionuclide half-life

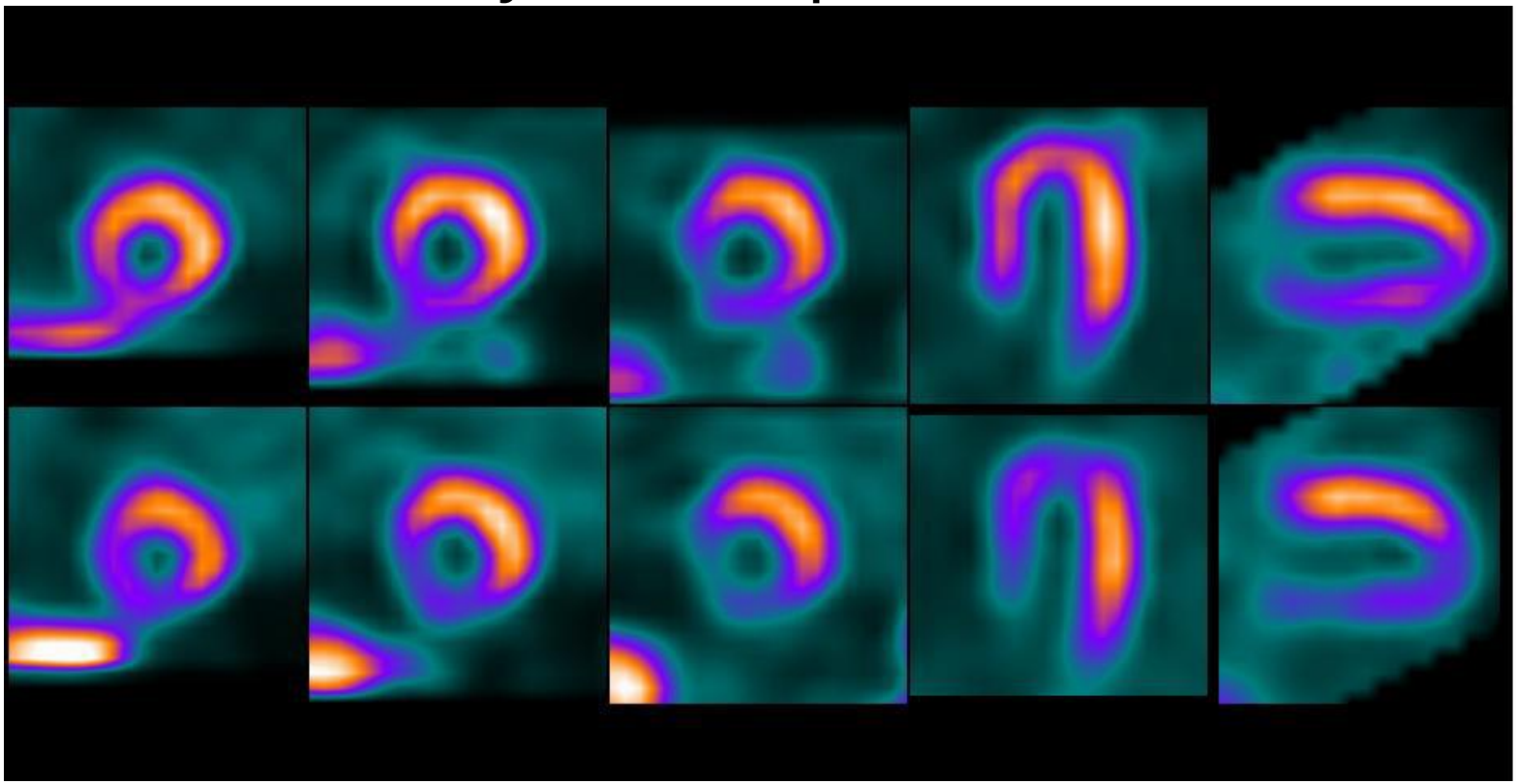
^{63}Zn $t_{1/2}$= 0.6 h	^{94m}Tc $t_{1/2}$= 0.9 h	^{45}Ti $t_{1/2}$= 3.1 h	^{99m}Tc $t_{1/2}$= 6 h	^{64}Cu $t_{1/2}$= 12.6 h	^{90}Nb $t_{1/2}$= 14.6 h	^{55}Co $t_{1/2}$= 17.5 h	^{89}Zr $t_{1/2}$= 78 h	^{52}Mn $t_{1/2}$= 134 h
					^{188}Re (359 keV) $t_{1/2}$ = 17 h	^{104}Rh (566 keV) $t_{1/2}$ = 35 h	^{67}Cu (580 keV) $t_{1/2}$ = 62 h	^{186}Re (791 keV) $t_{1/2}$ = 89 h

PET — SPECT — β^-

SPECT: Single Photon Emission Computed Tomography

γ emitters, 100 – 250 keV

Myocardial perfusion



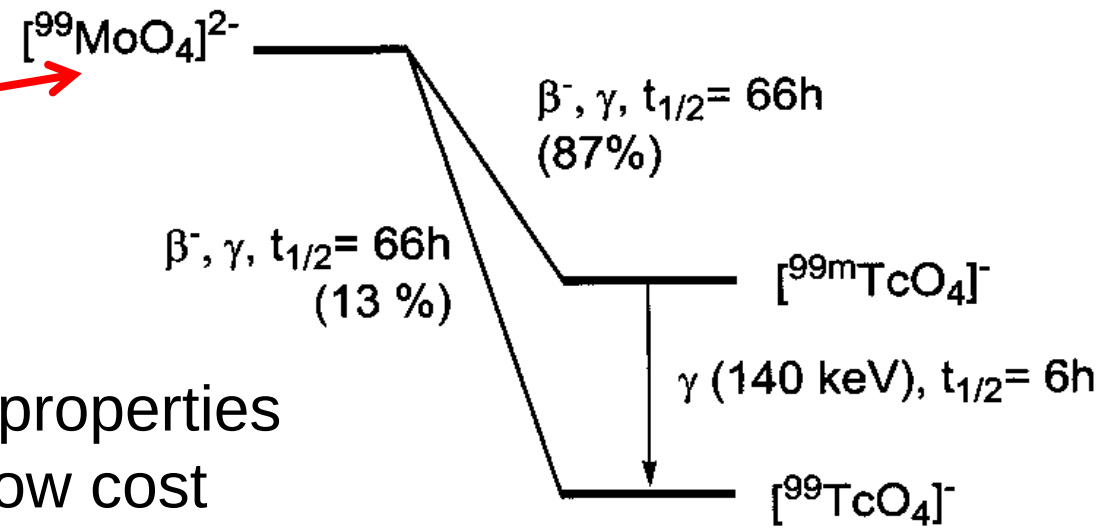
Main radionuclides for SPECT

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)

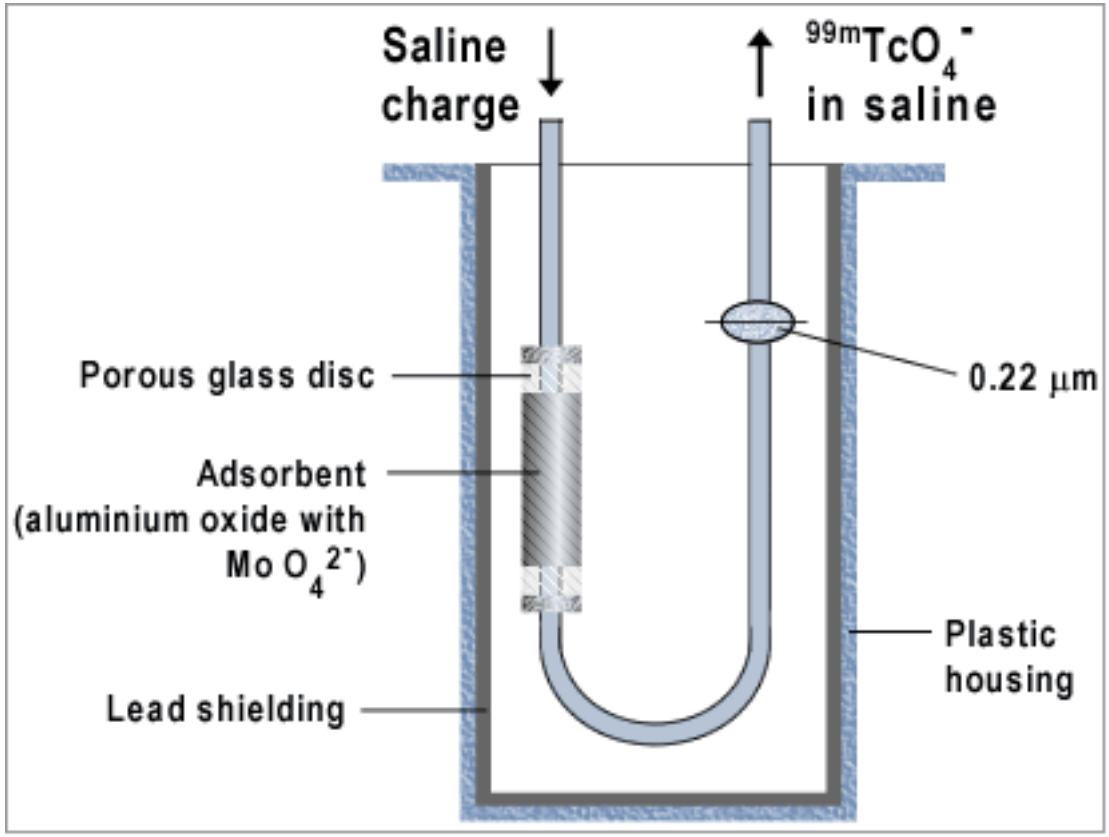
Obtained from fission of ^{235}U or from ^{98}Mo upon (n, γ) reaction



Pure β-emitter

- 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)

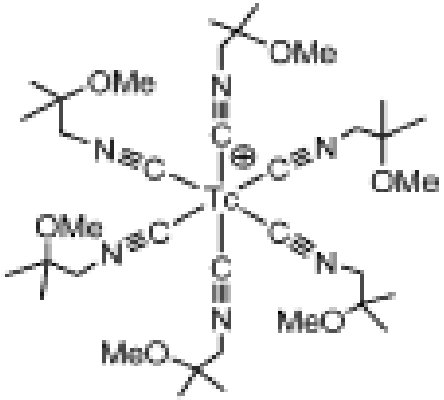
Generatore di $^{99m}TcO_4^-$



‘*Shake and bake*’ principle

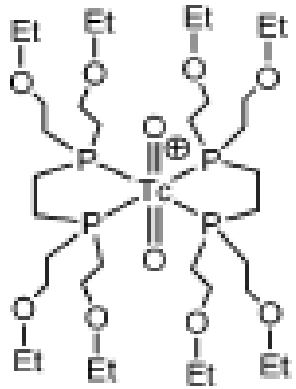
- Preparations must be performed in kits
- Yields must be > 98% (even at very low metal ion concentration)
- Compound must be ready for administration
- No lenghty purification or separation
- Aqueous solutions
- Non-toxic reagents (e.g. Sn(II) componds as reducing agents) and byproducts

Radiofarmaci di tecnezio di prima generazione



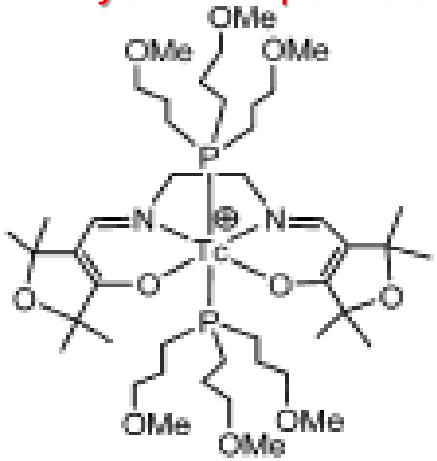
^{99m}Tc-Sestamibi

cardiac imaging



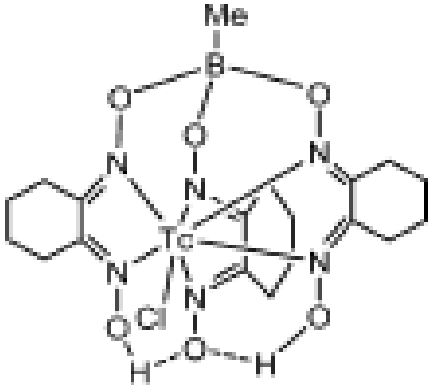
^{99m}Tc-Tetrofosmin

myocardial perfusion

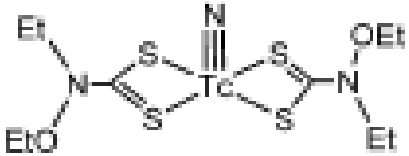


Q12

cardiac imaging

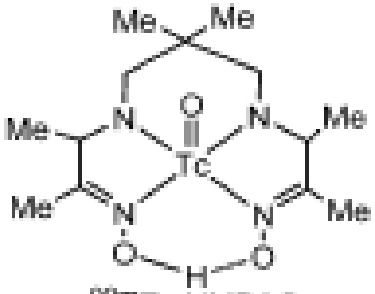


^{99m}Tc-Teboroxime



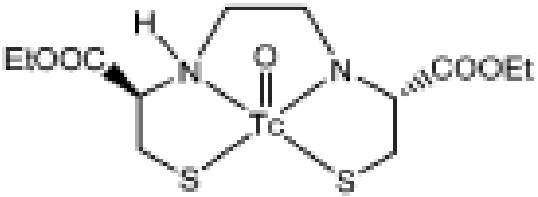
^{99m}TcN-NOET

myocardial perfusion



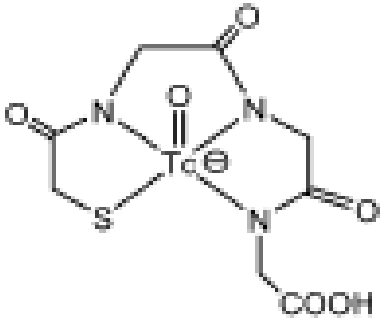
^{99m}Tc-HMPAO

cereberal perfusion



^{99m}Tc-Bicisate

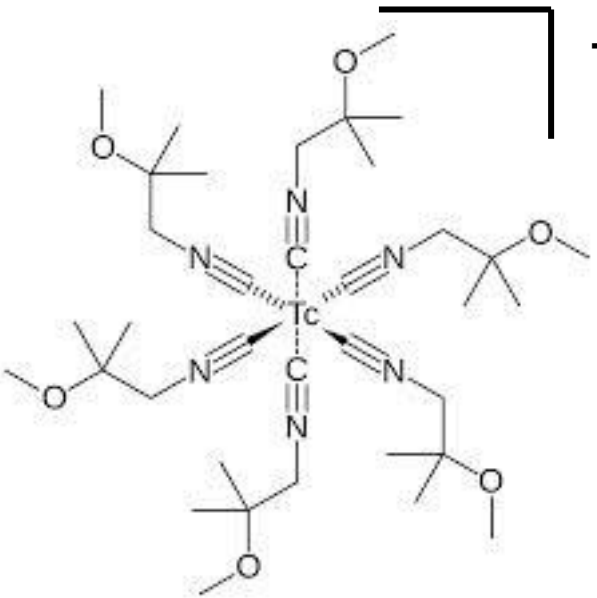
brain imaging



^{99m}Tc-MAG$_3$

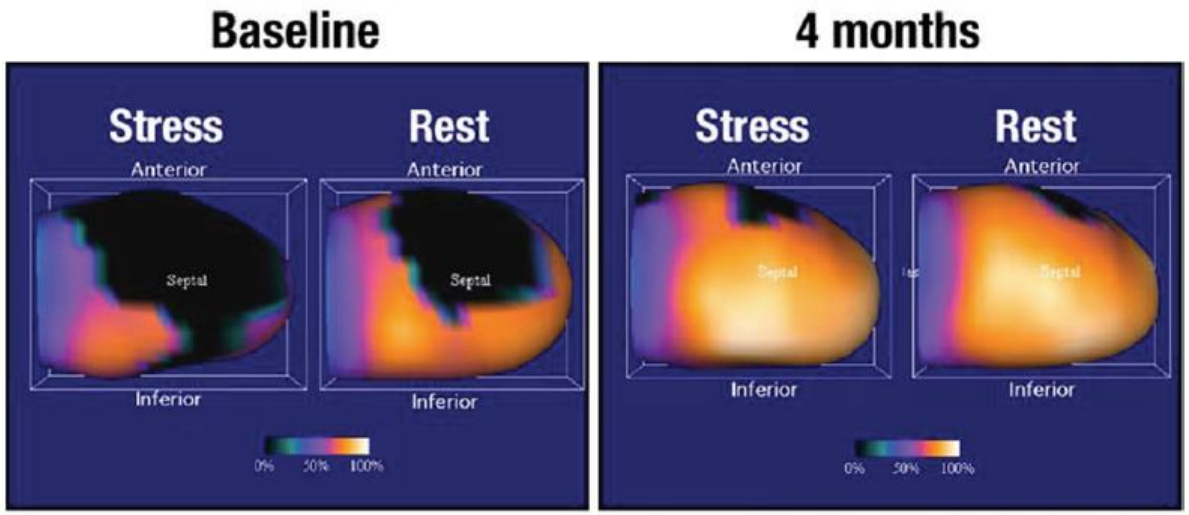
renal imaging

^{99m}Tc-sestamibi

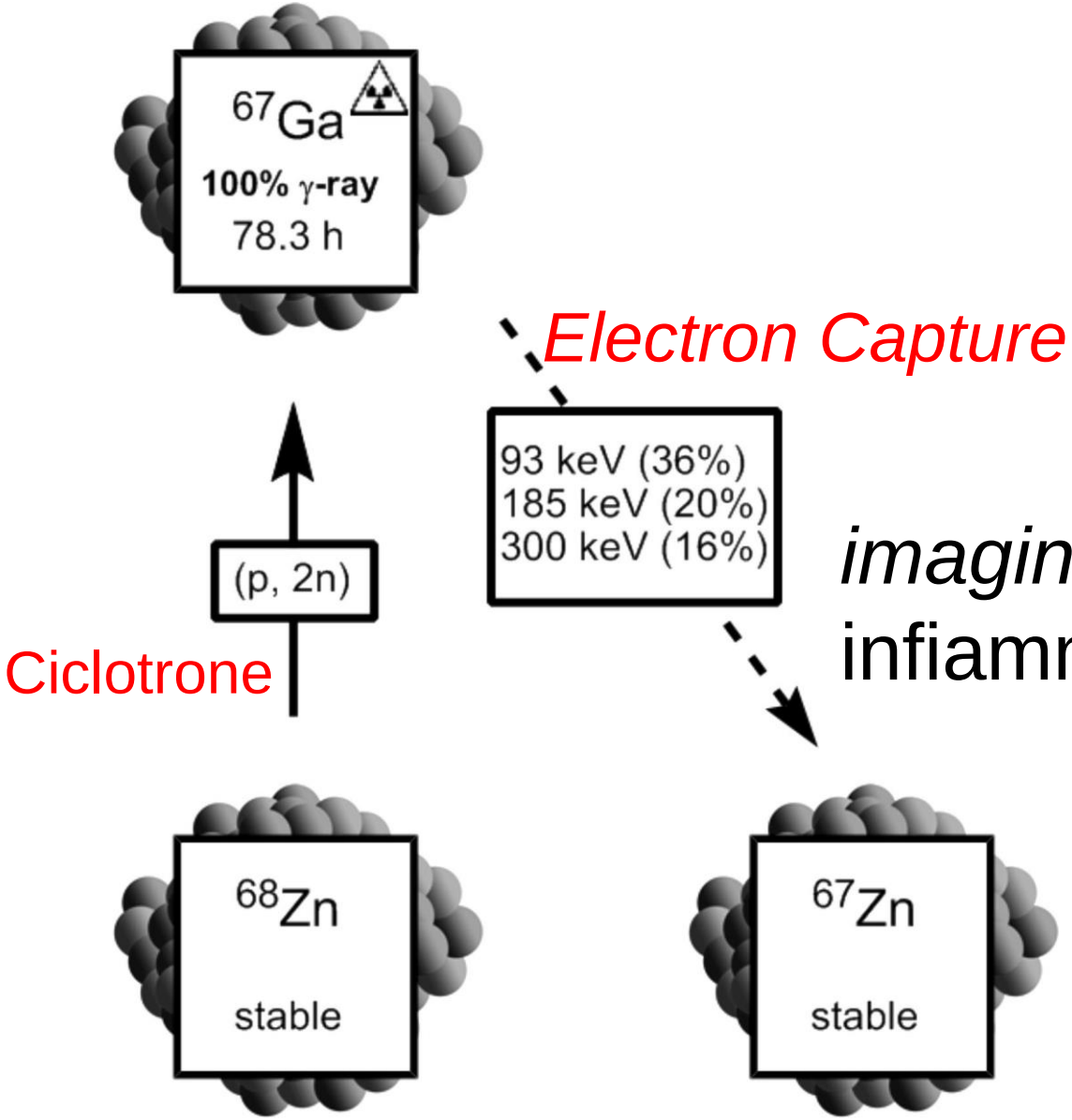


+

Localizzazione nei mitocondri

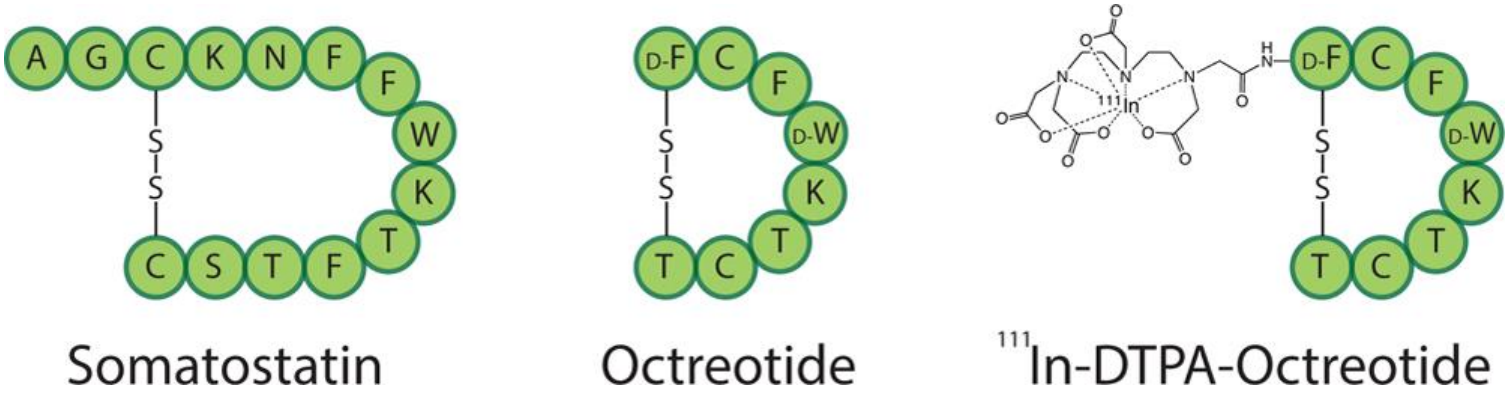


- Imaging cardiaco
- Diagnosi dei tumori (seno)
- Imaging della tiroide (adenomi)



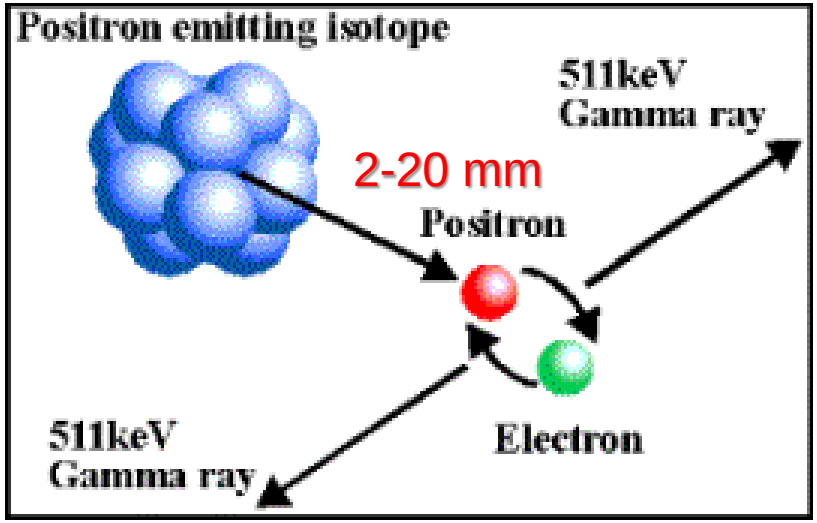
imaging di processi infiammatori e di tumori

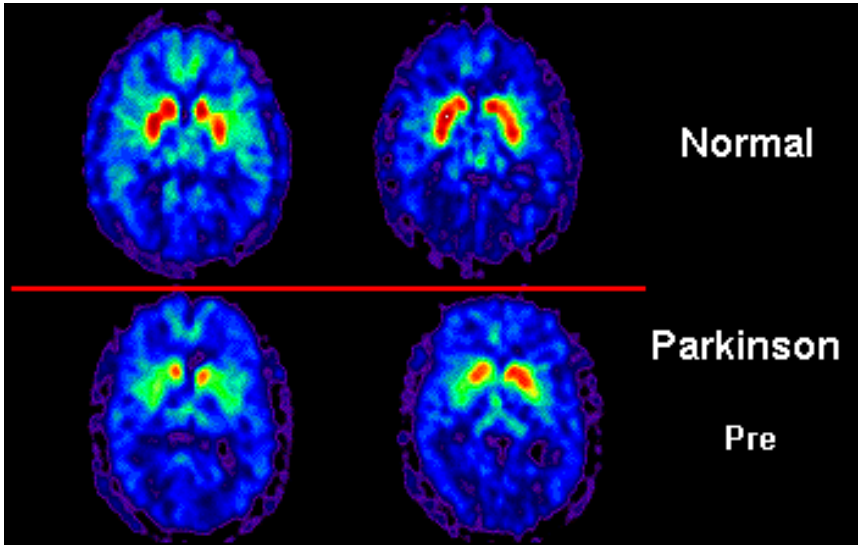
Radio-immuno-scintigrafia

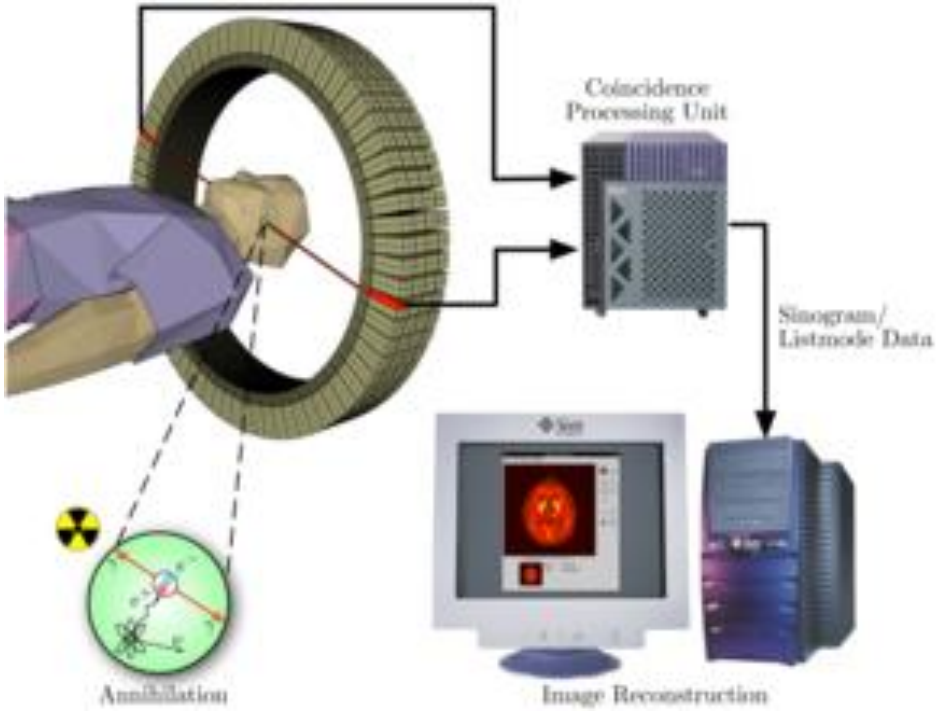


La somatostatina è un ormone polipeptidico che regola il sistema endocrino, la crescita e la proliferazione cellulare. I recettori della somatostatina sono proteine trans-membrana, sovra-espressi in molti tipi di tumori neuroendocrini. L'octreotide è simile alla somatostatina

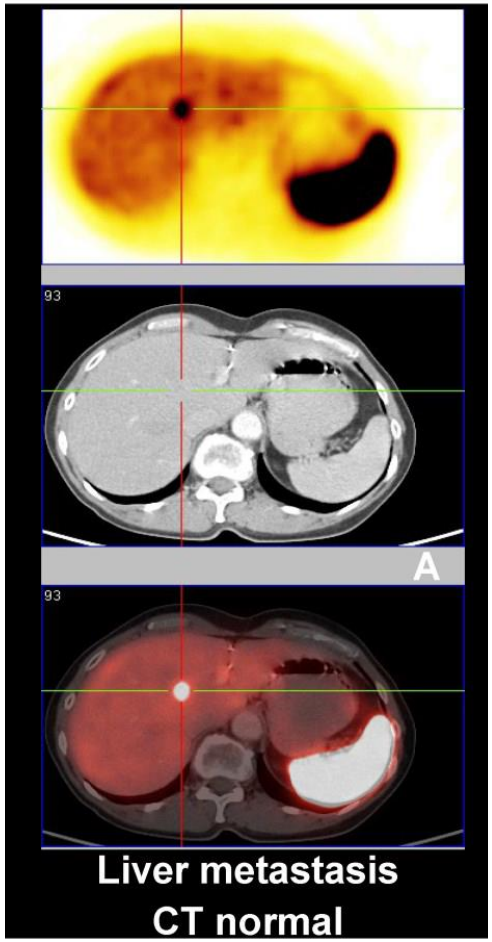
PET: Positron Emission Tomography







PET/CT: combinazione di imaging strutturale e funzionale



PET

CT

PET + CT

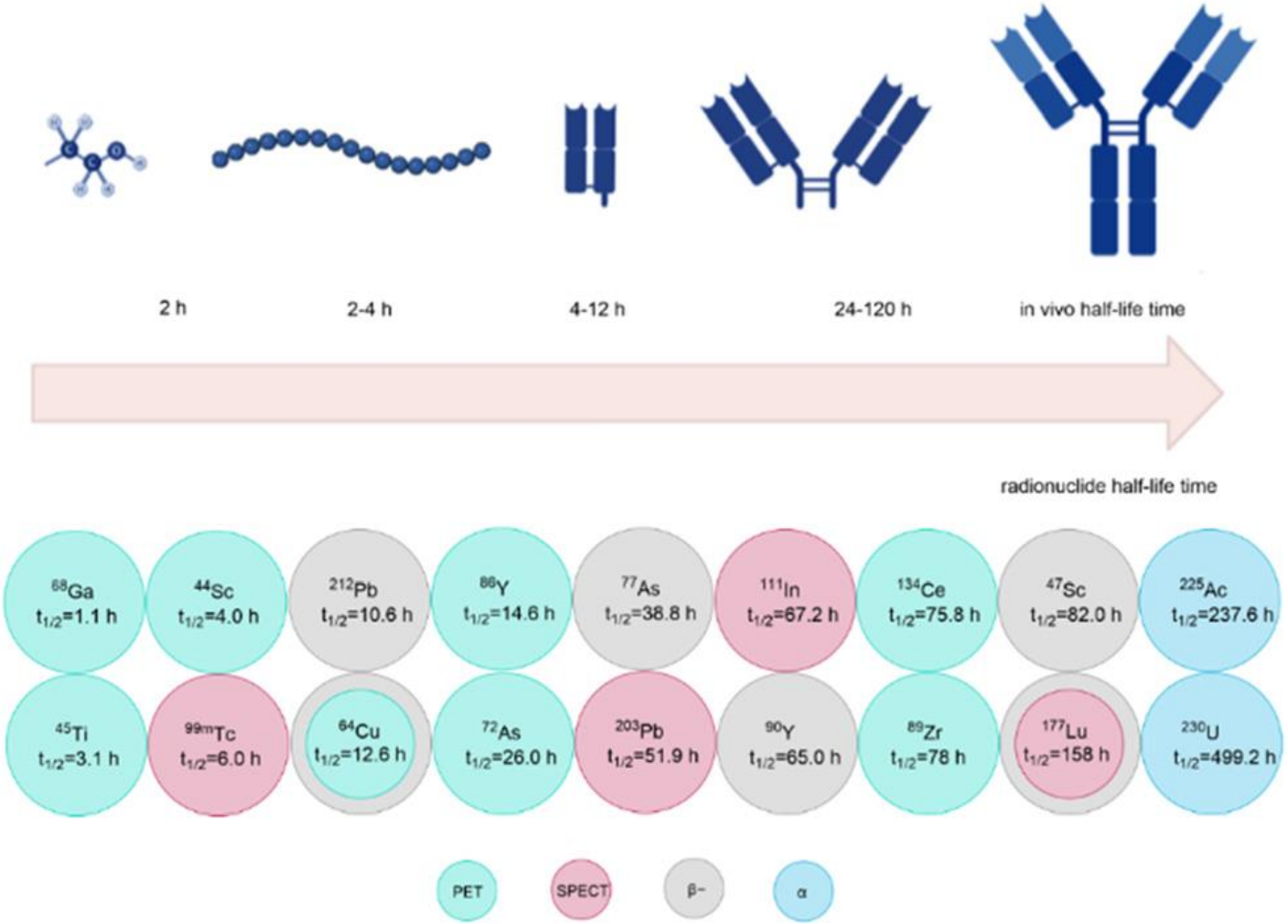
Principali radionuclidi per PET

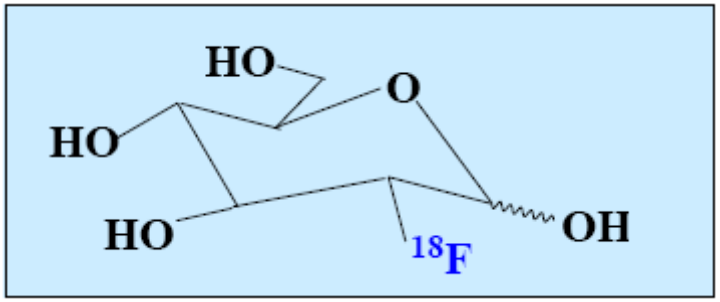
Table 1. Physical Properties of Commonly Used Positron-Emitting Radionuclides

nuclide	half-life (min)	maximum energy (MeV)	mode of decay (%)	theoretical specific activity (GBq/μmol)
^{18}F	110	0.64	$\beta+$ (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.

Tempo di semi-vita e tempo di biodistribuzione

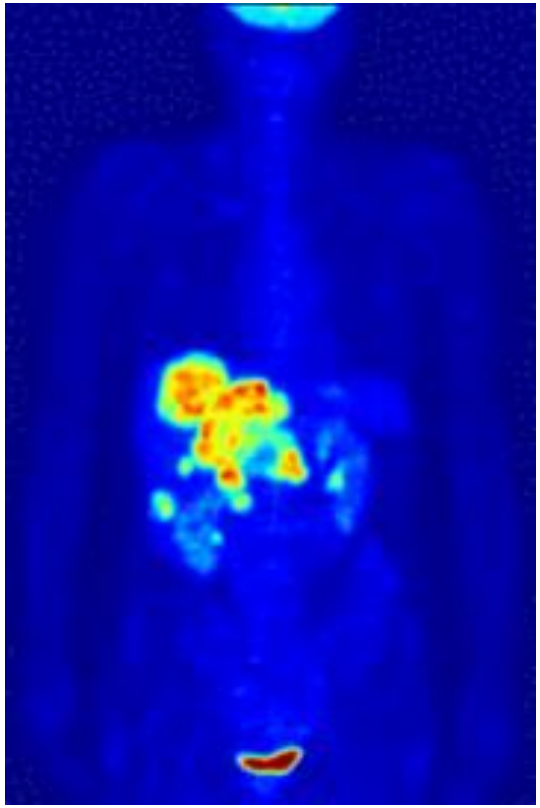


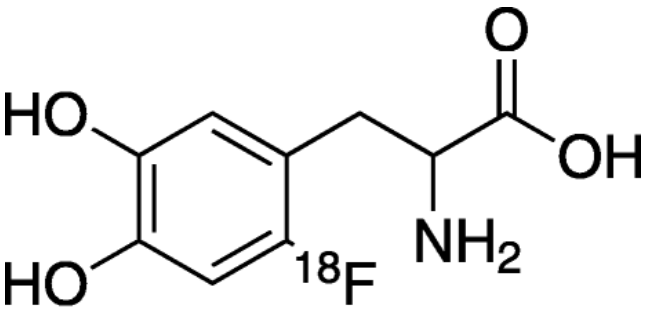


Fluorodeoxyglucose ([^{18}F] FDG)

Sostituzione bio-isosterica

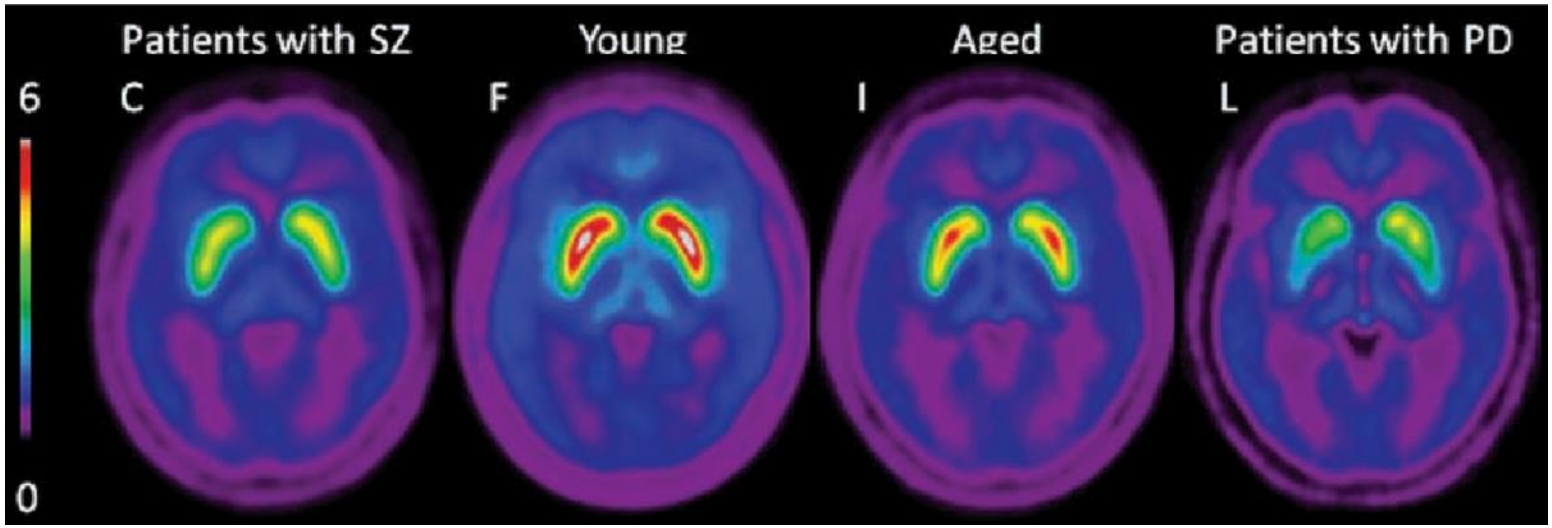
metabolismo del glucosio
localizzazione di tumori





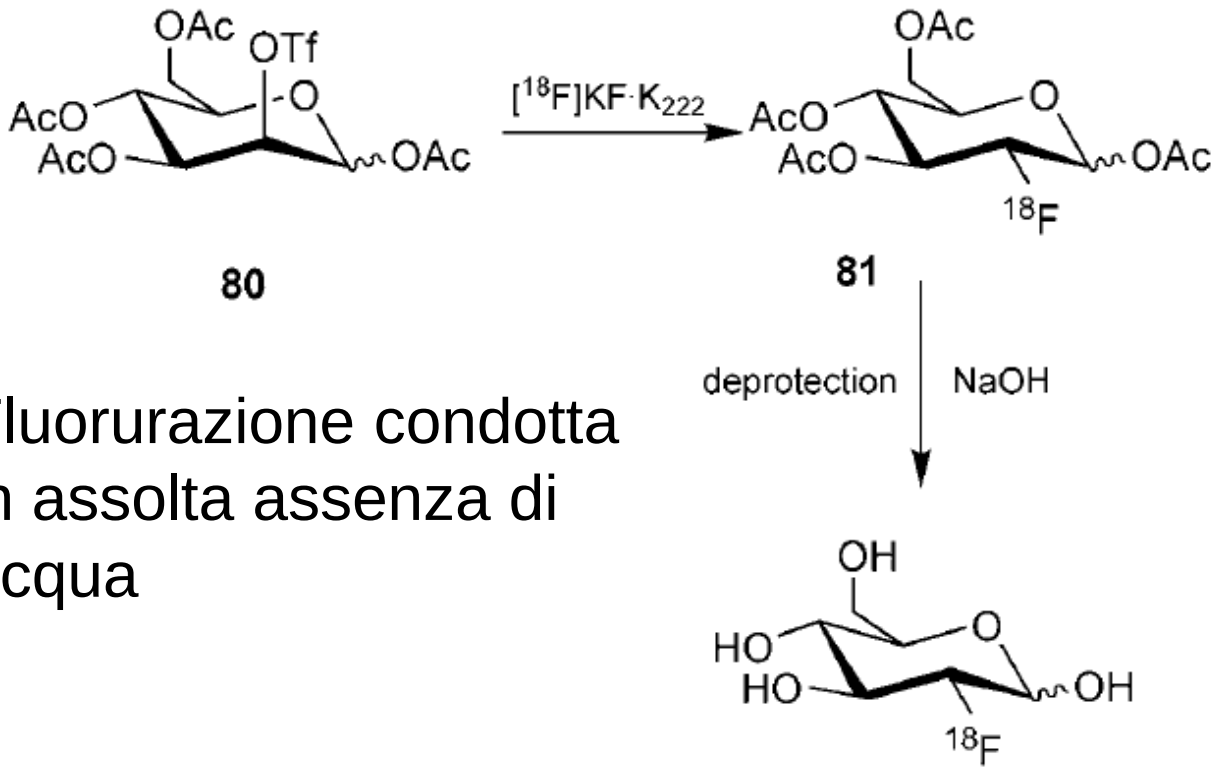
6-[18F]FDOPA,

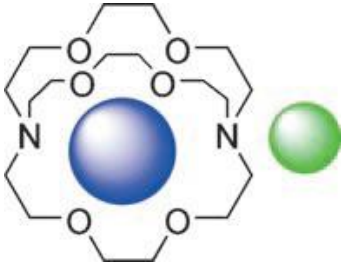
DOPA is the precursor of the neurotransmitter dopamine.
The neurotracer 6-[^{18}F]FDOPA is a powerful tool in PET imaging of neuropsychiatric diseases, movement disorders and brain malignancies. More recently, it also demonstrated good results in the diagnosis of other malignancies



Esempio di fluorurazione diretta nucleofila ($^{18}F^{-}$)

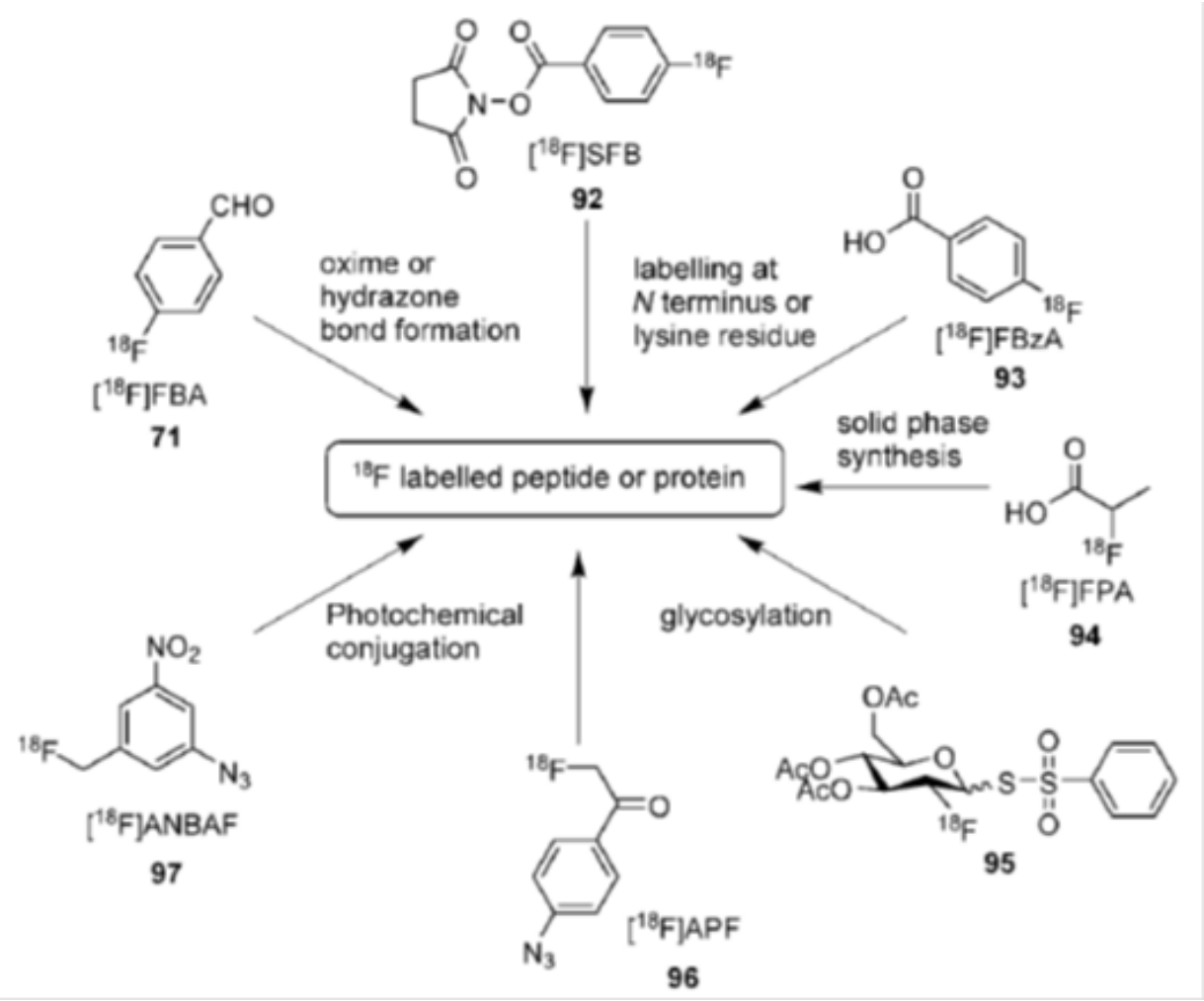
$^{18}O_{(da\ H_2O)}(p, n)^{18}F$





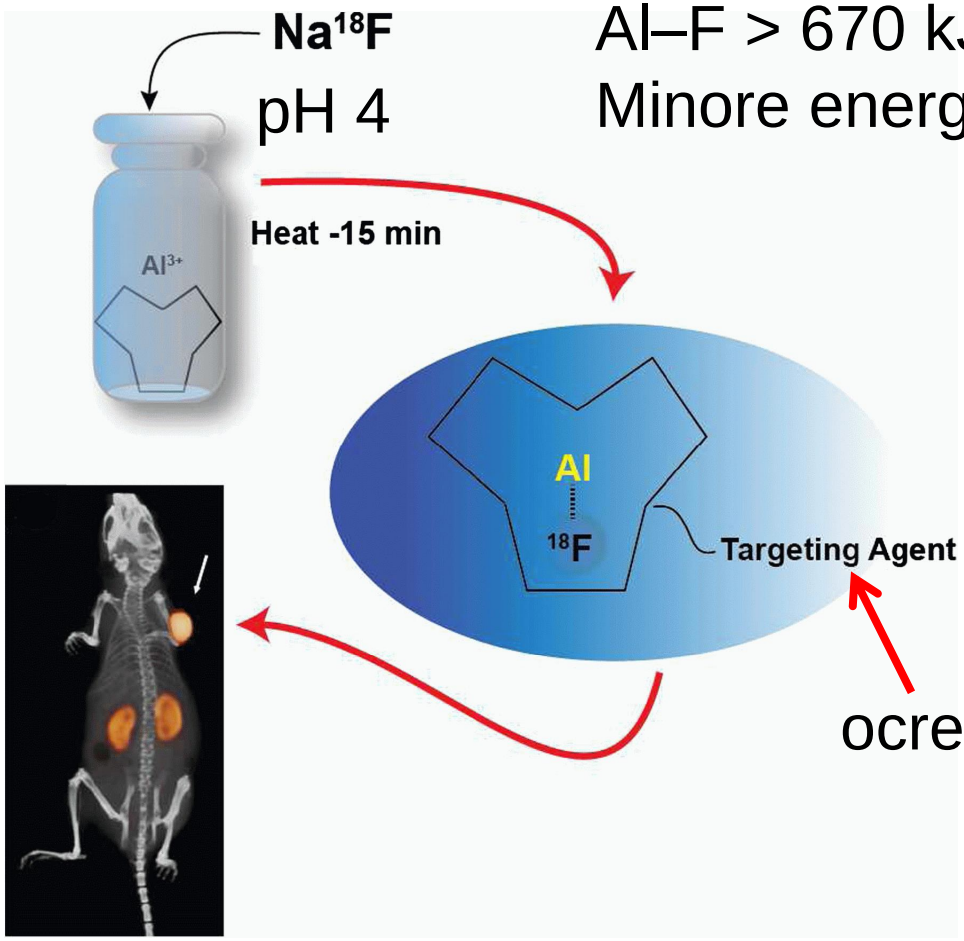
Fluorurazione condotta in assolta assenza di acqua

Gruppi prostetici per marcare biomolecole con ^{19}F



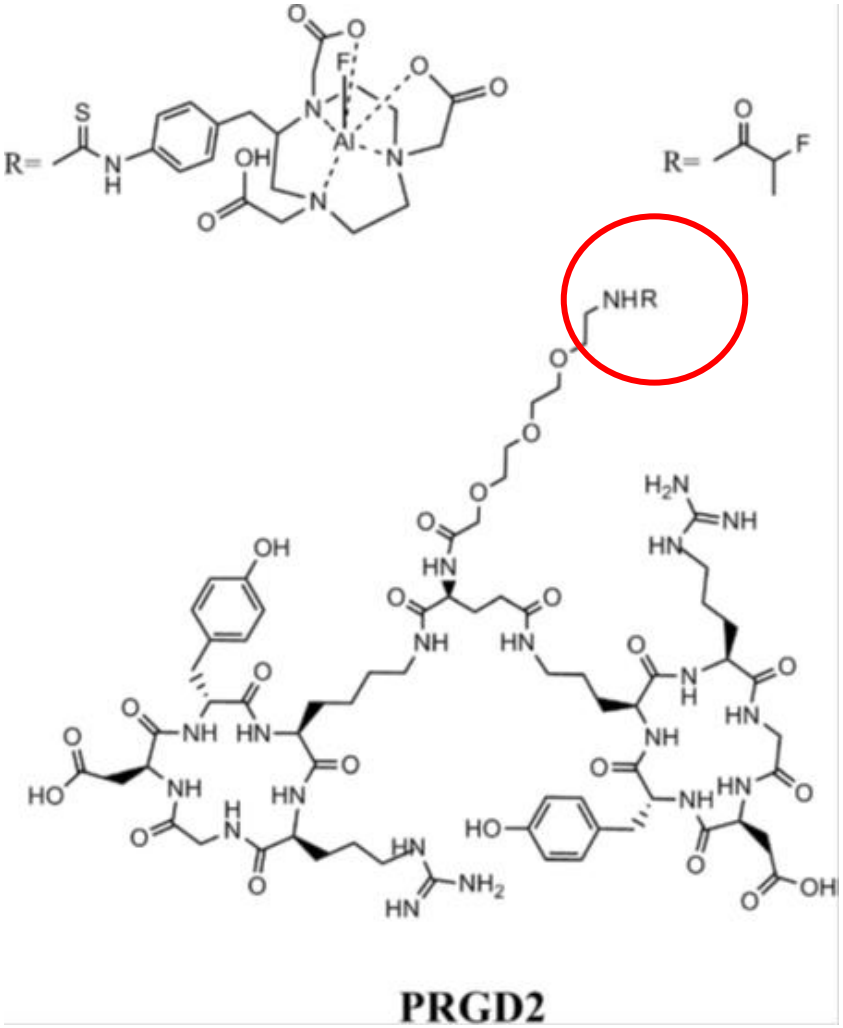
Fluorurazione inorganica (B, Si, Al…)

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



ocreotide

Studio clinico per l'*imaging* di un tumore al polmone



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

Radionuclidi metallici per PET

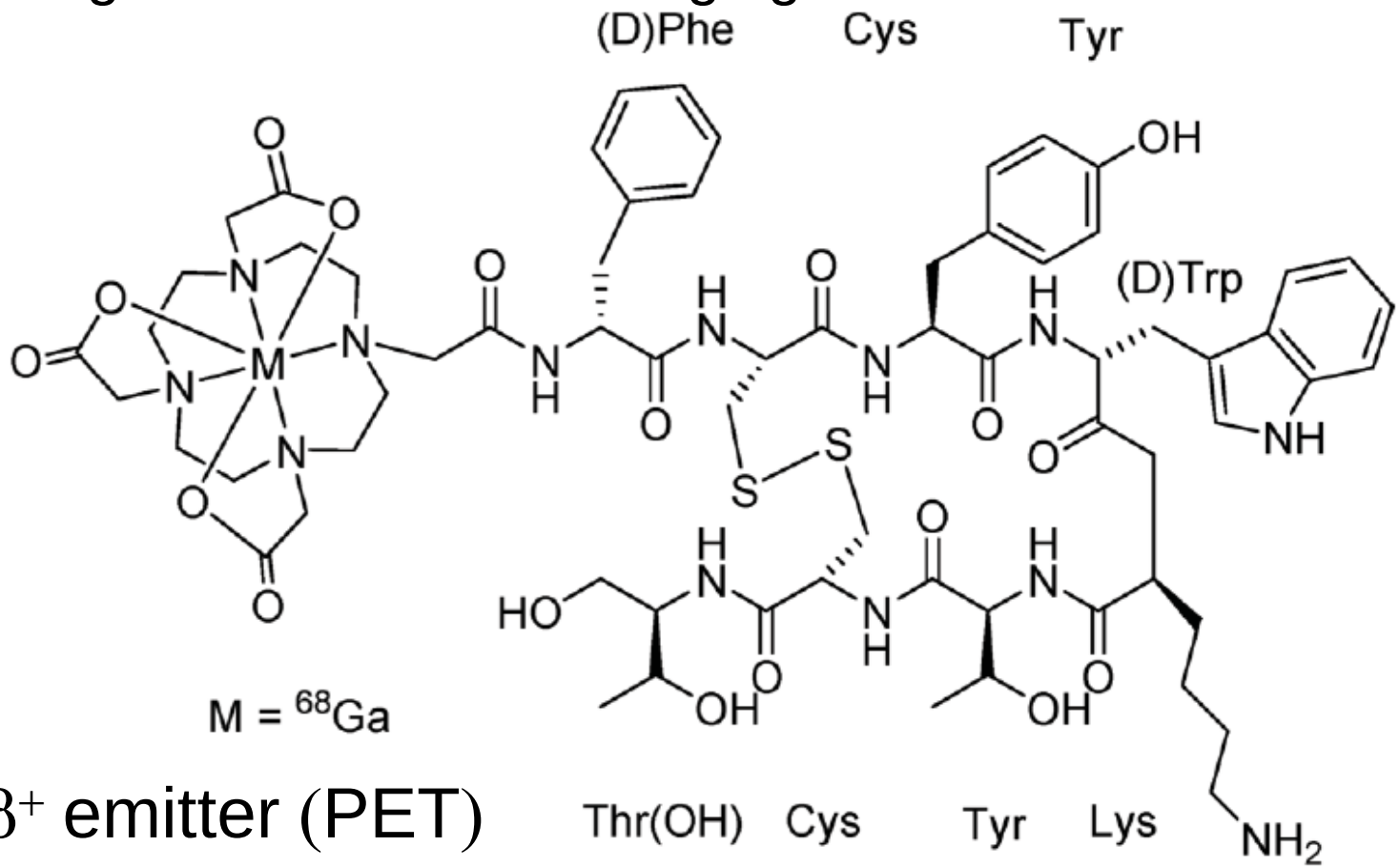
Table 1. Physical Properties of Some Common PET Radiometals[a]

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

^{68}Ga-DOTA-tyr3-Octreotide

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

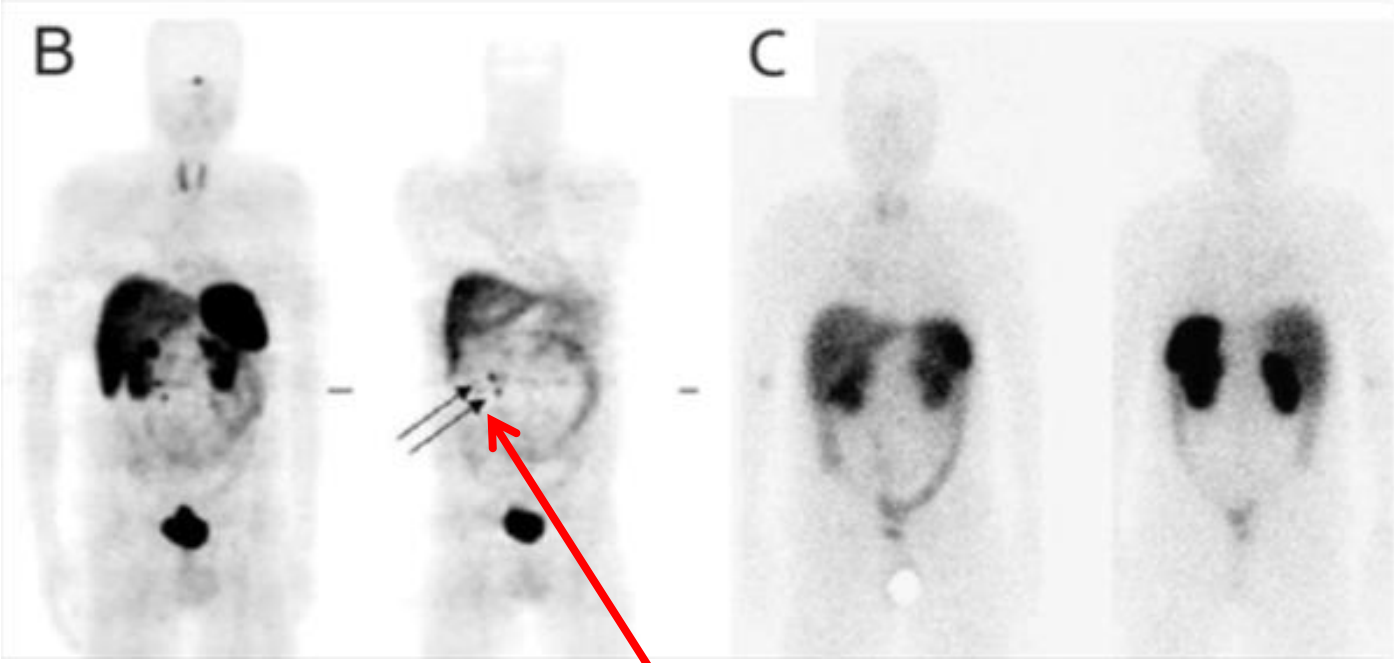
High resolution PET imaging of neuroendocrine tumors



β^+ emitter (PET)

^{68}Ga viene ottenuto in un generatore da ^{68}Ge per EC.

imaging di un tumore endocrino



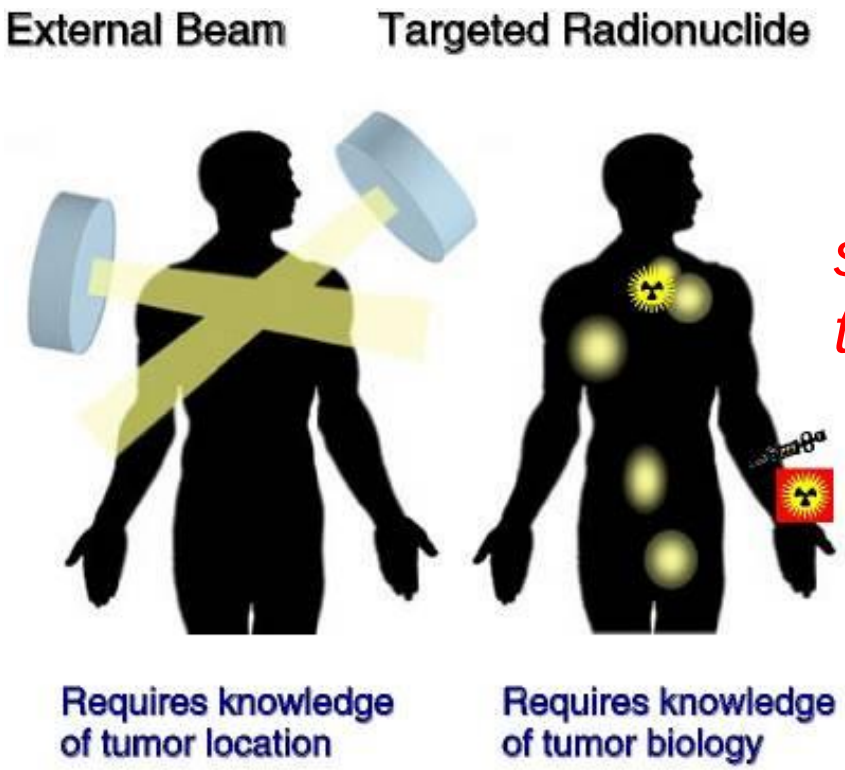
^{68}Ga-DOTATOC
(PET)

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

Linfonodi addominali

Targeted Radiotherapy (*Radio(immuno)therapy*)

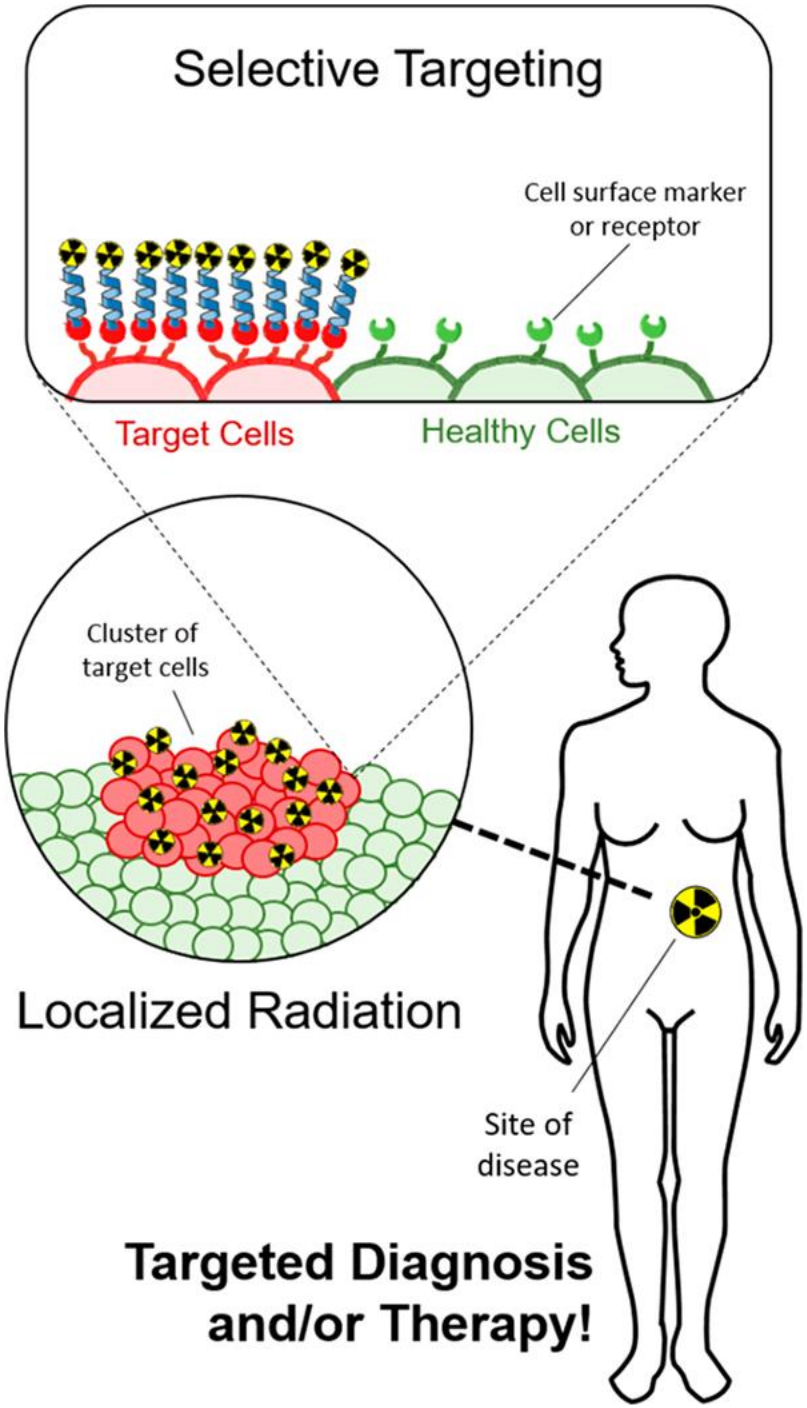
- Linfomi: 1500–2000 cGy
- Tumori solidi: 3500–10000 cGy



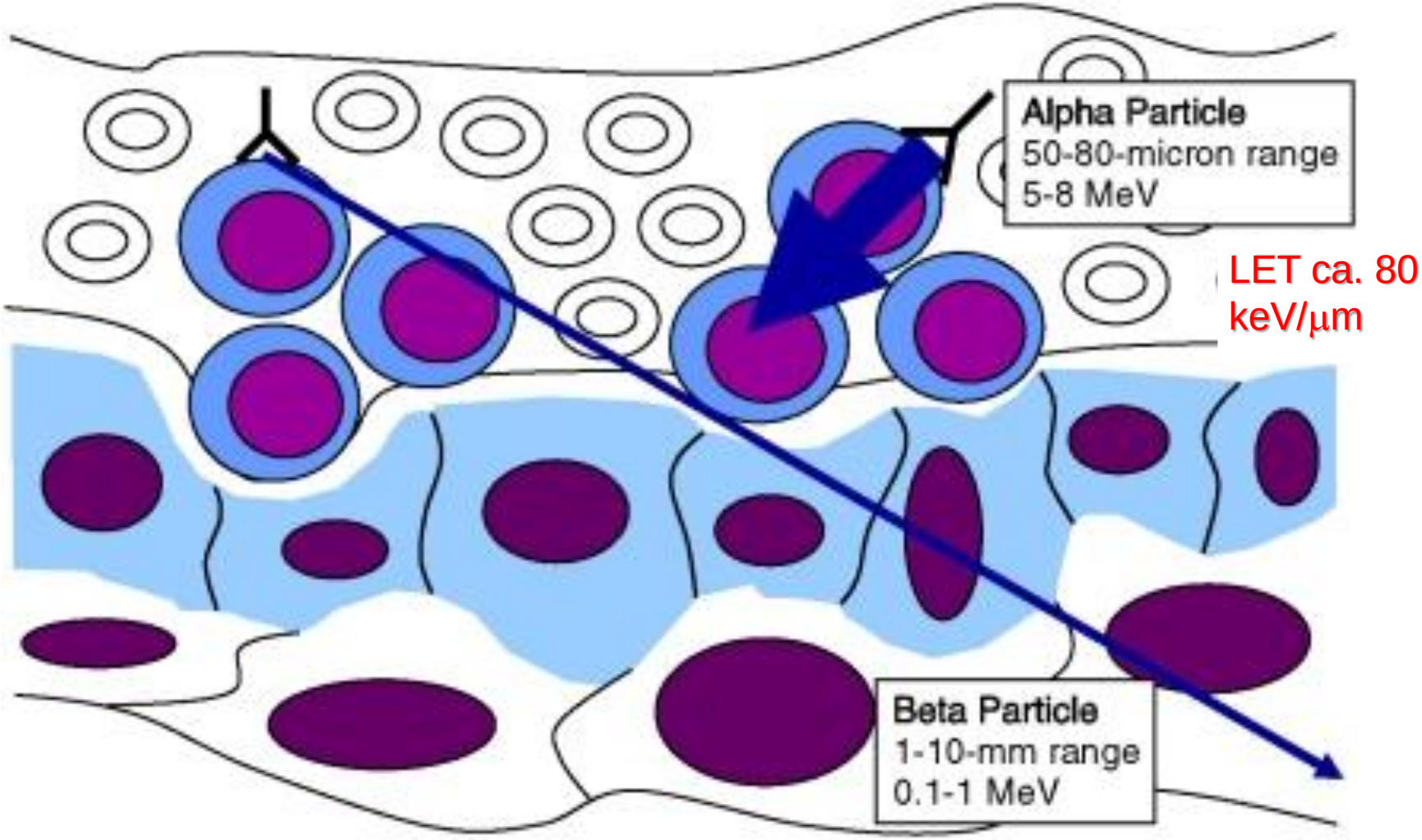
systemic treatment

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

TI = therapeutic index


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

Penetrating power of α and β particles

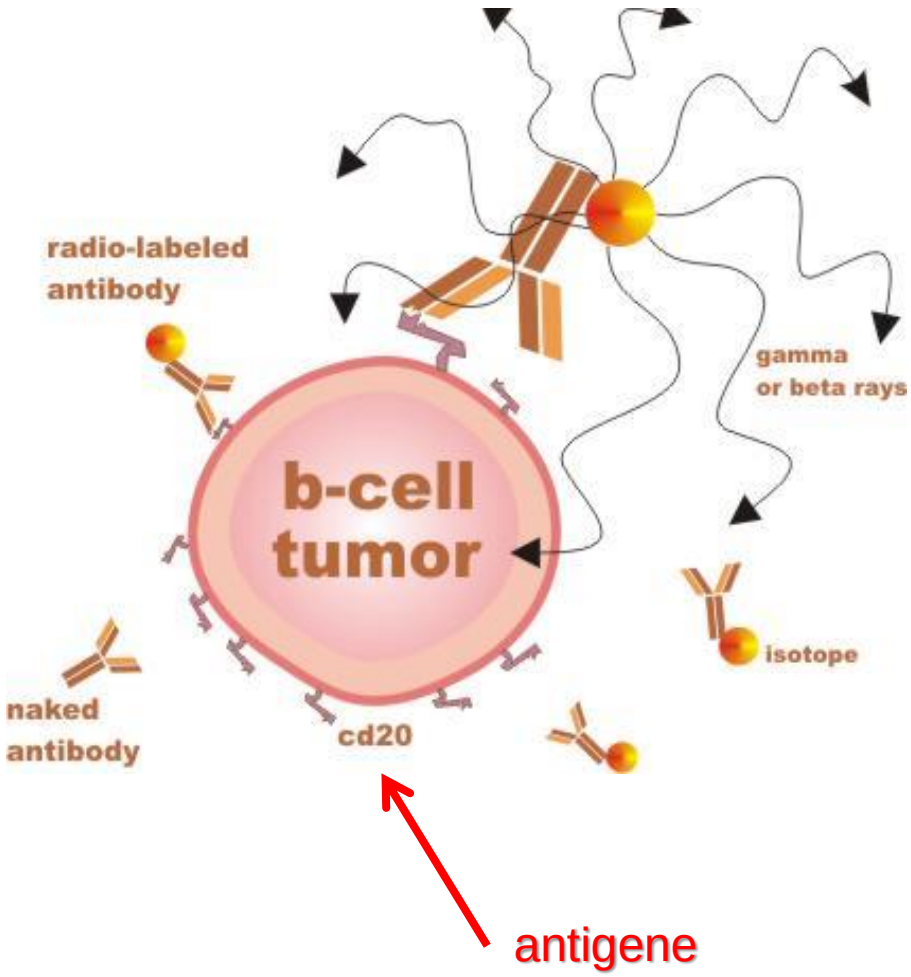


linear energy transfer (LET, keV/μm)

Main radionuclides for Targeted Radiotherapy

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

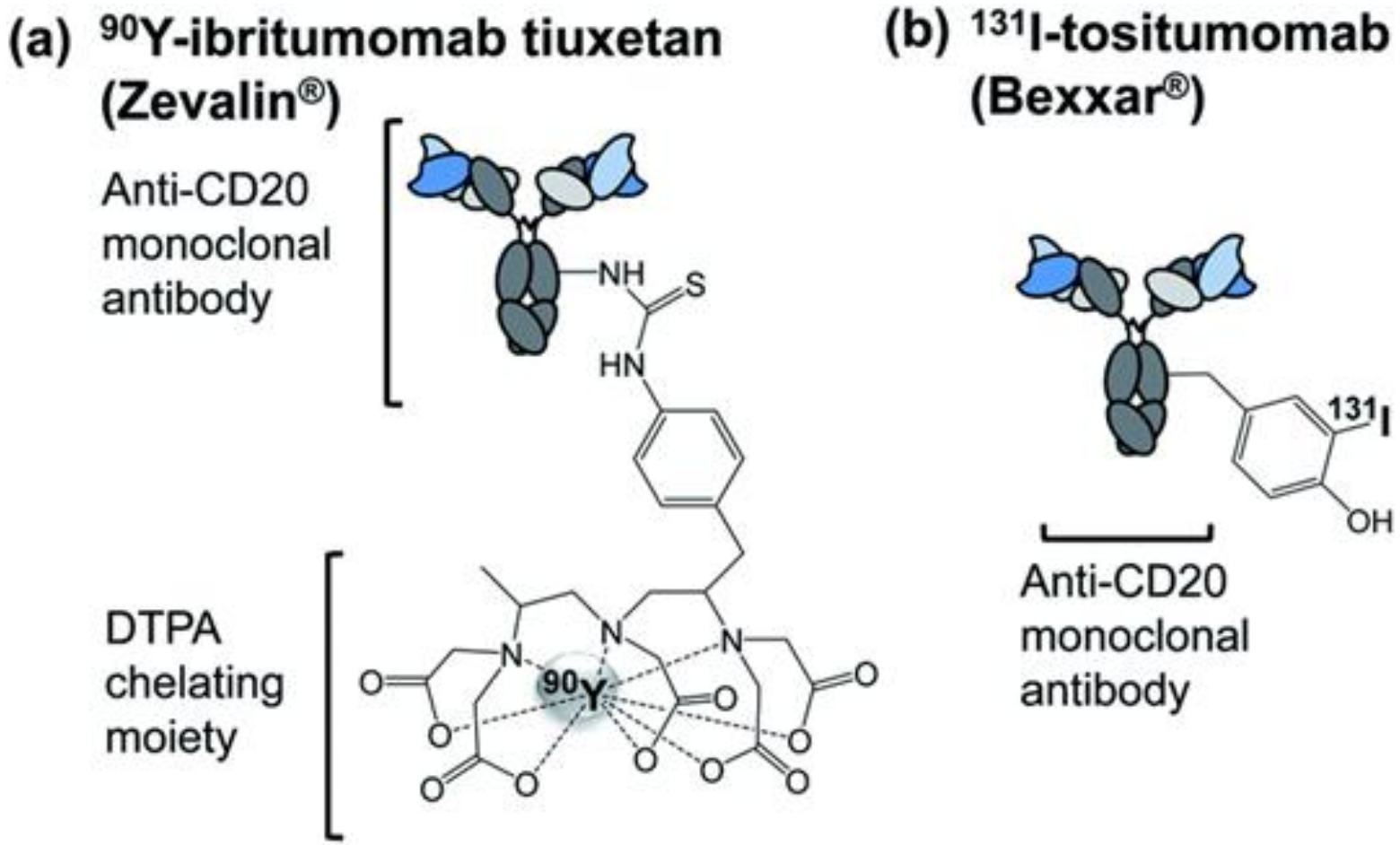
Treatment of B-cell non-Hodgkin's limphoma



Antigene ideale:

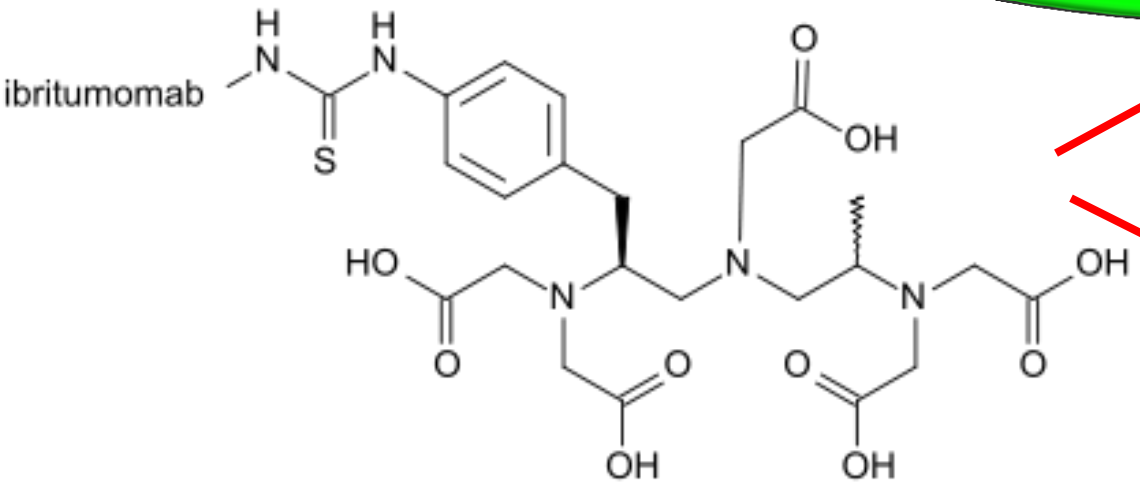
- altamente espresso con densità uniforme sulla superficie di tutte le cellule del tumore (> 10^5 siti per cellula),
- non deve essere espresso (o molto meno) nelle cellule sane,
- affinità antigene-anticorpo dell'ordine nanomolare
- internalizzazione

FDA approved



Zevalin®

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



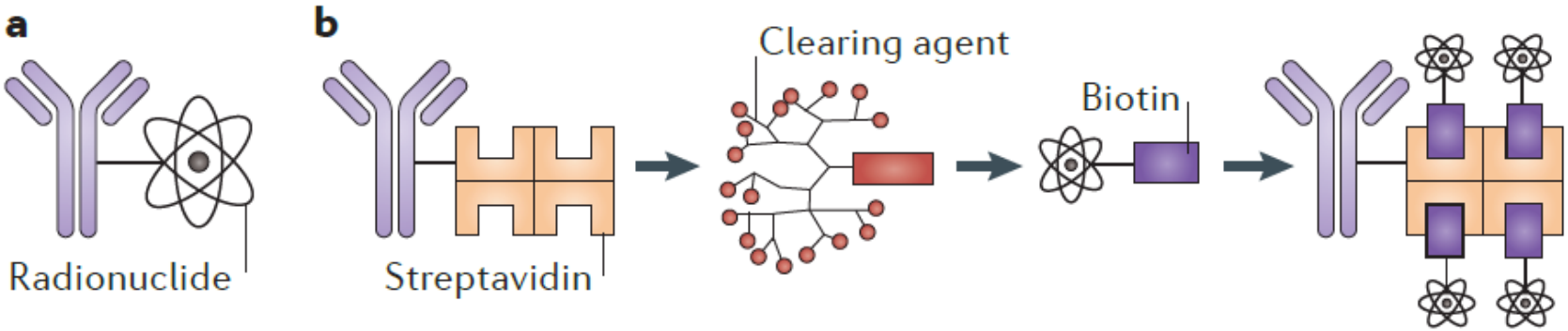
$^{111}In^{3+}$ or – better – $^{86}Y^{3+}$ for imaging

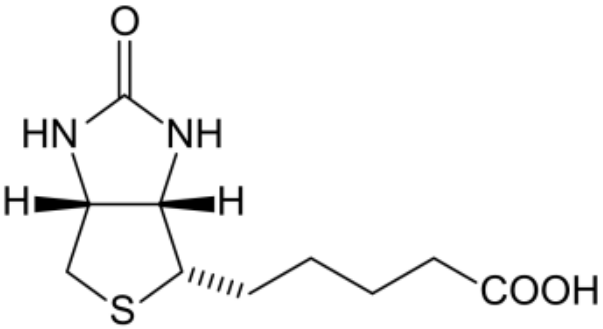
^{90}Y is a pure β^- emitter

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

Example of the matched-pair approach

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

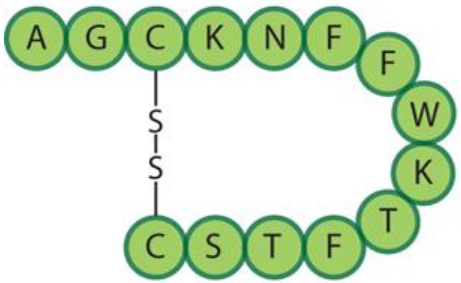




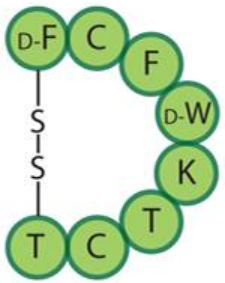
Biotina

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

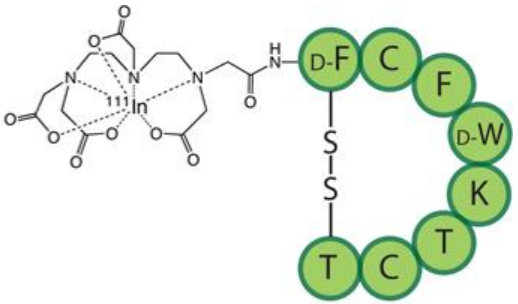
Radio-immunotherapy of neuroendocrine tumors



Somatostatin



Octreotide



^{111}In-DTPA-Octreotide

SPECT imaging of neuroendocrine tumors

^{68}Ga-DOTATOC for PET imaging

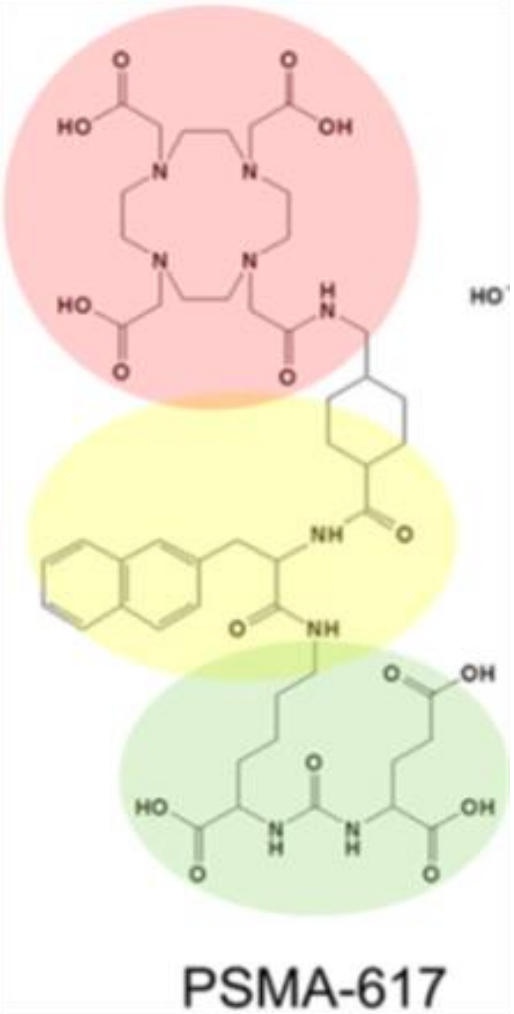
^{90}Y-DOTATOC and ^{177}Lu-DOTATATE for radiotherapy

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

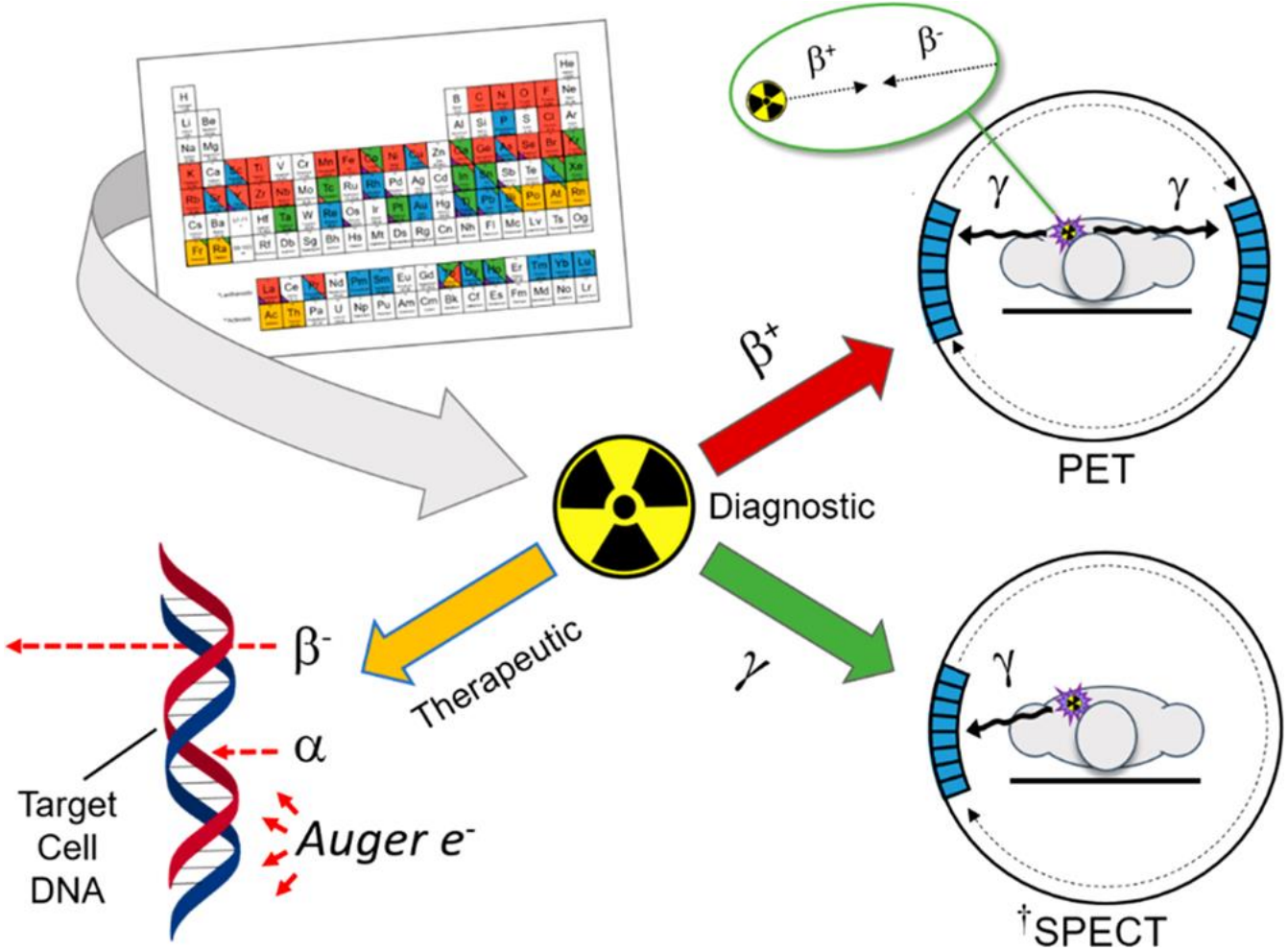
^{177}Lu-PSMA-167

Linker

Peptido-mimetico



PSMA = *prostate-specific membrane antigen*


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