

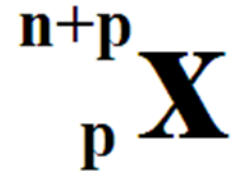
Radiopharmacy in Nuclear Medicine

By Dr. Fakhari, Radiopharmacist , PhD



What is?

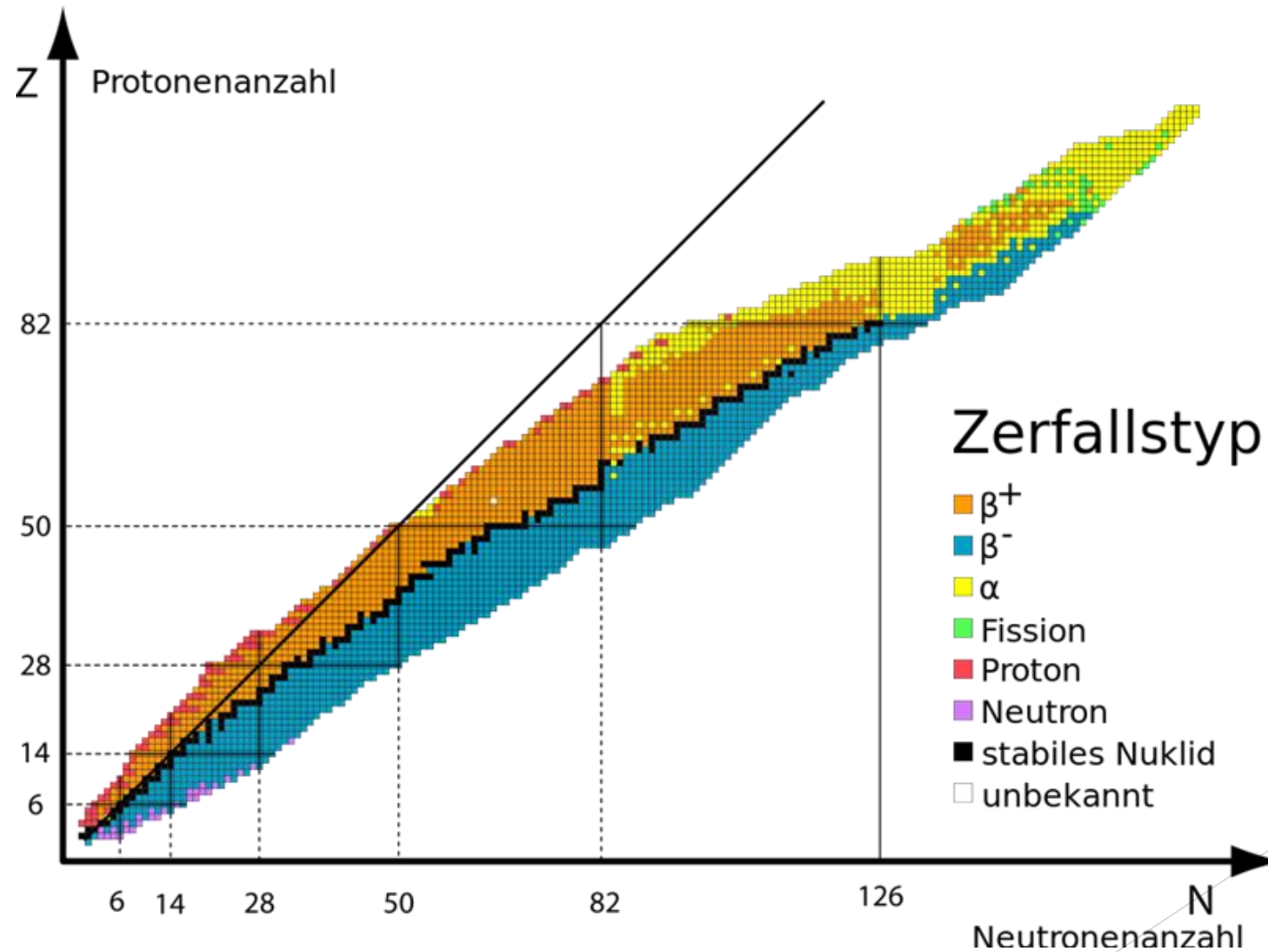
- ▶ Radioisotope
- ▶ Radiotracer
- ▶ Radiopharmaceutical
- ▶ Half time
- ▶ Effective half time



$$T(\text{eff}) = \frac{T(b) * T(p)}{T(b) + T(p)}$$



segre diagram



Units of radioactivity

► becquerel (Bq) → equal to one reciprocal second

► curie (symbol Ci) → $1 \text{ Ci} = 3.7 \times 10^{10} \text{ Bq} = 37 \text{ GBq}$



▶ Radioisotope production ways:

- ▶ Reactor
- ▶ Cyclotron
- ▶ generator



Radioisotope decay:

- ▶ Alpha
- ▶ **Beta**
- ▶ Gamma ray
- ▶ positron



kinds of radiopharmaceutical :

- ▶ **Diagnostic (gamma)**
- ▶ **Therapy (alpha , beta, auger)**



Therapeutic radiopharmaceuticals:

► Electron auge:

^{125}I

► Alpha emitters:

^{212}Bi , ^{212}At , **^{223}Ra**



Beta emitters:

- ▶ **131I** , 131I-MIBG (iodine-131-meta-iodobenzylguanidine)
- ▶ 32P
- ▶ 90Y
- ▶ 90Sr
- ▶ 198Au
- ▶ **89Sr**
- ▶ 186/188Re
- ▶ 177Lu
- ▶ **153Sm**

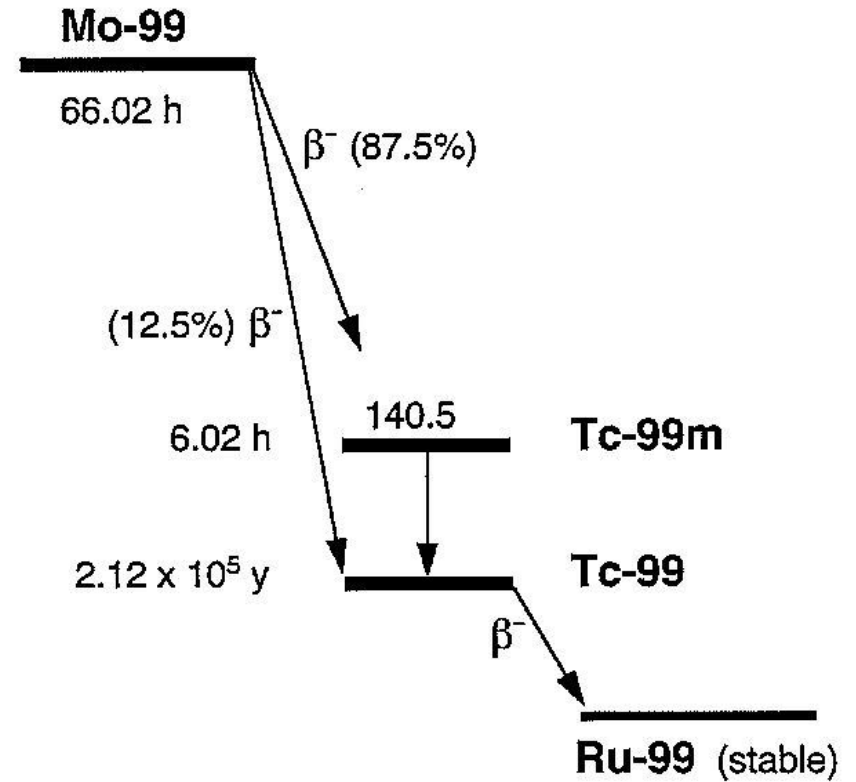
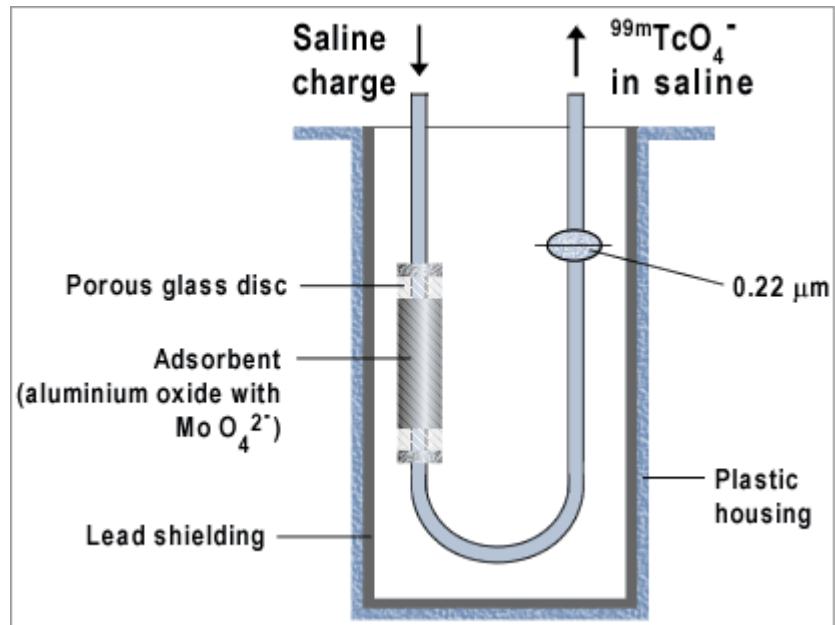


Diagnostic radiopharmaceuticals

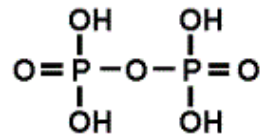
- ▶ ^{123}I
- ▶ ^{67}Ga
- ▶ ^{201}Tl
- ▶ $^{99\text{m}}\text{Tc}$
- ▶ Positron emitters(PET based radiotracers)



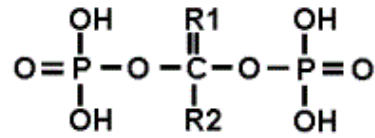
99mTc generator



bone ^{99m}Tc -Radiopharmaceuticals

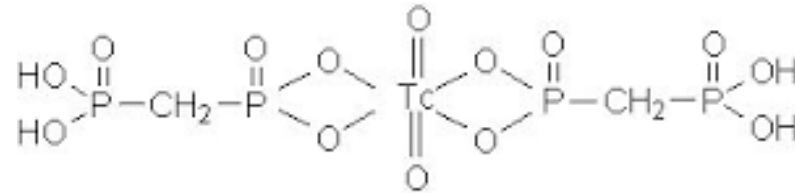
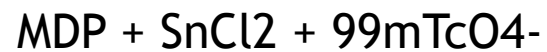
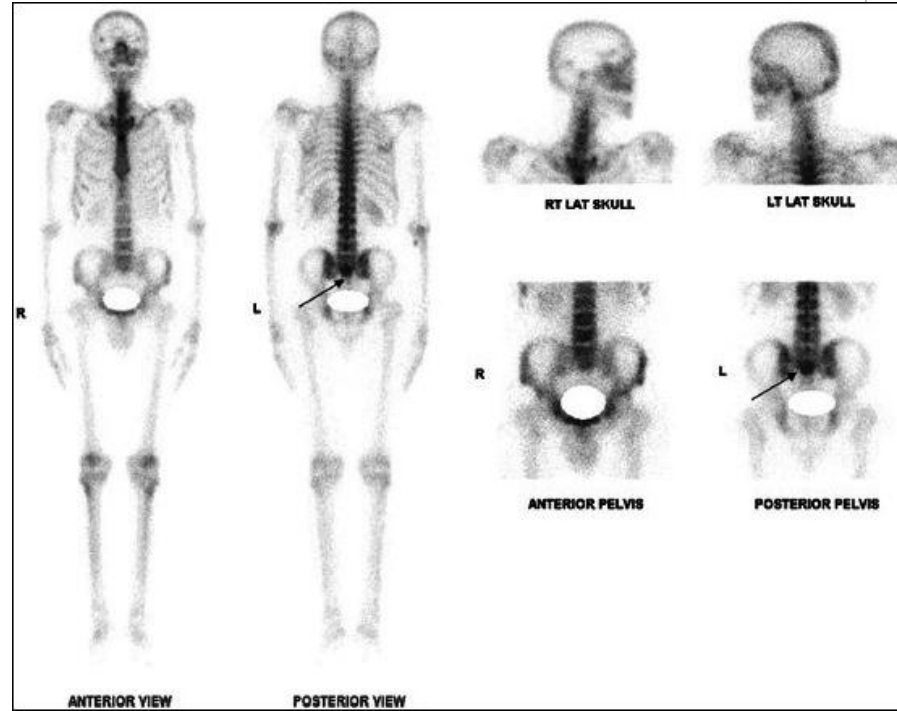


Pyrophosphate



Diphosphonate

	R1	R2
HEDP	OH	CH ₃
MDP	H	H
HMDP	OH	H



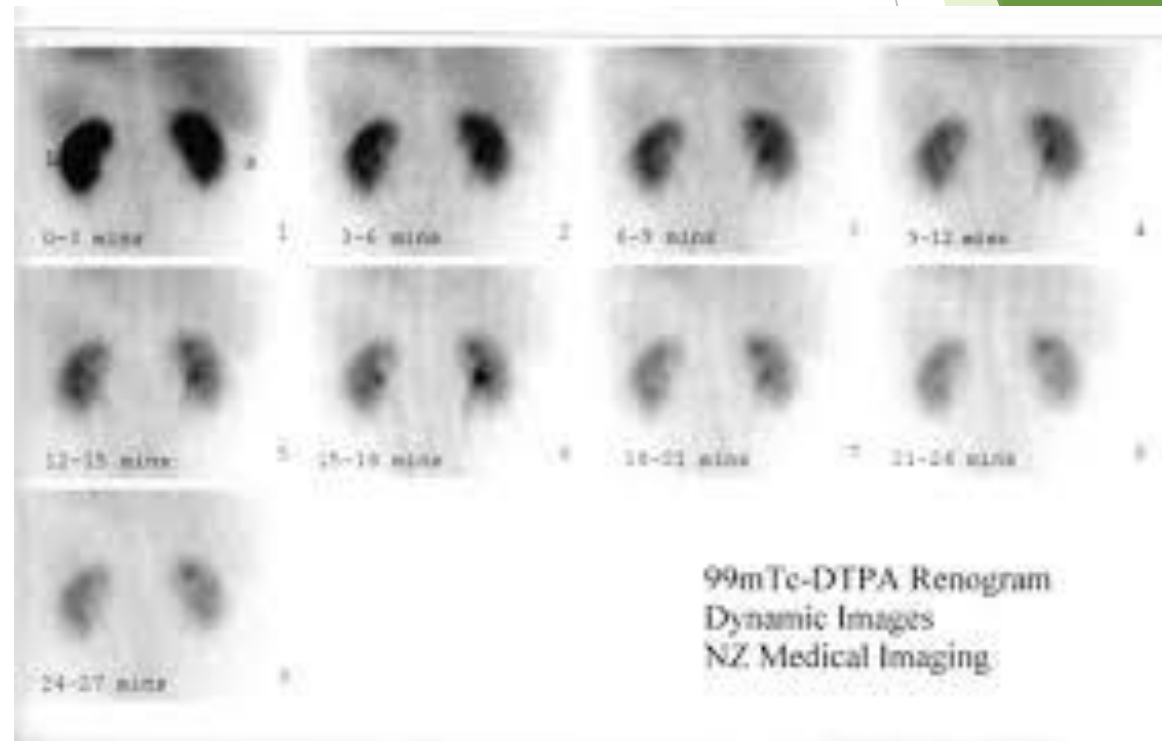
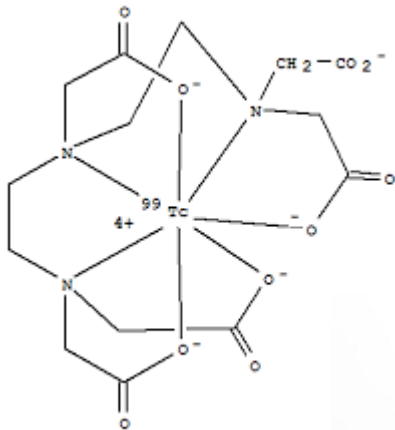
$[^{99m}\text{Tc}]$ Medronate



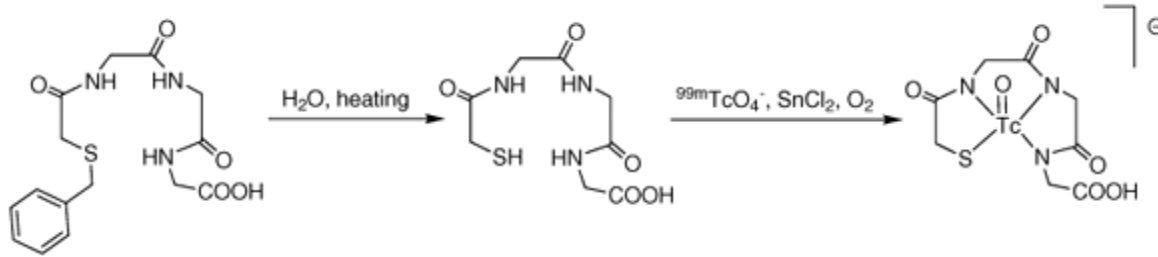
Renal ^{99m}Tc -Radiopharmaceuticals

- ▶ 1: Glomerular filtration rate (GFR)
- ▶ ^{99m}Tc -DTPA (diethylenetriaminepentaacetic acid)

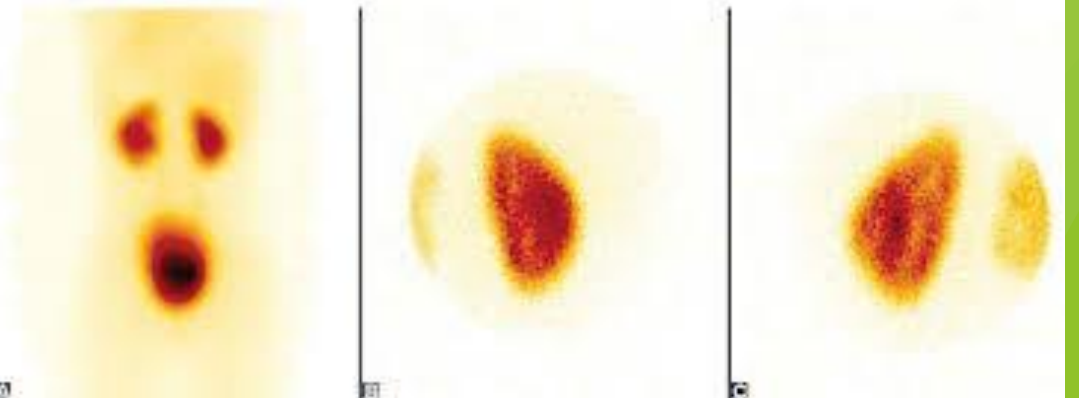
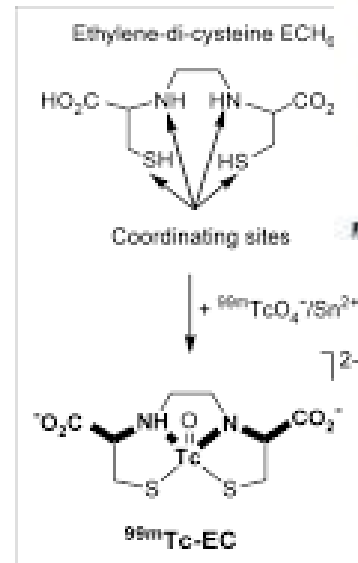
DTPA + SnCl_2 + $^{99m}\text{TcO}_4^-$



- **2: Effective Renal Plasma Flow (ERPF)**
- **^{99m}Tc -MAG3 (mercaptoacetyltriglycine) , ^{131}I -OIH**



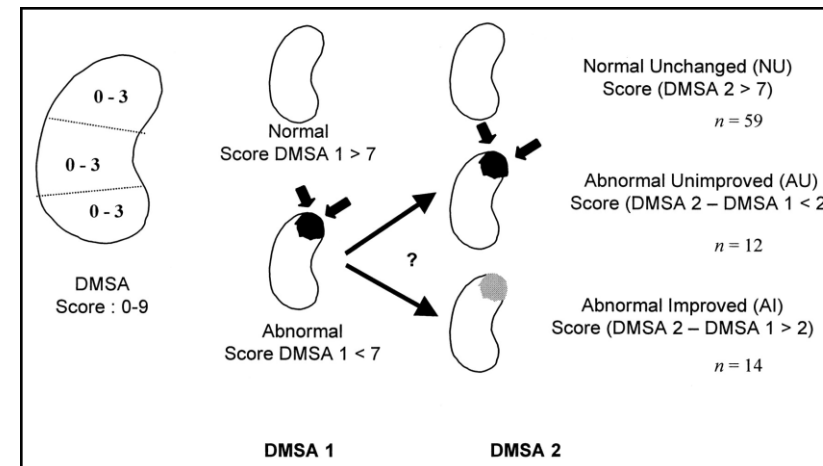
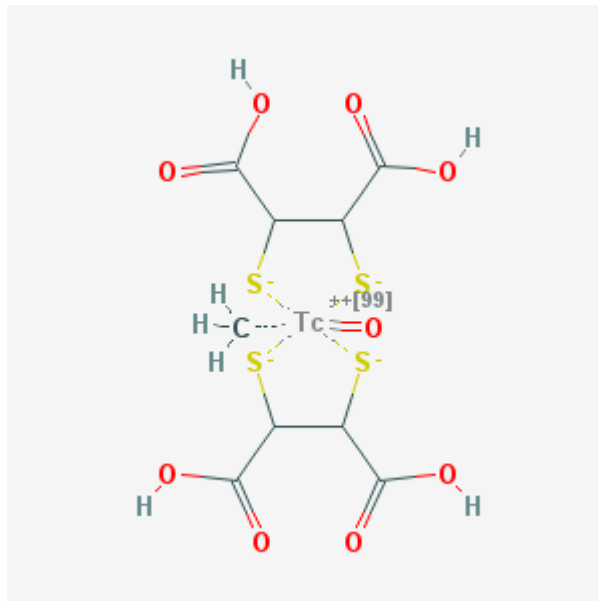
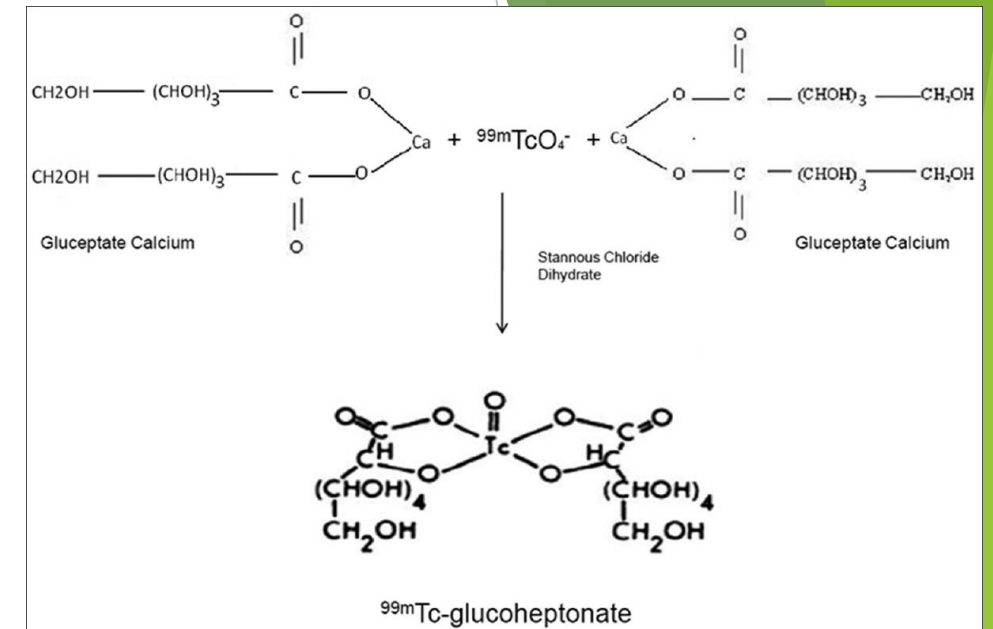
- **^{99m}Tc -EC (Ethylenedicysteine)**



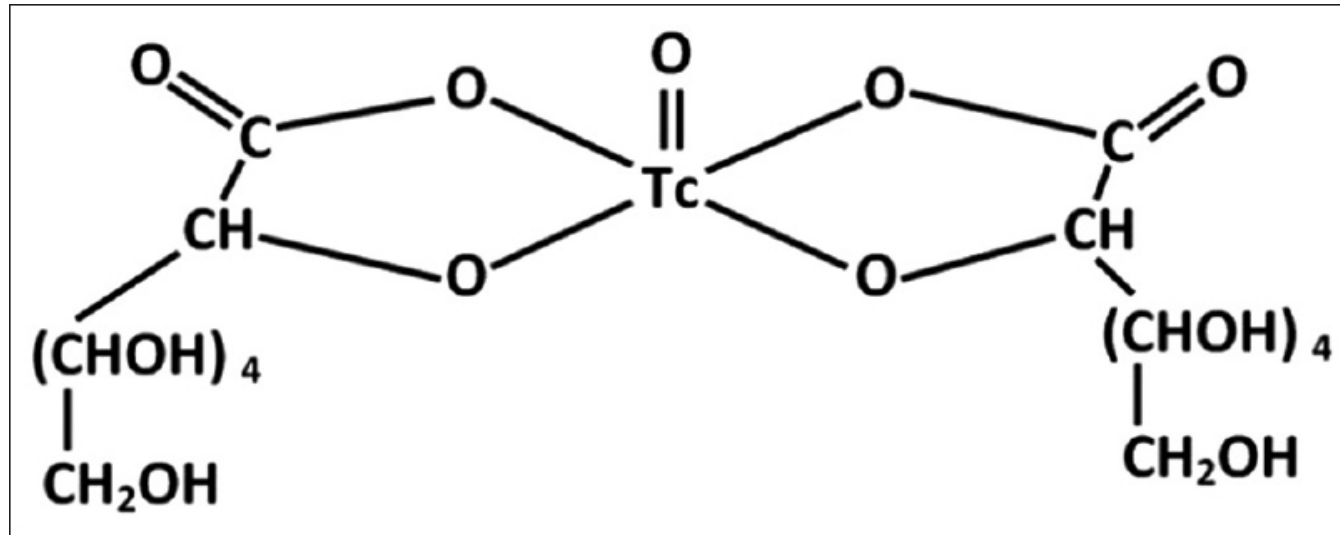
3: morphology

► 1: ^{99m}Tc-Glucoheptonate (GFR / morphology)

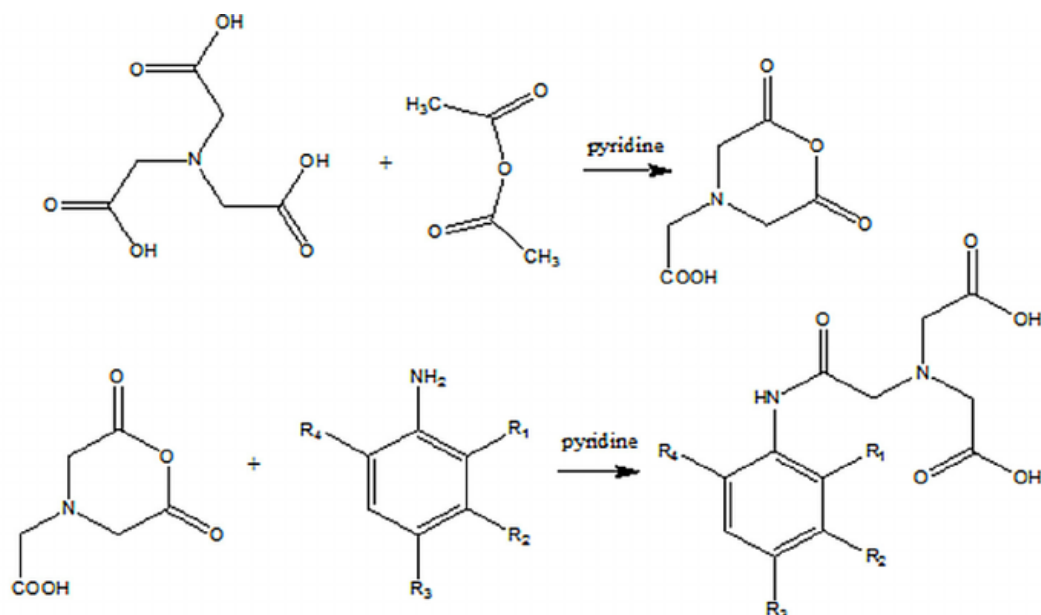
► 2: ^{99m}Tc-DMSA (Dimercaptosuccinic acid)



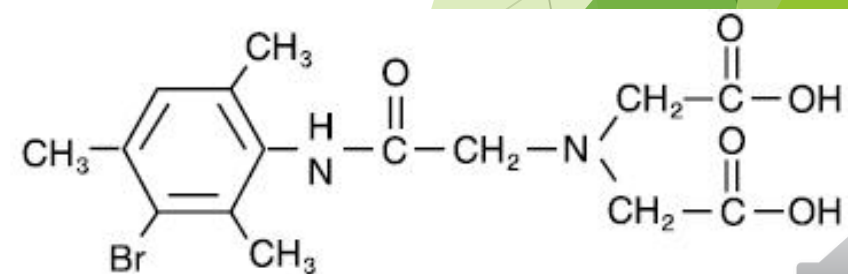
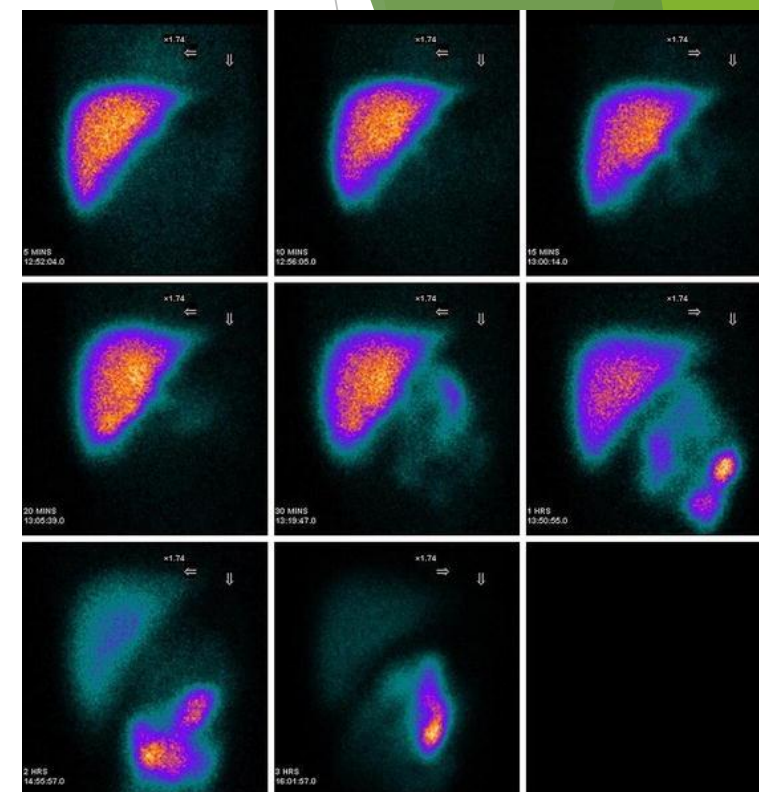
^{99m}Tc -GHA



Liver 99mTc-Radiopharmaceuticals



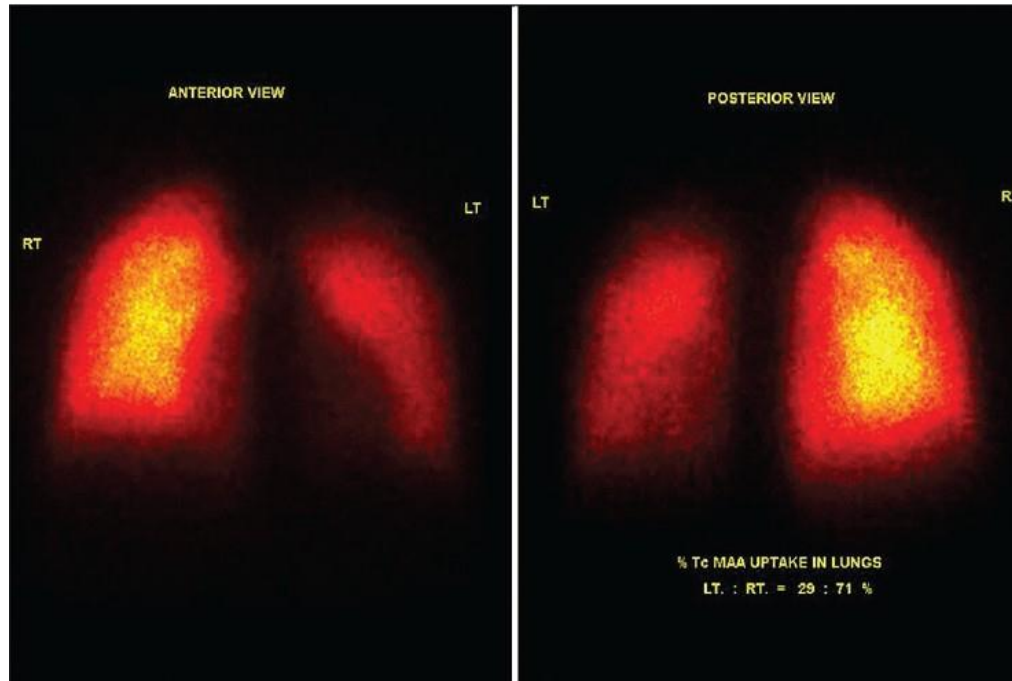
Synthesized compound	R ₁	R ₂	R ₃	R ₄
N-(4-methylacetanilide)iminodiacetic acid (Met-IDA)	H	H	CH ₃	H
N-(2,4-dimethylacetanilide)iminodiacetic acid (DMet-IDA)	CH ₃	H	CH ₃	H
N-(2,4,6-trimethylacetanilide)iminodiacetic acid (TMet-IDA)	CH ₃	H	CH ₃	CH ₃
N-(3-bromo-2,4,6-trimethylacetanilide)-iminodiacetic acid – mebrotfenin (MBR)	CH ₃	Br	CH ₃	CH ₃



Lung ^{99m}Tc -Radiopharmaceuticals

perfusion

- ▶ Particle including size 20-40 micron
- ▶ **^{99m}Tc -Macroaggregated Albumin (10-45)**



ventilation

^{133}Xe

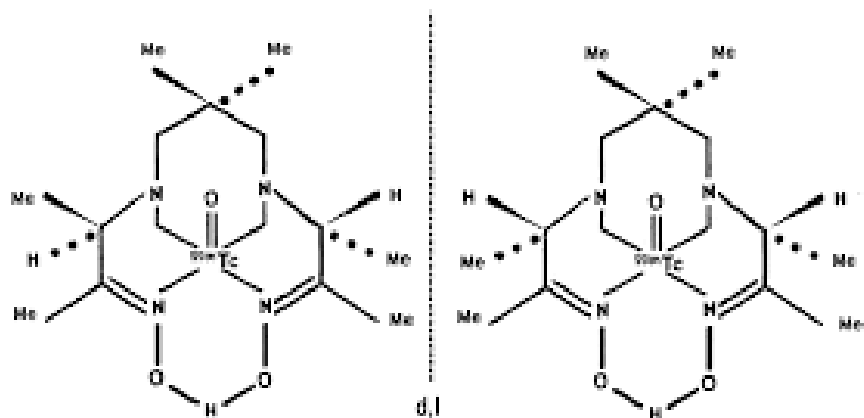
^{81m}Kr

^{99m}Tc -DTPA-Aerosol

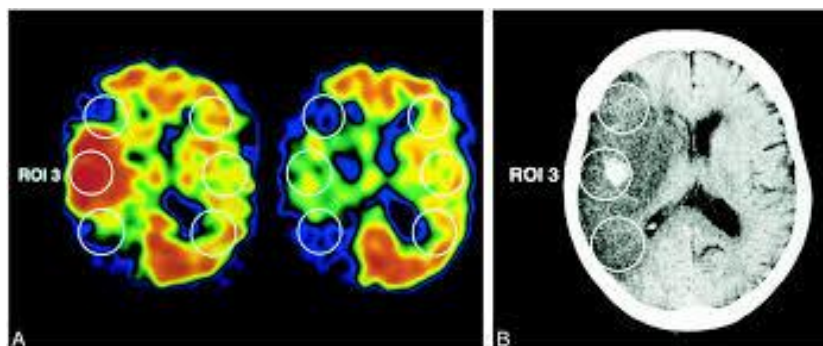
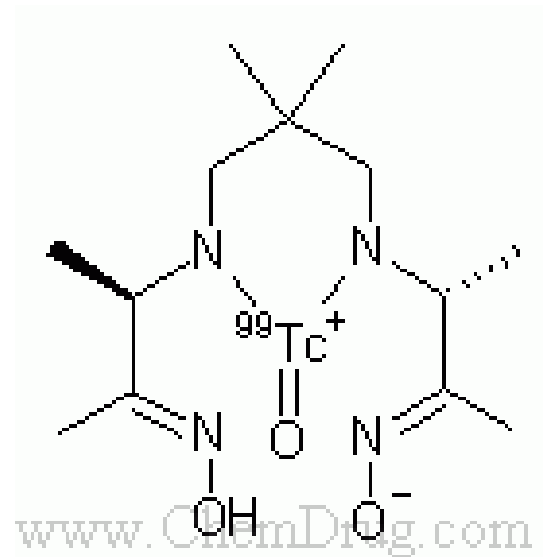


brain 99mTc-Radiopharmaceuticals

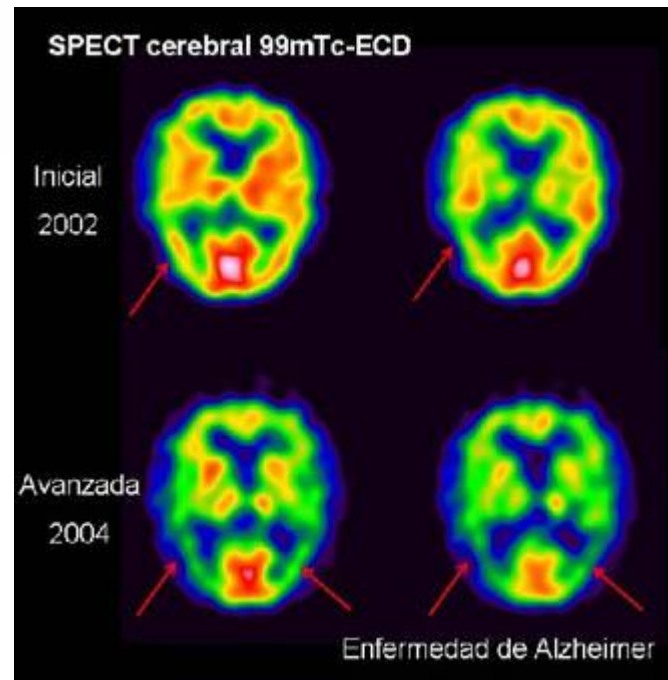
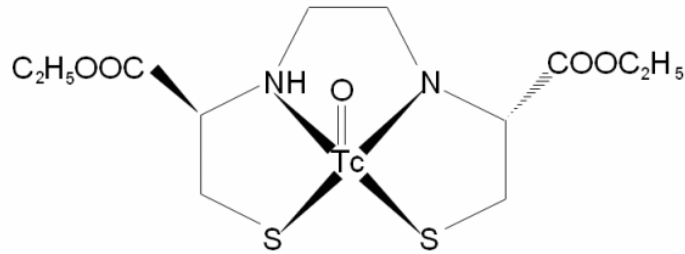
► 1: 99mTc-HMPAO (exametazime)



99mTc-labeled d,l Diastereoisomers of HMPAO

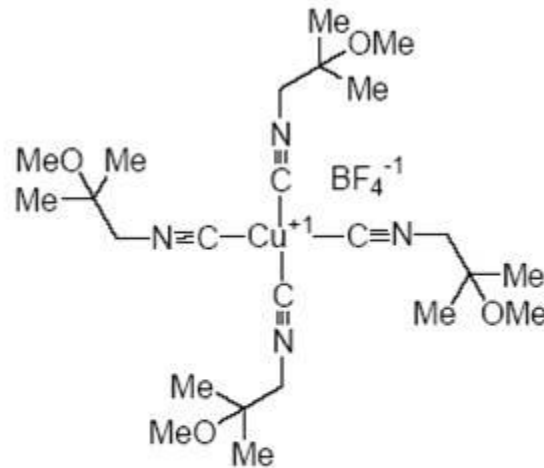
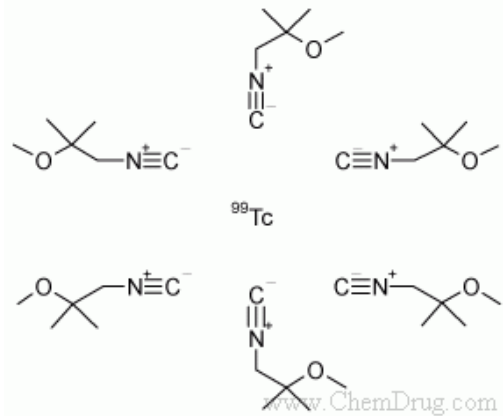


► **2:99mTc-ECD (ethyl cysteinate dimer)**



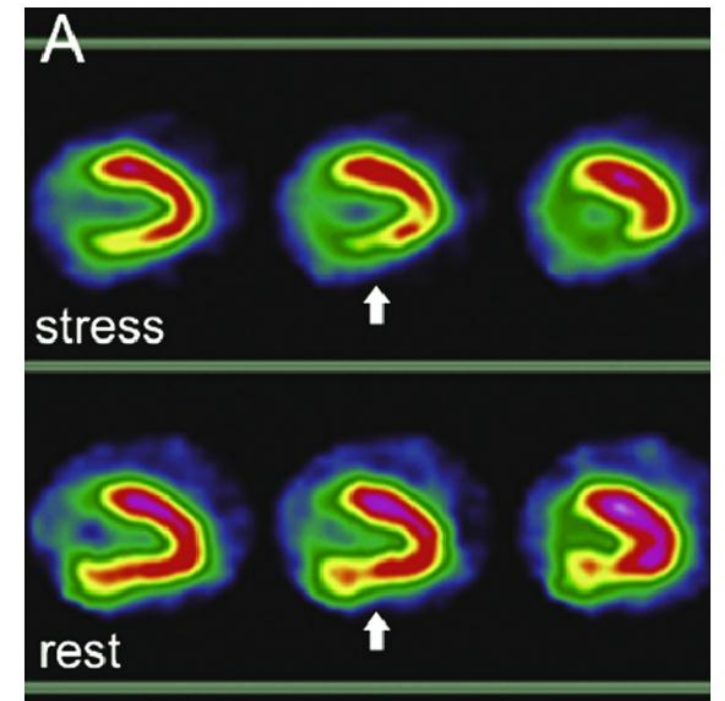
Heart ^{99m}Tc -Radiopharmaceuticals

► ^{99m}Tc -MIBI (methoxyisobutyl isonitrile)



Molecular Formula
 $\text{C}_{24}\text{H}_{44}\text{N}_4\text{O}_4\text{BF}_4\text{Cu}$

Molecular Weight
 602.98



RBC radiolabeling methods

► 1: in vitro

Blood $\Rightarrow$ centrifuge $\Rightarrow$ RBC $\Rightarrow$ SnCl₂
 $\Rightarrow$ 30min $\Rightarrow$ 15-12mCi (99mTcO₄⁻) $\Rightarrow$ **RBC***

► 2: in vivo

pyrophosphate + SnCl₂
or
pyrophosphate + DTPA + SnCl₂ $\Rightarrow$
1: mixing in saline
2: administering to patient

$\Rightarrow$ $\begin{matrix} \text{RBC} + \text{SnCl}_2 \\ 30\text{min} \end{matrix}$ $\Rightarrow$ 15-12mCi (99mTcO₄⁻) $\Rightarrow$ **RBC***



RBC labeling with ^{99m}Tc

- ▶ **1: ejection fraction** $\% \text{ EF} = \frac{\text{AED} - \text{AE}}{\text{AED}} * 100$
- ▶ **2: Vascular malformations and internal bleeding**
- ▶ **3: Spleen scan**
- ▶ $\text{TcO}_4^- + (\text{Sn}^{+2}, \text{RBC}) = \text{RBC}^*$



► 3: invivitro:

5 micro/Kg (SnCl_2) $\Rightarrow$ adminestred 30min

$\Rightarrow$ Blood $\Rightarrow$ $^{99}\text{TcO}_4^-$ $\Rightarrow$ **RBC***

► 4: New invitro:

Blood $\Rightarrow$ citrate + SnCl_2 $\Rightarrow$ ACD (acid citrate dextrose)

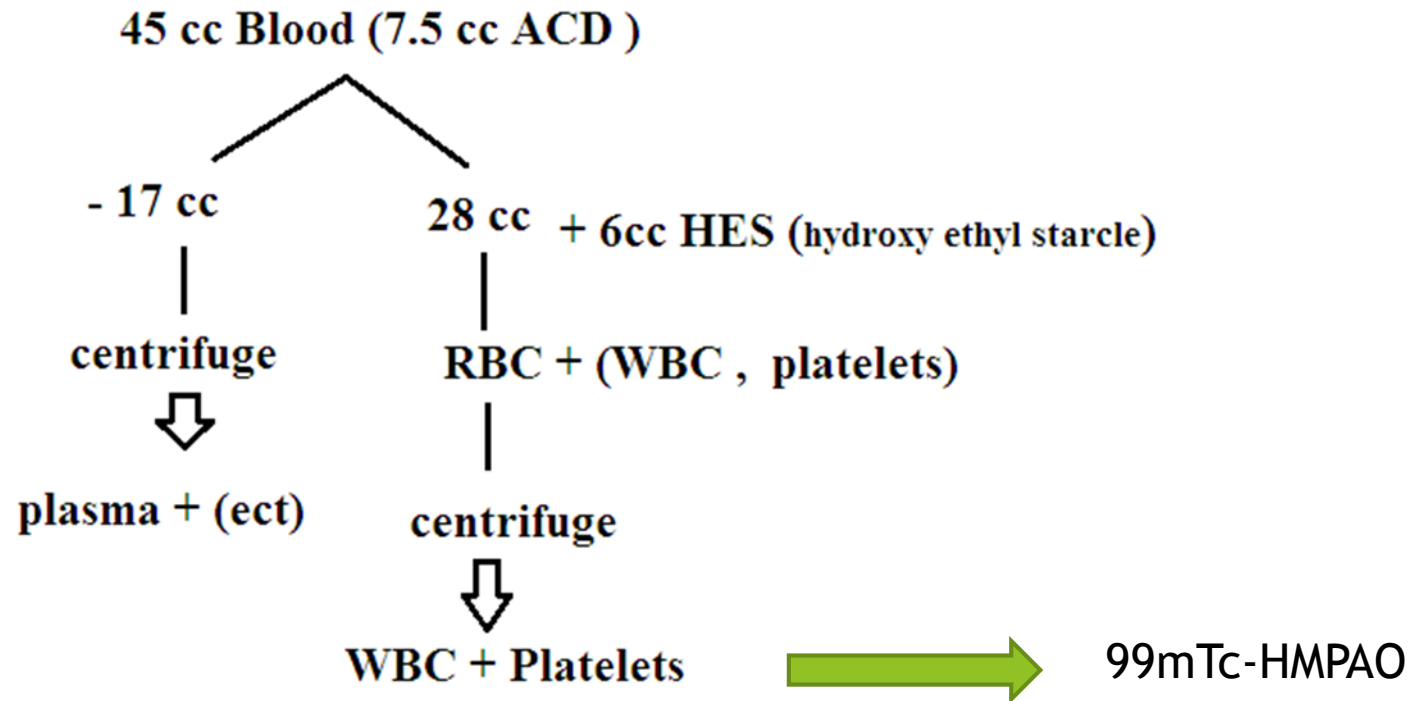
$\Rightarrow$ NaOCl $\Rightarrow$ 10-20 mCi ($^{99}\text{TcO}_4^-$) 20min $\Rightarrow$ centrifuge

$\Rightarrow$ **RBC***

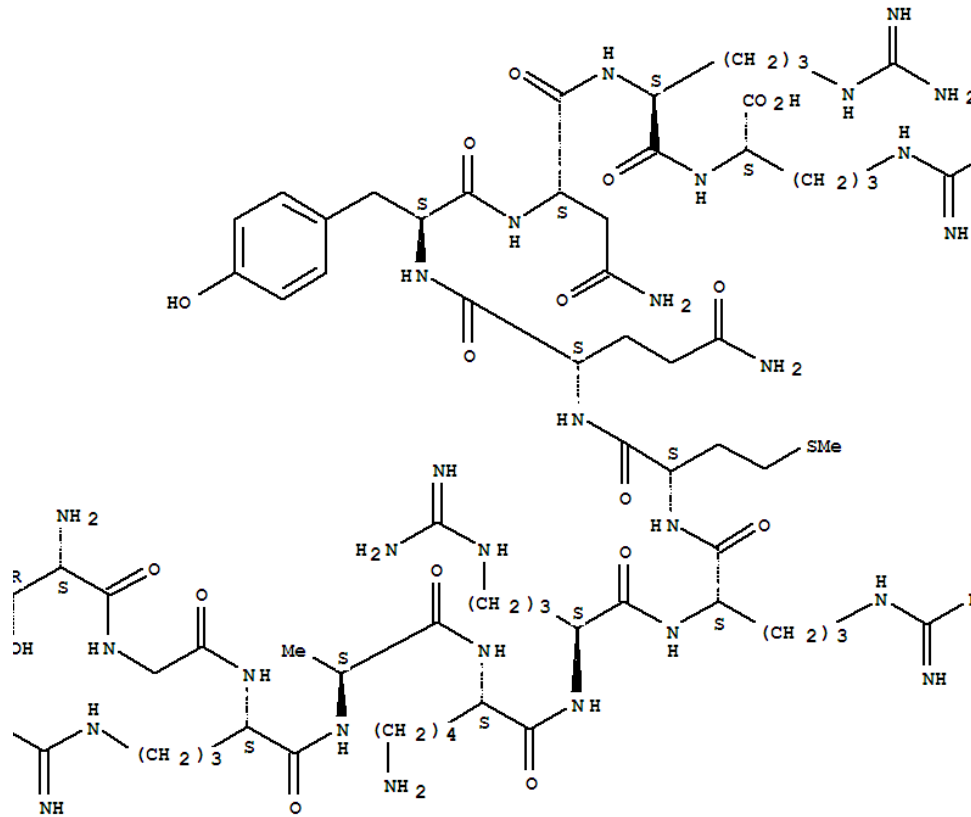


Radiolabeling of WBC

1: infection



^{99m}Tc -ubiquicidin

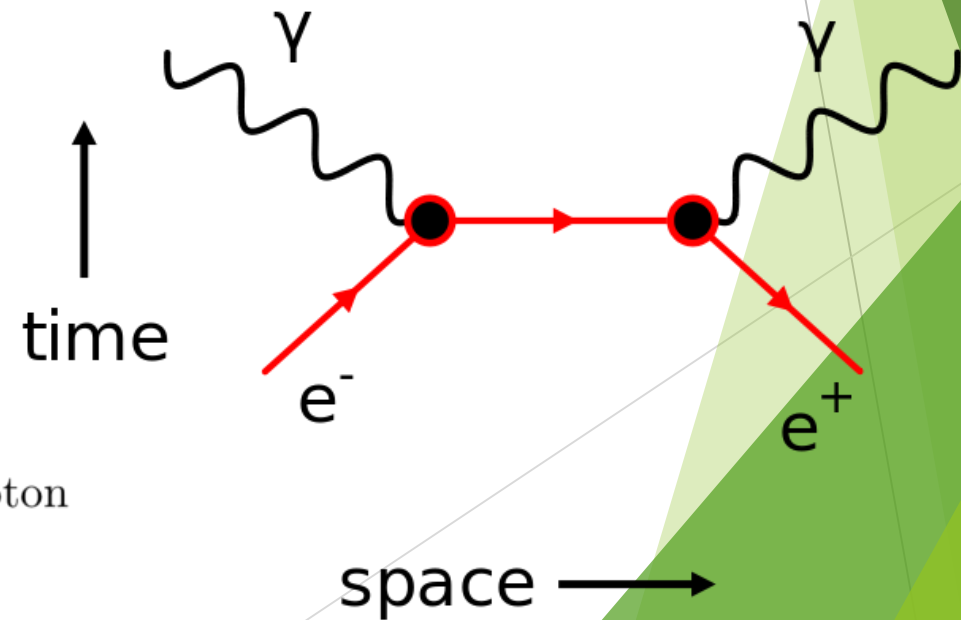
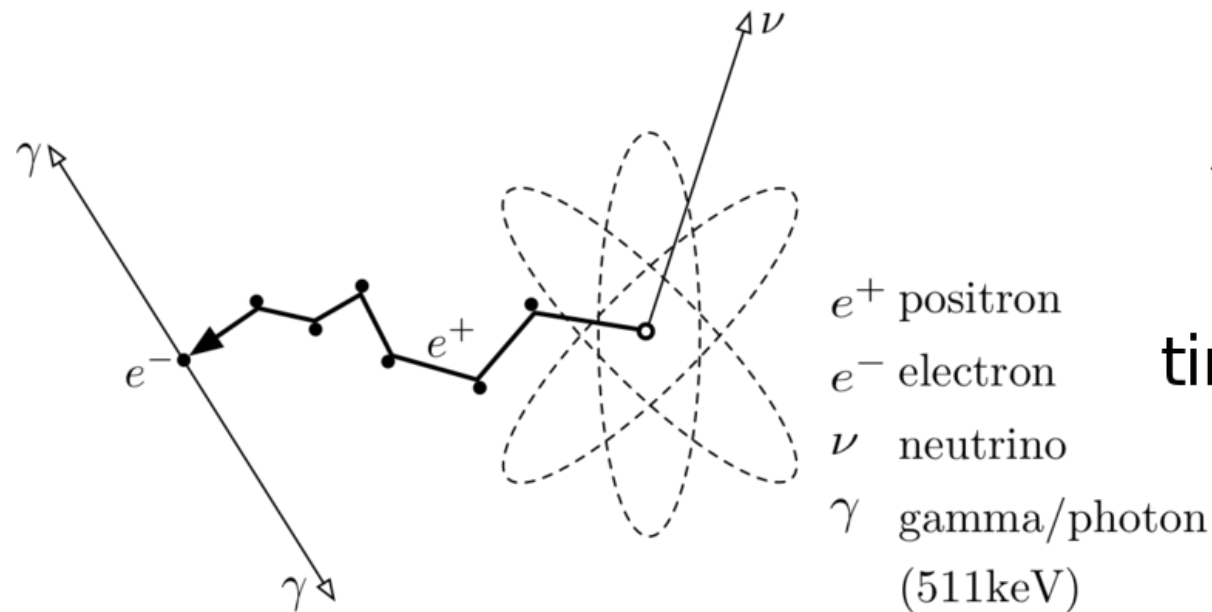


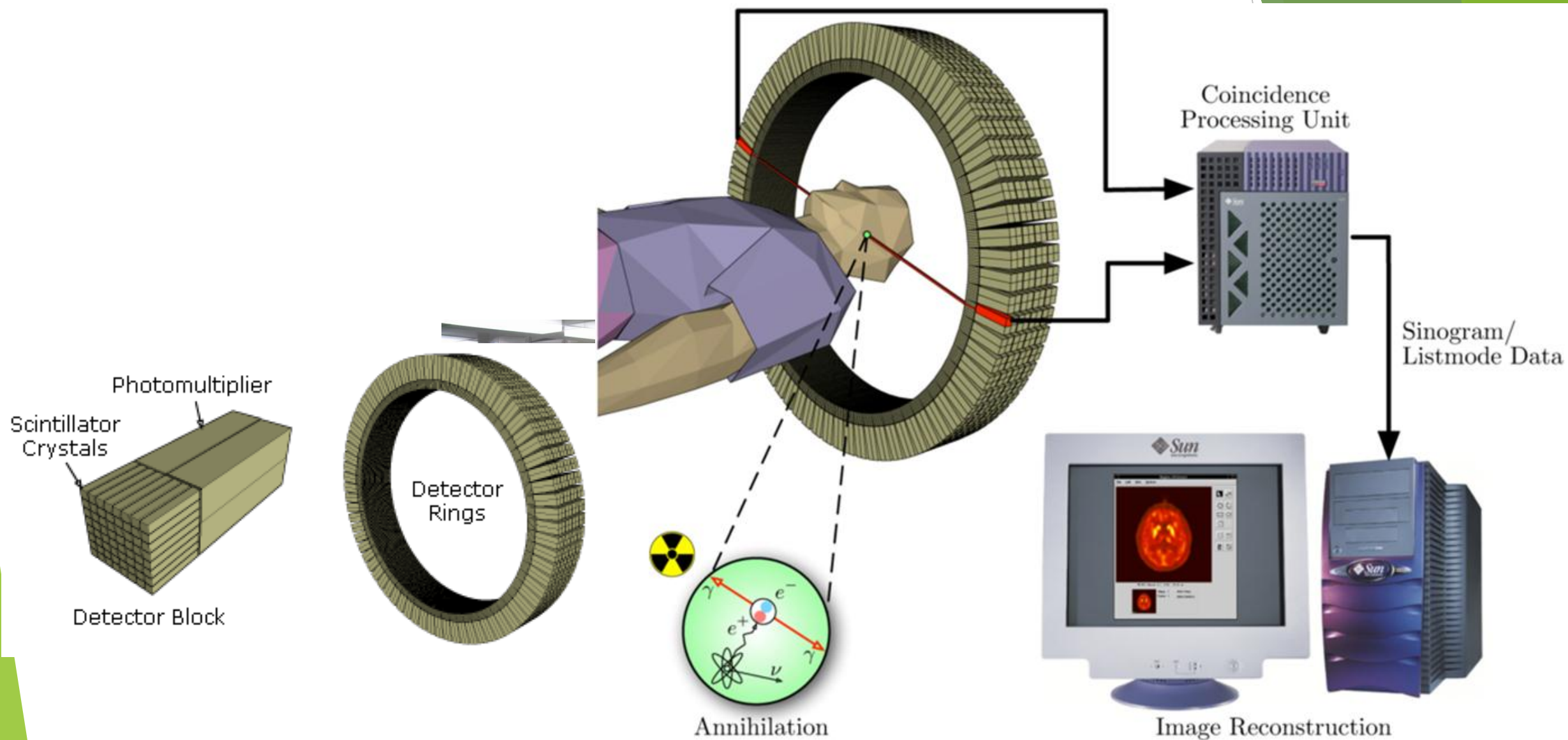
PET radiopharmaceuticals



Electron–positron annihilation

- ▶ Electron–positron annihilation occurs when an electron (e^-) and a positron (e^+ , the electron's antiparticle) collide. The result of the collision is the annihilation of the electron and positron, and the creation of gamma ray photons or, at higher energies, other particles:





Isotope	Halflife	fraction Max.	Energy range(mm)	production
C-11	20.4 mins	0.99 0.96 MeV	0.4 mm	cyclotron
N-13	9.96 mins	1.00 1.20 MeV	0.7 mm	cyclotron
O-15	123 secs	1.00 1.74 MeV	1.1 mm	cyclotron
F-18	110 mins	0.97 0.63 MeV	0.3 mm	cyclotron
Cu-62	9.74 mins	0.98 2.93 MeV	2.7 mm	generator
Cu-64	12.7 hours	0.19 0.65 MeV	0.3 mm	cyclotron
Ga-68	68.3 mins	0.88 1.83 MeV	1.2 mm	generator
Br-76	16.1 hours	1.00 1.90 MeV	1.2 mm	cyclotron
Rb-82	78 secs	0.96 3.15 MeV	2.8 mm	generator
I-124	4.18 days	0.22 1.50 MeV	0.9 mm	cyclotron



^{18}F is the most important

- ▶ **1: Low positron energy (0.64 MeV) with a short range in tissue (Max. 2.4 mm)**
- ▶ **2: Can be produced in high specific activity**
- ▶ **3: Fluorine is the most electronegative of all elements and can react with many organic and inorganic chemicals.**
- ▶ **4: It can react as an electrophile or a nucleophile chemical species.**
- ▶ **5: Relatively high labeling yields (20–70%) in the synthesis of ^{18}F -PET tracers**
- ▶ **7: Acceptable radiation dosimetry for multiple studies in a patient**
- ▶ **8: The physical $T_{1/2}$ (110 min) allows for the transport from the production site to the PET centers**



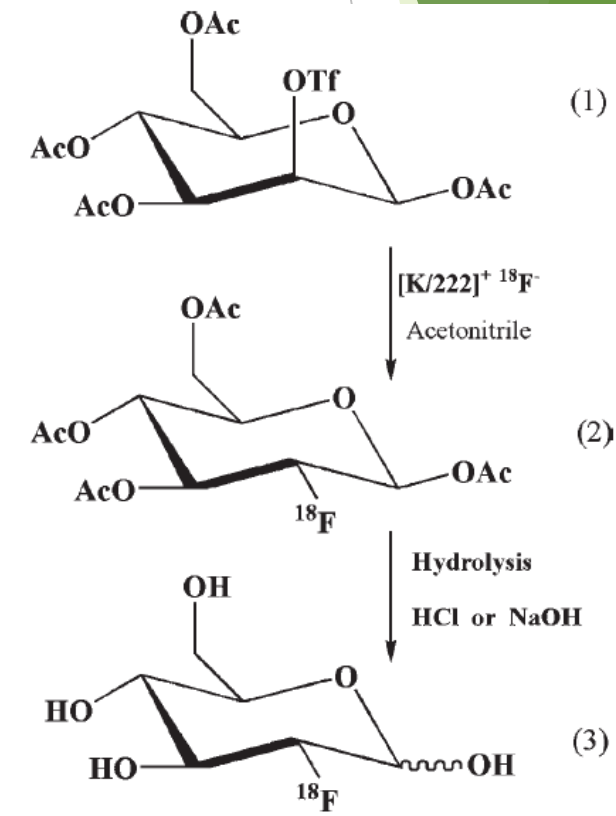
Biochemical process	Radiotracer	Mechanism of uptake or localization
Glucose metabolism	[¹⁸ F]FDG	Substrate for <i>hexokinase</i> in glucose metabolism
Bone metabolism	¹⁸ F-fluoride	Incorporation in the hydroxyapatite crystals in bone
Membrane synthesis	[¹⁸ F]Fluorocholine	Substrates for <i>choline kinase</i> in choline metabolism
Lipid synthesis	[¹⁸ F]Fluoroacetate	Substrate for <i>acetyl-CoA synthetase</i>
DNA synthesis	[¹⁸ F]Fluorothymidine (FLT)	Substrates for <i>thymidine kinase</i> in DNA synthesis
	[¹⁸ F]FMAU	
Hypoxia	[¹⁸ F]FMISO	Intracellular reduction and binding
	[¹⁸ F]FAZA	
Receptor Binding	[¹⁸ F]FES	Specific binding to estrogen receptors
Somatostatin Receptors	[¹⁸ F]Gluco-TOC	Specific binding to somatostatin receptor (SSTR-II)
Dopamine receptors	[¹⁸ F]Fallypride	Specific binding to D2/D3 receptors
Dopamine transporters	[¹⁸ F]FP-CIT	Binding to presynaptic dopamine transporters
Benzodiazepine receptors	[¹⁸ F]Flumazenil	Specific binding to central benzodiazepine receptors to assess neuronal integrity
Amino Acid transport and protein synthesis	[¹⁸ F]FDOPA	Precursor for the synthesis of dopamine
	[¹⁸ F]Fluoroethyltyrosine	
	[¹⁸ F]Fluoro- α -methyltyrosine	Brain amino acid transport
	[¹⁸ F]FCCA	
Apoptosis	¹⁸ F-Annexin V,	Specific binding to Phosphatidylserine (PS)
Angiogenesis	¹⁸ F-FB-E[c(RGDyK)] ₂	Integrin receptors ($\alpha_v\beta_3$) on endothelial cells
Gene expression	[¹⁸ F]Oligonucleotide	In vivo hybridization with mRNA
	[¹⁸ F]FHBG	Substrate to herpes virus <i>thymidine kinase</i>



Synthesis of **[18F]FDG**

Following production of ^{18}F in the cyclotron, the target water ($^{18}\text{O}[\text{H}_2\text{O}]$), containing several curies of ^{18}F fluoride ion, is trapped on a small column of anion exchange resin

The ^{18}F fluoride ion is eluted into a reaction vial using a solution of aqueous base, potassium carbonate (K_2CO_3), and Kryptofix 222 in acetonitrile. Some procedures substitute Kryptofix with either tetramethyl ammonium carbonate or tetrabutyl ammonium bicarbonate or hydroxide.





Baseline

12 weeks

24 weeks

43 weeks
(before retreatment)

56 weeks
(after retreatment)

20/08/2010

17/11/2010

15/02/2011

28/06/2011

27/09/2011

