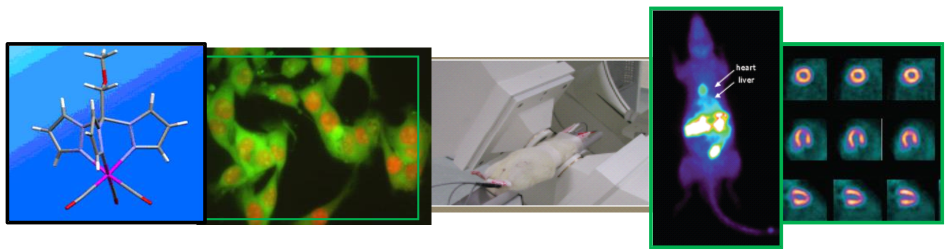
Radiochemistry



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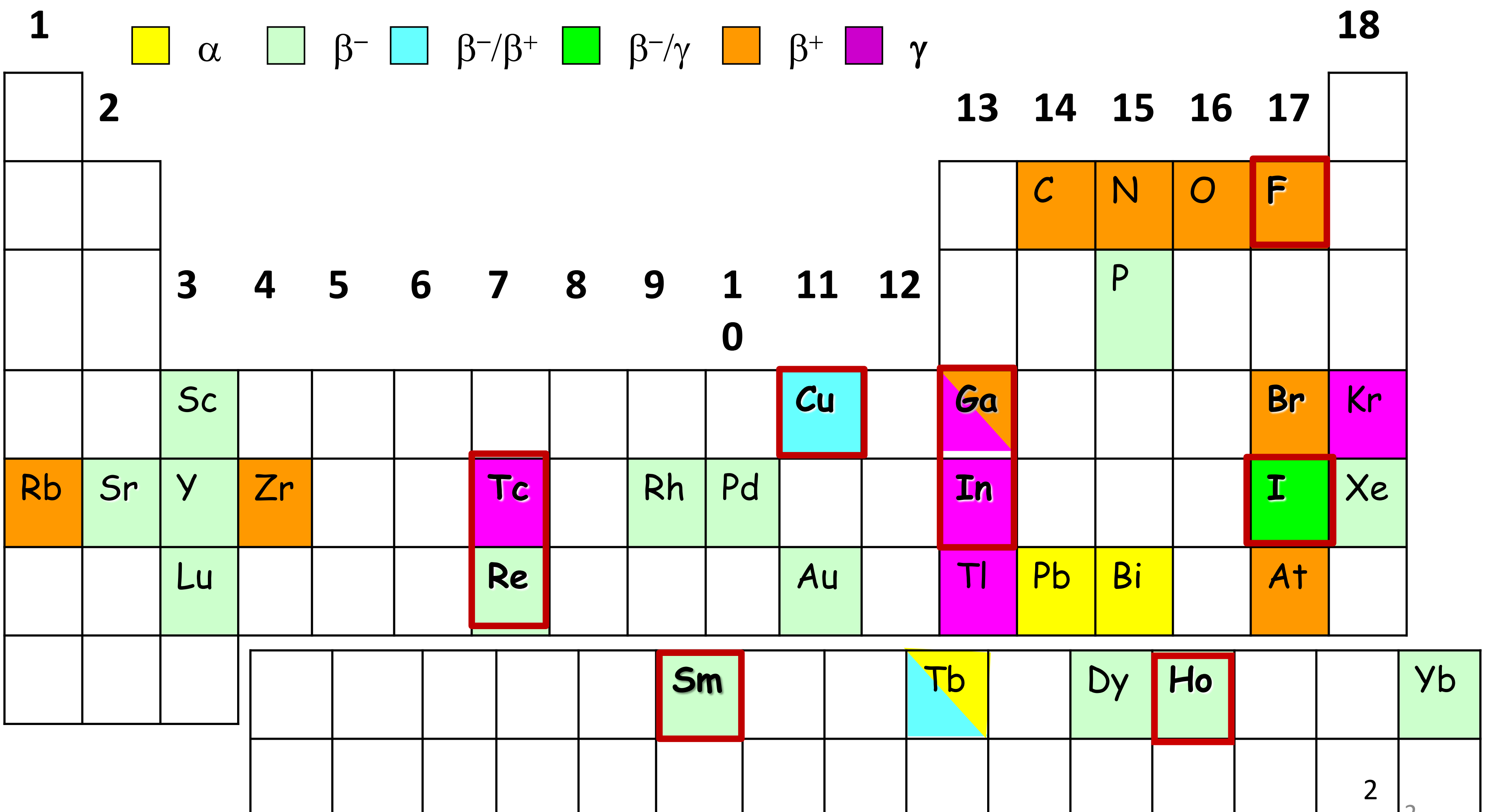
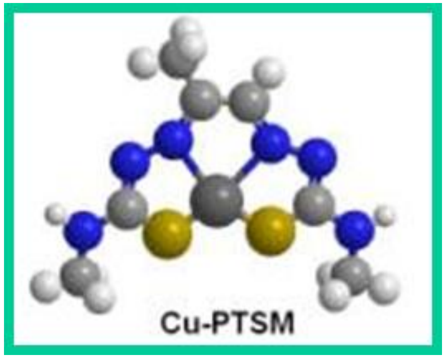
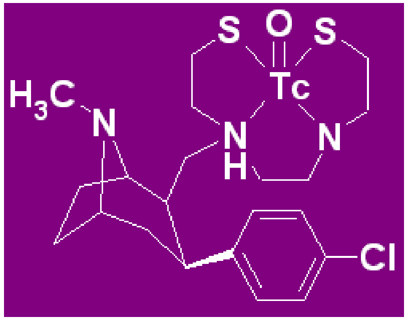
Química Biológica
Programa Doutoral ChemMedTrain
FF-UL, 19 de Janeiro, 2016

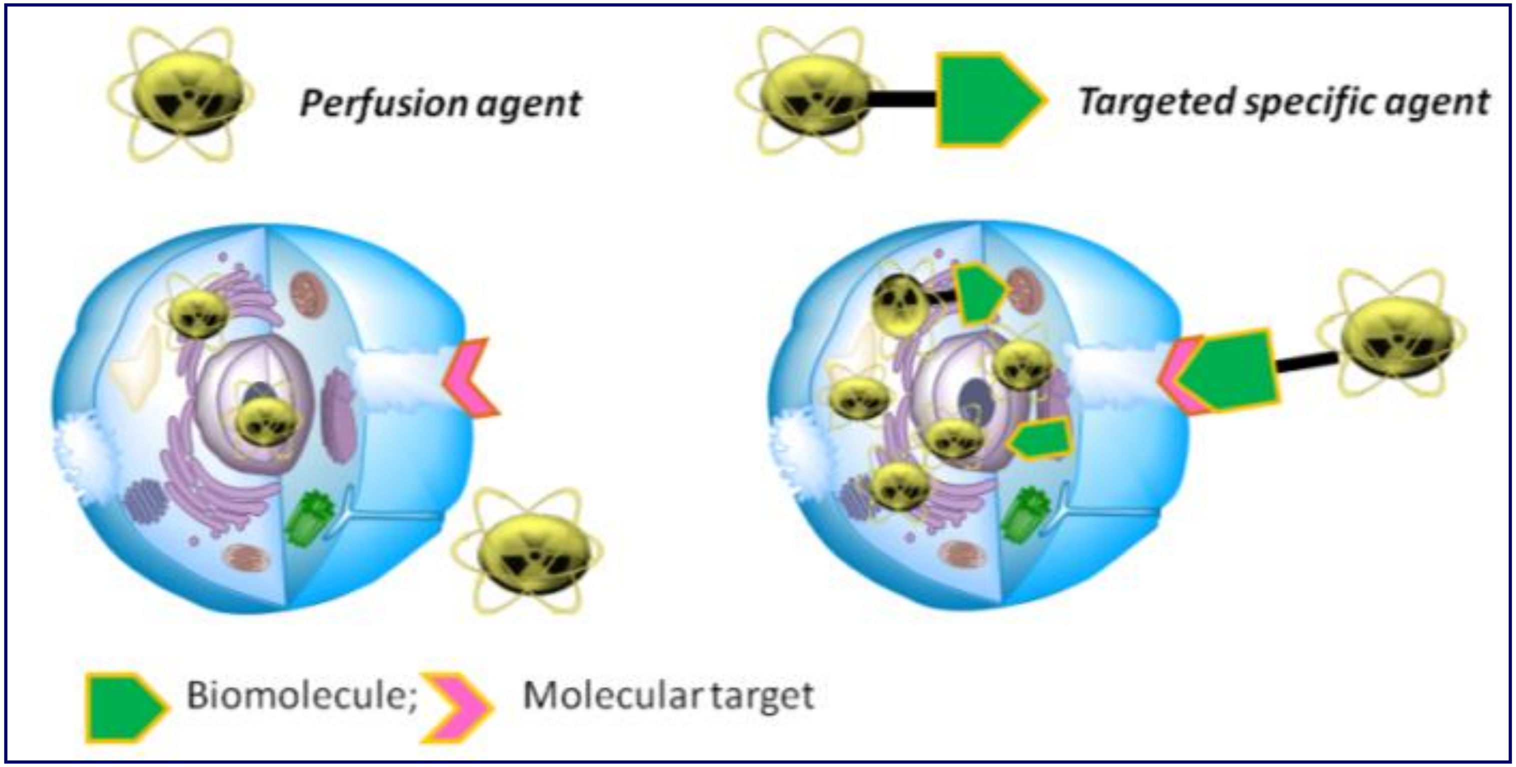
Periodic Table of Medical Radioisotopes



Target-Specific vs Perfusion Agents







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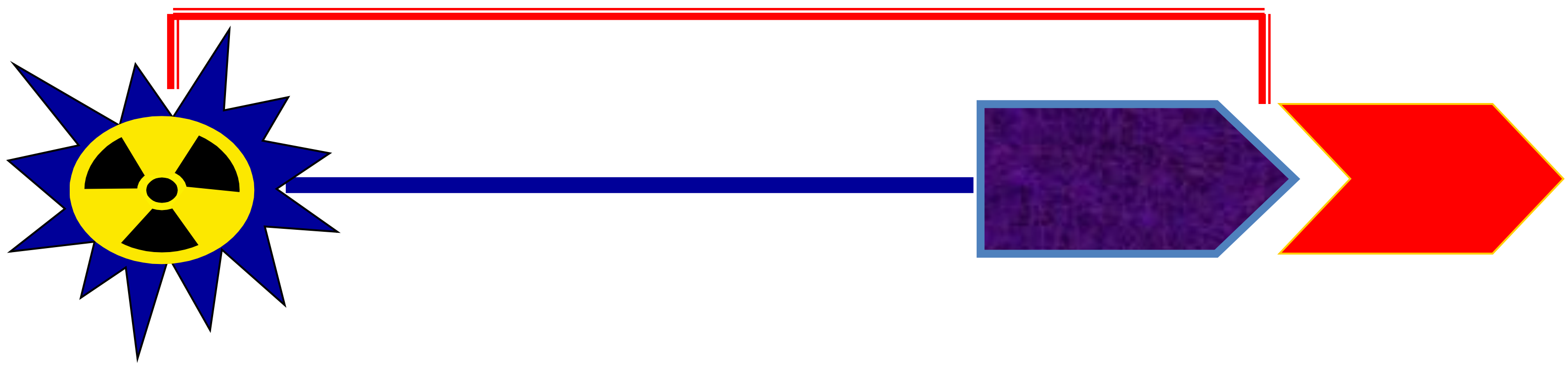
Design of Target-Specific Radioactive Probes



Radionuclide	Linker	Carrier	Target
IMAGING			
PET: β^+	Length	Antibody	Receptors
SPECT: γ	Flexibility	Protein	Enzyme
THERAPY	Hydrophilicity	Peptide	Transporters
α, β^-, Auger e-	Overall Charge	Small-Molecule	Transcription, etc

Radiolabeling: Synthetic Methods

- **Labeling Chemistry** depends on the chemical nature of the radioisotope:

  - Organic Molecules: Formation of **Covalent Bonds** (e.g. ^{11}C, ^{18}F, ^{123}I)
  - Metal Complexes: **Chelation** reactions (e.g. ^{99m}Tc, ^{111}In, $^{67/68}Ga$, ^{64}Cu)
  - **Optimization** of different **reaction parameters**: concentration of reagents, solvent, Temperature, pH, etc.

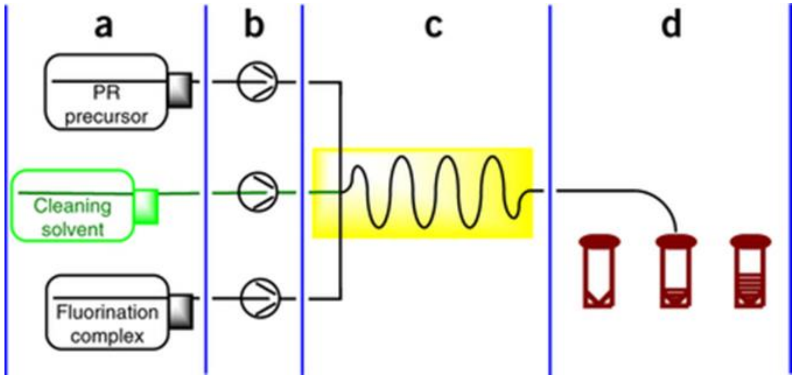
Short-Lived radioisotopes:

- Fast and high yield synthesis
- Simple purification processes
- Radiological Protection issues
- Automated Processes

Radiosynthesis: Other Differences Compared with Conventional Synthesis

- **Stoichiometry**: There is no stoichiometry between the reaction partners (i.e., the radionuclide and the precursor molecule)! A huge excess of the precursor is present in the reaction solution compared to the amount of radionuclide.

- Very low mass of reaction partners (often 1 mg precursor or less). For this reason, **microfluidic techniques** are increasingly being used to synthesize radiopharmaceuticals



Microfluidic techniques vs traditional vessel-based techniques:

- higher yields,
- shorter reaction times
- reduced amounts of reagents

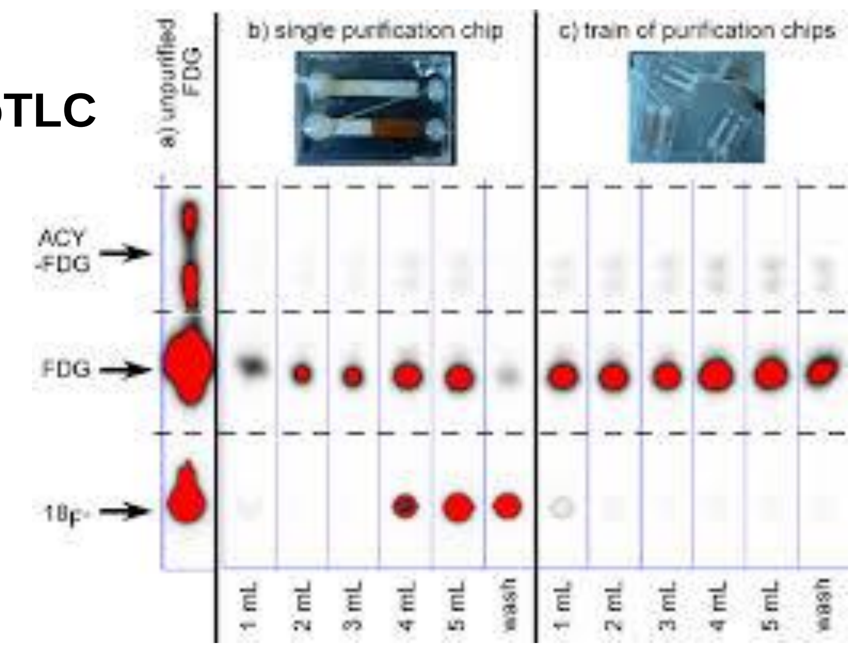
- **Radiolysis**: in solutions with high radioactivity concentrations radiolysis processes can be a major factor in the formation of unwanted by-products.

Characterization of the Radioprobes

-The low mass of the radionuclides (high specific activity) precludes the characterization of the radioprobes by the common structural analytical techniques (e.g. NMR, X-ray diffraction analysis, MS).

-The radiochemical purity of the probes is determined by chromatographic techniques (RadioTLC or RadioHPLC) using γ-detection.

RadioTLC

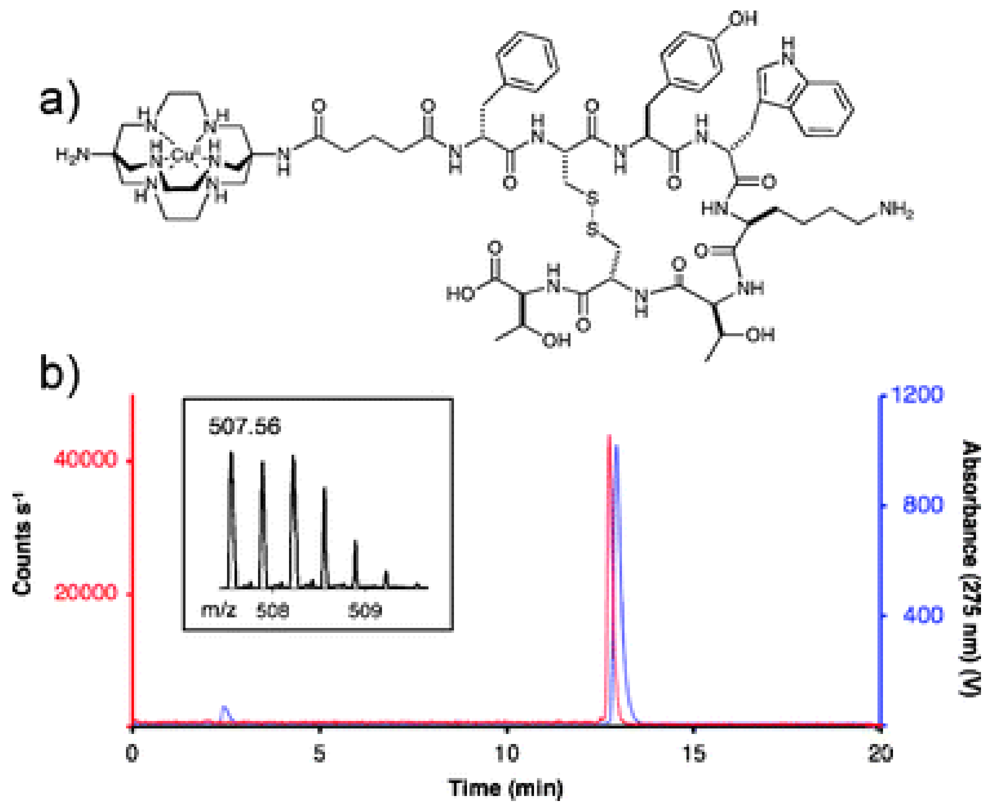


Characterization of the Radioprobes

- RadioHPLC is used to determine the radiochemical purity of the probe but also to assess its chemical nature by comparison with the non-radioactive congener fully characterized by the common analytical techniques

γ detector

UV detector



P.S. Donnelly et al., ***Chem. Commun.***, 2009, 3237-3239

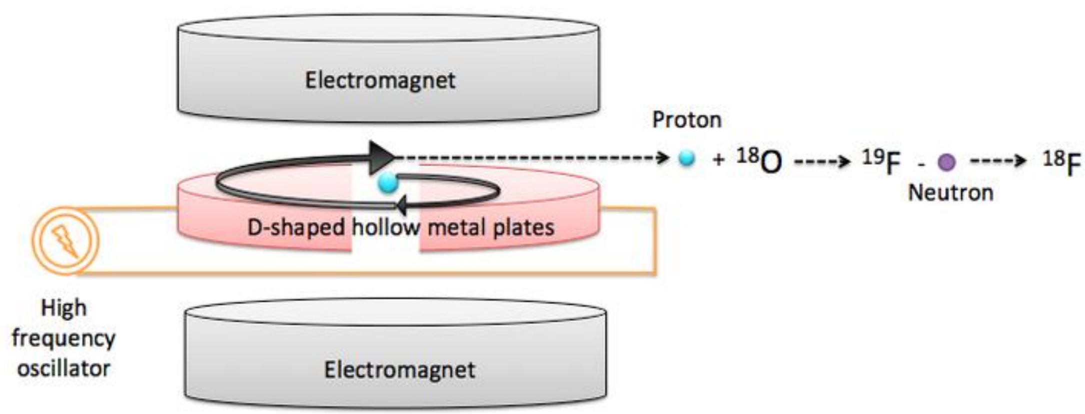
^{18}F-Labelling/Production of ^{18}F

- Most important PET radionuclide

- $T_{1/2} \approx 110$ min: enough to perform the radiosynthesis and with minimization of radiation burden

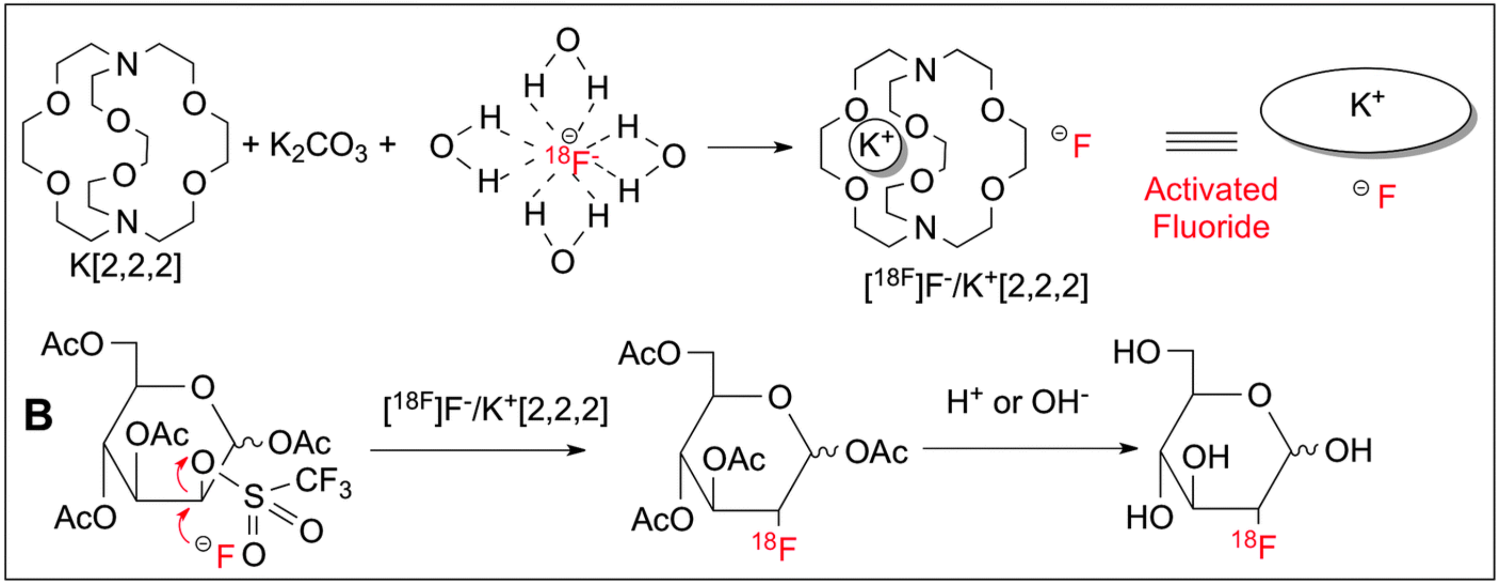
- Radiosynthesis usually starts with $Na^{18}F$ that reacts with appropriate precursors in dried organic solvents.

- $Na^{18}F$ is produced in a cyclotron by a $^{18}O(p,n)^{18}F$ reaction using a target of enriched $H_2{}^{18}O$



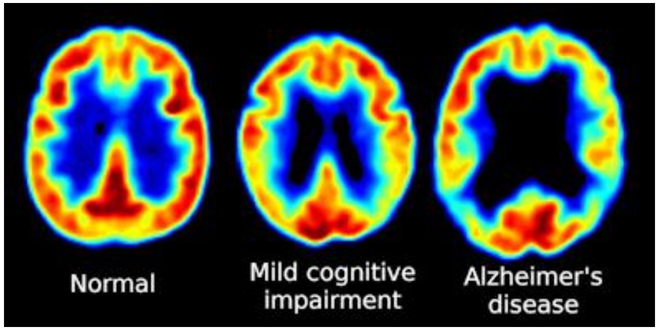
^{18}F-Labelling/ Nucleophilic Aliphatic Substitution

- **[^{18}F]FDG synthesis**



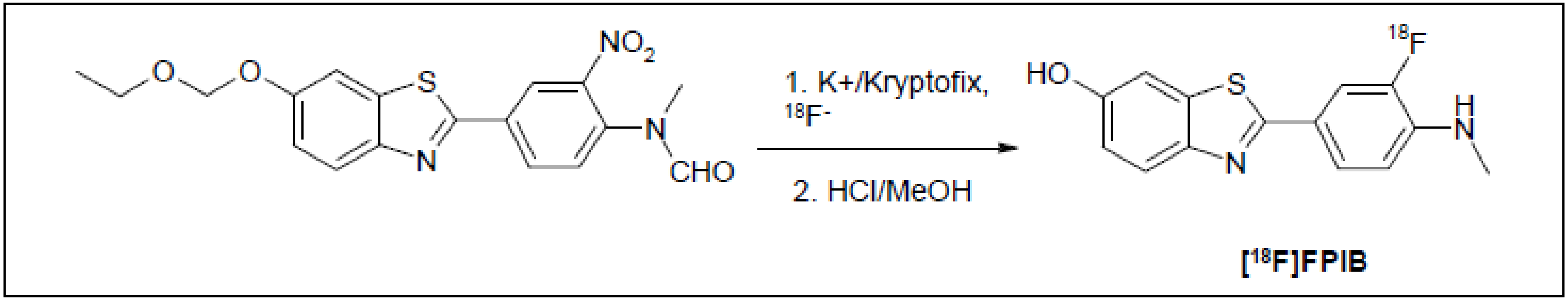
- Automated Synthesis Modules

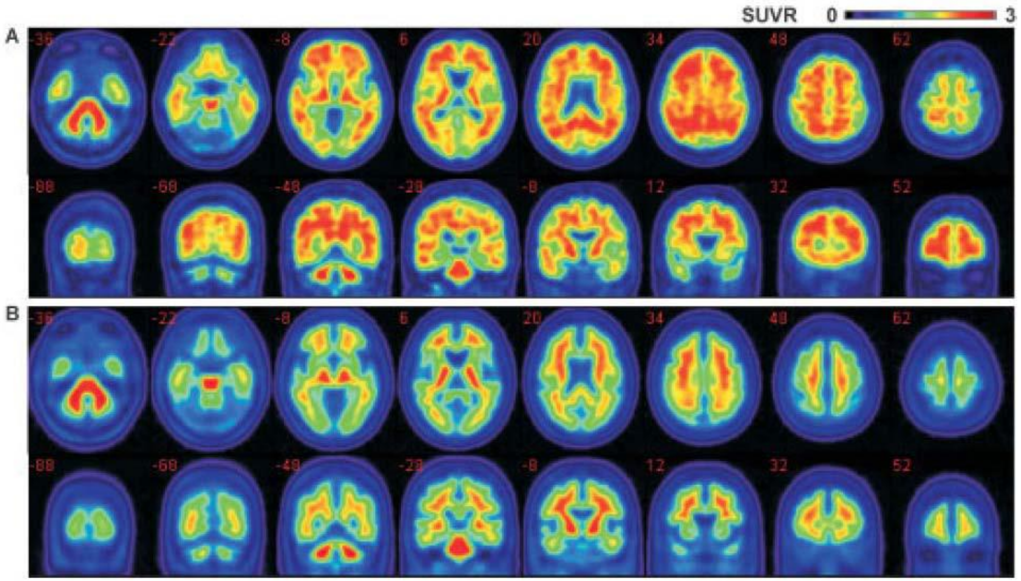
- [^{18}F]FDG is the most important PET radiopharmaceutical (oncology, cardiology, neurology)



^{18}F-Labelling/Nucleophilic Aromatic Substitution

- **[^{18}F]Flutemetamol (^{18}FPIB) synthesis**

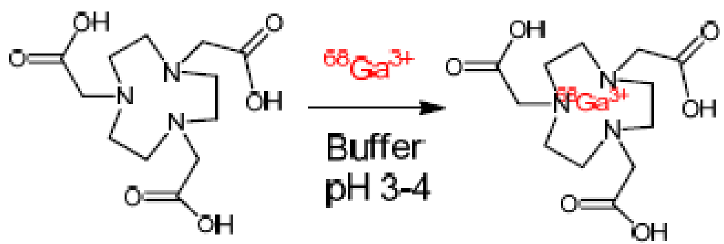




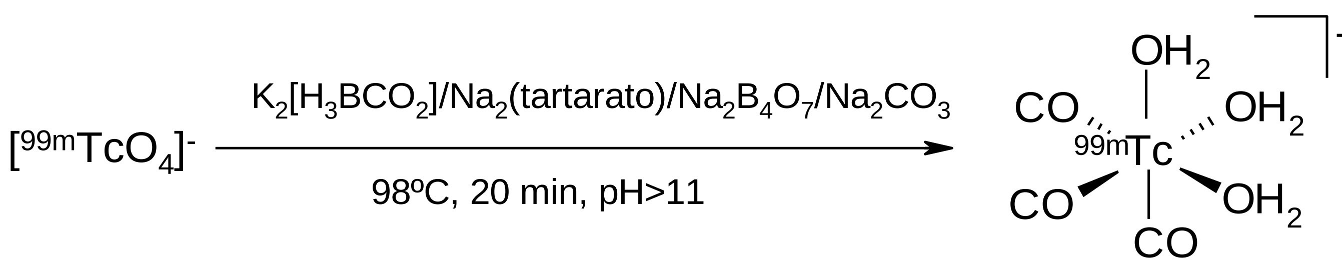
Diagnostic tool for Alzheimer's disease (AD) based on the detection of β-amyloid plaques

Labelling with Radiometals

-The labelling is performed via chelation reactions between simple inorganic forms of the radiometals and appropriate chelators



- Unlike covalent radiolabelling (e.g with ^{11}C, ^{18}F, $^{123}I/^{131}I$), the radiometallation reactions are performed under aqueous conditions and often using freeze-dried kits.



R. Alberto et al., *J. Am. Chem. Soc.,* **1998,** 120, 7987–7988.

Labelling with Radiometals

- Chemical nature of the radiometal defines the type of radioactive precursor, the labelling strategy and the choice of proper chelators:

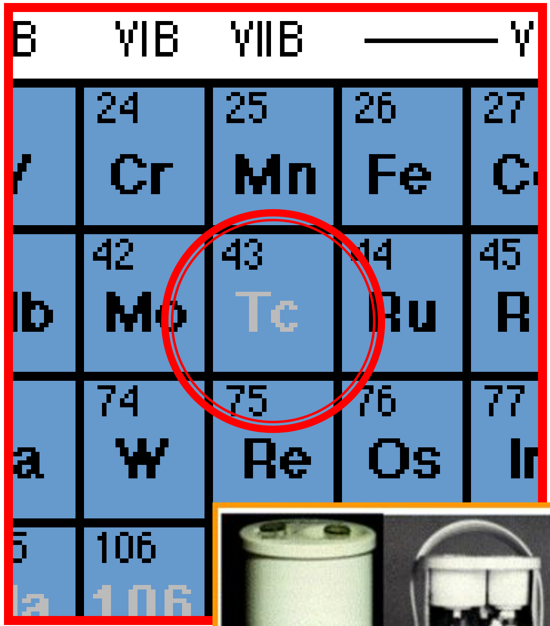
i) ^{99m}Tc, ^{186}Re, ^{188}Re: radiosynthesis always starts with $NaMO_4$ (M= Re, Tc); the radiopharmaceutical chemistry of these radiometals has unique features if compared with other radiometal

ii) ^{64}Cu/^{67}Cu: radiosynthesis starts with CuX_2 (X = Cl, CH_3COO) salts.

iii) Trivalent Radiometals (e.g. ^{68}Ga, ^{111}In, ^{90}Y, ^{177}Lu, ^{161}Tb): radiosynthesis starts with MX_3 (X = Cl, CH_3COO) salts.

Technetium-99m

RICH CHEMISTRY



^{99m}Tc generator

- The most important SPECT Radionuclide

  - ^{99m}Tc: γ 140 Kev; $T_{1/2}$= 6 h

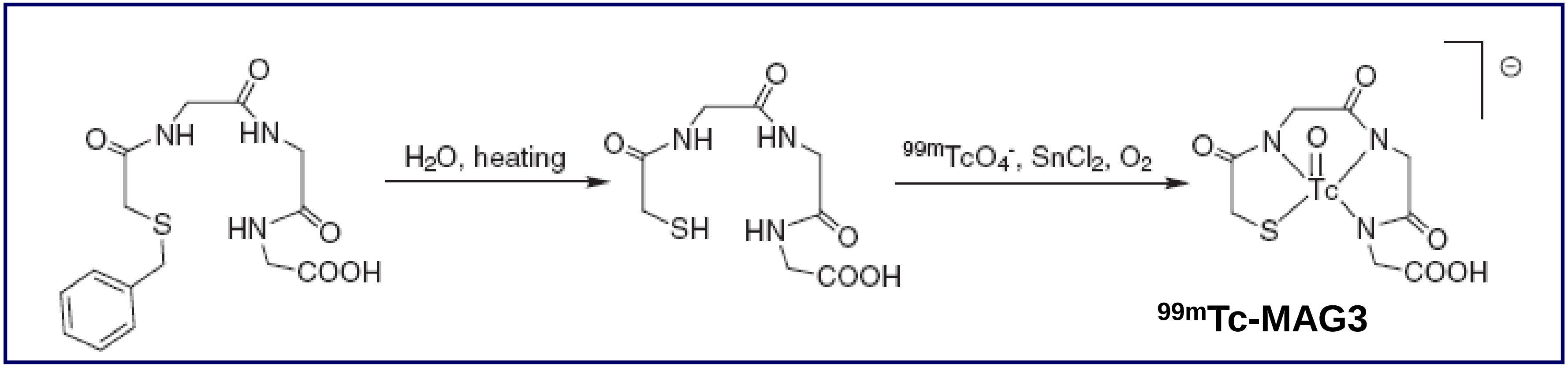
  - ^{99}Mo/^{99m}Tc Generator

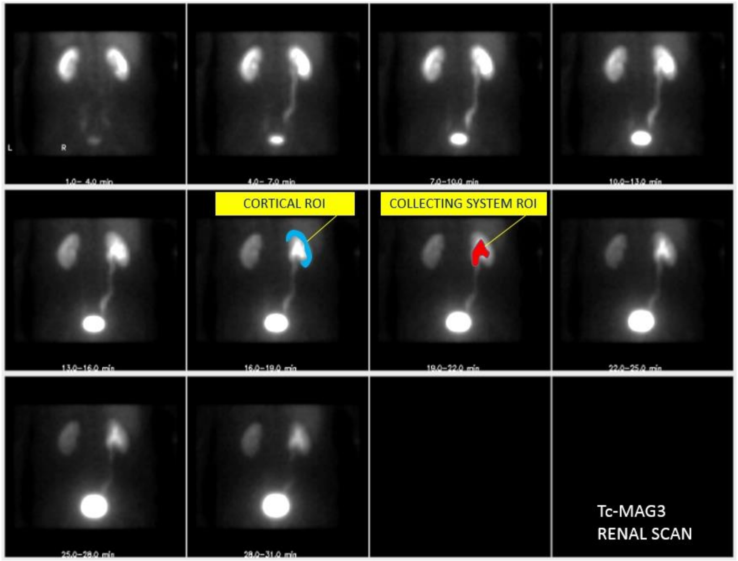
  -Variety of kits available

  - Radiopharmaceuticals in different oxidation states: Tc(I), Tc(III), Tc(IV), Tc(V)

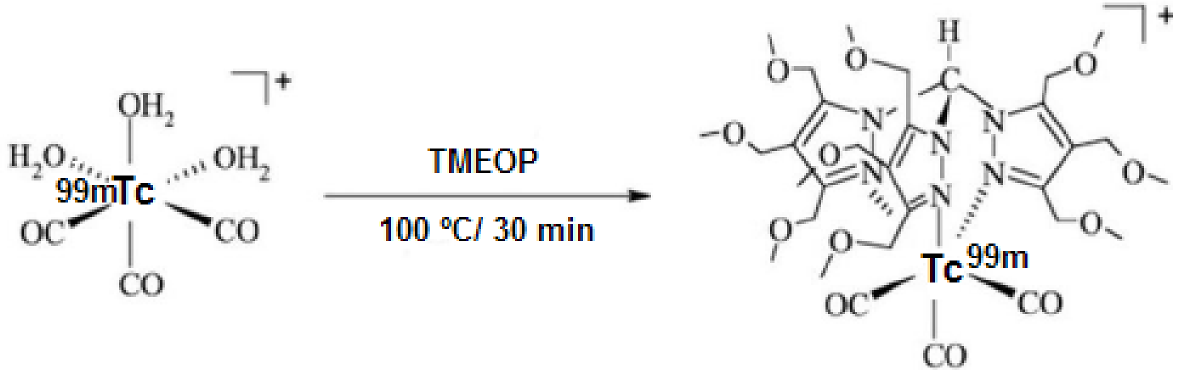
J. F. Valliant et al., *Chem. Rev.* **2010**, 110, 2903

^{99m}Tc-Labelling: Oxocomplexes

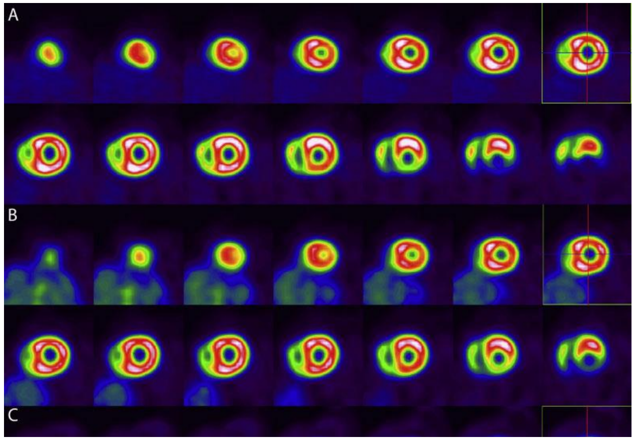




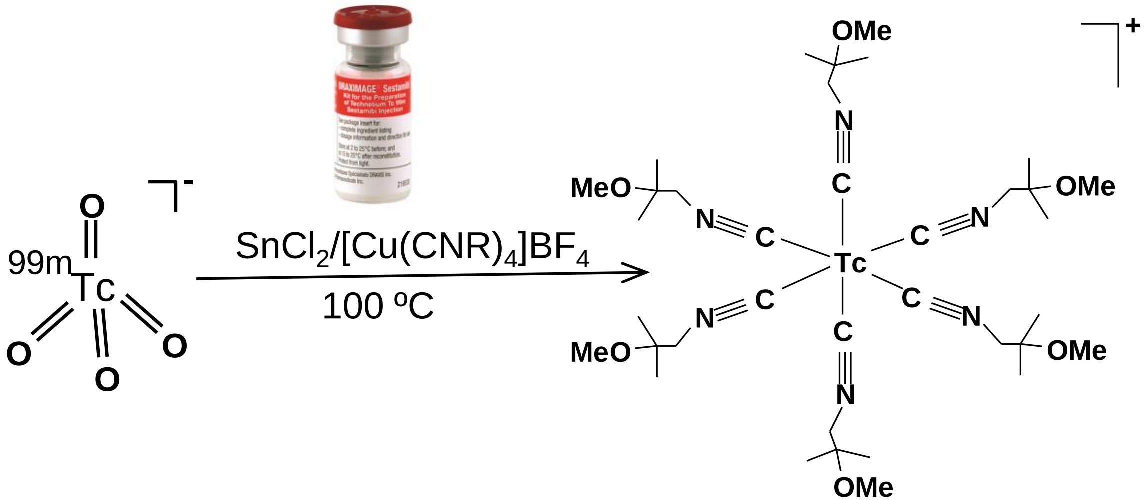
^{99m}Tc-Labelling: Organometallic Complexes



^{99m}Tc-TMEOP



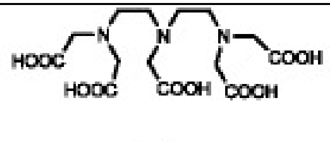
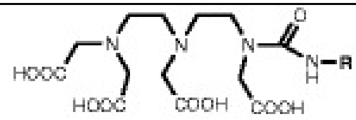
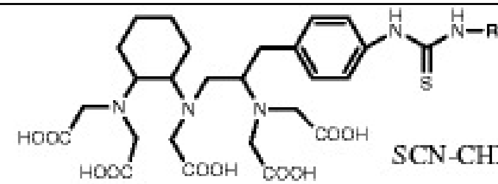
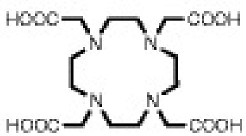
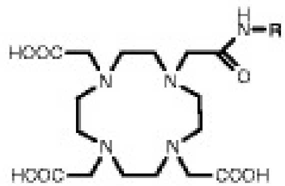
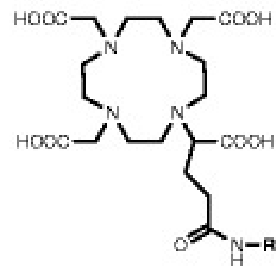
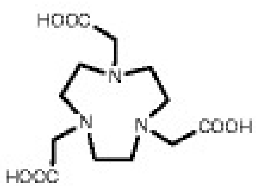
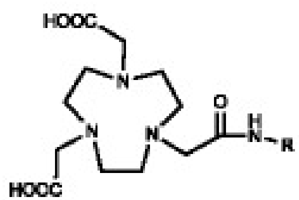
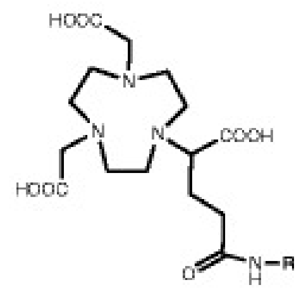
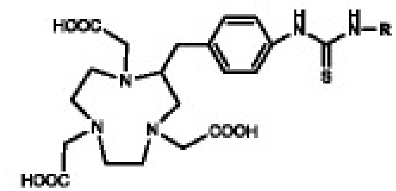
A. Paulo et al. *Contrast Media Mol. Imaging* **2011**, *6*, 178-188
I. Santos, A. Paulo, US20130131327 A1



^{99m}Tc-SESTAMIBI

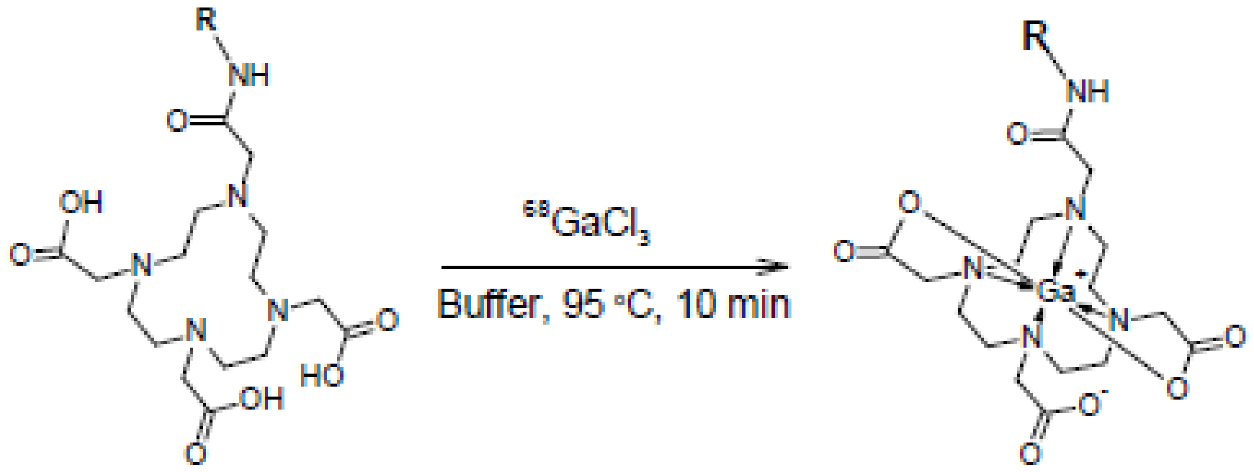
A. Jones , A. Davison et al. *Int. J. Nucl. Med. Biol.*, **1984**, 11, 225.

Labelling with Trivalent Radiometals/Chelators

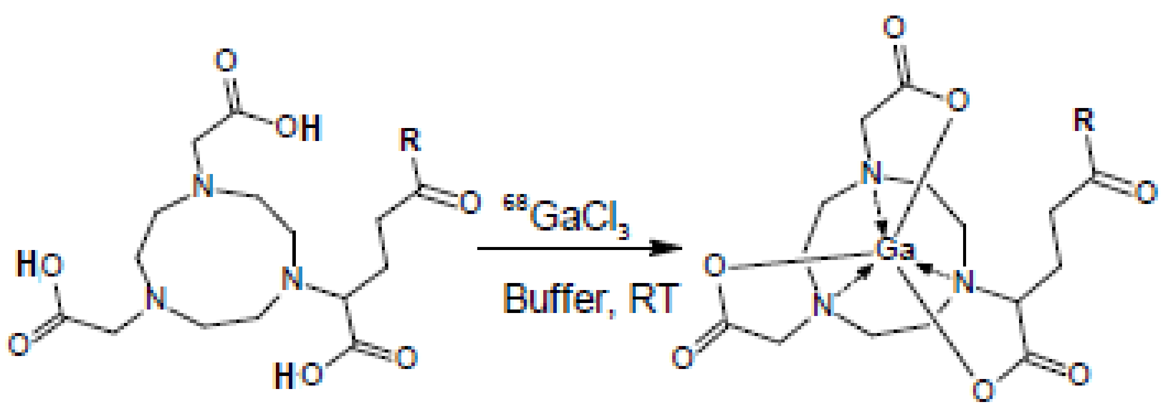
Radiometal	Chelators	Bifunctional chelators			
^{111}In	 DTPA	 DTPA-R	 SCN-CHX-A''-DTPA-R		
^{111}In $^{86/90}$Y ^{177}Lu $^{67/68}$Ga	 DOTA	 DOTA-R	 DOTAGA-R		
$^{67/68}$Ga ^{111}In $^{64/67}$Cu	 NOTA	 NOTA-R	 NODAGA-R	 SCN-Bz-NOTA-R	

A. Paulo et al., *Dalton Trans.* **2011**, *40*, 6144.

^{68}Ga-Labelling/Macrocyclic Chelators

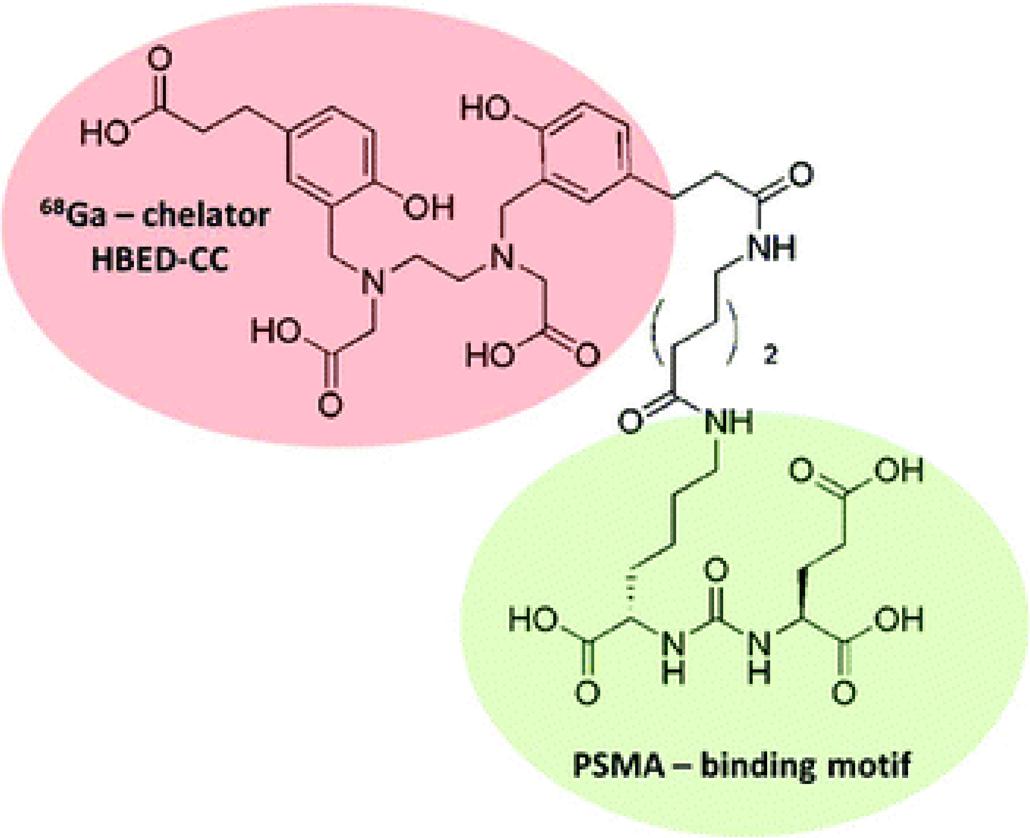


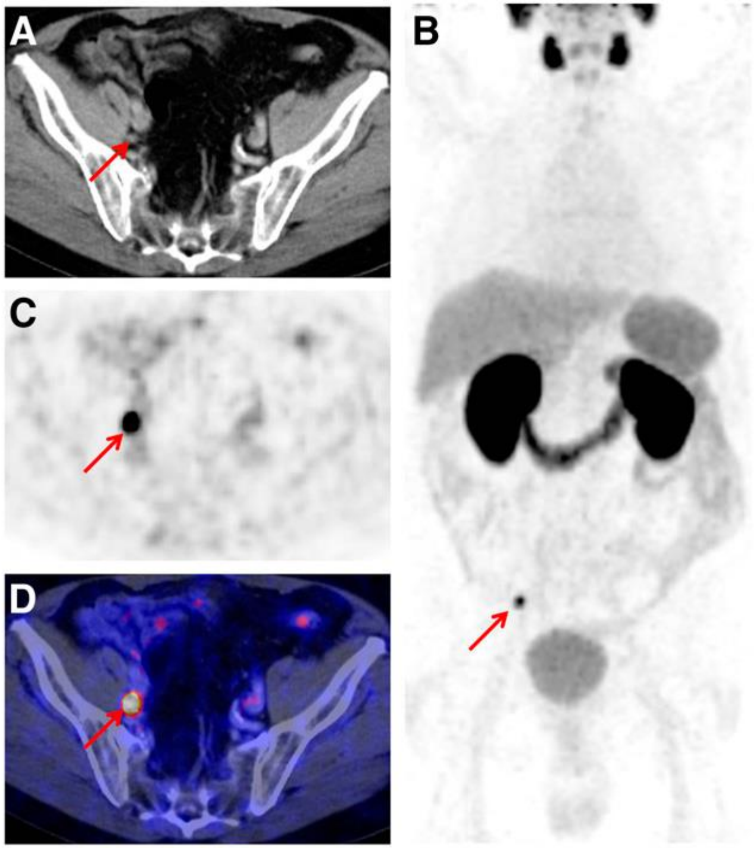
DOTA-based



NOTA-based

^{68}Ga-Labelling/Acyclic Chelators

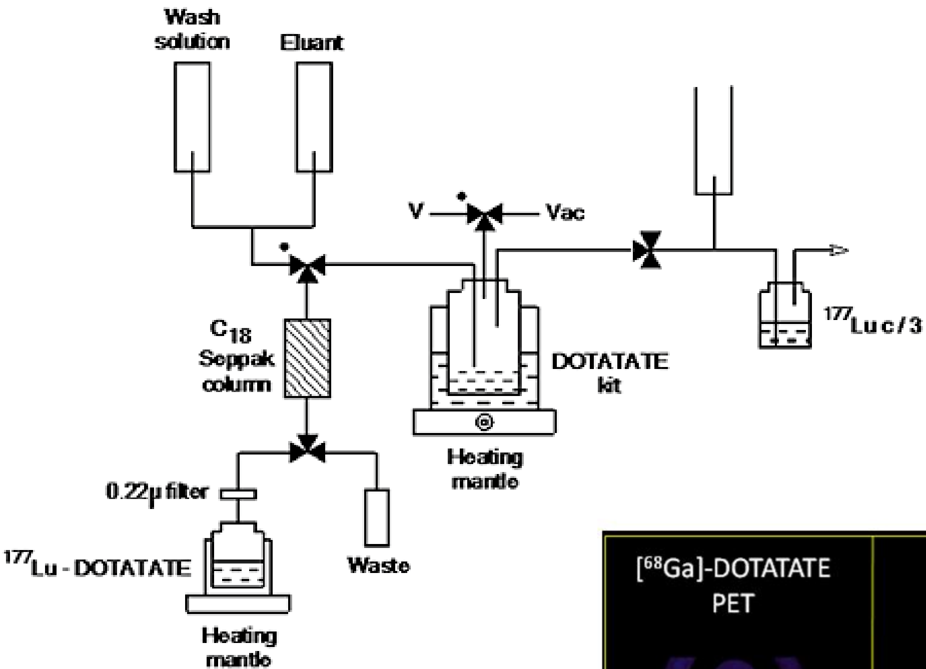


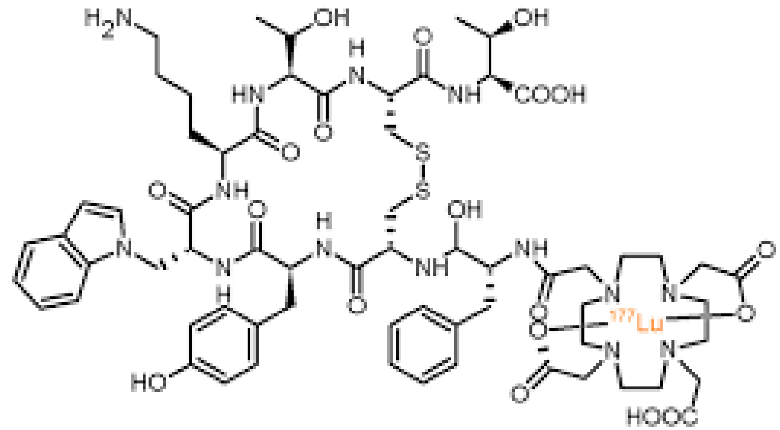


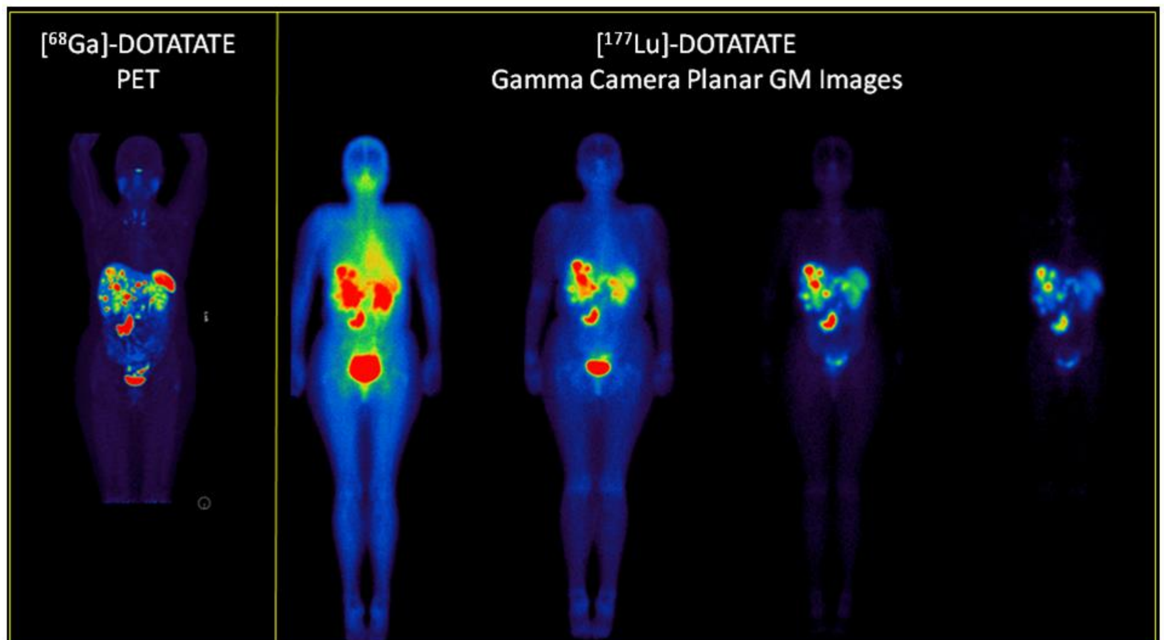
M. Eiber et al., *J Nucl Med* **2015**; 56:668–674

M. Einsenhut, *Bioconjugate Chem.,* **2012**, 23 (4), pp 688–697

Labelling with ^{117}Lu







Time after injection (hrs)	0.5	2.3	20.8	92.9
Radioactivity retained (MBq)	6378	2745	997	484

A. Mukherjee et al., *J. Label Compd. Radiopharm* **2015**, *58*, 166–172; P. J Roach et al., *Asia Oceania J Nucl Med Biol.* **2015**; 3(2):107-115