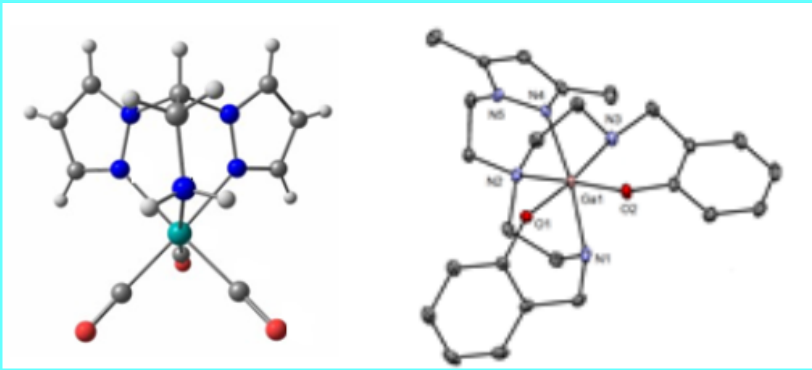
Matching Chelators and Radiometals



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Outline

- General concepts on radiopharmaceuticals, nuclear imaging and theranostics

- Radiometals in nuclear medicine

- Metal-based radiopharmaceuticals: Synthesis and characterization

- Matching Chelators with Radiometals

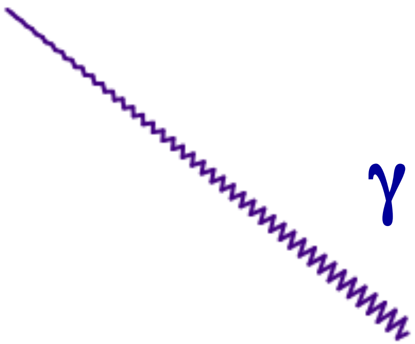
Nuclear Modalities: Imaging/Therapy

Radiopharmaceuticals:

Compounds that contain a radionuclide and are used in Nuclear Medicine for diagnostic and therapeutic applications; usually do not display a pharmacological effect

Radionuclide Therapy

Auger



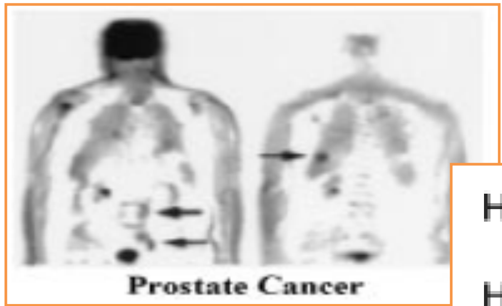
γ

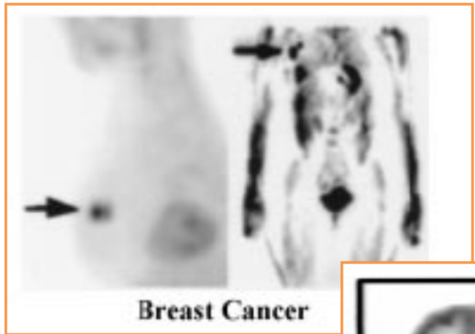
PET: Positron Emission Tomography

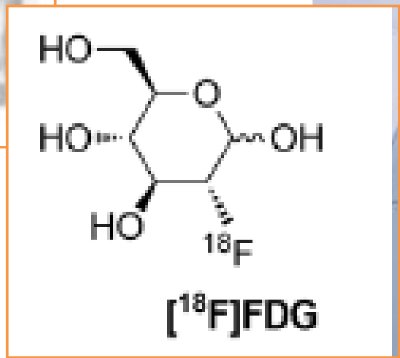
SPECT: Single Photon Emission Computorized Tomography

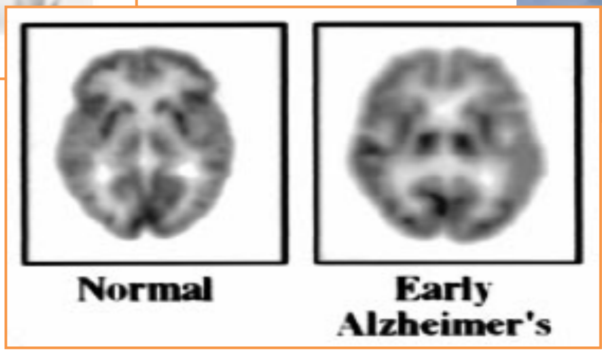
Nuclear Modalities: Imaging

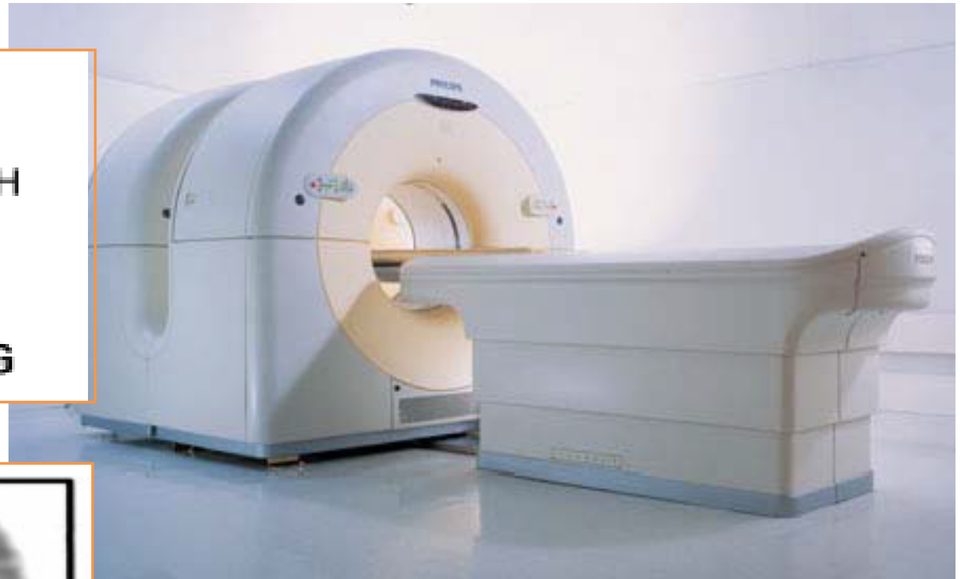
The radiopharmaceutical is injected into a subject and *a detector* outside the body detects the emitted γ rays: 50-250 keV (**SPECT**); 511 keV (**PET**)





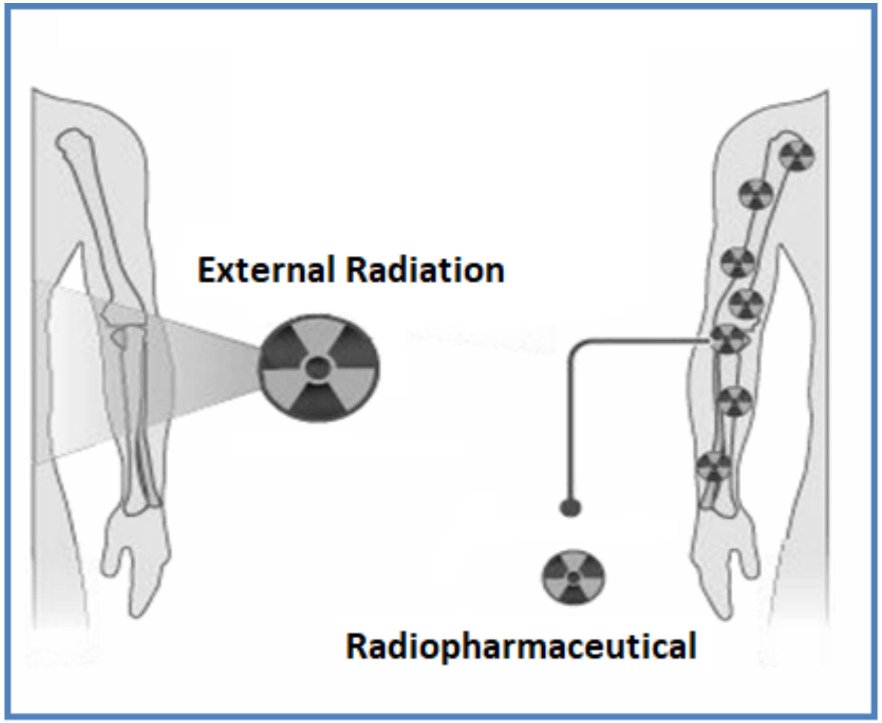


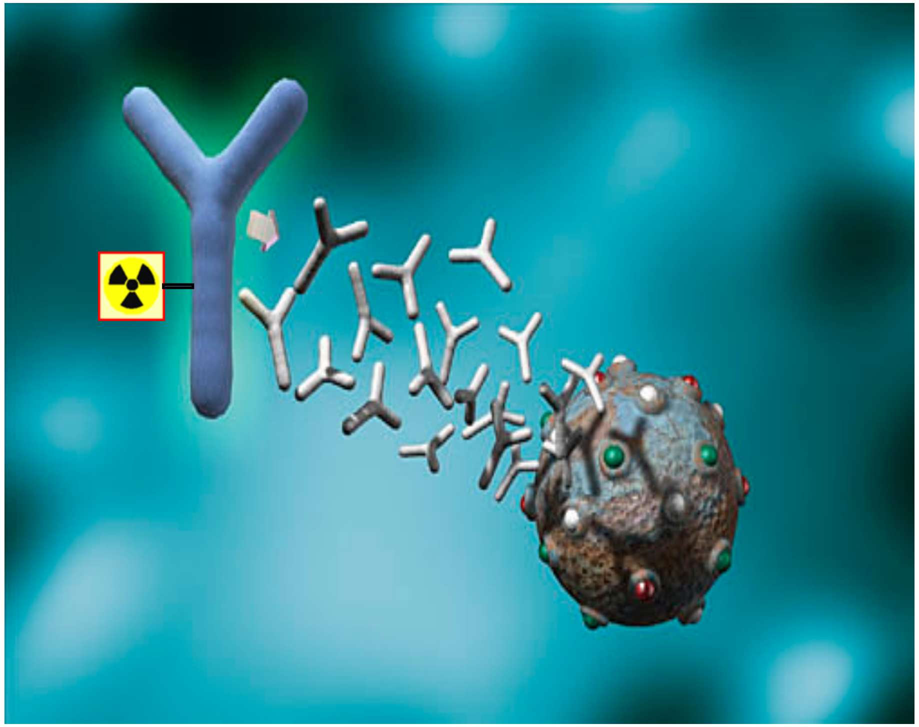




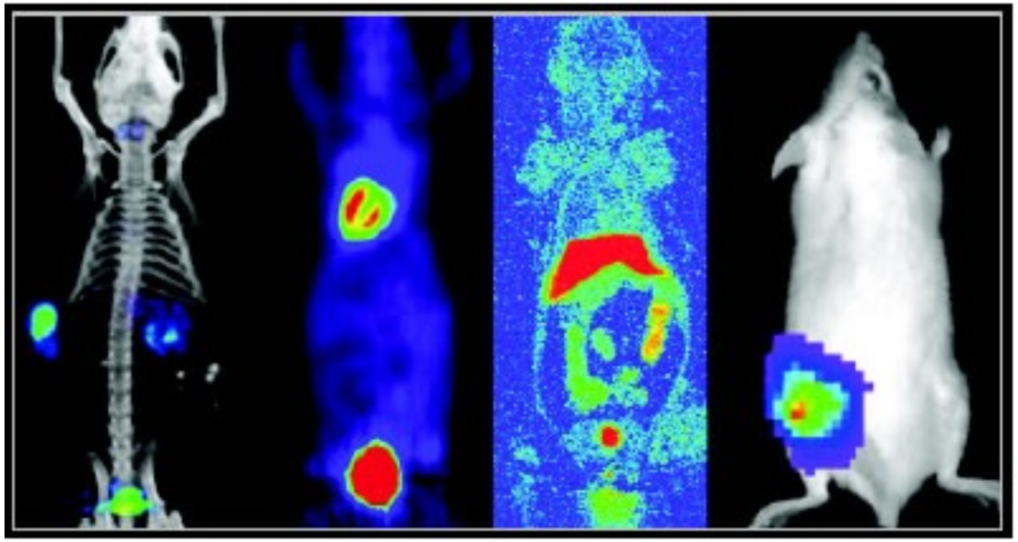
Nuclear Modalities: Therapy

The radiopharmaceutical is injected into a subject and the emitted ionizing radiation (β^- or α particles, Auger e-) exert a therapeutic effect mainly within antitumor therapies





Nuclear Imaging *vs* Other Modalities



- **MRI** :
  - High spatial resolution
  - Low sensitivity

- **Optical**
  - Cheap
  - High sensitivity
  - Low tissue penetration

- **SPECT and PET**
  - High sensitivity
  - No limit tissue penetration
  - Radionuclides both for imaging and Therapy
  - **Molecular Imaging and Theranostics**

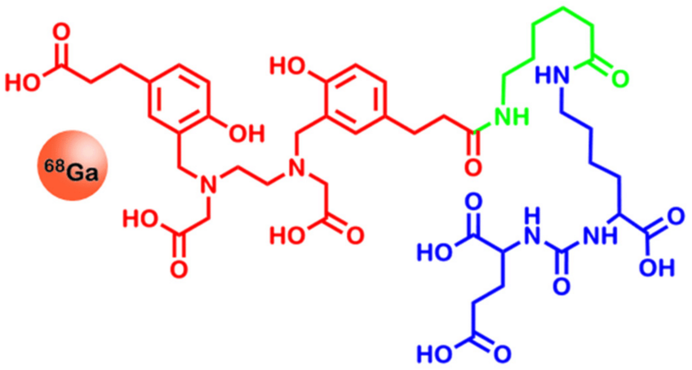
Theranostics Concept

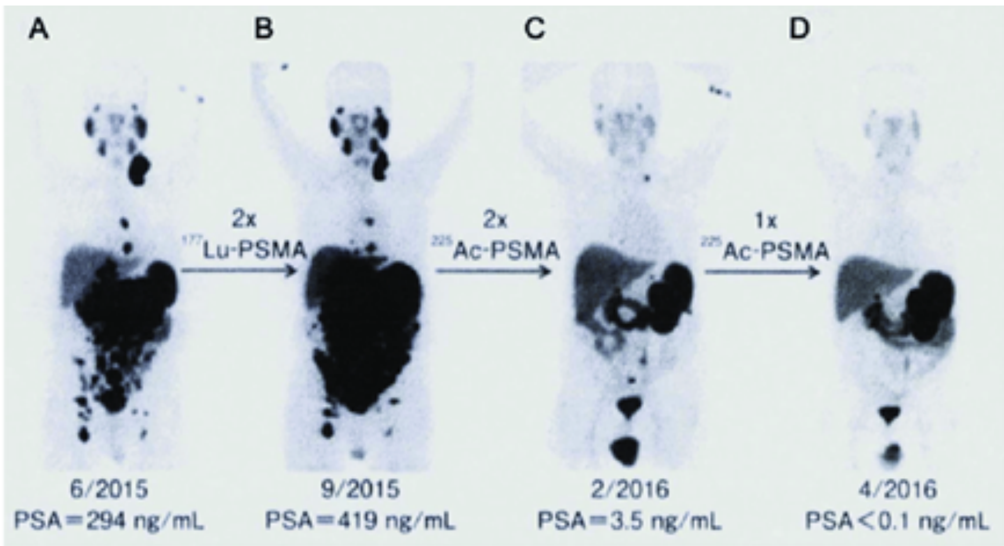
- Concept more than 20 years old.

- **Definition**: Theranostics (Tx) is the combination of a Diagnostic (Dx) tool that helps to define the right Therapeutic (Rx) tool for a specific disease.

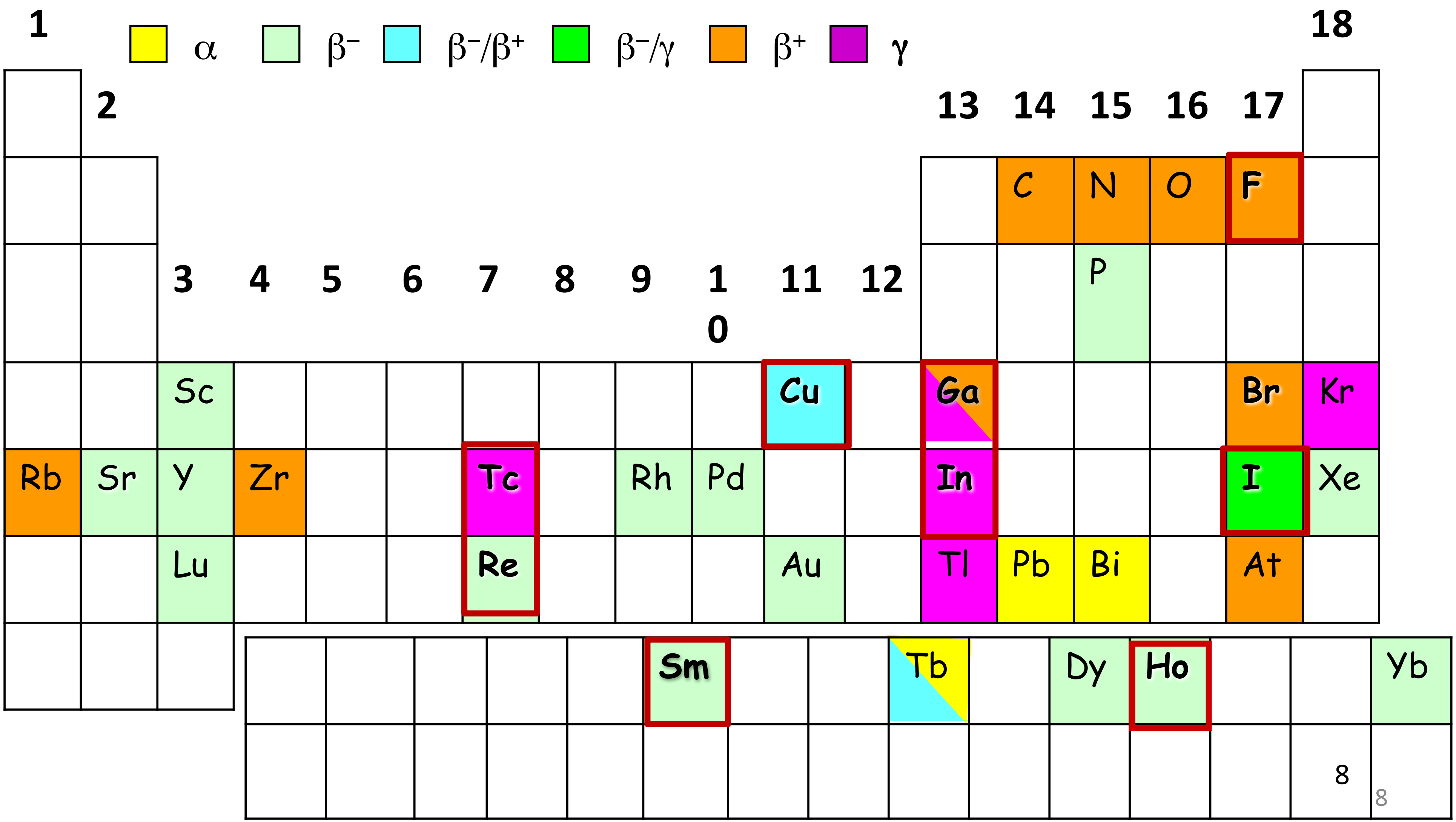
- Not specific to radiopharmaceuticals, but developed by pharma industry at the beginning of the 90's at the same time the concept of Personalized Medicine (PM) appeared.

- In NM, Theranostic is easy to apply by switching from a radionuclide from Dx to Rx using the same biological vector.





Periodic Table of Medical Radioisotopes



Radiometals in Nuclear Medicine

Diagnostic

- Gamma (γ) emitters (SPECT)
- Positron (β^+) emitters (PET)

Therapy

– β or α emitters
- Auger emitters

SPECT		PET	
Radionuclide	$T_{1/2}$ (h)	Radionuclide	$T_{1/2}$ (h)
^{99m}Tc	6.02	^{86}Y	14.7
^{111}In	67.9	^{89}Zr	78.5
^{67}Ga	78.3	^{68}Ga	1.13
^{155}Tb	5.6 d	^{64}Cu	12.7

Radionuclide	$T_{1/2}$ (h)	Decay mode
^{177}Lu	159.4	β^-, γ
^{161}Tb	165.4	β^-, γ
^{67}Cu	61.9	β^-, γ
^{90}Y	64.1	β^-
^{149}Tb	4.12 h	α
^{225}Ac	10.0 d	α
^{213}Bi	45.6 min	α
^{223}Ra		α

Many theranostic pairs available, based on PET/SPECT radionuclides and β or α emitters:

"matched pairs"

^{99m}Tc/^{188}Re

^{67}Ga/^{177}Lu

^{68}Ga/^{177}Lu

"isotopic pairs" (or "true pairs")

^{64}Cu/^{67}Cu **^{86}Y/^{90}Y**

^{155}Tb/^{149}Tb **^{152}Tb/^{161}Tb**

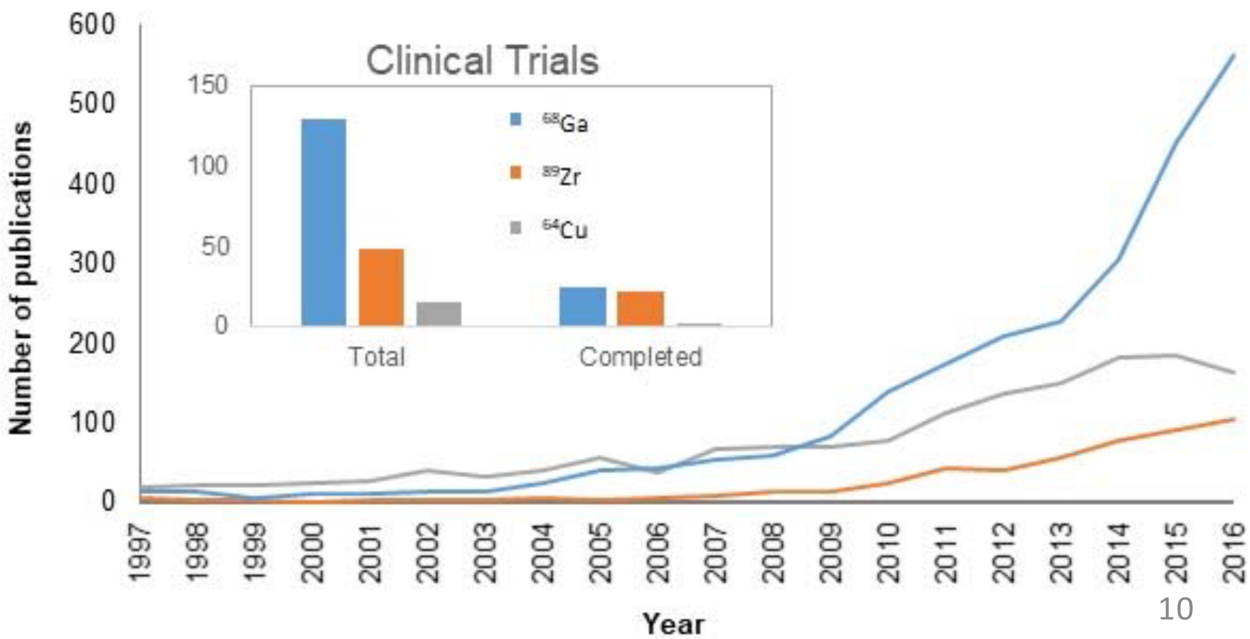
Metal-based radiopharmaceuticals

- Approved **metal-based pharmaceuticals** are scarce corresponding mostly to cis-platin derivatives

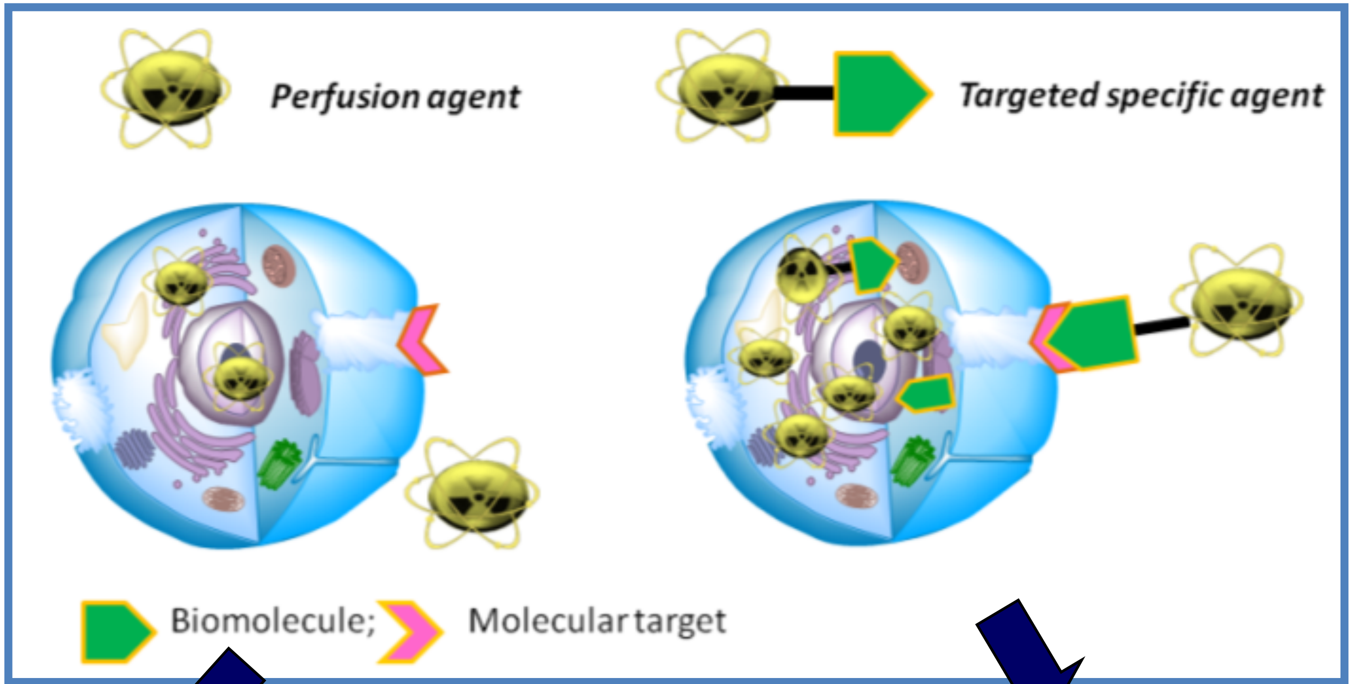
cisplatin carboplatin oxaliplatin

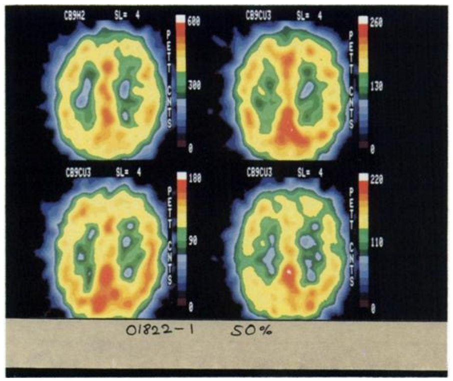
- Contrastingly, **metal-based radiopharmaceuticals** have a prominent role in nuclear medicine

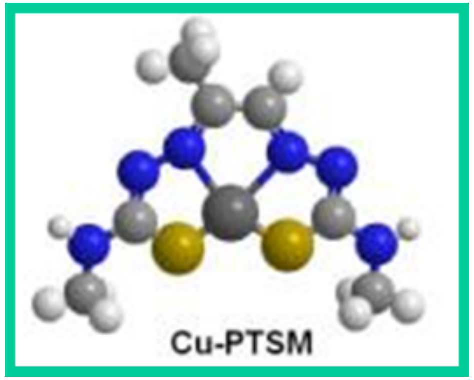
$^{223}RaCl_2$



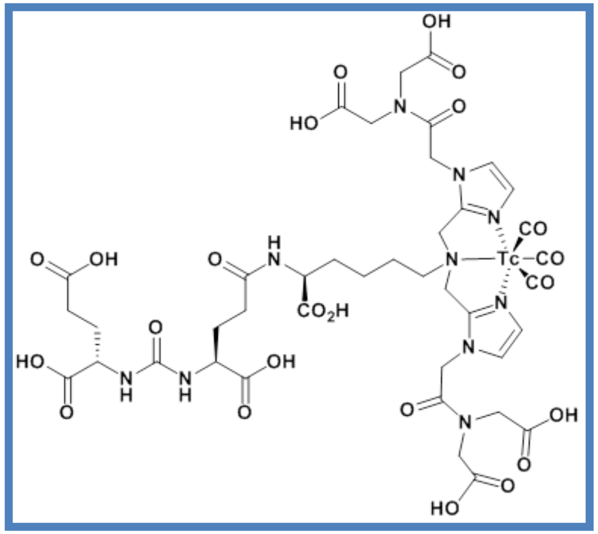
Types of metal-based radiopharmaceuticals

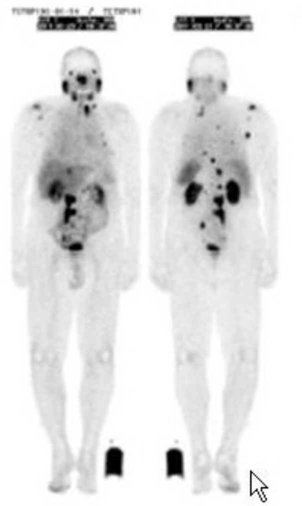






M. Welch et al. *J. Nucl. Med.* **1990**, *31*, 1989-1996





Hillier et al. et al. *J. Nucl. Med.* **2013**, *54*, 1-8

Synthesis of Metal-Based Radiopharmaceuticals

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

  - Involves **chelation** reactions using appropriate ligands and starting from simple inorganic precursors (e.g $^{99m}TcO_4^-$, $^{64}CuCl_2$, $^{177}LuCl_3$, $^{89}ZrCl_4$)

  - Requires the **optimization** of different **reaction parameters** (concentration of reagents, solvent, temperature, pH, etc.)

Short-Lived radioisotopes:

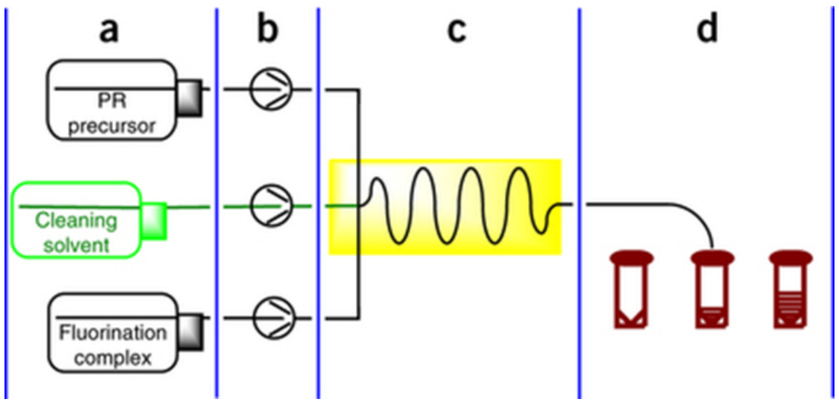
- Fast and high yield synthesis
- Simple purification processes
- Radiological Protection issues
- Automated Processes

2

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

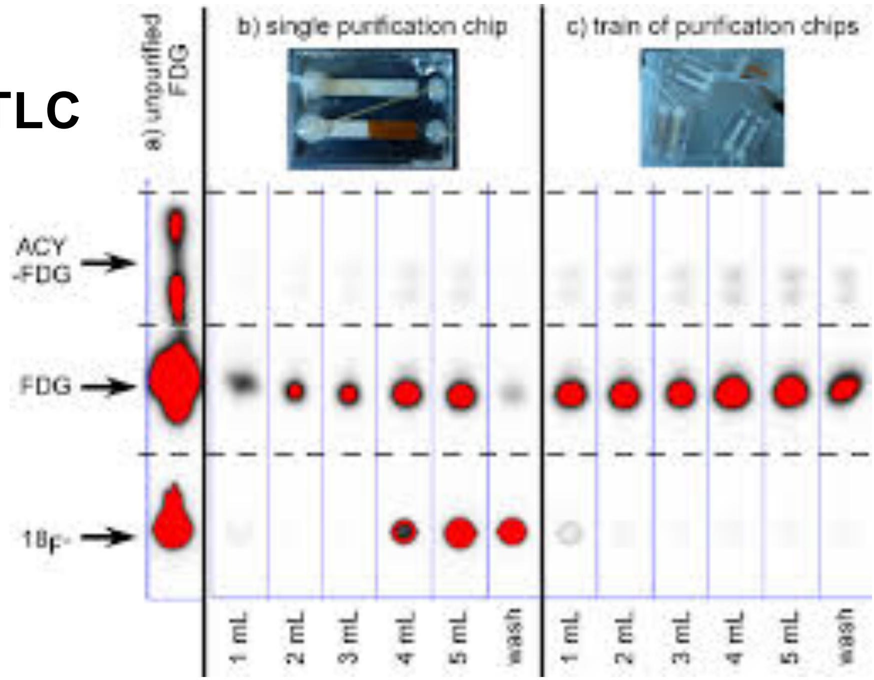
- **Radiolysis**: in solutions with high radioactivity concentrations radiolysis processes can be a major factor in the formation of unwanted by-products.

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).

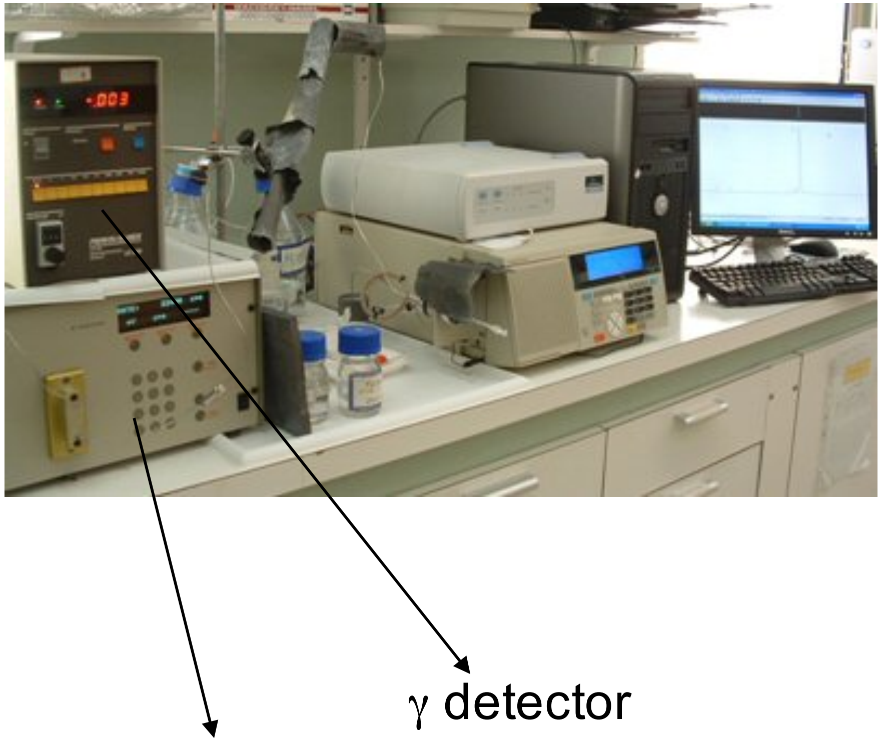
-The radiochemical purity of the probes is determined by chromatographic techniques (RadioTLC or RadioHPLC) using γ-detection.

RadioTLC



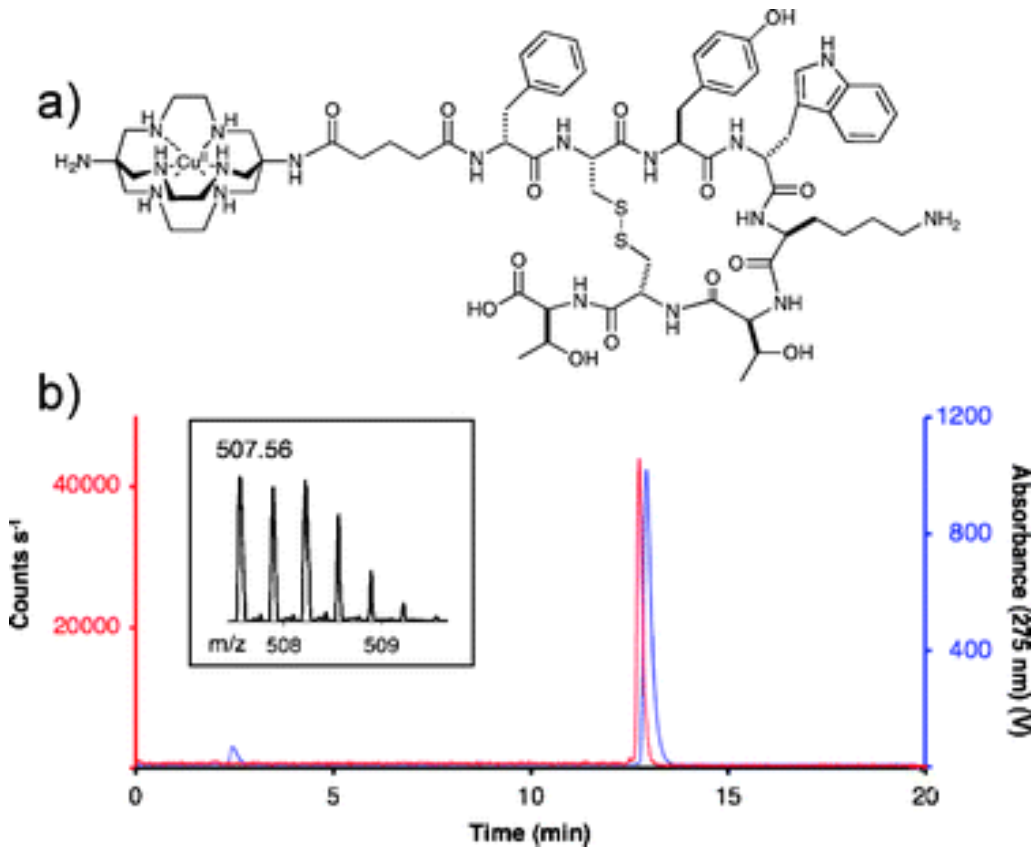
Characterization of the Radioprobes

- 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



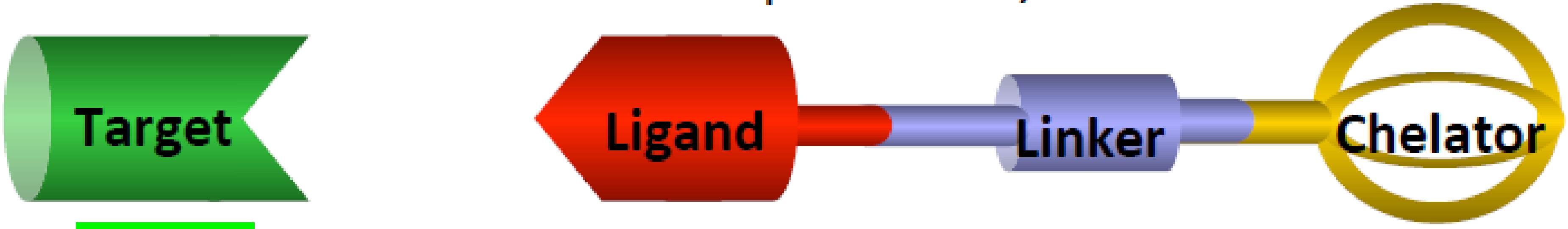
γ detector

UV detector



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

Design of the Target-Specific Radiocomplexes



Lock	Key	^{68}Ga, ^{90}Y, ^{177}Lu

Target

- Antigens (e.g. CD20, HER2)
- **GPCRs**
- Transporters

Molecular Address

- Antibodies, minibodies, Affibodies, SHALs, Aptamers
- **Regulatory peptides and analogs thereof**
- Amino Acids

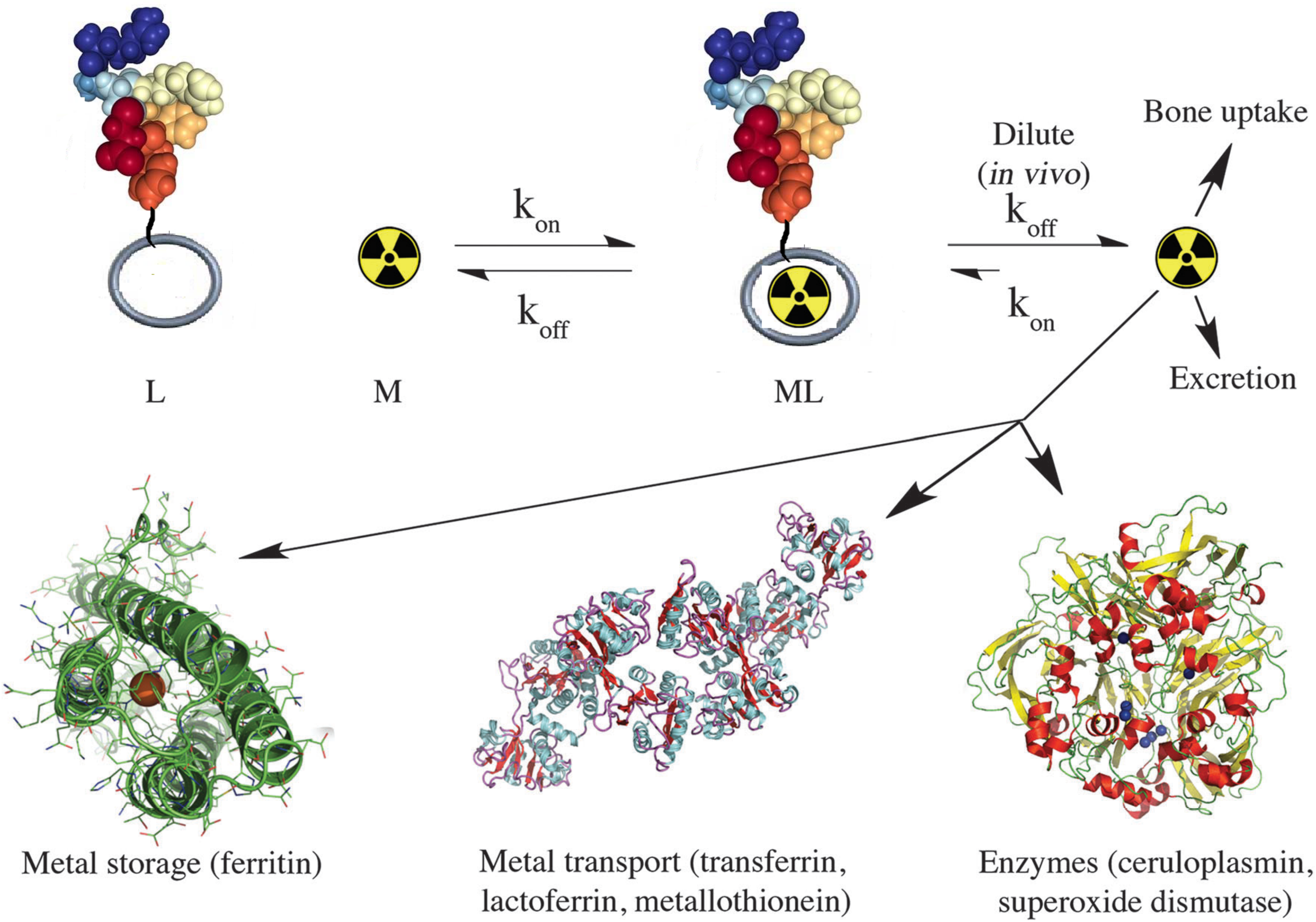
Reporting Unit

- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{68}Ga
- Gd^{3+}

Cytotoxic Unit

- ^{90}Y, ^{177}Lu, ^{213}Bi
- ^{105}Rh, ^{67}Cu, $^{186,188}Re$

Biological fate of Target-Specific Radiocomplexes



Selection of the Chelator

A good chelator of a given radiometal must provide:

- A fast reaction at room temperature with adequate radioactive precursor.

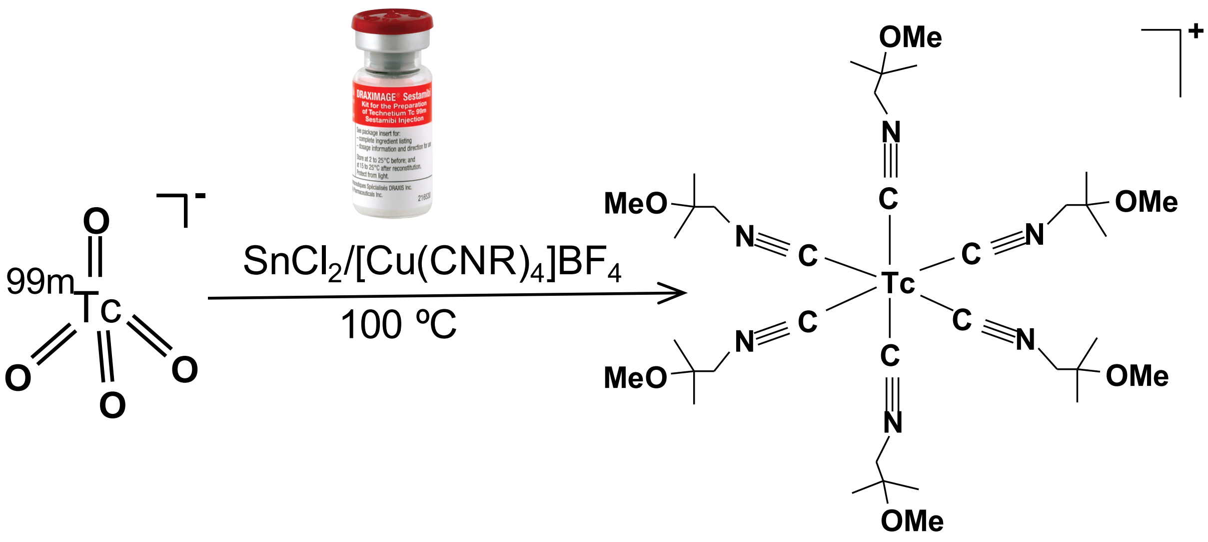
- Form kinetically stable radiocomplexes *in vitro* and *in vivo.*

- Allow easy functionalization with the biomolecules and versatile chemical modification for pharmacokinetics optimization.

There is no universal chelator, one that fits all!

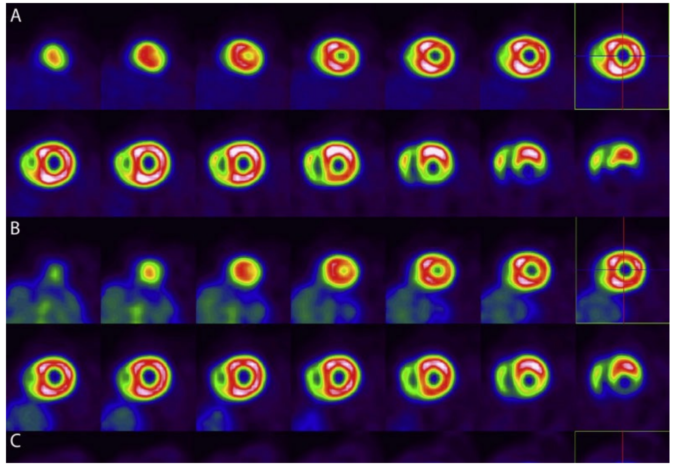
(Depends on size, oxidation state and electronic properties of the metal ion)

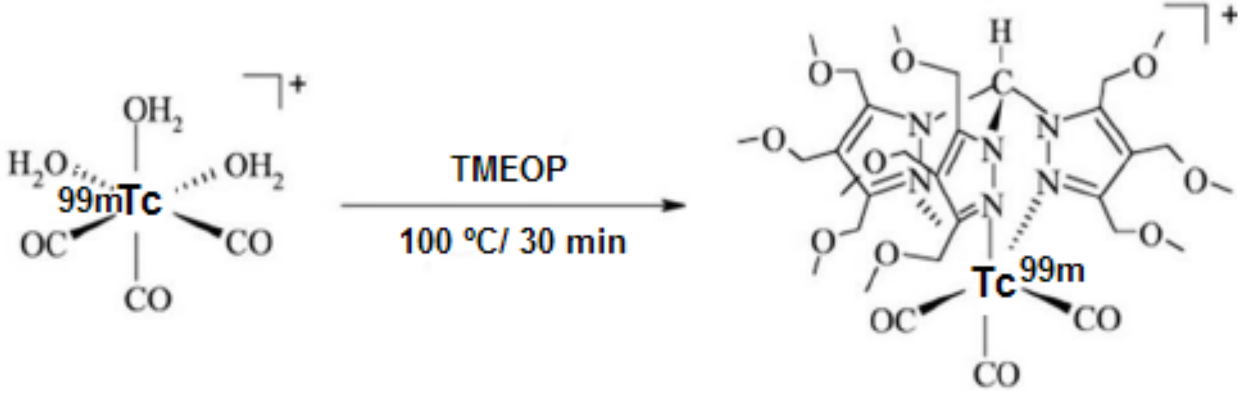
Organometallic ^{99m}Tc Complexes



^{99m}Tc-SESTAMIBI

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





^{99m}Tc-TMEOP

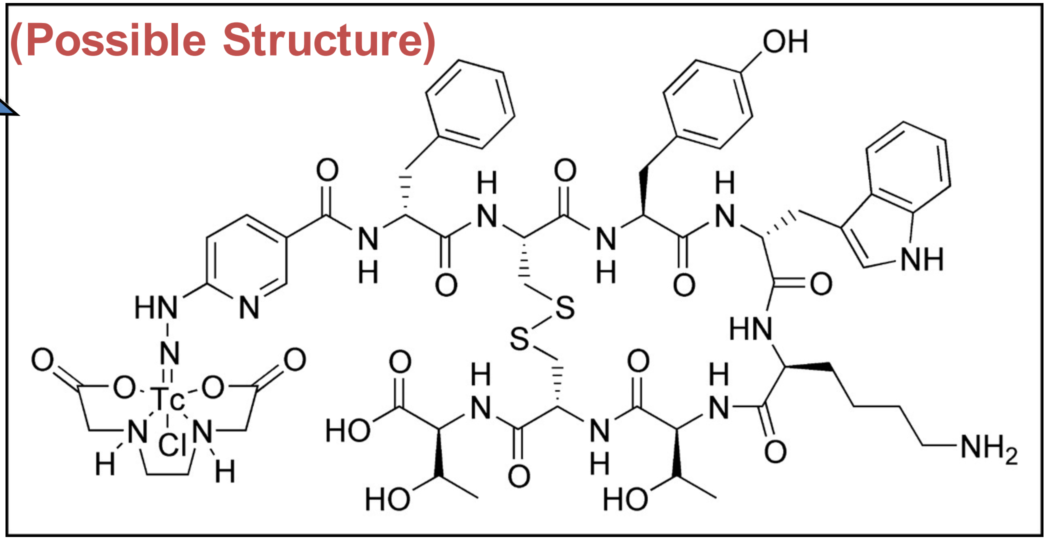
A. Paulo et al. *Contrast Media Mol. Imaging* **2011**, *6*, 178-188

Mixed-Ligand ^{99m}Tc Complexes

$+ ^{99m}TcO_4^-$

80 °C/20 min

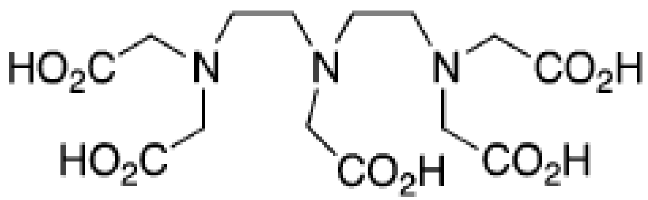
Tc-EDDA-HYNIC-octreotate



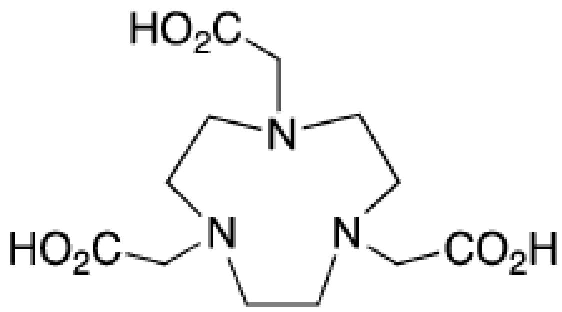
H. R. Maecke et al. J Nucl Med, 2005;46:1561-1569.

^{99m}Tc-HYNIC-TOC

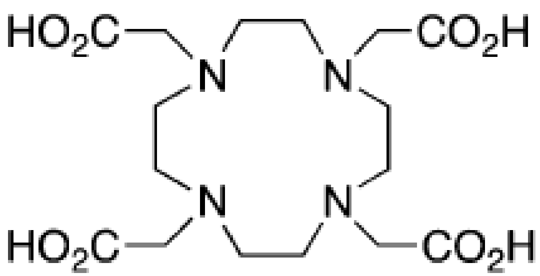
Acyclic and Macrocyclic N,O-Chelators



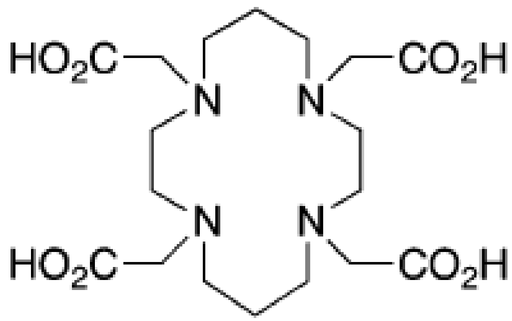
DTPA, diethylenetriaminepentaacetic acid, N_3O_5, CN = 8



NOTA, 1,4,7-triazacyclononane-1,4,7-triacetic acid, CN = 6, N_3O_3

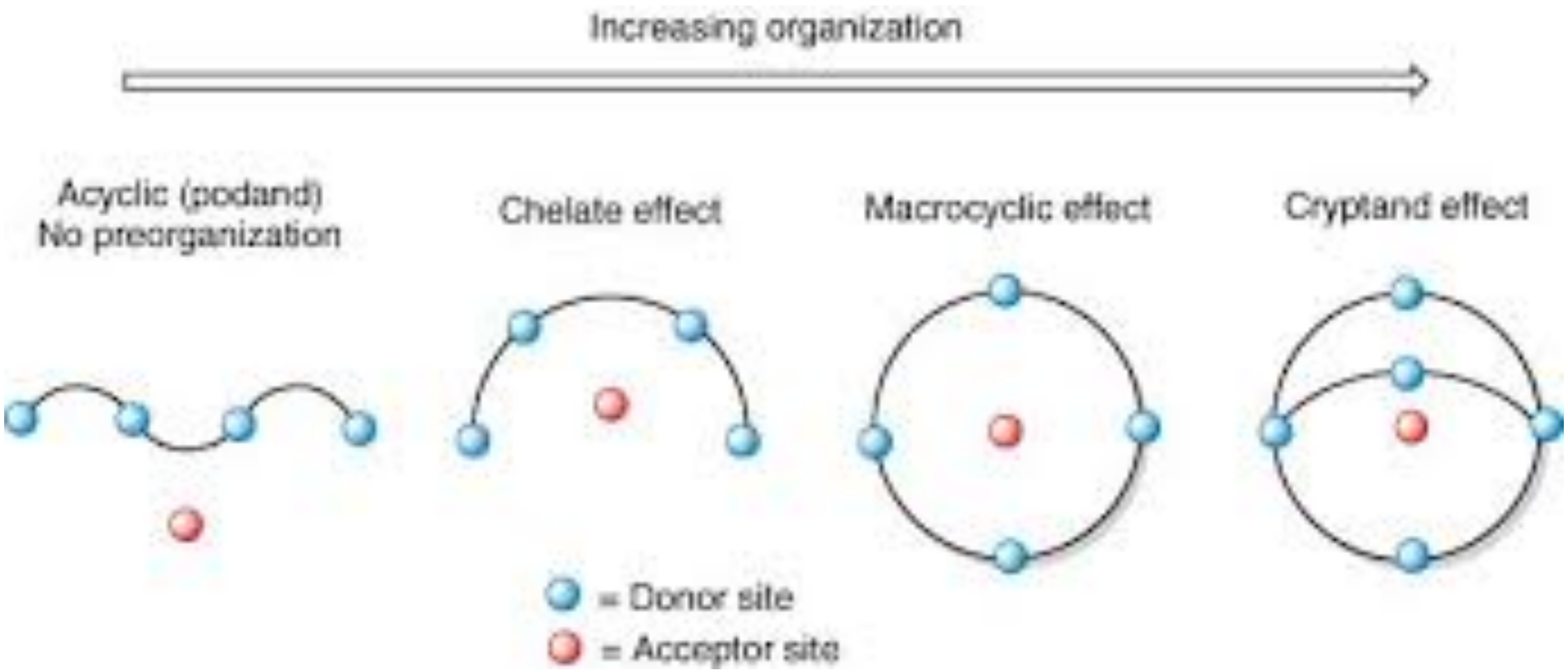


DOTA, 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid, maximum CN = 8, donor set N_4O_4



TETA, 1,4,8,11-tetra-azacyclotetradecane-1,4,8,11-tetraacetic acid, N_4O_4 CN = 8

Macrocyclic Effect



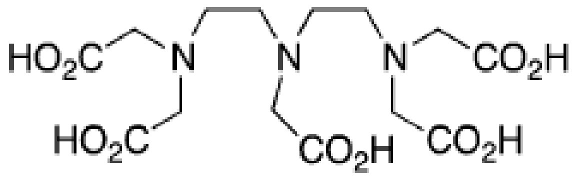
Stability constants of Lu complexes with common chelators

chelating agent	log stability constant
diethylenetriaminepentaacetic acid (DTPA)	12.5
1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)	25.4
1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A)	23.0
1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA)	15.3

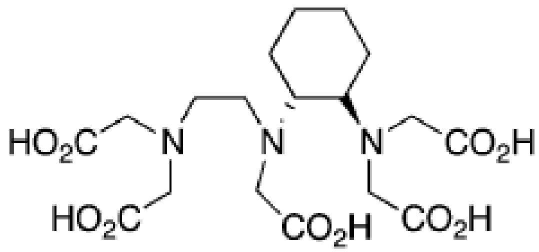
S. Banerjee et al., *Chem. Rev.* **2015**, 115, 2934–2974

Macrocycles tend to form more stable complexes than the acyclic counterparts

DTPA Derivatives



DTPA



CHX-A"-DTPA

DTPA

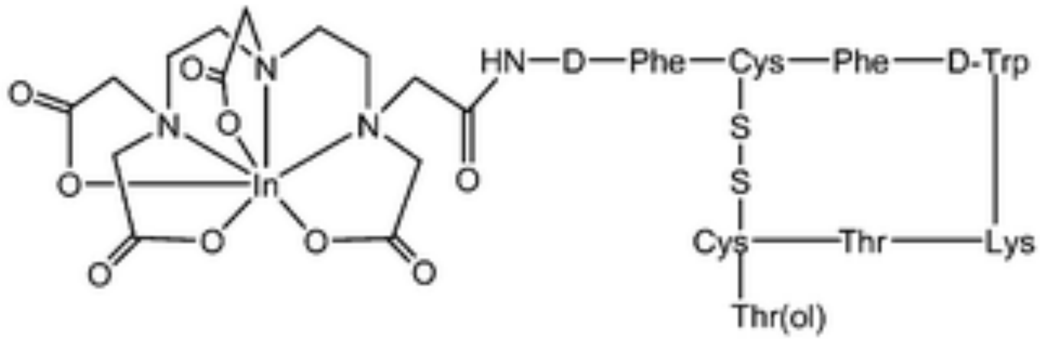
	$\log K_{ML}$		Radiolabelling Conditions
$^{67/68}Ga^{3+}$	24.3	✗	25 °C, 30 min, pH 3.5
$^{111}In^{3+}$	29.0	~	25 °C, 5–10 min, pH 4.5–5.5
$^{177}Lu^{3+}$	22.6	~	25 °C, 10–20 min, pH 5.5
$^{86/90}Y^{3+}$	21.2	~	25 °C, 10–20 min, pH 5.5

CHX-A"-DTPA

		Radiolabelling Conditons
$^{67/68}Ga^{3+}$	✗	85 °C, 20 min, pH 5.5
$^{111}In^{3+}$	✓	25–60 °C, 30–60 min, pH 5.5
$^{177}Lu^{3+}$	✓	37–75 °C, 30–60 min, pH 5–5.5
$^{86/90}Y^{3+}$	✓	37–75 °C, 30–60 min, pH 5–5.5

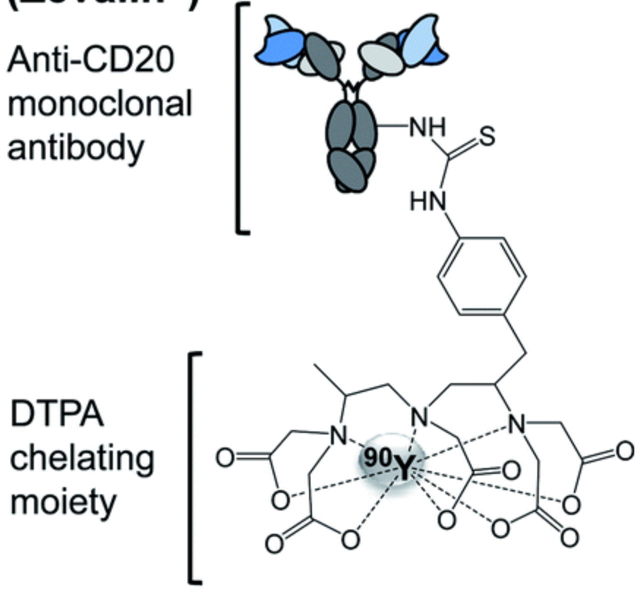
E. W. Price, C. Orvig, *Chem. Soc. Rev.* **2014**, 43, 260-290

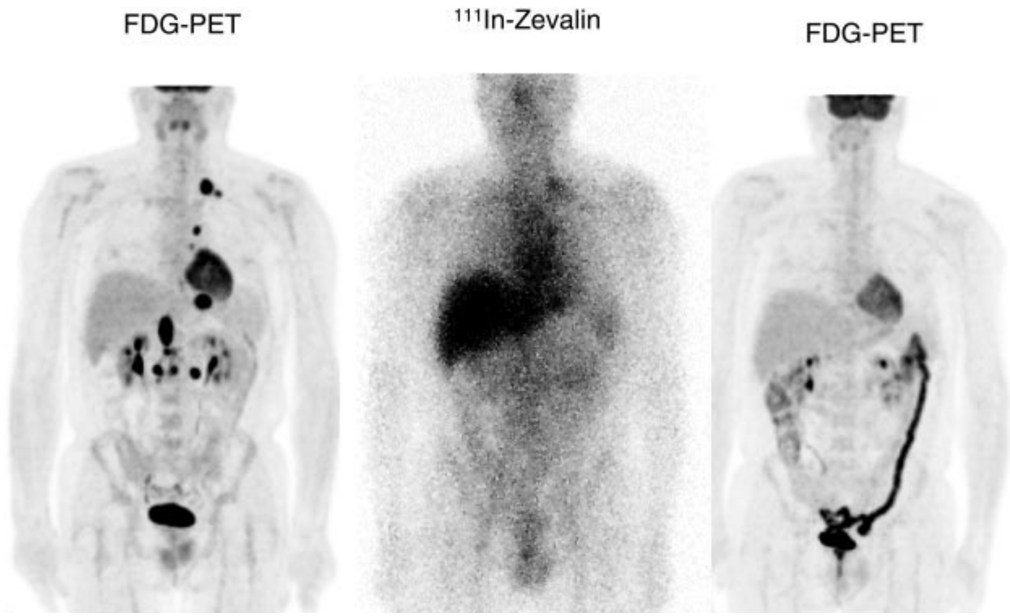
DTPA Derivatives: Examples of Clinical Applications



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

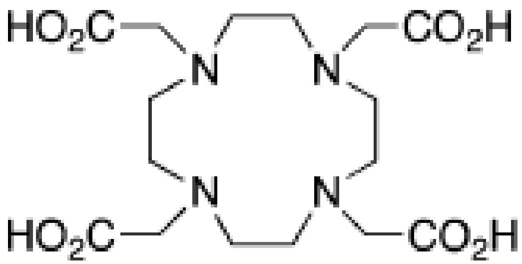
^{90}Y-ibritumomab tiuxetan (Zevalin®)





Before Therapy **After Therapy**

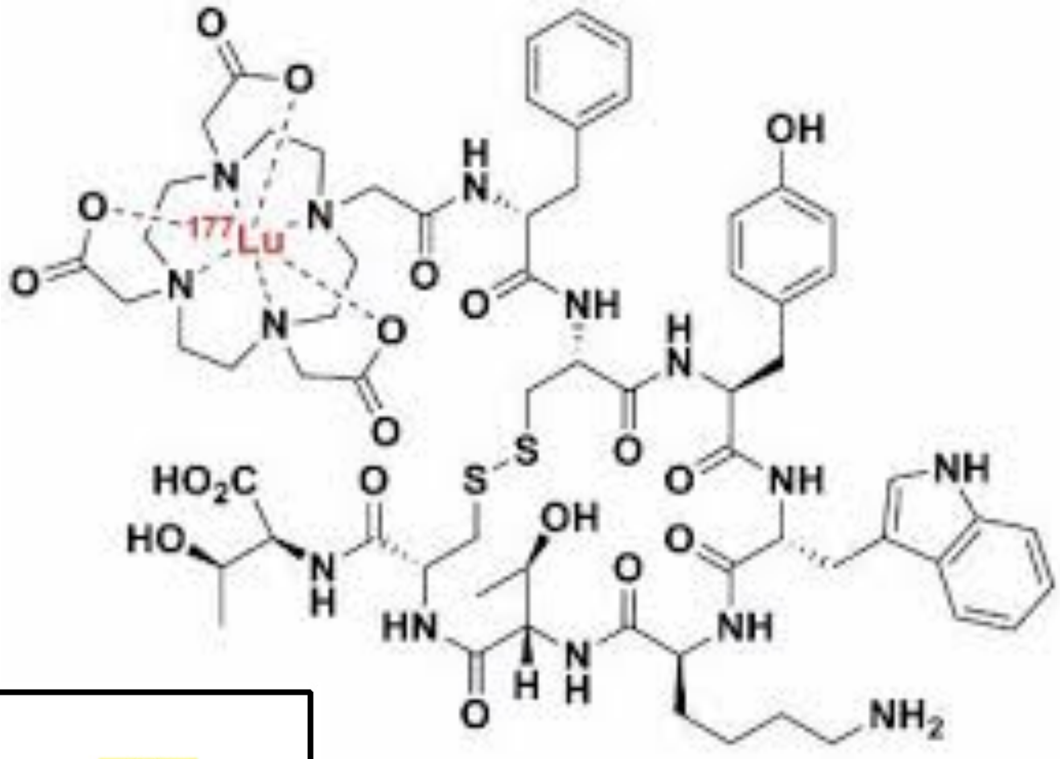
DOTA Derivatives



DOTA

	$\log K_{ML}$		**Radiolabelling Conditons**
$^{64}Cu^{2+}$	22.2	~	25–90 °C, 30–60 min, pH 5.5–6.5
$^{67/68}Ga^{3+}$	21.3	~	37–90 °C, 10–30 min, pH 4.0–5.5
$^{44/47}Sc^{3+}$	27.0	✓	95 °C, 20–30 min, pH 4.0
$^{111}In^{3+}$	23.9	✓	37–100 °C, 15–60 min, pH 4.0–6.0
$^{177}Lu^{3+}$	23.5	✓	25–100 °C, 15–90 min, pH 4.0–6.0
$^{86/90}Y^{3+}$	24.3	✓	25–100 °C, 15–90 min, pH 4.0–6.0

DOTA Derivatives: Examples of Clinical Applications



Lutathera
lutetium Lu 177 dotatate injection
For Intravenous Infusion
Single-dose vial. Discard Unused Portion. Rx Only

CAUTION RADIOACTIVE MATERIAL Rx Only

Advanced Accelerator Applications

Usual Dosage: See Prescribing Information
Store below 25°C (77°F)

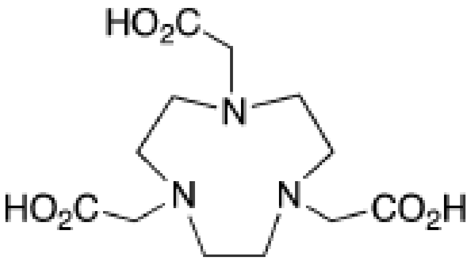
MANUFACTURER
< Adress 1 >
< Adress 2 >
< Postal Code >
< City >
< Country >

AAA-P-RA-668-00

Lot #: {LTYYMMDDX-nn} **NDC#** 69488-003-01
Vial #: {X} **Volume:** {Y} mL
Activity at calibration time: 370 MBq/mL (10 mCi/mL)
{DD/MM/YYYY hh:mm am UTC}
Activity at infusion time: {Z} MBq - ({A} mCi)
{DD/MM/YYYY hh:mm am UTC}
EXP: {DD/MM/YYYY hh:mm am UTC}

S. Banerjee et al., *Chem. Rev.* **2015**, 115, 2934–2974

NOTA Derivatives



NOTA

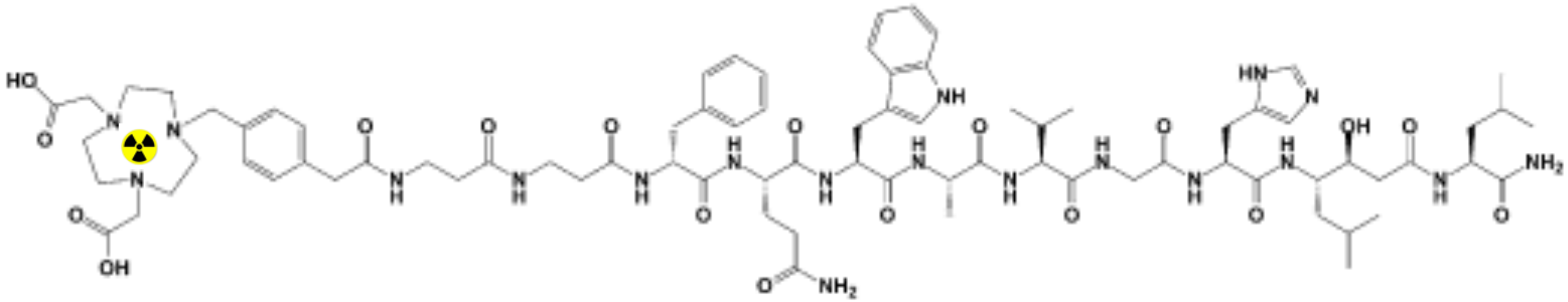
	$\log K_{ML}$		Radiolabelling Conditions
$^{64}Cu^{2+}$		✓	25 °C, 30–60 min, pH 5.5–6.5
$^{67/68}Ga^{3+}$		✓	25 °C, 30–60 min, pH 4.0–5.5
$^{44/47}Sc^{3+}$		~	95 °C, 20–30 min, pH 4.0
$^{111}In^{3+}$		~	60–95 °C, 20–30 min, pH 4.0–5.0

E. W. Price, C. Orvig, *Chem. Soc. Rev.* **2014**, 43, 260-290

NOTA Derivatives: Labelling with ^{18}F

NOTA derivatives can be also labelled with ^{18}F using $Al^{18}F$ precursors.

The same radioconjugate can be labelled with ^{18}F and other PET radionuclides (^{68}Ga or ^{64}Cu)!!

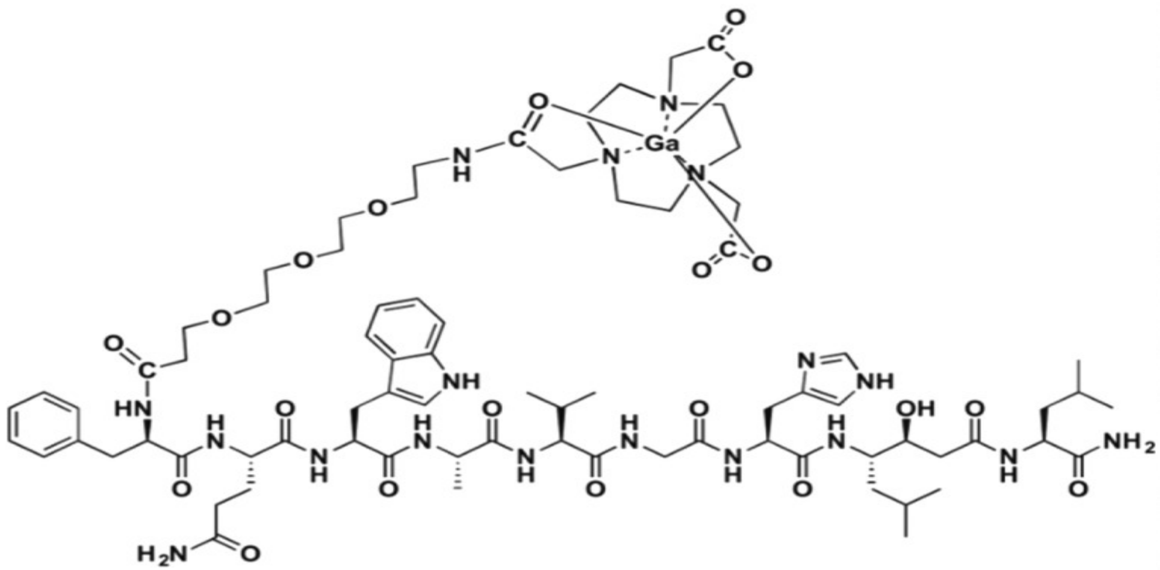


= $Al^{18}F$, ^{68}Ga

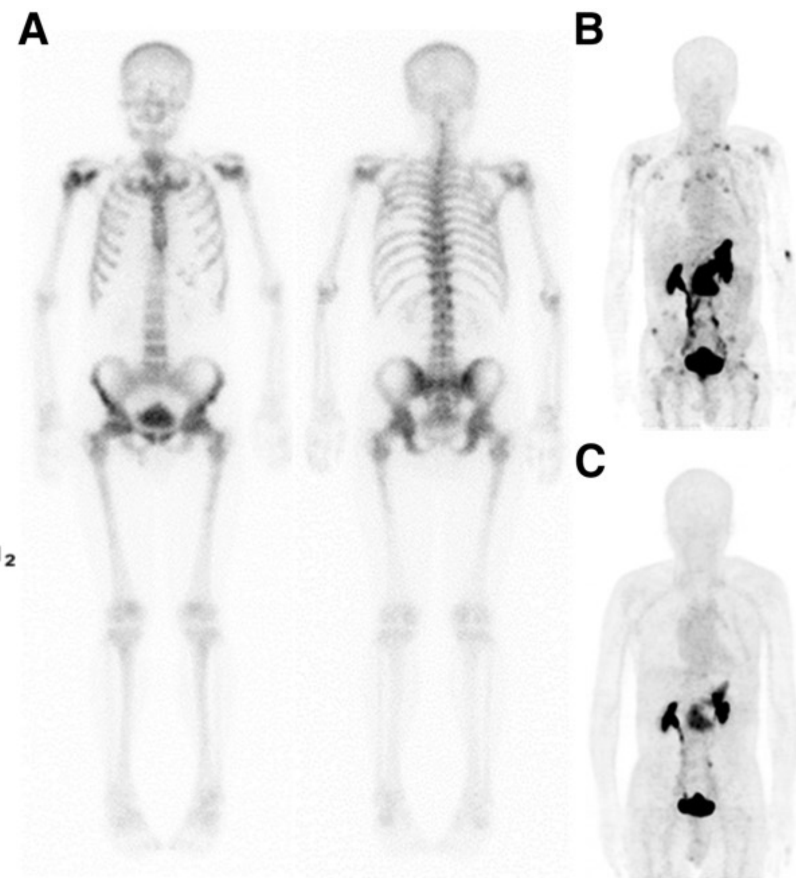
(JMV5132/BBN antagonist)

M. de Jong et al., *J Nucl Med* **2014**, 55:1–7

NOTA Derivatives: Examples of Clinical Applications



^{68}Ga–NOTA–PEG$_3$–RM26/ BBN antagonist

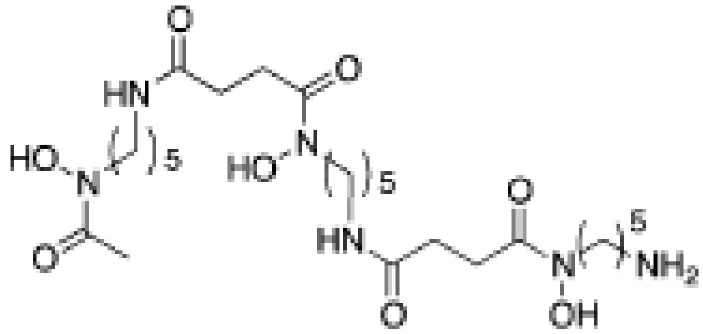


A) ^{99m}Tc-MDP bone scintigraphy
B) ^{68}Ga-RM26 PET/CT
C) ^{68}Ga-BBN PET/CT

X. Chen et al., *J. Nucl. Med.* **2018**, 59:922–928

https://clinicaltrials.gov/ct2/show/NCT03347864

Less-Common Chelators

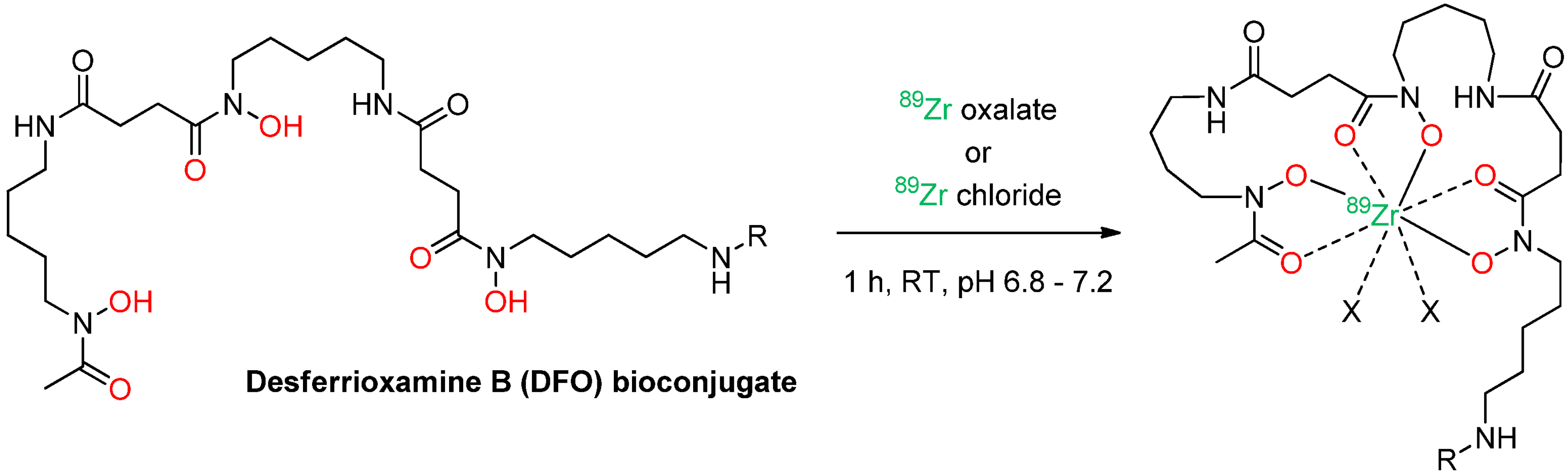


DFO

$^{89}Zr^{4+}$

Radiolabelling Conditions

25 °C, 60 min, pH 7–7.3

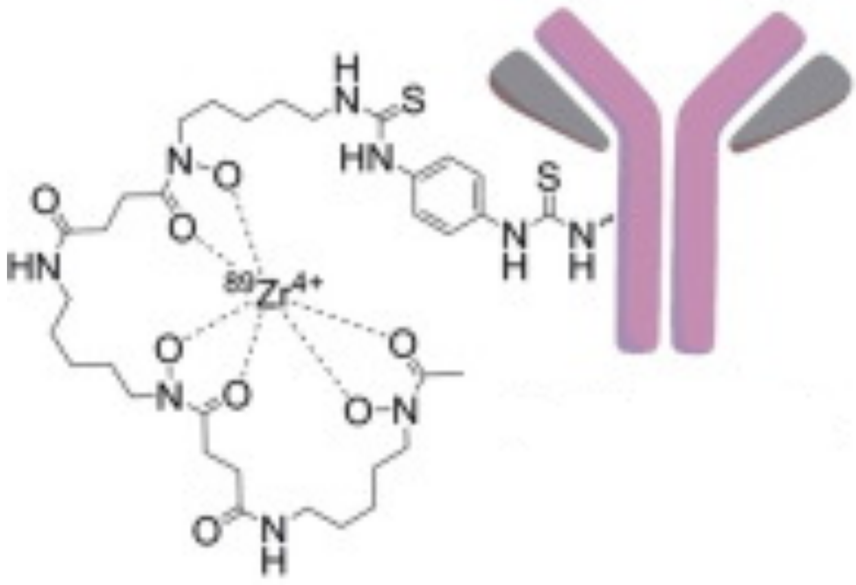


^{89}Zr-DFO bioconjugate

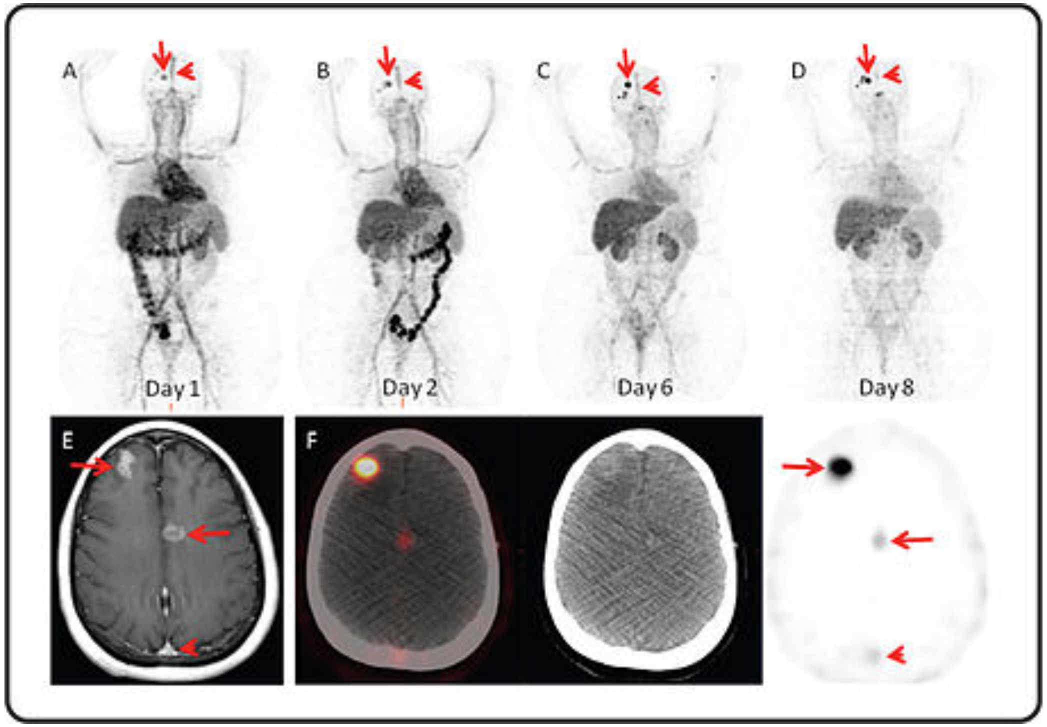
X = H_2O or anion
R = biomolecule

E. W. Price, C. Orvig, *Chem. Soc. Rev.* **2014**, 43, 260-290

Less-Common Chelators: : Examples of Clinical Applications



^{89}Zr-Pertuzumab



Detection of HER2-positive breast cancer metástases (HER2: *Human Epidermal growth factor Receptor 2*)

G. A. Ulaner et L., *J Nucl Med* **2018**, 59:900-906

Final Remarks

The contribution of inorganic chemists/radiochemists is still needed to introduce new chelators and new radiolabelling strategies?

New chelators combining the thermodynamic stability and kinetic inertness of macrocyclic chelators with the facile radiolabeling of acyclic chelators are still needed, namely for the **soft labelling of antibodies with trivalent radiolanthanides**.

New chelators to profit from the intrinsic luminescence of lanthanide complexes, avoiding the use of conjugated exogenous fluorophores: **Design of dual optical/nuclear probes**.

Efficient chelators for complexation of ^{223}Ra are not available to explore this radioisotope in targeted alpha therapy (**TAT**), unlike other alpha emitters (e.g. ^{227}Th, ^{225}Ac, ^{212}Pb, ^{213}/^{212}Bi)

Further Readings

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- M. Brandt, J. Cardinale, M. L. Aulsebrook, Gilles Gasser3, Thomas L. Mindt, AN OVERVIEW ON PET RADIOCHEMISTRY: PART 2 – RADIOMETALS, *J. Nucl. Med.*, published on May 10, **2018** as doi:10.2967/jnumed.117.190801.

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