Radiochemistry: Radiolabeling and medical applications

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27/11/2025

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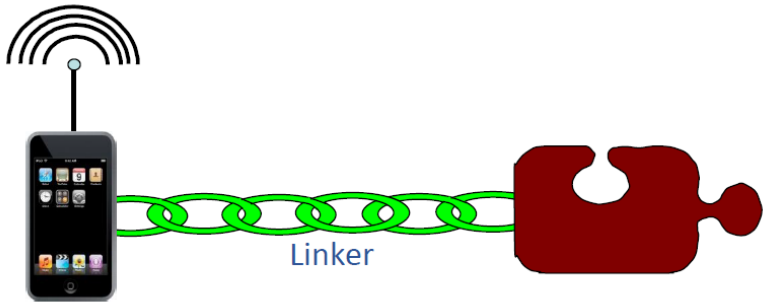
Medical applications

Nuclear Medicine

Diagnostic



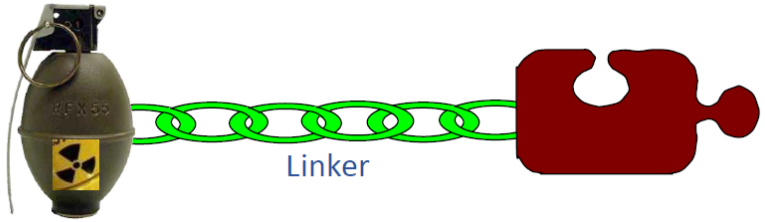
Radionuclide

Emits **radiation** upon decay, detectable by **PET** or **SPECT**.

Vector molecule

Responsible for a specific interaction with the target (enzyme, receptor, transporter,...)

Therapeutic



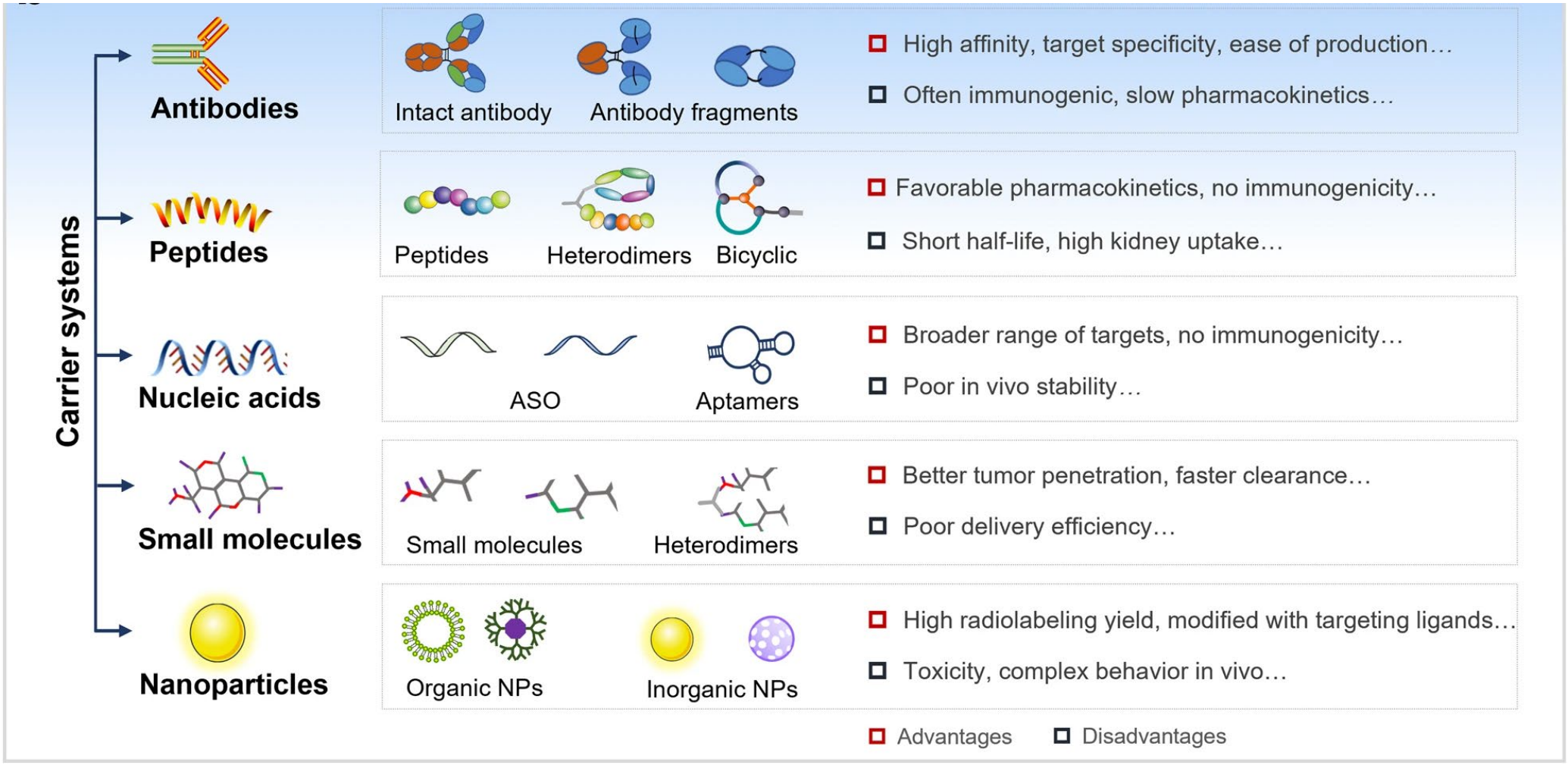
Radionuclide

Emits **particle radiation** upon decay, destroing target cells.

Vector molecule

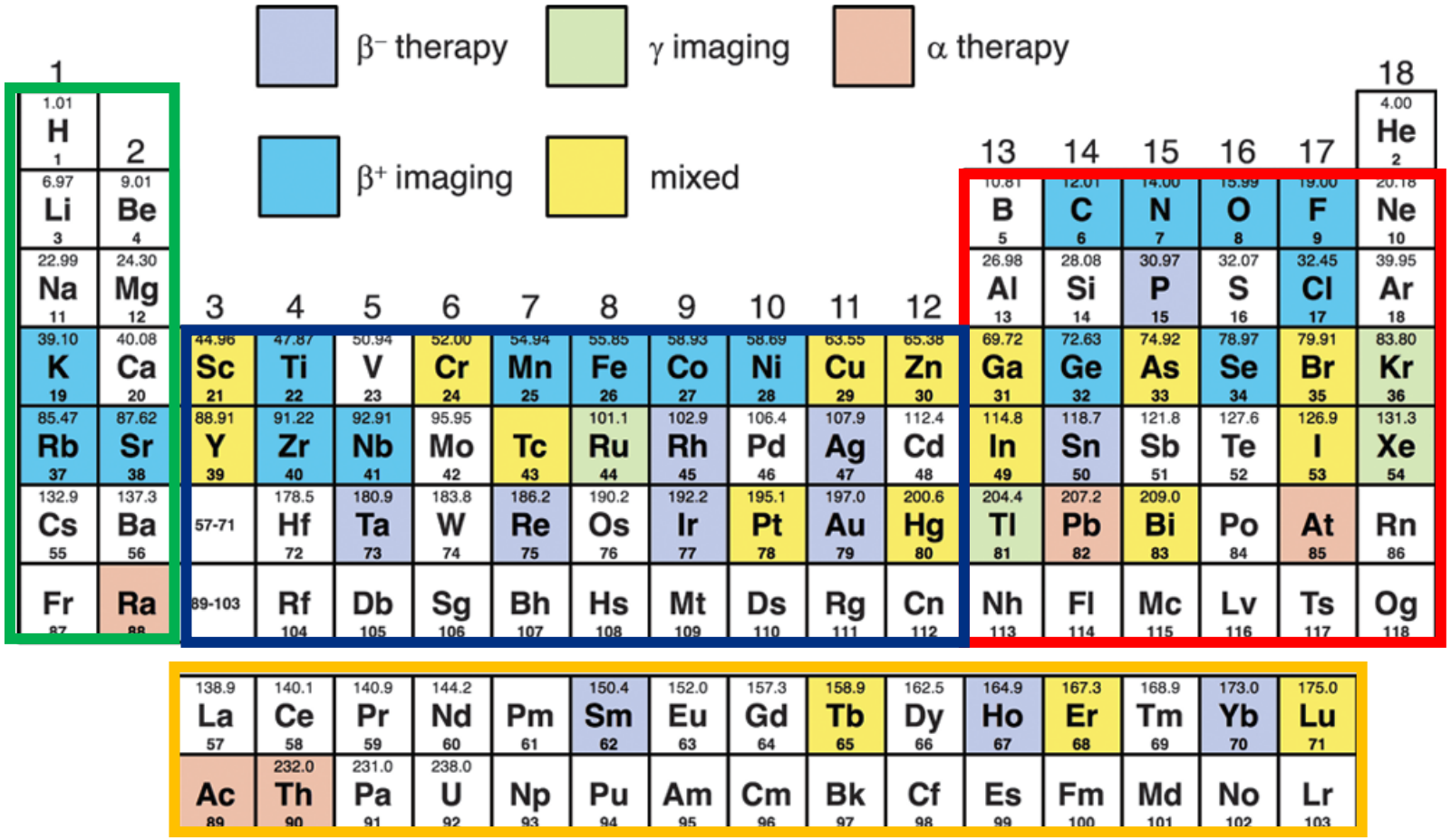
Responsible for a specific interaction with the target (enzyme, receptor, transporter,...)

Vectors



Zhang, T. et al. Carrier systems of radiopharmaceuticals and the application in cancer therapy. Cell Death Discov. 10, 16 (2024)

Radionuclide



s-block- Ionic reaction ([^{223}Ra]Cl_2)

d-f-block-Complexation ([^{177}Lu]PSMA)

p-block- Complexation,
Nucleophilic/ electrophilic substitution
([^{68}Ga]FAPI and [^{18}F]FDG, respectively)

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Radiolabeling

- Direct labelling
  - Complexation
  - Electrophilic substitution
  - Nucleophilic substitution
- Indirect labelling- Synthons
- Manual Vs automation

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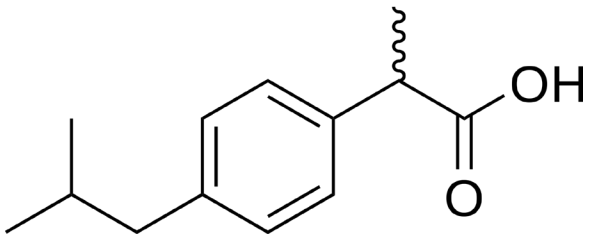
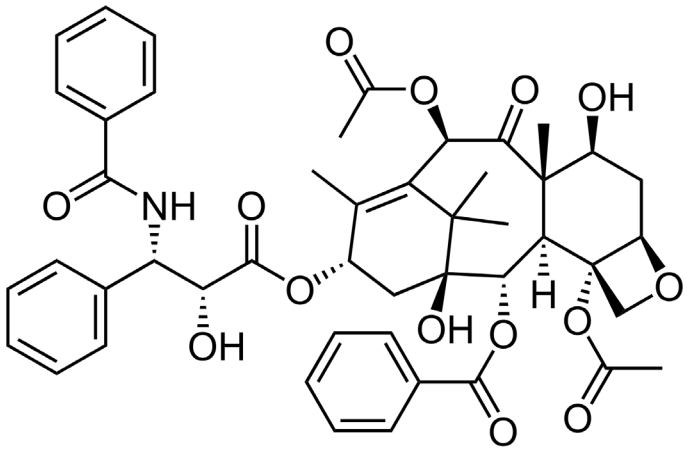
Radiolabeling

Radiochemistry is similar to chemistr… a few twists



Ibuprofen
3 steps



Taxol
39 steps!!

…dded and the reaction was stirred magnetically for 45 min (monitored by TLC). Then *N*-Boc-
…,7,10-trioxa-1,13-tridecanediamine(*8*) (3.93 g, 12.3 mmol) was added dropwise in 4 mL DMF
…nd the mixture was stirred for 24 h. The solvent was removed under reduced pressure and the
…esidue was dissolved in CH_2Cl_2 (150 mL) and the organic layer was washed with H_2O (3 ×
…00 mL) and brine (2 × 100 mL), then dried over $MgSO_4$, before filtration and removal of the
HA…
added and the reaction…
4,7,10-trioxa-1,13-tridecanediamine(…
and the mixture was stirred for 24 h. The solvent was…
residue was dissolved in CH_2Cl_2 (150 mL) and the organic layer…
100 mL) and brine (2 × 100 mL), then dried over $MgSO_4$, before filtration and remo…
solvent under reduced pressure. The crude sample was purified by column chr…
(SiO_2, AcOEt) to give compound **1** as a slightly…
400 MHz, 298 K) δ (…

To a solution of compound **2** (348 mg, 0.952 mmol) in DMF (5 mL) was added succinic
anhydride (143 mg, 1.43 mmol) and the mixture was stirred for 48 h at r.t. under an atmosphere
of N_2. After evaporation of the solvent, the crude was purified by flash chromatography (C18.
…(C=O), 156.1 (C=O), 166.3 (C=O). **HR-ESI-**
…O_6+Na]$^+$ 488.24795, found 488.24801.

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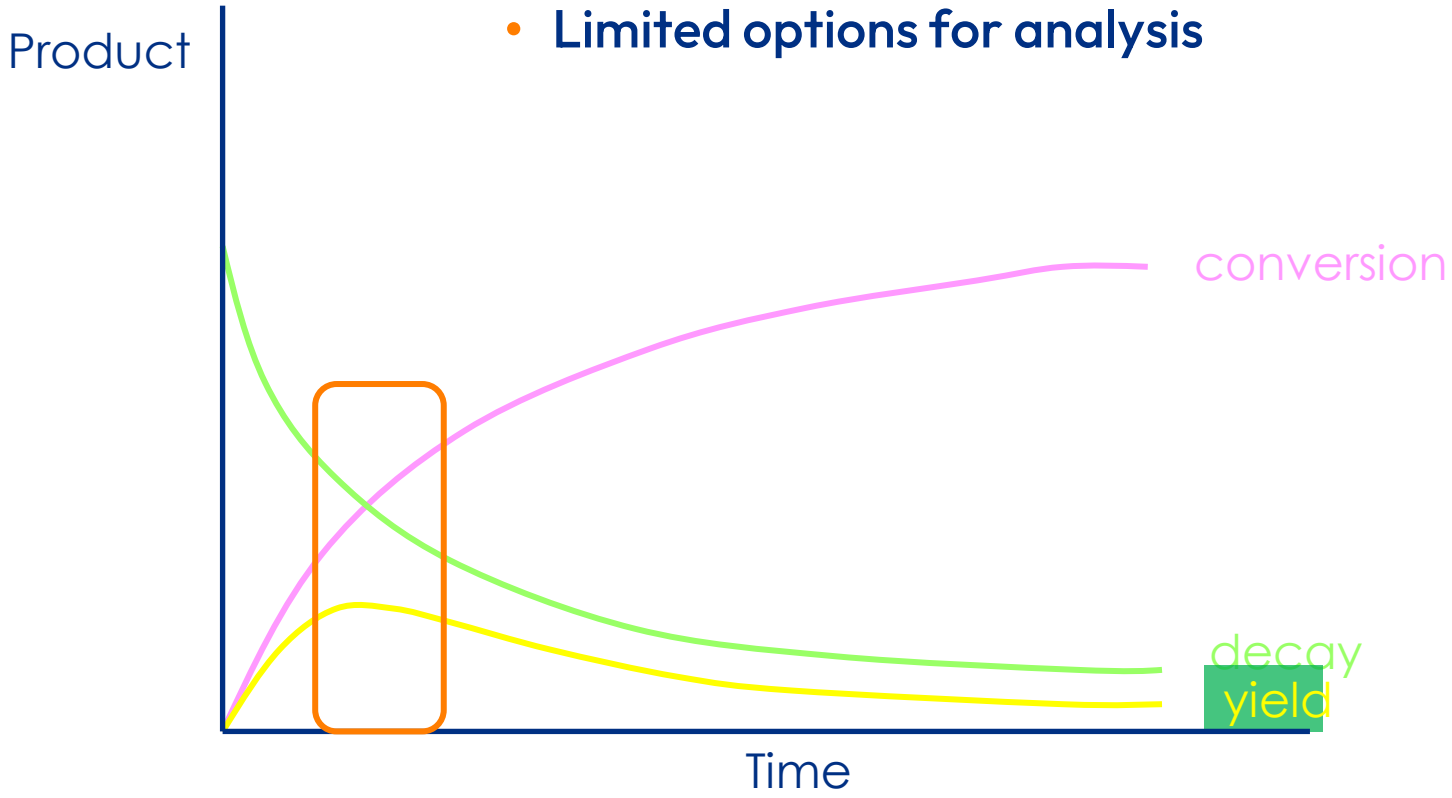
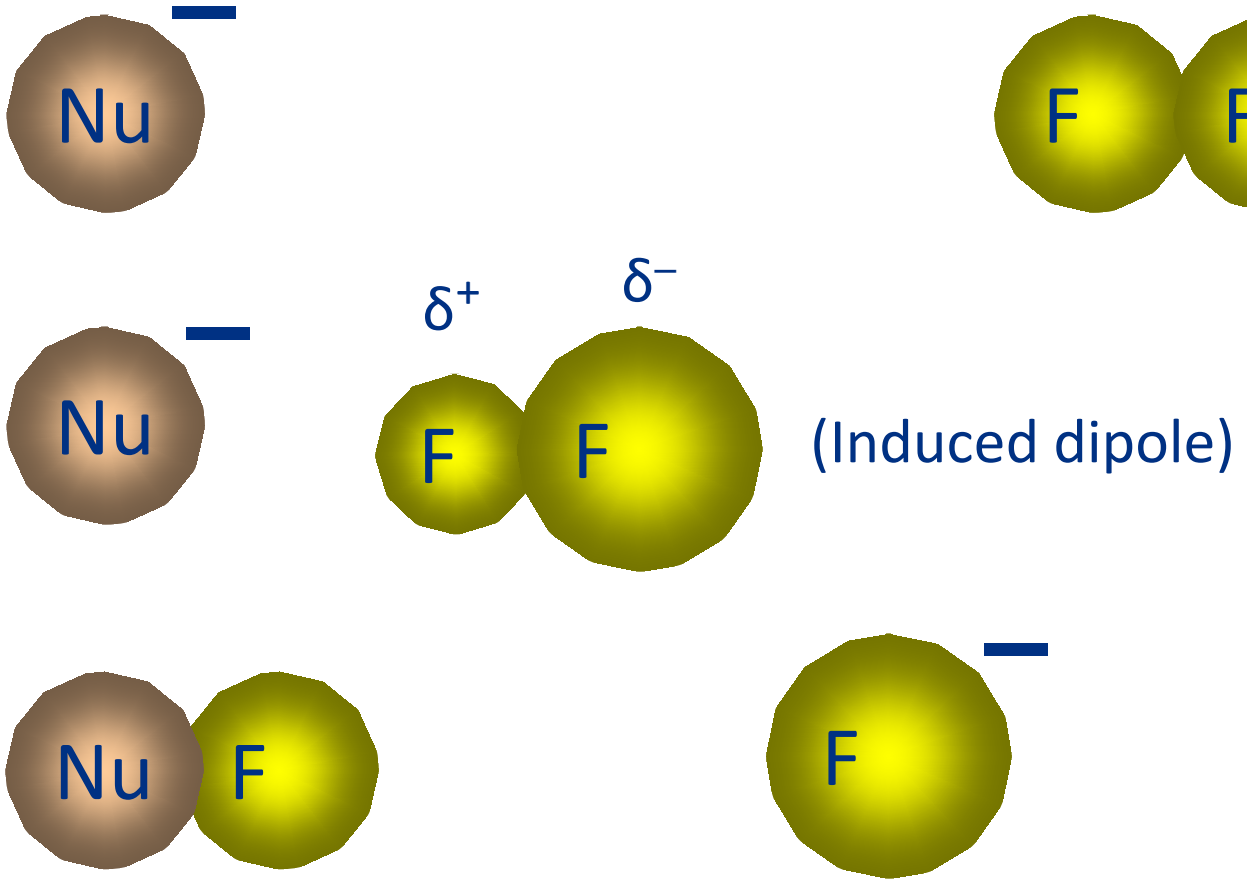
Radiolabeling

- Time (short-lived radionuclides)-Need simple and late-stage incorporation
- Radiation safety (need to start with high amounts of activity)
- Stoichiometry of reagents (Radionuclide always limiting reagent (pmol to nmol)
- Sensitive to impurities
- Limited options for analysis



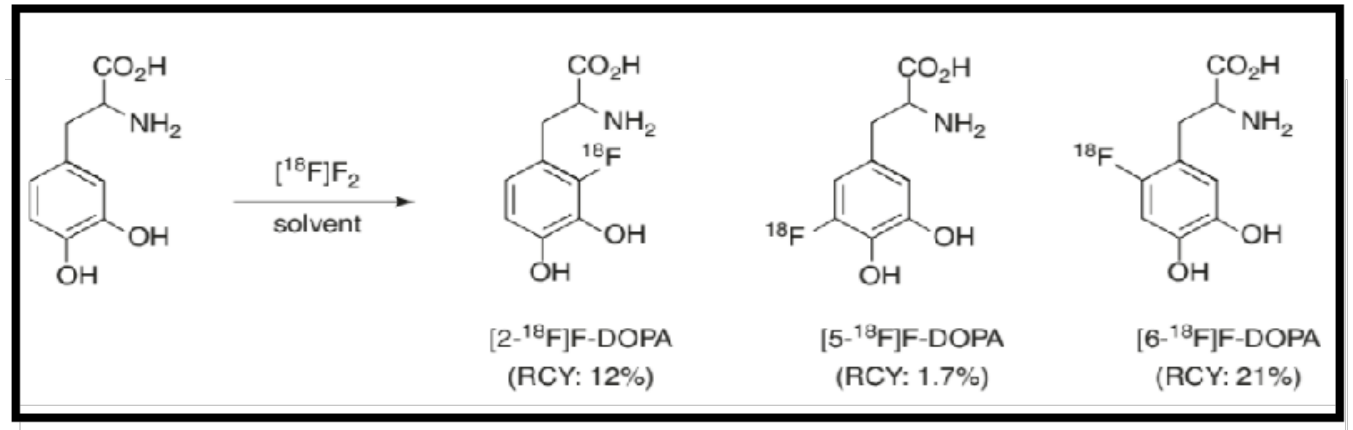
Radiolabeling

Electrophilic substitution



Radiolabeling

Electrophilic substitution

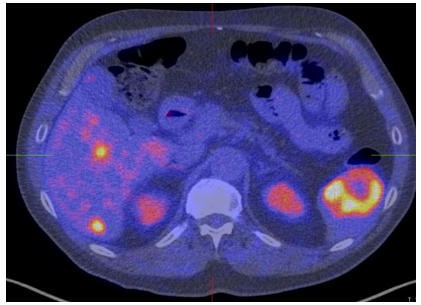


Main issues with $[^{18}F]F_2$ electrophilic substitution:

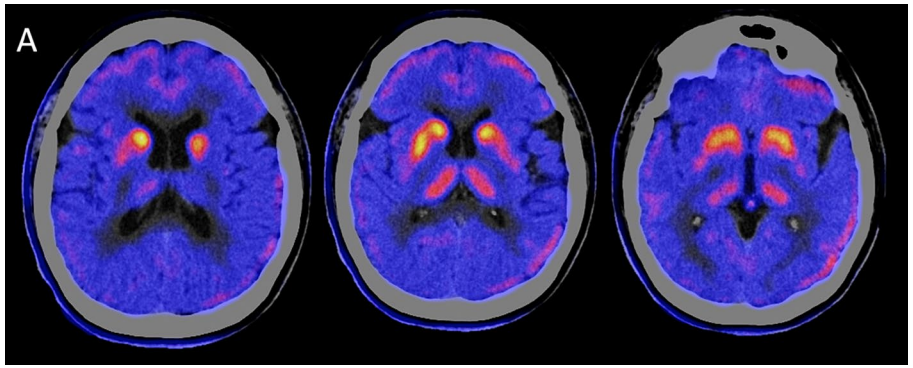
1. Maximum achievable theoretical radiochemical yield is 50%
2. Product form with low Molar Activity
3. $[^{18}F]F_2$ is highly reactive → Several by-products

Bone, liver, spleen metastases

Liver, spleen metastases



Parkinson's disease



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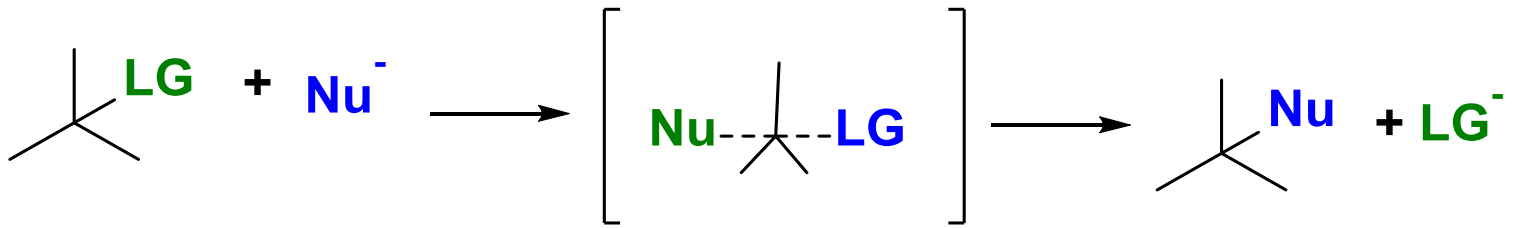
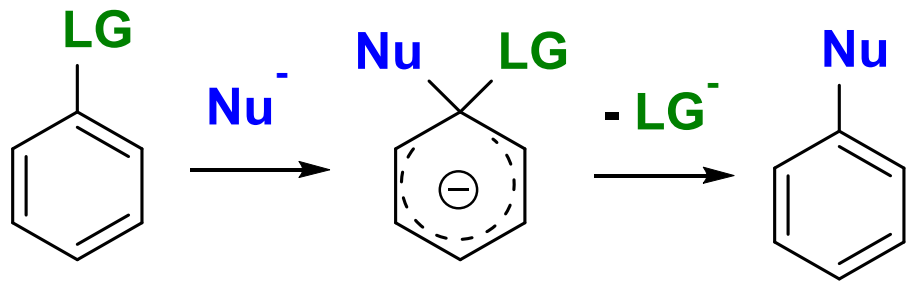
Radiolabeling

Nucleophilic substitution

S_N2



S_NAr



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Radiolabeling

Nucleophilic substitution

- ^{18}F-fluoride must be dehydrated
- high temperatures (~80–100 °C)
- presence of weak nucleophilic bases (K_2CO_3;$KHCO_3$ bicarbonate $K_2C_2O_4$)
- Polar aprotic solvents ACN, DMF or DMSO.
- ↑ solubility of ^{18}F- in organic solvent with Kryptofix 222 or a bulky tetrabutylammonium cation.
- With very reactive leaving groups → lower temperatures to avoid competitive elimination reaction
- Need of protecting groups
- Activating groups (SNAr)

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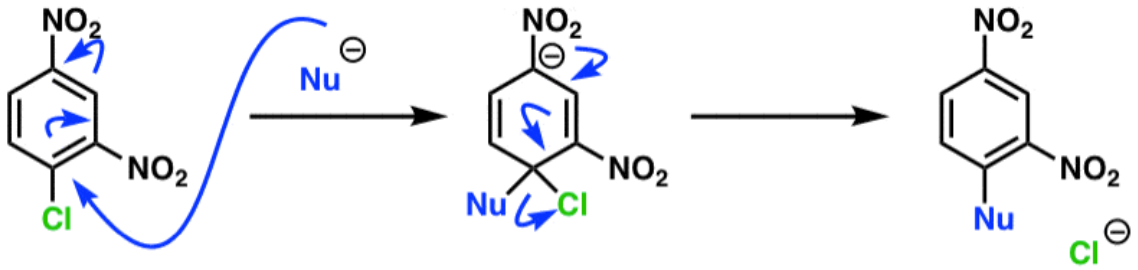
Radiolabeling

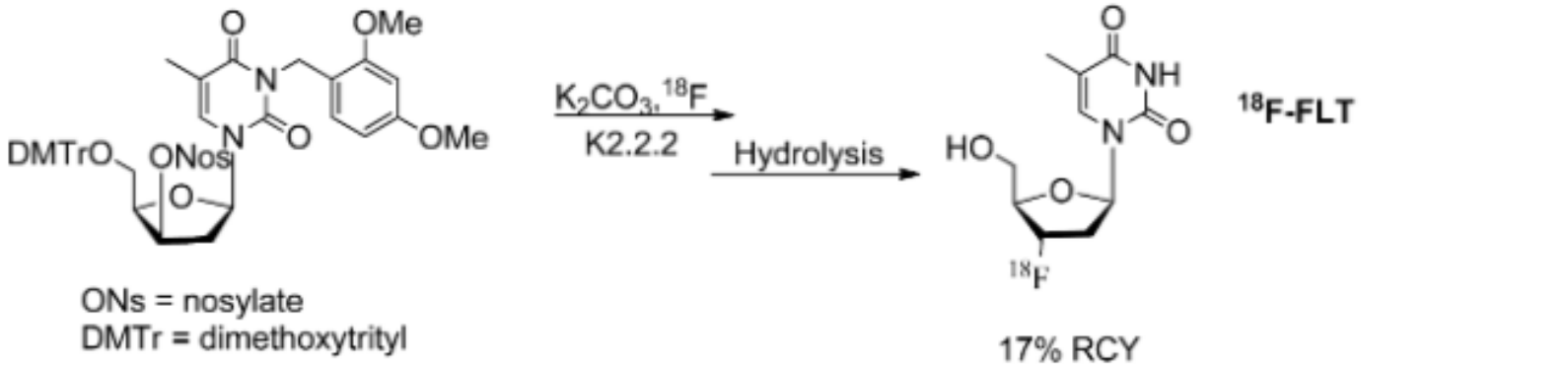
Nucleophilic substitution

- It requires sufficient activation or the phenyl ring→ electron withdrawing groups (EWG: -NO_2, –CN, –CF_3 , or carbonyl groups)



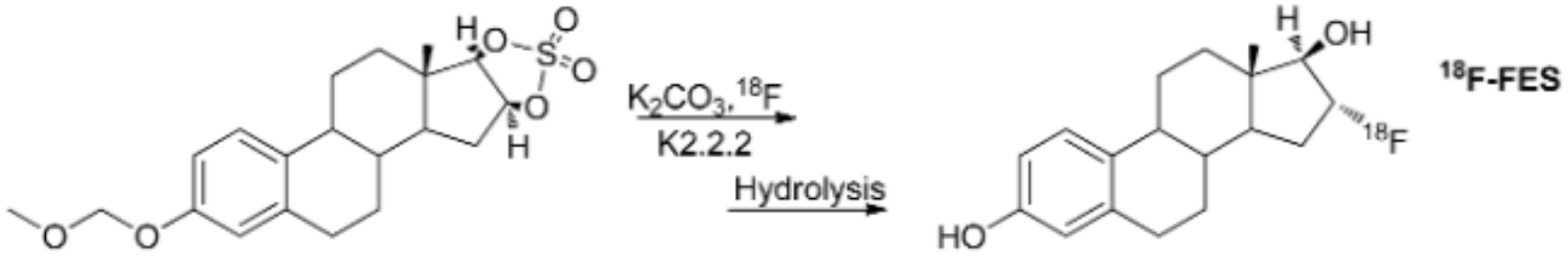
Radiolabeling

Nucleophilic substitution



ONs = nosylate
DMTr = dimethoxytrityl

17% RCY



76% RCY

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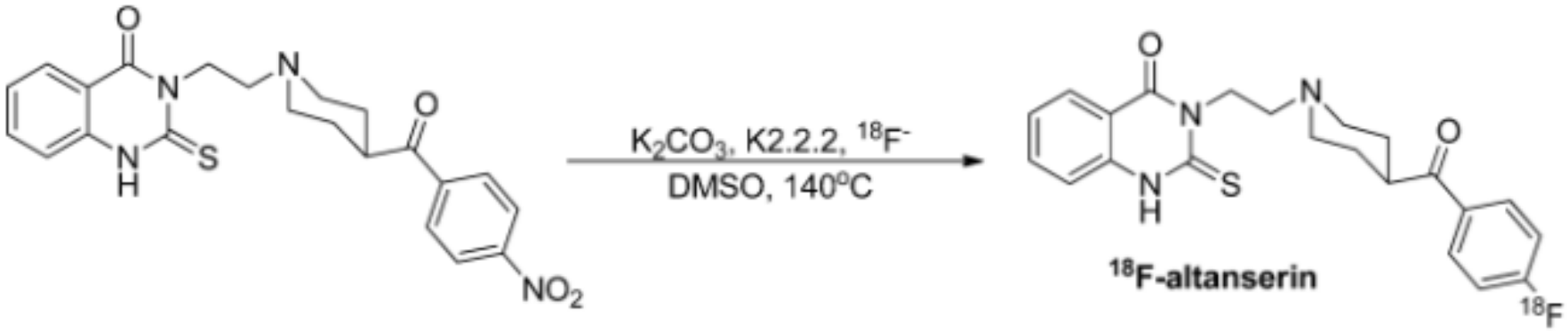
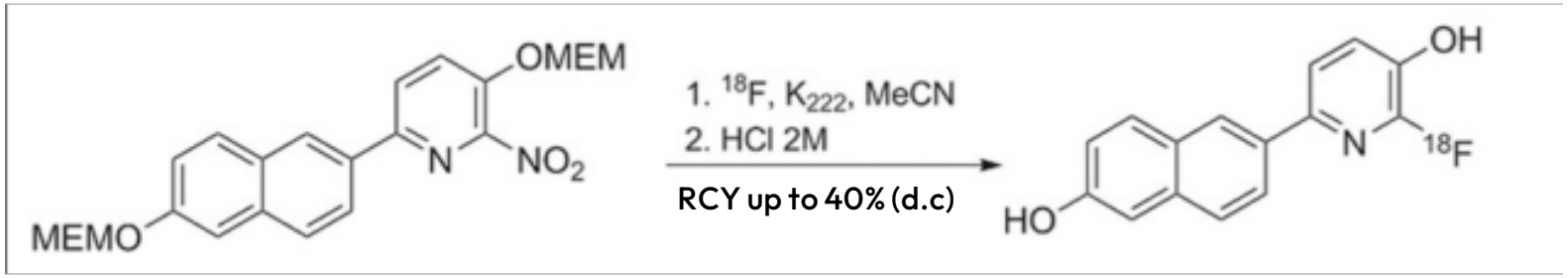
Radiolabeling

Nucleophilic substitution



^{18}F-altanserin

23% RCY



[^{18}F]FHNP for ERβ

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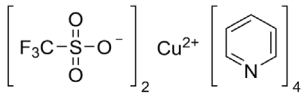
dx.doi.org/10.1021/bc500475e | Bioconjugate Chem. 2015, 26, 1−184
Antunes et.al. J Nucl Med. 2017 Apr;58(4):554-559 DOI: https://doi.org/10.2967/jnumed.116.180158

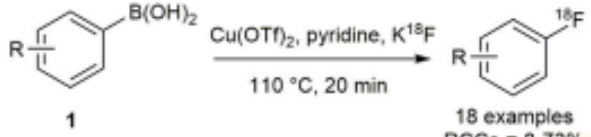
Radiolabeling

Metal-mediated radiofluorination



$Cu(OTf)_2(py)_4$

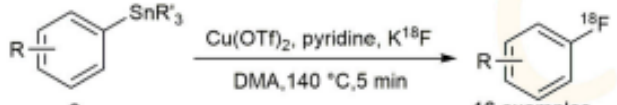
Reaction 1 (Mossine et al., 2015):



1

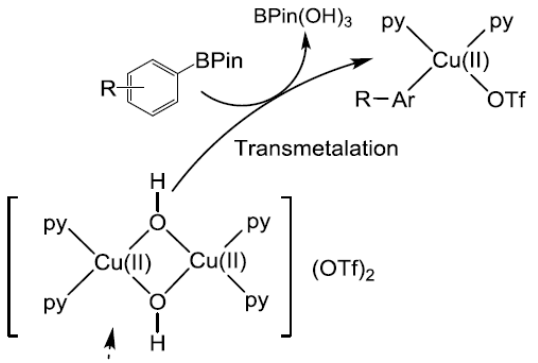
18 examples
RCCs = 8-73%

Reaction 2 (Makaravage et al., 2016):



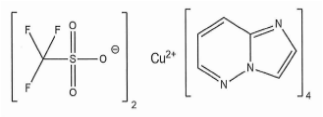
2

16 examples
RCCs = 9-70%



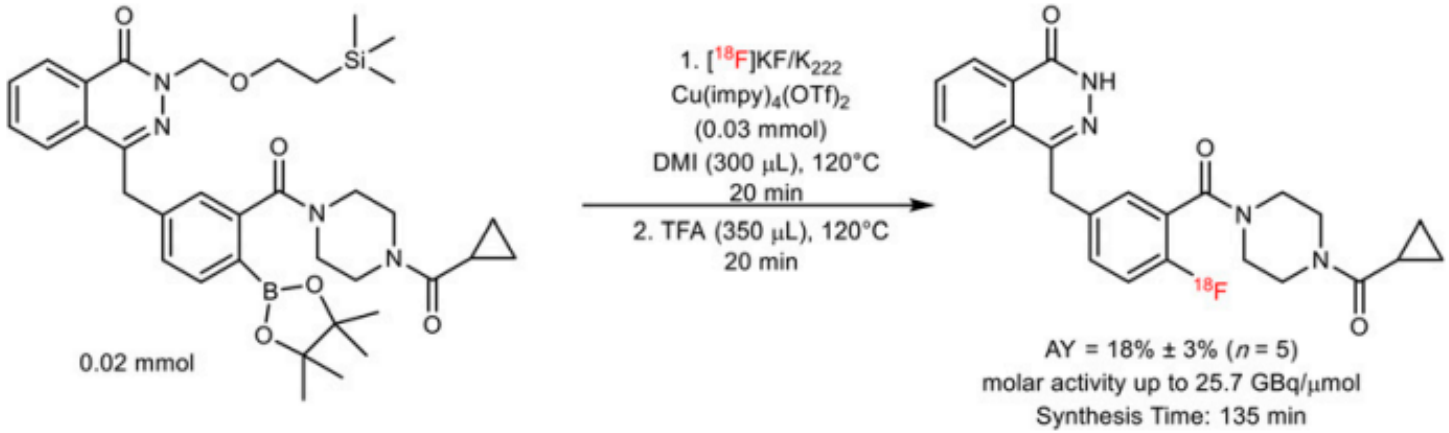
Radiolabeling

Metal-mediated radiofluorination

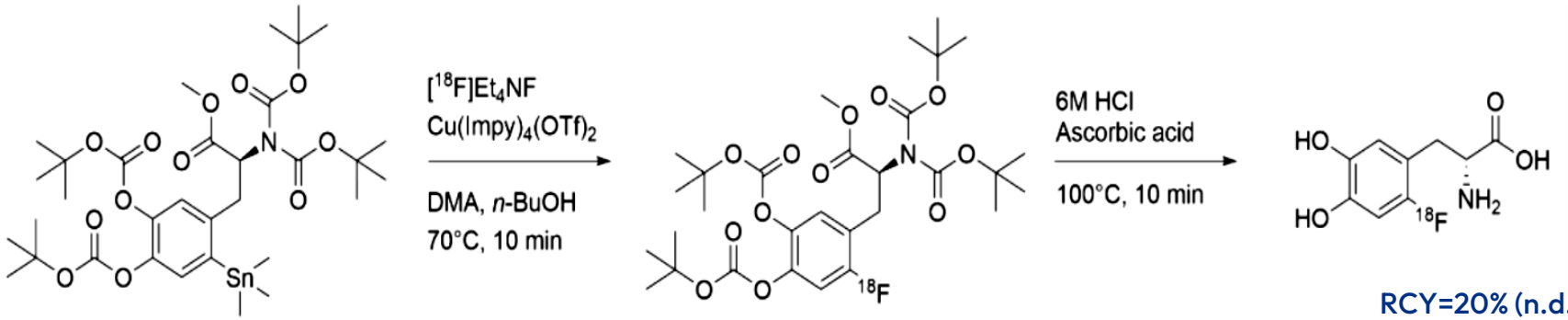


$Cu(OTf)_2(impy)_4$

[^{18}F]-Olaparib



[^{18}F]-FDOPA



RCY=20% (n.d.c) M_A>25GBq/µmol

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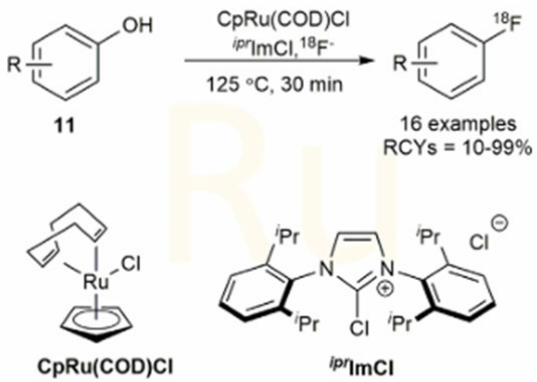
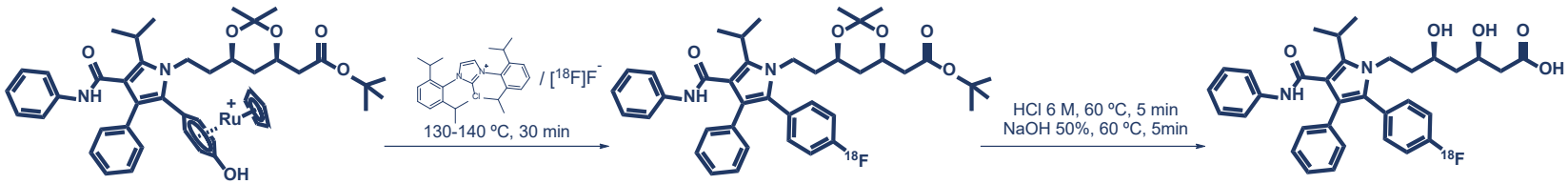
Wilson et al. 2019 and Kwizera C et.al.2024):

Radiolabeling

Metal-mediated radiofluorination

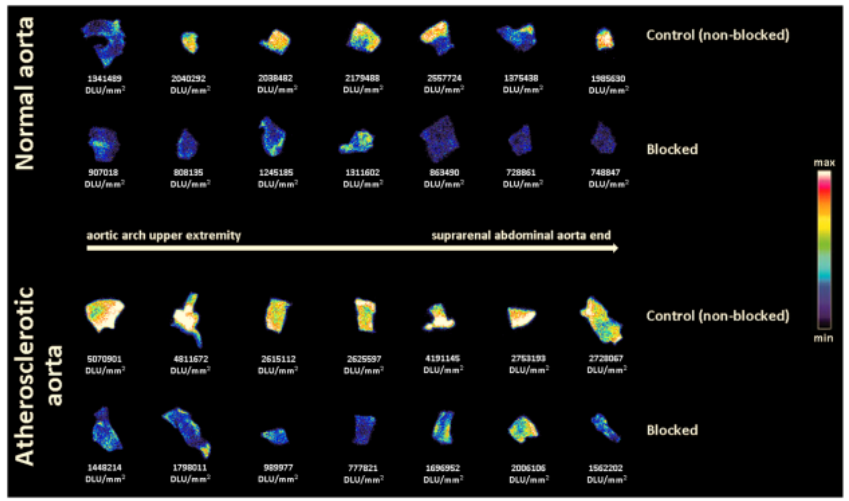


- Aryl systems
- Heterocyclic compounds
- Wide variety of functional groups
- Some basic amines



RCY=19% (d.c)

M_A=65GBq/μmol



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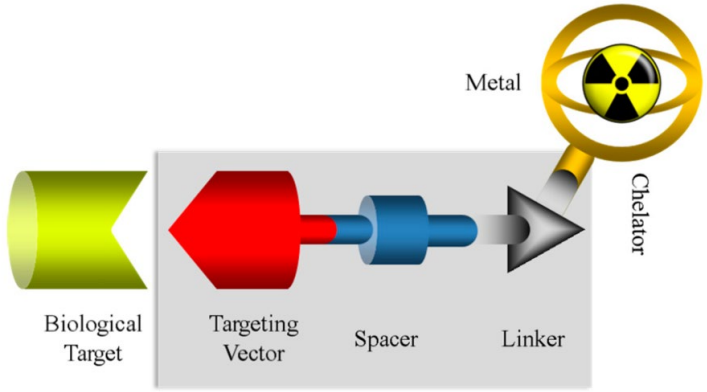
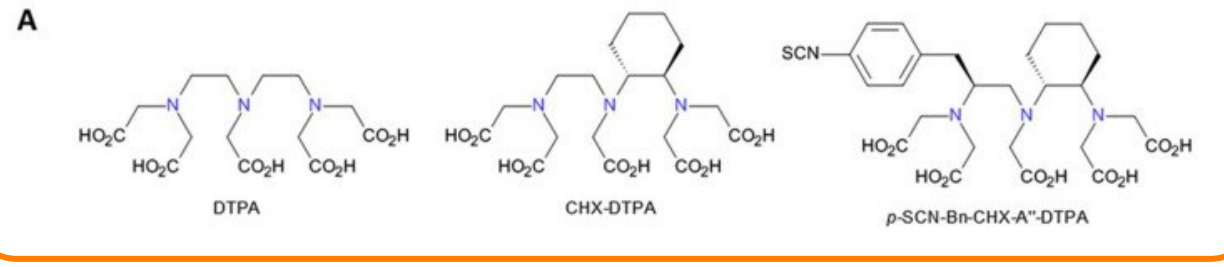
Clemente et al. EJNMMI Research 2020, 10,
Beyzavi et al., ACS Central Science 2017 3 (9), 944-948

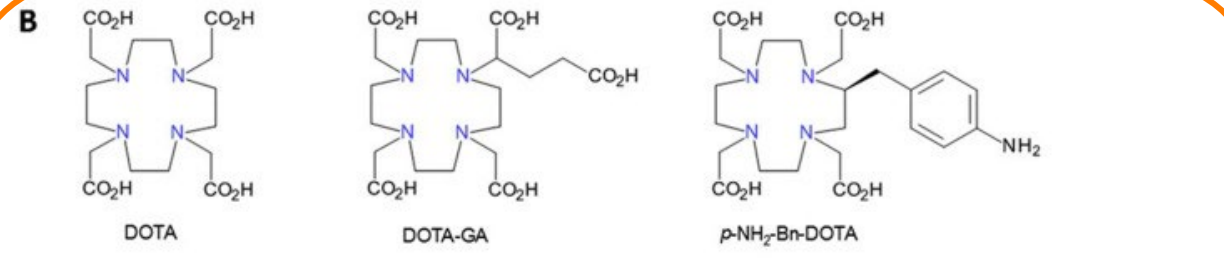
Radiolabeling

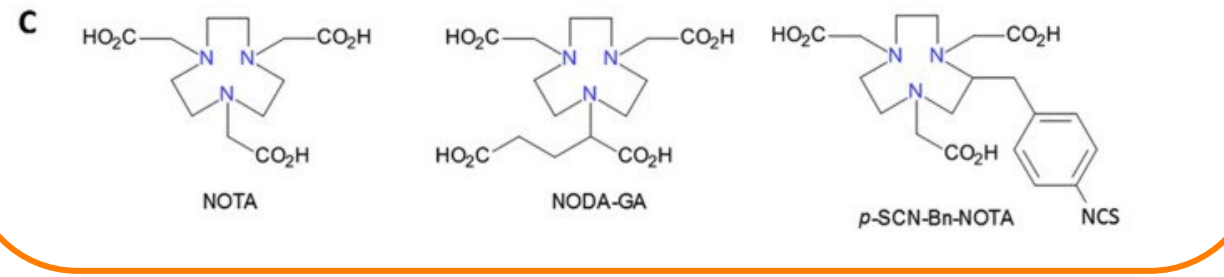
Complexation



Acyclic chelators VS cyclic chelators







Acyclic chelators

\+ Incorporation of the radiometal even at room temperature

\- More Kinetically labile

Cyclic chelators

\+ thermodynamically stable and kinetically inert

\- Incorporation of the radiometal at high temperatures

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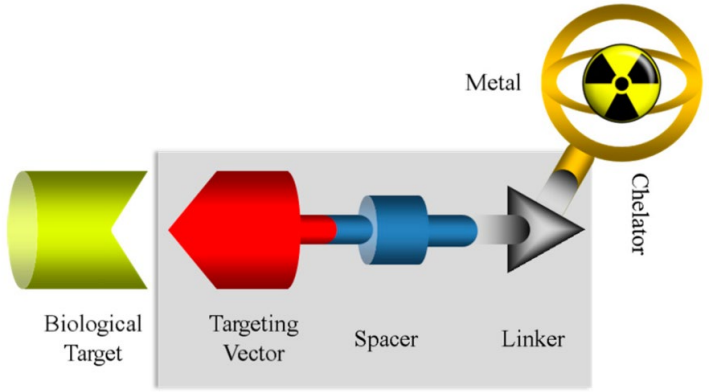
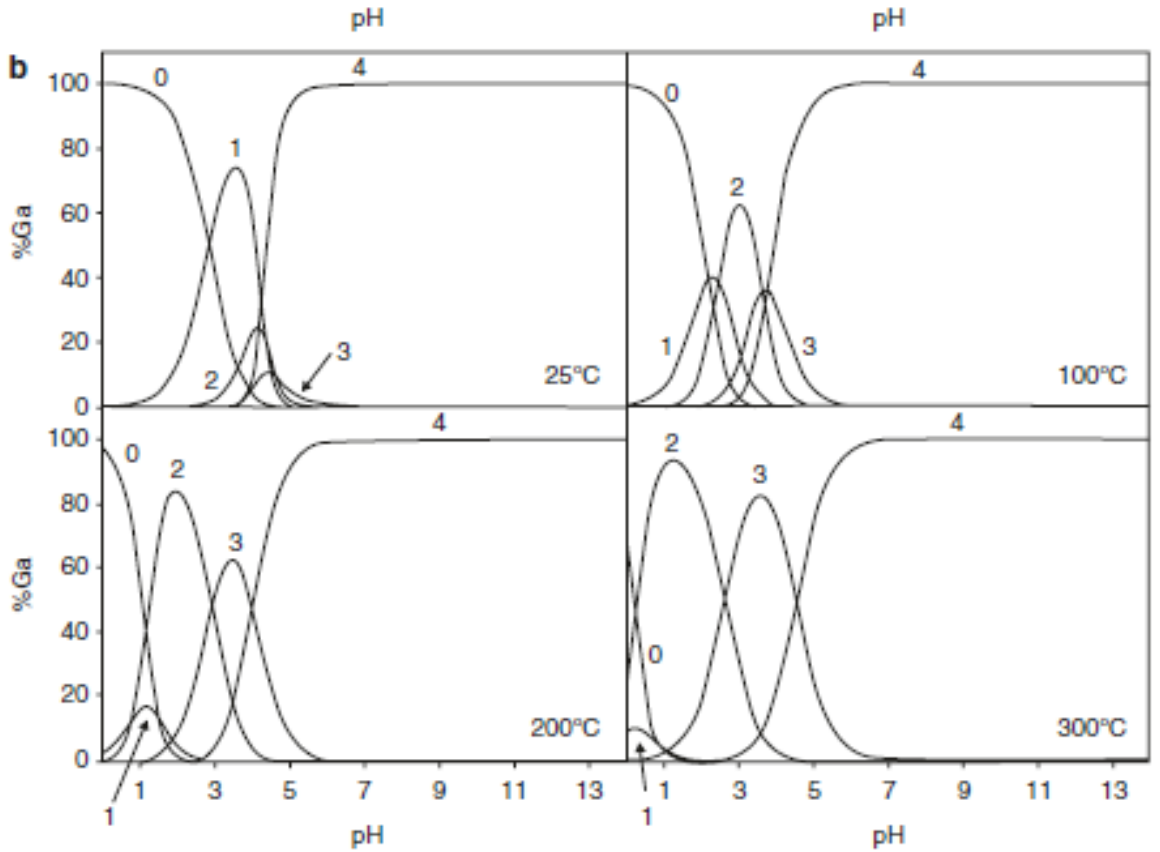
Radiolabeling

- *Size*
- *Oxidation state*
- *pH*
- *temperature*

Complexation





and Ga-hydroxide (**b**) species as a function of temperature and pH at infinite dilution. The species shown are (M = Ga or In): 0 = M^{3+}, 1 = $M(OH)^{2+}$, 2 = $M(OH)_2^{+}$, 3 = $M(OH)_3$ and 4 = $M(OH)_4^{-}$ (From Wood and Samson [17], with permission)

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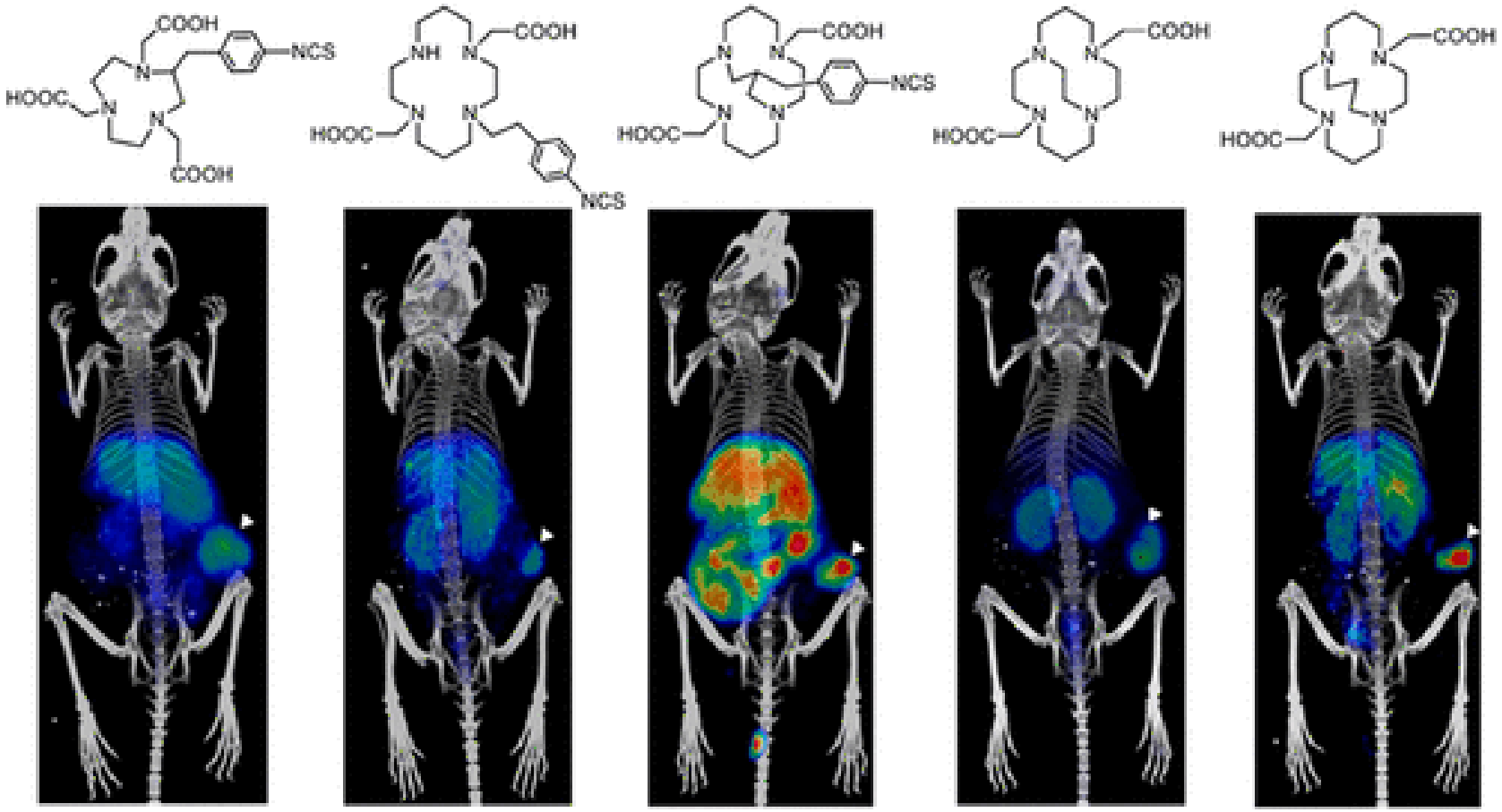
Radiolabeling

Complexation



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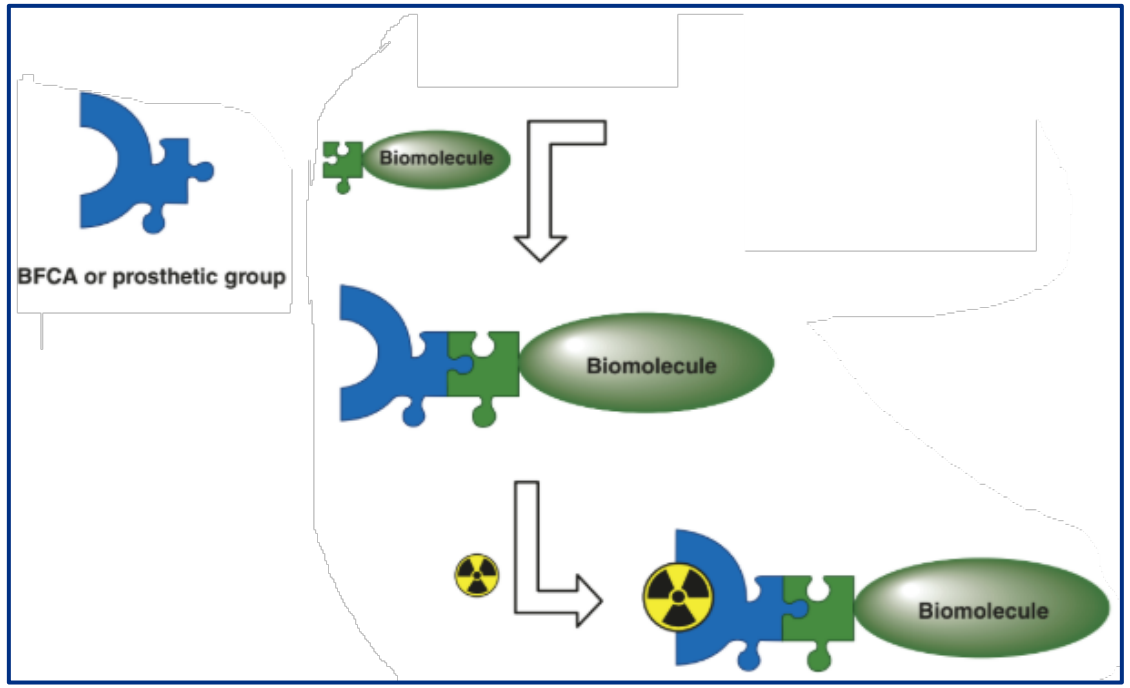
Sarkar el al. J. Med. Chem. 2018, 61, 1, 385-395

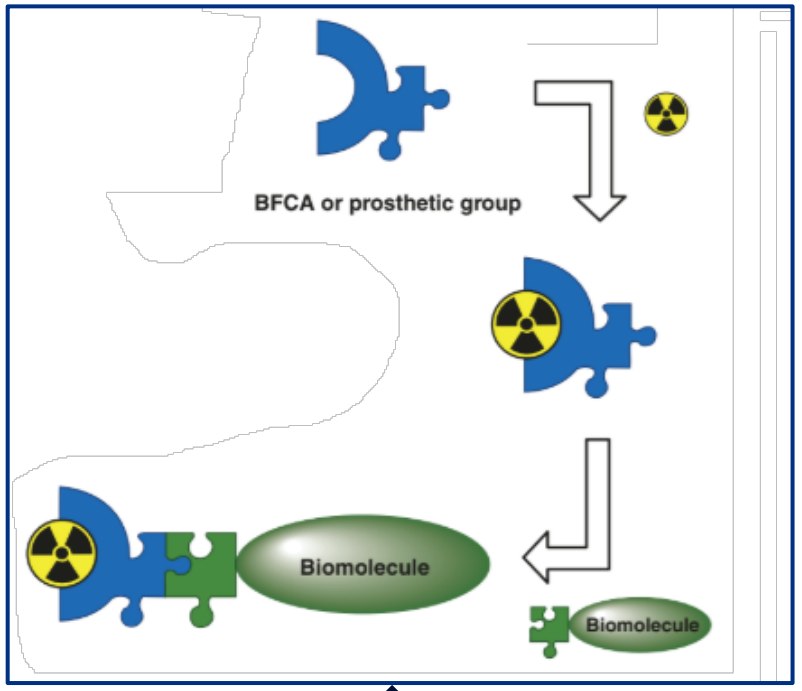
Radiolabeling

Indirect-labelling

Direct Radiolabelling



Indirect Radiolabelling



Non physological pH
High temperatures

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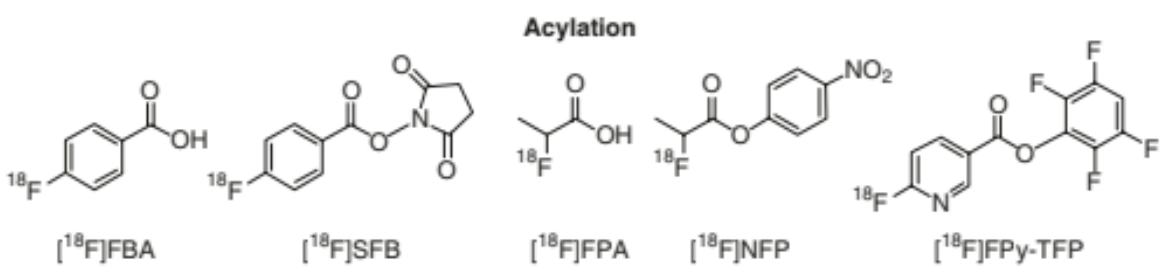
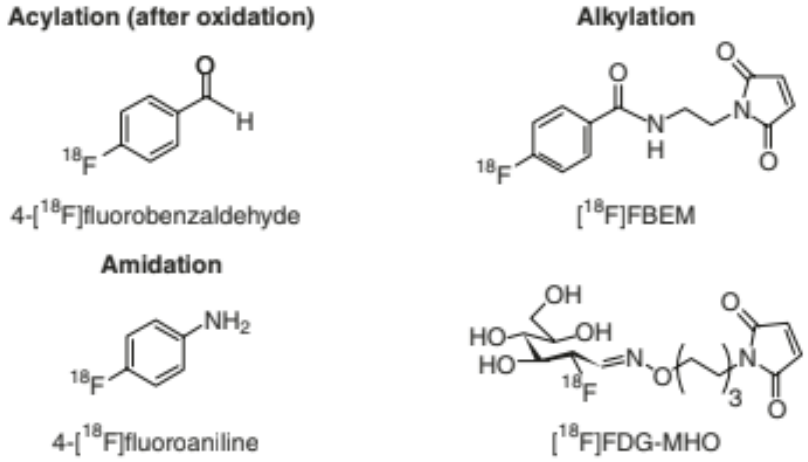
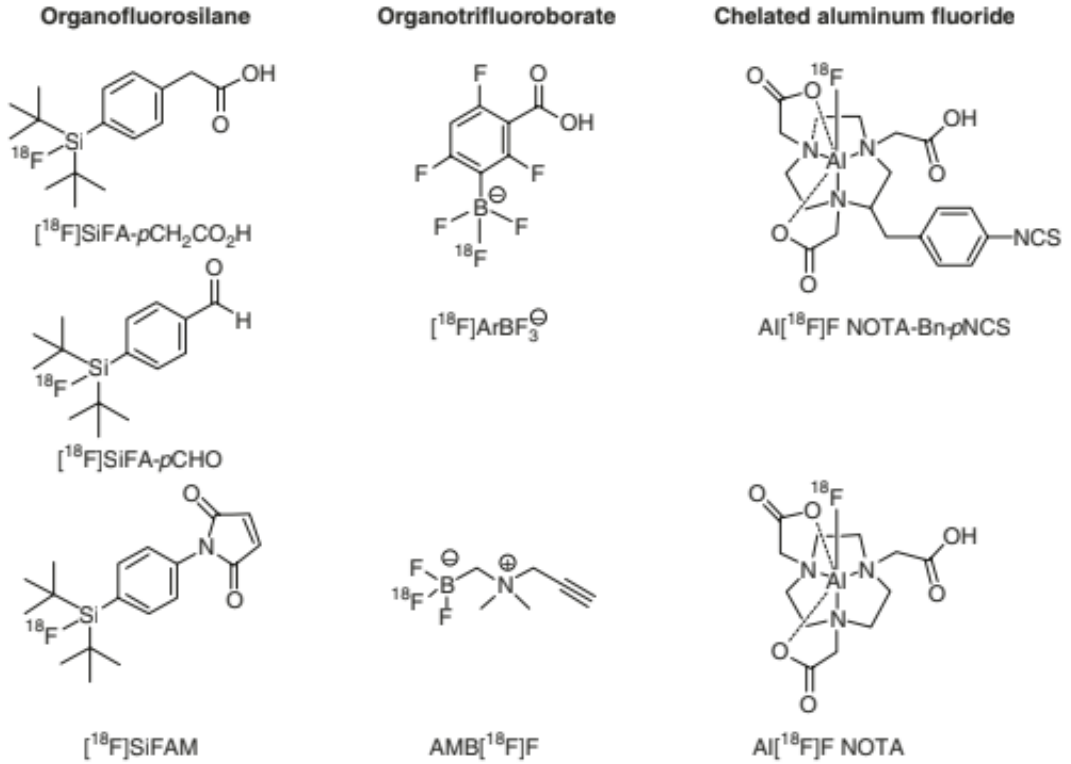
Radiolabeling

Indirect-labelling







Versatility

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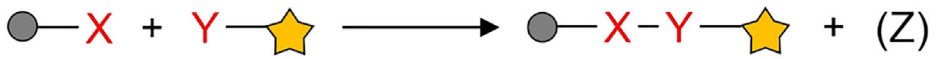
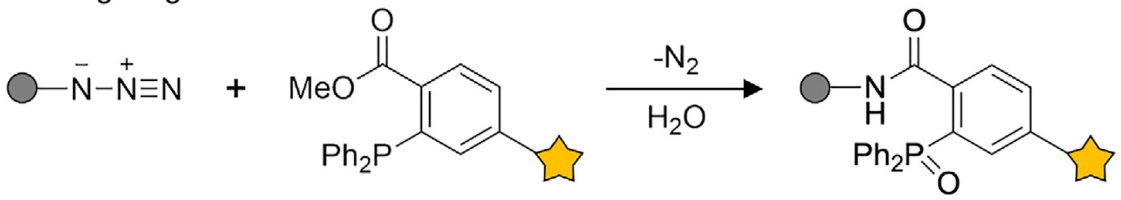
Rickmeier, J. et al. Nat Protoc 18, 3614–3651 (2023), Verhoog et al., Synlett. 2016;27:25, Sadasivam et al., J. Med. Chem. 2024, 67, 5064−5074

Radiolabeling

Indirect-labelling



Staudinger ligation

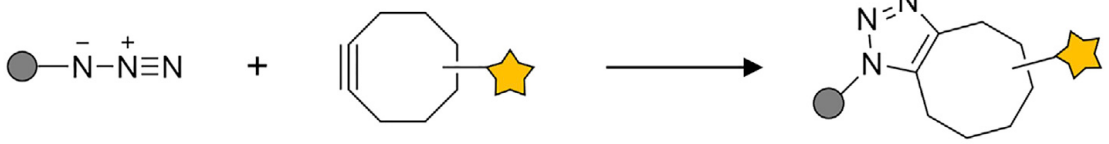


+ Versatility (Fast and low temp 40°C)

Cu-catalyzed azide-alkyne cycloaddition

+ Insensitive to water/oxygen
+ No need of protecting groups/Fast
- Needs Copper

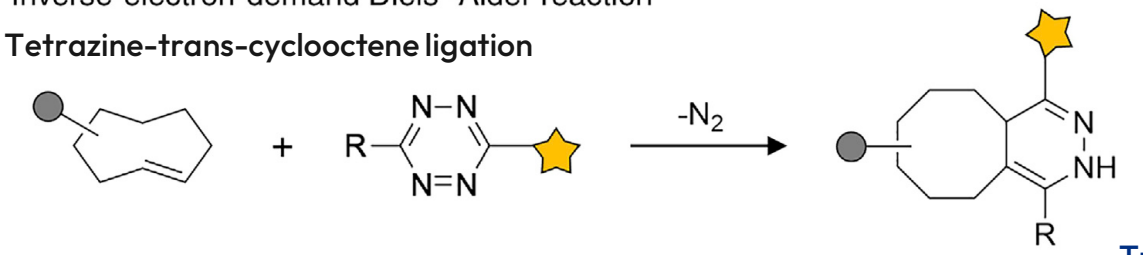
Strain-promoted azide-alkyne cycloaddition



+ Insensitive to water/oxygen
+ No need of protecting groups/Fast

Inverse-electron-demand Diels–Alder reaction

Tetrazine-trans-cyclooctene ligation



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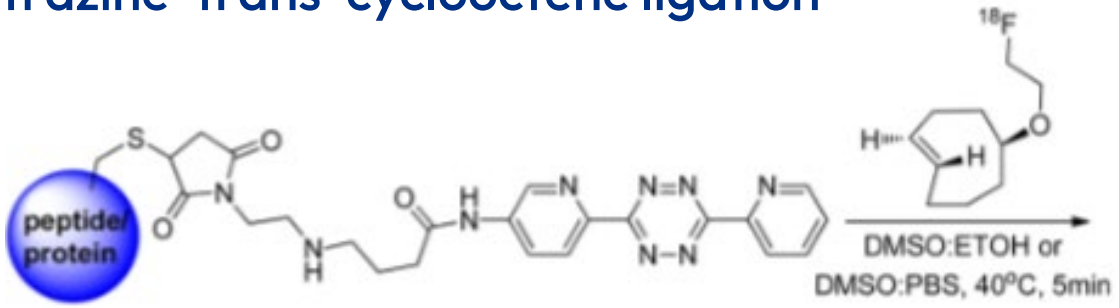
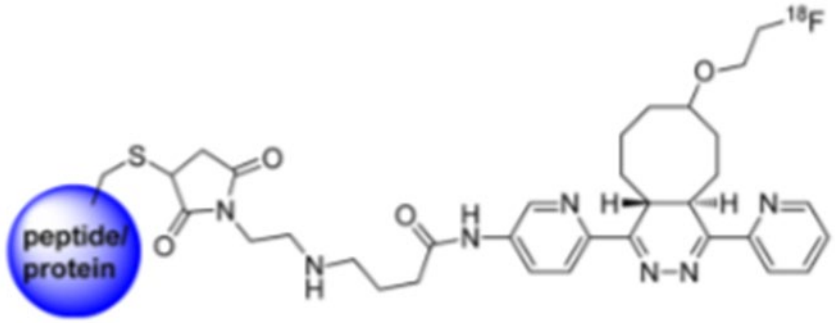
Trends in Chemistry, November, Vol. 1, No. 8 https://doi.org/10.1016/j.trechm.2019.08.003

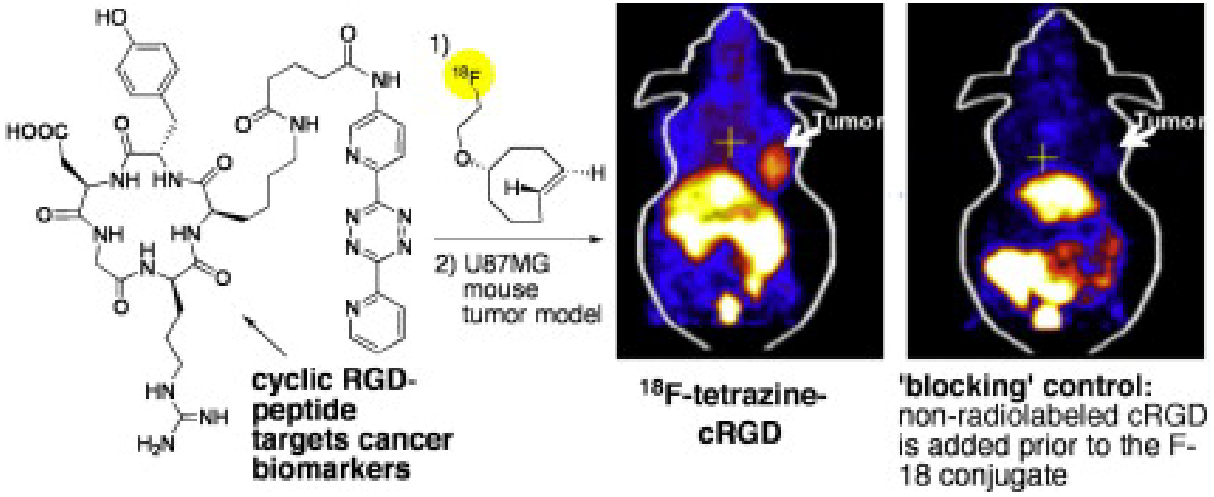
Radiolabeling

Indirect-labelling

Tetrazine-trans-cyclooctene ligation







^{18}F-tetrazine-cRGD

'blocking' control: non-radiolabeled cRGD is added prior to the F-18 conjugate

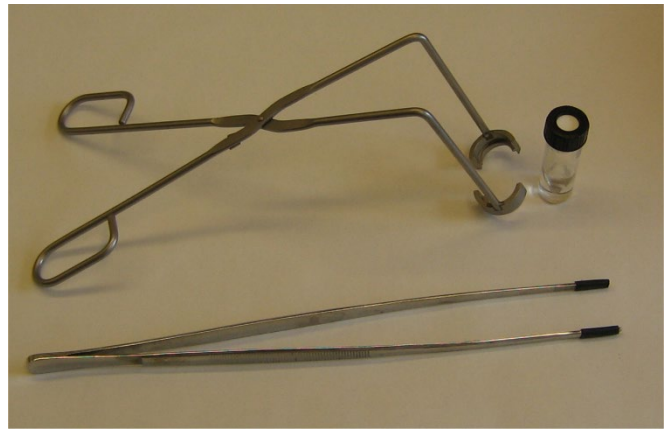
Reaction	RGD derivative (amount µM)	Labelling Yield (%)
TTCA	78	90
CUAAC	940	30
Conjugation 18F-SFB	1800	70

Conti et al., Bioorganic & Medicinal Chemistry Letters, 2011 ,21, 5011-5014


Blonde
Tripels
Dark
Amber
Sour
Wheat
Wheat & Fruity
Saison
Flavours
I.P.A.
Draft
Softs
DELIRIUM CAFÉ
BRUSSELS
Network
DELIRIUM VILLAGE
WIFI Code
delirium
Join Us
Delirium Village
WWW.DELIRIUMVILLAGE.COM/MENUCAFE

Radiolabeling

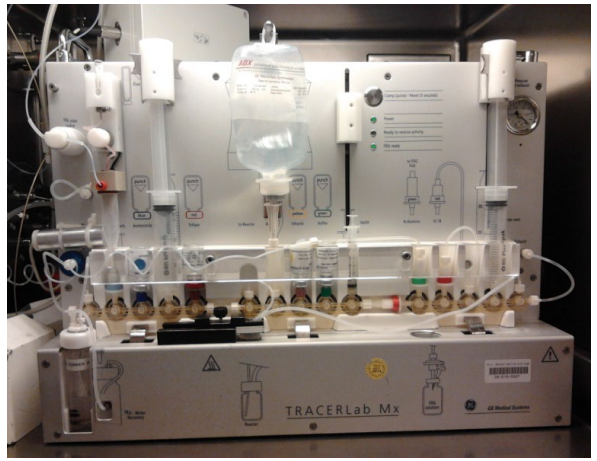
Manual



Radiolabeling

Automated

Cassette



Fixed tubing

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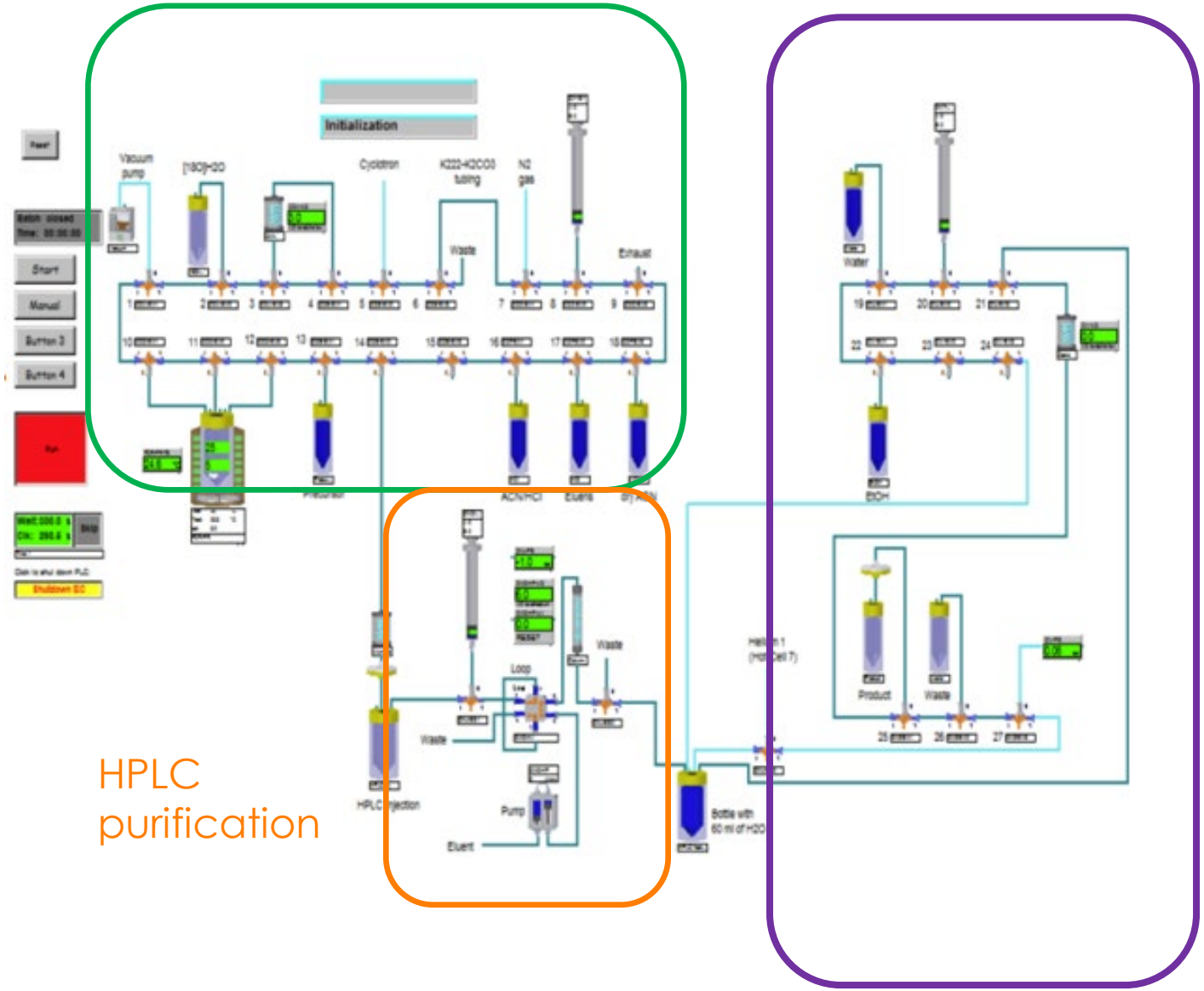
Radiolabeling

Automated

Synthesis

Formulation



HPLC purification

Challenges in automation

- Dependence on mechanical parts: regulators, valves, lines
- Compatibility of hardware with chemicals and radiation
- Clogging or leakage
- Human mistakes in case of complex syntheses

Advantages of automation

- Audit trail
- Reduction of radiation dose
- Can make life easy

Radiolabeling

Automated

Type of automated synthesis module matters!!

[^{18}F]FES synthesis in E&Z Vs IBA

E&Z

Synthera

Figuur 2. Synthera met HPLC module.

- Simpler (Fixed cassette Vs assembled cassete)
- Shorter synthesis steps
- Shorter time
- More robust

Higher yields!! ($\eta \cong 6\%$ Vs $\eta = 25\%$)

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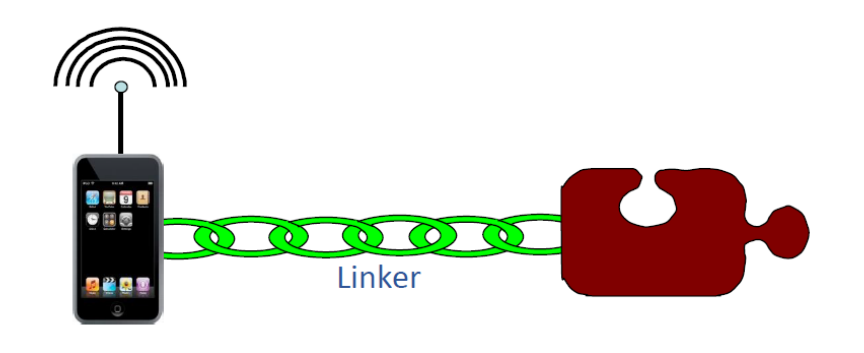
Medical applications

Nuclear Medicine

Diagnostic



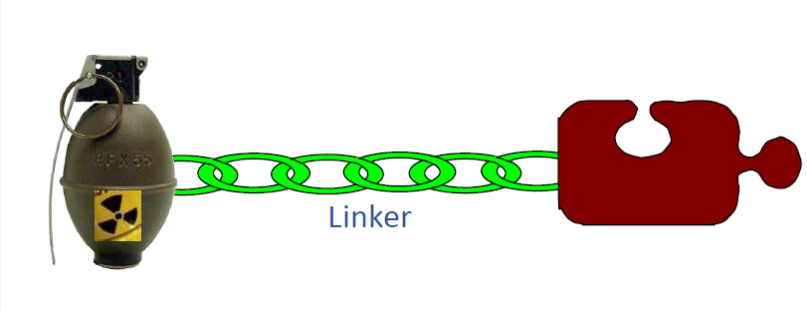
Radionuclide

Emits **radiation** upon decay, detectable by PET or SPECT.

Vector molecule

Responsible for a specific interaction with the target (enzyme, receptor, transporter,...)

Therapeutic



Radionuclide

Emits **particle radiation** upon decay, destroing target cells.

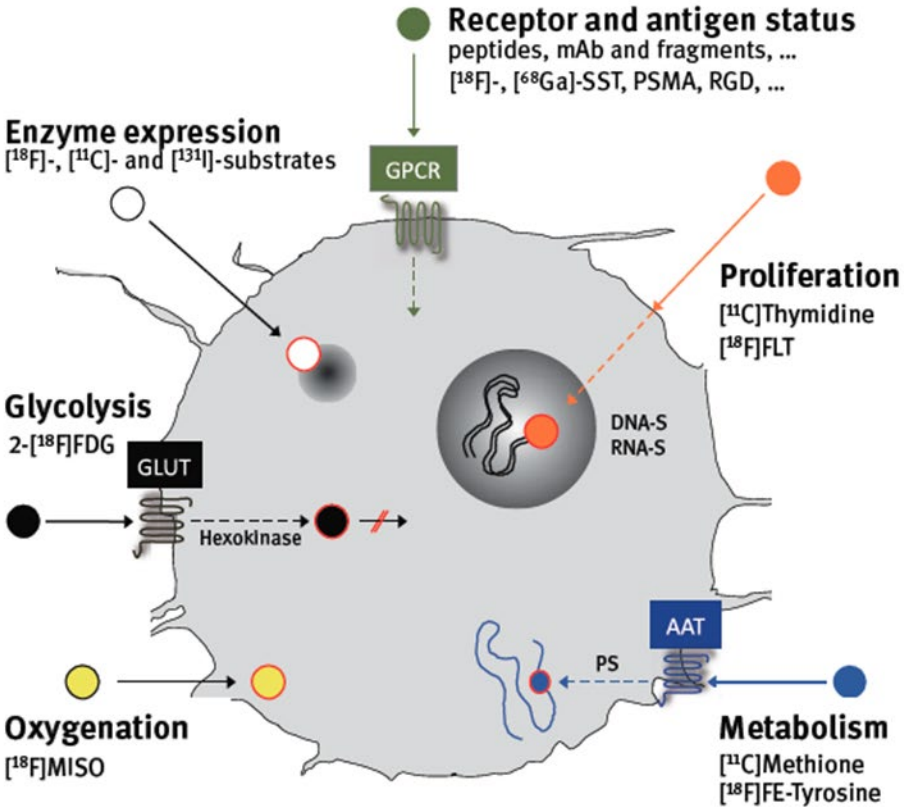
Vector molecule

Responsible for a specific interaction with the target (enzyme, receptor, transporter,...)

Applications

What can be measured with SPECT/PET?

- Receptor density
- Receptor occupancy by a drug
- Enzyme activity
- Membrane transporter activity
- Energy metabolism
- Protein synthesis
- Membrane synthesis
- DNA synthesis
- Oxygenation
- Blood flow
- Perfusion
- Etc, etc .....



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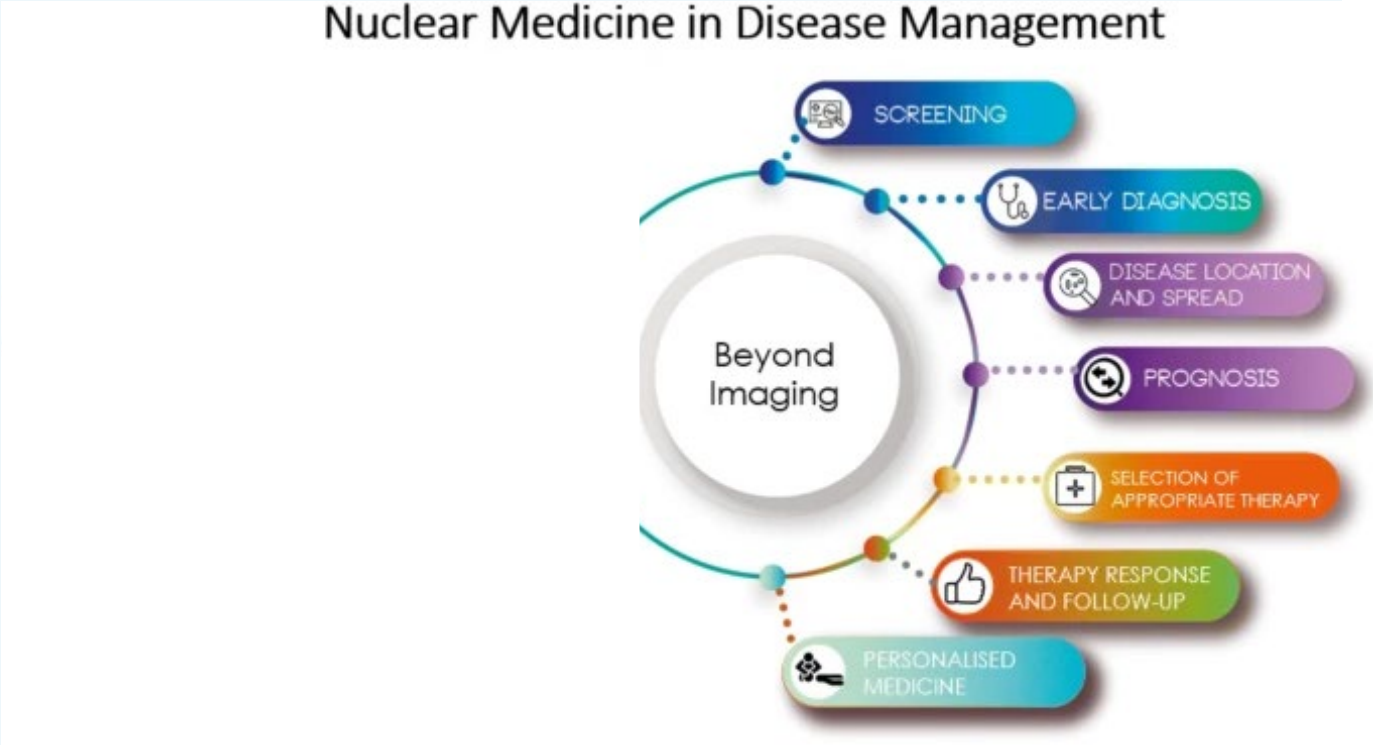
Applications

What information can PET/SPECT provide?

- Differential diagnosis
- Insight the pathology and etiology of disease
- Mechanism of action of drugs
- Monitoring disease progression
- Assessment of treatment efficacy
- Distribution of drugs
- Drug kinetics and receptor occupancy
- …



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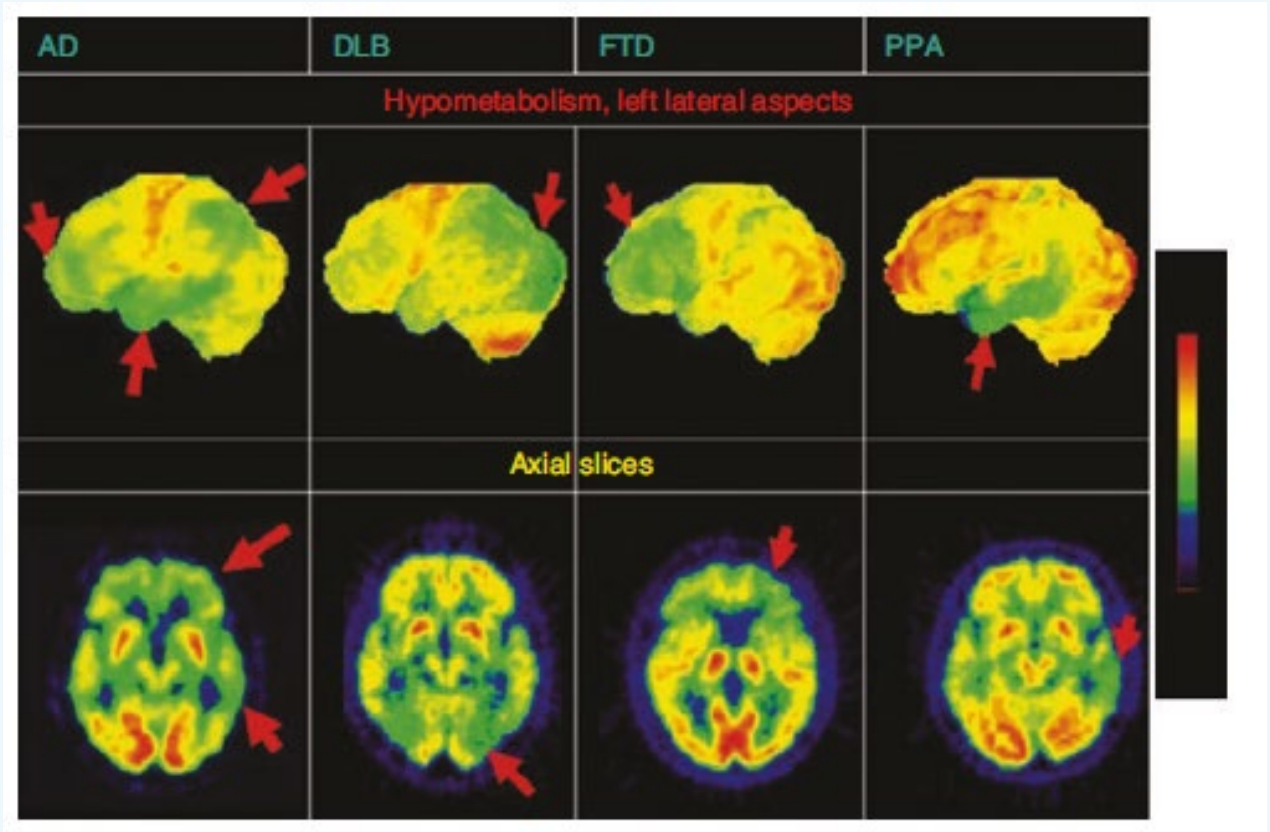
Paez, D., Giammarile, F. & Orellana, P. Nuclear medicine: a global perspective. Clin Transl Imaging 8, 51–53 (2020).

Applications

Diagnostics

Measuring neurological function

[18F]FDG-PET in the differential diagnosis of various degenerative dementias



AD Alzheimer dementia
FTD frontotemporal dementia
DLB dementia with Lewy body (Parkinson's disease)
PPA primary progressive aphasia

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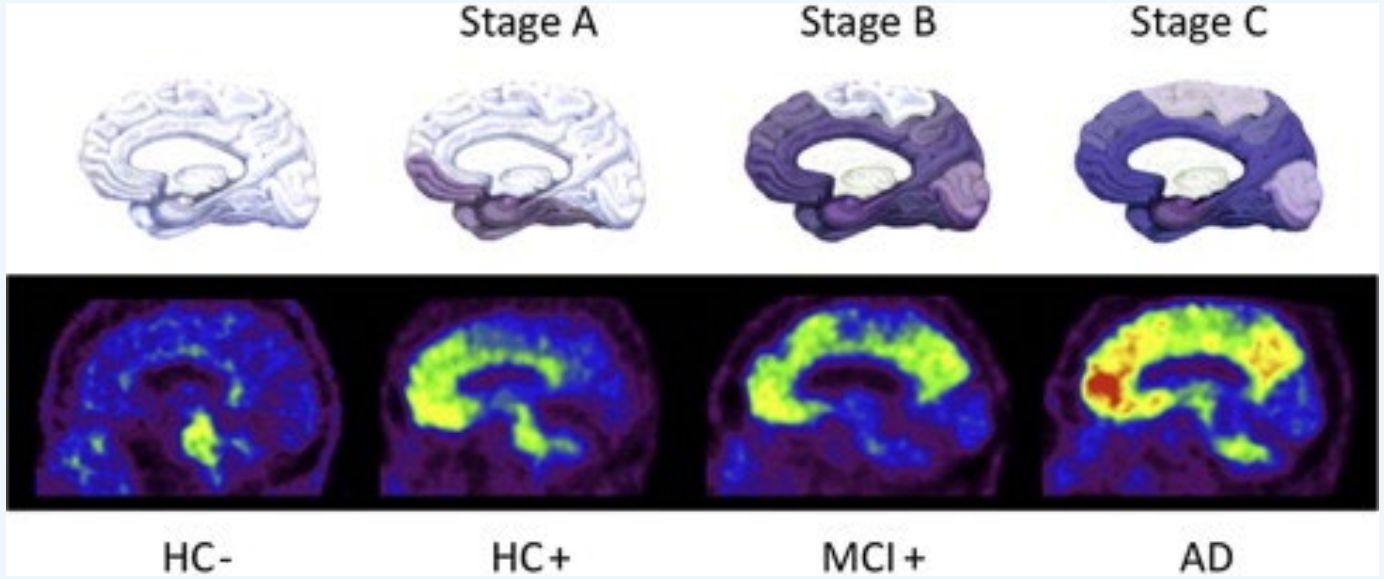
Applications

Follow disease evolution

[^{11}C]PiB for β-amyloid formation



1. asymptomatic healthy control with low (HC−) Aβ burden
2. asymptomatic healthy control with high (HC+) Aβ burden
3. A patient with mild cognitive impairment (MCI+)
4. an AD patient

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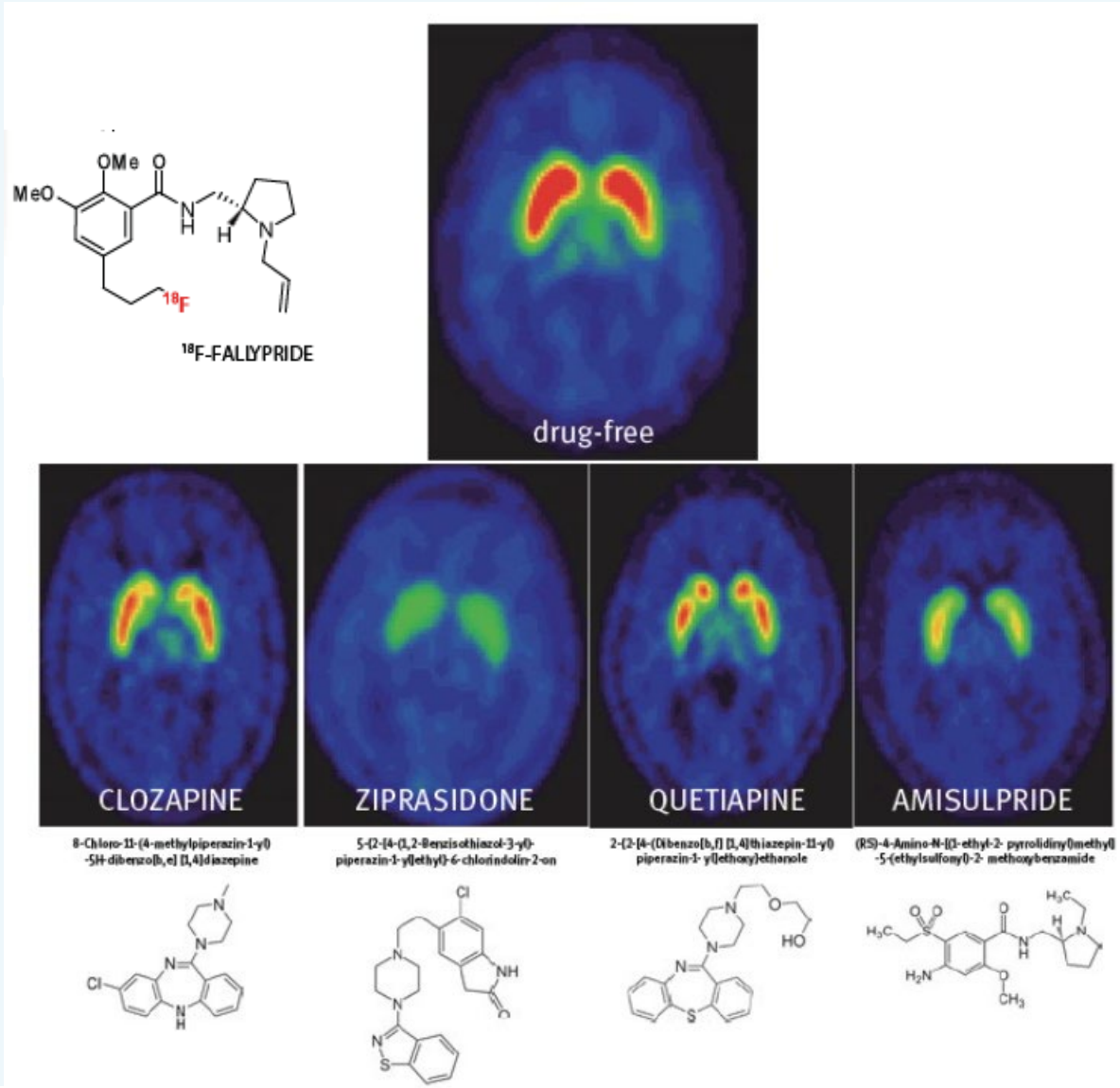
Applications Drug development

Fast access to *in vivo* data (pre-clinical or clinical) to:

- Verify proof-of-concept
- Determine the drug dose
- Determine the efficacy of the drug
- Determine the selectivity of the drug to a certain target

Applications

Drug development



Sagittal view of the striatum injected with D2/D3 receptor PET tracer, [^{18}F]Fallypride in health volunteers showing endogenous levels of receptor availability VS when taken different neuroleptics.

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Applications Therapeutic drug monitoring

To determine the individual optima dose (personalized treatment)

Patient-characteristics properties :

- Metabolism
- The penetrability of the BBB.
- Metastasized cancer Vs primary cancer

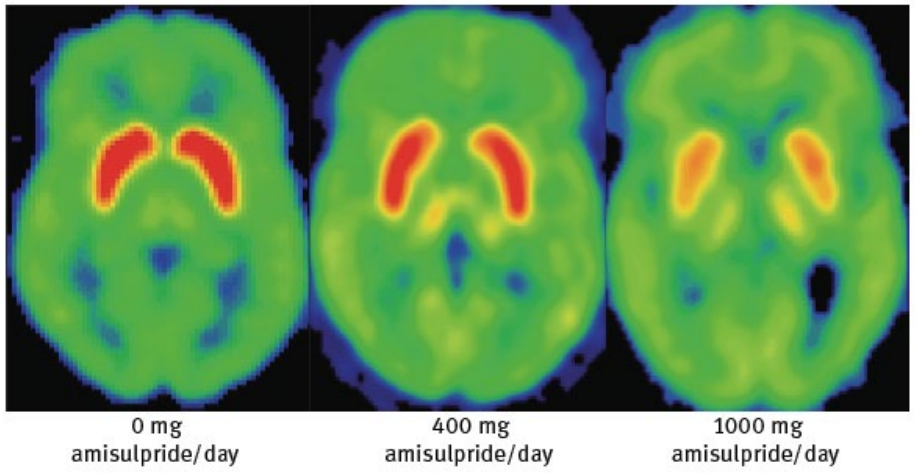

Fig. 12.60: Increasing occupation of postsynaptic $D_{2/3}$ receptors as analyzed by [^{18}F]DMFP PET depending on the daily dose of the neuroleptic drug amilsulpride.

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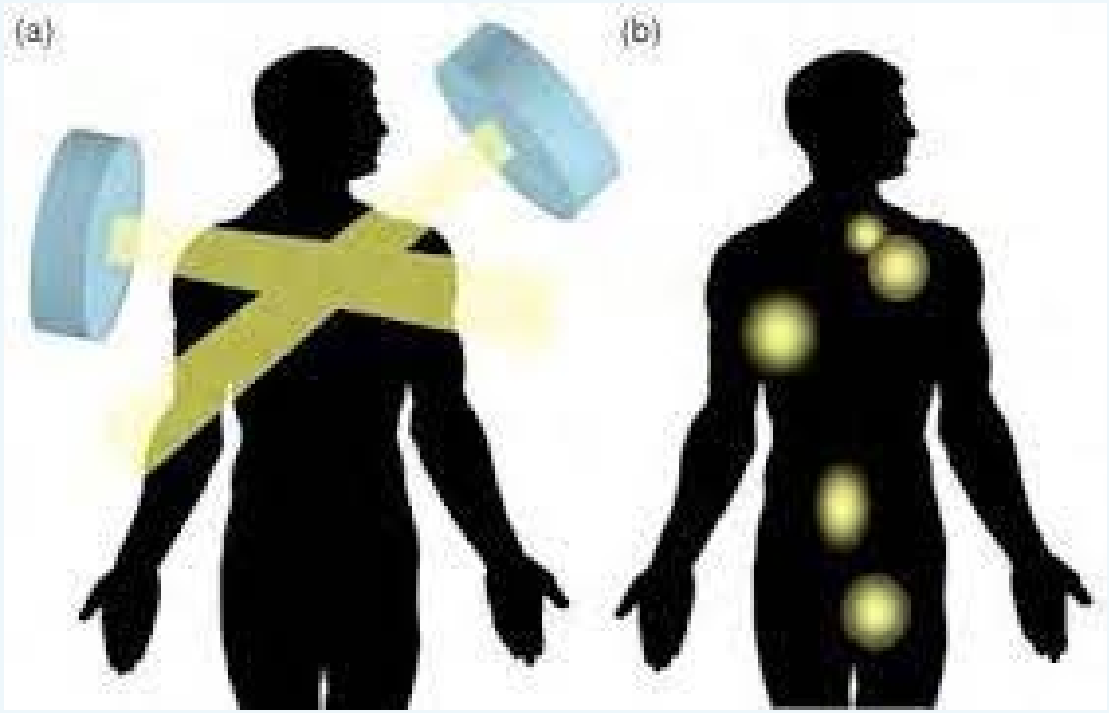
Applications

Theranostics

External Beam

Targeted Radionuclide



Requires knowledge of tumor location

Requires knowledge of tumor biology

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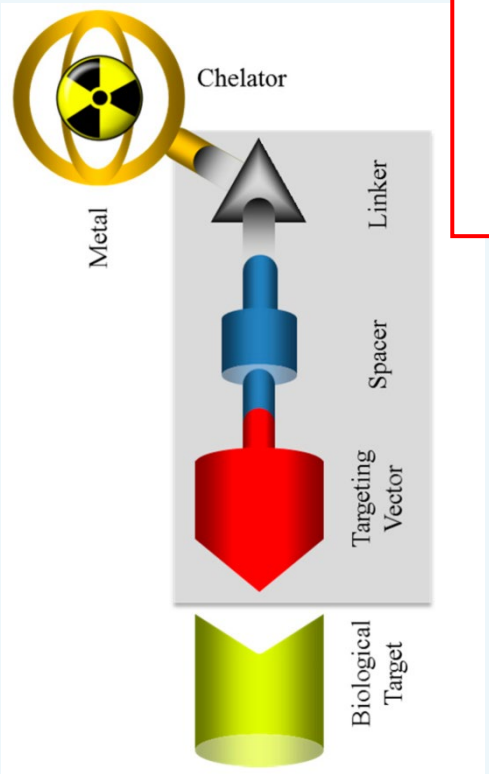
Applications

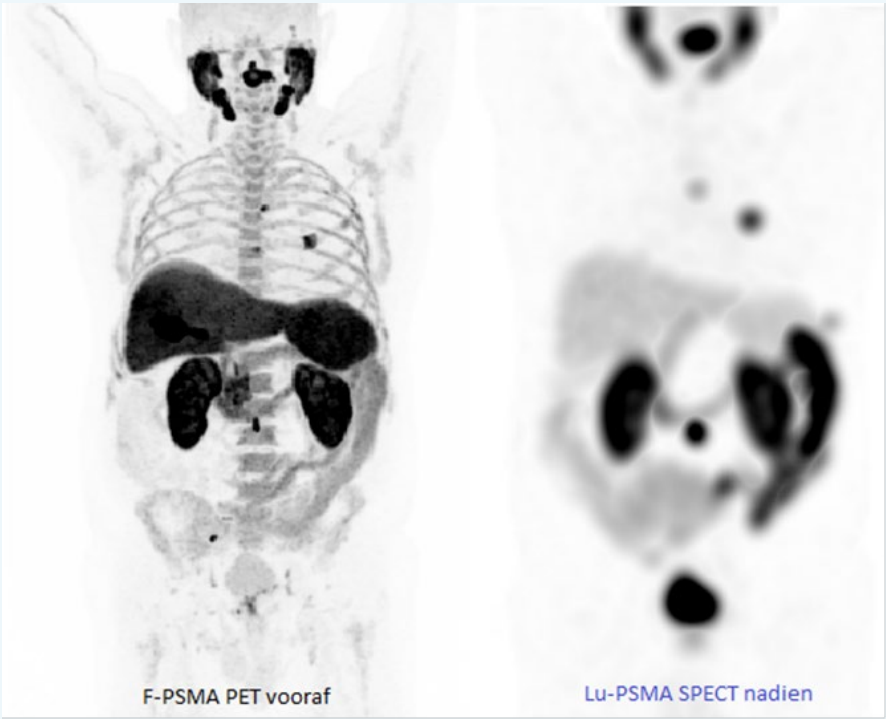
Theranostics

^{99m}Tc (SPECT)

$^{68}Ga/^{18}F$ (PET)



^{177}Lu (Beta emitter)
^{161}Tb (Beta emitter + Auger e-)
^{225}Ac (Alpha emitter)



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TARGETED
RADIONUCLIDE
THERAPY
cost
EUROPEAN COOPERATION IN
IN SCIENCE AND TECHNOLOGY

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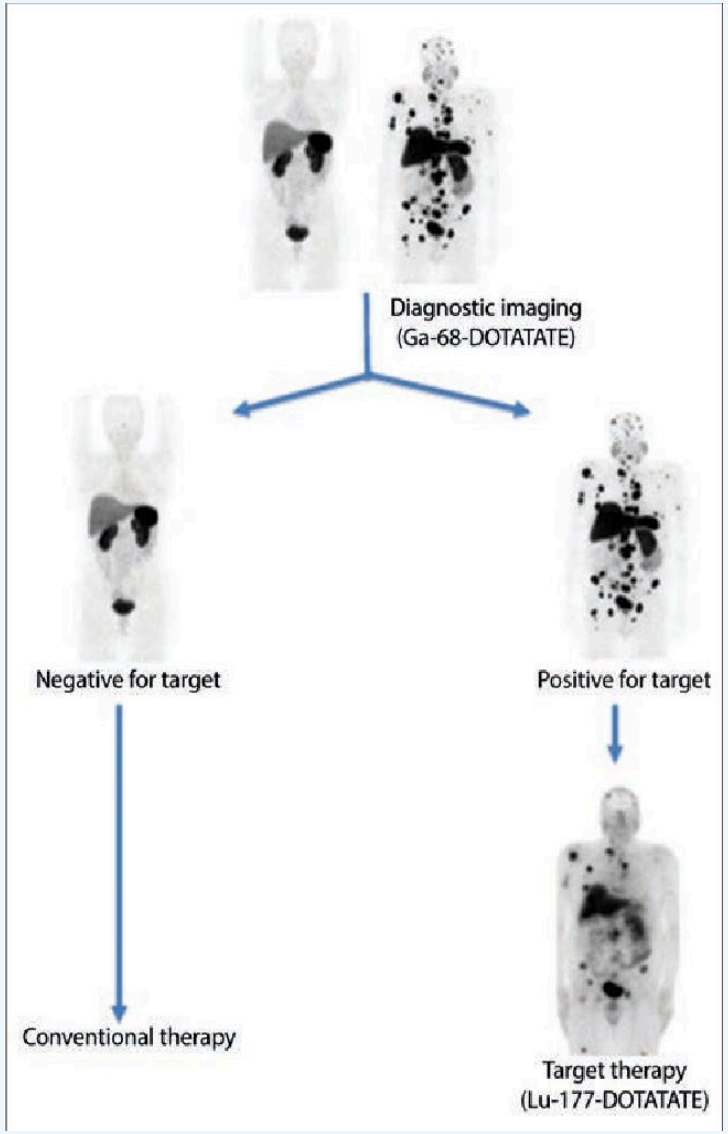
Applications

Theranostics

1. You treat what you see!

Personalized treatment (therapy selection based on specific molecular features of disease)



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Applications Theranostics

2. Estimate the effective absorbed dose and therefore reduce side effects

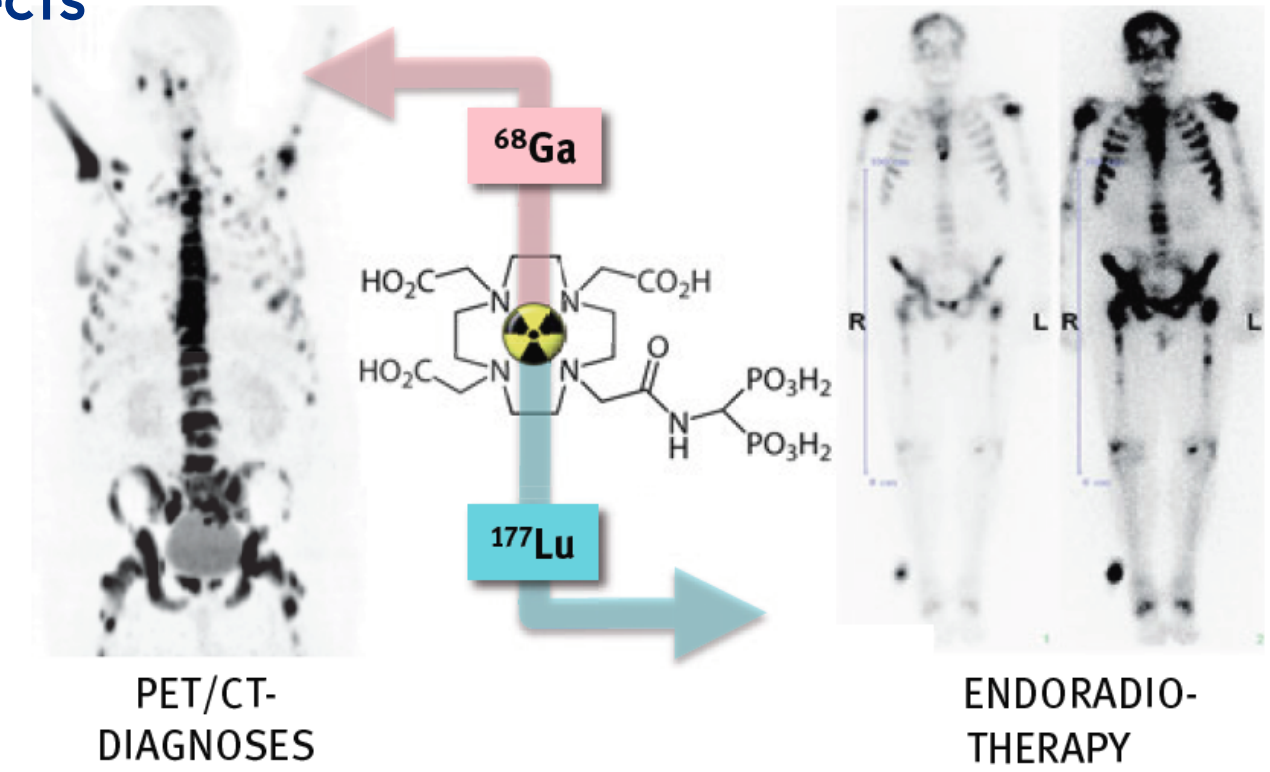

Fig. 13.31: Example of a theranostic approach in nuclear medicine: The same targeting vector, the DOTA-conjugate bisphosphonate BPAMD, is labeled first with ^{68}Ga for quantitative PET to verify the bone metastases expression and the intensity of the tracer uptake (in SUV). Next the same patient undergoes therapy with the ^{177}Lu-BPAMD analog (courtesy Roesch 2011).

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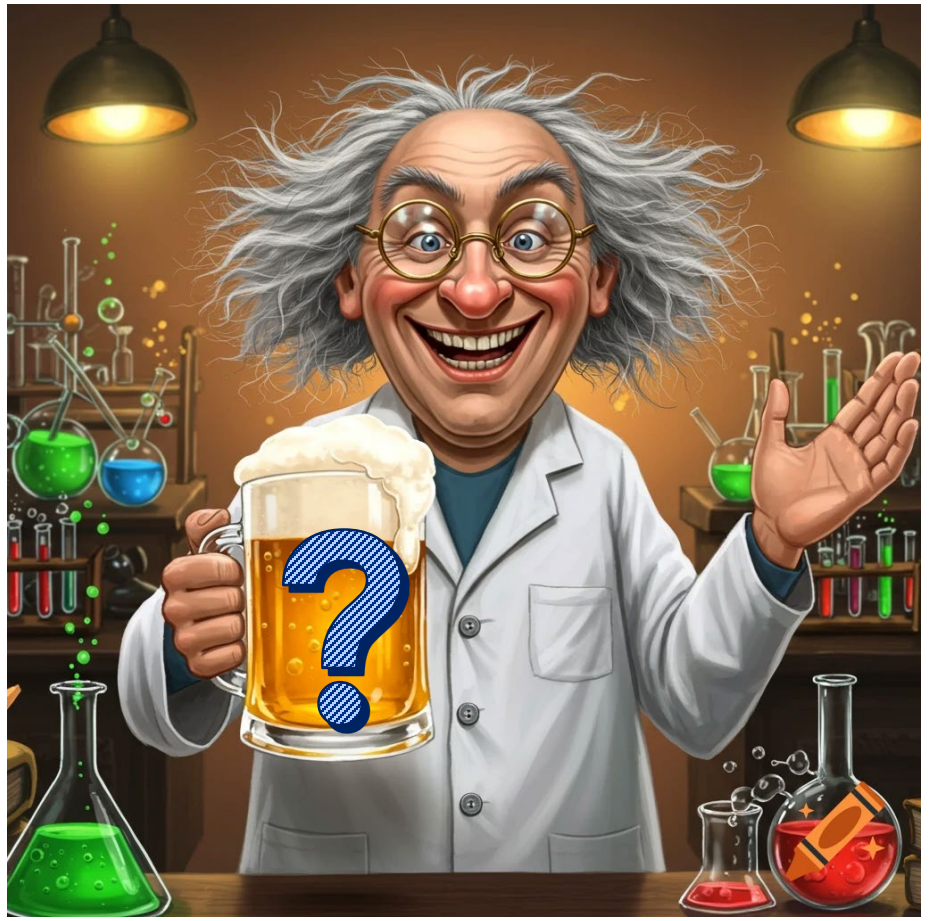
Conclusion:

- The properties of the radionuclide and vector will mostly dictate what synthesis method to use
- Radionuclide needs to match the biological half-life of the vector.
- Radiopharmaceuticals can be both applied for diagnostic and therapeutic to improve Precision medicine



One size doesn't fit all!!

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