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Radiochemistry in nuclear medicine

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Do not say “contrast media” (but *molecular imaging*)

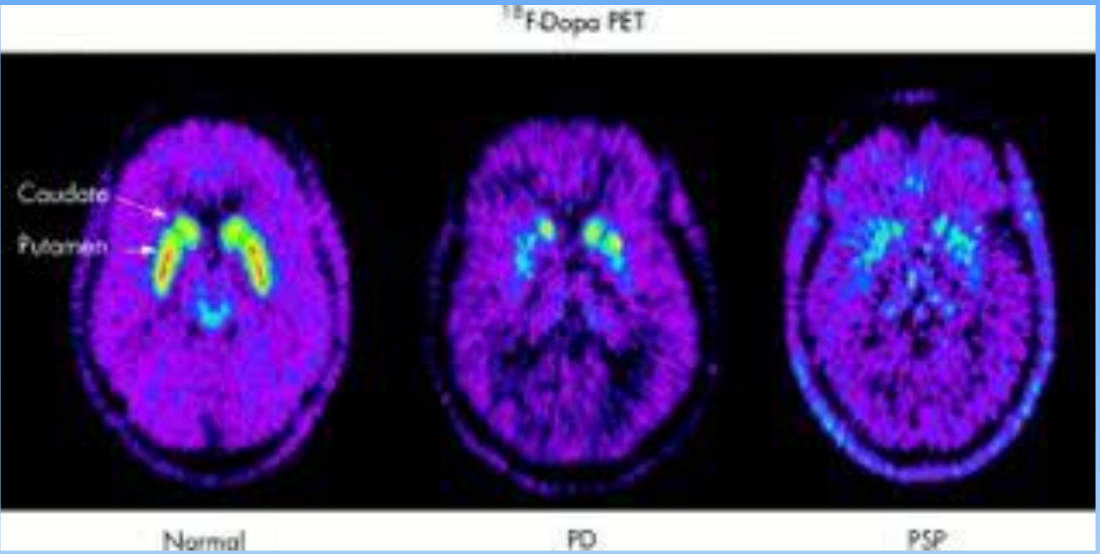
Contrast media

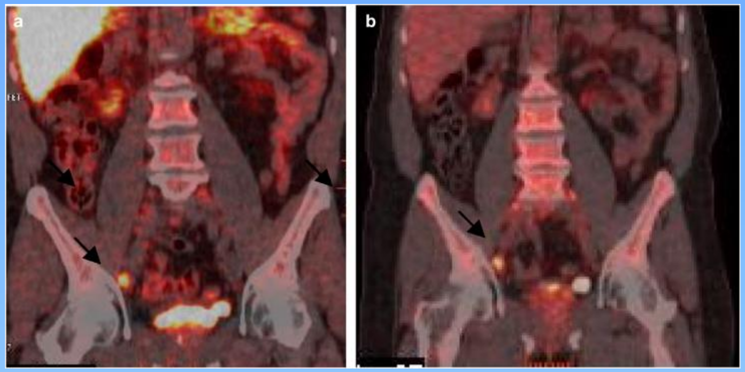
- Mainly anatomical
- High injected mass
  - Mild invasive
  - Patient reactions
- Non natural molecules
- Stability issues
- Easy purchase media
- MRI, CT

Radiopharmaceuticals

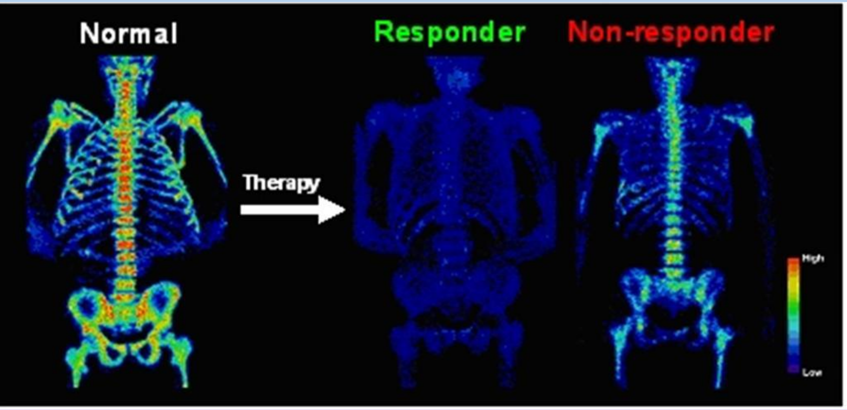
- Mainly functional
- Low injected mass
  - Low invasive
  - Rare patient reactions
- Some natural molecules or analogues
- Few stability issues
- Limited purchase or GMP prepared tracers
- PET, SPECT

The final aim of Nuclear Medicine



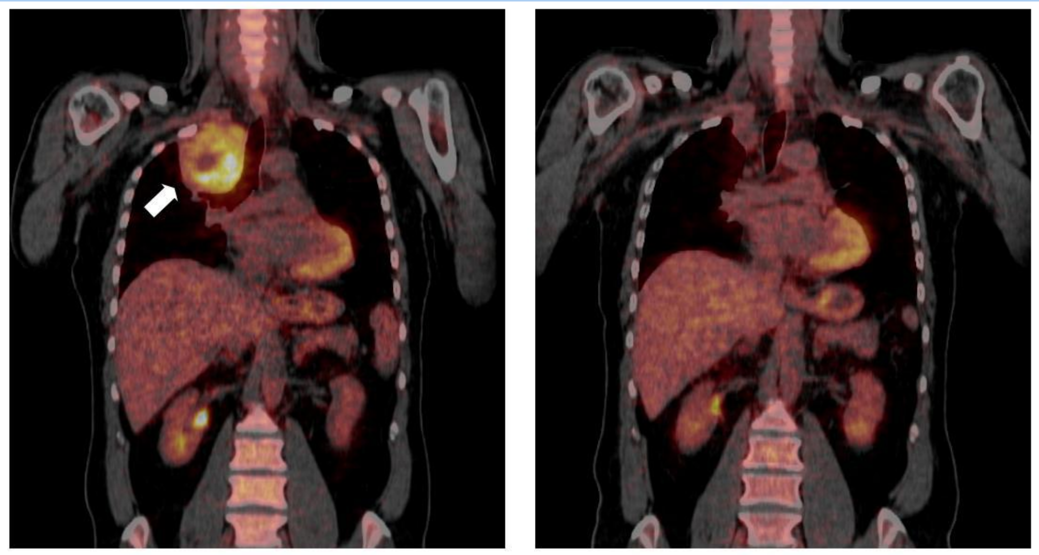


FDG Fluorocholine

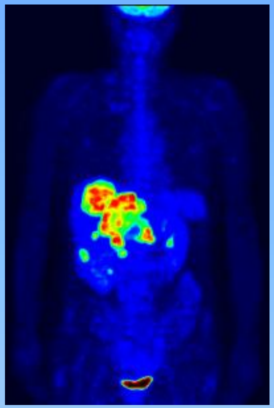


FLT

FDG



A successful PET study



Data processing, medical diagnosis

Physician

Patient handling, scanning protocols

Physician
Paramedics
Physic
Engineer

Tracer radiosynthesis

Chemist
Engineer

Nuclide production

Physic
Engineer

Big interplay among different fields of knowledge

Outlook

- Radionuclides in nuclear medicine
- Radiochemical reactions
- Radiopharmaceuticals

Employed radionuclides

Elements	For PET			For SPECT		
	Radionuclide	$T_{½}$	$β^+$ (MeV)	Radionuclide	$T_{½}$	γ (MeV)
Organic compound elements	^{11}C	20.4 months	0.959			
	^{13}N	9.96 months	1.197			
	^{15}O	2.03	1.738			
Halogens	^{18}F	109.8 months	**0.635**			
	^{75}Br	98 months	1.74			
	^{76}Br	16.1 h	3.98			
	^{124}I	4.2 days	2.13	^{123}I	13.2 h	0.159
				^{131}I	8.04 days	0.364
Metals	^{66}Ga	9.45 h	4.153	^{67}Ga	78.2 h	0.093, 0.184, 0.300
	^{68}Ga	68.3 months	1.898			
	^{83}Sr	32.4	1.150			
	^{110}In	66 months	2.250	^{111}In	67.2 h	0.173, 0.247
Transition metals	^{44}Sc	3.92 h	1.470			
	^{45}Ti	3.09 h	1.040			
	^{51}Mn	46.2 months	2.170			
	^{52}Mn	5.6 days	0.575			
	^{52}Fe	8.2 h	0.800			
	^{55}Co	17. h	1.500			
	^{61}Cu	3.32 h	1.220	^{67}Cu	2.6 days	0.185, 0.92
	^{62}Cu	9.76 months	2.910			
	^{64}Cu	12.8 h	**0.656**			
	^{86}Y	14.74 h	3.150			
	^{89}Zr	78.4 h	0.900			
	^{94m}Tc	52 months	2.440	^{99m}Tc	6.0 h	0.140

months = minutes
Error in table!!!

Singol Photon Emission Computed Tomography (SPECT) nuclides

^{99m}Tc ($T_{1/2}$=6.02h, E_γ=140 keV) is used in more than 70% of all medical applications in many pharmaceutical preparations

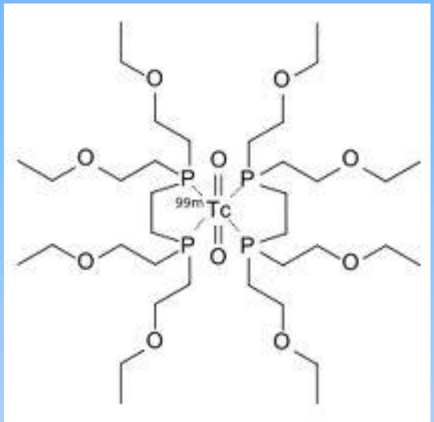
^{67}Ga ($T_{1/2}$=78.3h, $E\gamma$ =93 keV, 185 keV, 300 keV) is often used as tumor localizing agent (gallium citrate)

^{123}I ($T_{1/2}$=13h, $E\gamma$=159 keV) can be covalently bound to several molecules ande proteins. It has replaced ^{131}I ($T_{1/2}$=6d, $E\gamma$=364 keV) because of the reduced radiation exposure

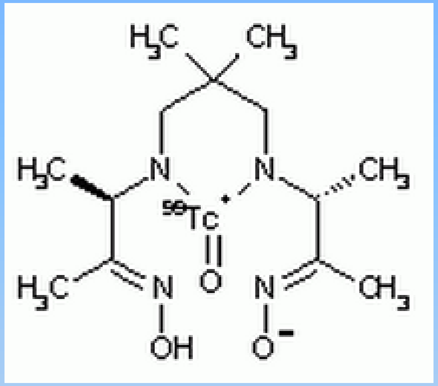
^{81m}Kr ($T_{1/2}$=13s, $E\gamma$=190 keV) is a very short-lived gas used to perform lung ventilation studies, (short half-life limits its application)

Some Tc-based radiopharmaceuticals

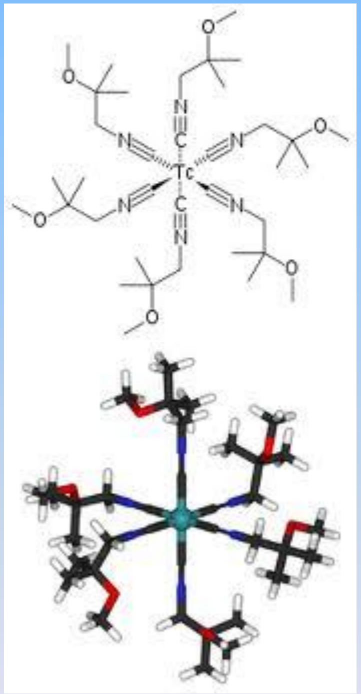
Tc-tetraphosmin (Myoview)

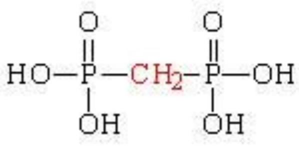


Tc-HMPAO (Ceretec)

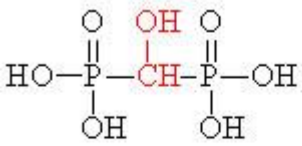


Tc-Sestamibi (Cardiolite)

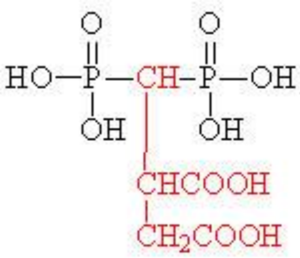




MDP



HDP



DPD

Bone scan tracers

PET working principle

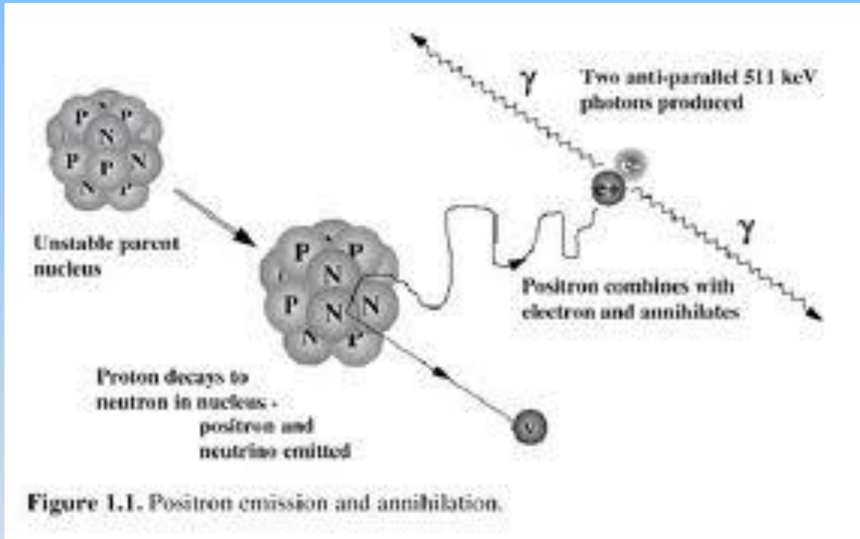
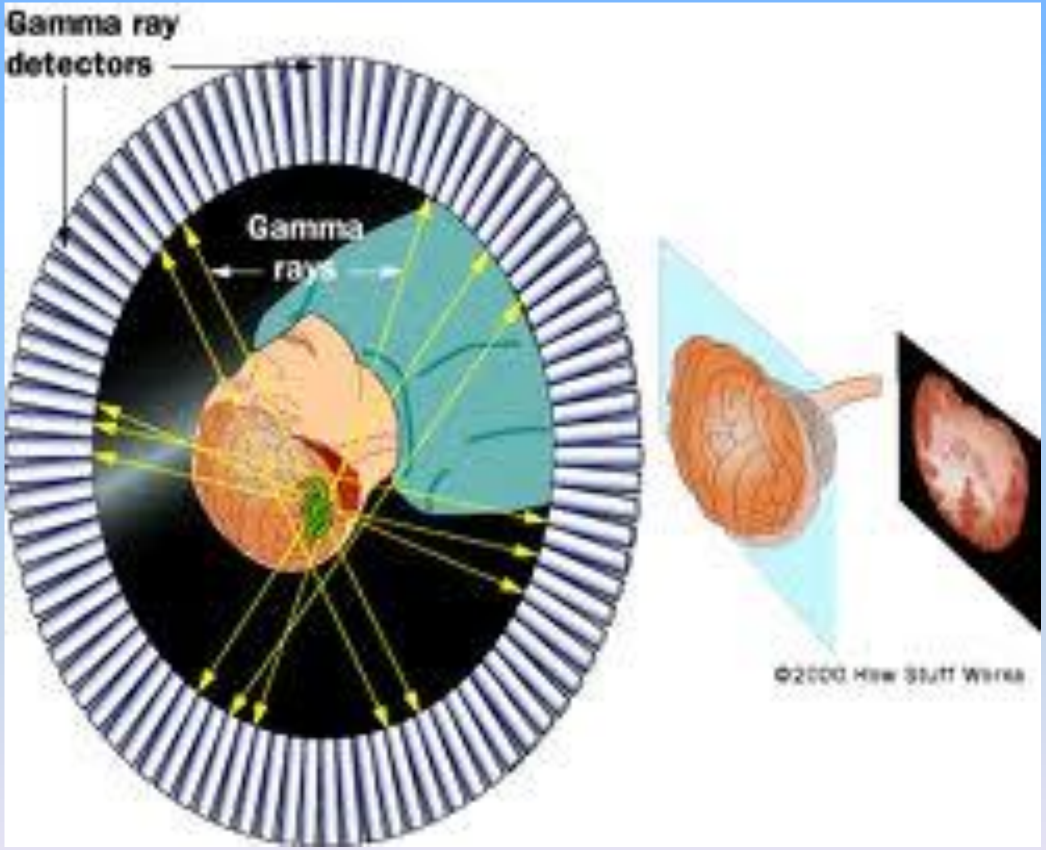


Figure 1.1. Positron emission and annihilation.



Positron Emission Tomography (PET) nuclides

Important for PET studies are neutron deficient isotopes which decay by positron emission. Positrons annihilate with electrons emitting two $E\gamma$=511 keV photons in opposite direction.

^{18}F ($T_{1/2}$=110 m, $E\gamma$ = 511 keV), (used in more than 80% of all PET applications)

^{13}N ($T_{1/2}$=10 m, $E\gamma$ = 511 keV)

^{11}C ($T_{1/2}$=20.4 m, $E\gamma$ = 511 keV)

^{68}Ga ($T_{1/2}$=68 m, $E\gamma$= 511 keV)

^{82}Rb ($T_{1/2}$=1.3 m, $E\gamma$ = 511 keV)

Nuclides for radiotherapy

Radionuclide	Emission type	Half-life	Emax (keV)	Range in tissue	Production
^{186}Re	β, γ (9.4%)	89.2 h	(β): 1069	Maximum (5 mm)	^{185}Re (n, γ) ^{186}Re
^{166}Ho	β, γ (6.7%)	26.9 h	(β): 1853	Maximum (10.2 mm)	^{165}Ho (n, γ) ^{166}Ho
^{188}Re	β, γ (15.1%)	17.0 h	(β): 2120	Maximum (11 mm)	$^{188}W/^{188}Re$-generator
^{89}Sr	β	52.7 days	1463	Maximum (3 mm)	^{88}Sr (n,y) ^{89}Sr
^{32}P	β	14.3 days	1710	Maximum (8.7 mm)	^{32}S (n,p) ^{32}P or ^{31}P (n, γ) ^{32}P
^{90}Y	β	64.1 h	2280	Maximum (12 mm)	$^{90}Sr/^{90}Y$-generator
^{225}Ac	α	10 days	5830, 5792, 5790, 5732	40–80 μm	^{225}Ra-generaor
^{211}At	α	7.2 h	5870	60–80 μm	Accelerator
^{213}Bi	α	45.7 min	5869	50–80 μm	^{225}Ra-generaor

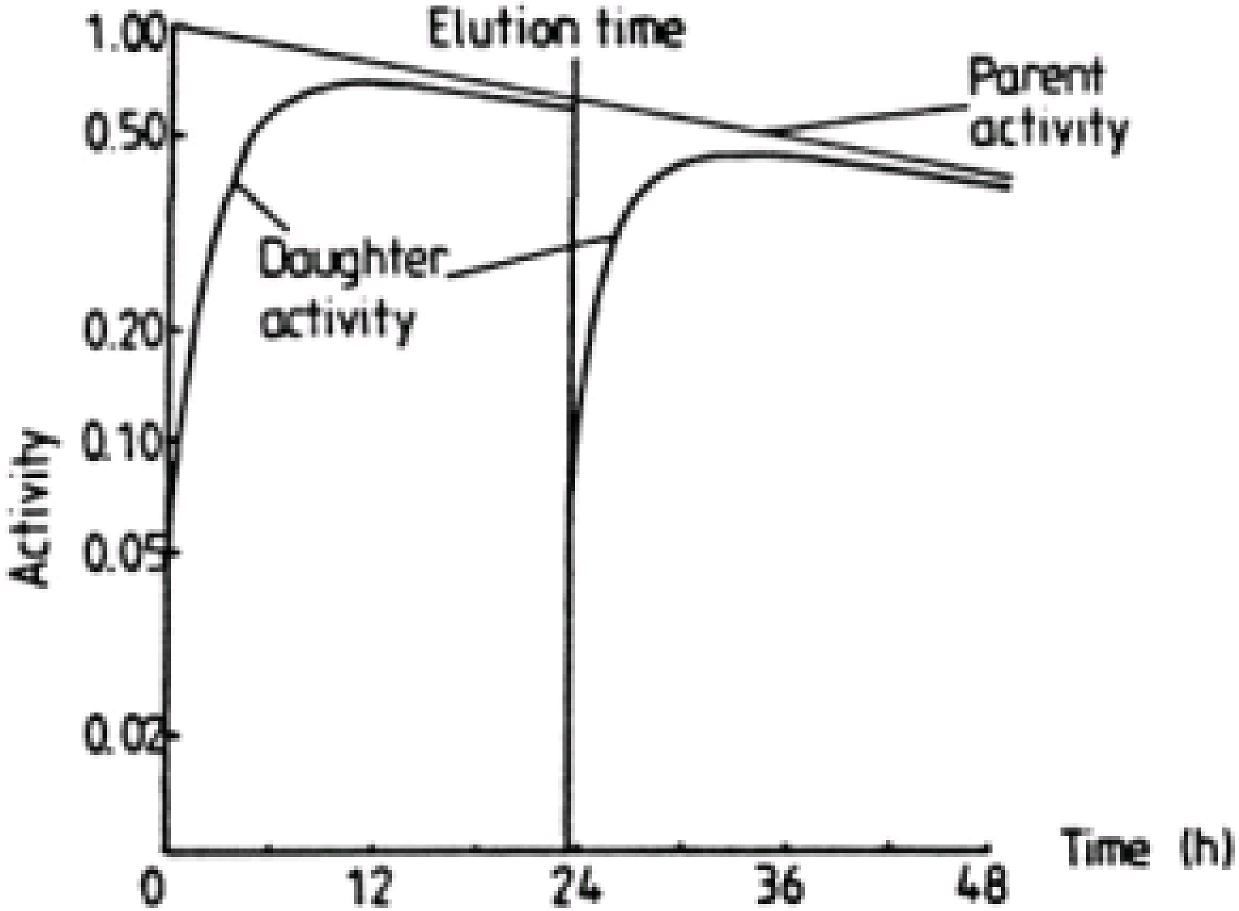
Generating radionuclides

Generators

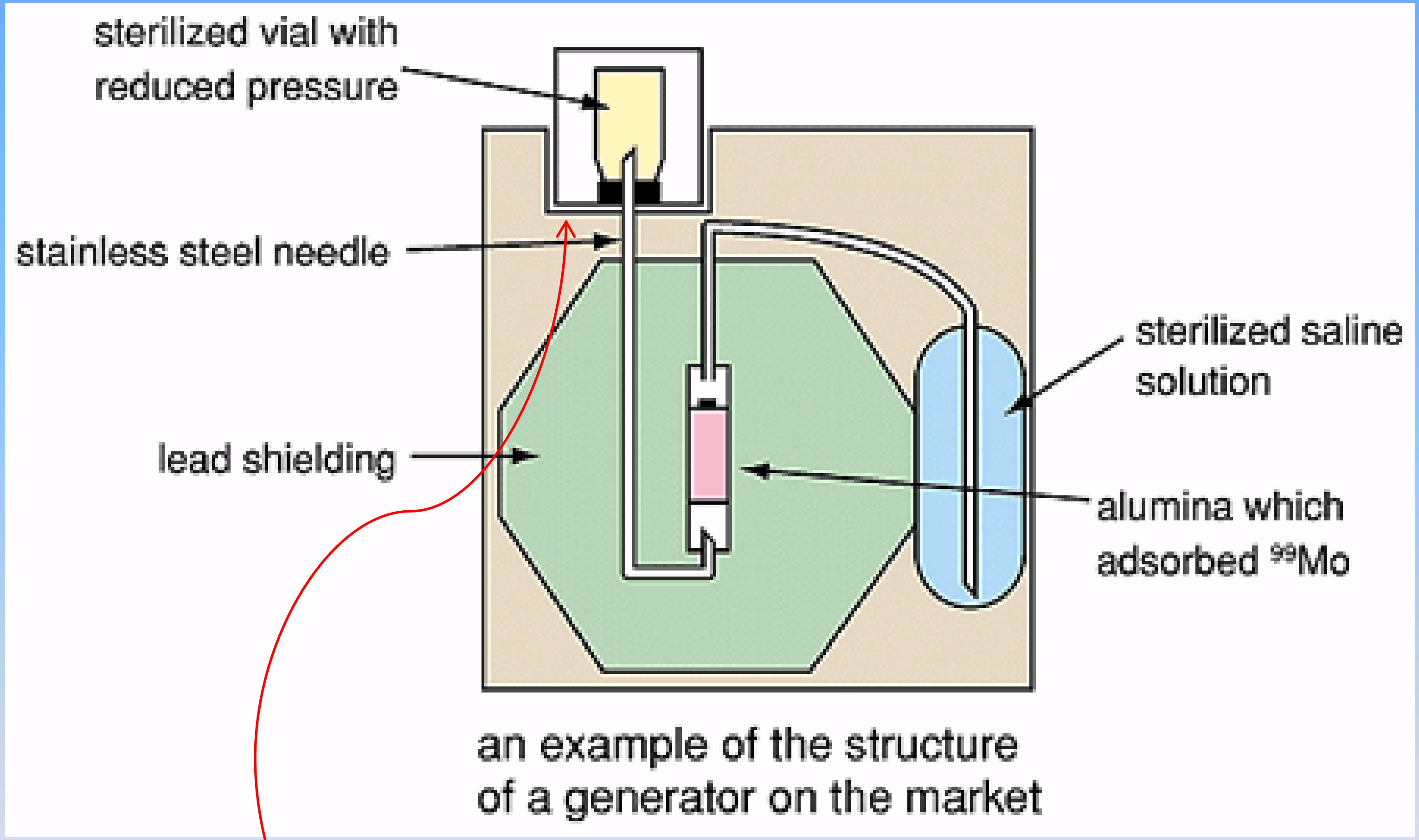
Parent P	Parent half-life	Mode of decay P→D	Daughter D	Mode of decay of D	Daughter half-life	Gamma-ray energy from daughter (keV)
^{99}Mo	2.7 d	β^-	$^{99}Tc^m$	IT	6 h	140
^{82}Sr	25 d	EC	^{82}Rb	EC β^+	1.3 min	777 511
^{68}Ge	280 d	EC	^{68}Ga	EC β^+	68 min	511
^{52}Fe	8.2 h	EC β^+	$^{52}Mn^m$	EC β^+ IT	21 min	511
^{81}Rb	4.7 h	EC	$^{81}Kr^m$	IT	13 s	190
^{62}Zn	9.1 h	EC β^+	^{62}Cu	EC β^+	9.8 min	511
^{178}W	21.5 d	EC	^{178}Ta	EC	9.5 min	93

Generator elution principle

$$A_2(t) = A_1^0 \cdot [e^{-\lambda_1 \cdot t} - e^{-\lambda_2 \cdot t}]$$



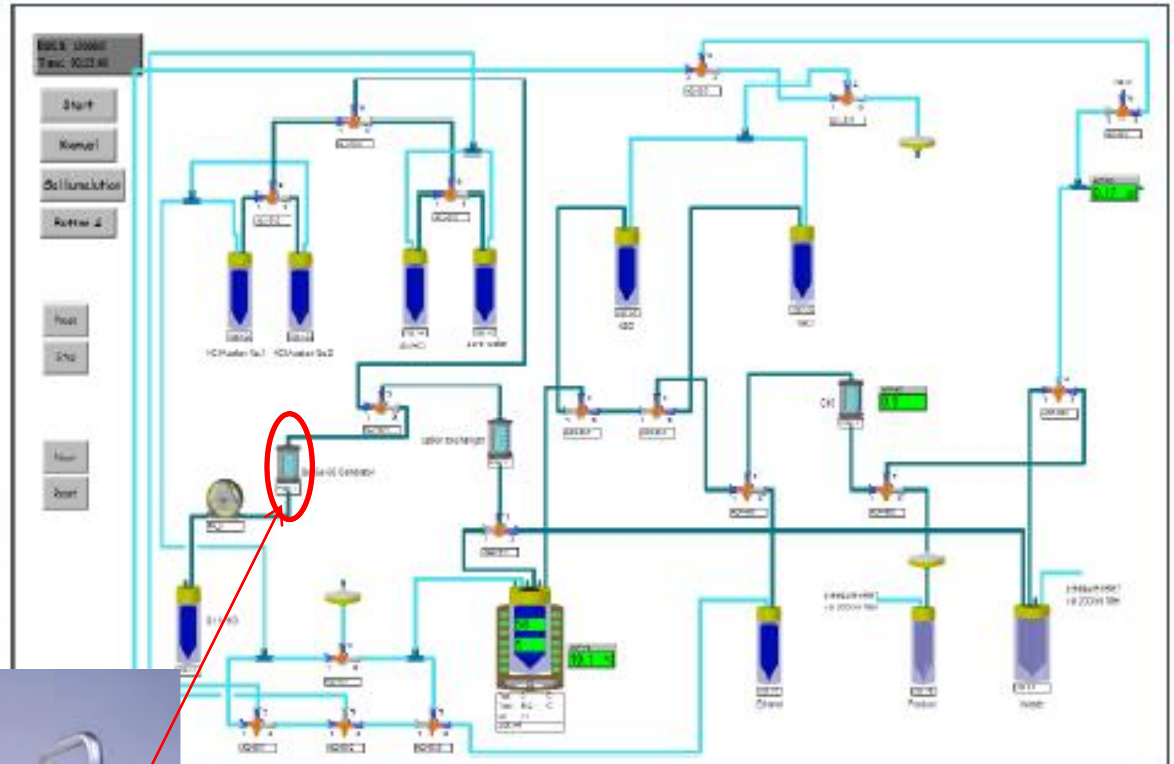
99mTc Generator Scheme



The reaction vial is ready for instantaneous preparation of tracer

$$[^{99m}TcO_4]^- + \boxed{Sn^{+2} + nL} \xrightarrow[\text{complexation}]{\text{reduction}} {}^{99m}Tc(L)_n$$

68Ga Generator and utilization



68Ga-DOTATOC synthesis apparatus scheme

Cyclotron as seen by

Biomedical cyclotron generated nuclides

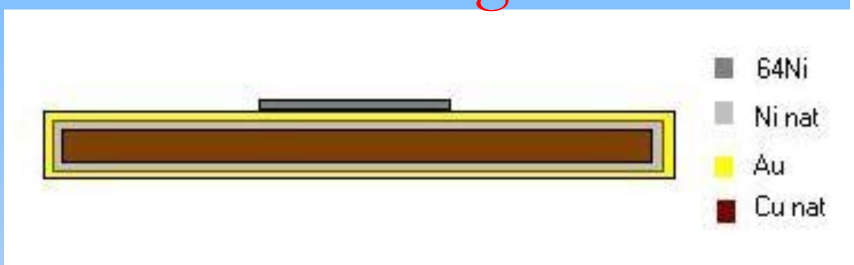
Isotope	Principal gamma-ray energy (keV)	Half-life	Reaction
^{11}C	511 (β^+)	20.4 min	$^{14}N(p,\alpha)^{11}C$
^{13}N	511 (β^+)	9.96 min	$^{13}C(p,n)^{13}N$
^{15}O	511 (β^+)	2.07 min	$^{15}N(p,n)^{15}O$
^{18}F	511 (β^+)	109.7 min	$^{18}O(p,n)^{18}F$
^{67}Ga	93 184 300	78.3 h	$^{68}Zn(p,2n)^{67}Ga$
^{111}In	171 245	67.9 h	$^{112}Cd(p,2n)^{111}In$
^{123}I	159	13 h	$^{124}Te(p,2n)^{123}I$ $^{127}I(p,5n)^{123}Xe \rightarrow {}^{123}I$
^{201}Tl	68–80.3	73 h	$^{203}Tl(p,3n)^{201}Pb \rightarrow {}^{201}Tl$

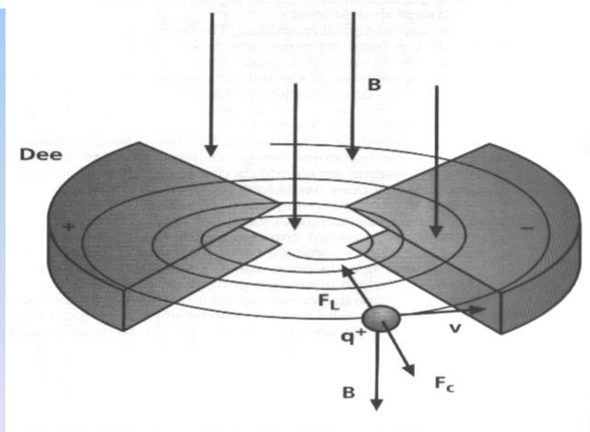
^{94m}Tc, ^{76}Br, ^{60}Cu, ^{64}Cu

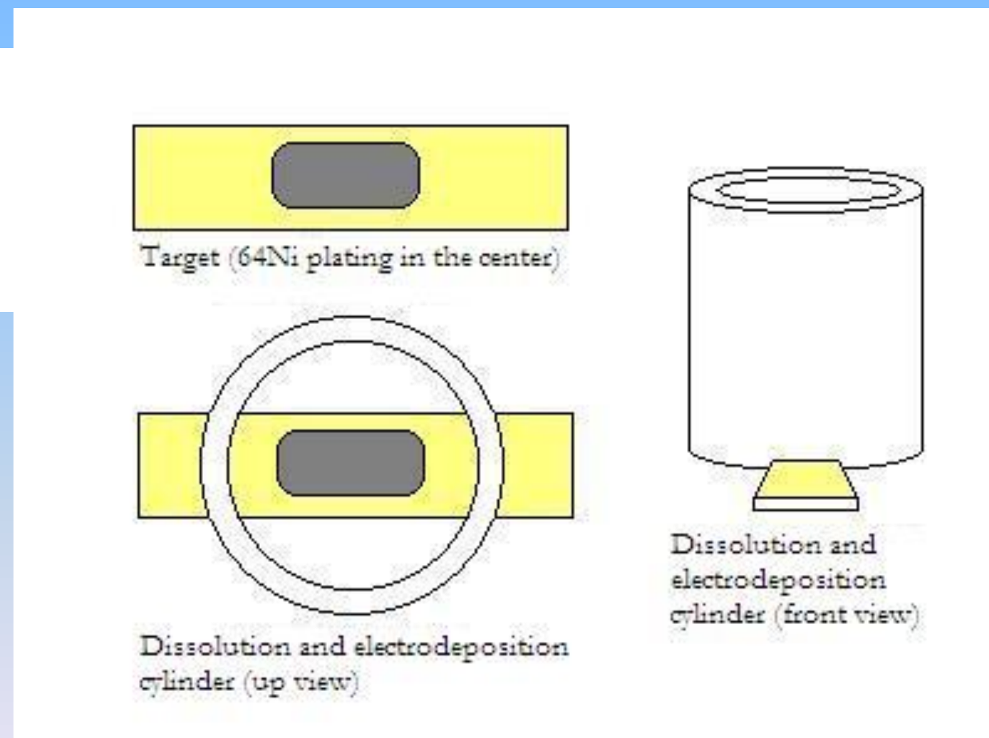
Production example: ^{64}Cu

Cyclotron reaction $^{64}Ni(p,n)^{64}Cu$ → 6N HCl dissolution of target material → ^{64}Cu separation by elution through AG1-X8 column → $^{64}CuCl_2$ aqueous solution

Slant target



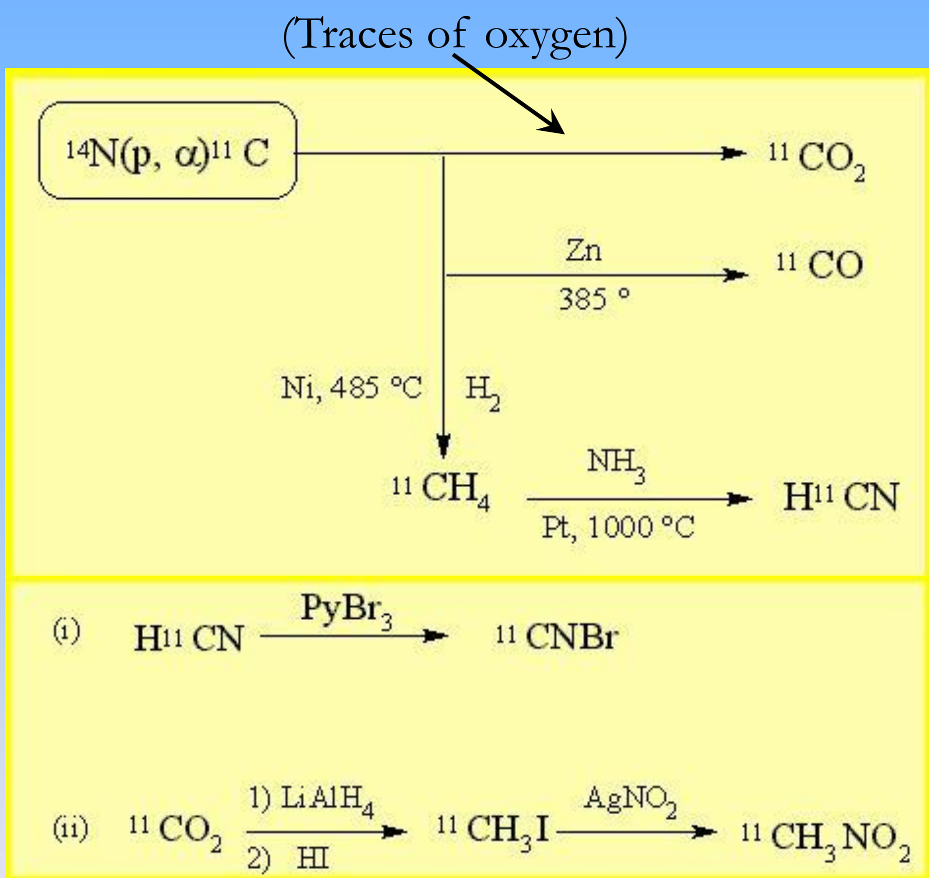


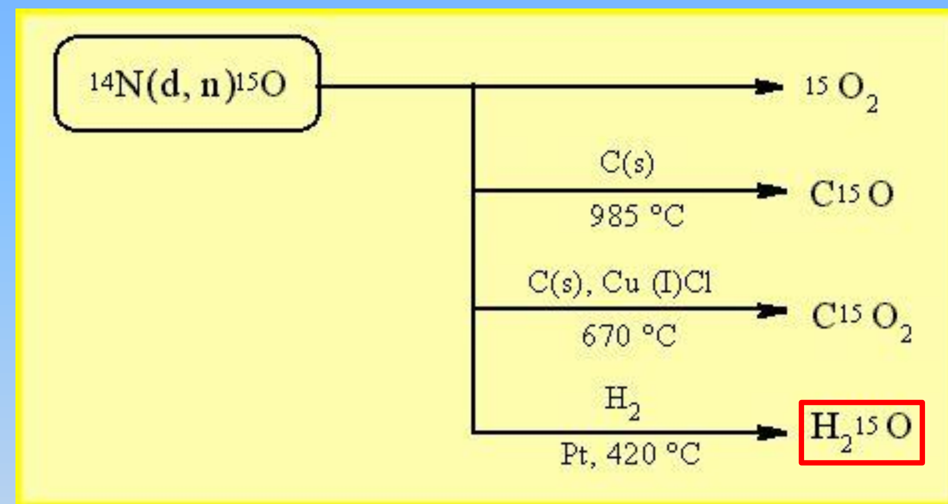


$CuCl_2$ is not a useful tracer; must be converted into a **RADIOPHARMACEUTICAL**

Main PET nuclides: Chemical forms

Chemical forms of produced radionuclides: ^{11}C, ^{15}O, ^{13}N





$H_2{}^{16}O(p,pn)H_2{}^{15}O$

$H_2{}^{16}O(p,\alpha)^{13}NH_3$

(3-10 mM ethanol)

Real tracer

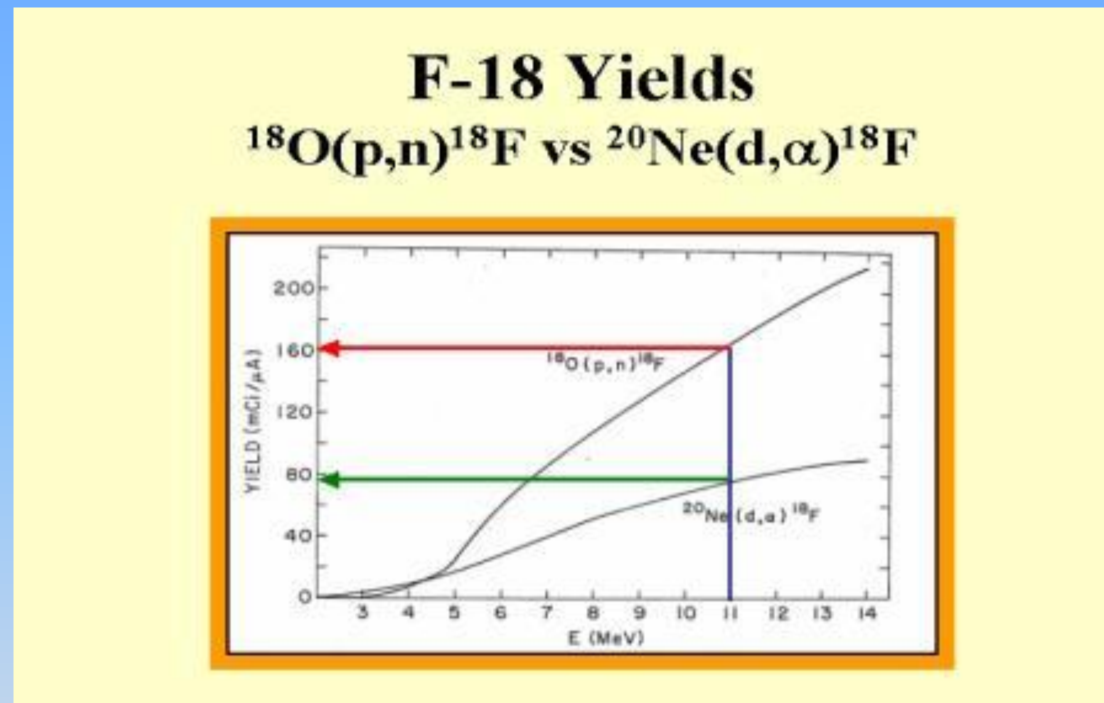
Chemical forms of produced radionuclides: ^{18}F

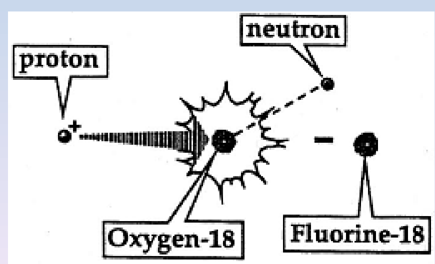
<u>$[^{18}F]F_2$</u>:

- Difficult handling
- Too high reactivity (conversion to $[^{18}F]AcOF$, $[^{18}F]N$-fluorolactams, $[^{18}F]XeF_2$)
- Maximum rcy 50%
- Lower production rate
- c.a. production only
- Electrophilic approach

<u>$[^{18}F]HF$</u>:

- Easy handling
- High s.a.
- Nucleophilic approach
- Low reactivity

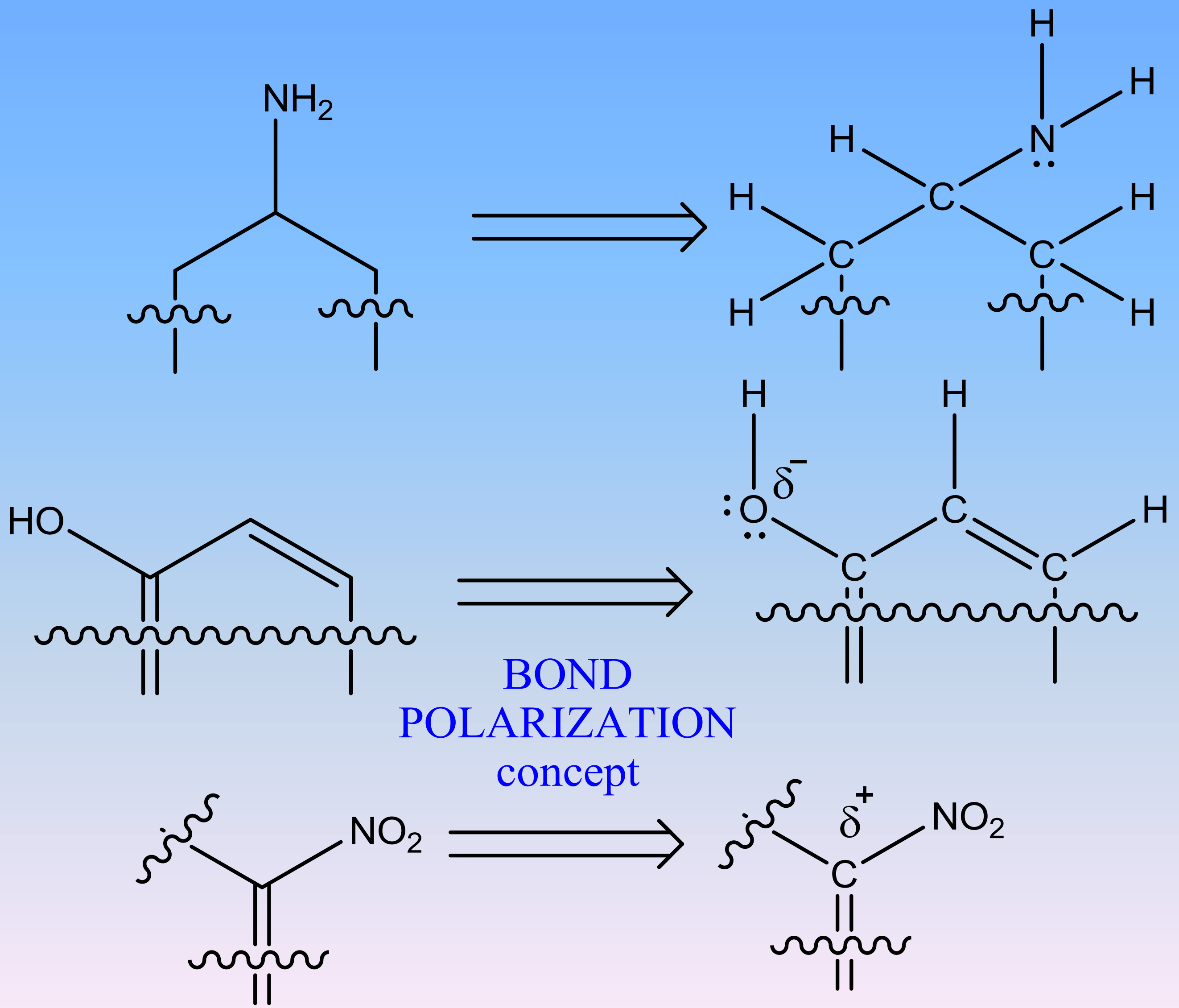




<u>On a 13MeV GE PETrace:</u>

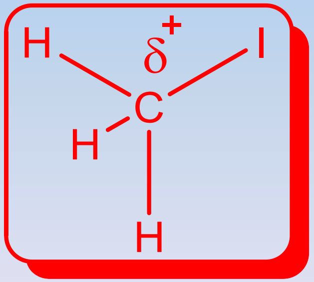
- 1,5 mL ^{18}O-H_2O target
- 30-35 μA
- 2 hours irradiation
- 100-150 GBq

Basic organic chemistry update…



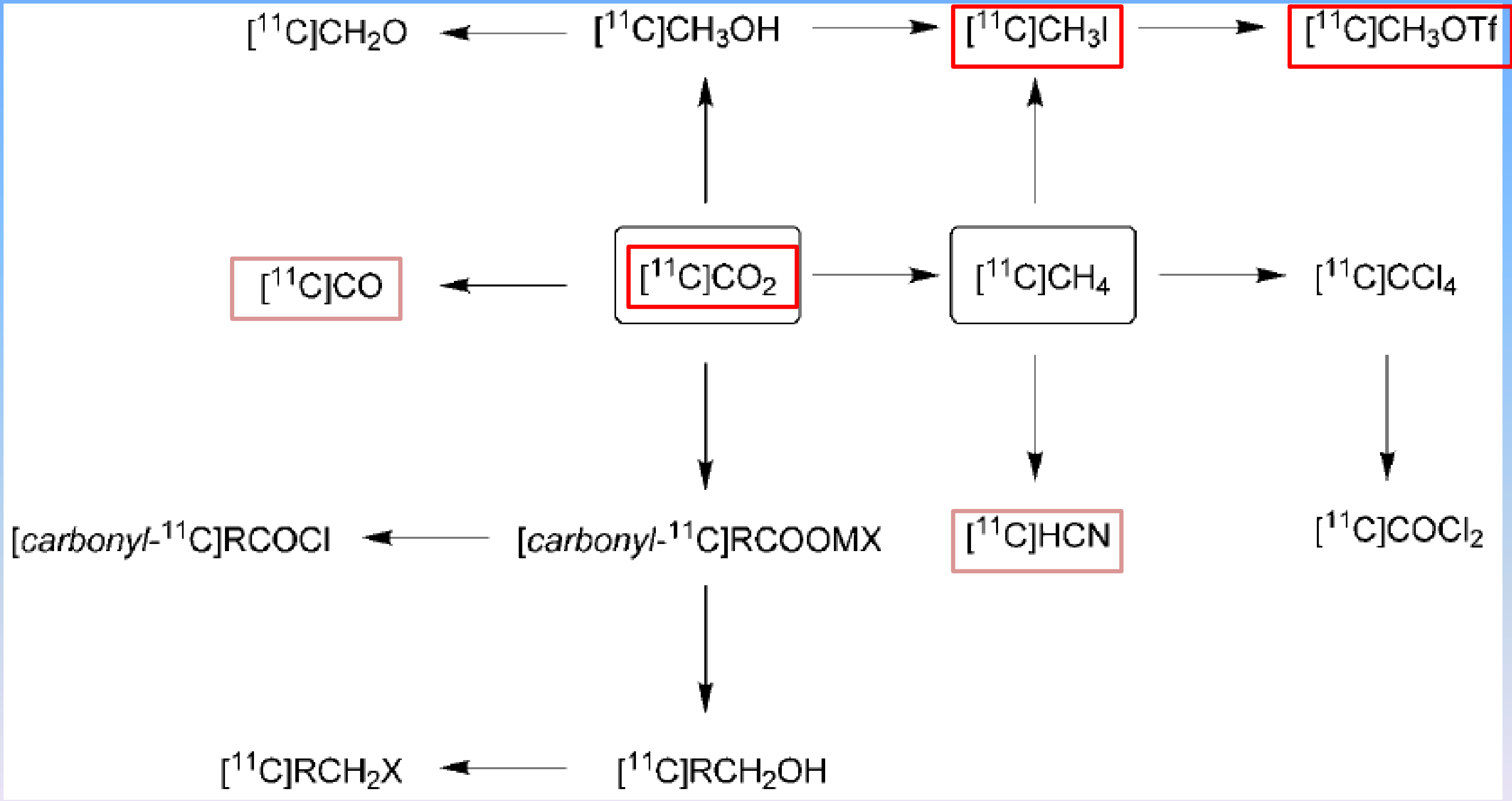
$KF = K^+F^-$

$F_2 = \langle F^+ \rangle$

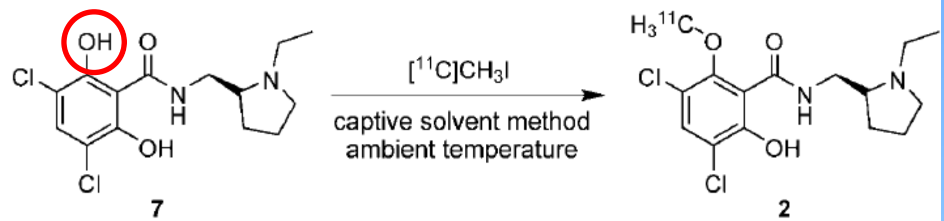


11C radiochemistry

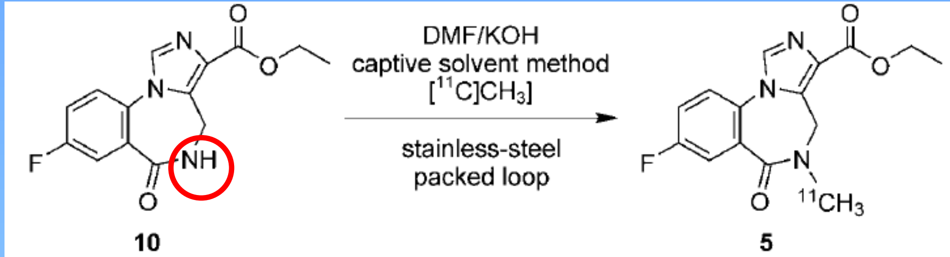
11C radiochemistry



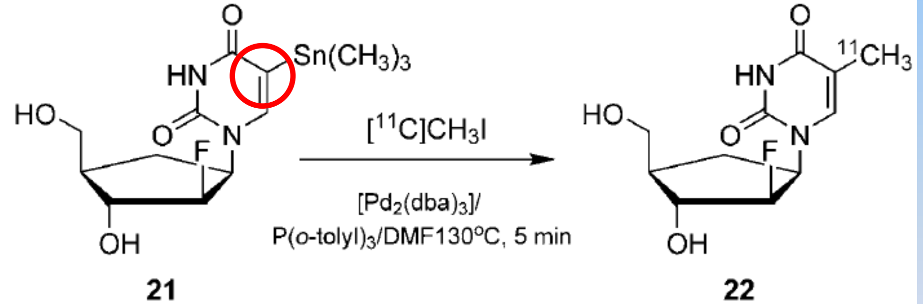
11C methylation reactions



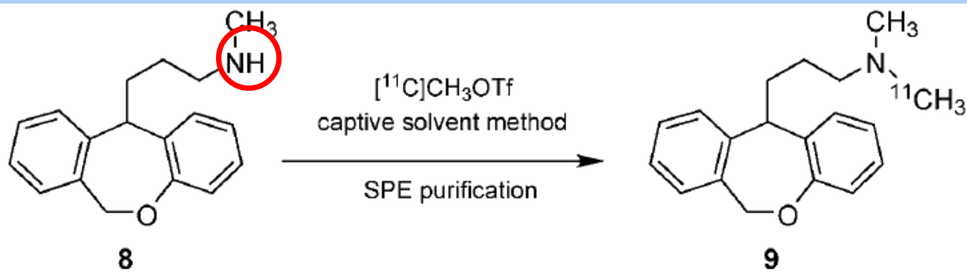
Scheme 4. O-Selective ^{11}C methylation of **7** to form [^{11}C]raclopride (**2**), which is used to image dopamine D2/D3 receptors.



Scheme 6. N-Selective ^{11}C methylation of **10** to form [^{11}C]flumazanil (**5**), a benzodiazepine antagonist that prevents the enhancement of GABA activity.

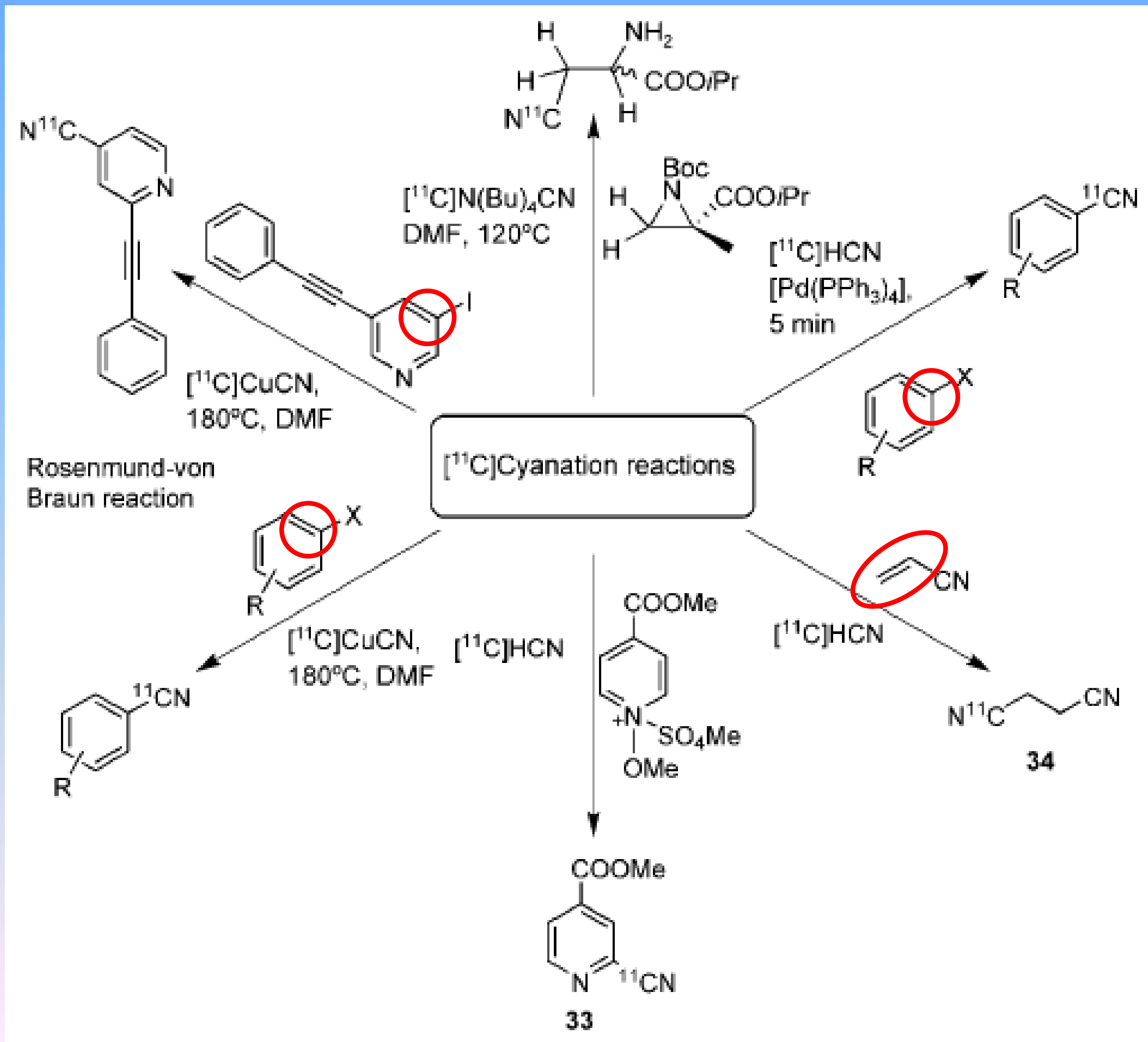


Scheme 13. Synthesis of [^{11}C]FMAU (**22**) by palladium-mediated [^{11}C]CH_3I Stille cross-coupling reactions.



Scheme 5. N-Selective ^{11}C methylation of nordoxepin (**8**) to form [^{11}C]doxepin (**9**), a histamine H1 receptor antagonist and antidepressant.

11C cyanation reactions

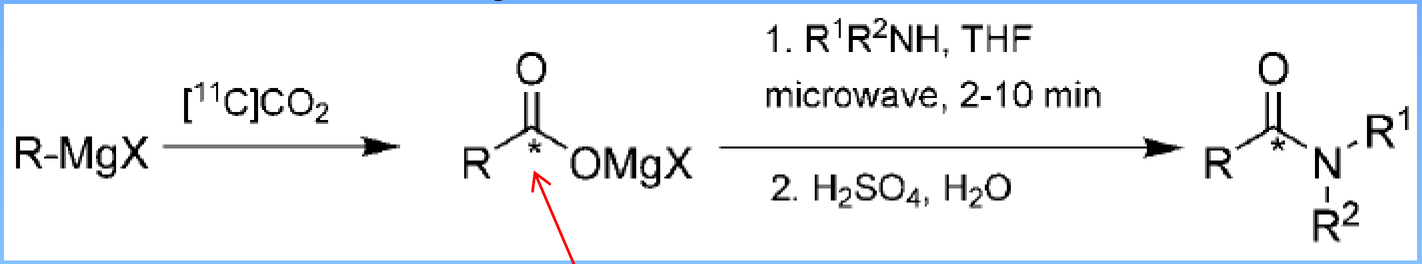


Nucleophilic substitution

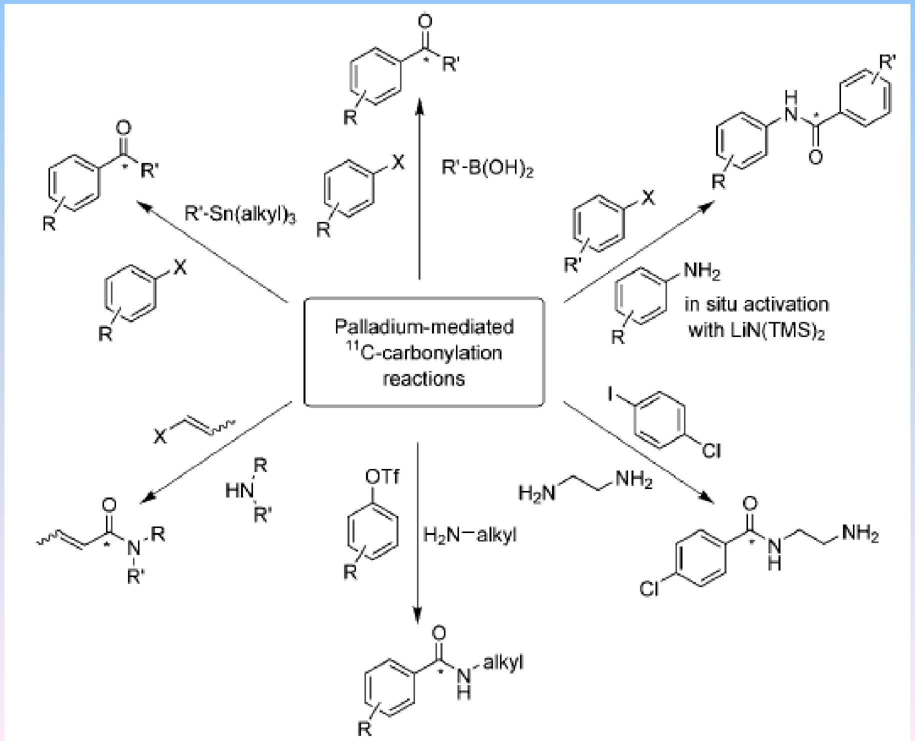
KCN? Poisonous?

NO!! (*s.a.*)

11C carbonylation and carboxylation reactions



Simple route to 11C-acetic acid and 11C-fatty acids

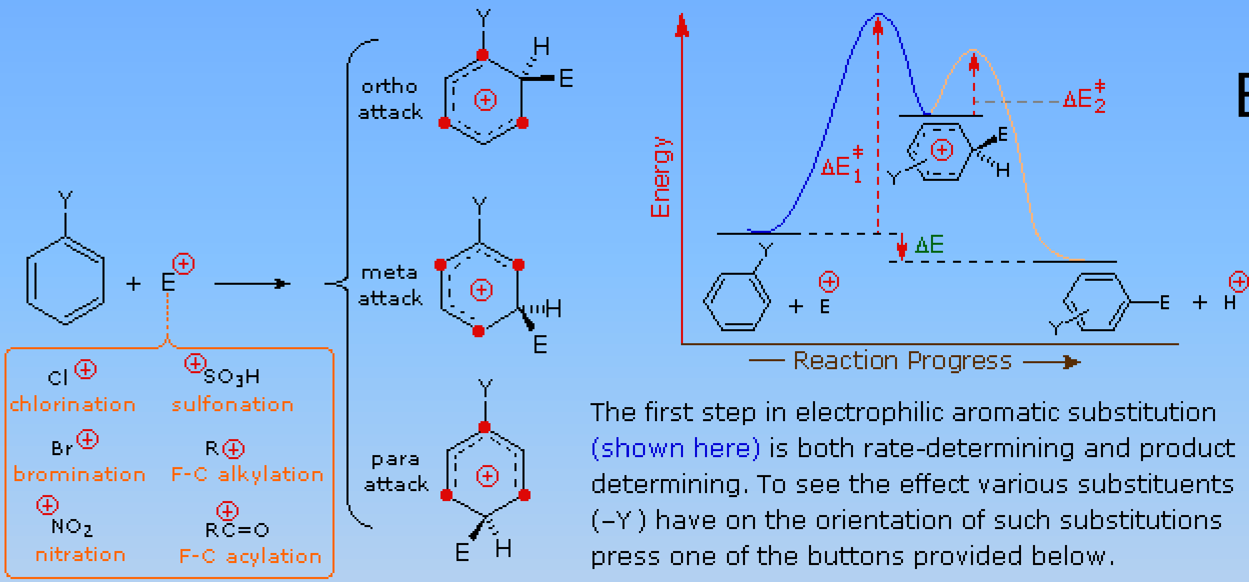


Carbonylation =

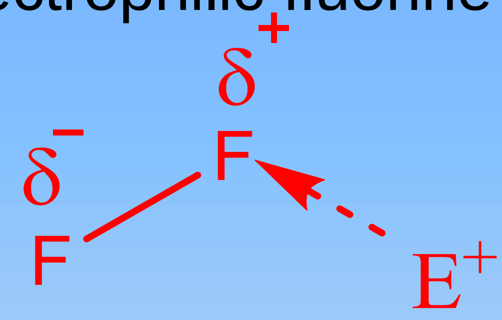
Insertion of a C=O group between two carbon atoms

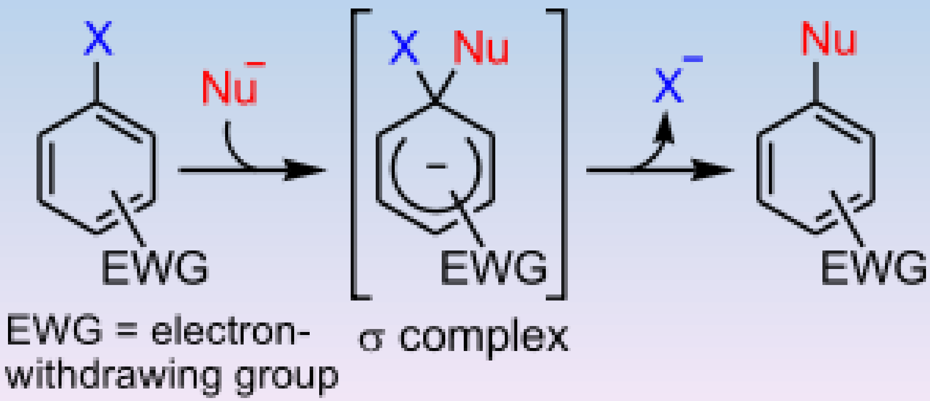
18F radiochemistry

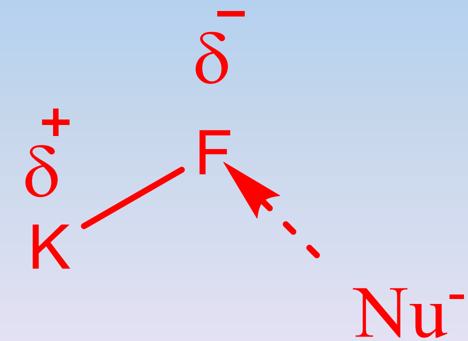
Electrophilic and nucleophilic aromatic substitution



Electrophilic fluorine

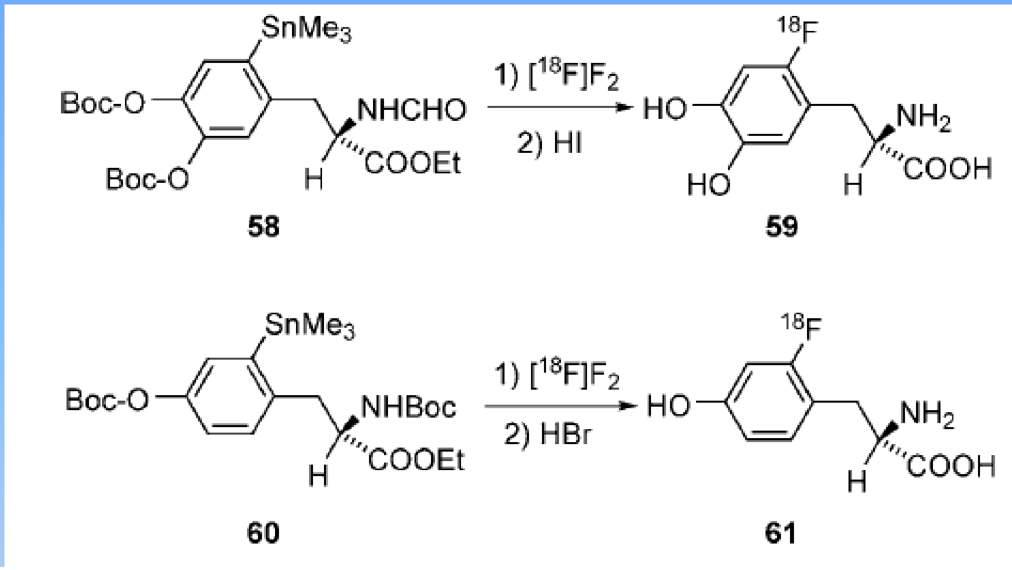




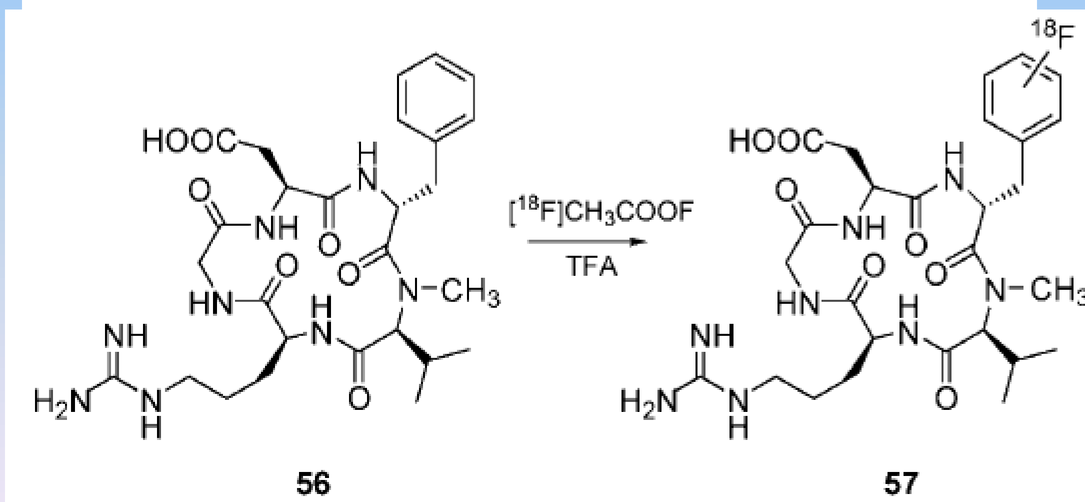


Nucleophilic fluorine

18F electrophilic reactions



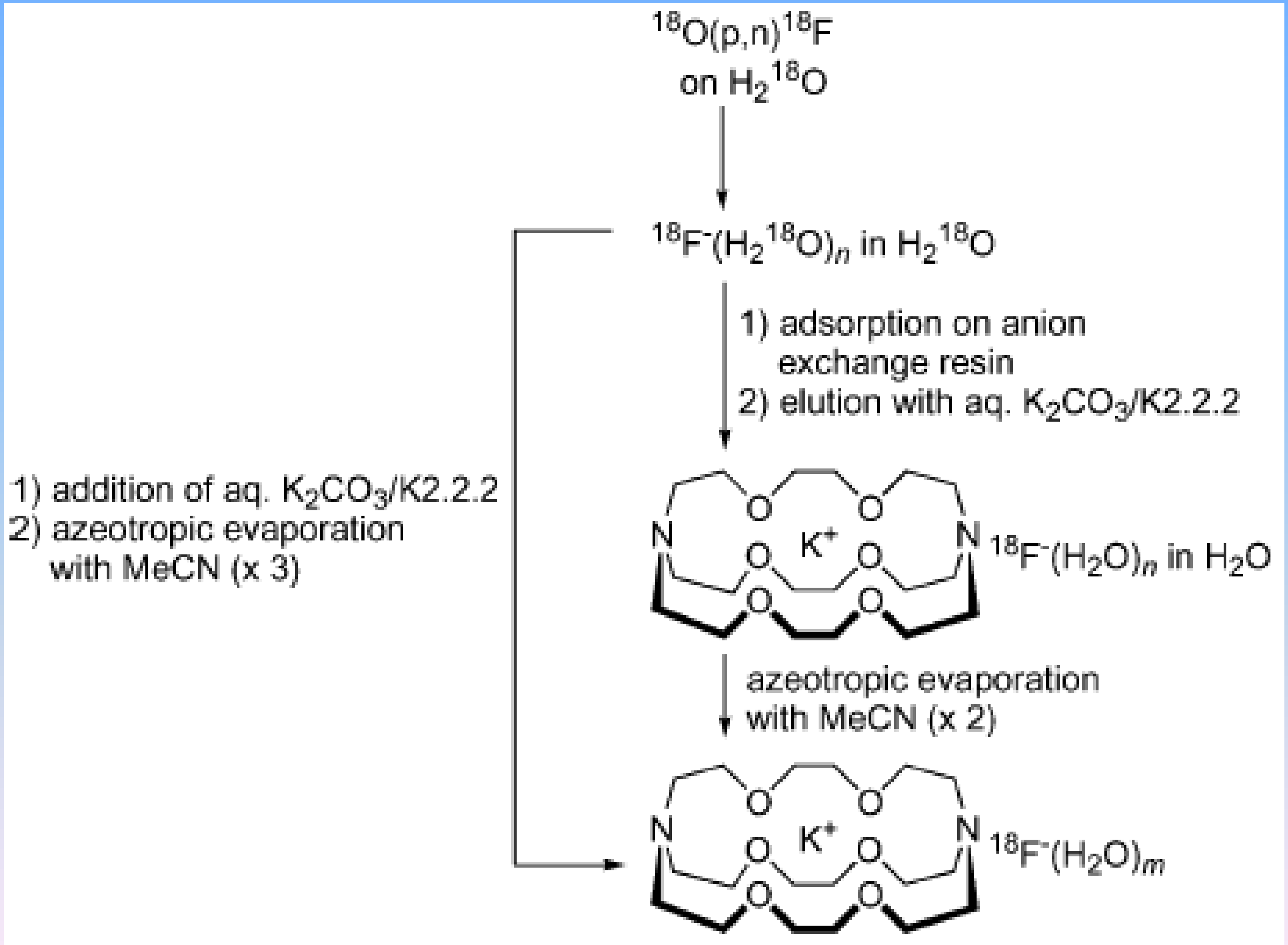
F_2 is a very reactive reagent (needs carrier added conditions in target) and its direct use must be regioselective by use of organometallics

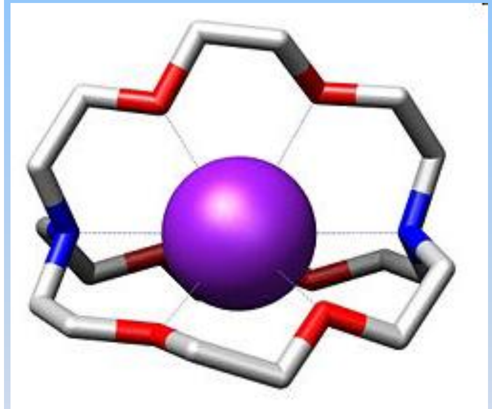


Scheme 33. Electrophilic ^{18}F fluorination of cyclic RGD peptides using [^{18}F]CH_3COOF.

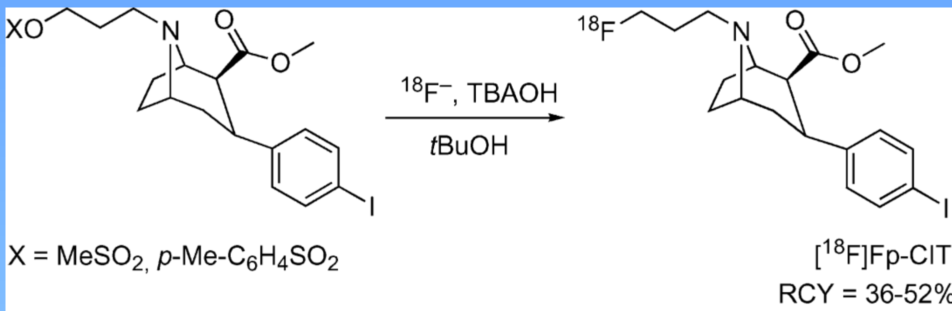
F2 activity can be "tamed" by generating milder fluorinating species, such as acetylipofluorite or XeF_2

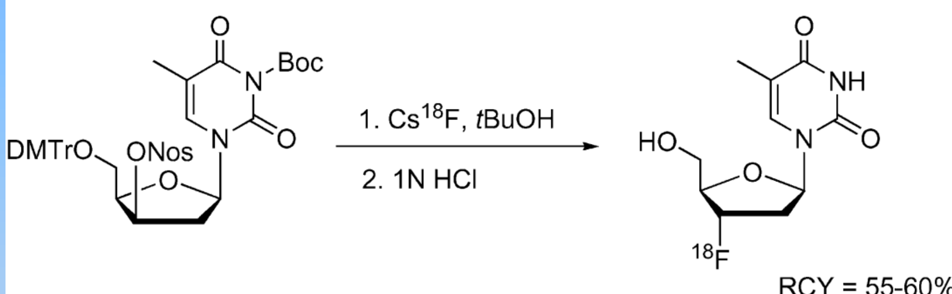
18F nucleophilic reactions: activation step



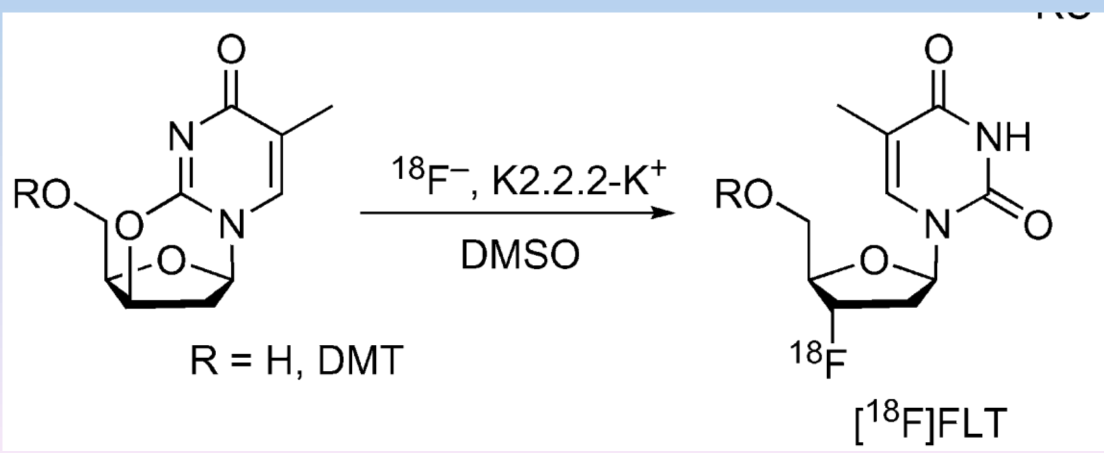


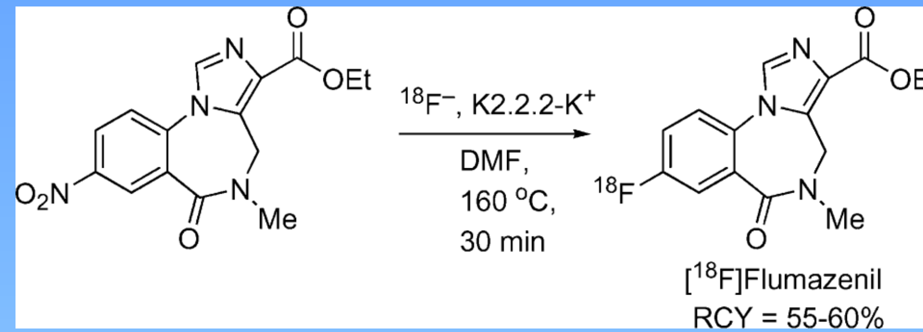
18F nucleophilic reactions: direct



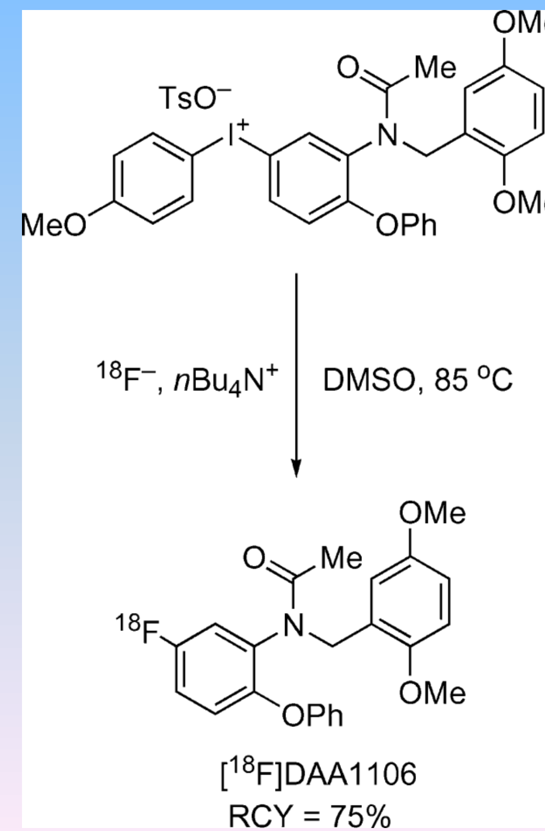


Aliphatic substitution

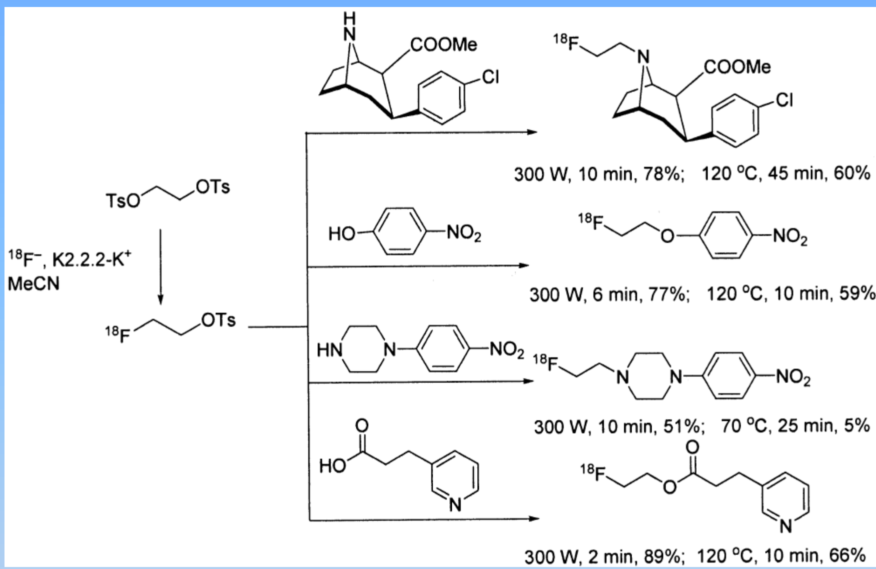


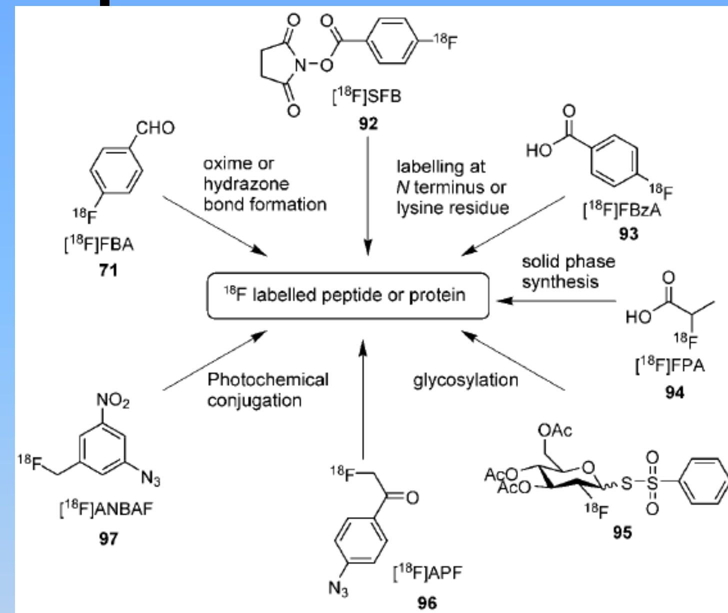


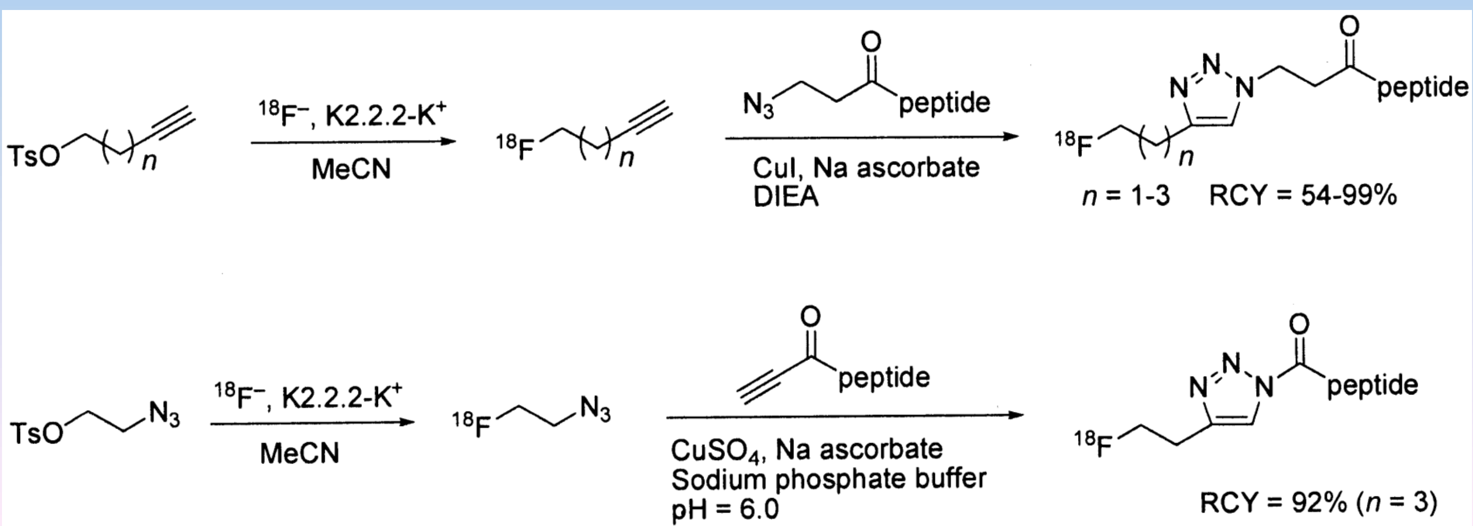
Aromatic substitution



18F nucleophilic reactions: prostetic groups use







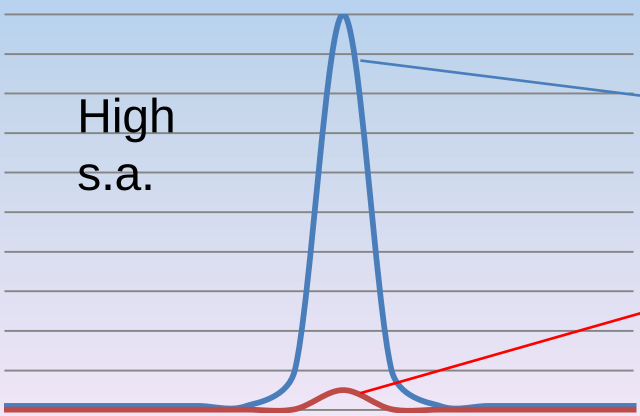
Specific activity

	Maximum SA		Practical SA
Nuclide	mCi µg^{-1}	Ci µmole^{-1}	Ci µmole^{-1}
^{11}C	838,000	9,220	<100
^{18}F	95,000	1,170	10–20 as F^- < 0.03 as F_2
^{68}Ga	40,600	2,766	
^{67}Ga	597	47	<3.35
^{111}In	423	40	<5.55
^{123}I	1,926	237	
^{124}I	250	31	

Carrier added (c.a.): The correspondent stable nuclide is added to the reaction/preparation

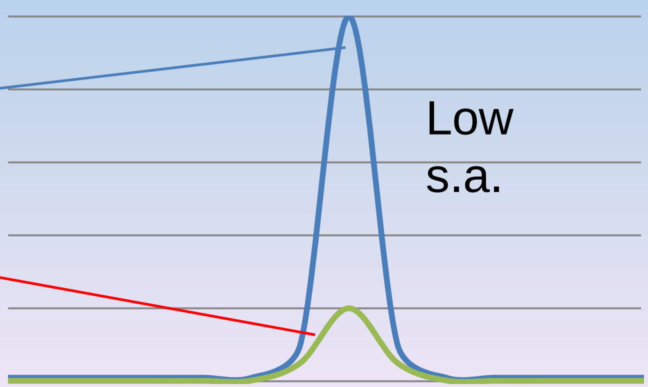
No carrier added (n.c.a.): no addition of carrier

Carrier free (c.f.): no stable isotope is present in preparation



$$s.a. = \frac{activity_{trac}}{mass_{trac}}$$

Quantify the chemical entity generating the activity



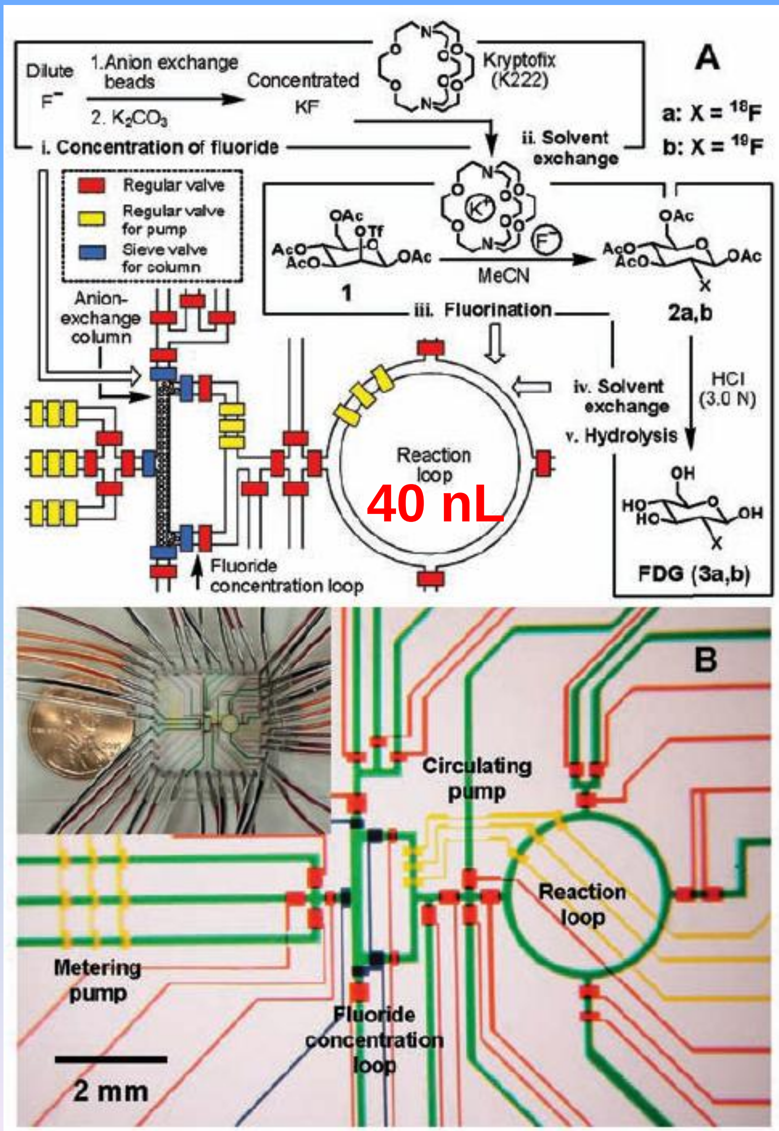
Automated synthesis systems

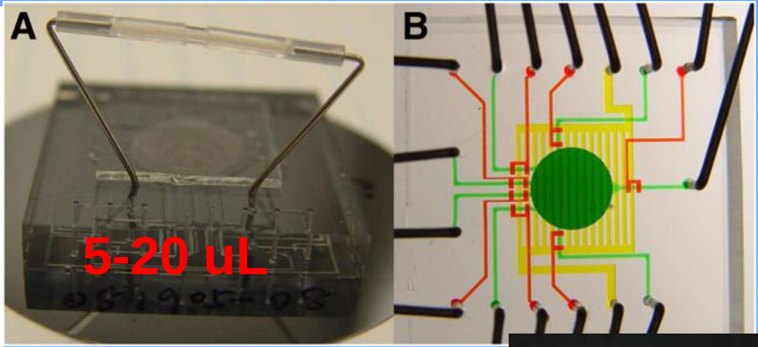
Need for automation

GE, Siemens
Eckert&Ziegler, Raytest, IBA, Scintomics, Advion

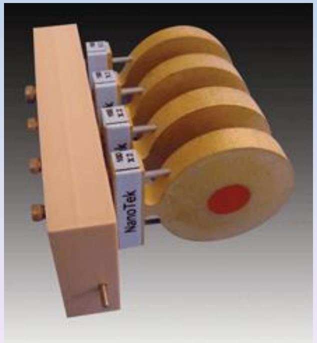
Need for automation: price…

New avenues for automation

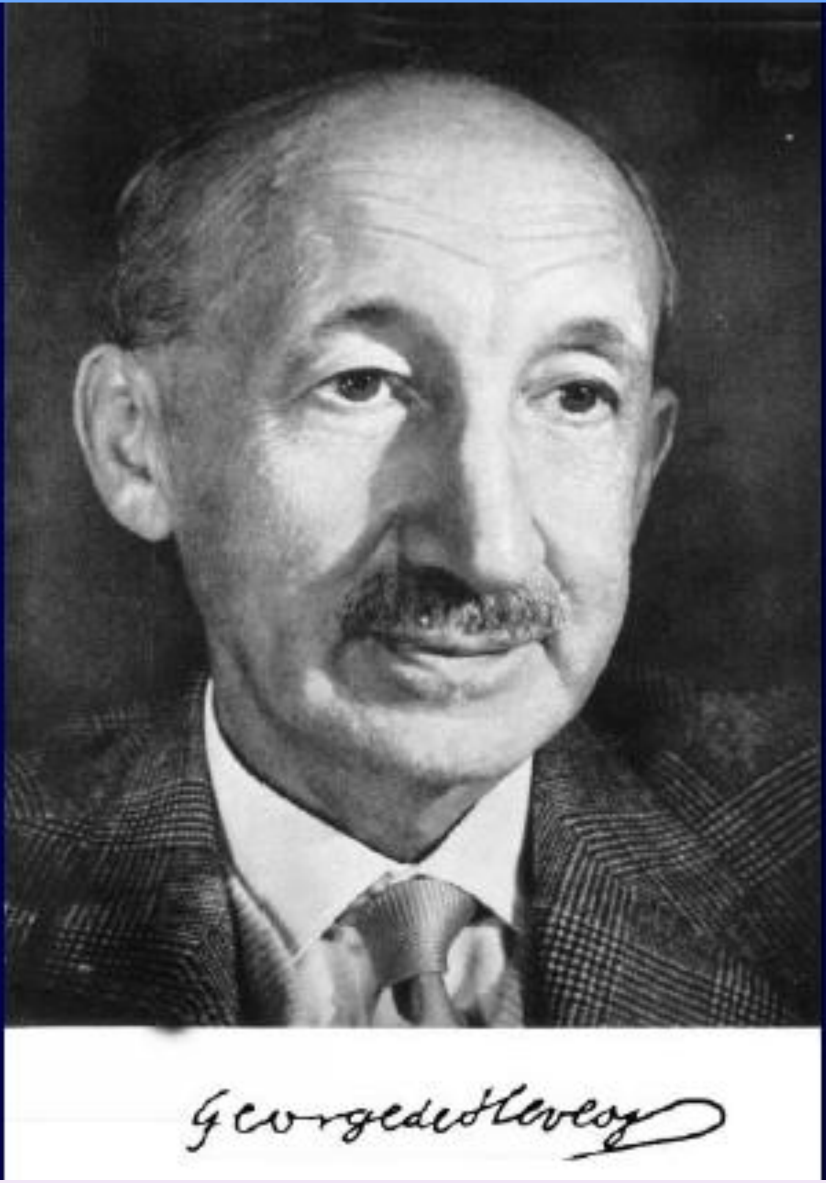




Microfluidics



Radiopharmaceuticals: general



The Father of Nuclear Medicine:

George de Hevesy

(1885 - 1966)

Received Nobel Prize in 1943 for his pioneering work with isotopes as tracers. Winner of Atom for Peace Award 1959.

The first practical application of radioisotopes

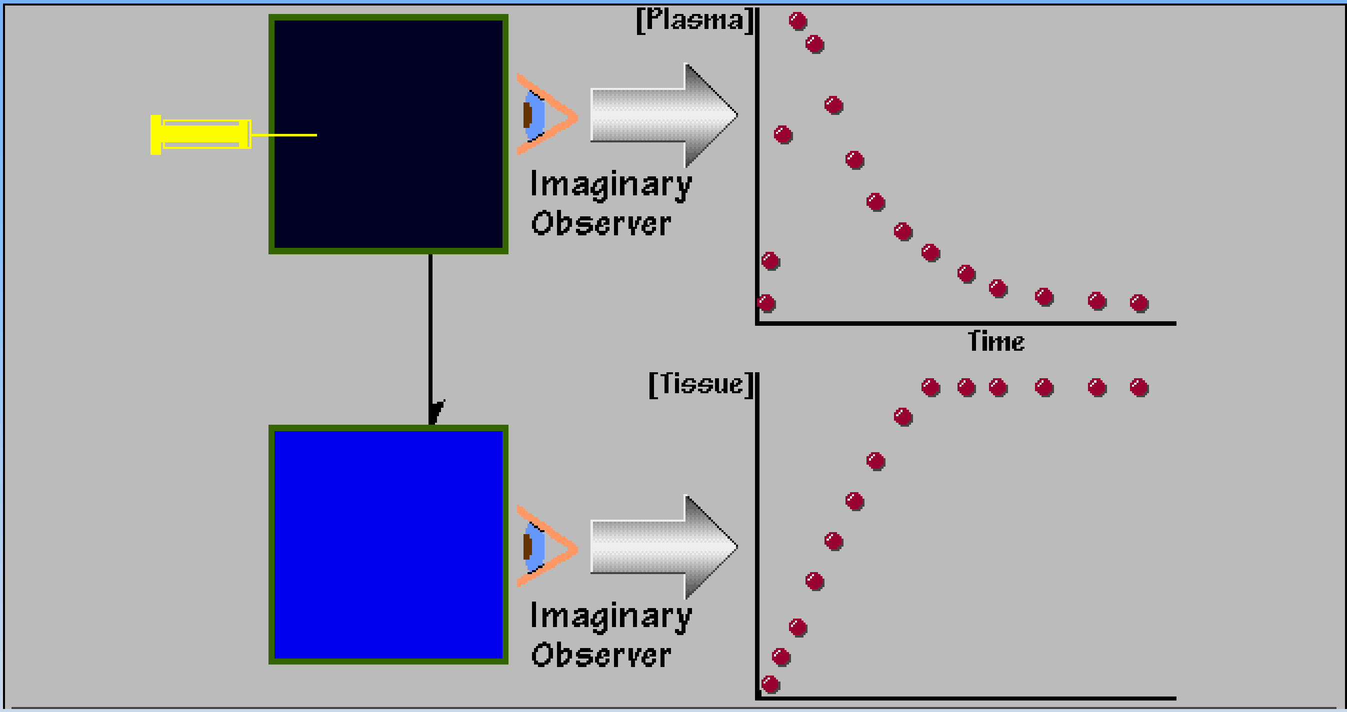
George de Hevesy & his landlady:

- **Using radioactive material he proved two things:**
  - The landlady was indeed "recycling" leftovers from their plates!
  - More importantly, that small amounts of radioactive materials could be used to "trace" the fate of a substance in a system.

Biodistribution generalities

<u>Target/non-target ratio</u>

Blood extraction of the radiopharmaceutical to accumulate selectively on target organs

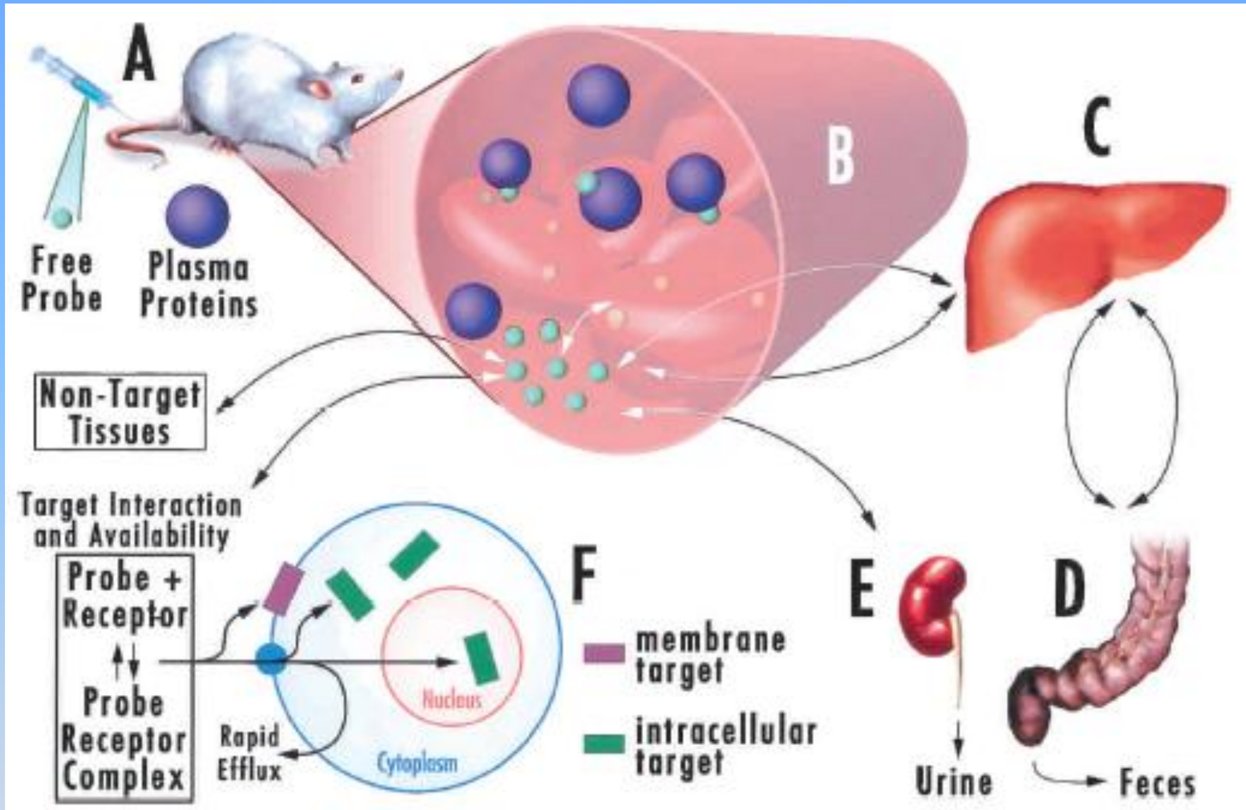


Simple 2 compartment model

<u>Factors</u>

- Chemical nature of tracer
- Blood flow
- Membrane permeation
- Competition with endogenous ligands

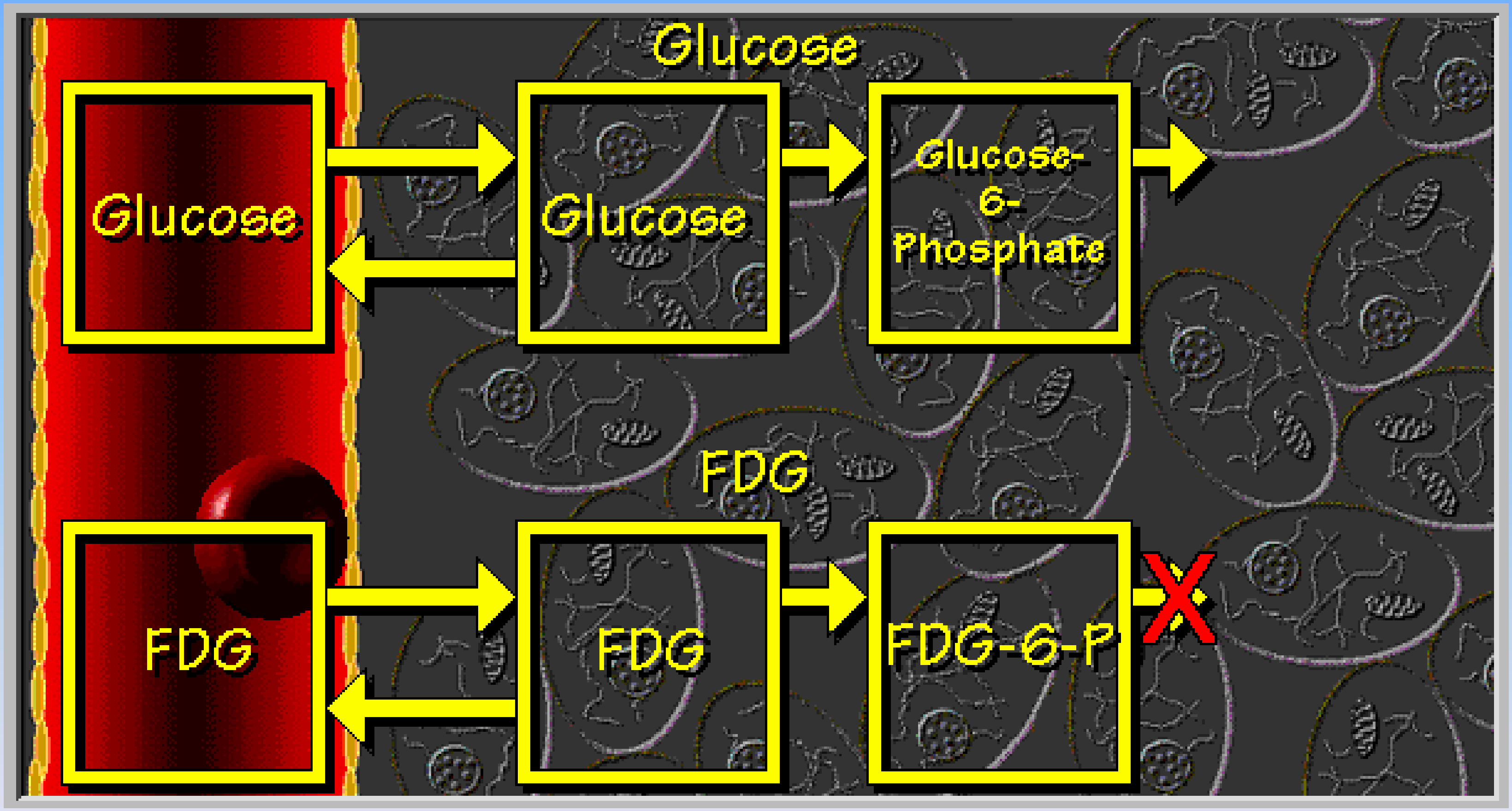
A more complete scheme…



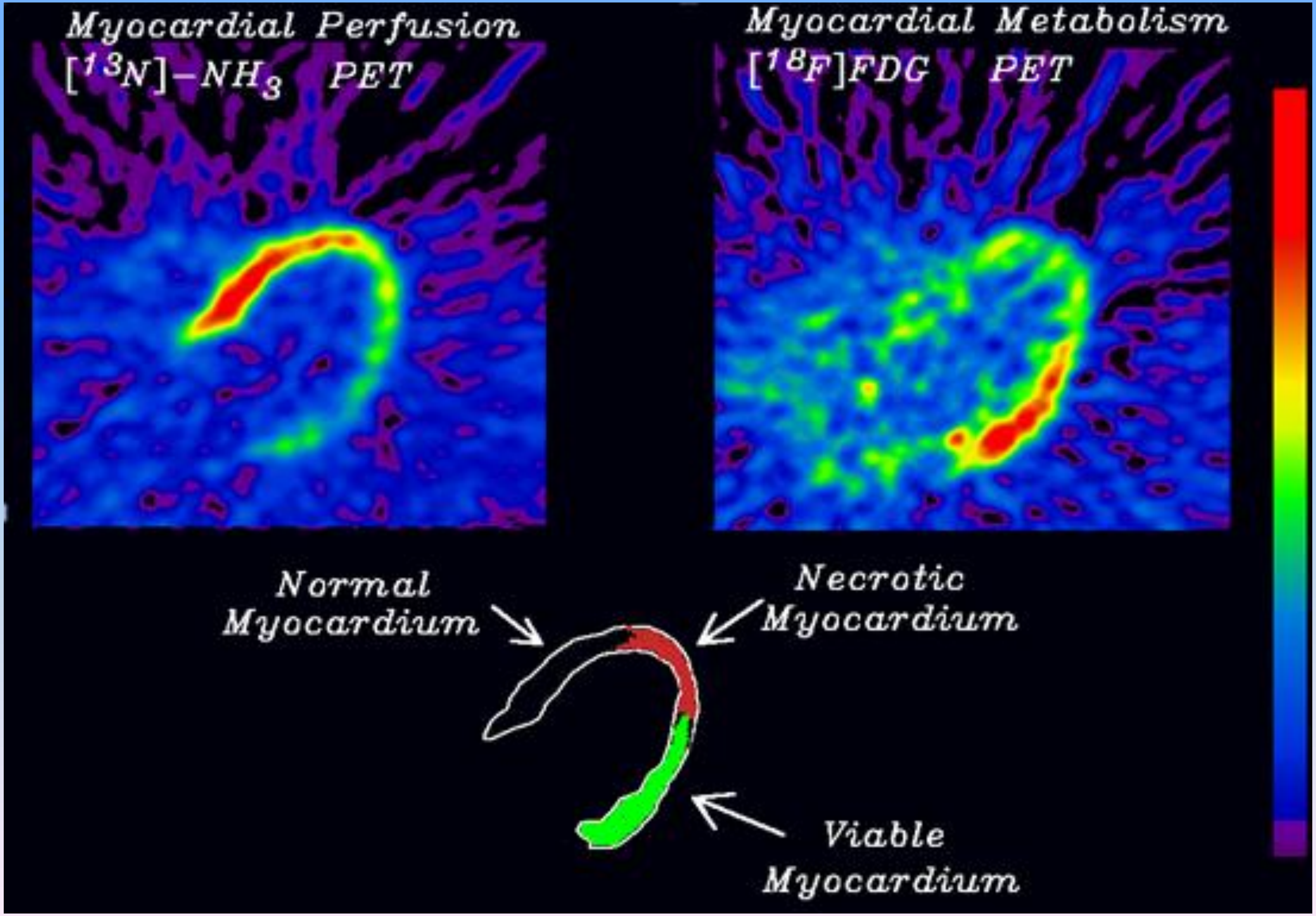
Pharmacokinetics of molecular imaging probes. Molecular imaging probes need to overcome many biological barriers when administered to living subjects. These probes are subject to all the pharmacokinetic rules and constraints that govern the concentration of "drugs" in plasma, including absorption/delivery (*A*), distribution (*B*), metabolism (*C*), excretion/reabsorption in the enterohepatic circulation (*D*), urinary excretion (*E*), and other factors within the vascular compartment (*B*; e.g., plasma half-life, protein binding). Rapid excretion, nonspecific binding/trapping in nontarget tissues, metabolism, and delivery barriers are all important obstacles to be overcome before availability to target(s) for interaction (*F*).

A: Administration — A
D: Distribution — D
M: Metabolism — M
E: Excretion — E
T: Toxicology — T

[^{18}F]FDG model



Classical example: 13NH3 for perfusion, 18F-FDG for metabolism

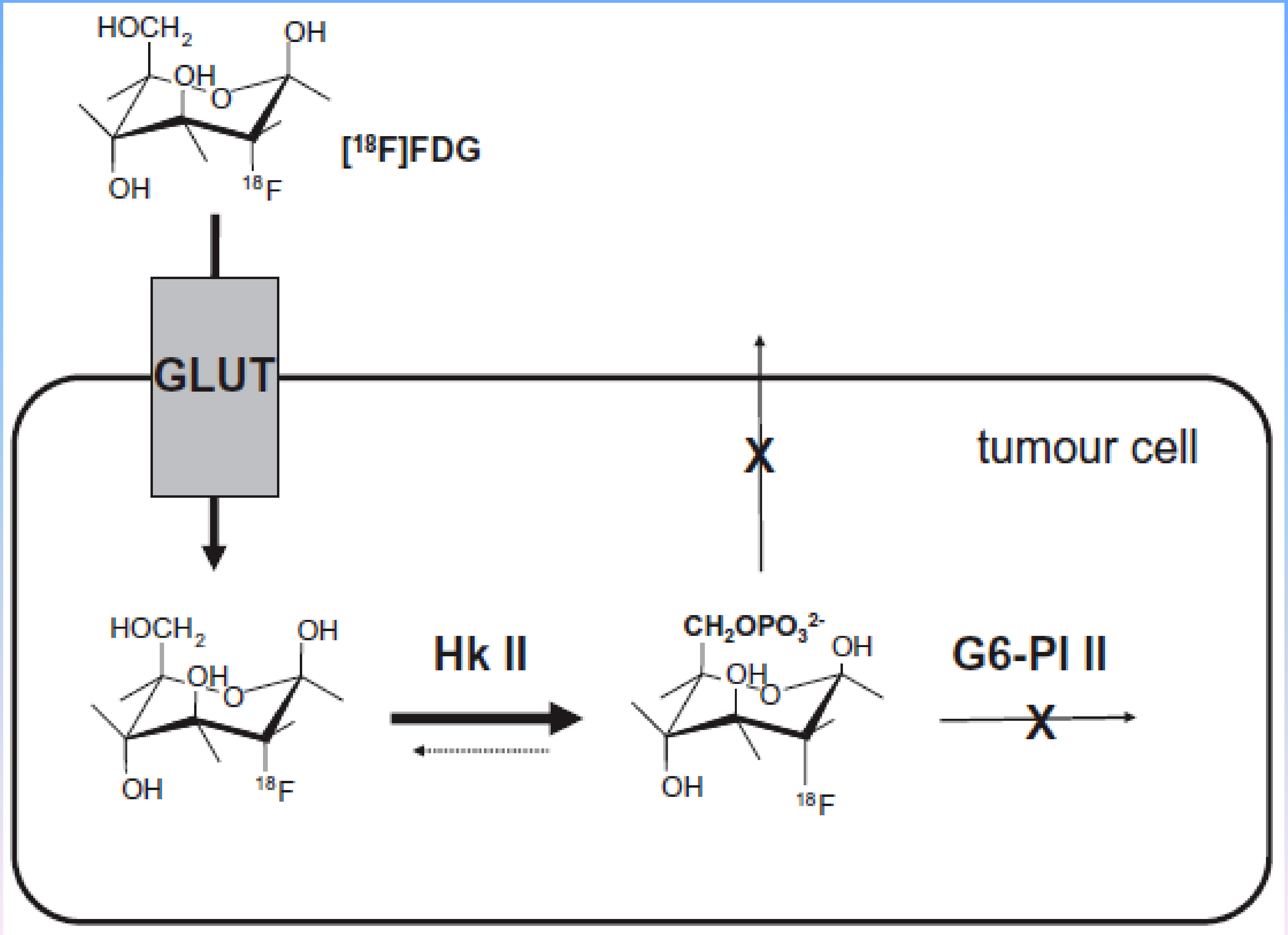


Working principles of Selected radiotracers

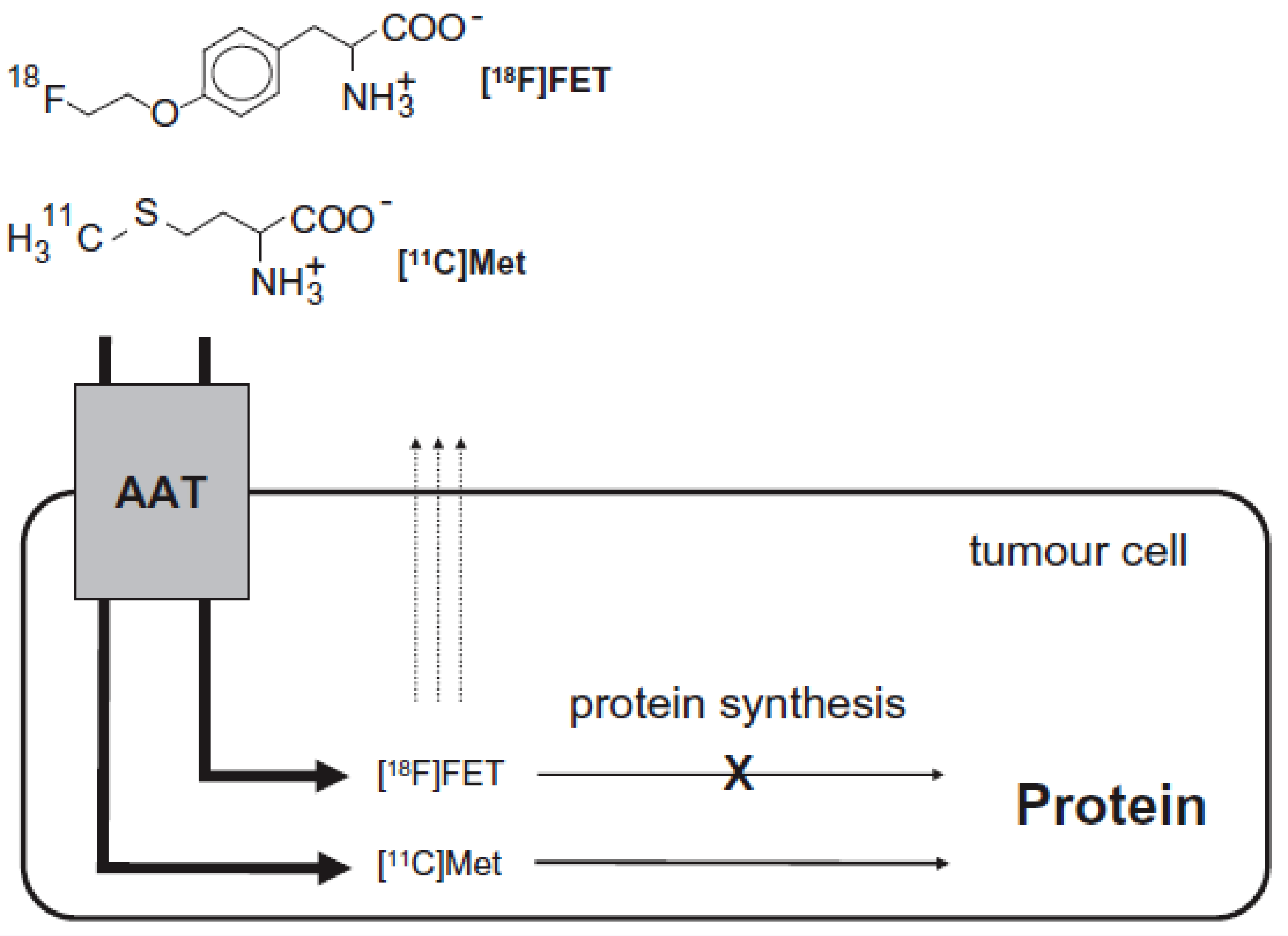
PET radiopharmaceuticals

Molecular uptake mechanism	Tracer	Isotope	Organs of highest physiological uptake[a]	Availabiltiy
Amino acid transport and protein synthesis	Methionine	C-11	Liver, salivary glands, lachrymal glands, bone marrow, pancreas, bowels, renal cortical, urinary bladder	In-house production/cyclotron
	Fluoroethyltyrosine	F-18	Pancreas, kidneys, liver, heart, brain, colon, muscle	In-house production/cyclotron[b]
	FDOPA	F-18	Pancreas, liver, duodenum, kidneys, gallbladder, biliary duct	Commercially available
Glucose metabolism	FDG	F-18	Brain, myocardium, breast, liver, spleen stomach, intestine, kidney, urinary bladder, skeletal muscle, lymphatic tissue, bone marrow, salivary glands, thymus, uterus, ovaries, testicle, brown fat	Commercially available
Proliferation	FLT	F-18	Bone marrow, intestine, kidneys, urinary bladder, liver	In-house production/cyclotron[b]
Hypoxia	FMISO	F-18	Liver, urinary excretion	In-house production/cyclotron[b]
	FAZA	F-18	Kidneys, gallbladder, liver, colon	In-house production/cyclotron
	Cu-ATSM	Cu-64	Liver, kidneys, spleen, gallbladder[c]	In-house production/cyclotron[b]
Lipid metabolism	Choline	C-11	Liver, pancreas, spleen, salivary glands, lachrymal glands, renal excretion, bone marrow, intestine	In-house production/cyclotron
	Fluoroethylcholine	F-18	Liver, kidneys, salivary glands, urinary bladder, bone marrow, spleen	In-house production/cyclotron[b]
	Acetate	C-11	Gastrointestinal tract, prostate, bone marrow, kidneys, liver, spleen, pancreas	In-house production/cyclotron
Angiogenesis/integrin binding	Galacto-RGD	F-18	Bladder, kidneys, spleen, liver	In-house production/cyclotron
	AH111585	F-18	Bladder, liver, intestine, kidneys	In-house production/cyclotron
SSTR binding	DOTATOC	Ga-68	Pituitary and adrenal glands, pancreas, spleen, urinary bladder, liver, thyroid	In-house production/generator
	DOTATATE	Ga-68	Spleen, urinary bladder, liver	In-house production/generator

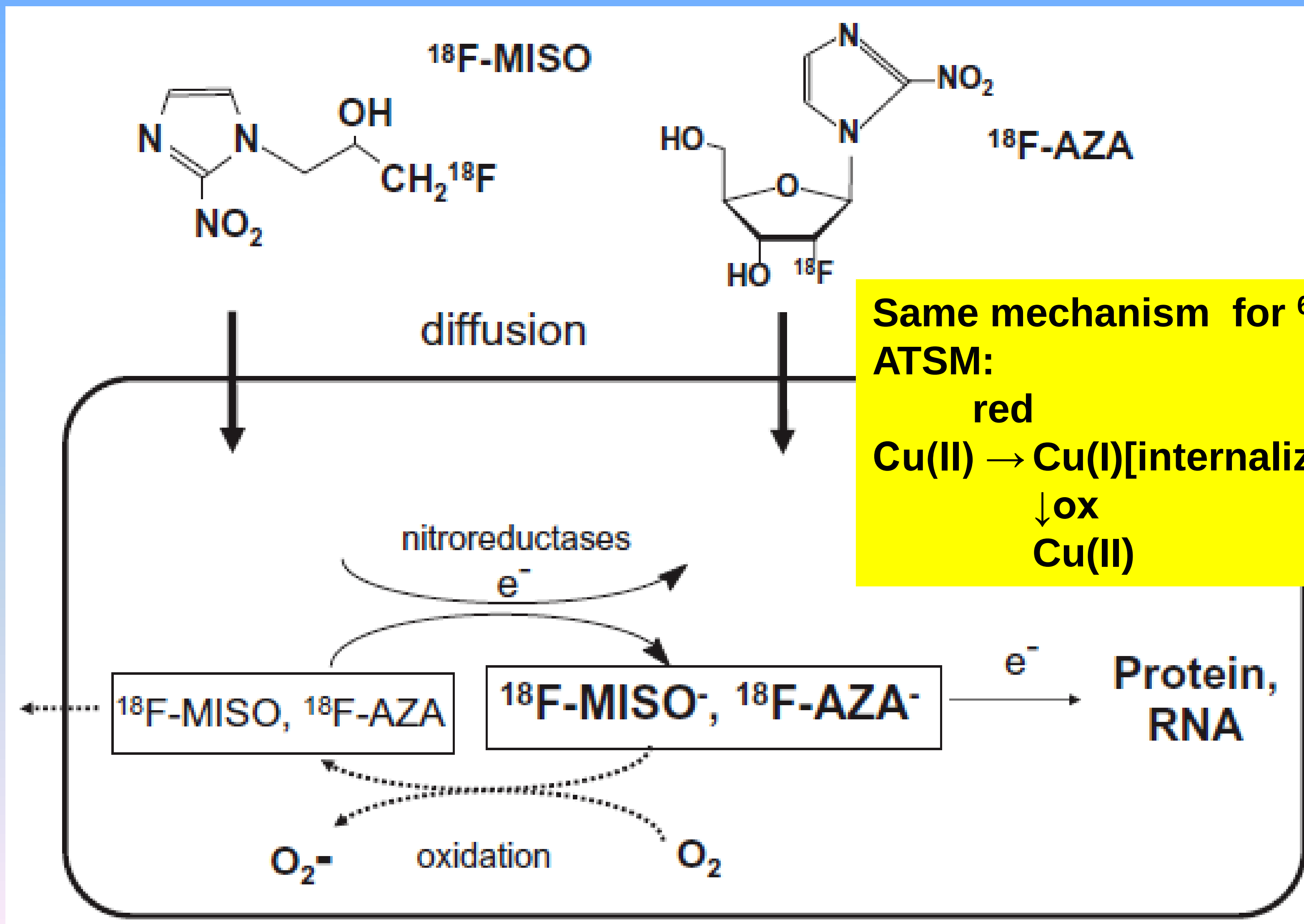
Working principle: FDG



Working principle: labelled aminoacids



Working principle: hypoxia agents



Same mechanism for ^{64}Cu-ATSM:

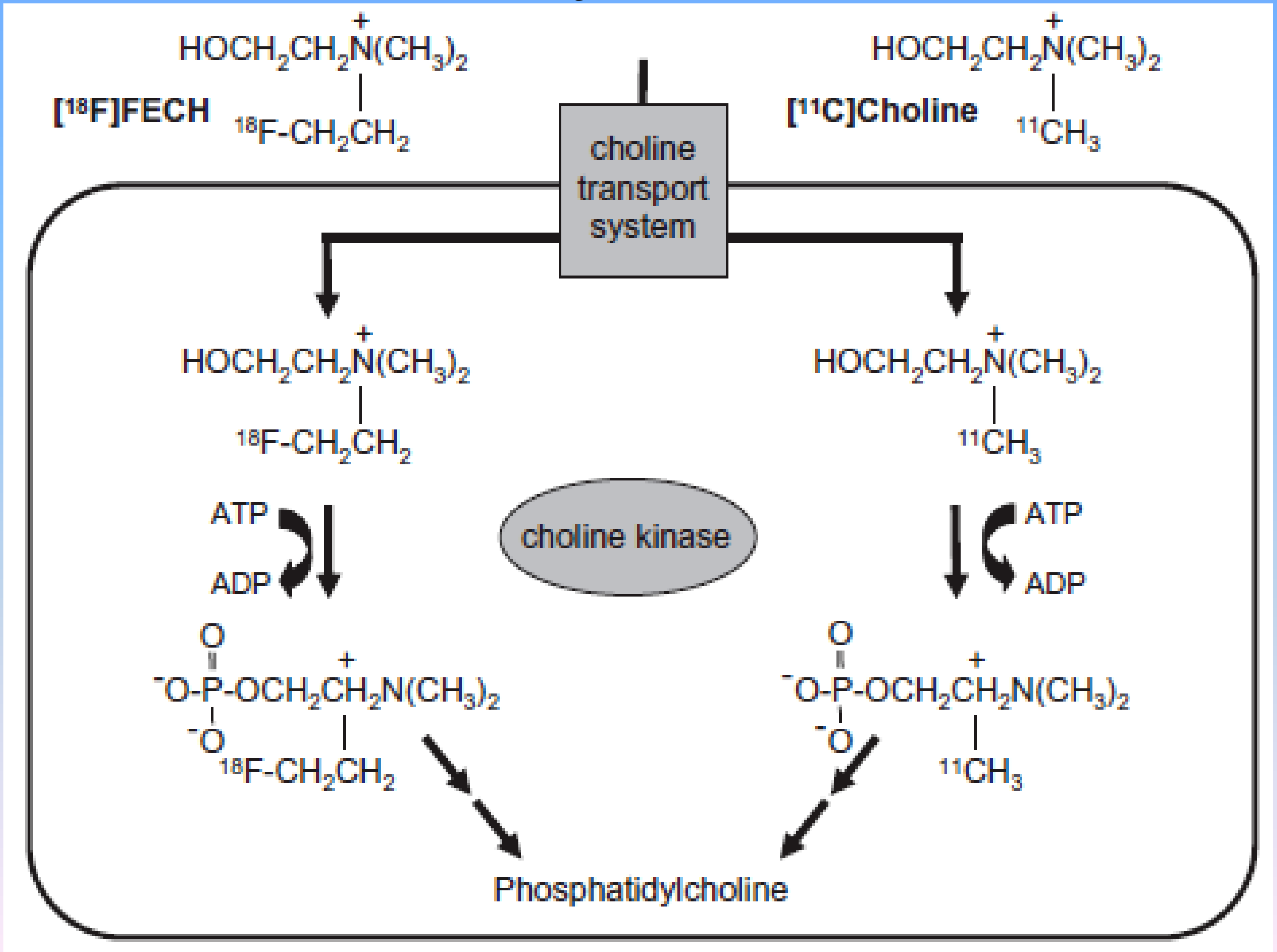
red

Cu(II) → Cu(I)[internalized]

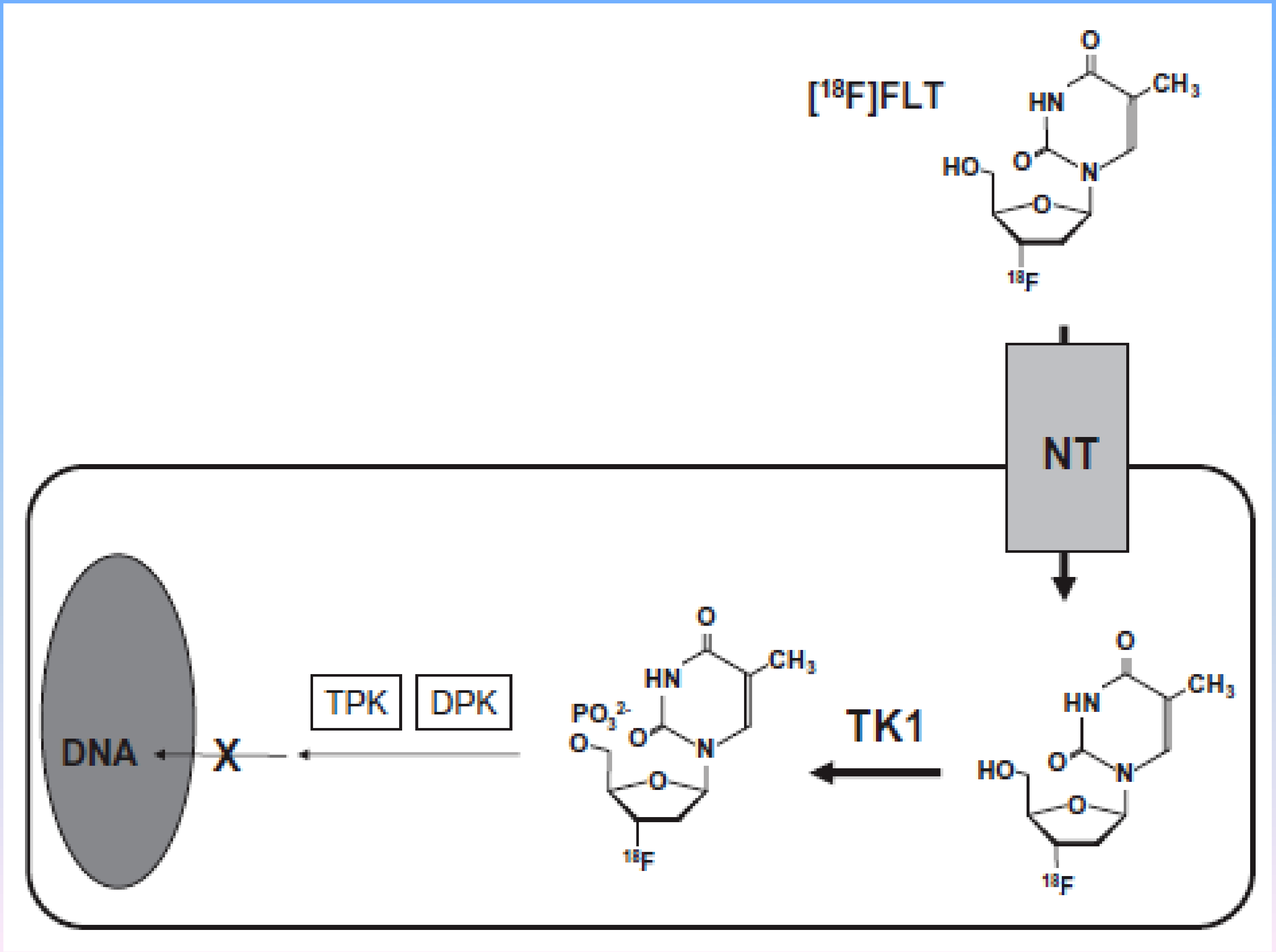
↓ox

Cu(II)

Working principle: membrane biosynthesis



Working principle: labelled nucleosides



Working principle: angiogenesis and somatostatin tracers

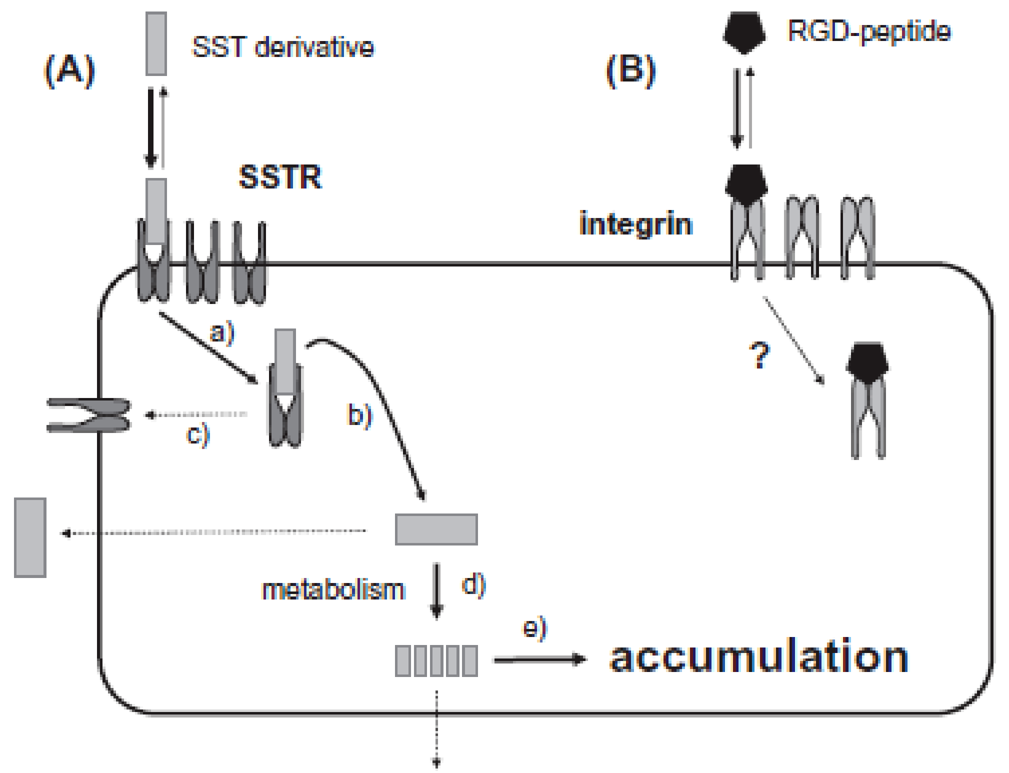
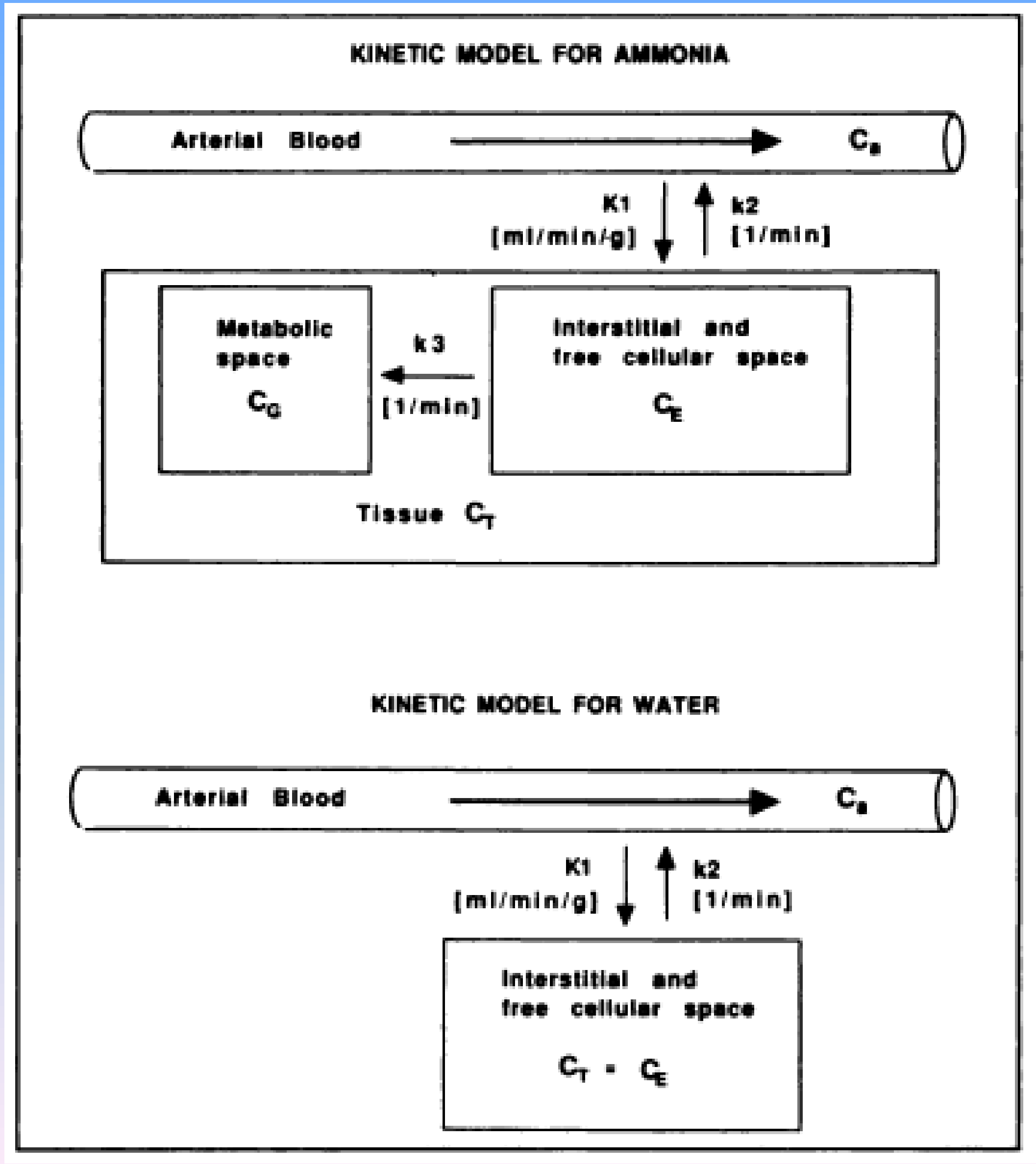


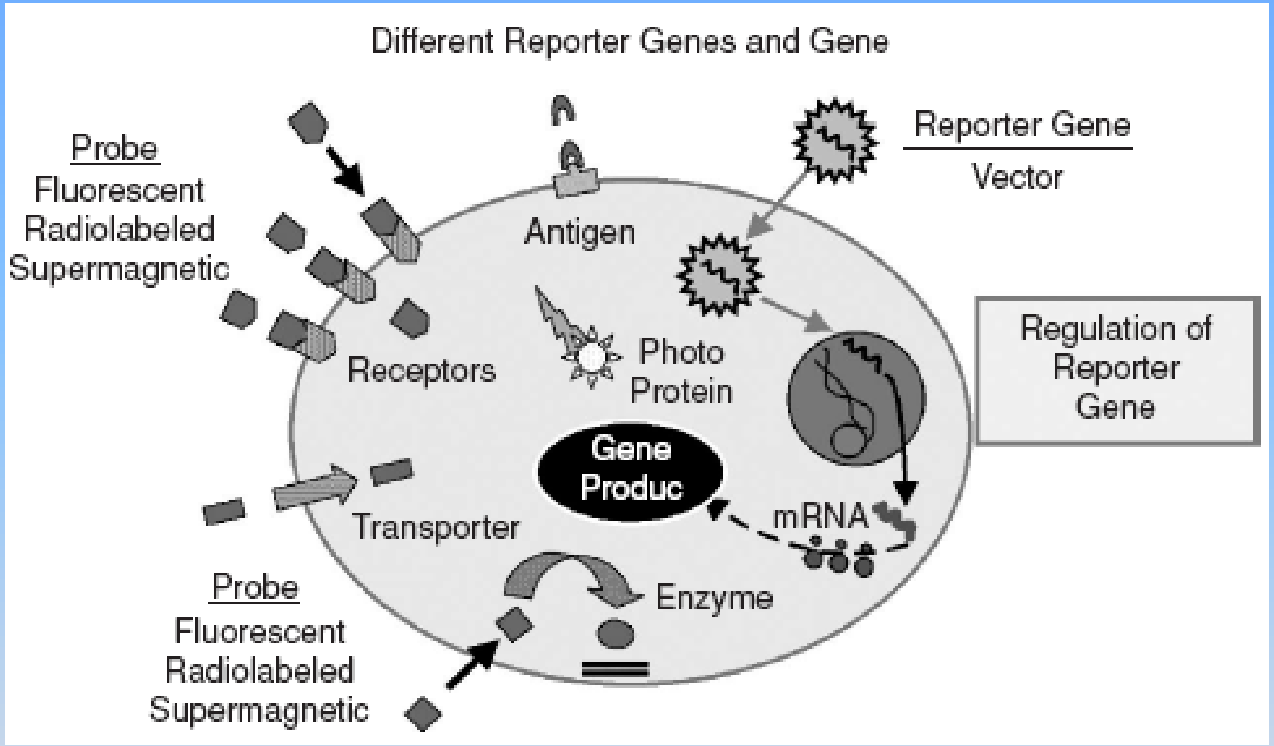
Fig. 6. Schematic presentation of uptake of radiolabelled-somatostatin derivatives and radiolabelled-RGD-peptides: (A) Somatostatin derivatives (e.g. radiolabelled DOTATOC and DOTATATE) bind to the somatosatin receptor (SSTR) and are internalized via endocytosis (a). After release of the tracer (b) the receptor can be recycled (c). The major amount of the radiolabelled somatostatin derivative is metabolized (d) resulting in fragments which can not penetrate the cell membrane (e). (B) Radiolabelled RGD-peptides bind with high affinity to the integrin (especially $\alpha v\beta 3$). It is discussed that the receptor ligand complex can also be internalized. However, at the moment corresponding studies are missing. In in vitro internalization assays only small amounts of activity are found inside the cell (see e.g. Ref. [69]). Thus, it is unclear if in vivo accumulation is mainly based on receptor-binding or internalization.

Tracer model for $^{15}O\text{-}H_2O$ and $^{13}N\text{-}NH_3$



Multiparametrical analysis allows to asses exactly the blood volume

Tracers for gene therapies

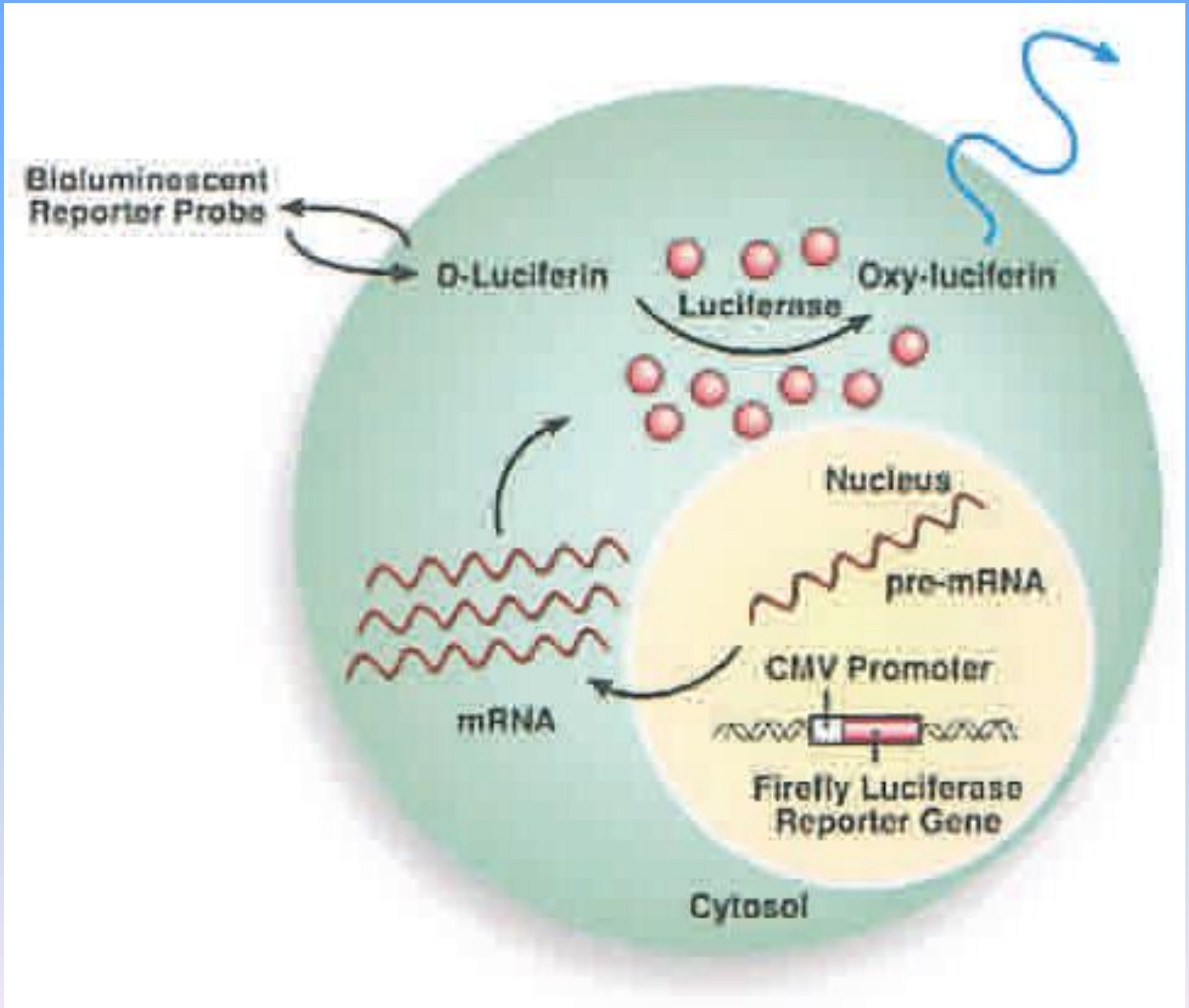


- Modify genome of a given cell population for study or curative reasons
- Problem: quantify gene expression, that is evaluation of ***location***, ***magnitude*** and ***persistence***

- A gene coexpresses curative protein/enzyme and a secondary agent (enzyme, receptor, protein)
- The radiotracer has a binding selectivity for the secondary agent
- Radioactive uptake will give information on the main expression

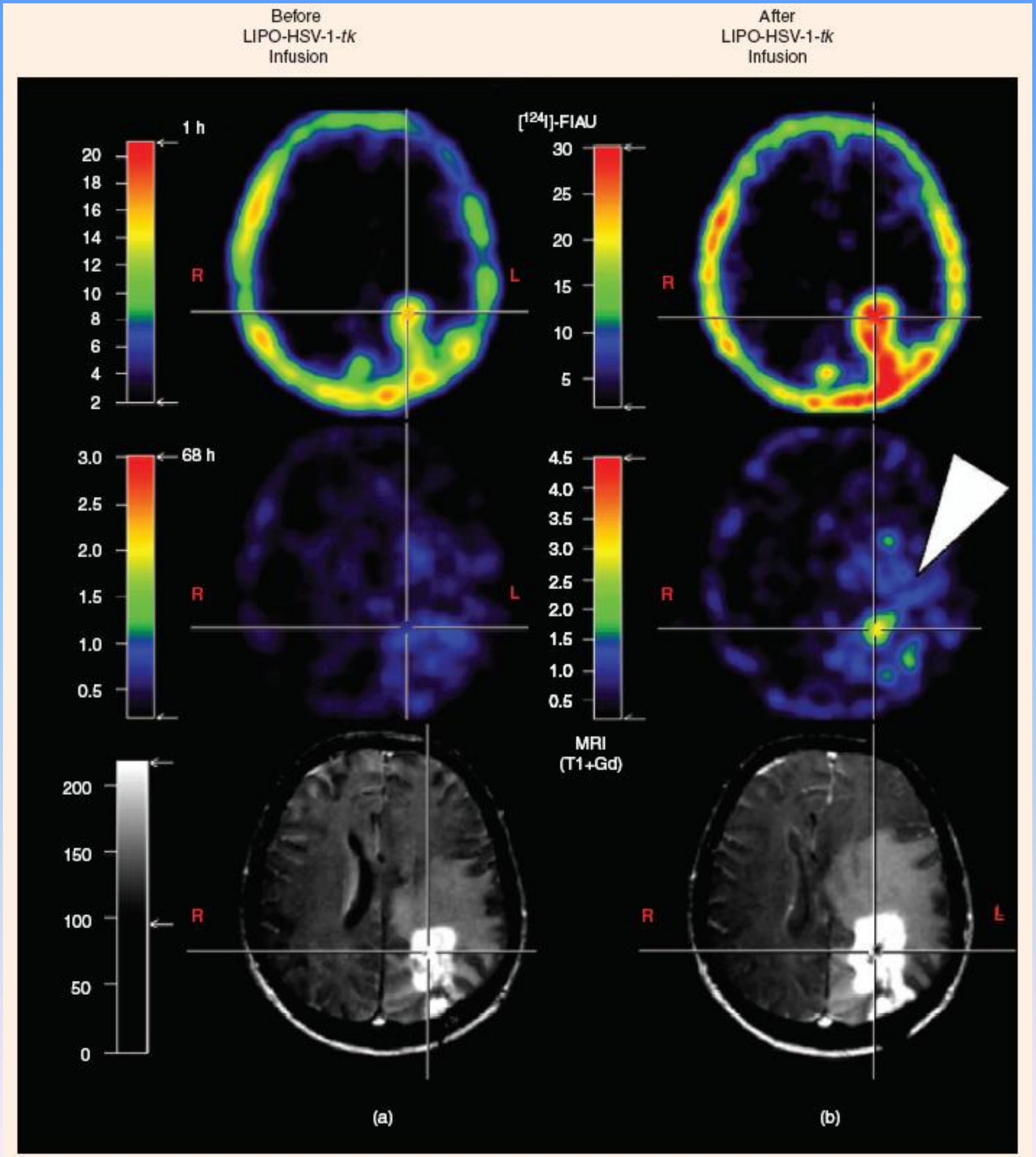
Reporter gene *technique uses a small, selected set of secondary agents to be coupled with virtually any kind of curative gene*

Working principle of Luciferase system



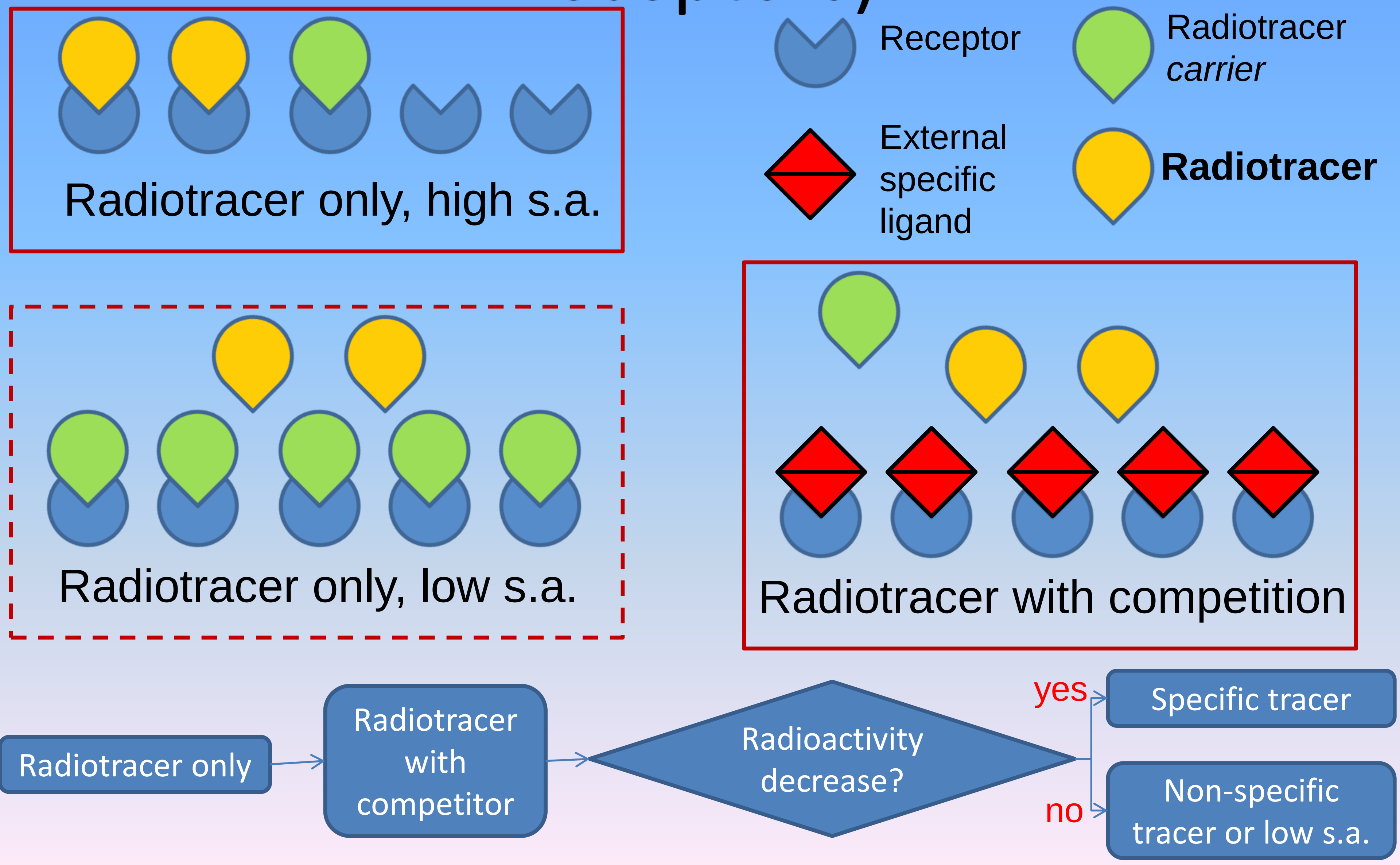
Luciferase = secondary agent

Luciferin (or luciferin analogues) = reporter gene tracer



Before
LIPO-HSV-1-tk
Infusion
After
LIPO-HSV-1-tk
Infusion
1 h
[124I]-FIAU
68 h
MRI
(T1+Gd)
R
L
(a)
(b)

Specific binding assessment (brain receptors)



Concluding remarks

Testing of new radiopharmaceuticals

In vitro

- Cell culture of target tissue

Ex vivo

- Binding on tissue slices
- Biodistribution on excised organs

In vivo

- “Simulated” animal model
- Bioengineered animal model
- Human

Good Manufacturing Practice: GMP

- Or “Generate More Paperwork”…
- Injectable preparations for human (and for animal also) must respect GMP preparation rules
- Guidelines on hardware, software and paperwork validation
- Radiopharmaceuticals are drugs, but up to 4 batches produced every day (*vs* few batches per year of traditional products)

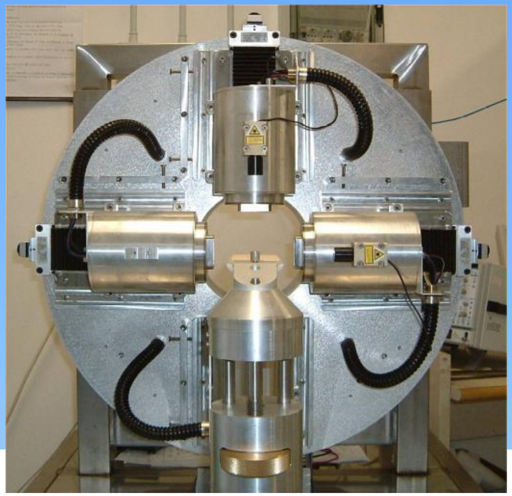
Physics research in Nuclear Medicine field

- Nuclide production/optimization by accelerator or generator
- Accelerator construction/maintenance/optimization
- Imaging apparatuses prototypization: PET, SPECT, CT
- Image extraction, based on matter interaction phenomena (theory) and mathematical iterative methods (practice)
- Radiotherapy machines building
- Radiosurvelliance, controlled are site planning, personnell control

Preclinical multimodal imaging at IFC

Xalt$_{HR}$

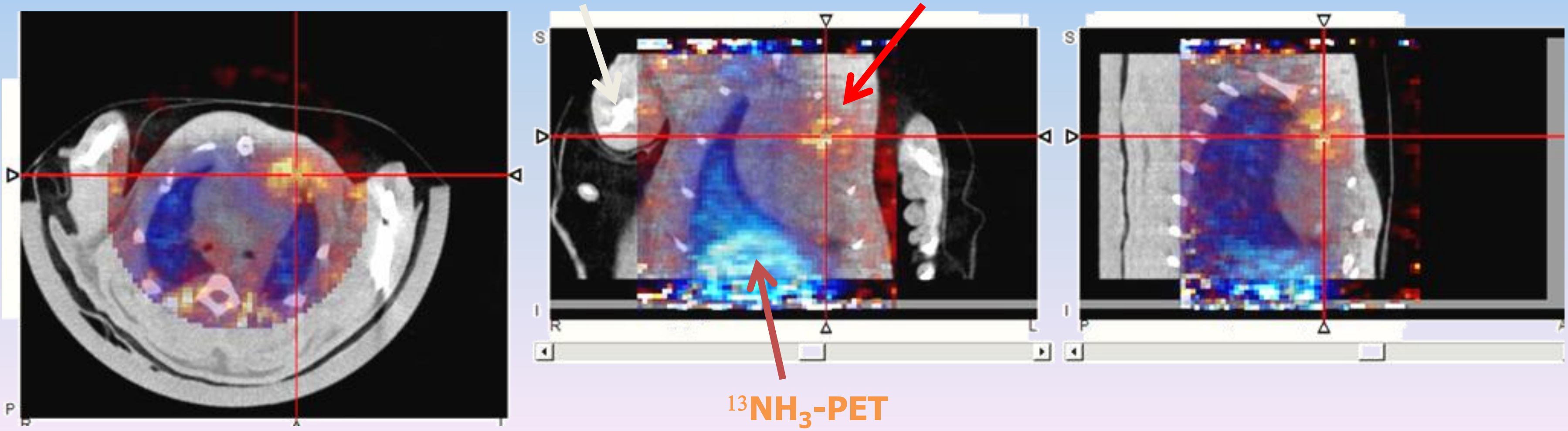
YAP-(S)PET II



ISE Ingegneria dei Sistemi Elettronici

CT

^{68}Ga-PET



$^{13}NH_3$-PET

Dr. Daniele Panetta (dpanetta@ifc.cnr.it)

Examples of new prototypes

Mini-cyclotron
(Ron Nutt, ABT)

Automated chemistry

Automated Quality
Control

Thanks for the attention