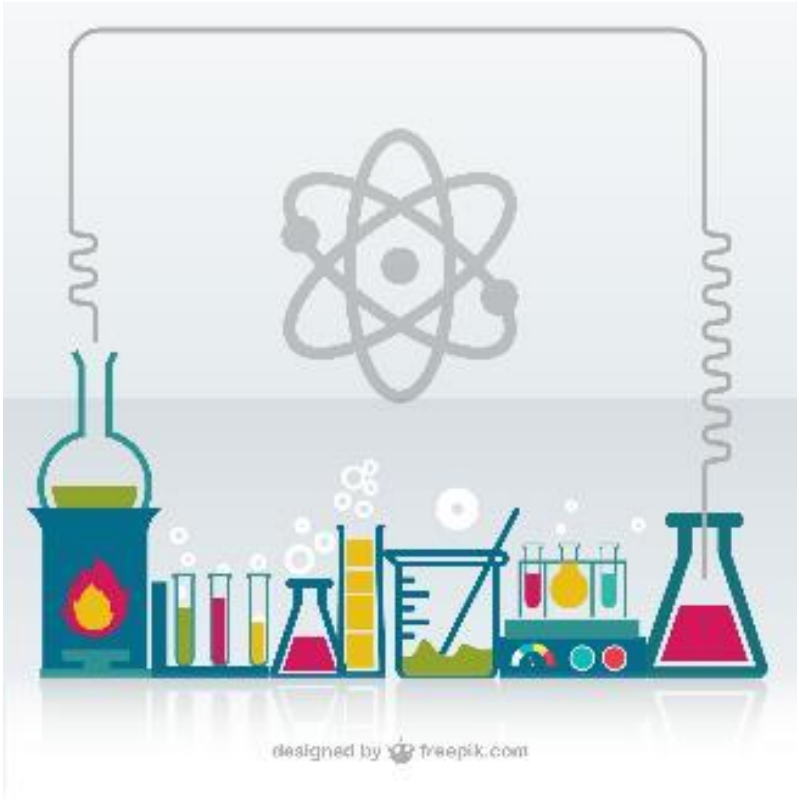


基礎放射化學:以 C-11 與 F-18 為例

放射核種物理與化學性質、
放射藥物分離純化技術

臺北榮民總醫院
核子醫學部
張文議

Molecular Imaging Probe Design

Signal agent:
- PET: ^{18}F, ^{11}C, ^{64}Cu, etc.
- SPECT: ^{99m}Tc, ^{111}In, etc.
- Optical: near IR fluoresent dyes
- MR: magnetically active elements
  Gd (III) chelates; Iron oxide nanoparticles;
  Dynamic nuclear polarization; Para-Hydrogen
- Ultrasound: microbubbles; micelles; liposomes
- Multimodal agents
  MR/PET; MR/optical; CT/optical;
  MR/fluoresence/bioluminescence

Targeting moiety:
- Viruses
- Small molecules
- Peptides
- Proteins
- Antibodies
- Nanoparticles
- Dual recognition

Target:
- Enzyme
- Receptor
- DNA/RNA
- Physiological state

Fig. (1).
Schematic representation of molecular imaging probe.

Molecular Imaging Probe Design

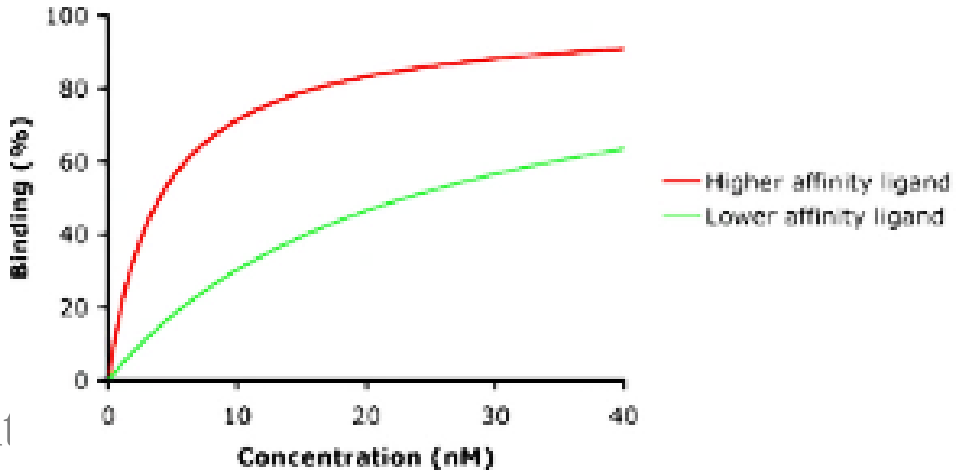
- **1.** High binding affinity to target
- **2.** High specificity to target
- **3.** High sensitivity
- **4.** High contrast ratio
- **5.** High stability in vivo
- **6.** Low immunogenicity and toxicity
- **7.** Production and economical feasibility

Molecular Imaging Probe Design

- **1.** High binding affinity to target

Molecular imaging generally favors the acquisition of the images at early time after administration of a molecular probe. To obtain high uptake of the imaging probe to the target within limited circulation time frame requires that the imaging probe has binding property of fast on-rate (K_{on}) and slow off-rate (K_{off}).

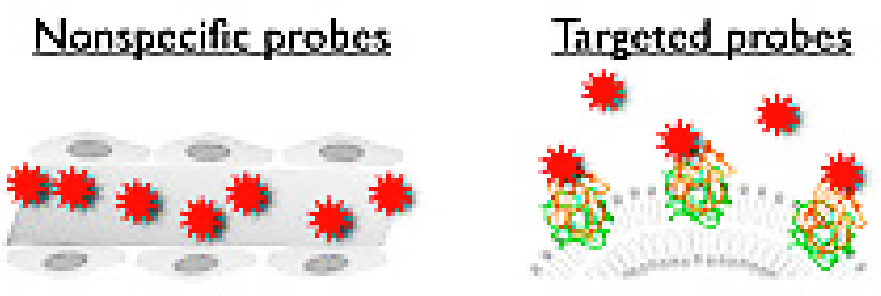
- **2.** High specificity to target.
- **3.** High sensitivity.
- **4.** High contrast ratio.
- **5.** High stability in vivo.
- **6.** Low immunogenicity and toxici
- **7.** Production and economical feasibility.



Molecular Imaging Probe Design

- **1.** High binding affinity to target
- **2.** High specificity to target

In contrast, target-specific molecular imaging probes can interact with particular biomarkers, such as enzyme, receptor, and transporters, which are involved in various biological processes associated with particular cell populations and subcellular compartments.



- **3.** High sensitivity
- **4.** High contrast ratio
- **5.** High stability in vivo
- **6.** Low immunogenicity and toxicity
- **7.** Production and economical feasibility

Molecular Imaging Probe Design

- **1.** High binding affinity to target
- **2.** High specificity to target
- **3.** High sensitivity

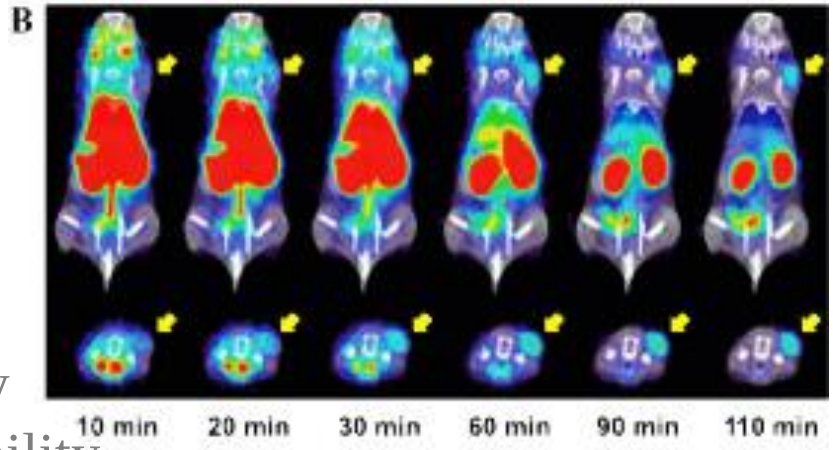
  To detect the biochemical process of the disease, especially at an early stage, frequently requires spying on the aberrant of a very small amount of targets.

- **4.** High contrast ratio
- **5.** High stability in vivo
- **6.** Low immunogenicity and toxicity
- **7.** Production and economical feasibility

Molecular Imaging Probe Design

- **1.** High binding affinity to target
- **2.** High specificity to target
- **3.** High sensitivity
- **4.** High contrast ratio.

  High contrast images with high target-to-background or signal-to-noise ratio ensure appropriate interpretation of physiological and pathological conditions of the diseases.



- **5.** High stability in vivo
- **6.** Low immunogenicity and toxicity
- **7.** Production and economical feasibility

Molecular Imaging Probe Design

- **1.** High binding affinity to target
- **2.** High specificity to target
- **3.** High sensitivity
- **4.** High contrast ratio
- **5.** High stability in vivo

Although only trace amount of imaging probe is normally given to the living subjects, maintenance of the intact structure of an imaging probe is a big challenge because numerous enzymes or proteases present in serum or targeted tissue may degrade the imaging probe. The image information given from the metabolites of the imaging probe undoubtedly complexifies the imaging readout and usually makes the understanding of disease highly vague.

- **6.** Low immunogenicity and toxicity
- **7.** Production and economical feasibility

Molecular Imaging Probe Design

- **1.** High binding affinity to target
- **2.** High specificity to target
- **3.** High sensitivity
- **4.** High contrast ratio
- **5.** High stability in vivo
- **6.** Low immunogenicity and toxicity

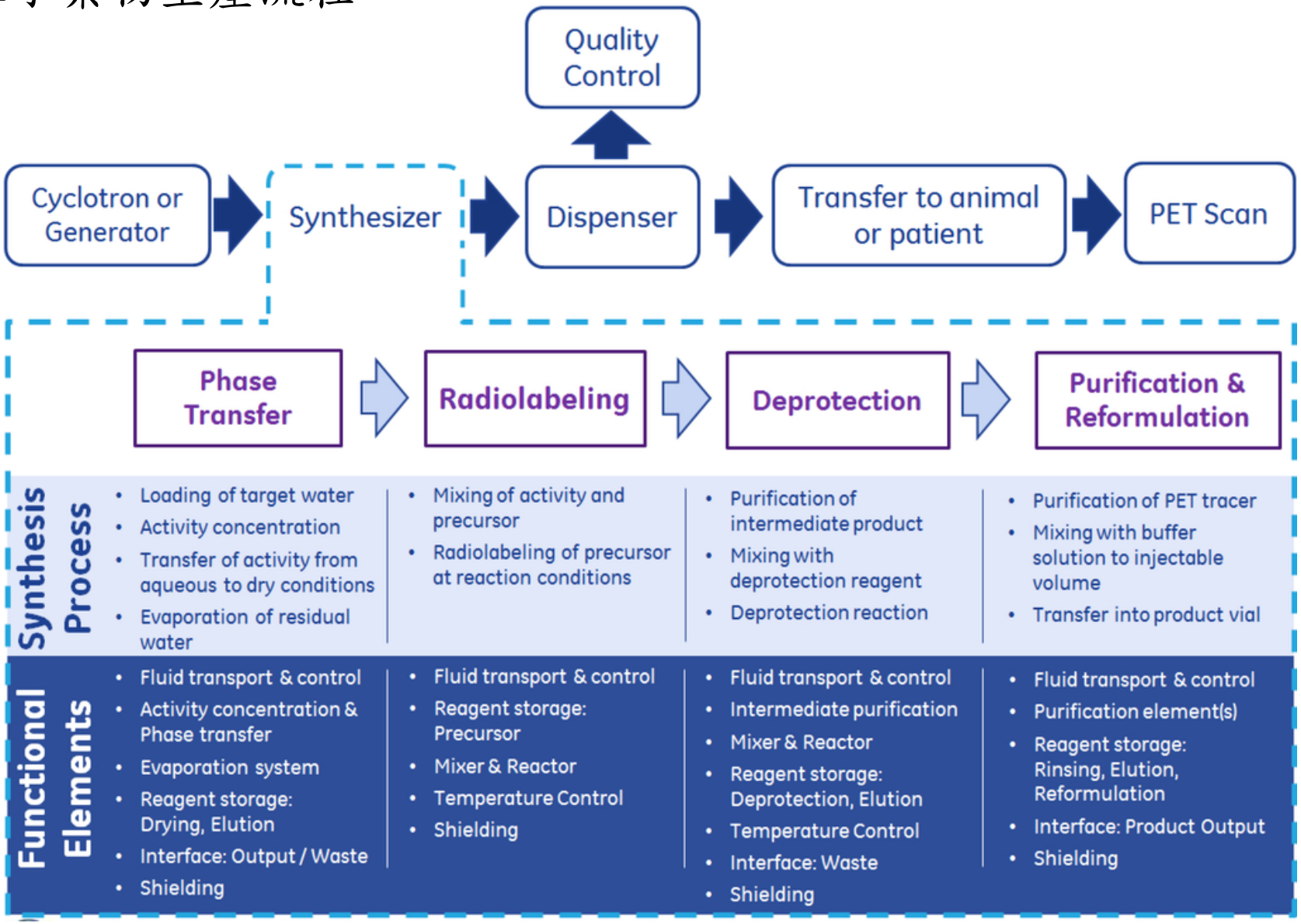
  A molecular imaging probe should have minimal or acceptable level of immunogenicity and toxicity before it can be safely employed in human.
- **7.** Production and economical feasibility

  The low cost and excellent availability of molecular imaging probes are advantageous for their wide distribution and clinical routine use.

正子藥物生產流程


1 Radioisotope production and delivery
2 Radioisotope preparation
3 Radiosynthesis
4 Purification
5 Formulation
6 Sterile filtration
7 Quality control (QC) testing
8 Radiotracer Injection
9 PET scan and image analysis

正子藥物生產流程


Quality Control
Cyclotron or Generator
Synthesizer
Dispenser
Transfer to animal or patient
PET Scan
Phase Transfer
Radiolabeling
Deprotection
Purification & Reformulation
Synthesis Process
Loading of target water
Activity concentration
Transfer of activity from aqueous to dry conditions
Evaporation of residual water
Mixing of activity and precursor
Radiolabeling of precursor at reaction conditions
Purification of intermediate product
Mixing with deprotection reagent
Deprotection reaction
Purification of PET tracer
Mixing with buffer solution to injectable volume
Transfer into product vial
Functional Elements
Fluid transport & control
Activity concentration & Phase transfer
Evaporation system
Reagent storage: Drying, Elution
Interface: Output / Waste
Shielding
Fluid transport & control
Reagent storage: Precursor
Mixer & Reactor
Temperature Control
Shielding
Fluid transport & control
Intermediate purification
Mixer & Reactor
Reagent storage: Deprotection, Elution
Temperature Control
Interface: Waste
Shielding
Fluid transport & control
Purification element(s)
Reagent storage: Rinsing, Elution, Reformulation
Interface: Product Output
Shielding

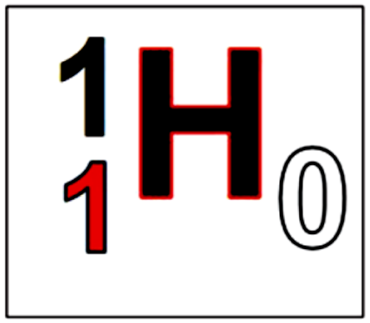
質量數 ← A X → 元素符號

原子序 ← Z

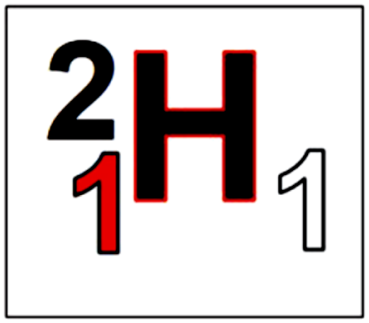
帶電荷粒子	英文	表示方式	
質子	Proton	p	$^{1}_{1}p$
中子	Neutron	n	$^{1}_{0}n$
阿法粒子	α 或 Helium	α	$^{4}_{2}\alpha$ $^{4}_{2}He$
電子	Electron	e	$^{0}_{-1}e$
氘核子	Deuterium	d	$^{2}_{1}d$
氫元子	Hydrogen	H	$^{1}_{1}H$

The main isotopes of hydrogen and their natural abundance:

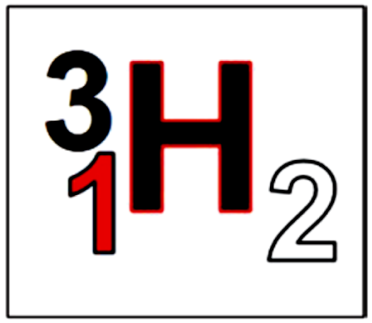
HYDROGEN
99.9885%



DEUTERIUM
0.0115%



TRITIUM
10^{-15}%

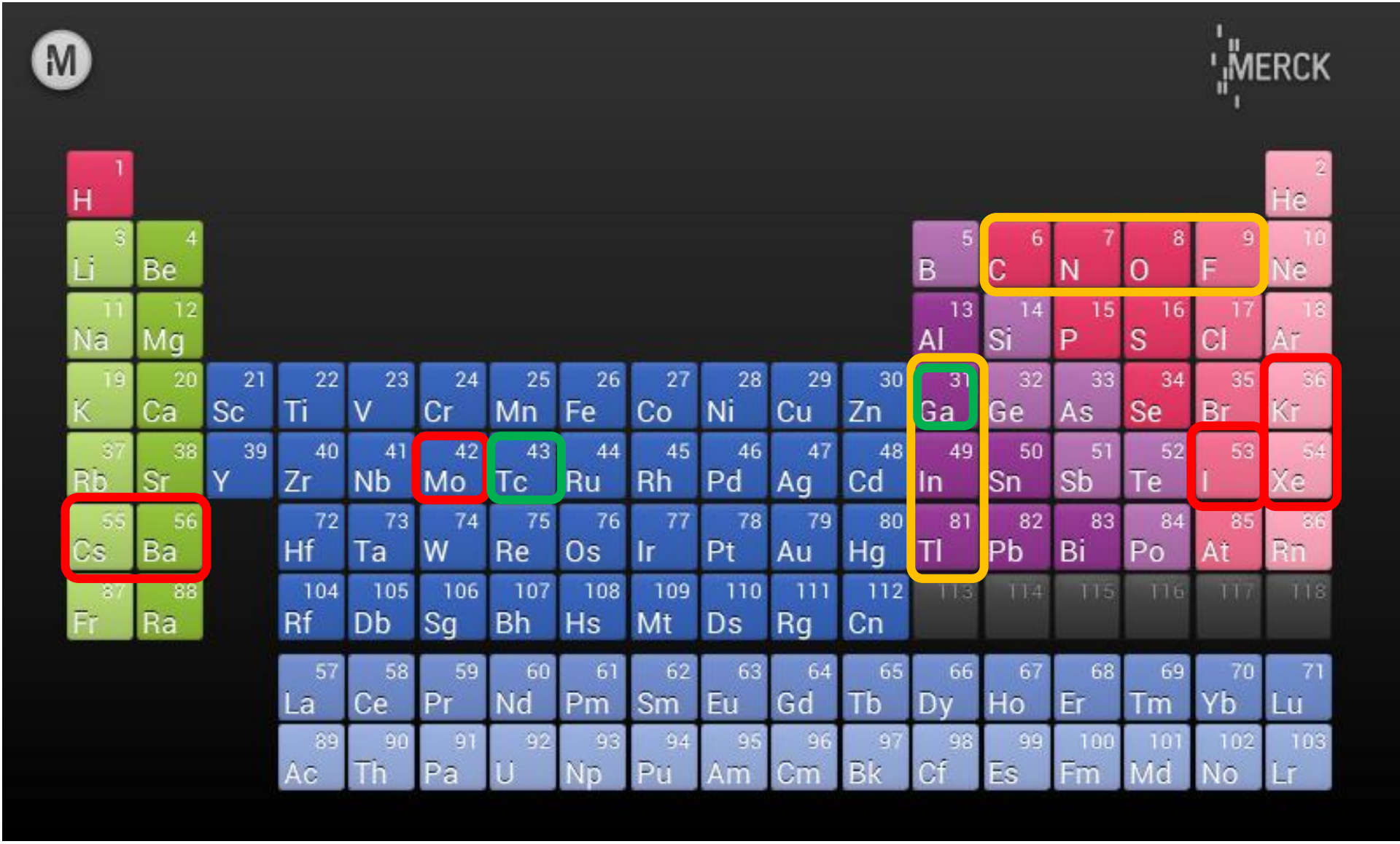


元素週期表
Periodic Table of the Elements

金屬元素　類金屬元素　非金屬元素　氣體　液體　固體

鹼金屬 IA 1	鹼土金屬 IIA 2	過渡金屬					VIII B					硼族 IIIA 13	碳族 IVA 14	氮族 VA 15	氧族 VIA 16	鹵素 VIIA 17	鈍氣 VIII A 18
		III B 3	IV B 4	V B 5	VI B 6	VII B 7	8	9	10	I B 11	II B 12						
1 H 氫 1.008																	2 He 氦 4.003
3 Li 鋰 6.941	4 Be 鈹 9.012											5 B 硼 10.81	6 C 碳 12.01	7 N 氮 14.01	8 O 氧 16.00	9 F 氟 19.00	10 Ne 氖 20.18
11 Na 鈉 22.99	12 Mg 鎂 24.31											13 Al 鋁 26.98	14 Si 矽 28.09	15 P 磷 30.97	16 S 硫 32.07	17 Cl 氯 35.45	18 Ar 氬 39.95
19 K 鉀 39.10	20 Ca 鈣 40.08	21 Sc 鈧 44.96	22 Ti 鈦 47.88	23 V 釩 50.94	24 Cr 鉻 52.00	25 Mn 錳 54.94	26 Fe 鐵 55.85	27 Co 鈷 58.93	28 Ni 鎳 58.69	29 Cu 銅 63.55	30 Zn 鋅 65.39	31 Ga 鎵 69.72	32 Ge 鍺 72.61	33 As 砷 74.92	34 Se 硒 78.96	35 Br 溴 79.90	36 Kr 氪 83.80
37 Rb 銣 85.47	38 Sr 鍶 87.62	39 Y 釔 88.91	40 Zr 鋯 91.22	41 Nb 鈮 92.91	42 Mo 鉬 95.94	43 Tc 鎝 98.91	44 Ru 釕 101.1	45 Rh 銠 102.9	46 Pd 鈀 106.4	47 Ag 銀 107.9	48 Cd 鎘 112.4	49 In 銦 114.8	50 Sn 錫 118.7	51 Sb 銻 121.8	52 Te 碲 127.6	53 I 碘 126.9	54 Xe 氙 131.3
55 Cs 銫 132.9	56 Ba 鋇 137.3	鑭系元素	72 Hf 鉿 178.5	73 Ta 鉭 180.9	74 W 鎢 183.9	75 Re 錸 186.2	76 Os 鋨 190.2	77 Ir 銥 192.2	78 Pt 鉑 195.1	79 Au 金 197.0	80 Hg 汞 200.6	81 Tl 鉈 204.4	82 Pb 鉛 207.2	83 Bi 鉍 209.0	84 Po 釙 (209)	85 At 砈 (210)	86 Rn 氡 (222)
87 Fr 鈁 (223)	88 Ra 鐳 226.0	錒系元素	104 Rf 鑪 (261)	105 Db 𨧀 (262)	106 Sg 𨭆 (263)	107 Bh 𨨏 (262)	108 Hs 𨭉 (265)	109 Mt 鏌 (267)	110 Ds 𫟼 (269)	111 Rg 錀 (272)	112 Cn 鿔 (277)	113 Uut (286)	114 Fl 鈇 (289.2)	115 Uup (288)	116 Lv 鉝 (293.2)	117 Uus (294)	118 Uuo (294)

鑭系元素	57 La 鑭 138.9	58 Ce 鈰 140.1	59 Pr 鐠 140.9	60 Nd 釹 144.21	61 Pm 鉕 (145)	62 Sm 釤 150.4	63 Eu 銪 152.0	64 Gd 釓 157.3	65 Tb 鋱 158.9	66 Dy 鏑 162.5	67 Ho 鈥 164.9	68 Er 鉺 167.3	69 Tm 銩 168.9	70 Yb 鐿 173.0	71 Lu 鑥 175.0
錒系元素	89 Ac 錒 227.0	90 Th 釷 232.0	91 Pa 鏷 231.0	92 U 鈾 238.0	93 Np 鎿 237.0	94 Pu 鈽 (244)	95 Am 鋂 (243)	96 Cm 鋦 (247)	97 Bk 錇 (247)	98 Cf 鉲 (251)	99 Es 鑀 (252)	100 Fm 鐨 (257)	101 Md 鍆 (258)	102 No 鍩 (259)	103 Lr 鐒 (262)


MERCK
H 1
He 2
Li 3
Be 4
B 5
C 6
N 7
O 8
F 9
Ne 10
Na 11
Mg 12
Al 13
Si 14
P 15
S 16
Cl 17
Ar 18
K 19
Ca 20
Sc 21
Ti 22
V 23
Cr 24
Mn 25
Fe 26
Co 27
Ni 28
Cu 29
Zn 30
Ga 31
Ge 32
As 33
Se 34
Br 35
Kr 36
Rb 37
Sr 38
Y 39
Zr 40
Nb 41
Mo 42
Tc 43
Ru 44
Rh 45
Pd 46
Ag 47
Cd 48
In 49
Sn 50
Sb 51
Te 52
I 53
Xe 54
Cs 55
Ba 56
Hf 72
Ta 73
W 74
Re 75
Os 76
Ir 77
Pt 78
Au 79
Hg 80
Tl 81
Pb 82
Bi 83
Po 84
At 85
Rn 86
Fr 87
Ra 88
Rf 104
Db 105
Sg 106
Bh 107
Hs 108
Mt 109
Ds 110
Rg 111
Cn 112
113
114
115
116
117
118
La 57
Ce 58
Pr 59
Nd 60
Pm 61
Sm 62
Eu 63
Gd 64
Tb 65
Dy 66
Ho 67
Er 68
Tm 69
Yb 70
Lu 71
Ac 89
Th 90
Pa 91
U 92
Np 93
Pu 94
Am 95
Cm 96
Bk 97
Cf 98
Es 99
Fm 100
Md 101
No 102
Lr 103

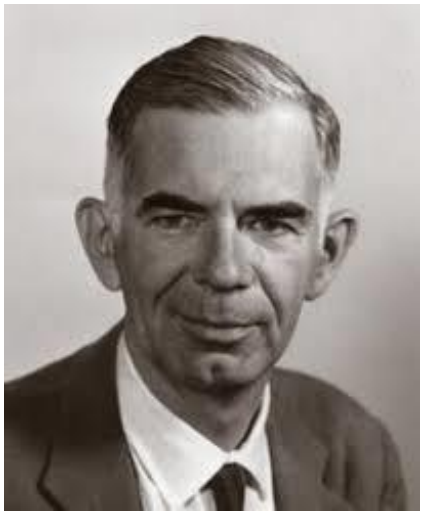
Radionuclides for positron emission tomography (PET)

Isotope	Half-life	Primary decay mode (branching ratio)	Mean β^+ energy (keV)	β^+ end-point energy (keV)	% abundance β^+	Production route
^{11}C	20.364 (14) min	β^+ (1)	385.70 (44)	960.4 (10)	99.7669 (25)	$^{14}N(p,\alpha)^{11}C$
^{13}N	9.965 (4) min	β^+ (1)	491.82 (12)	1198.5 (3)	99.8036 (20)	$^{16}O(p,\alpha)^{13}N$
^{15}O	122.24 (16) s	β^+ (1)	735.28 (23)	1732.0 (5)	99.9003 (10)	$^{15}N(p,n)^{15}O$
						$^{14}N(d,n)^{15}O$
^{18}F	109.77 (5) min	β^+ (1)	249.8 (3)	633.5 (6)	96.73 (4)	$^{18}O(p,n)^{18}F$
						$^{20}Ne(d,\alpha)^{18}F$

- **The Radiopharmaceutical Chemistry of Carbon-11: Basic Principles**
- **The Radiopharmaceutical Chemistry of Carbon-11: Tracers and Applications**
- **The Radiopharmaceutical Chemistry of Fluorine-18: Nucleophilic Fluorinations**
- **The Radiopharmaceutical Chemistry of Fluorine-18: Electrophilic Fluorinations**

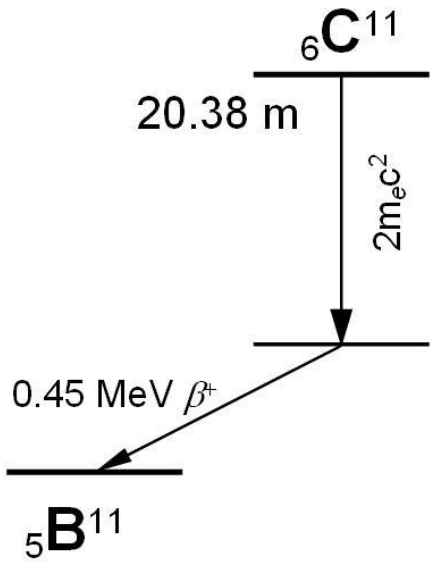
The Radiopharmaceutical Chemistry of Carbon-11: Basic Principles

Historic View on Carbon-11 Chemistry



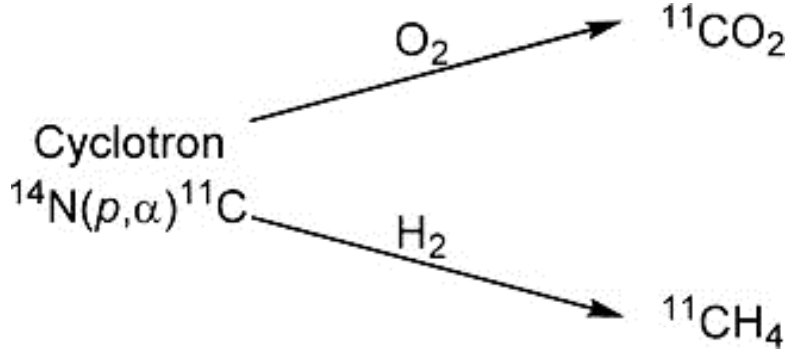
Carbon-11 was produced for the first time in 1934 by Crane and Lauritsen.

Decay Characteristics of Carbon-11

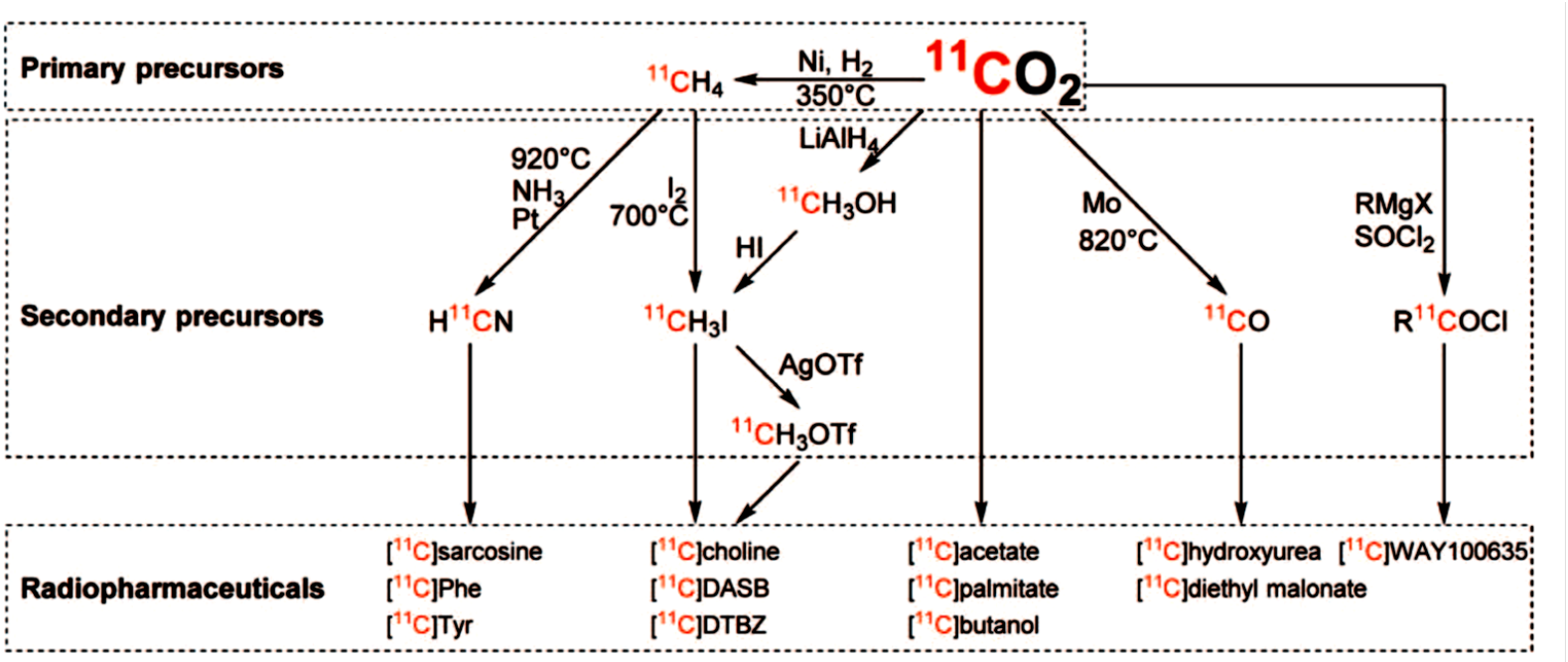


Carbon-11 Precursors for Labeling

Production of Carbon-11



In-Target-Produced Primary Precursors
Secondary Precursors

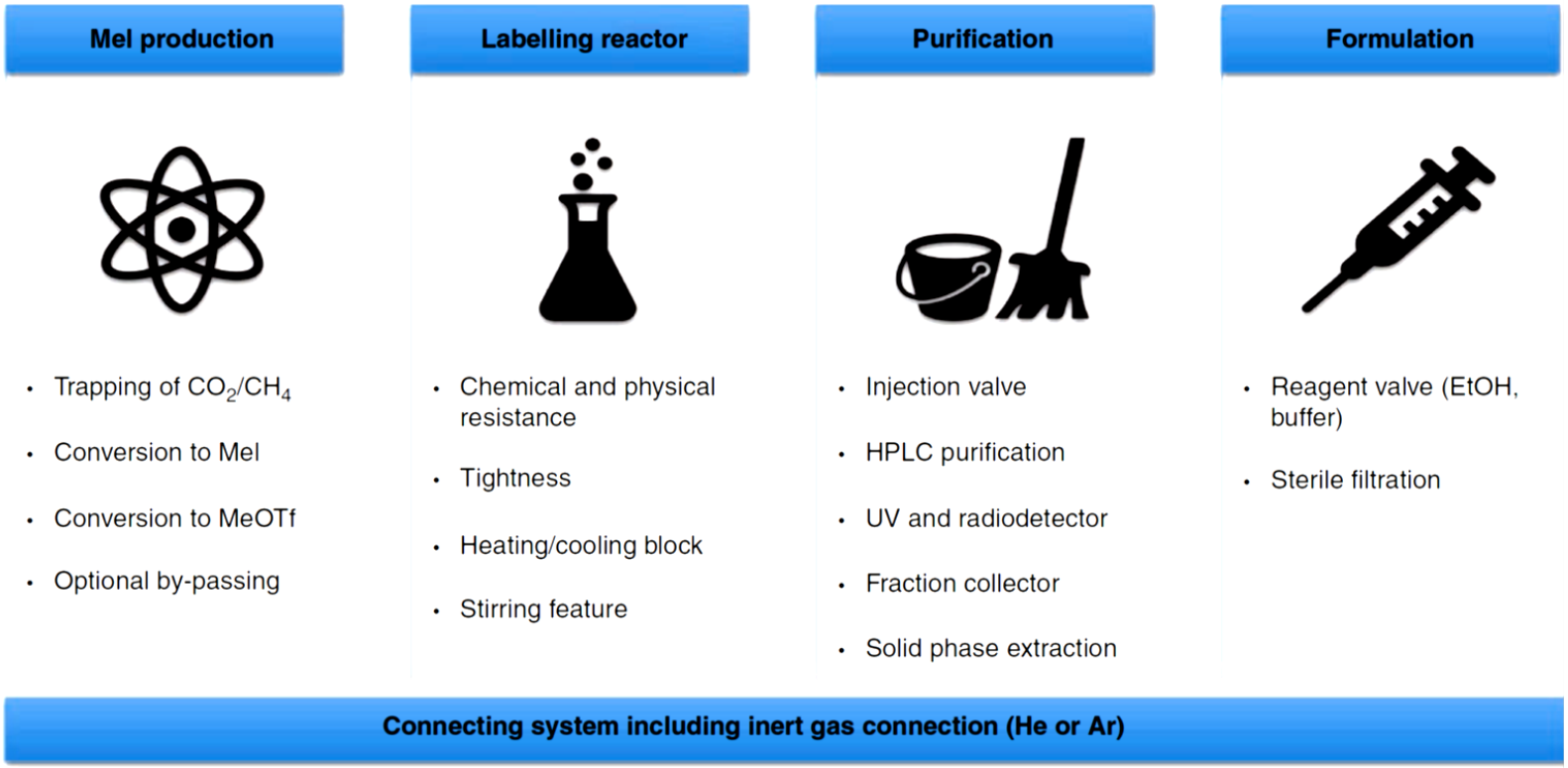


[^{11}C]Carbon Dioxide: Starting Point for Labeling PET Radiopharmaceuticals
http://dx.doi.org/10.5772/intechopen.72313

The Radiopharmaceutical Chemistry of Carbon-11: Tracers and Applications

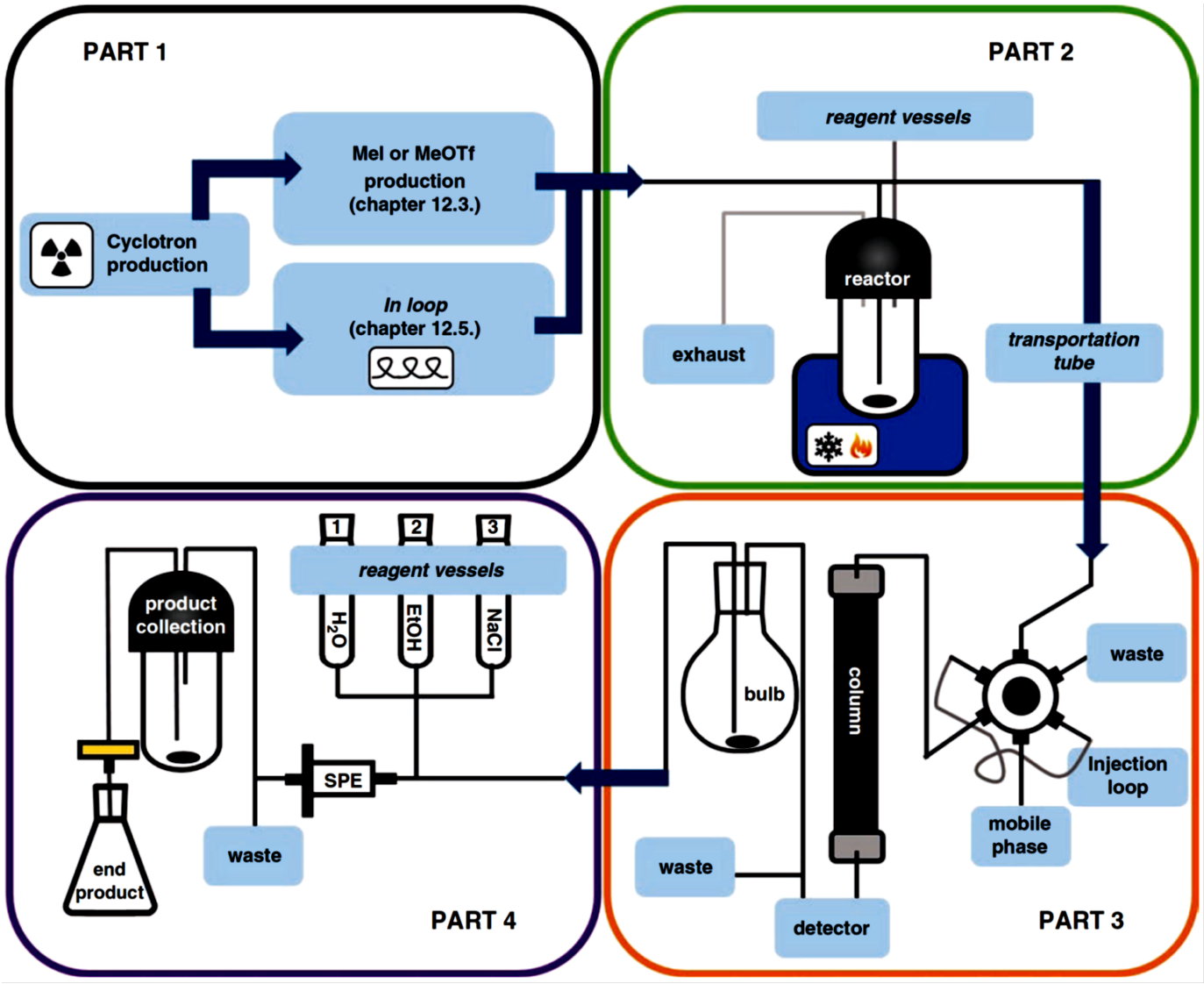
Technical Aspects of Carbon-11: Commercially Available Synthesizers and Optimization

Overview of the four necessary procedures for a successful radiosynthesis

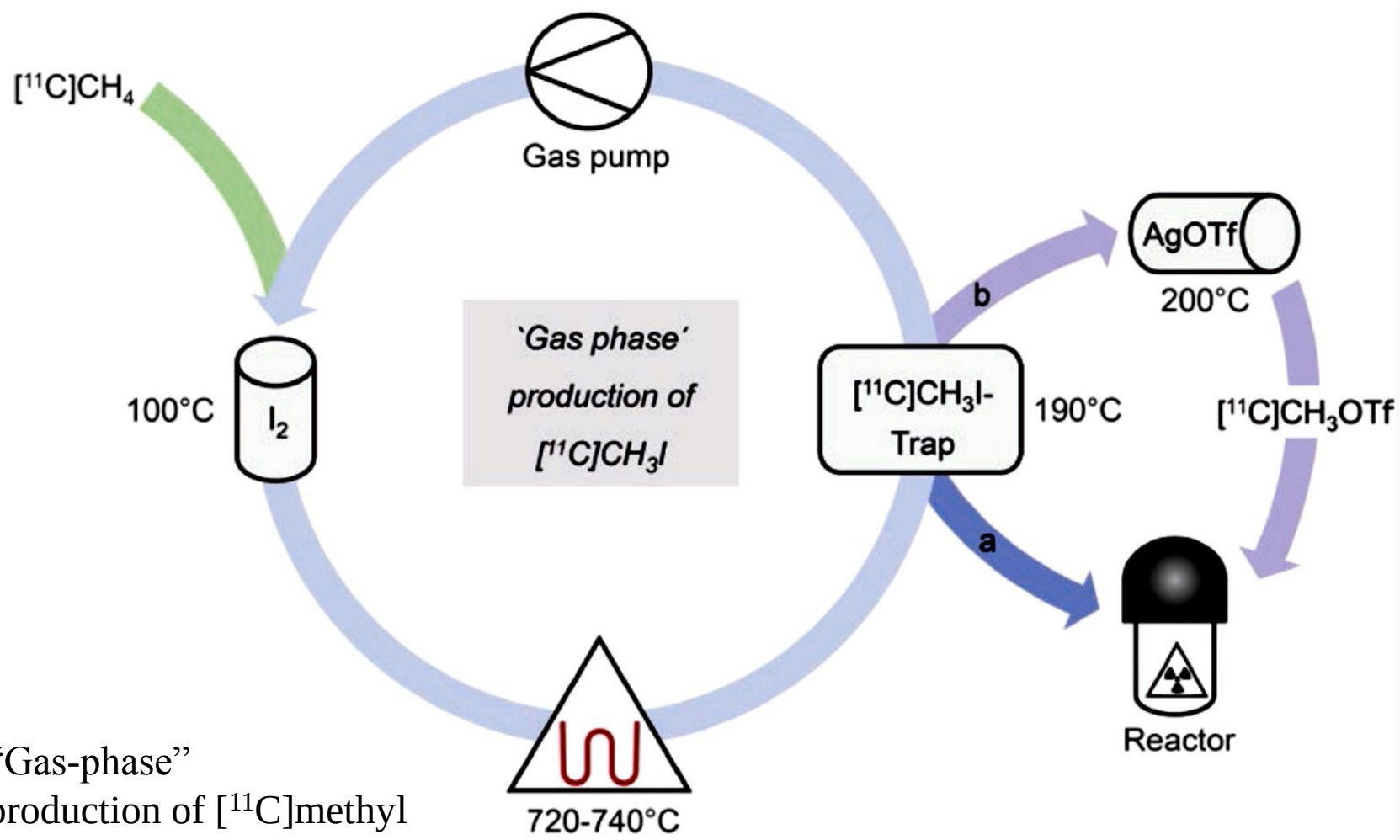


General Considerations for Radiotracer Production and the Setup of Synthesizers

Reactors and Reagent Vessels

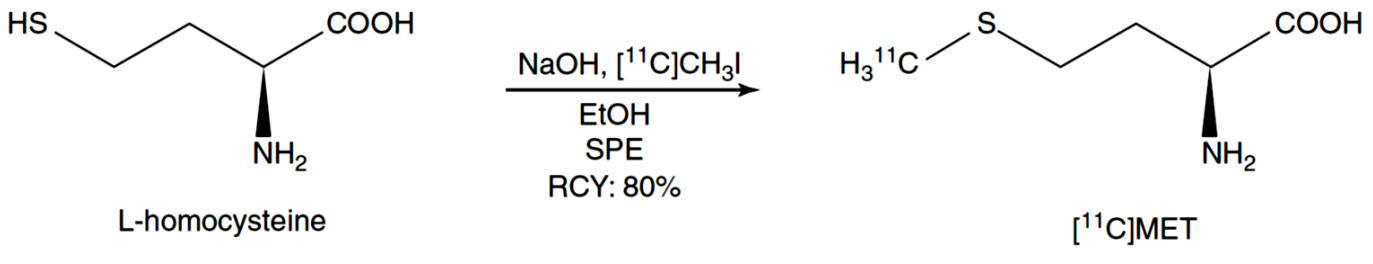


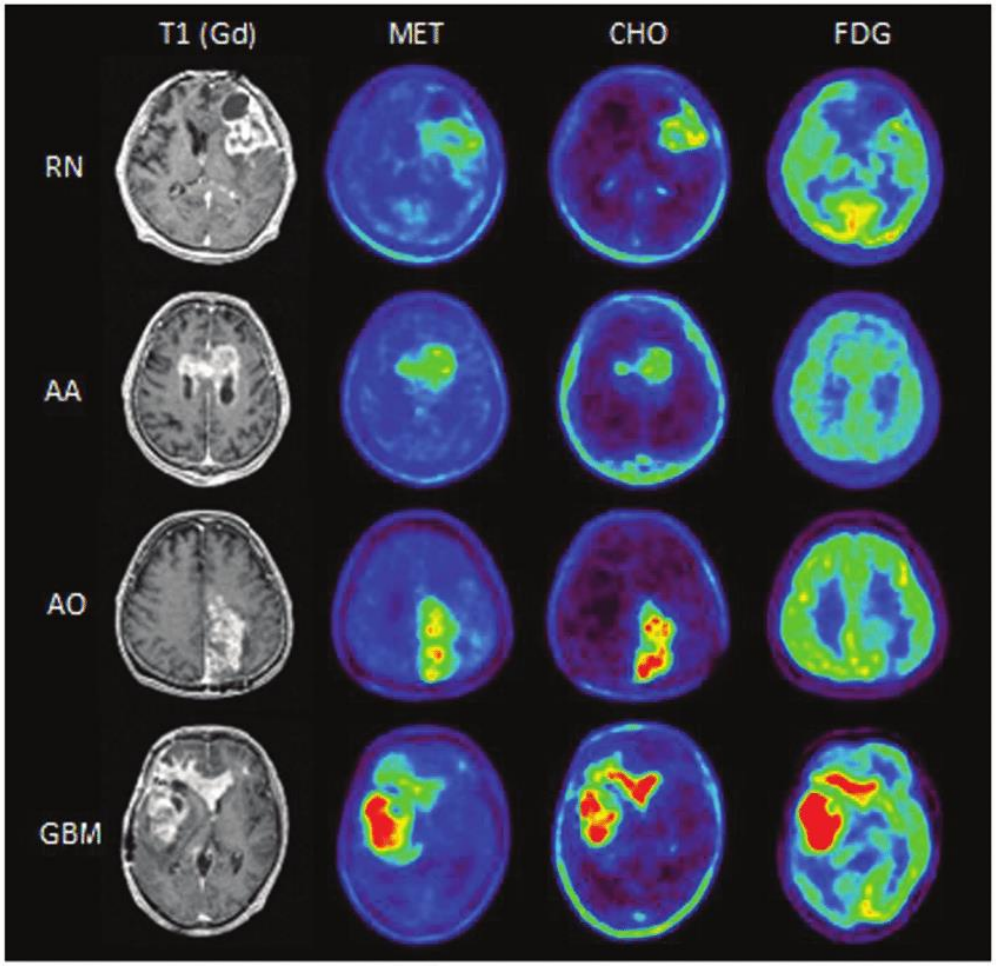
The four essential parts of carbon-11 radiosynthetic modules



"Gas-phase" production of [^{11}C]methyl iodide. (a) Direct delivery of [^{11}C]CH_3I into the reactor and (b) online passage of [^{11}C] CH_3I through AgOTf for conversion into [^{11}C]CH_3OTf

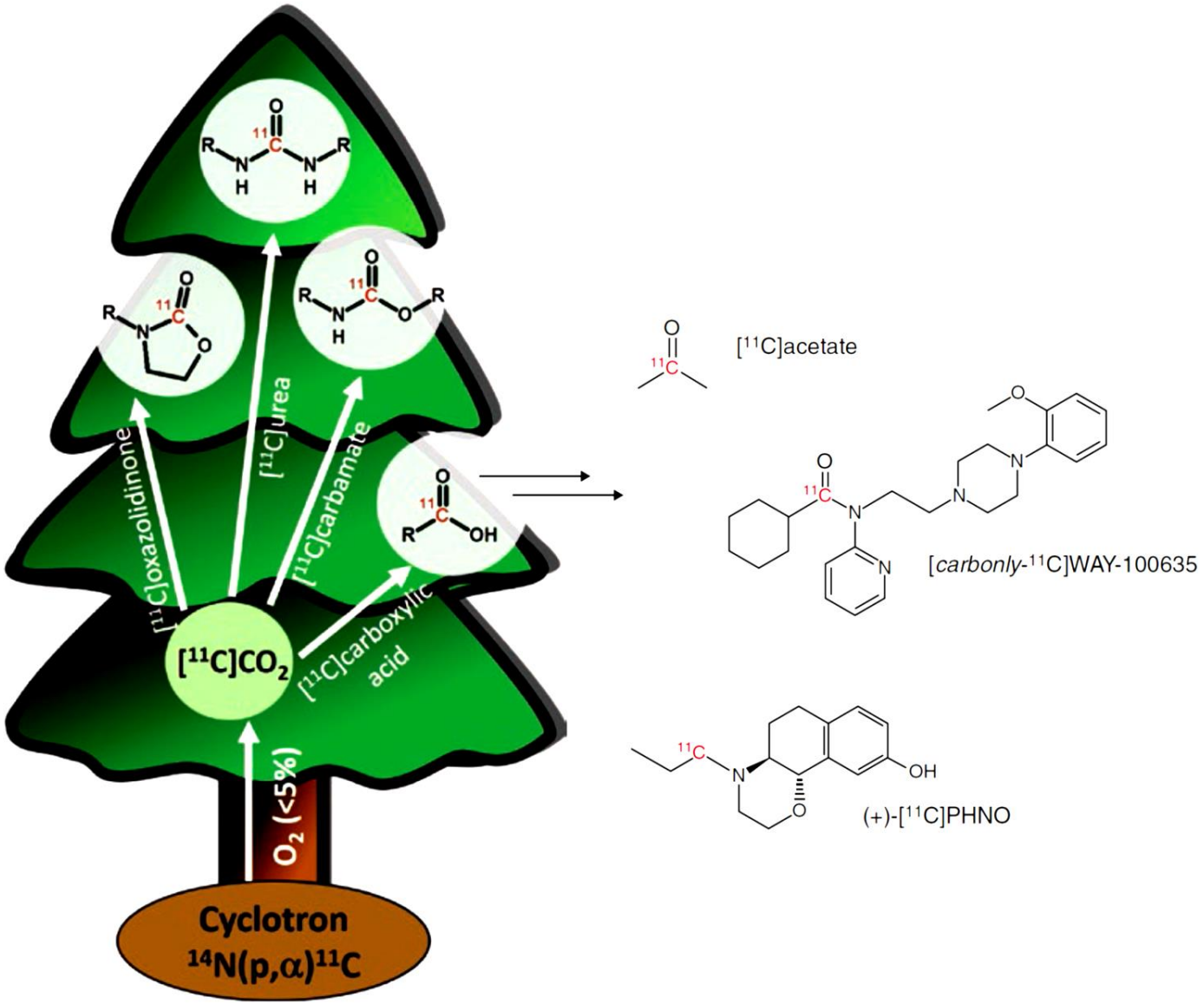
Radiochemical synthesis of [^{11}C]MET





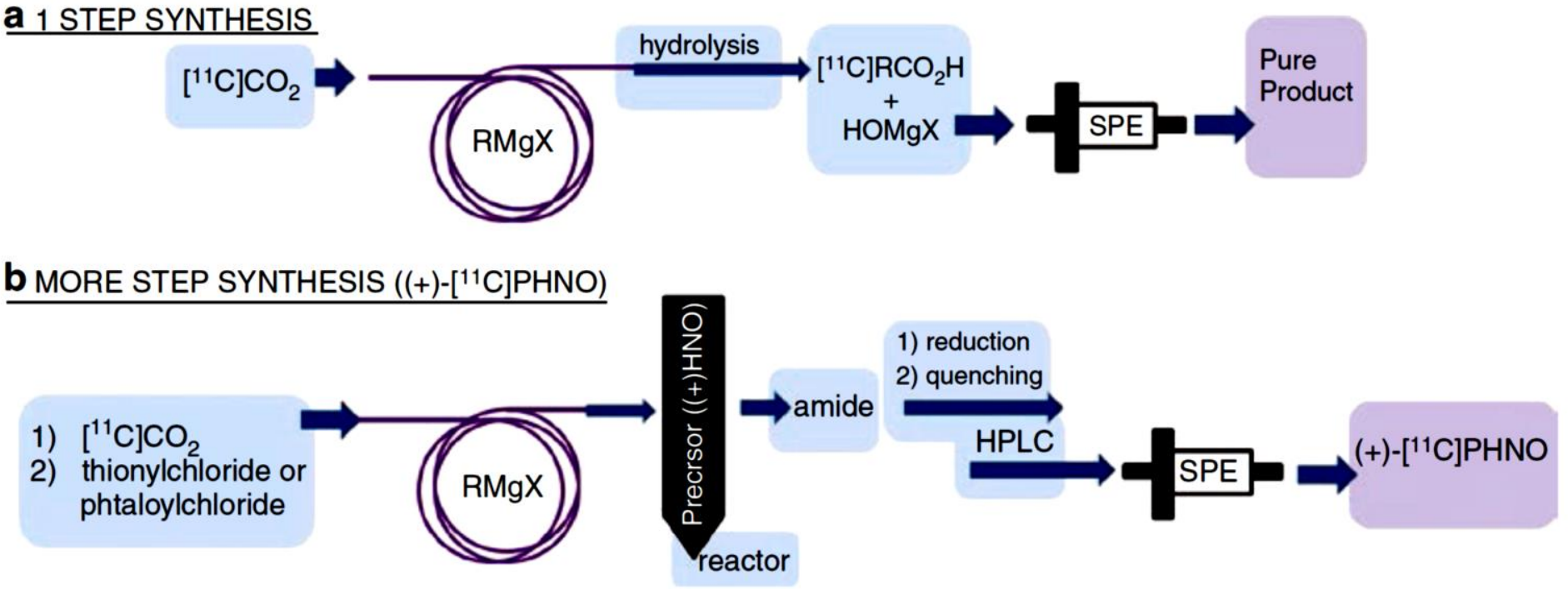
Article *in* Neurologia medico-chirurgica · December 2013

Reaction pathways to $[^{11}C]CO_2$ fixation products yielding in high oxidation state functional groups

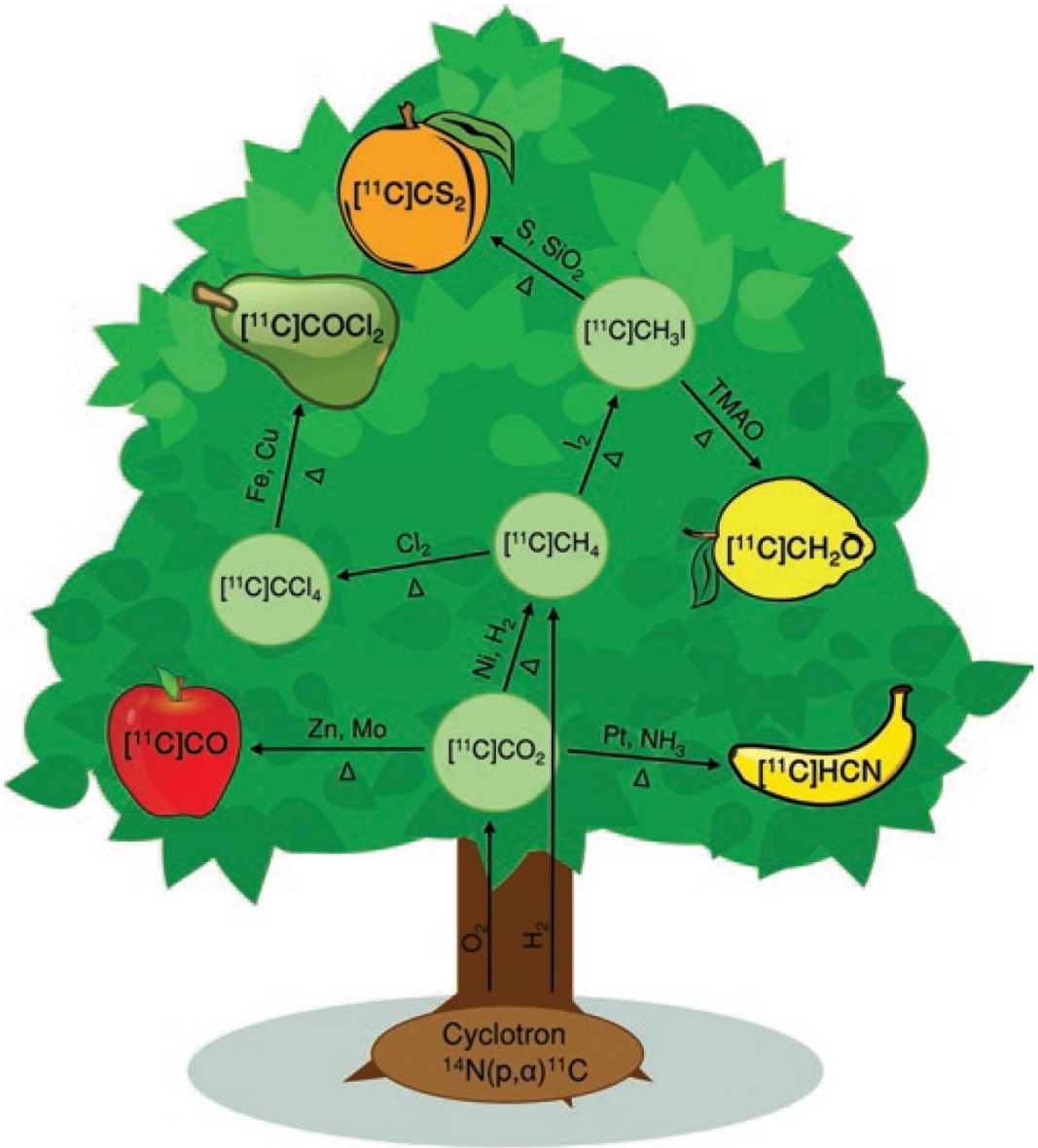


1. **Grignard Reactions in Carbon-11 Radiochemistry (In-Loop)**
2. **Moisture Sensitivity, Solvents, and Preparation**
3. **Technical Considerations: Reaction Vessels Versus In-Loop Syntheses for Grignard**

Scheme of in-loop syntheses for (**a**) a one-step reaction and (**b**) a multistep synthesis of (+)-[^{11}C]PHNO

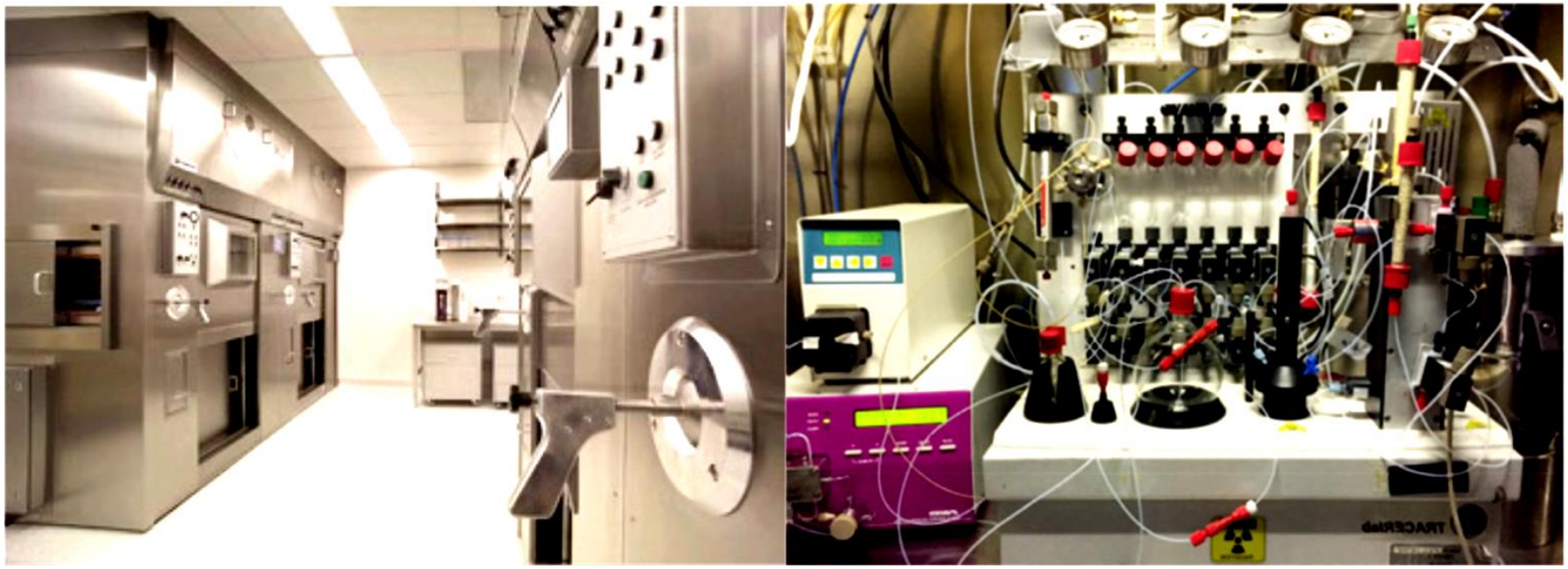


Overview of Other Methodologies for the Production of ^{11}C-Labeled Radiotracers



Reaction pathways to less-common carbon-11 precursors

Automatical synthesis equipment in lead-shielded fume hoods



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Automatical synthesis equipment in lead-shielded fume hoods

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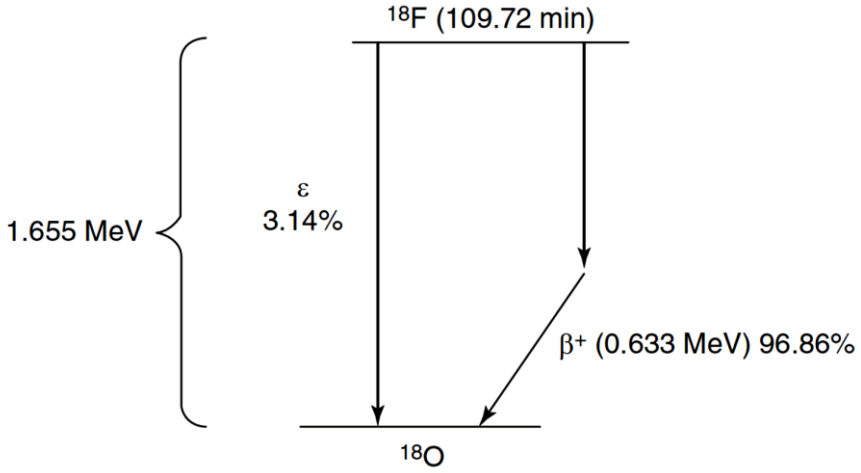
The Radiopharmaceutical Chemistry of Fluorine-18: Nucleophilic Fluorinations

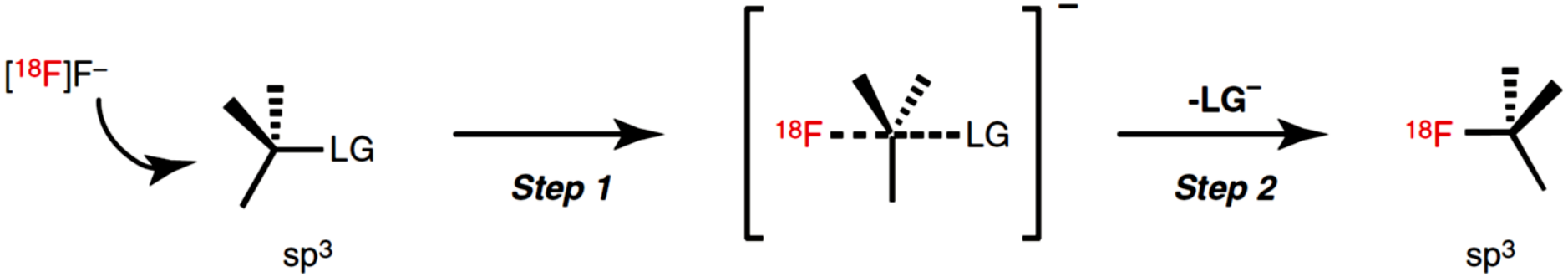
Introduction of Fluorine-18

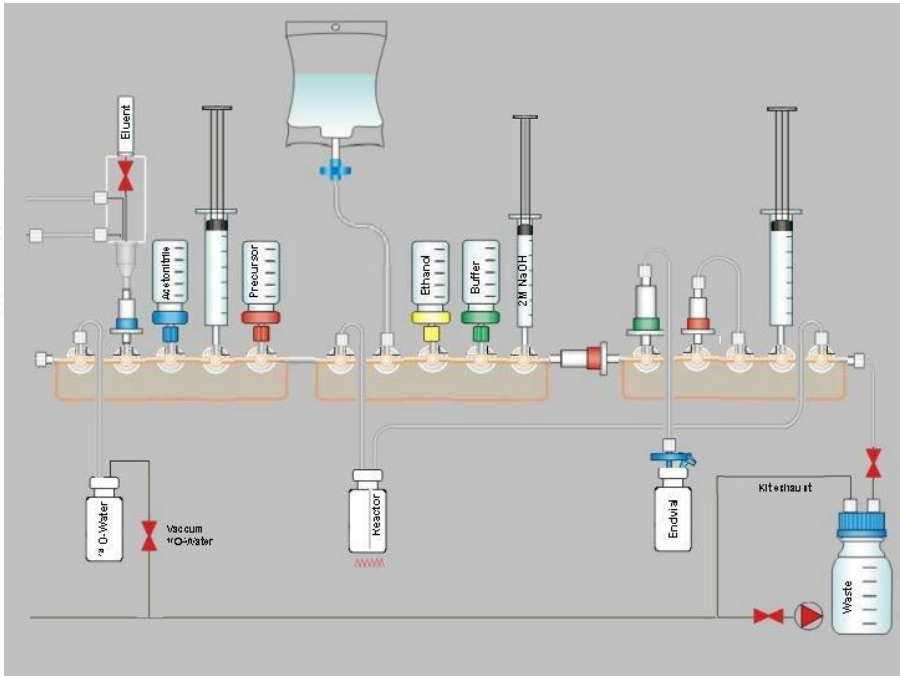
Decay scheme of ^{18}F



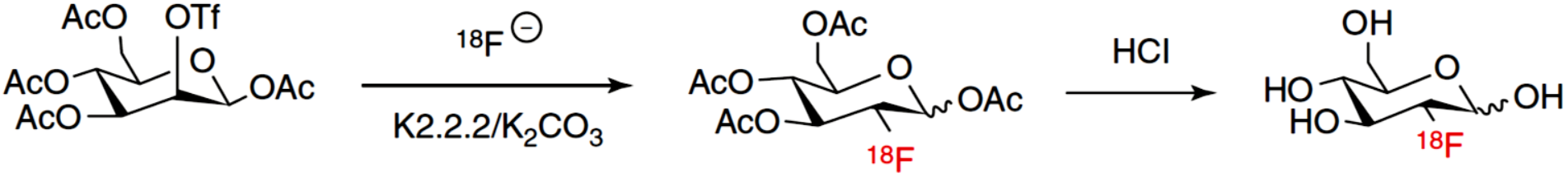
1. **Nucleophilic ^{18}F-Substitution**
2. **General Aspects of ^{18}F-Labeling**
3. **^{18}F-Preprocessing**
4. **Aliphatic ^{18}F-Substitution**

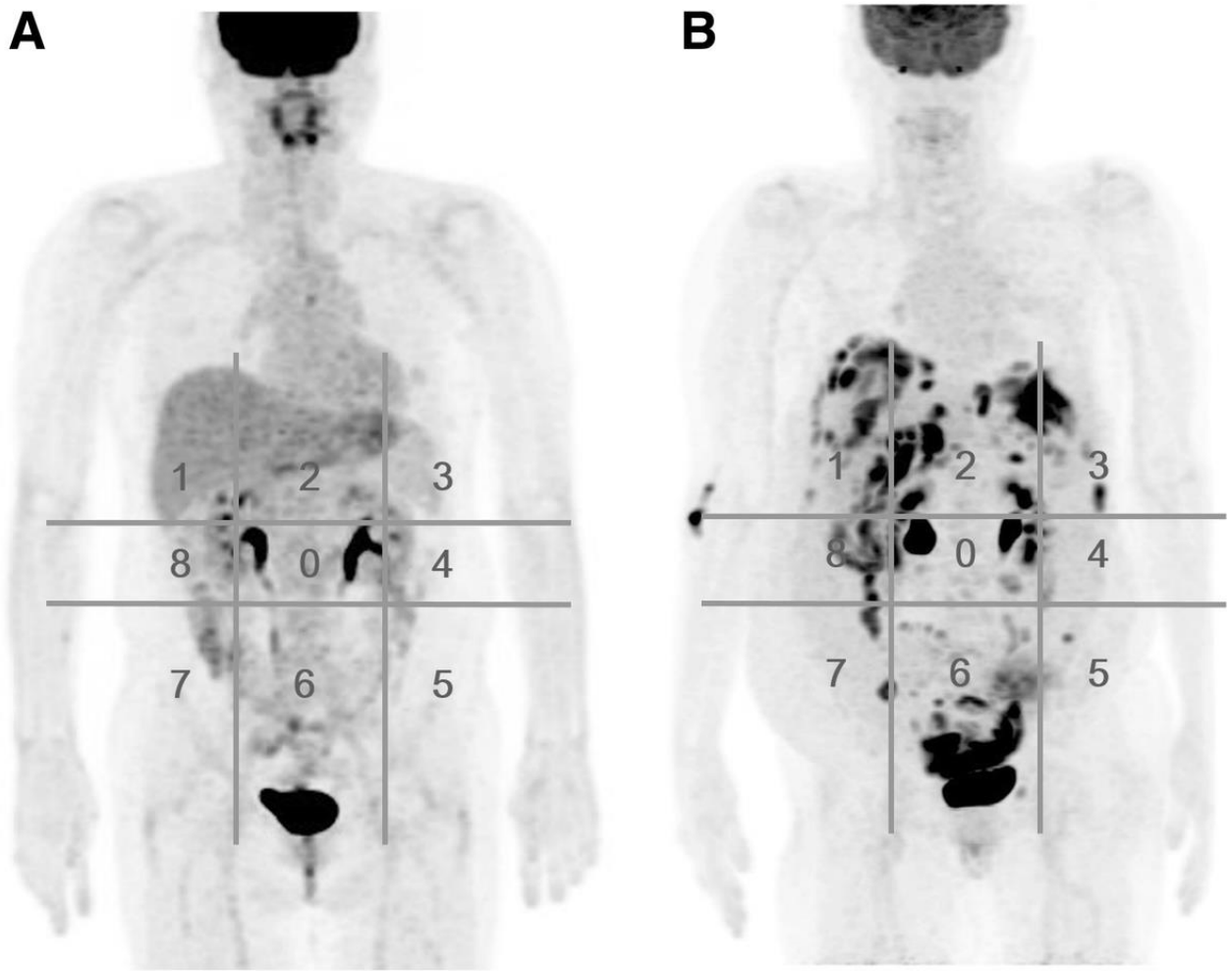
SN2 mechanism with Walden inversion





Nucleophilic synthesis – of [^{18}F]FDG





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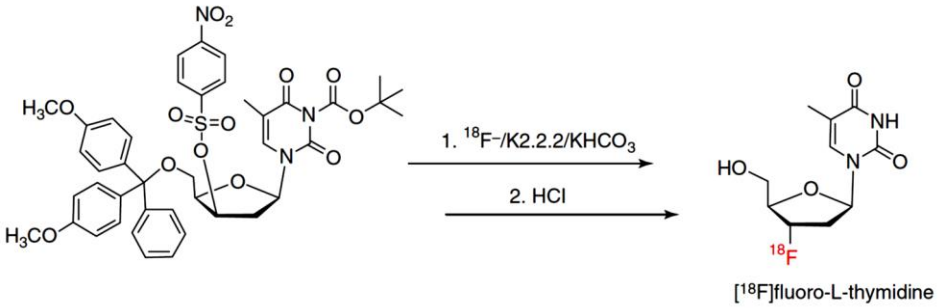
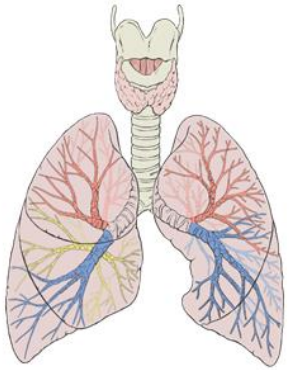
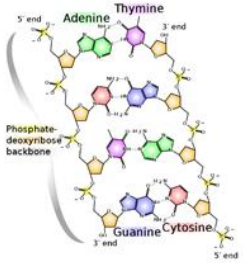
Synthesis of [^{18}F]FLT from the corresponding precursor using a nosyl leaving group and *tert*butoxycarbonyl and dimethoxytrityl protecting groups for the amide and hydroxyl, respectively



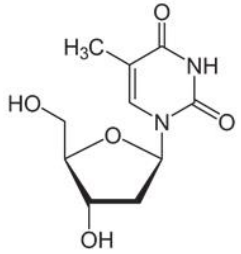
Early Response Assessment to Targeted Therapy using ^{18}F-FLT-PET/CT in Lung Cancer



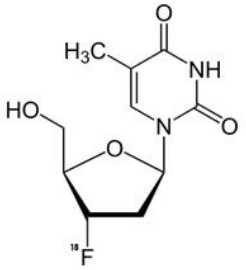
FLT indicates changes in tumor cell proliferation



DNA

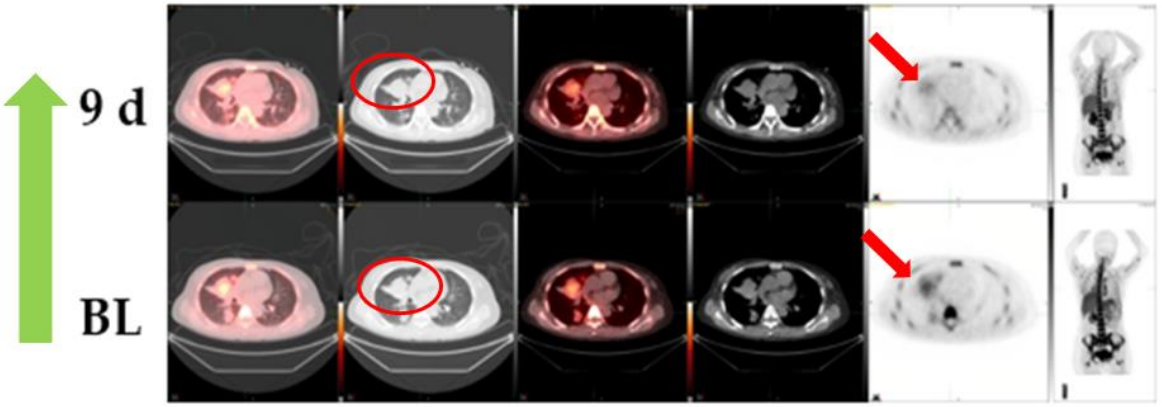


Thymidine



3′-deoxy-3′[(18)F]-fluorothymidine (FLT)

Baseline → 9 day CT vs FLT-PET imaging post targeted therapy



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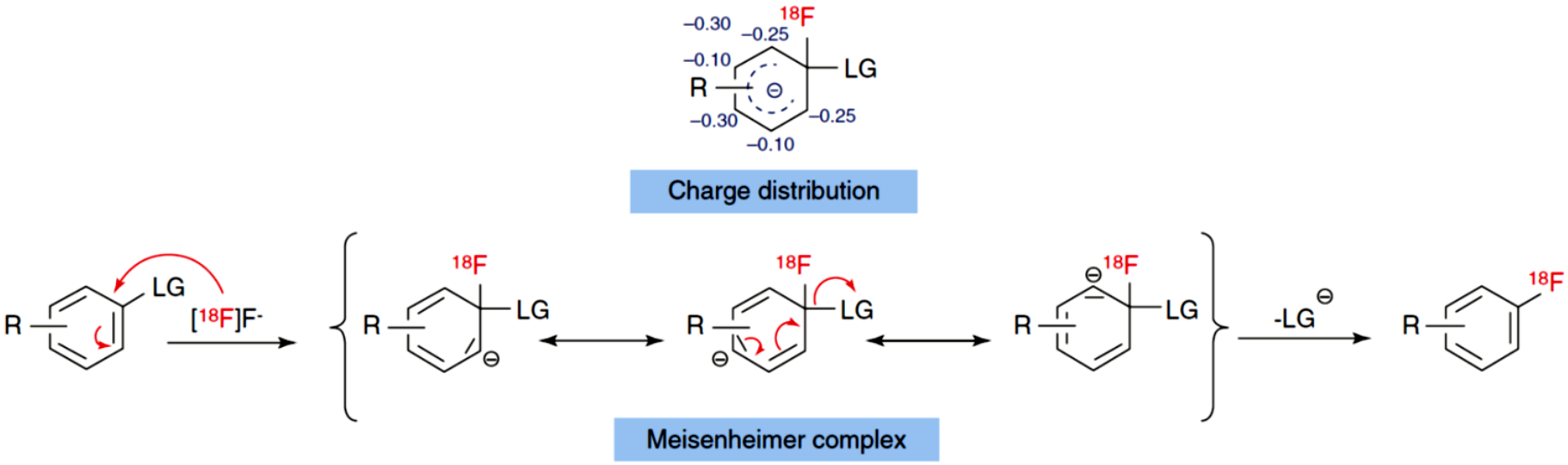
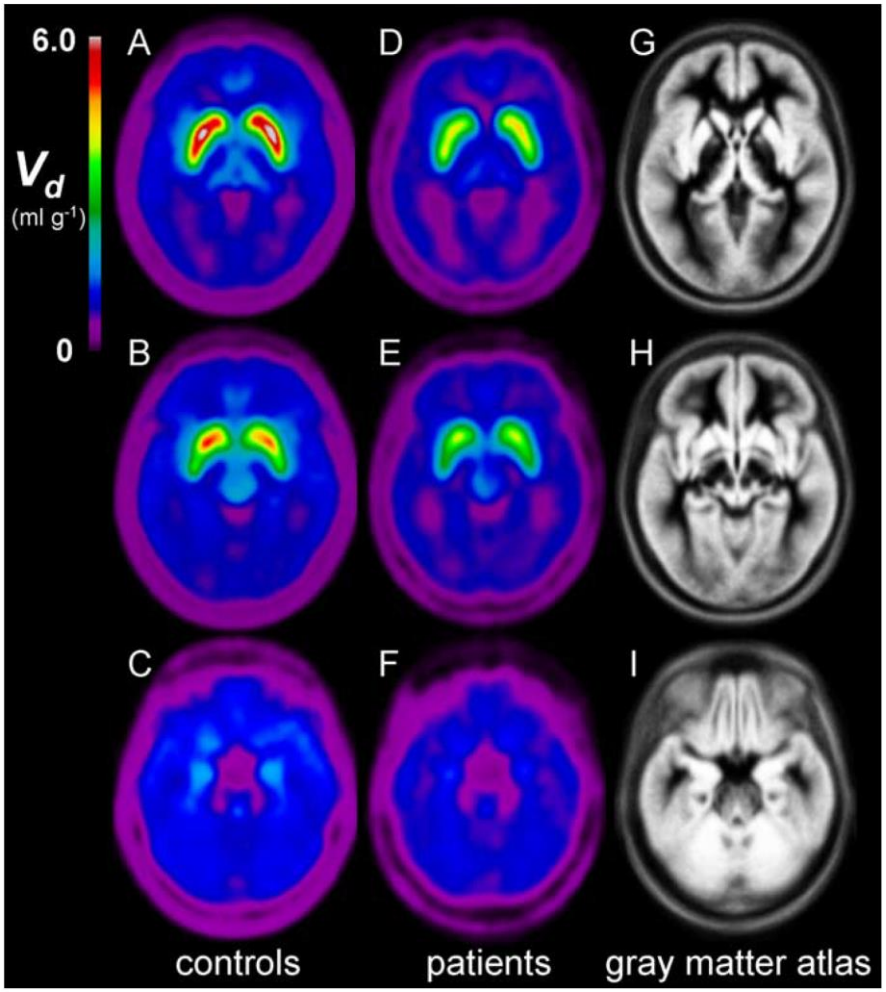
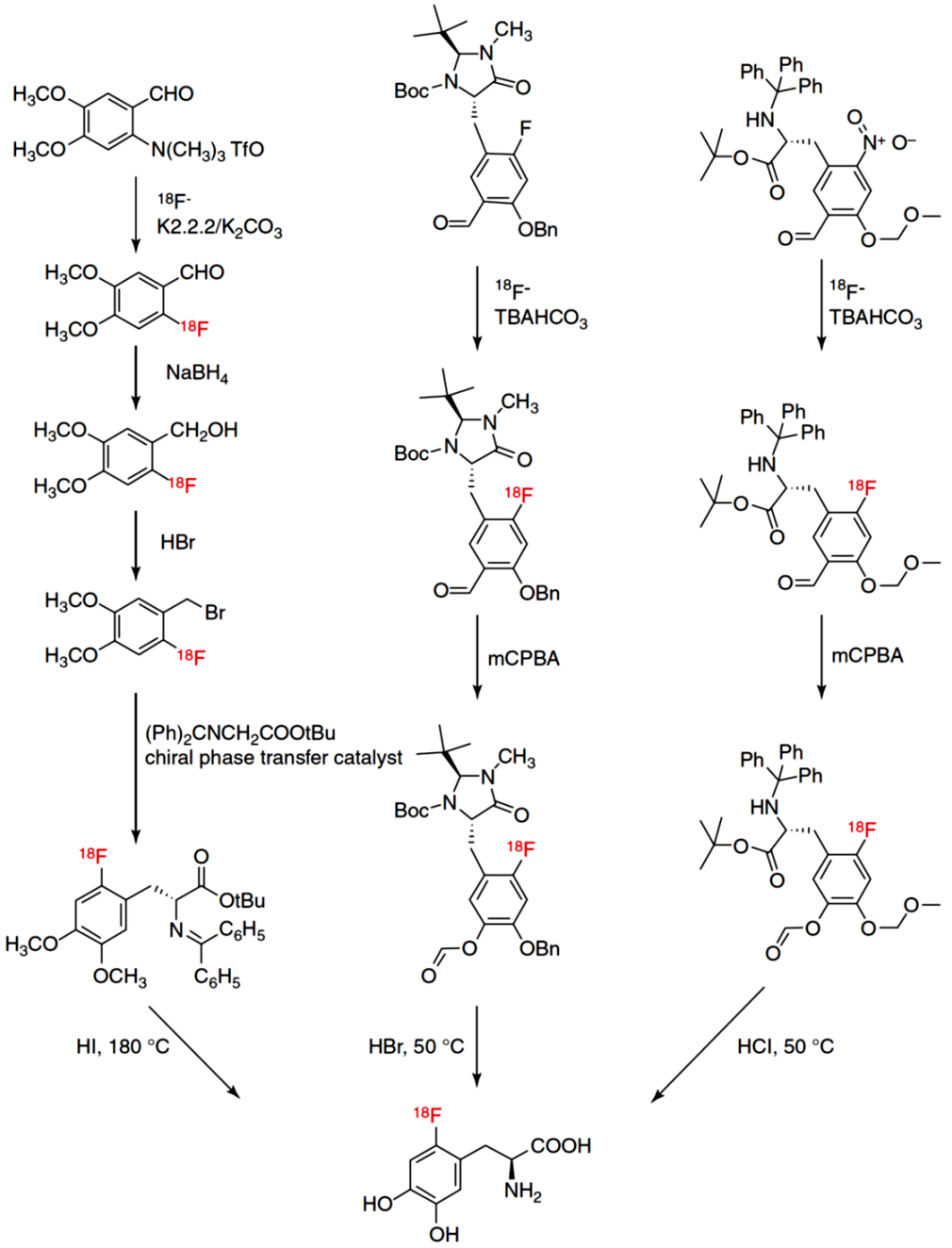
Synthesis of ^{18}F-Labeled Arenes by Aromatic Nucleophilic ^{18}F-Substitution (SNAr)



Aromatic nucleophilic substitution (S_NAr)

Three multistep, nucleophilic syntheses of 6-[^{18}F]FDOPA





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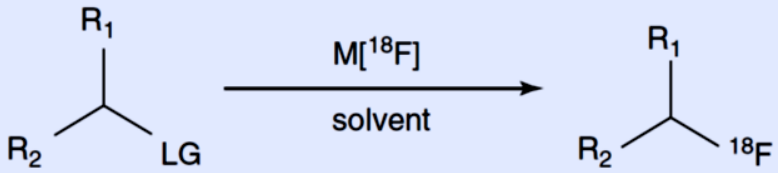
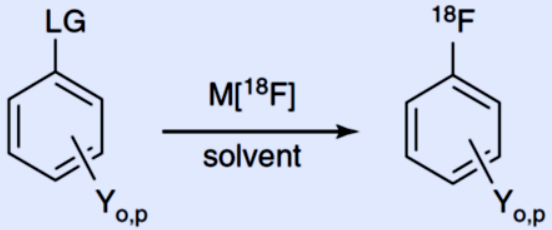
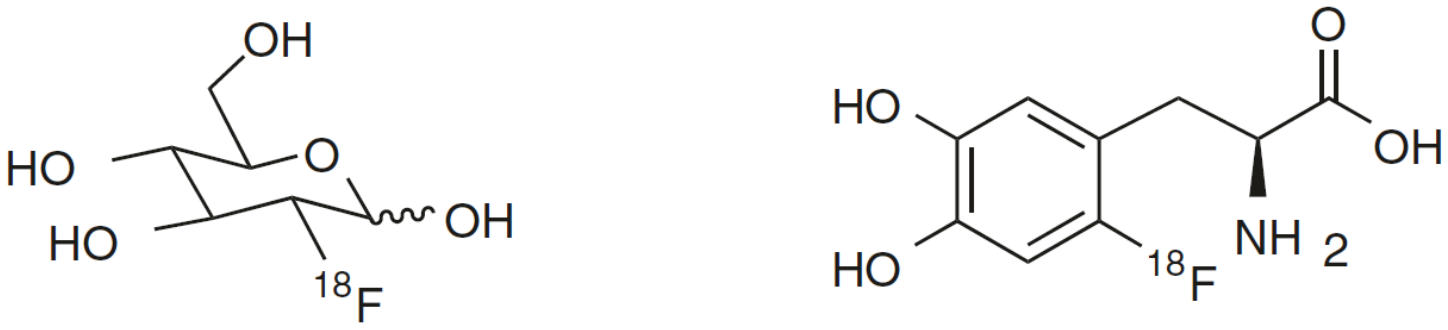
Prerequisites for nucleophilic ^{18}F-substitutions

Aliphatic ^{18}F-substitution	Aromatic ^{18}F-substitution
	
LG = Cl, Br, I, sulfonates	LG = Cl, Br, I, F, NO_2 [35], $(CH_3)_3N^+$ [36], Ar_2S^+ [37], ArI^+ [38], IL_2 [39, 40], $I(OAc)_2$ [41], ArSO [42], ArSeO [43], N-arylsydnones [44]
R_1 = alkyl, aryl; R_2 = alkyl, aryl, H	Y = COOR, COR, CHO, CN, NO_2
M = Cs^+, Rb^+, R_4N^+, K2.2.2./K^+, R = alkyl	M = Cs^+, Rb^+, R_4N^+, K2.2.2./K^+ R = alkyl
Solvent: acetonitrile, DMF, DMSO, *tert*-butanol/acetonitrile	Solvent: DMSO, DMF, DMA

LG = leaving group, *Y* = activating group, *DMSO* = dimethyl sulfoxide, *DMF* = *N,N*-dimethylformamide, *DMA* = *N,N*-dimethylacetamide

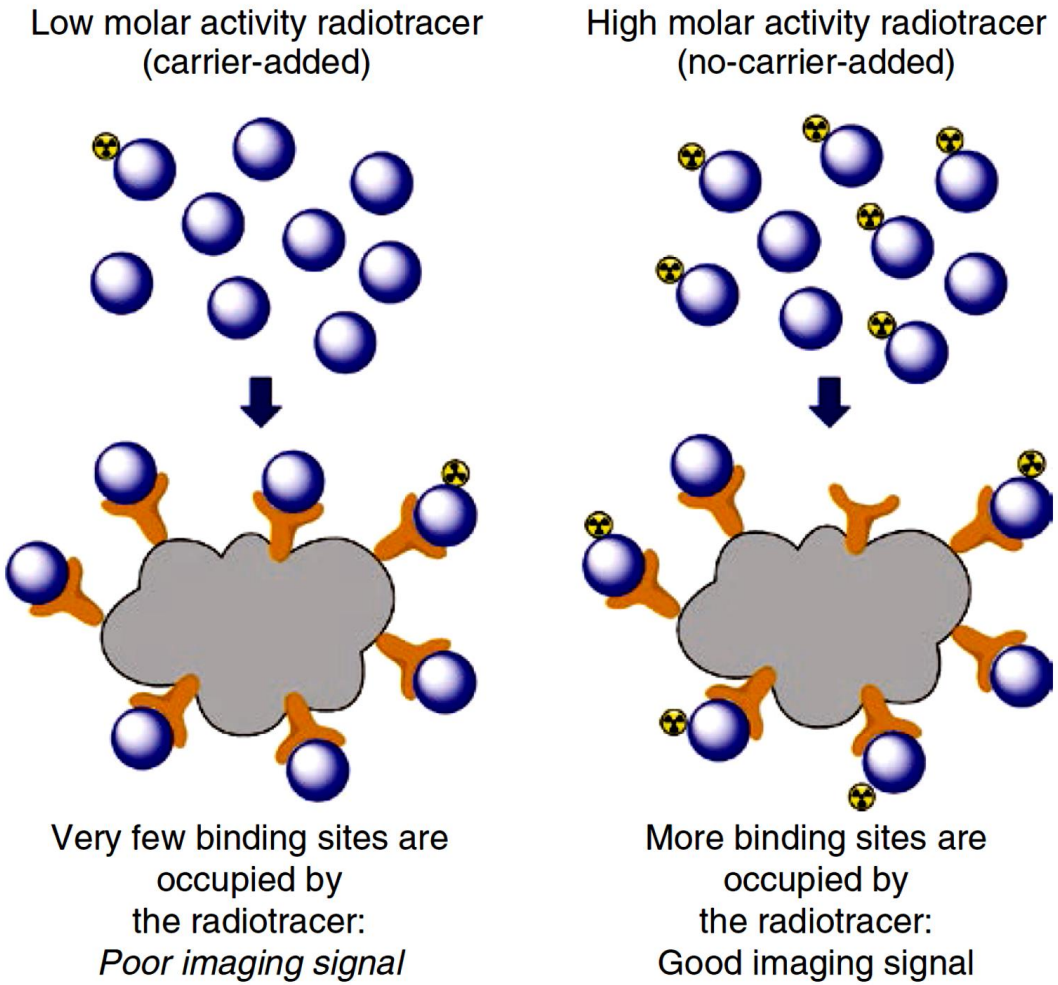
The Radiopharmaceutical Chemistry of Fluorine-18: Electrophilic Fluorinations

The Fundamentals of Electrophilic Radio-fluorination Chemistry



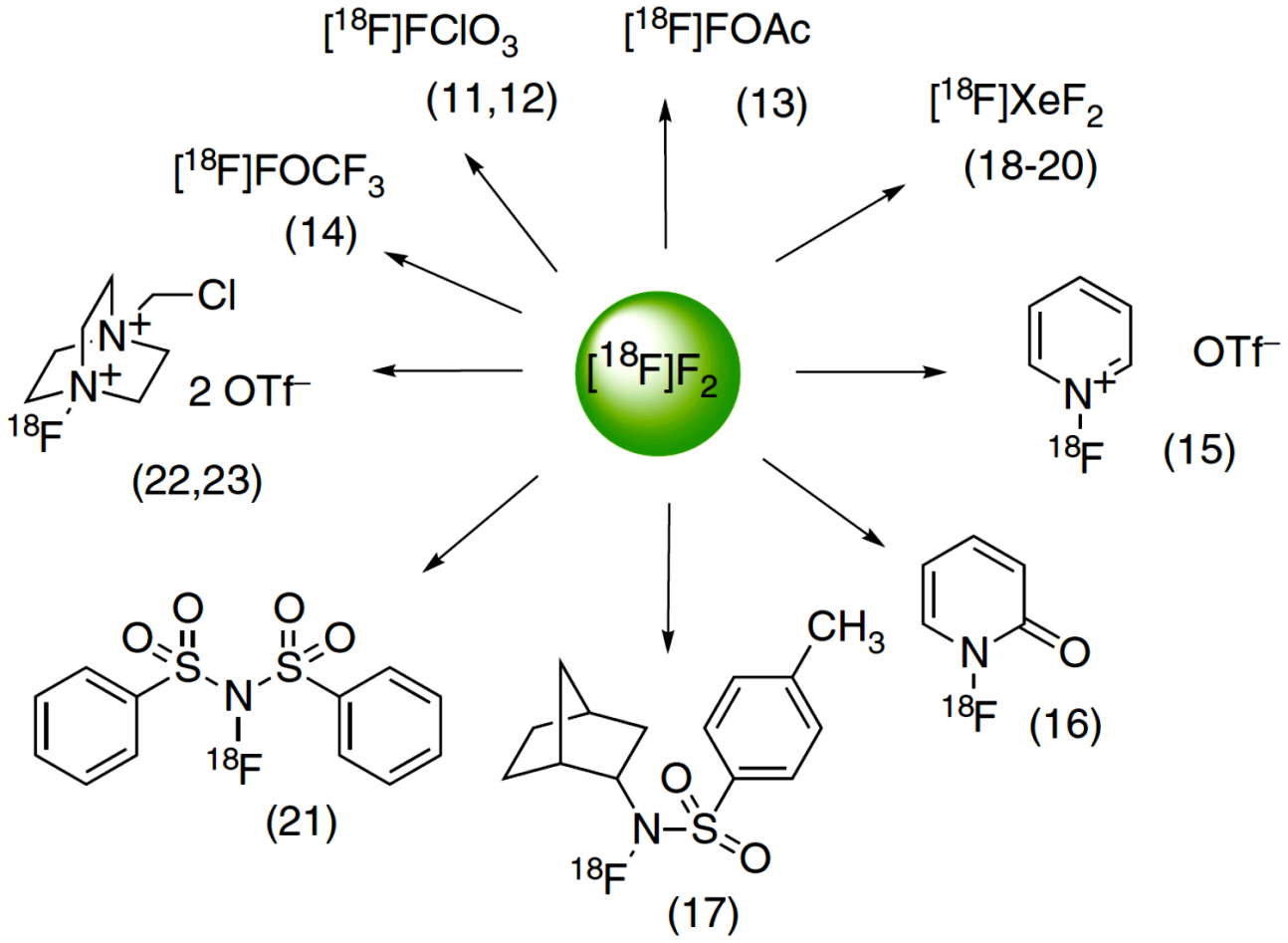
Structures of 2-[^{18}F]FDG (left) and 6-[^{18}F]F-DOPA (right)

The Fundamentals of Electrophilic Radio-fluorination Chemistry



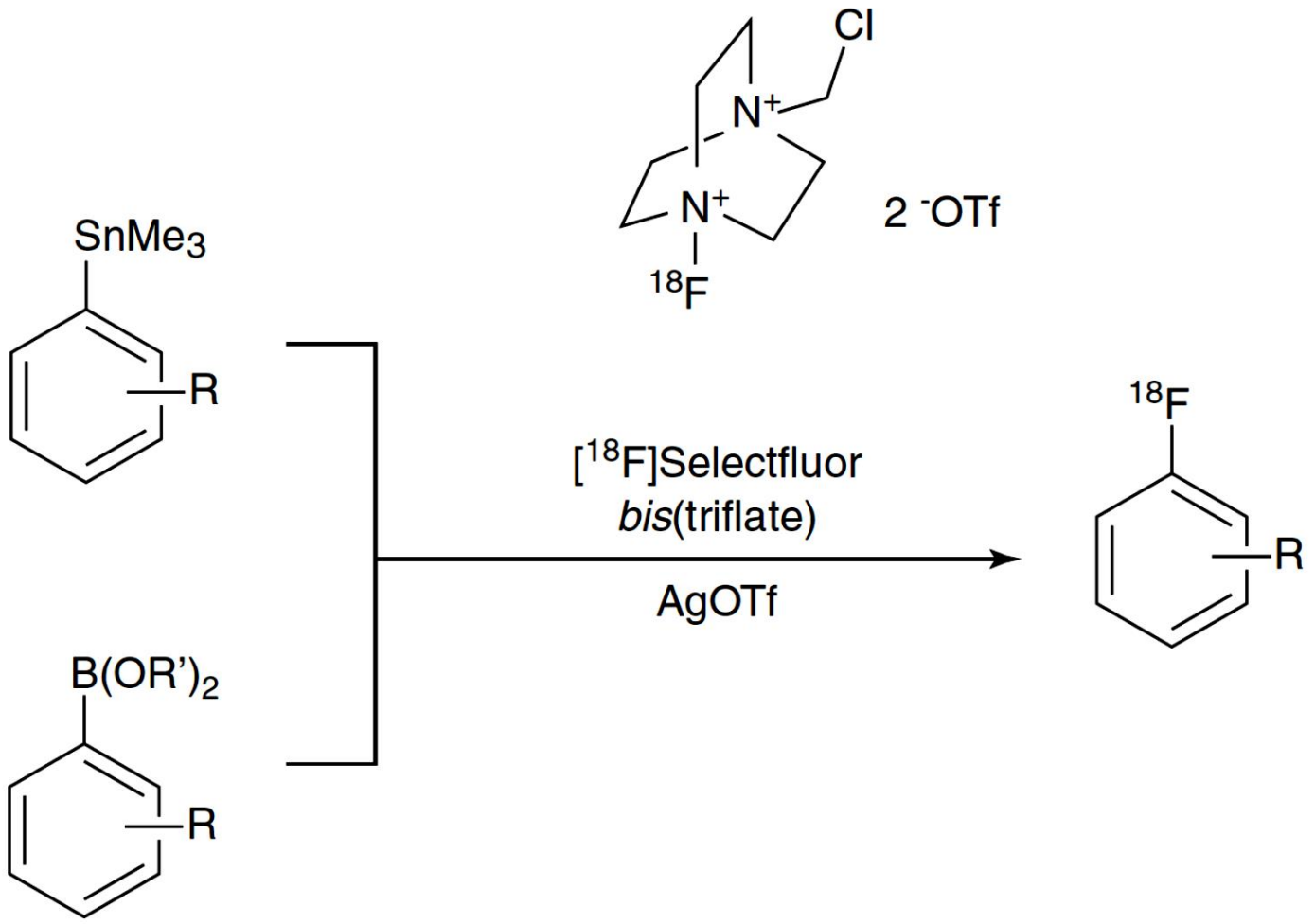
Influence of molar activity on the quality of the imaging signal

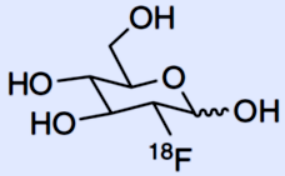
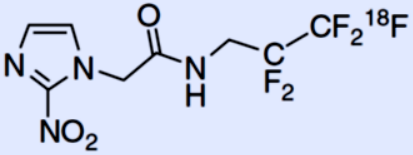
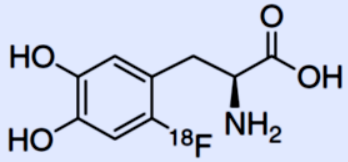
Secondary Labeling Precursors and Building Blocks for Electrophilic Radio-fluorinations with ^{18}F

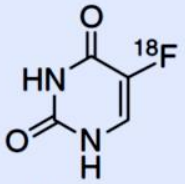
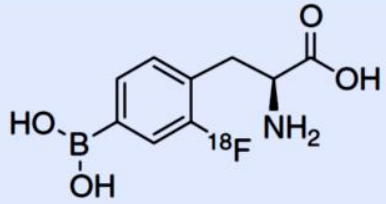
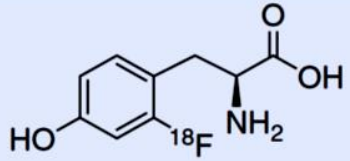


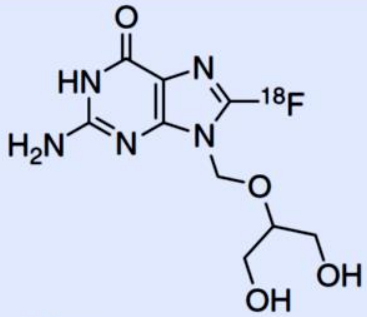
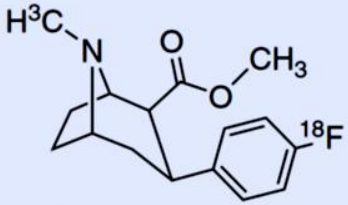
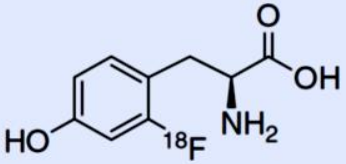
Secondary precursors for electrophilic ^{18}F-labeling derived from $[^{18}F]F_2$

Ag-mediated radiofluorinations with [^{18}F]Selectfluor® *bis*(triflate)



Radiopharmaceutical	Synthesis method	Application	References
 2-[^{18}F]Fluoro-deoxyglucose (2-[^{18}F]FDG) 2-[^{18}F]Fluorodeoxyglucose (2-[^{18}F]FDG)	Addition of [^{18}F]F_2, [^{18}F]XeF_2, or [^{18}F]FOAc to the double bond in triacetoxyglucal precursor	PET imaging of glucose metabolism	[1] ([^{18}F]F_2) [34] ([^{18}F]XeF_2) [35] ([^{18}F]FOAc)
 [^{18}F]-2-(2-Nitro-1[H]-imidazole-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)-acetamide ([18F]EF5) [^{18}F]-2-(2-Nitro-1[H]-imidazole-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)-acetamide ([^{18}F]EF5)	Addition of [^{18}F]F_2 to the double bond in trifluoroallyl precursor	PET imaging of hypoxia	[36]
 6-[^{18}F]Fluoro-3,4-dihydroxy-L-phenylalanine (6-[^{18}F]F-DOPA) 6-[^{18}F]Fluoro-3,4-dihydroxy-L-phenylalanine (6-[^{18}F]F-DOPA)	Direct electrophilic radiofluorination with [^{18}F]F_2 or [^{18}F]FOAc	PET imaging of dopamine metabolism	[22] ([^{18}F]F_2) [37] ([^{18}F]FOAc)
	^{18}F-fluorodemetallation using HgR_2 or $SnMe_3$ precursors with [^{18}F]F_2 or [^{18}F]FOAc		[25, 26] ([^{18}F]FOAc, HgR_2) [27, 29] ([^{18}F]F_2, $SnMe_3$) [29] ([^{18}F]FOAc, $SnMe_3$)

Radiopharmaceutical	Synthesis method	Application	References
 5-[^{18}F]Fluorouracil 5-[^{18}F]Fluorouracil	Direct electrophilic radiofluorination with [^{18}F]F_2 or [^{18}F]FOAc	Tumor imaging	[38, 39] ([^{18}F]F_2) [40] ([^{18}F]FOAc)
 4-Borono-2-[^{18}F]fluoro-L-phenylalanine 4-Borono-2-[^{18}F]fluoro-L-phenylalanine	Direct electrophilic radiofluorination with [^{18}F]FOAc	PET imaging of amino acid metabolism	[41, 42]
 2-[^{18}F]Fluoro-L-tyrosine 2-[^{18}F]Fluoro-L-tyrosine	^{18}F-fluorodestannylation with [^{18}F]F_2	PET imaging of amino acid metabolism	[31]

Radiopharmaceutical	Synthesis method	Application	References
 8-[^{18}F]Fluoroganciclovir 8-[^{18}F]Fluoroganciclovir	Direct electrophilic radiofluorination with [^{18}F]F_2	PET imaging of HSV1-tk expression	[43]
 [^{18}F]CFT [^{18}F]CFT	^{18}F-fluorodestannylation with [^{18}F]FOAc	PET imaging of dopamine metabolism	[44]
 [^{18}F]Fluorometaraminol [^{18}F]Fluorometaraminol	^{18}F-fluorodestannylation with [^{18}F]F_2	PET imaging of cardiac sympathetic nerve integrity	[30]

The Radiopharmaceutical Chemistry of Fluorine-18: Next-Generation Fluorinations

Comparison of the bond dissociation energies (kJ/mol) of the bond between fluorine and carbon as well as some heteroatoms

Bond	Bond dissociation energy (kJ/mol)
B-F	732
C-F	514
N-F	290
Al-F	675
Si-F	576
P-F	405

Thank you for your attention!!