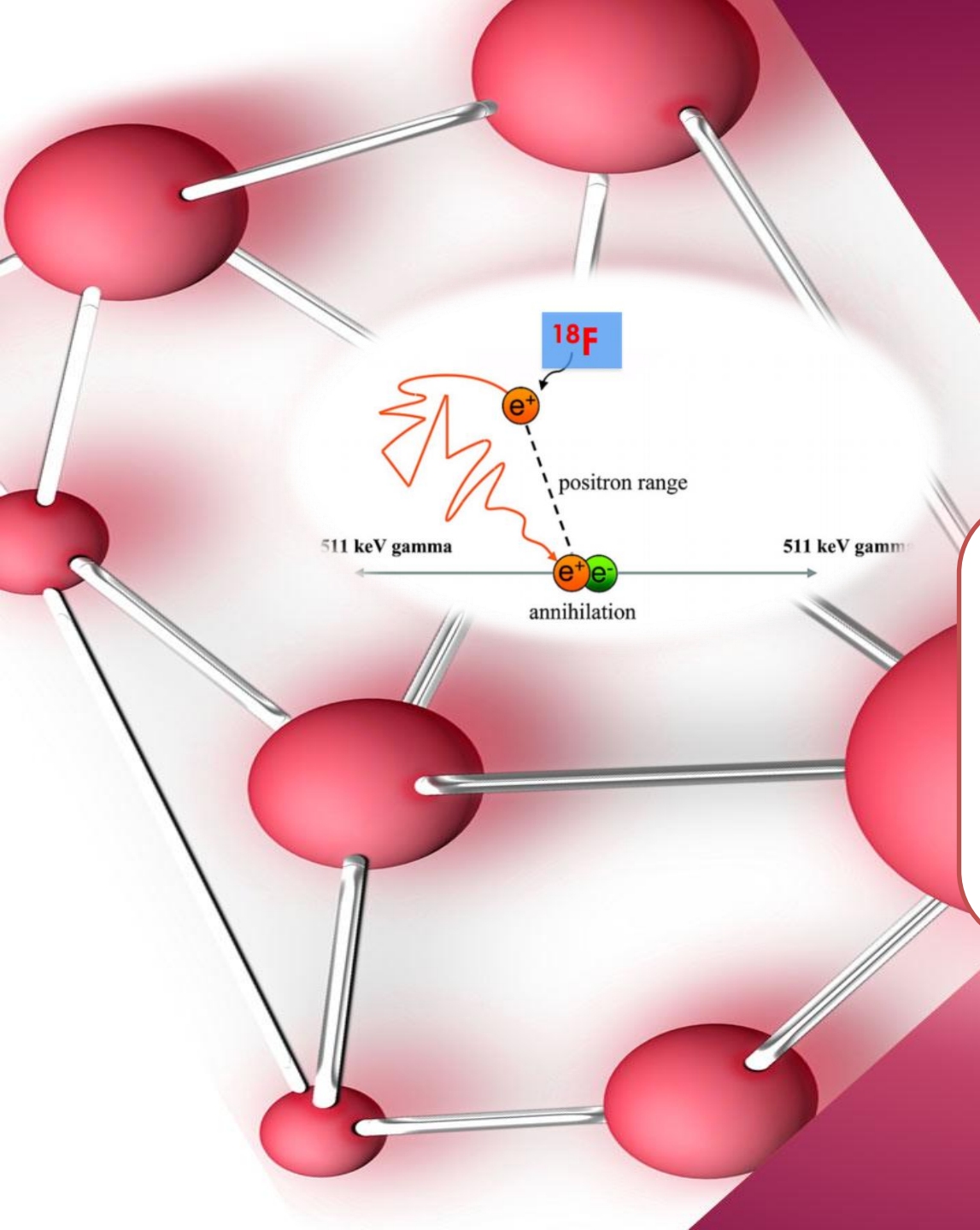

University Institute of Positron Emission Tomography

Skopje, Macedonia

The role of chemistry in the development of the radiosynthesis methods for fluorine-18 radiopharmaceuticals

Maja Chochevska

26th Congress of SCTM - Sep, 2023


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Универзитетски
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за позитронско
емисиона
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Typical workflow of radiopharmaceuticals production

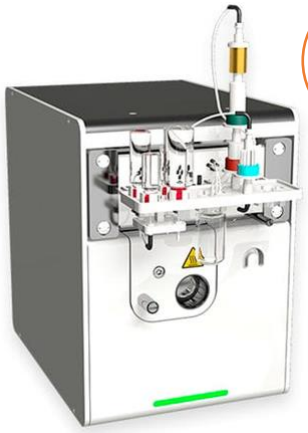
Radionuclide production

~ 0.5-1h

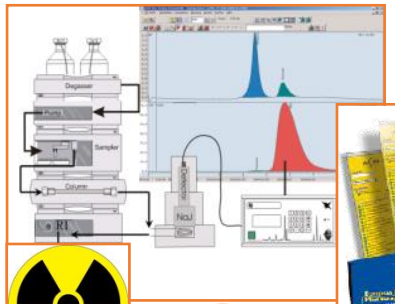
Time Required?

lasts 2-3 hours

Radiochemical synthesis



30 min



30 min

Quality control

Dispensing

~ 0.5-1h

Equipment for the Production of PET radionuclide

Targets for production of F-18, C-11 and N-13
(with possibility of additional embedding of solid targets)

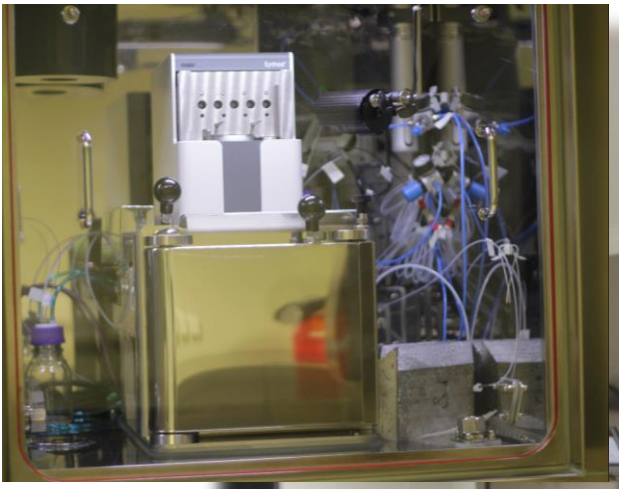
Isotope	Half-life	Production[a]	Mode of decay	Common source
^{18}F	109.8 min	$^{18}O(p,n)^{18}F$	β^+ (97%), EC (3%)	Cyclotron
^{11}C	20.4 min	$^{14}N(p,\alpha)^{11}C$	β^+ (100%)	Cyclotron
^{13}N	10 min	$^{16}O(p,\alpha)^{13}N$	β^+ (100%)	Cyclotron
^{15}O	2 min	$^{15}N(p,n)^{15}O$	β^+ (100%)	Cyclotron
^{124}I	4.2 d	$^{124}Te(p,n)^{124}I$	β^+ (23%), EC (77%)	Cyclotron
^{44}Sc	4.0 h	$^{44}Ti/^{44}Sc$	β^+ (94%), EC (6%)	Generator[b]
^{64}Cu	12.7 h	$^{64}Ni(p,n)^{64}Cu$	β^+ (17%), EC (44%), β^- (39%)	Cyclotron[c]
^{68}Ga	67.7 min	$^{68}Ge/^{68}Ga$	β^+ (89%), EC (11%)	Generator[d]
^{82}Rb	1.3 min	$^{82}Sr/^{82}Rb$	β^+ (95%), EC (5%)	Generator
^{86}Y	14.7 h	$^{86}Sr(p,n)^{86}Y$	β^+ (32%), EC (68%)	Cyclotron
^{89}Zr	78.4 h	$^{89}Y(p,n)^{89}Zr$	β^+ (23%), EC (77%)	Cyclotron

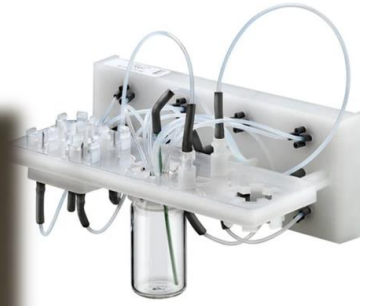
F-18: physical and nuclear characteristics

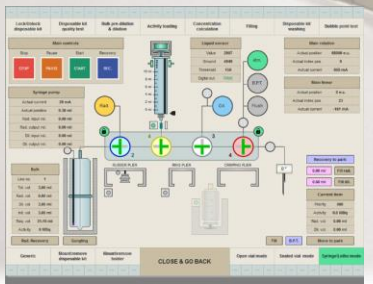
- ✓ Low positron energy and short range in tissue (high resolution)
- ✓ 97% β+ decay
- ✓ high specific activity
- ✓ can be produced in large amount in a cyclotron (>10 Ci)
- ✓ can be labeled in high radiochemical yields
- ✓ allow transportation from production site to PET centers ($T_{1/2}$= 109.7 min)

Cyclotron - 16,5 MeV GE PET Trace

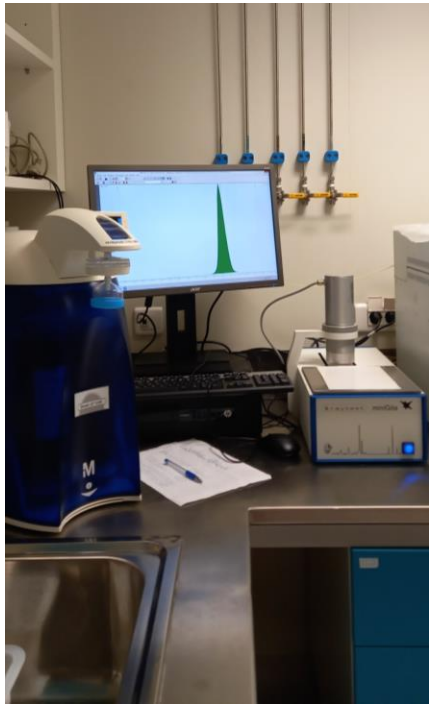
Radiochemistry Requirements







Radiochemistry Requirements



QC Laboratories

Fluorine-18 chemistry

^{20}Ne(d,α)18F

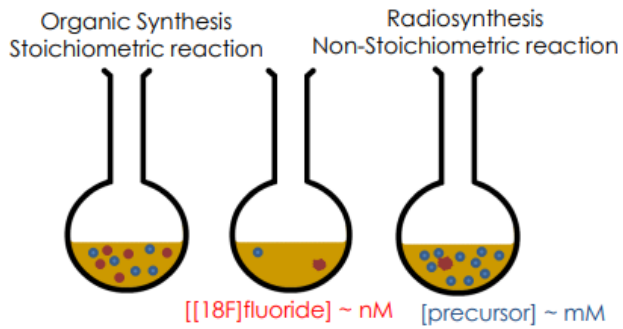
A solid target is bombarded and fluorine-18 is obtained in the form of molecular fluorine gas

⇩

$[^{18}F]F_2$

Electrophilic substitution

(Electrophilic radiofluorination)



^{18}O(p,n)18F

A liquid target is bombarded - enriched water with ^{18}O, and fluorine-18 is obtained in the form of fluoride anion

⇩

$[^{18}F]F^-$

Nucleophilic substitution

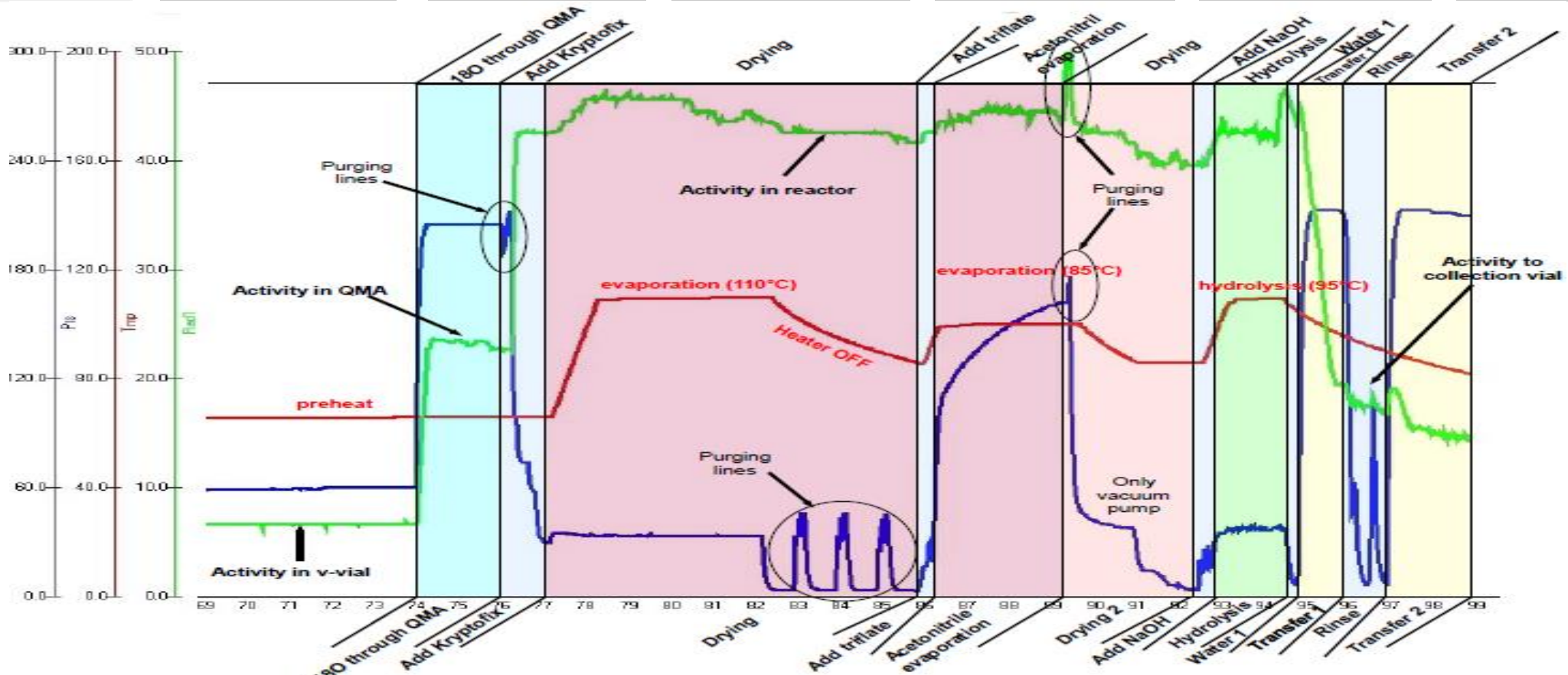
(Nucleophilic radiofluorination - S_N2 or S_NAr)

The utilization of nucleophilic $[^{18}F]F^-$ ions in the F-18 radiopharmaceutical synthesis process has many advantages over fluorine gas $[^{18}F]F_2$

Electrophilic ^{18}F-fluorination	Nucleophilic ^{18}F-Fluorination
$[^{18}F]F_2$ in gas form - possibility of contamination	$[^{18}F]F^-$ in liquid form - less chance of contamination
Molar activity typically in the range of 100-500 MBq/μmol	High molar activity in the range of 500-5000 GBq/μmol
Radiochemical yield (RCY) up to 50% due to the presence of a non-radioactive atom [^{19}F]	Radiochemical yield (RCY) up to 90% as a result of direct binding to precursor molecules
Highly reactive fluorine-18 gas	Less reactive nature of fluorine-18
Several automated synthesis modules (GMP)	Numerous automated synthesis modules (GMP)

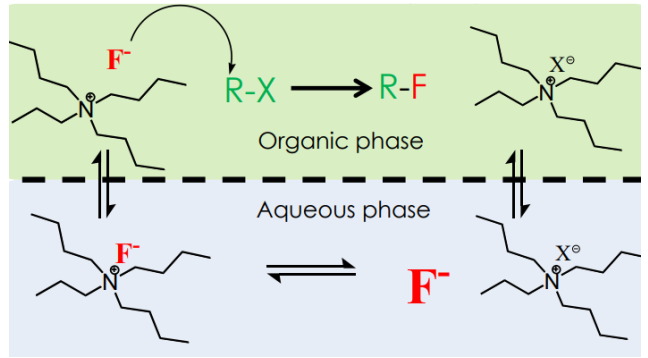
[^{18}F]-radiopharmaceuticals synthesis

1	2	3	4	5	6	7
Transfer of [^{18}F]F$^-$ from cyclotron to synthesizer	Transfer to QMA and trapping of [^{18}F]F$^-$	Elution of [^{18}F]F$^-$ to reaction vial and drying	Fluorination	Hydrolysis	Purification	Transferring to dispensing cell



Typical processing for preparation on $[^{18}F]F^-$ ions

Phase Transfer Catalysis (K2,2,2 or tetrabutylammonium carbonate) and azeotropic distillation in Radiochemistry?

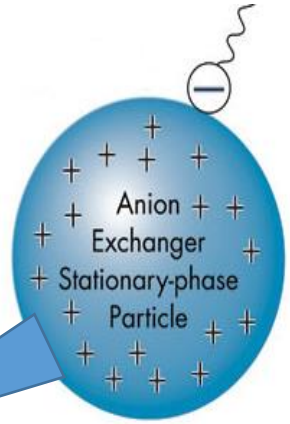


Role of K_2CO_3?

Base	pKb
K_2CO_3	3.8
$KHCO_3$	7.6
K^+ oxalate	10
H_2O	14

More basic

^{18}F - trapping

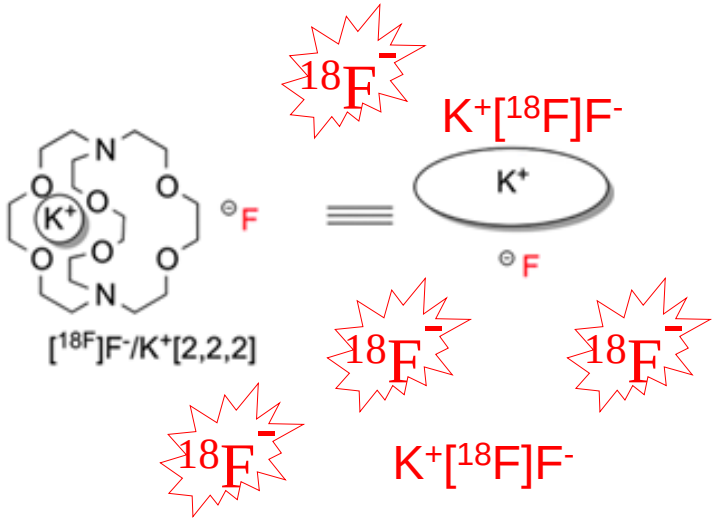


$K_{2,2,2}$; K_2CO_3 ; AcN

Elution

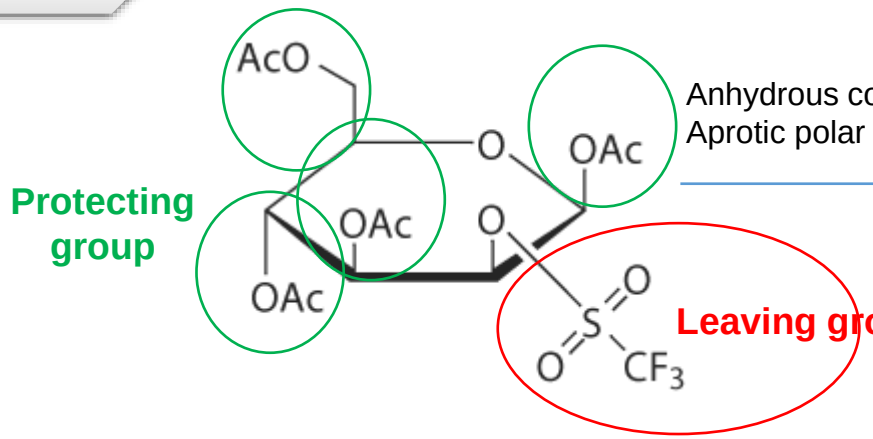
Azeotropic distillation

H_2O; AcN

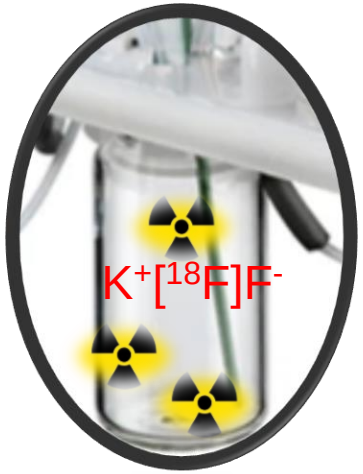


Waste $H_2{}^{18}O$ water collection vial

4 Fluorination

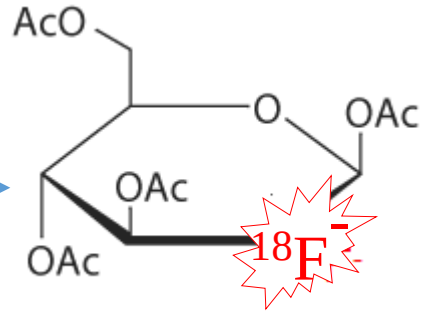


Anhydrous condition
Aprotic polar solvent



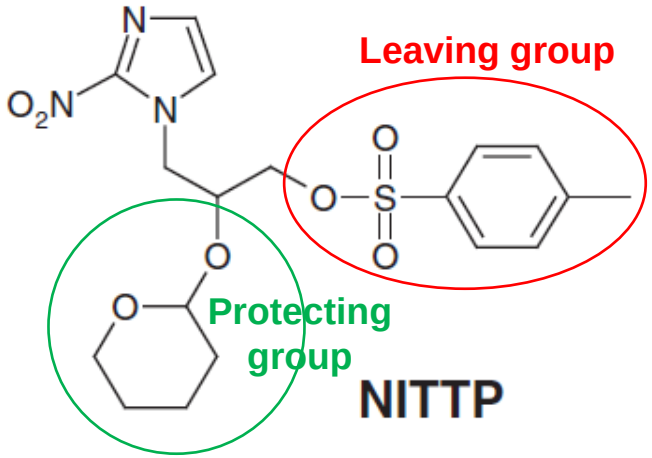
SN2 nucleophilic substitution

3 min, 85 ° C



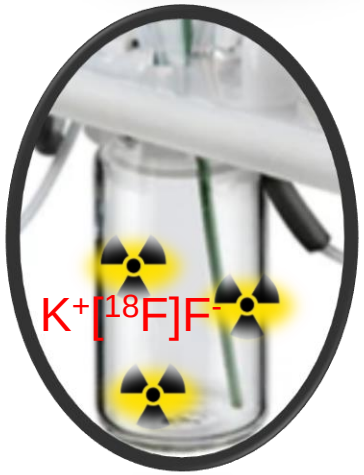
[18F] fluorinated intermediate

Mannose triflate
Precursor for [18F]FDG



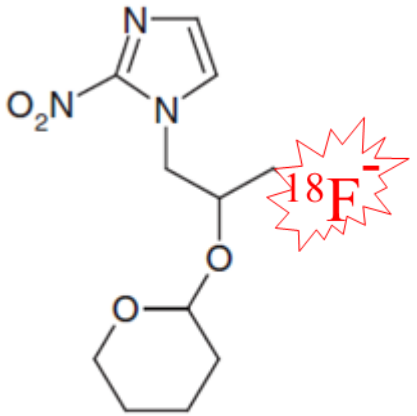
1H-imidazole-1-propanol, 2-nitro-β-[(tetrahydro-2H-pyran-2-yl)oxy]-, 4-methylbenzenesulfonate (ester)

Anhydrous condition
Aprotic polar solvent



SN2 nucleophilic substitution

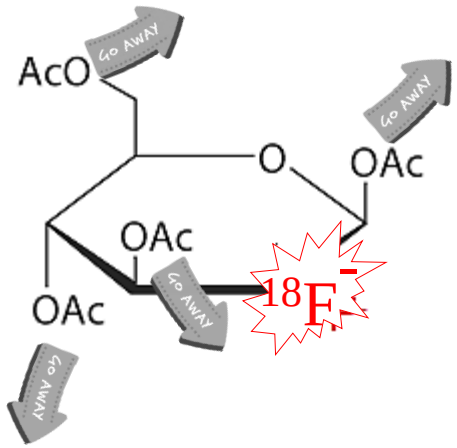
10 min, 120 ° C



[18F] fluorinated intermediate

Precursor for [18F]FMISO

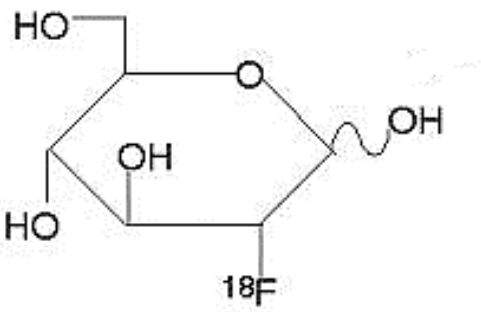
5 Removing protective groups



[^{18}F] fluorinated intermediate

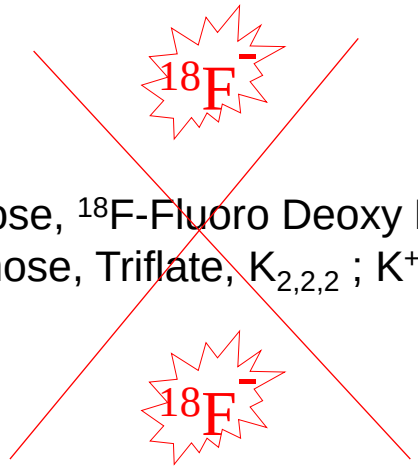
NaOH

Hydrolysis

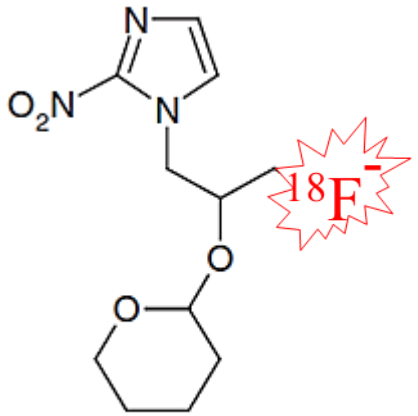


[^{18}F]Fluorodeoxyglucose ([^{18}F]FDG)

\+



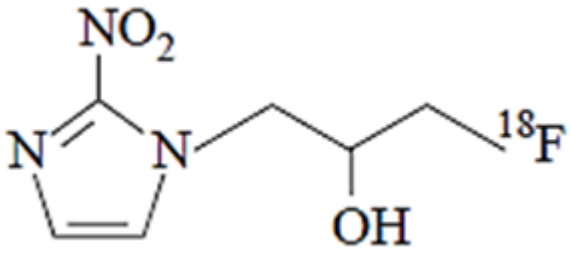
Glucose, ^{18}F-Fluoro Deoxy Mannose
Mannose, Triflate, $K_{2,2,2}$; K^+ e.t.c



[^{18}F] fluorinated intermediate

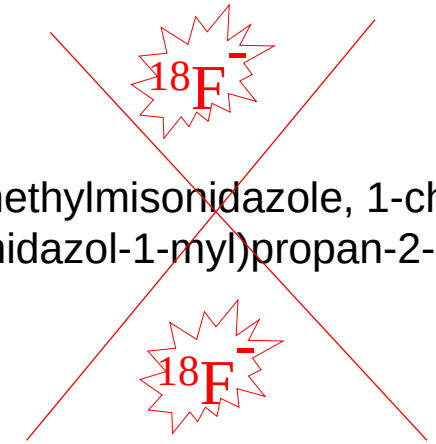
HCl

Hydrolysis



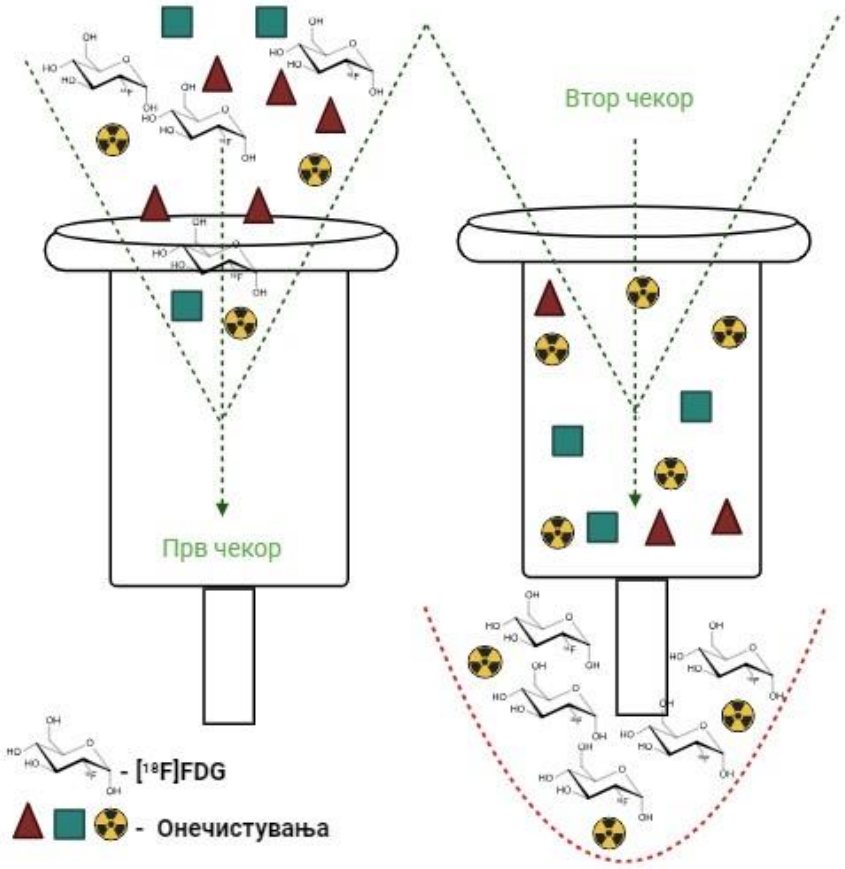
[^{18}F]Fluoromisonidazole ([^{18}F]FMISO)

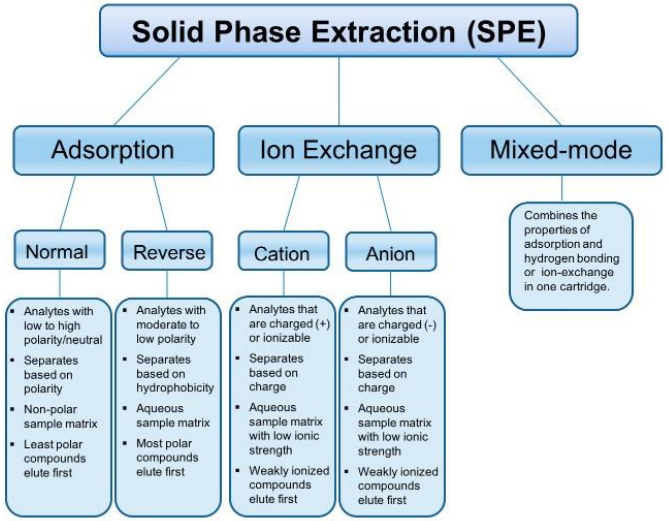
\+

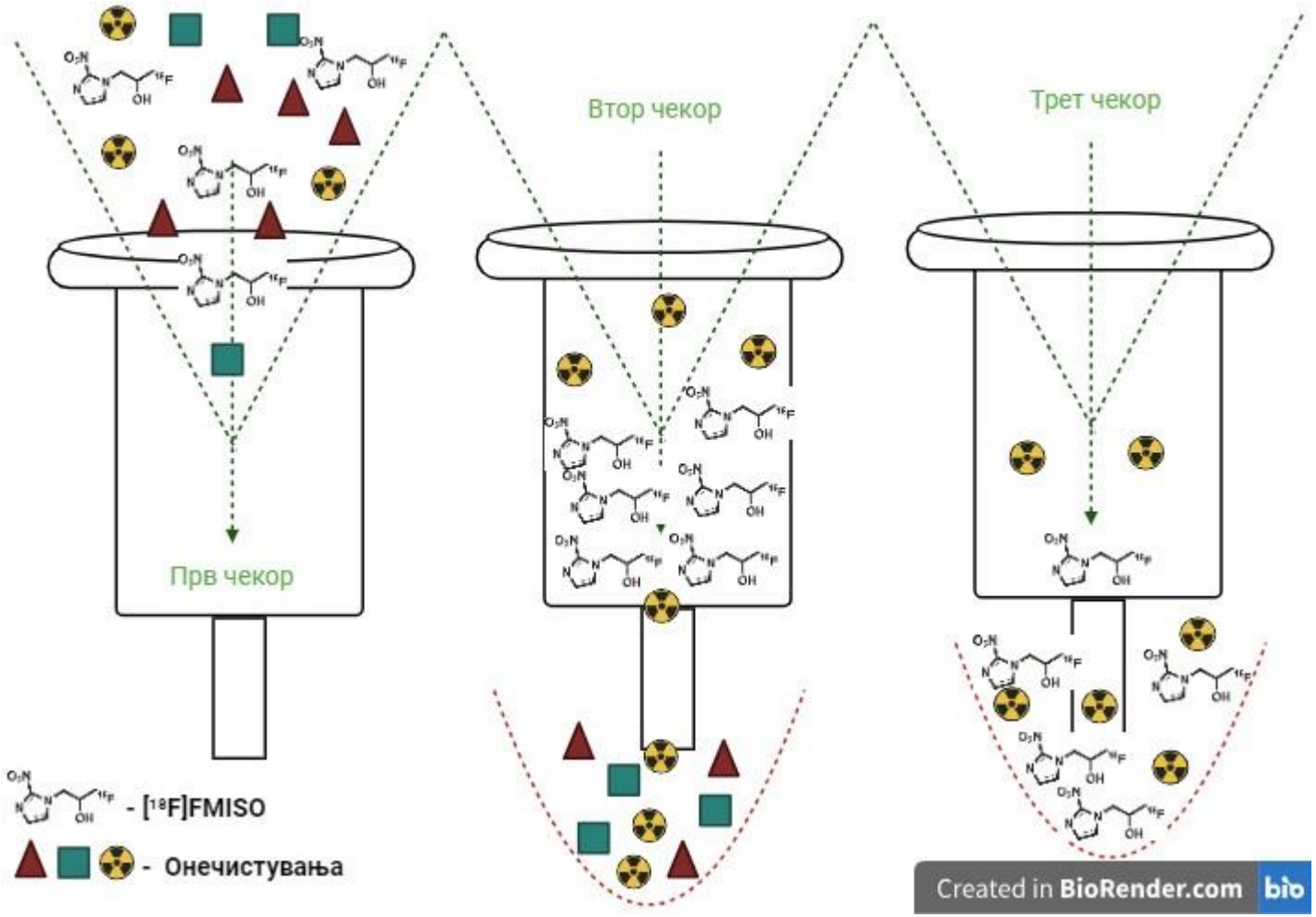


Desmethylmisonidazole, 1-chloro-3-(2-nitro-1H-imidazol-1-myl)propan-2-ol, $K_{2,2,2}$; K^+ e.t.c

Purification and final formulation





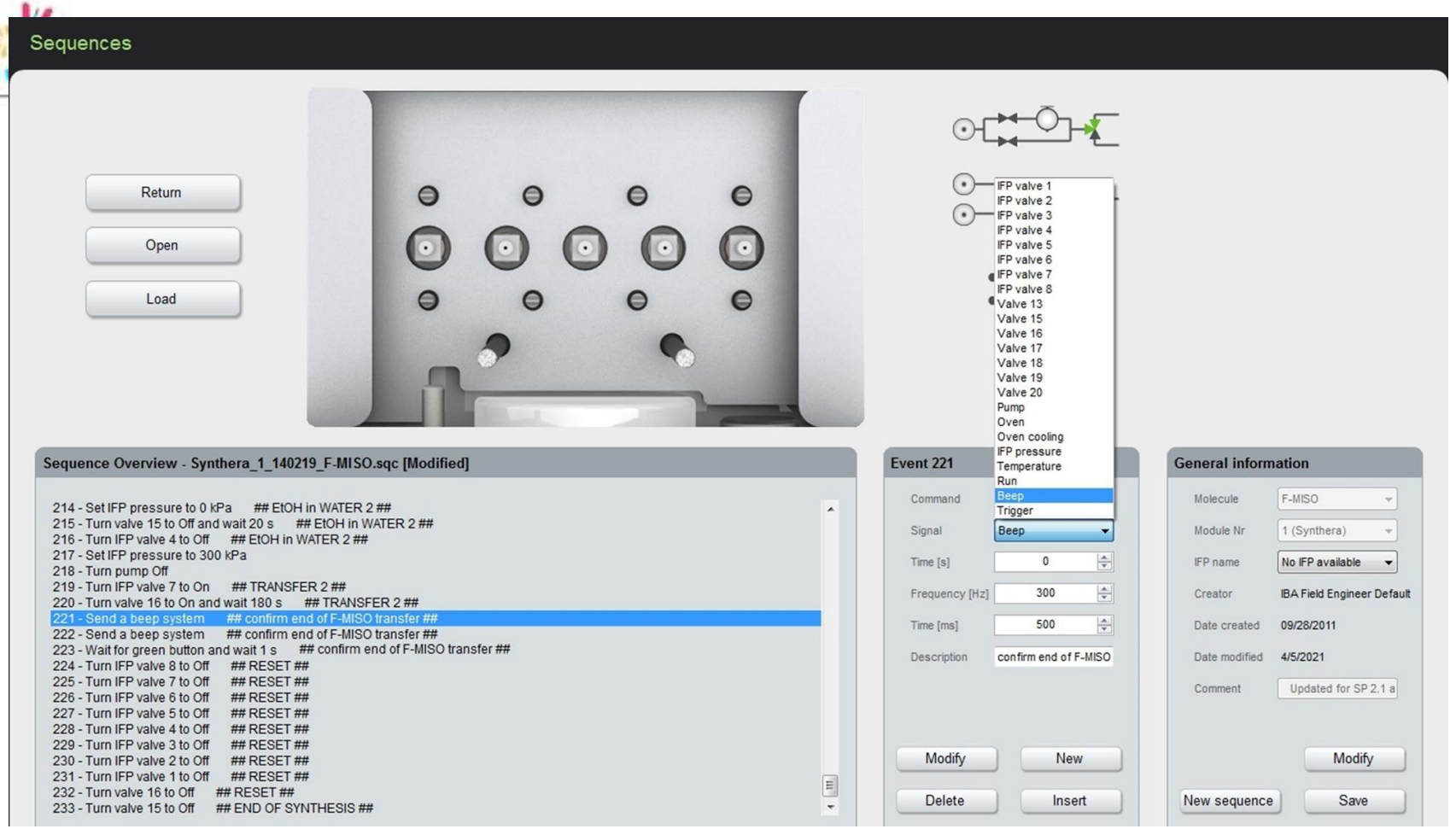


R & D Spending and New ^{18}F-radiopharmaceuticals Development

Developing a new and efficient automated radiosynthesis method takes time and therefore, planning is key!

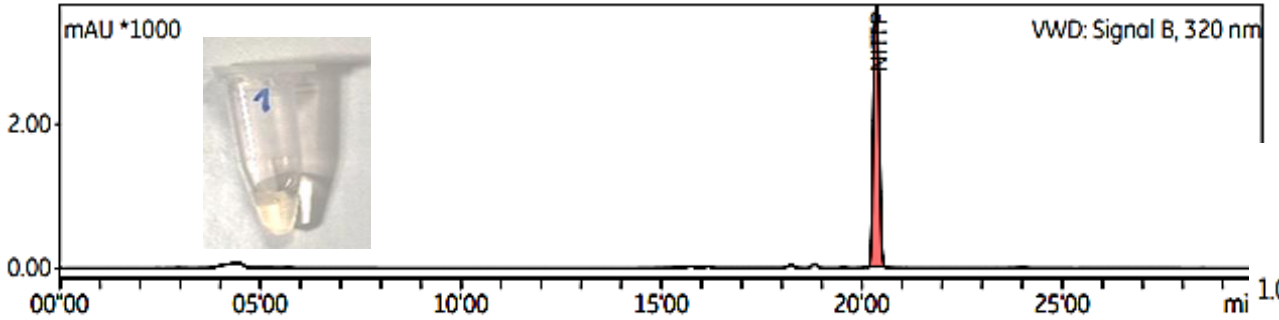
The capacity of the cassette (i.e. the number of reagents and consumables it can hold) is an important consideration when deciding how to best automate a radiosynthesis.

First step

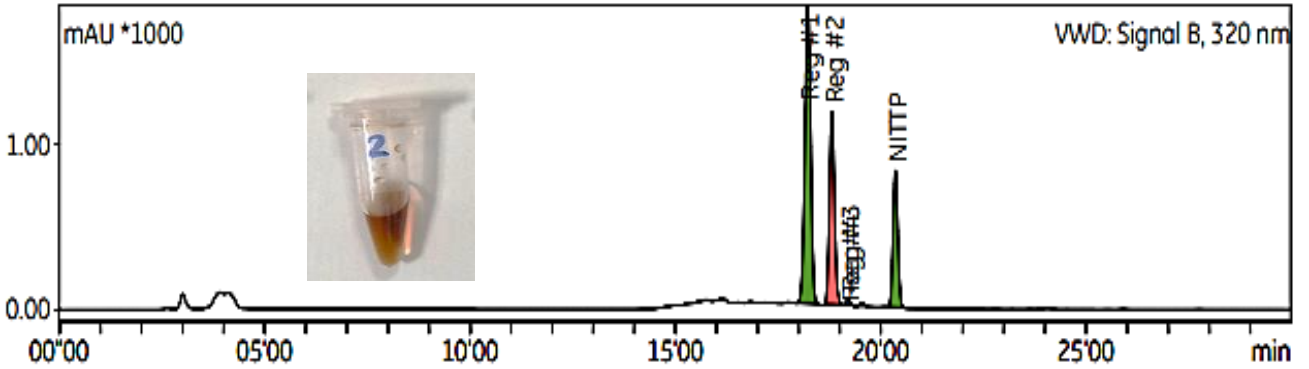


R & D Spending and New ^{18}F-radiopharmaceuticals Development

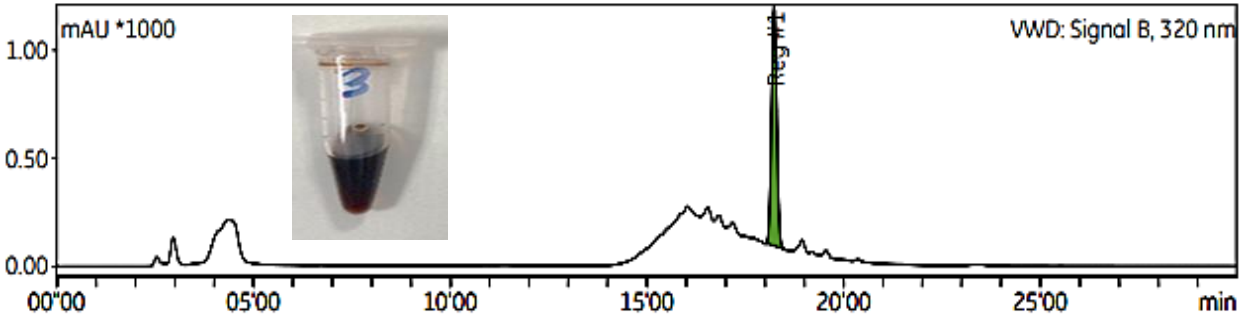
[^{19}F]F$^-$ chemistry practices – for analysis of the reaction mixture at different steps of synthesis (before/after fluorination reaction, unhydrolyzed/hydrolyzed intermediate mixture, unpurified product mixture)



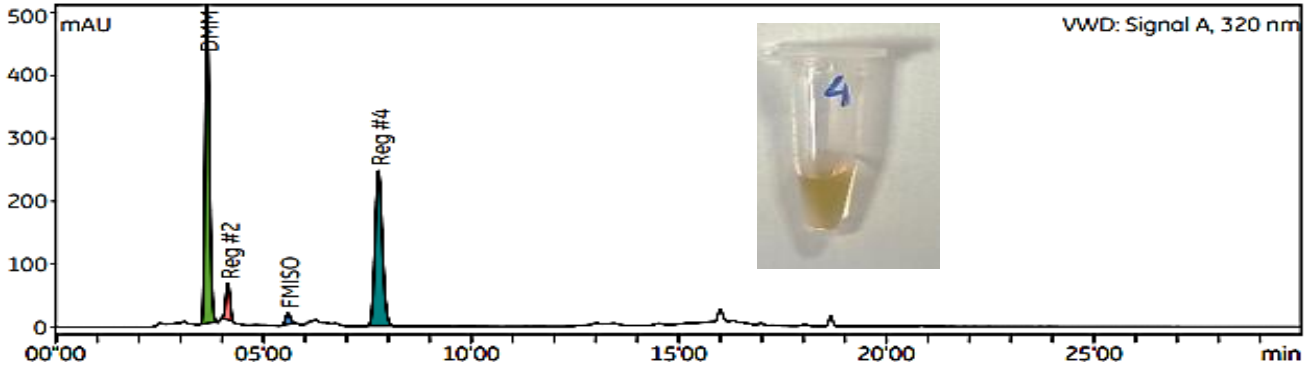
Before fluorination, after transferring the precursor (at first min)



Five min after starting the fluorination

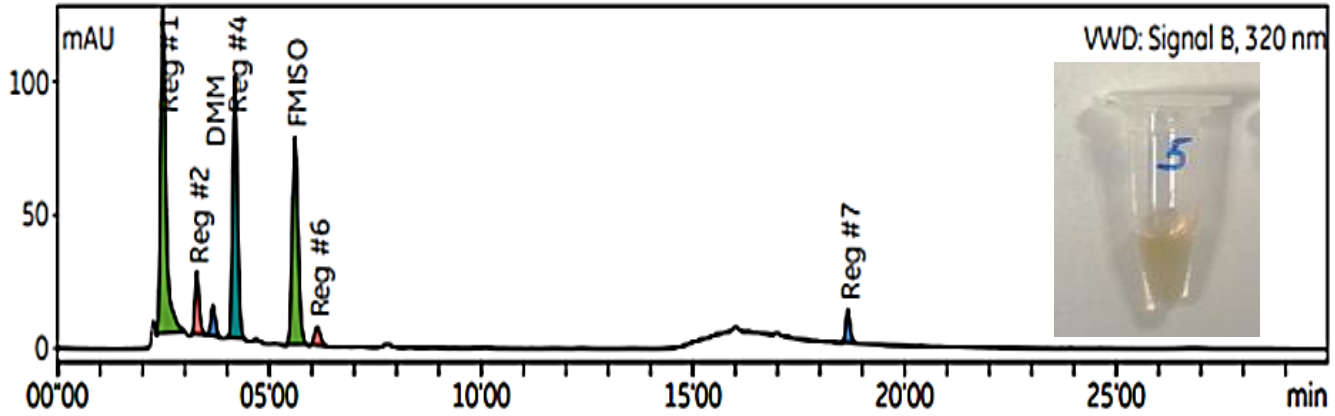


At the end of fluorination (after 10 min, post labeled unhydrolyzed intermediate reaction mixture)

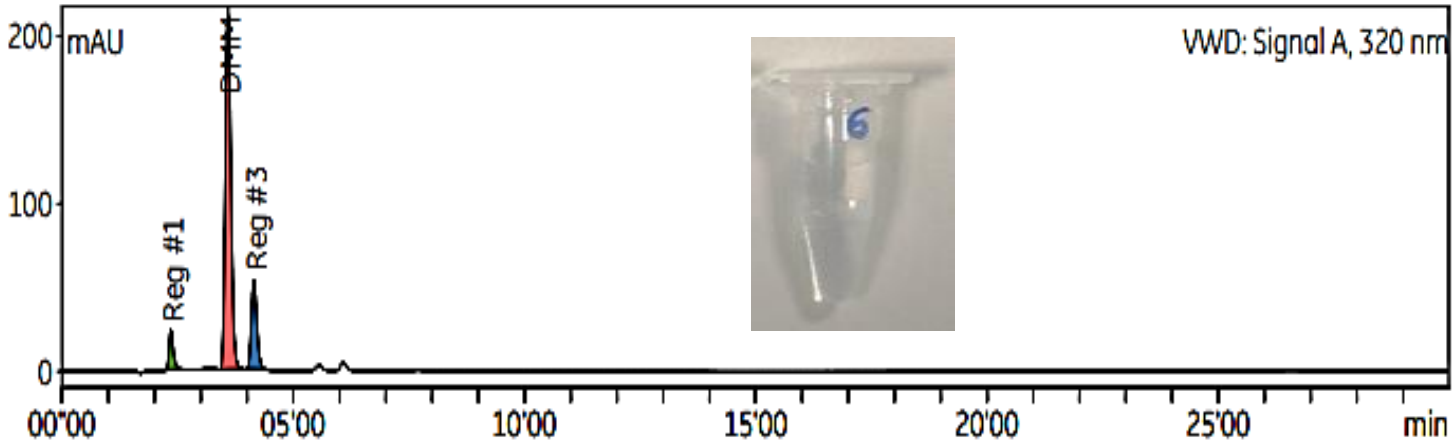


After drying of the acetonitrile (before hydrolysis)

R & D Spending and New ^{18}F- radiopharmaceuticals Development

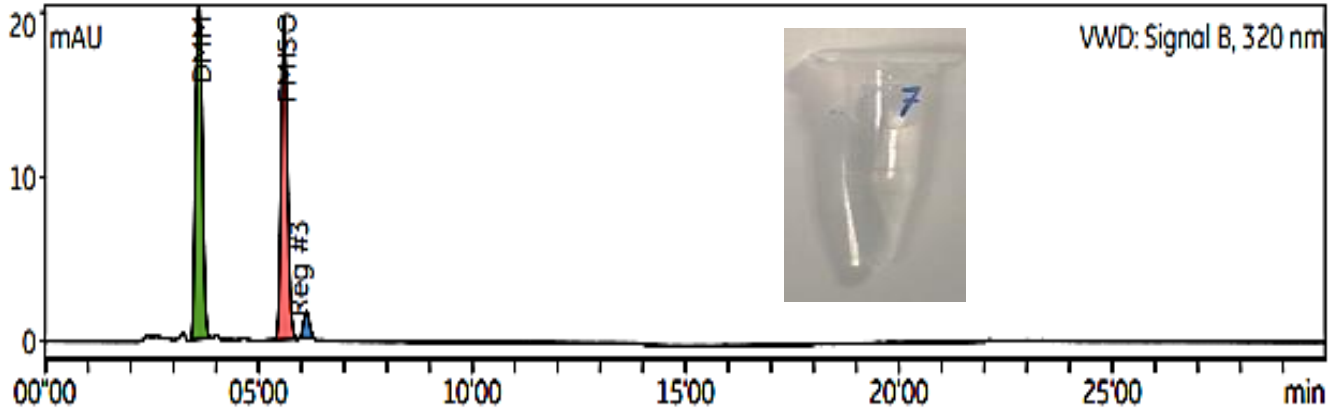


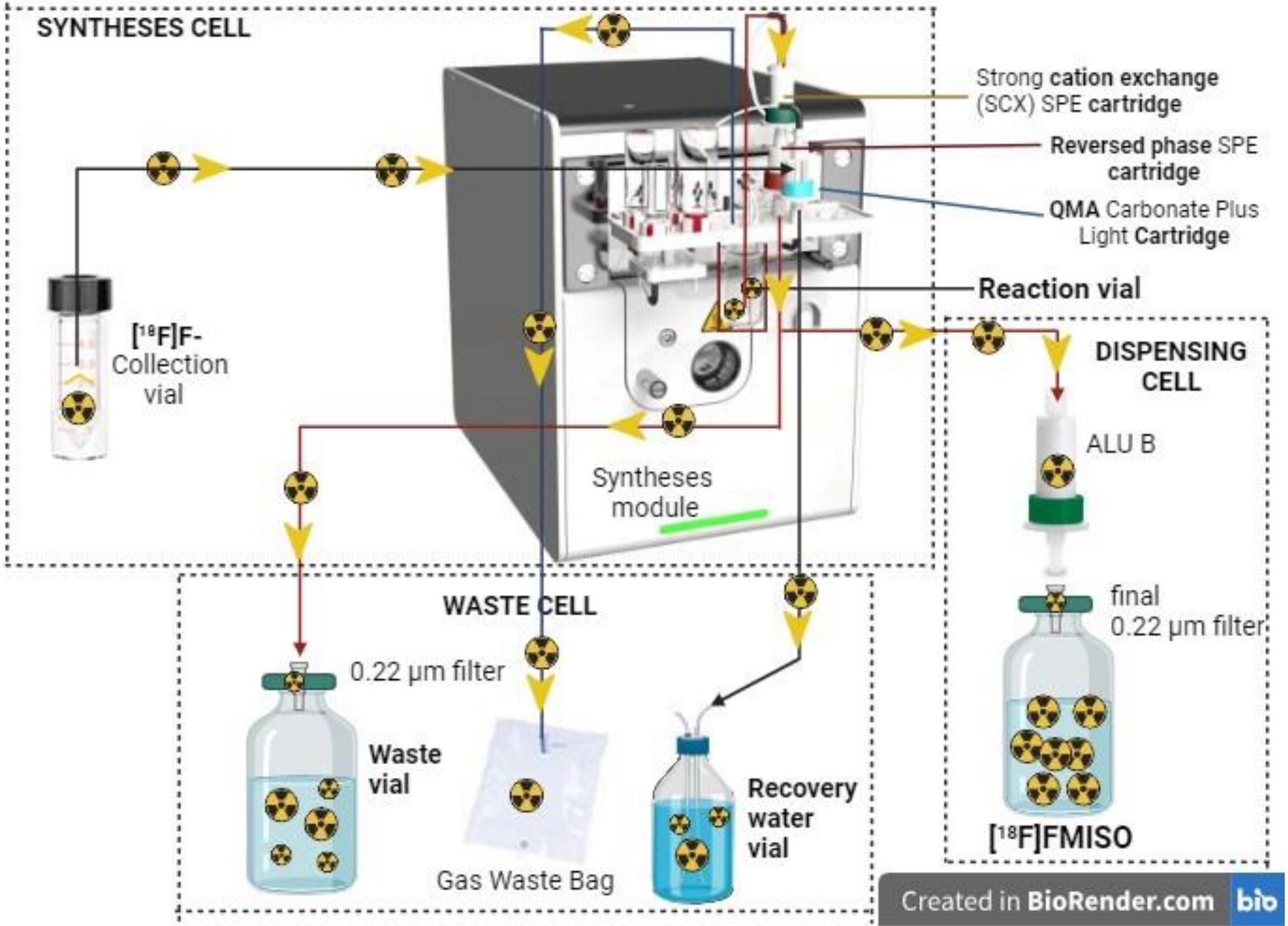
At the end of hydrolysis (hydrolyzed and unpurified mixture)



Waste wash out elution sample

Final purified product solution




SYNTHESES CELL
Strong cation exchange (SCX) SPE cartridge
Reversed phase SPE cartridge
QMA Carbonate Plus Light Cartridge
Reaction vial
[18F]F- Collection vial
Syntheses module
DISPENSING CELL
ALU B
final 0.22 µm filter
[18F]FMISO
WASTE CELL
0.22 µm filter
Waste vial
Gas Waste Bag
Recovery water vial
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