



Chemistry and Radiochemistry

Jonathan Cotton

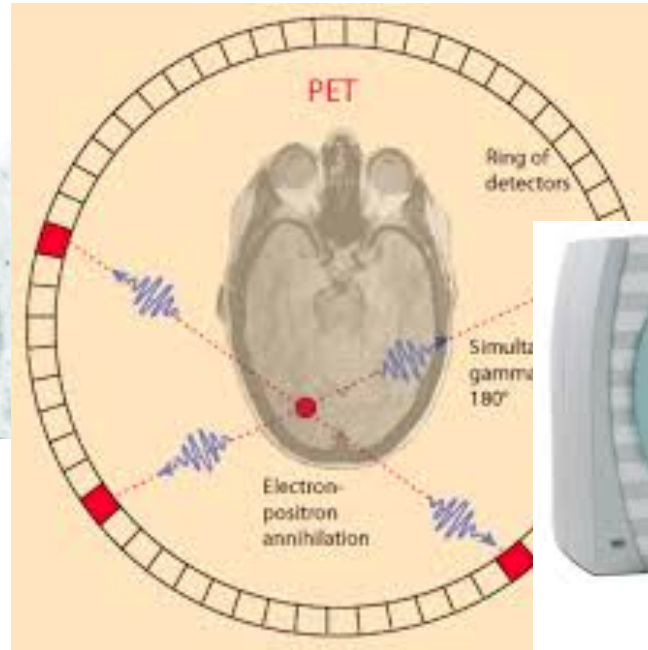
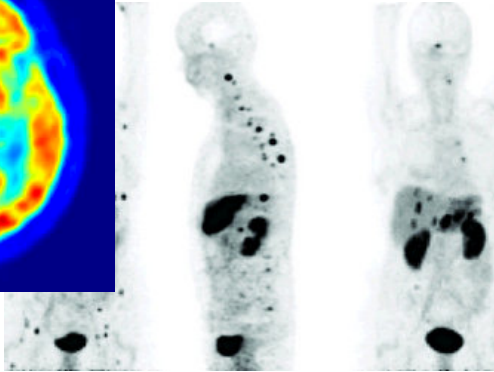
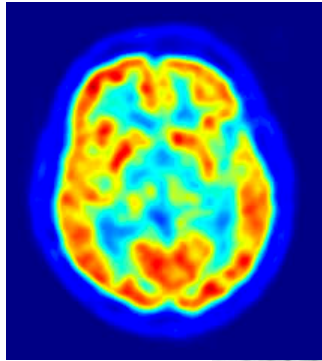
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- Introduction:
 - Radiopharmaceuticals.
 - PET Tracers
- Chemistry 101: Crash Course
 - Atomic structure
 - Essentials of Organic chemistry
 - Chelation Chemistry
- Radiochemistry:
 - Definitions
 - Specific Activity
 - Practical Radiochemistry

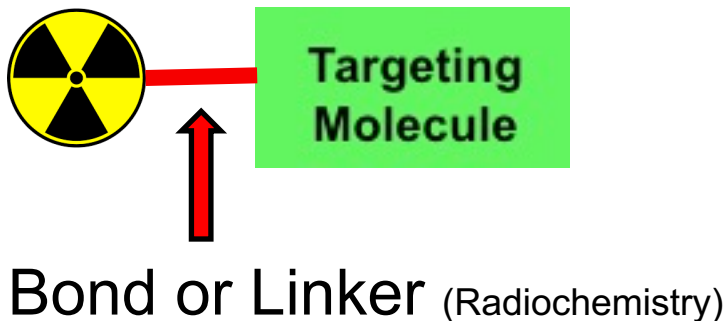
- F-18 Chemistry
 - Isotope production
 - Tracer production
- C-11 Chemistry
 - Isotope production
 - Tracer production
- Labeling of Biomolecules
 - Biomolecules
 - Antibodies
 - Prosthetic groups and radiometals

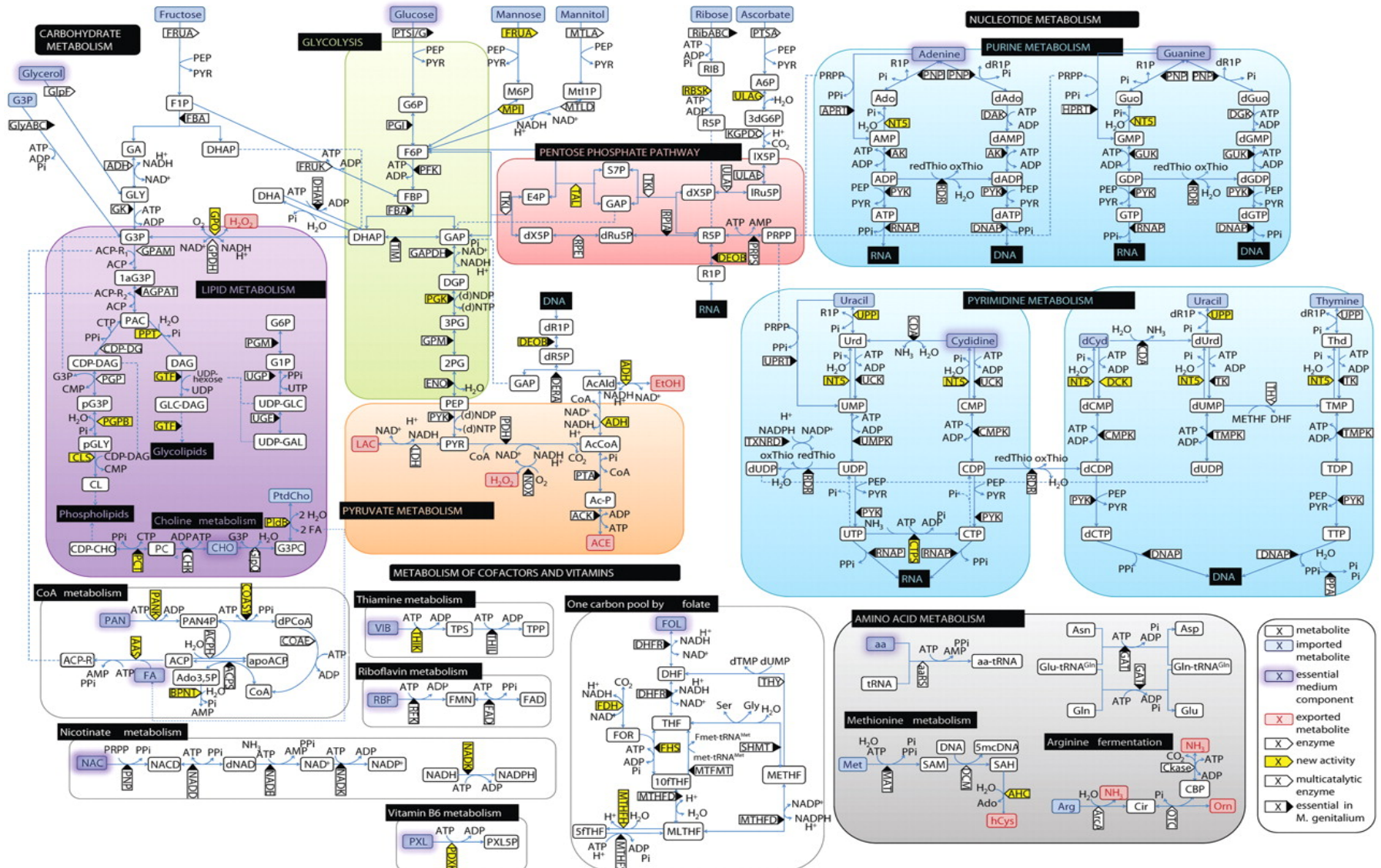
PET and Radiopharmaceuticals





- Radioactive substances used to **diagnose, treat** or prevent **disease**
- These compounds are made up of two components:
 1. A radioactive isotope which carries the energy for imaging or treatment (or both!!!)and
 2. (typically) a carrier molecule which delivers the isotope to the area to be treated or examined.







- George de Hevesy
- Nobel Prize 1943
 - “for his work on the use of isotopes as tracers in the study of chemical processes.”
- The Tracer Principal:
 - Radioactive isotopes have the same chemical properties as non-radioactive isotopes of the same element.
 - Radioactive decay is highly energetic and thus easy to detect.

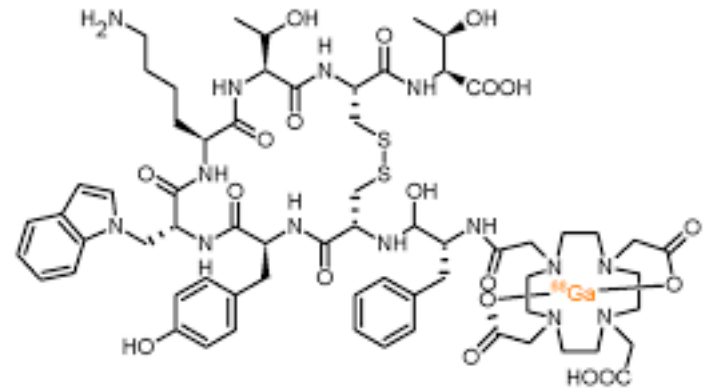
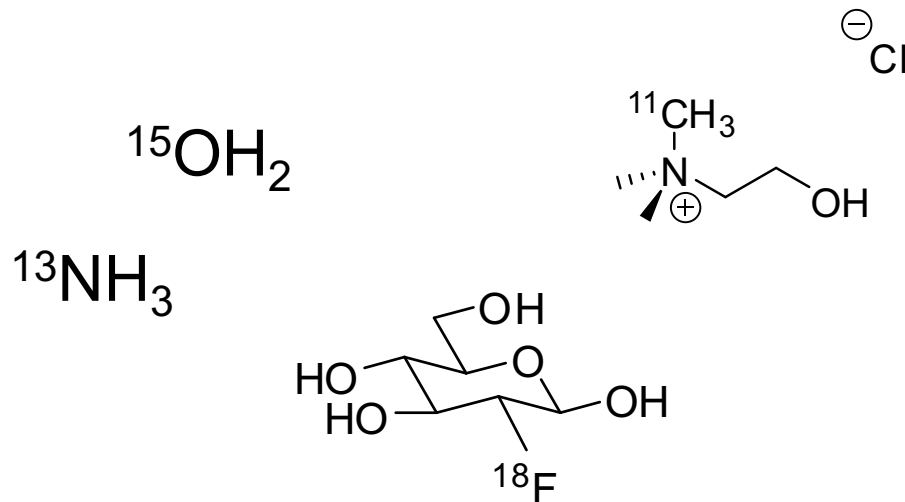


SAME CHEMISTRY
SAME BIOLOGICAL/METABOLIC BEHAVIOR.
HIGHLY SENSITIVE (Only small amounts of tracer needed)

!!Can observe chemical change with out
changing the process which is being observed!!

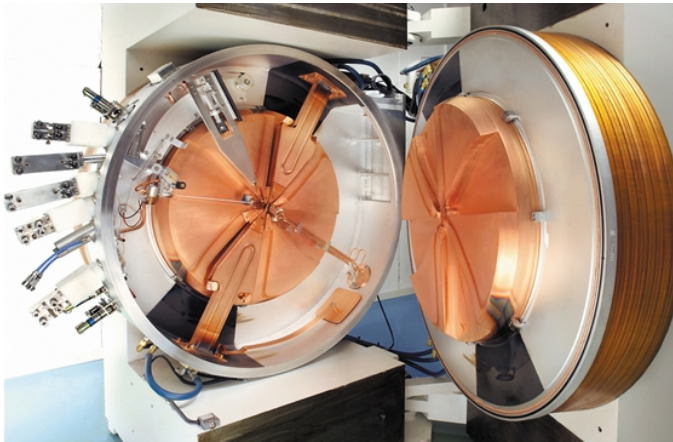


- PET uses radioactive molecules that are involved in biochemical processes.
- Image: tissue perfusion, metabolism, drug/receptor interactions, and gene expression.
- Isotopes should have short half-life and high percentage of positron emission. (C-11: 99.8%, N-13: 100%, O-15: 100%, F-18: 97%)
- High Specific activity.





Radionuclide Production



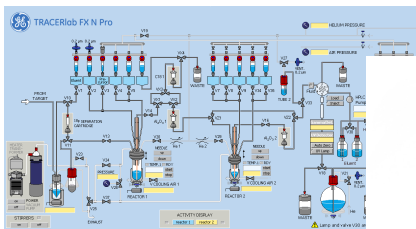
Cyclotron



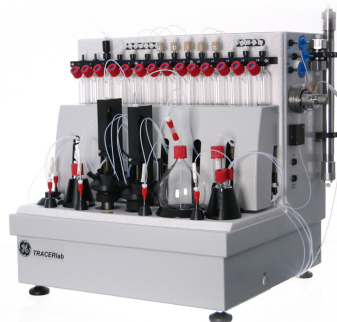
Generator



Radionuclide isolation and preparation.



Computer controlled
Synthesis module



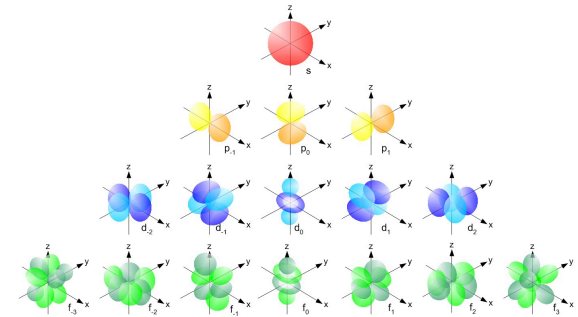
- Purification
- Dispensing
- Quality Control (QC)
- Lots of Paper Work!
- Delivery
- Patient!!



- Nucleus
 - generally not directly involved in chemical transformations

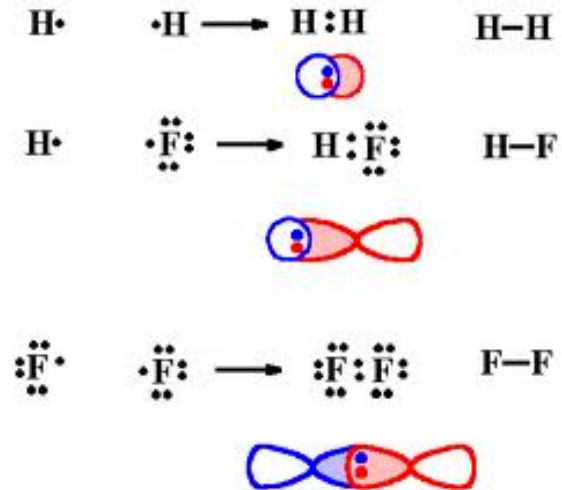
• Electrons

- Around the nucleus in “clouds” known as orbitals.
- Orbital: “quantum mechanically derived 3D distribution of where the electron has the highest chance of being found.”
- The 4 main types are S,P,D and F orbitals.
- The outer most electrons are called valence electrons.



• Valence electrons.

- Can be shared between atoms to form “Bonds.”
- This happens through a mixing of valence orbitals.
- Bonds always consist of **Two** shared electrons.
- This is called “**covalent bonding.**”



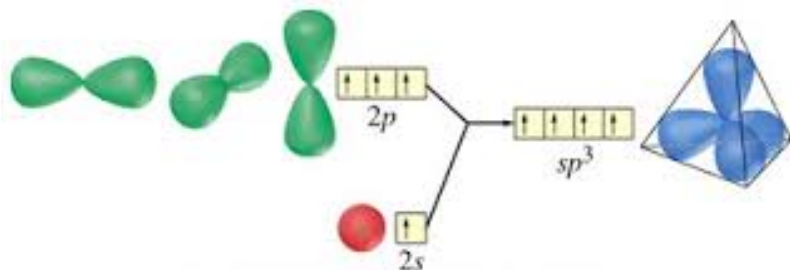


- A chemical bond describes the probability of the presence of two electrons within a certain space between two atoms.

The Golden Rule: Most atoms in Org.Chem (C,N,O,F) want a FULL valence shell of $8e^-$. stable Electrons ALWAYS exist in pairs.

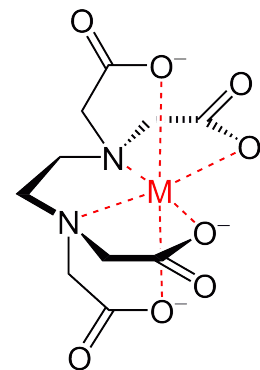
Therefore: These atoms can NEVER form more than 4 Bonds.
This is called the "**Octet Rule.**"

- There are different theories which are applied to describe atomic or Molecular Orbitals, such as **Hybridization**, **VSEPR** (valence shell electron pair repulsion) or the **ligand field theorem**.



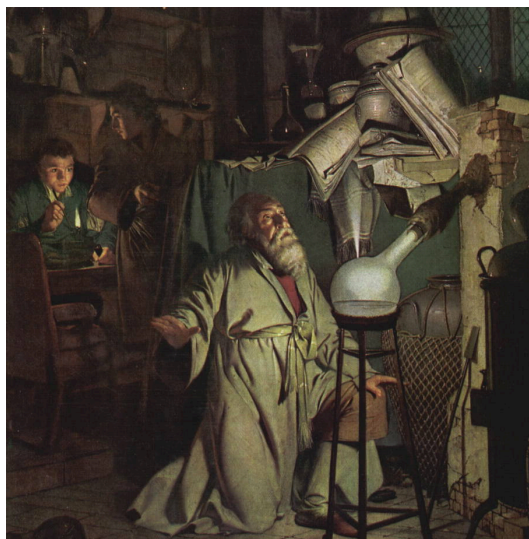
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VSEPR Theory



Ligand Field Theorem

“**Chemistry** is the science of atomic matter, its properties, structure, composition and its changes during interactions and (chemical) reactions.”



Organic Chemistry is the study of compounds containing Carbon **and** Hydrogen and how they change and can be changed

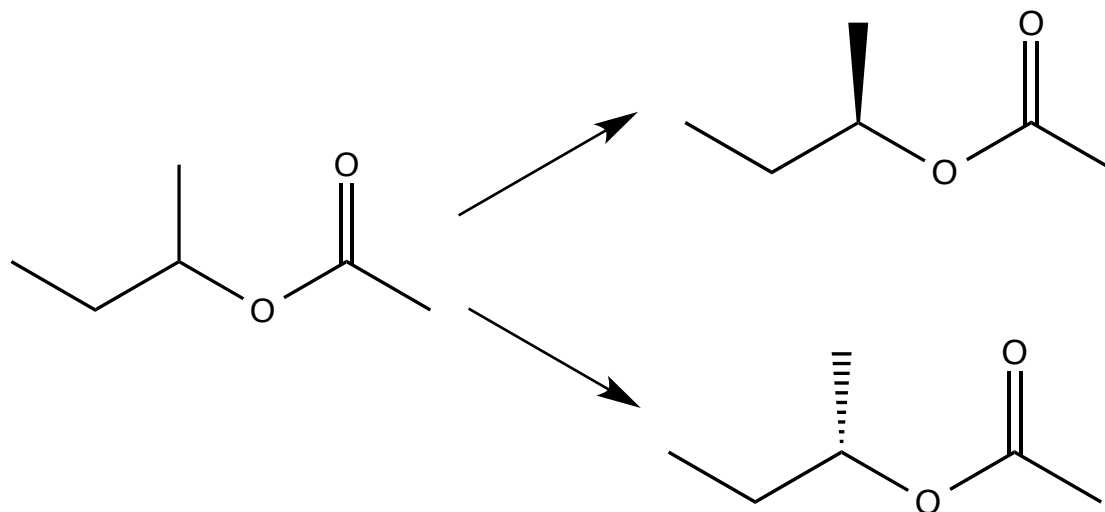
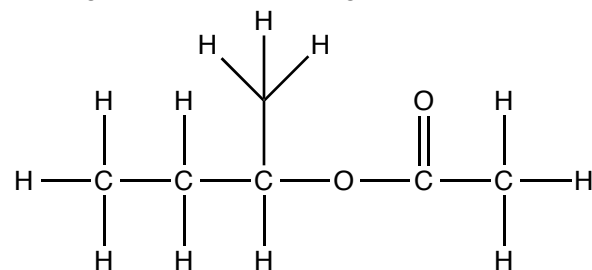
“Organic chemistry is the study of carbon compounds

Biochemistry is the study of carbon compounds that crawl.” – Mike Adams

Note: Representing Chemical Structure



- Drawing of organic molecules:
 - Any molecule is a 3D object in real space and the representation of molecules reflects that.
 - Lets take a molecule like sec-butyl acetate:
 - $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)\text{OC}(=\text{O})\text{CH}_3$ (condensed formula)





Organic Chemistry is principally divided in **four** classes:

1. Polar (or ionic) reactions:

Classical chemical reactions, chelating reactions.
e.g. methylation or fluorination reaction.

2. Pericyclic reactions:

thermal or (UV) light triggered.
electrons move together in cyclic system.
rearrangement reactions, e.g. “Click” chemistry.

3. Radical reactions:

Involve movements of single electrons.
Synthesis of Polymers, Combustion of organic compounds.

4. Reduction / Oxidation reactions (redox)

Involve a transfer of electrons



1. Nucleophiles:

Electron rich.

Looking for positive charge or partner to share electrons with

2. Electrophiles:

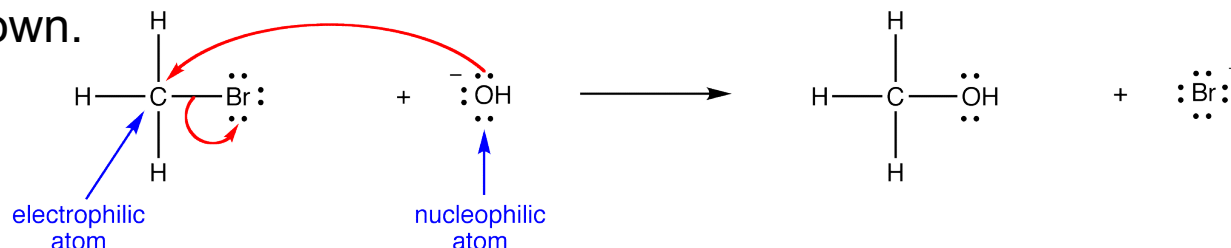
Electron deficient.

Looking for electron rich, negatively charged partner.

3. Leaving Group:

The group that is replaced.

Pretty stable on its own.



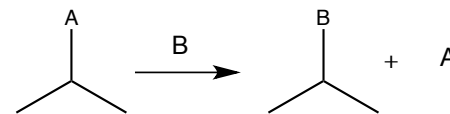


Polar reactions can be again divided into:

1. Nucleophilic/electrophilic **substitutions**:

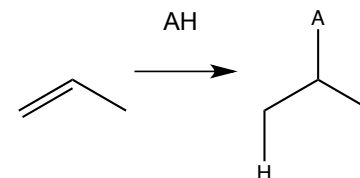
Switching one group for another.

^{11}C -methylations, ^{18}F -fluorinations, iodinations.



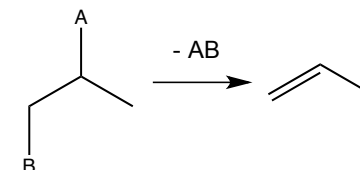
2. Nucleophilic/electrophilic **additions**:

Adding a new group to either a double or triple bond.



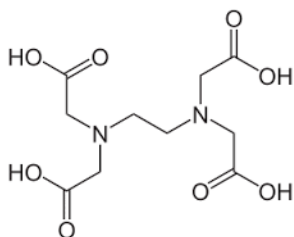
3. **Elimination** reactions:

Removing a group to form a double or triple bond.

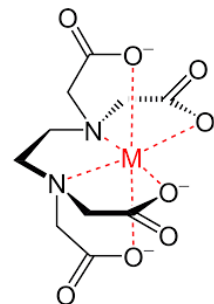


4. **Chelating** reactions / Complex chemistry / Coordination Chemistry:

Trapping a large metal ion in an organic “cage” known as a chelator to form a “Complex.”



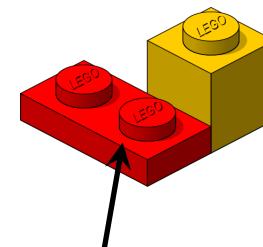
+ Metal =





- Substitution reactions (The players):

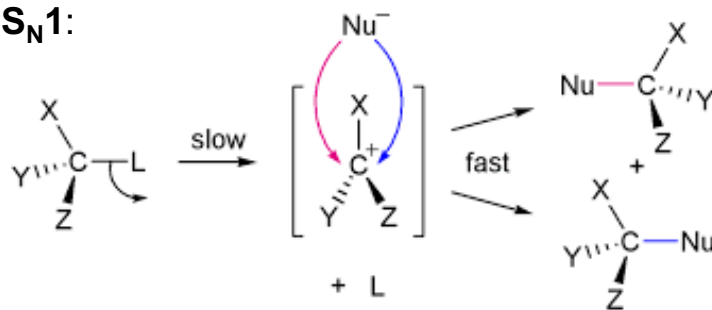
- Electrophile
- Nucleophile.
- Leaving group.



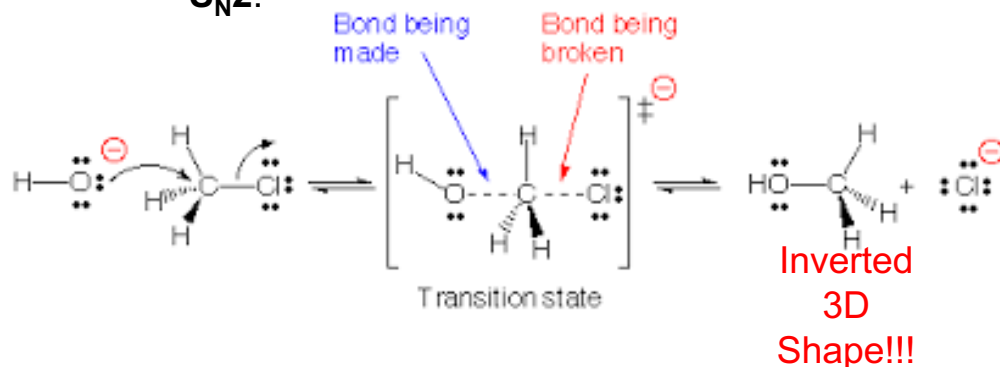
- Substitution reactions (The Mechanism):

- Three Types of substitution - S_N1 , S_N2 , S_NAr .

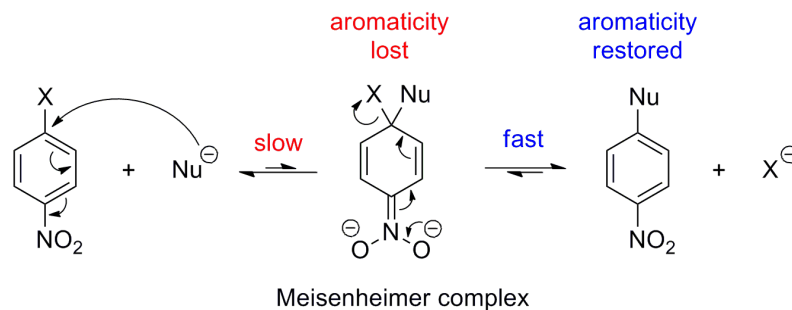
- S_N1 :



- S_N2 :

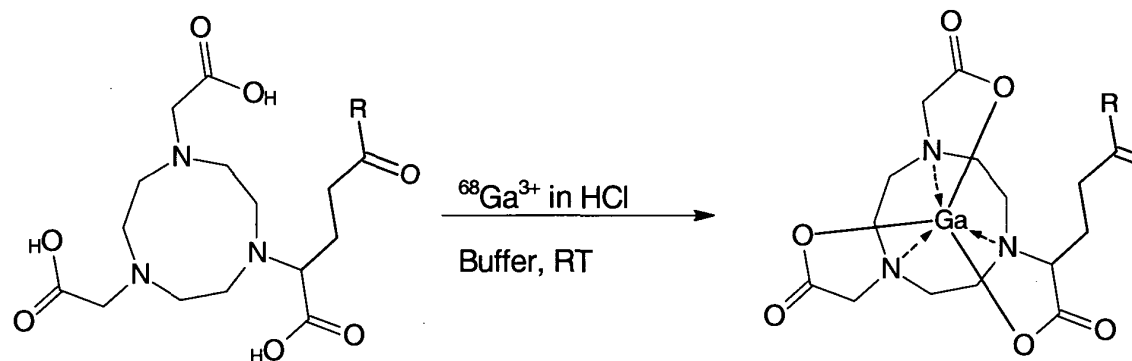


S_NAr :

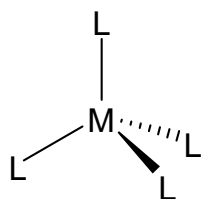




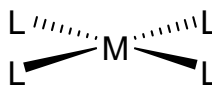
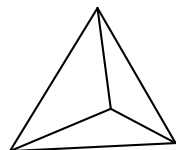
The term coordination compound describes stoichiometric compounds consisting of molecules and/or ions, which can also exist independently from each other.



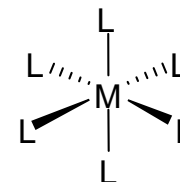
Through the formation of the complex, a compound is created which displays different properties to its individual components. Complexes are written with 'square brackets'. Within a complex unit there is the central atom (acceptor atom) and the ligands (donors).



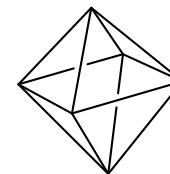
tetrahedral coordination



square-planar coordination



octahedral coordination

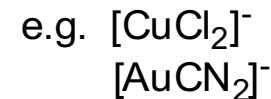
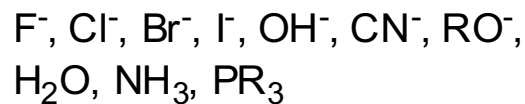


coordination number 4

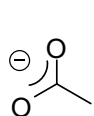
coordination number 6



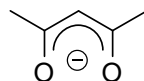
Monodentate ligands:



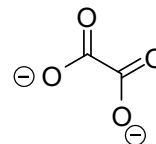
Bidentate ligands:



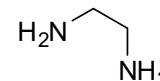
acetato



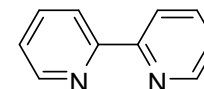
acetylacetonato



oxalato

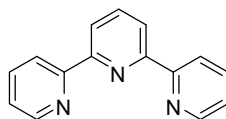


ethylenediamine
(en)

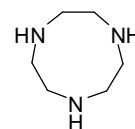


2,2'-Bipyridine

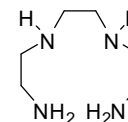
Tridentate ligands (tripod)
and higher order ligands



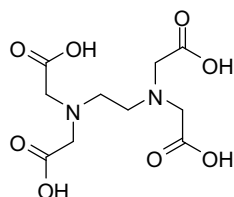
2,2',6',2''-Terpyridin
(terpy)



1,4,7-Triazacyclo-
nonane (9aneN₃)

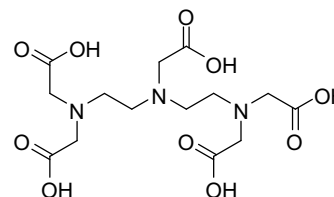


Triethyltetraamine
(trien)



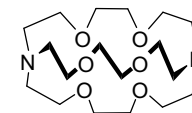
Ethylenediaminetetraacetic
acid (edta)

ideal for: Mn(II), Cu(II), Fe(II),
Pb(II), Co(III)



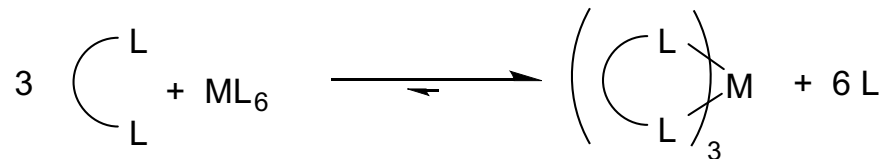
Diethylenetriaminepentaacetic acid
(dtpa)

ideal for: Fe(III), U(IV),
Th(IV), Ce(III/IV)



Kryptofix 2.2.2

Definition: If a monodentate and a multidentate ligand with the same donor atoms in an ideally identical chemical environment compete for the same metal center, empirical data indicates that the multidentate ligand replaces the respective number of monodentate ligands.



$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad \text{Gibb's free enthalpy}$$

$$\Delta G^\circ = -RT \ln \beta$$

$$\text{with } \beta = \frac{[\text{M}(\text{L-L})_3] [\text{L}]^6}{[\text{ML}_6] [\text{L-L}]^3}$$

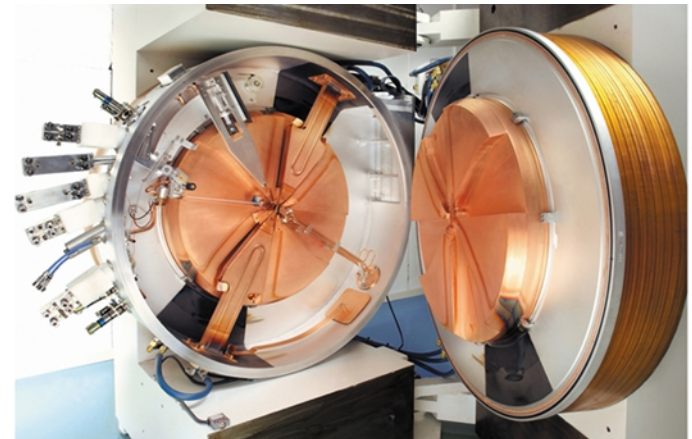
In general the formation of complexes between a metal and higher order ligands is thermodynamically and entropically favoured.

Chelators can be readily conjugated on to biomolecules and then “complexed” with radio-metals like ^{68}Ga , ^{64}Cu , ^{89}Zr or ^{111}In .

Very effect strategy for labelling big biomolecules!!



- Radiochemistry:
 - The chemistry of, and using, radioactive isotopes.
 - PET radiochemistry mainly uses:
 - ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{64}Cu , ^{68}Ga , ^{89}Zr and ^{124}I



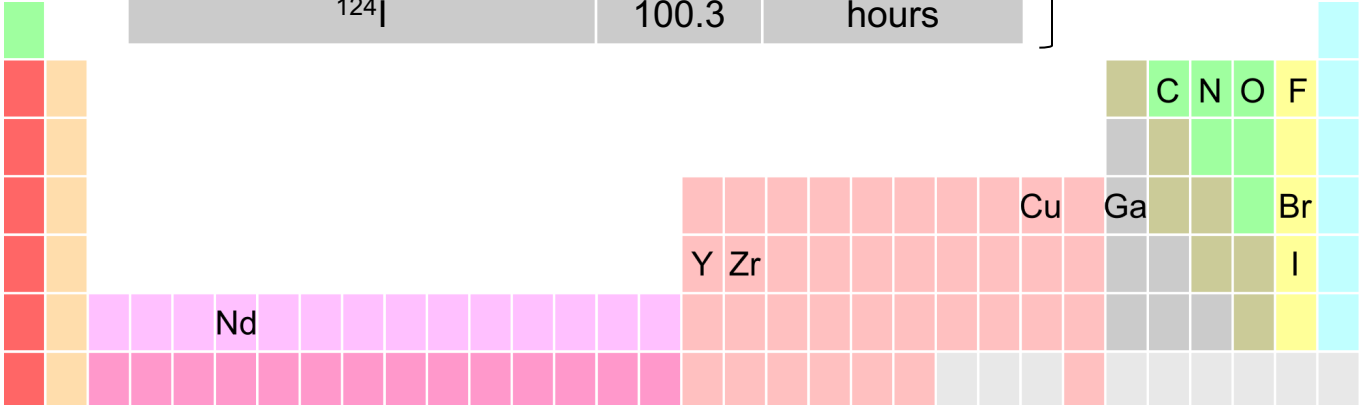
Radionuclide		$t_{1/2}$	
^{15}O		122	seconds
^{13}N		9.9	minutes
^{11}C		20	minutes
^{68}Ga		68.3	minutes
^{18}F		110	minutes
^{64}Cu		12.7	hours
^{86}Y		14.7	hours
^{76}Br		16.2	hours
^{89}Zr		78.4	hours
$^{140}\text{Nd} \rightarrow ^{140}\text{Pr}$		80.8	hours
^{124}I		100.3	hours

metals

short-living

intermediate-living

long-living



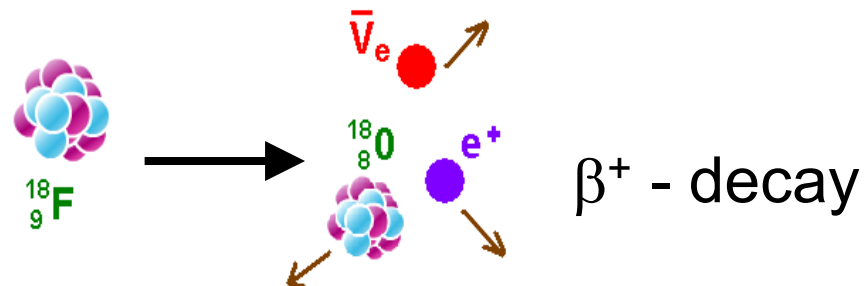
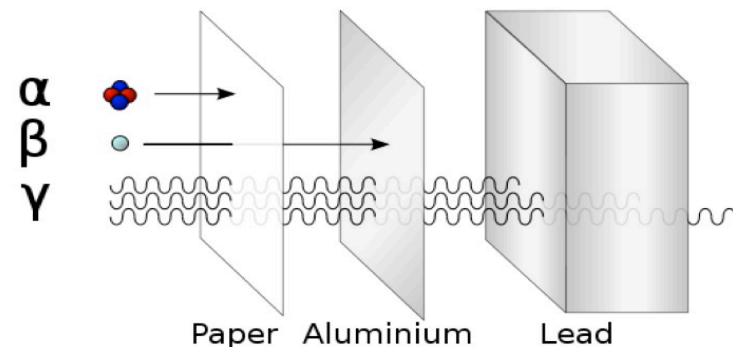
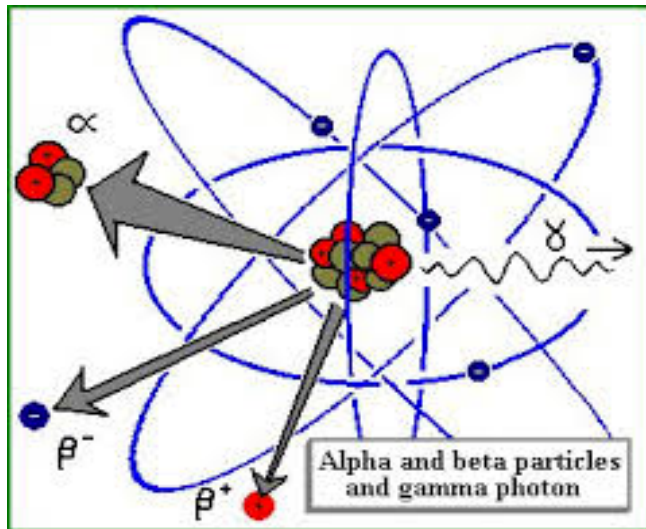


Radioactivity:

a property of certain nuclides to spontaneously emit a:

- Particle (alpha- or beta-)
- High energy (x-ray or gamma) photon

Through radioactive decay an unstable radioactive isotope undergoes a change into a more stable isotope.



Radioactive decay:

- Statistical event
- Each decay is independent from neighbouring nuclei
- The moment of decay can not be predicted for a single atom
- Measured in Becquerel's (Bq) (counts per second)

Half-life:

- The time it takes for half the radioactive sample to decay. A statistical constant of the decaying element. ^{18}F has a $T_{1/2} \approx 110\text{min}$, ^{11}C $T_{1/2} \approx 20\text{min}$, ^{64}Cu $T_{1/2} \approx 12\text{hrs}$.

- Radioactive decay:
$$N(t) = N_0 * e^{-\lambda t} \quad T_{1/2} = \frac{\ln 2}{\lambda} \quad \lambda: \text{decay constant } 1/\text{s}$$

Specific activity: Defined as Bq/kg, but often given in Molar Activity: Bq/mol.

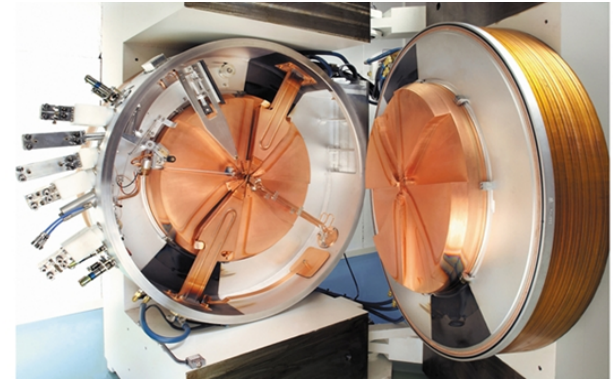
- The specific (radio-)activity tells you how many decays per second take place in a certain amount of substance. A higher value means a higher ratio of the radioactive compound in comparison to the non-radioactive compound.



Theoretical values:

- ^{11}C 370 TBq / μmol ($8.4 \cdot 10^8$ Ci/g)
- ^{18}F 62 TBq / μmol ($9.3 \cdot 10^7$ Ci/g)
- ^{64}Cu 9 TBq / μmol ($3.8 \cdot 10^6$ Ci/g)
- ^{125}I 78 GBq / μmol ($1.7 \cdot 10^4$ Ci/g)
- ^{235}U 18 Bq / μmol ($2.1 \cdot 10^{-6}$ Ci/g)

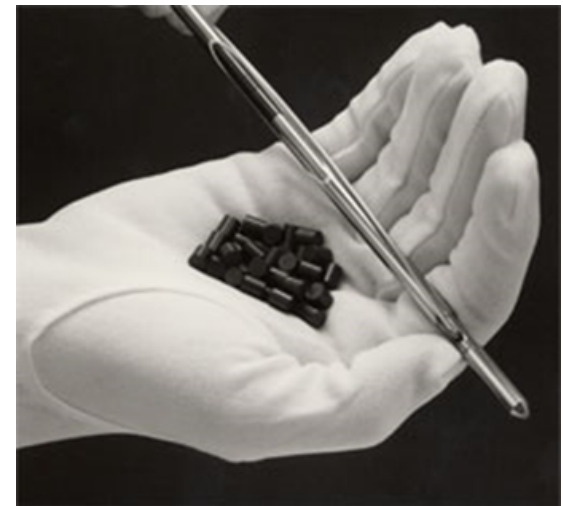
$$18 \text{ Bq} / 0.235 \text{ mg} \Rightarrow 18 \text{ kBq} / 0,235 \text{ g} \Rightarrow 76 \text{ MBq} / \text{kg}$$



In general, the higher a radionuclide's specific activity, the shorter its half-life (decay rate), and the more "radioactive" it is when compared to one with a lower specific activity.

Experimental results (Radiopharmacy Tübingen)

- ^{11}C 100 – 400 GBq / μmol
(after radiosynthesis)
- ^{18}F 50 – 100 GBq / μmol
- ^{64}Cu ~ 50 GBq / μmol





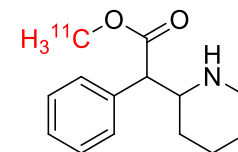
Various factors effect specific activity.

Carrier: the non-radioactive version of a radiopharmaceutical

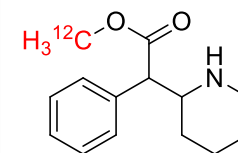
Pseudo-carrier: material closely resembling the true carrier (e.g. similar biological activity or receptor binding affinity)

For synthetic radiotracers there is (often) a substantial dilution with a carrier. The carrier usually remains constant, while the radioactivity decays. So, specific radioactivity generally decreases according to the half-life of the radioisotope.

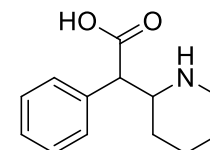
Specific radioactivities for PET tracers should be cited with respect to a particular time e.g. end of radionuclide production (**EOB**), end of synthesis (**EOS**) or time of injection (**TOI**).



^{11}C -Methylphenidat
(Ritalin)



Methylphenidat
(Ritalin)



Ritalinic acid

Carrier-Free (CF)

A radiopharmaceutical is carrier-free (CF) when there is no accompanying carrier (more or less an ideal but unreachable state).

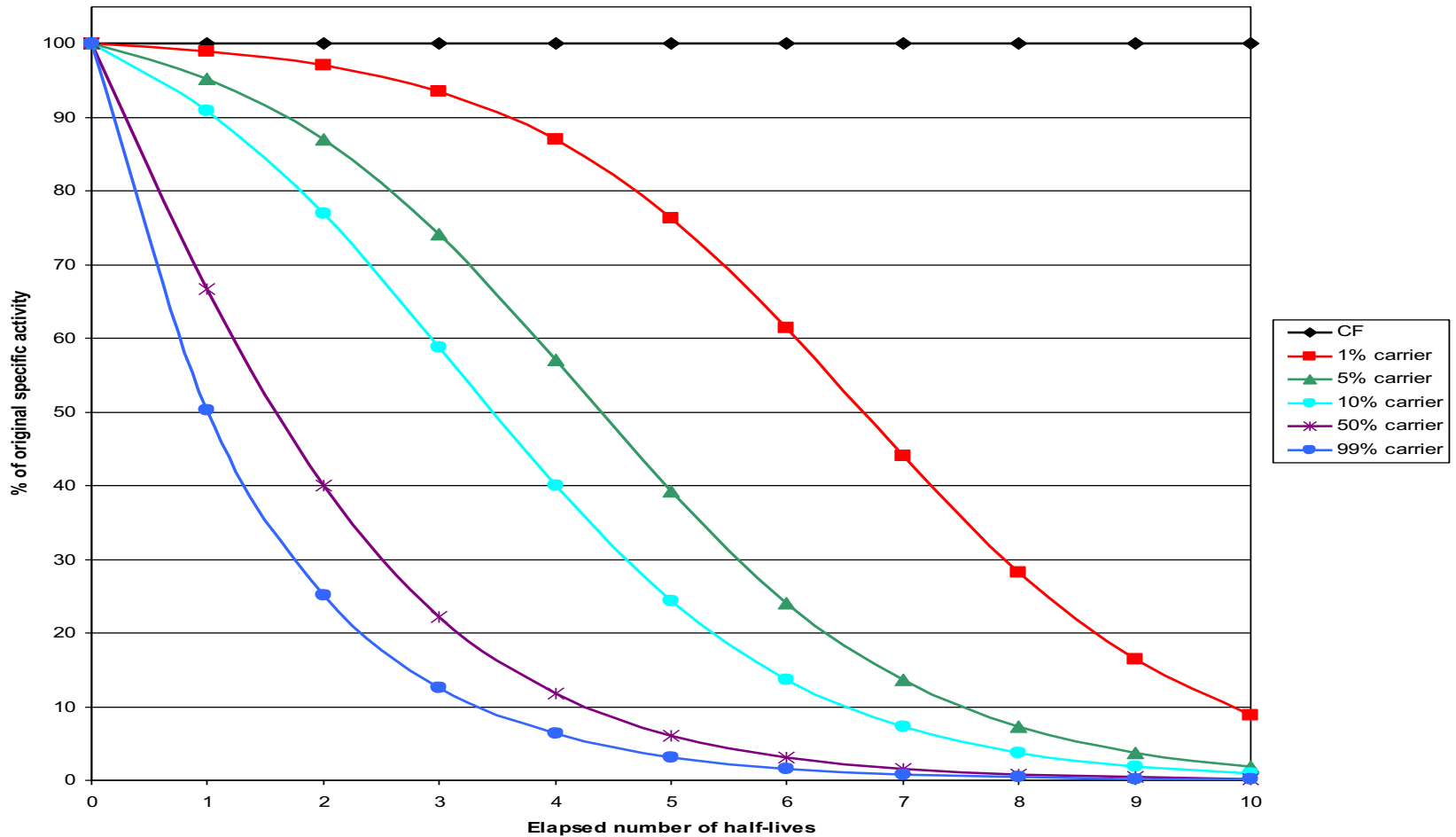
No Carrier-Added (NCA)

A radiopharmaceutical is no carrier-added (NCA) when no source of carrier has been added deliberately during its production, and when all reasonable precautions have been taken against the intrusion of sources of carrier.

Carrier Added (CA)

A radiopharmaceutical is carrier-added (CA) when a source of carrier has been added deliberately during its production.

Time-dependence of specific radioactivity on dilution with carrier





- Practical Factors effecting specific activity:

1. Ion contamination from the target.

- Ni^{64} contamination is a particular problem in ^{64}Cu production.

2. Contamination from materials.

- Radiolysis in Teflon tubing and components.
- Contamination from reagents.
- Contamination from air (CO_2).
- QMA resins

Table 1. Carrier mass from 11.1 GBq (300 mCi) exposure to system components

Teflon item	Surface (cm ²)	Time (min)	Mass (nmol)
1.5 mm Teflon tubing (790 cm)	252	1.25	72
Teflon resin holder	3.8	3	47
Teflon tube in reaction vessel	1.7	20	170
Rheodyne slider valve	2.3	1.25	6.3
Control-reagents only	0	0	25
Control-mock target water	0	0	23
All components	267	N/A	357

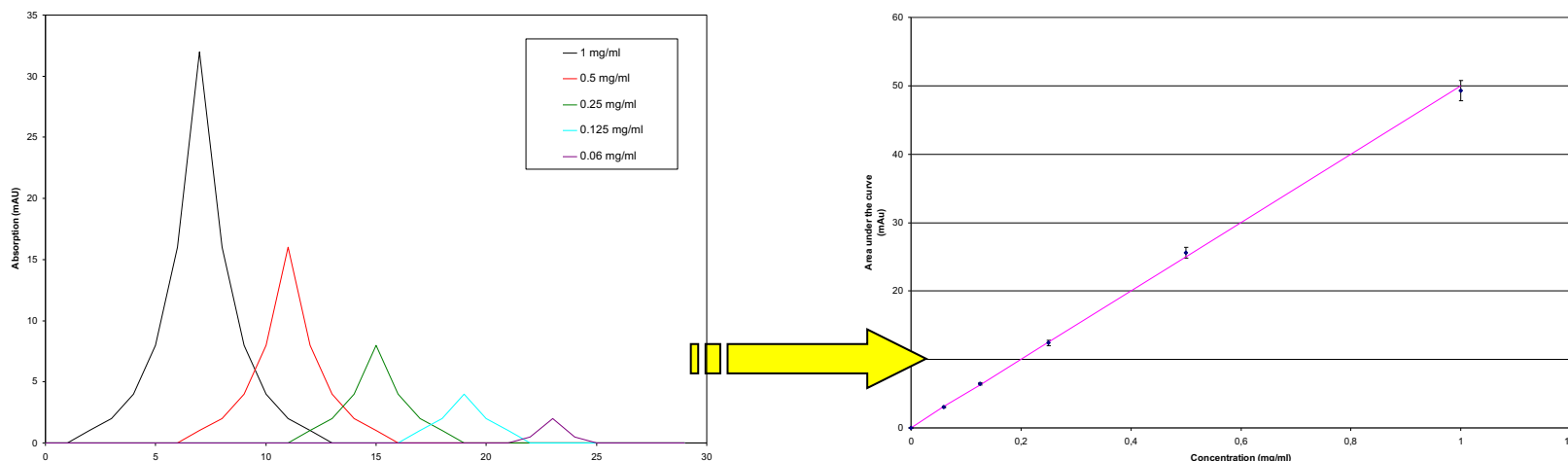
- Why is Specific activity so important??

- Cold tracer can block your targets.
- Can reduce your labelling efficiency.
- Contaminates are usually present in much greater amounts than your activity which is present only in ultra-trace quantities (even for high amounts of radiation)
- **A large amount of effort goes into ensuring the max SA possible!**



Experimental determination of the specific activity

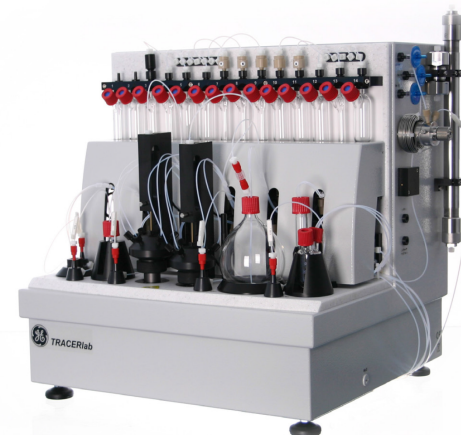
- Serial dilution of the non-radioactive („cold“) standard
- Consecutive measurement with signal integration on a HPLC or GC system



- Perform a radiosynthesis and run a sample of defined volume of your reaction solution under the same conditions as the serial dilution
=> concentration of total amount (sum of hot and cold product).
- With the knowledge of the total volume of the reaction solution, the concentration of the reaction solution determined via HPLC or GC and the measured radioactivity
- calculate the specific activity to the time of the HPLC/GC run

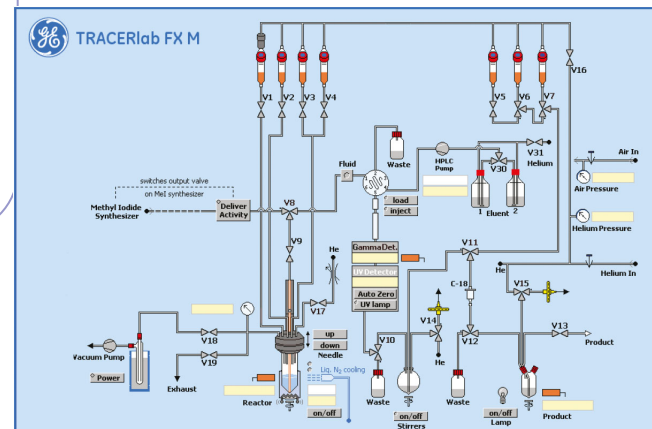
Setup Synthesiser

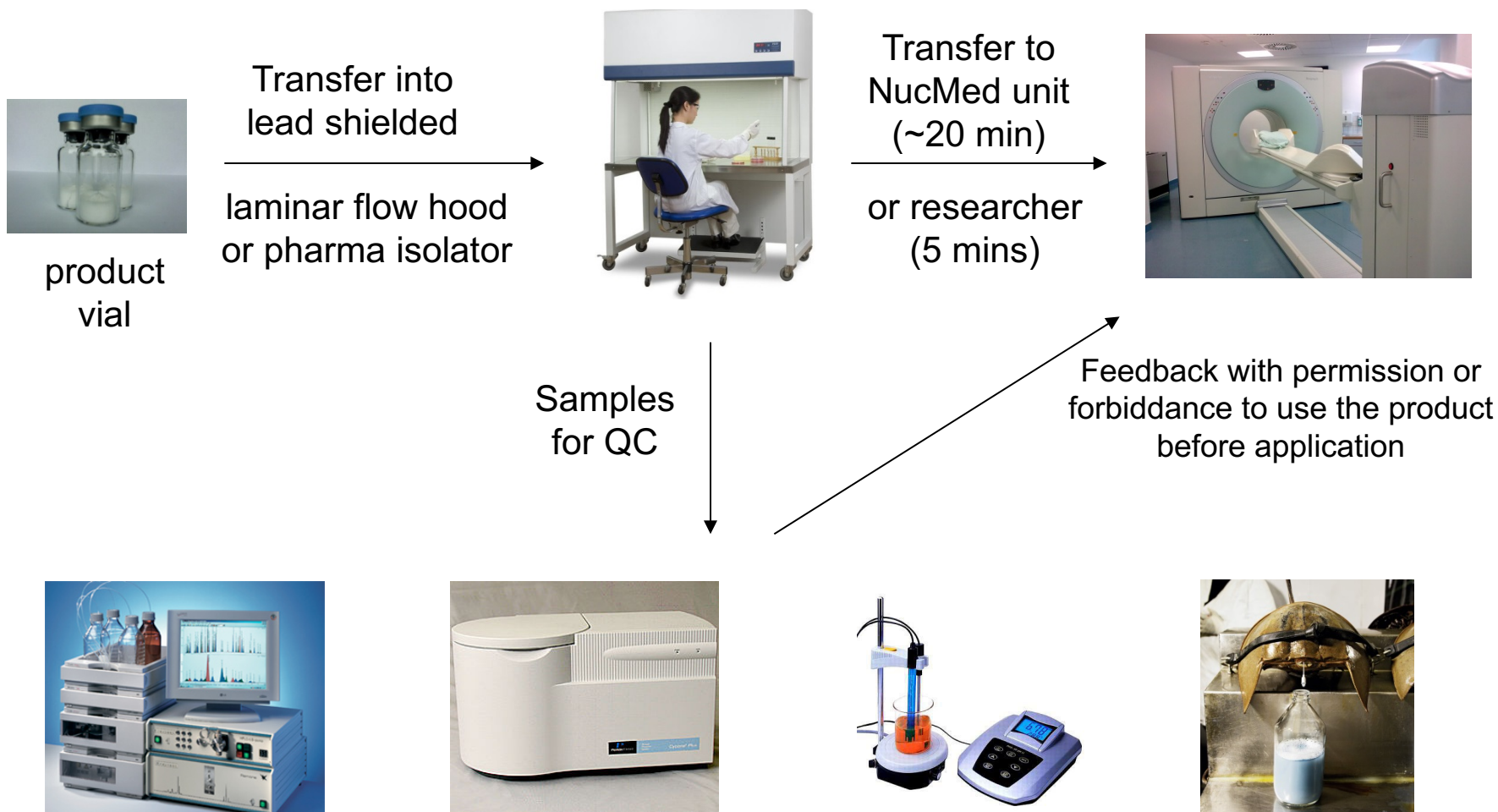
- Load reagents, chemicals, solvents, etc.



Run synthesis program

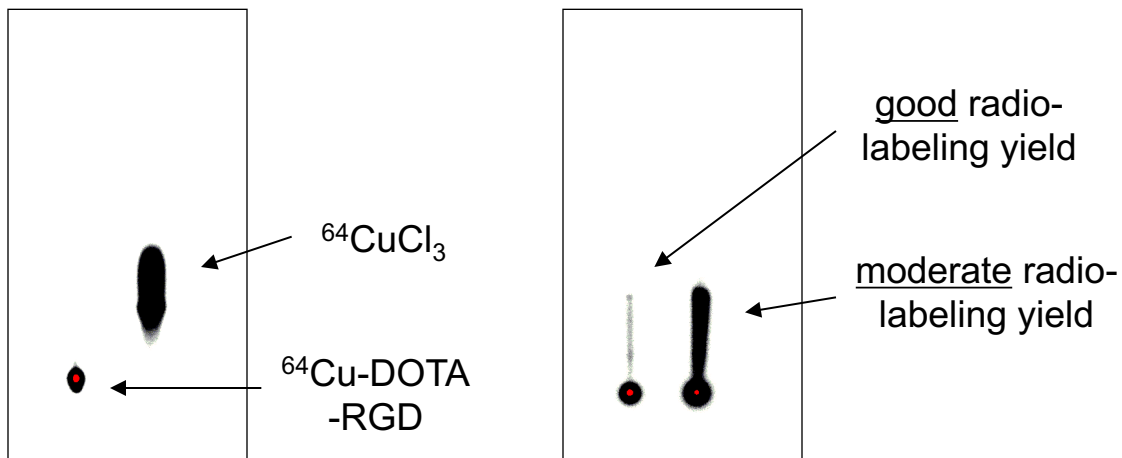
- Run a pre-made program based on a time list of scheduled events.



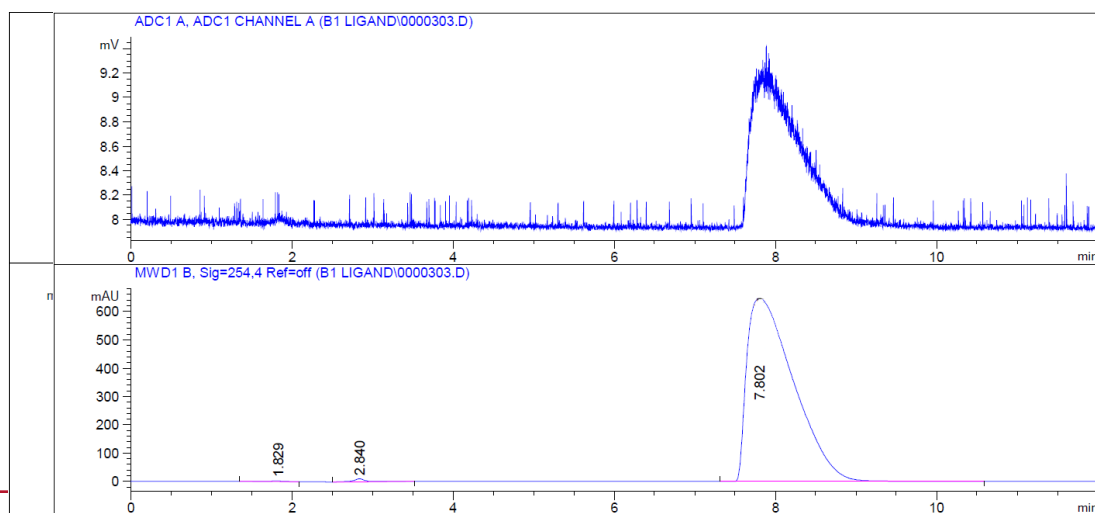


Tests for chemical identity, (radio-)chemical purity, pH value, osmolality, endotoxins and sterility (~30 mins).

Radio-TLC

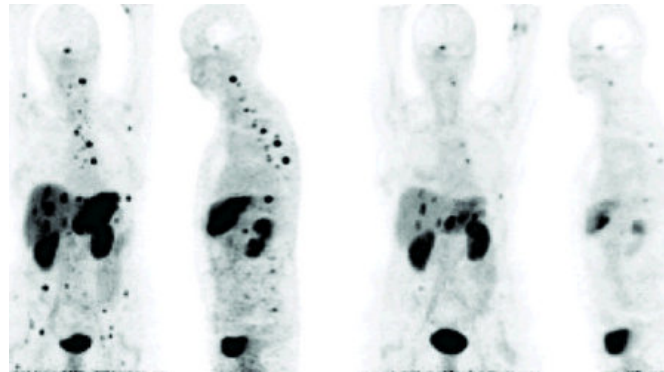
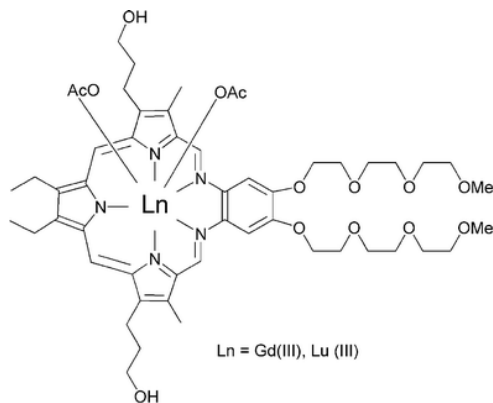


Radio-HPLC





- Radioactivity
- Radiochemistry
- Radiopharmaceuticals
- Specific activity
- Radioactive decay ($t_{1/2}$)
- Pharmakokinetics
- Metabolism

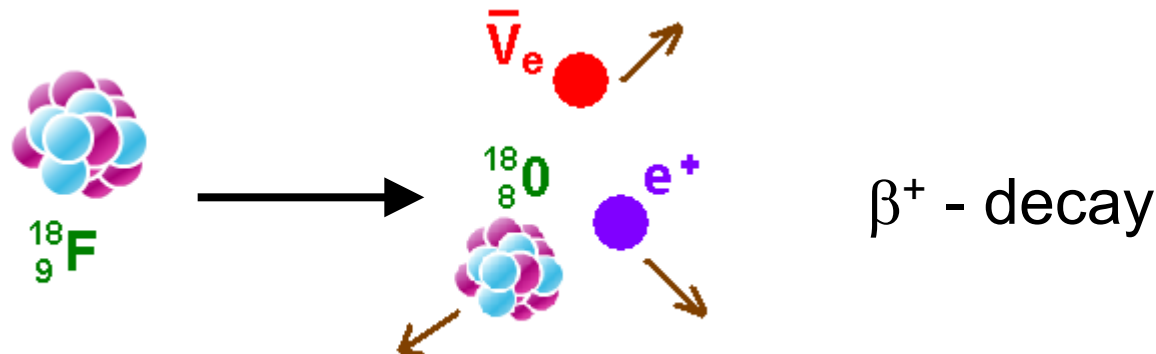


Treatment with Bi-213



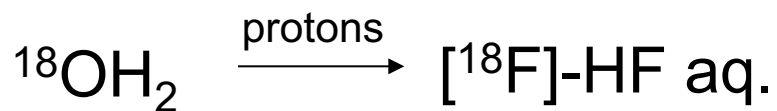
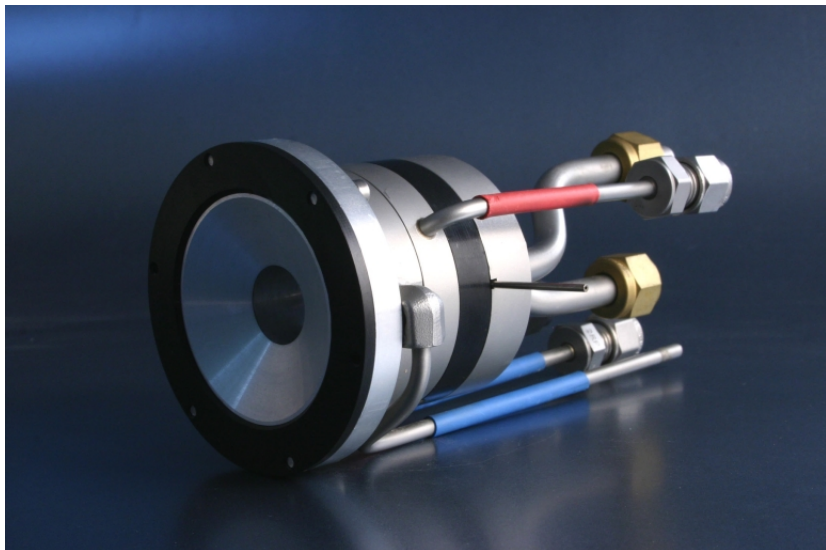


- Fluorine-18 is a **synthetic isotope**, which does not occur in nature and typically is produced *via* a proton accelerator (i.e. a **cyclotron**).
- Half-life time of ~110 mins**; almost exclusive **β^+ - decay** (positron emission 97% and 3% electron capture).
- Fluorine has the **highest electronegativity of 4.0** (Pauling scale) of all elements and therefore all chemical bonds with fluorine are polarized towards it .



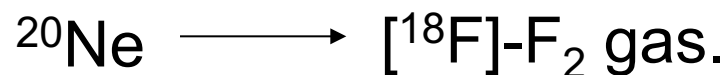
Production of F-18

via ,water target' $^{18}\text{O}[\text{p},\text{n}]^{18}\text{F}$



↓
Nucleophilic
Substitution

via ,gas target' $^{20}\text{Ne}[\text{d},\alpha]^{18}\text{F}$

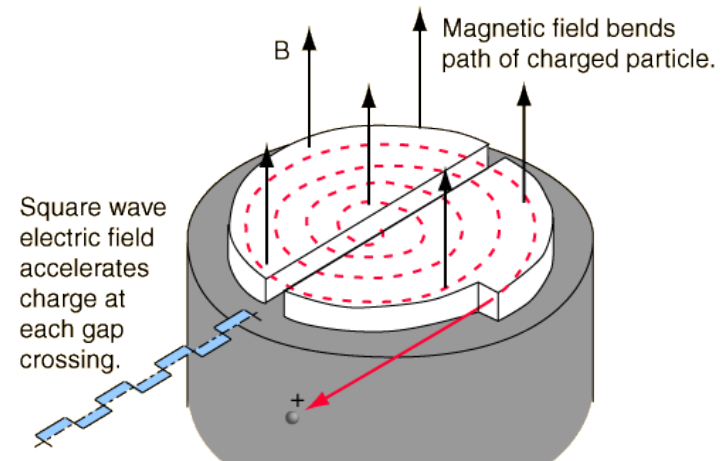
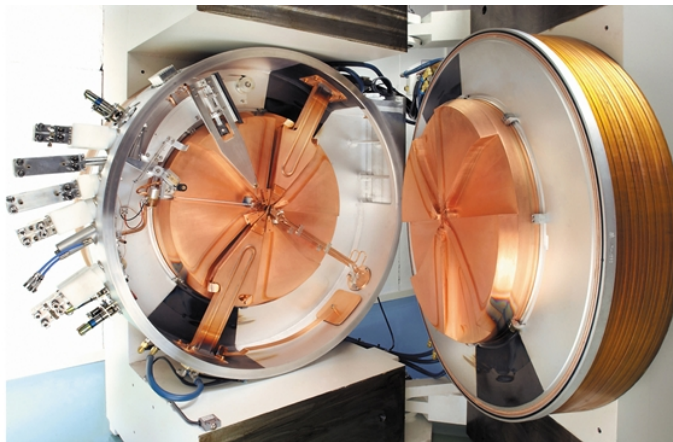
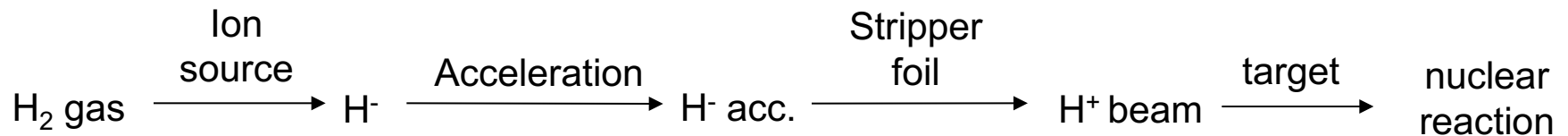


↓
Electrophilic
Addition

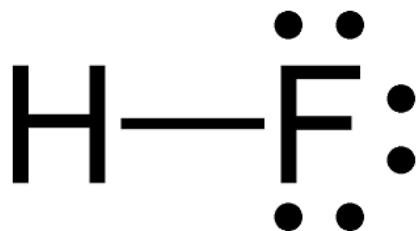


A 60 min of bombardment of a water target with protons produces around 40-80 GBq of aqueous [^{18}F]-HF. Depending on the target, the volume is usually 1-5 ml.

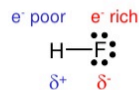
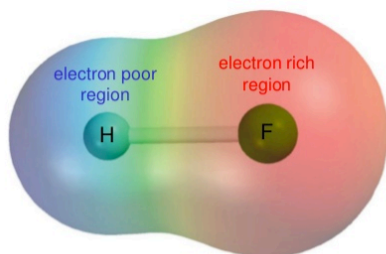
Rule of thumb: The maximum activity within the target is reached after 5-6 half-lives of the radioisotope during an irradiation on the target. But an irradiation of one half-life time gives 50% of the maximum activity.



The Problem With Fluorine chemistry

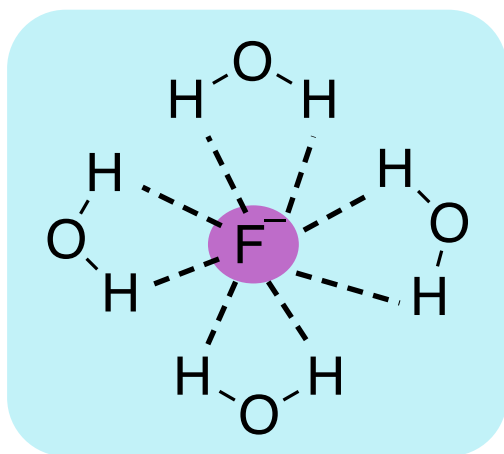


Polar covalent bond or **polar bond** is a covalent bond with greater electron density around one of the two atoms



1A	2A	3B	4B	5B	6B	7B	8B	8B	8B	1B	2B	3A	4A	5A	6A	7A	8A
1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57-71	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89-103	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo

■ Other Nonmetals ■ Metalloids ■ Alkaline Earth Metals
■ Halogens ■ Alkali Metals ■ Post-Transition Metals
■ Noble Gases ■ Transition Metals



X	H-X Bond Strength	Electronegativity	pK _a
F	565 kJ/mol	4.0	3.1
Cl	427 kJ/mol	3.0	-7.0
Br	363 kJ/mol	2.8	-9.0
I	295 kJ/mol	2.5	-11.0

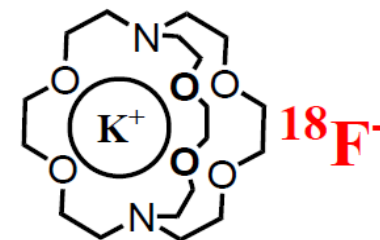
F-18 Nucleophilic Sources



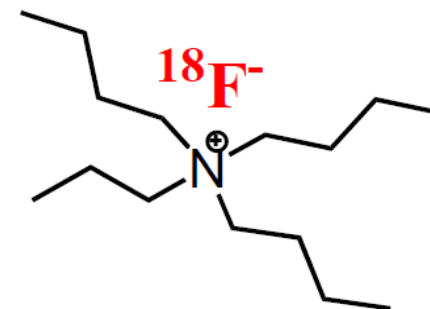
1A	2A	3B	4B	5B	6B	7B	8B	8B	8B	1B	2B	3A	4A	5A	6A	7A	8A
1 H																	2 He
3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
55 Cs	56 Ba	57-71	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
87 Fr	88 Ra	89-103	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Uut	114 Fl	115 Uup	116 Lv	117 Uus	118 Uuo

Other Nonmetals Metalloids Alkaline Earth Metals
Halogens Alkali Metals Post-Transition Metals
Noble Gases Transition Metals

KF/Cryptand

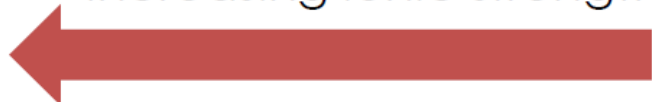


Tetraalkylammonium fluoride



Common alkali metal fluorides

Increasing ionic strength



$\text{LiF} < \text{NaF} < \text{KF} < \text{CsF}$



Increasing nucleophilicity
Increasing solubility

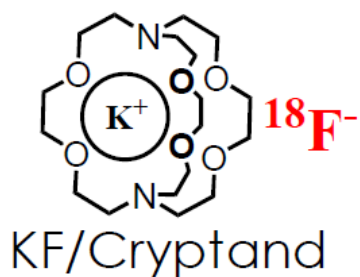
(1) Role of PTC?

(2) Role of base?

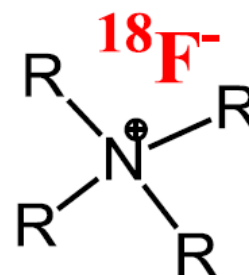
32



Kryptofix ($\text{K}_{2.2.2}$)
 K_2CO_3



Tetrabutylammonium
carbonate
or bicarbonate

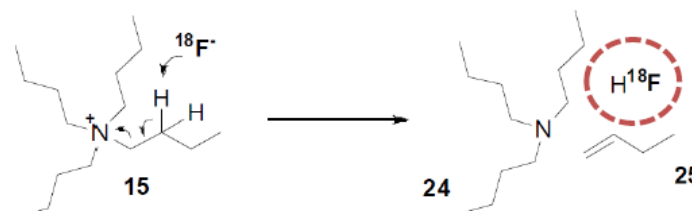


Cesium carbonate
or bicarbonate

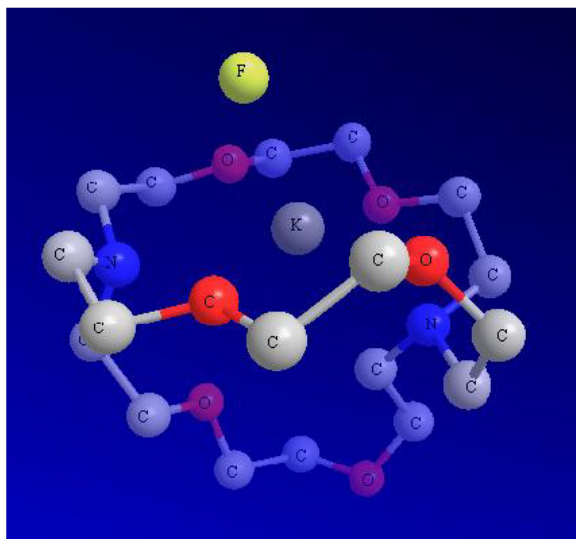


Tetraalkylammonium fluoride

R = methyl, ethyl, butyl

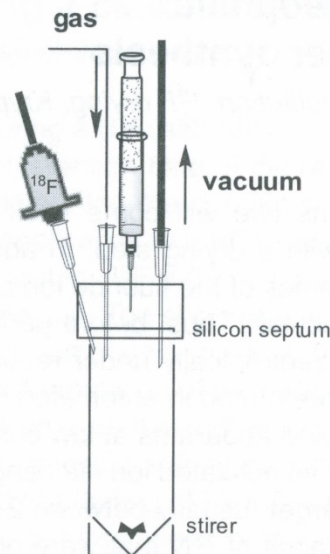


Thermal decomposition of TB⁺F⁻



Nucleophilic Substitution (most commonly applied method)

[^{18}F]-HF acquired from a water target is unreactive and requires a laborious drying process, to gain 'water-free' [^{18}F]-KF. Potassium fluoride is the reactive species for **most nucleophilic substitution reactions** in radiochemistry.

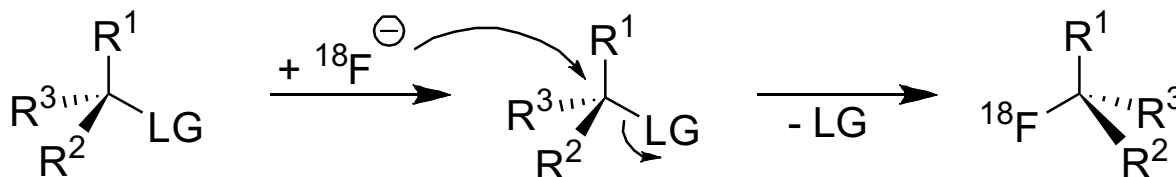


Equipment:

- reaction vial 5 mL + silicon septum lid
- vacuum tubing
- gas tubing for He or N₂
- syringe 1 mL
- gas cylinder (He or N₂)
- oil bath or heating block
- heater with thermometer
- magnetic stirring bar
- QMA light cartridge

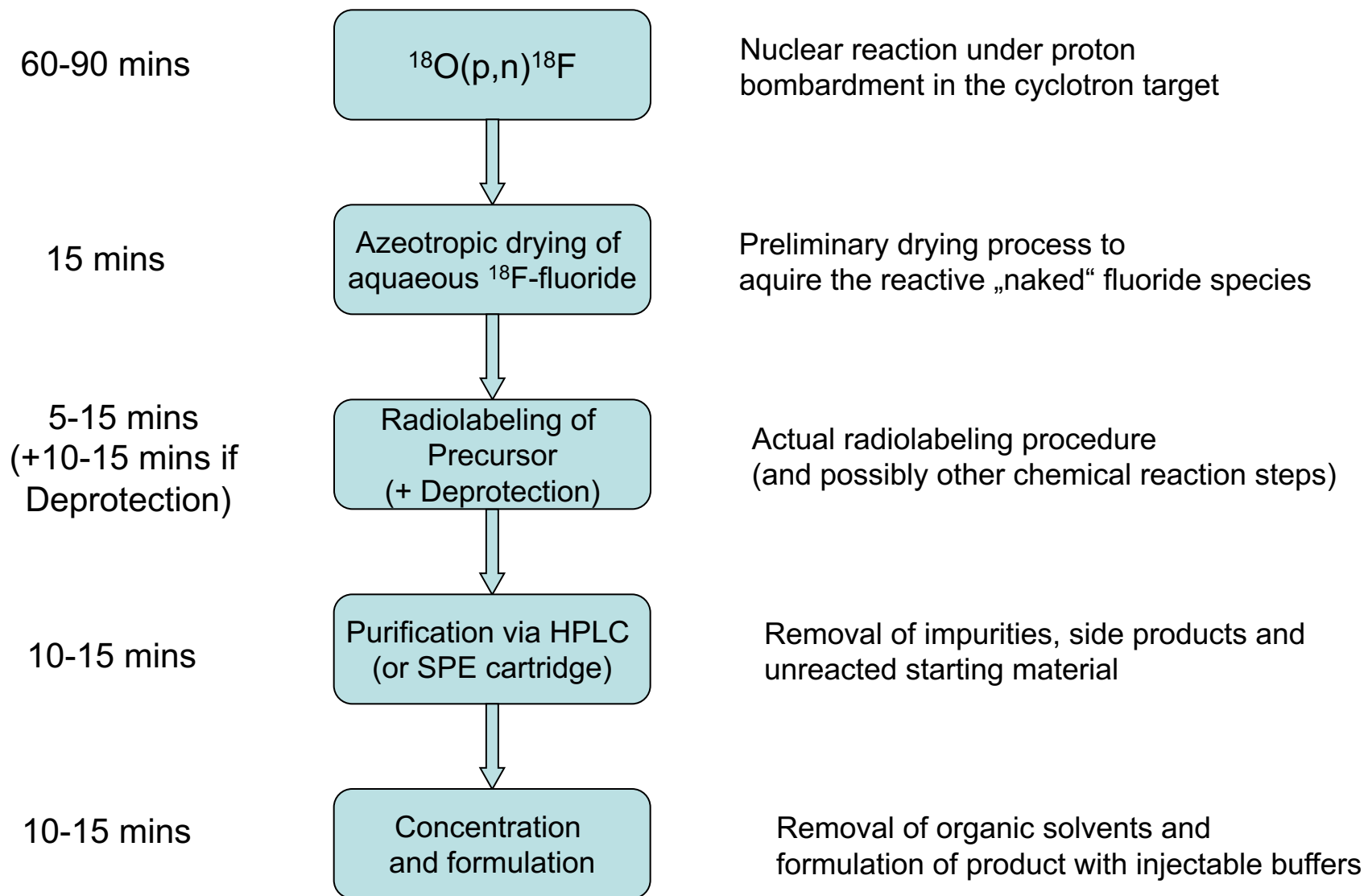
Chemicals:

- Kryptofix 2.2.2 or Cs₂CO₃ or NBu₄⁺HCOO⁻
- K₂CO₃ or potassium oxalate (only when Kryptofix 2.2.2 is used)
- acetonitrile



LG: leaving group

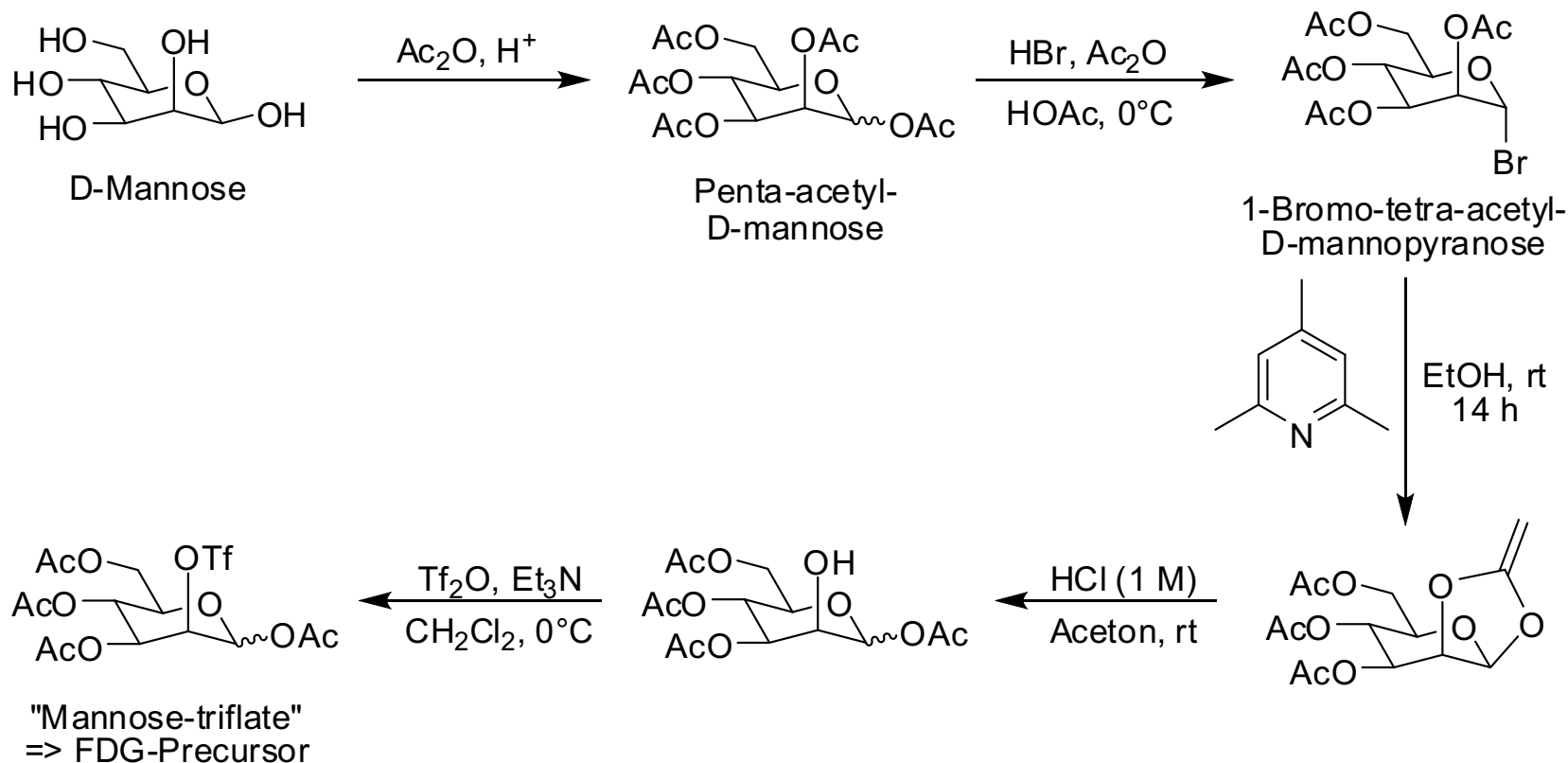
- Cl, -Br, -I
- OMs, -OTs, -ONs
- ⁺NMe₃

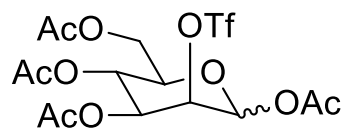




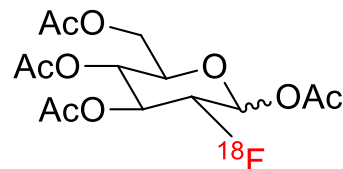
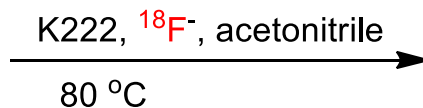
Synthesis of FDG

(1) Precursor synthesis



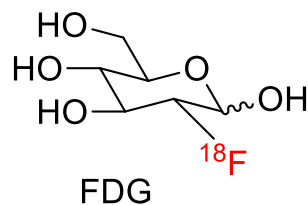


"Mannose-triflate"
=> FDG-Precursor



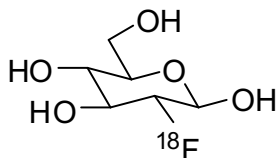
1. QMA clean up

2. NaOH

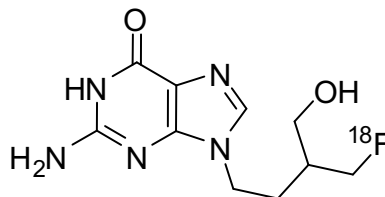


formulated in buffer

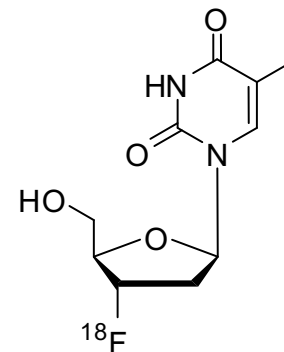




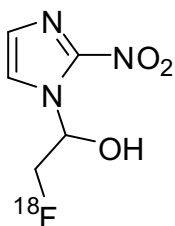
FDG
(2-Fluor-desoxy-glucose)



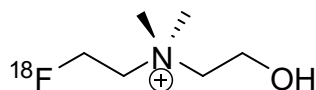
FHBG



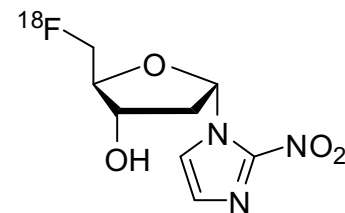
FLT



FMISO

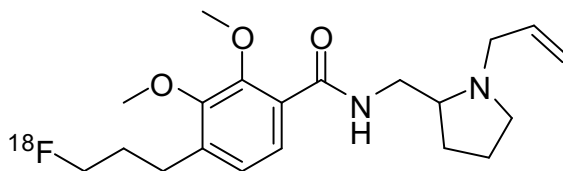


FEC

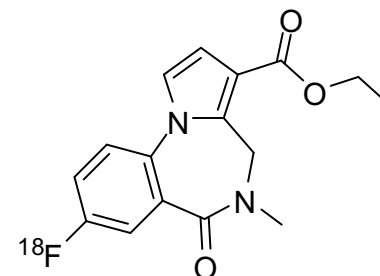


FAZA

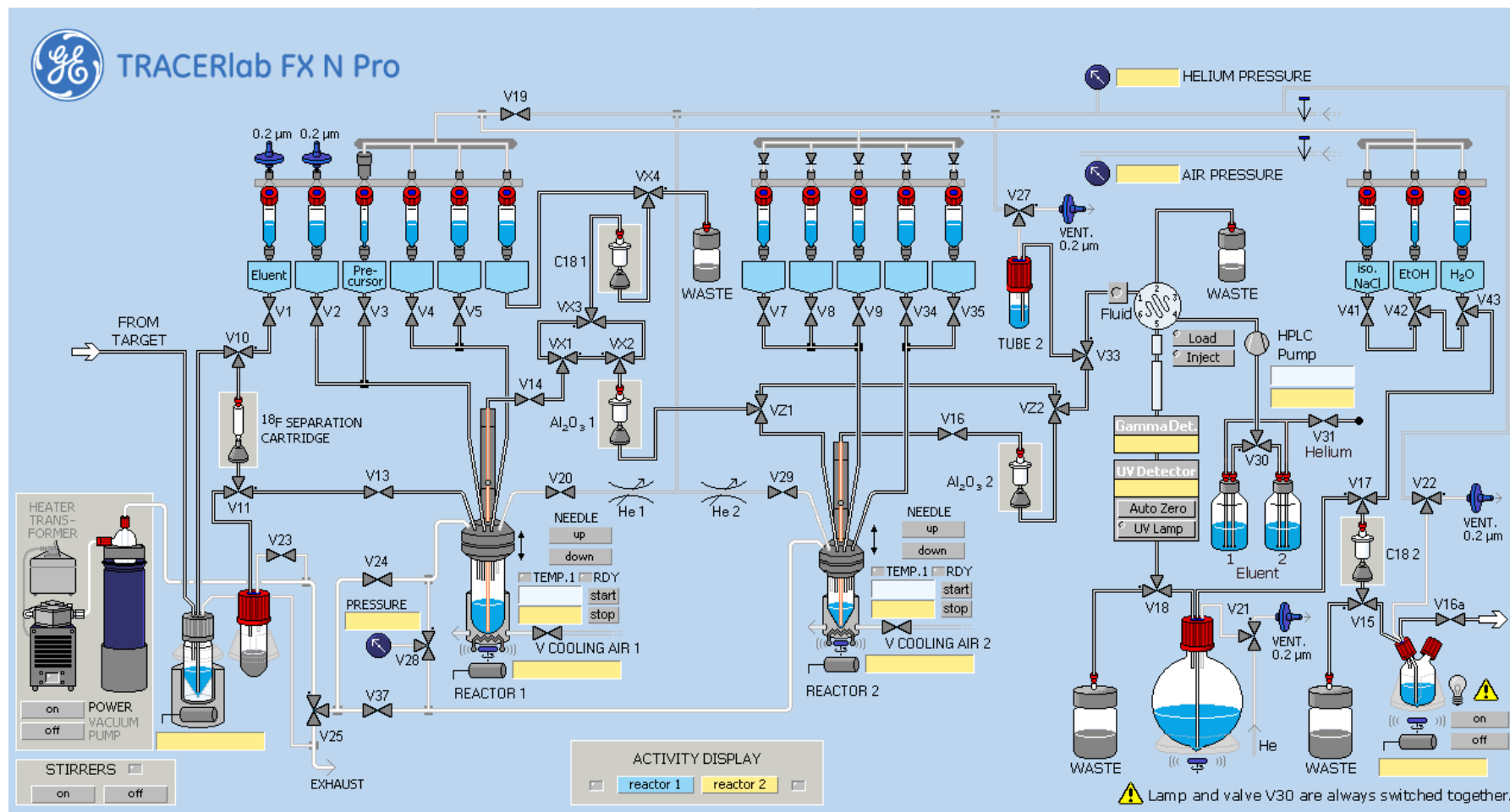
Fallypride

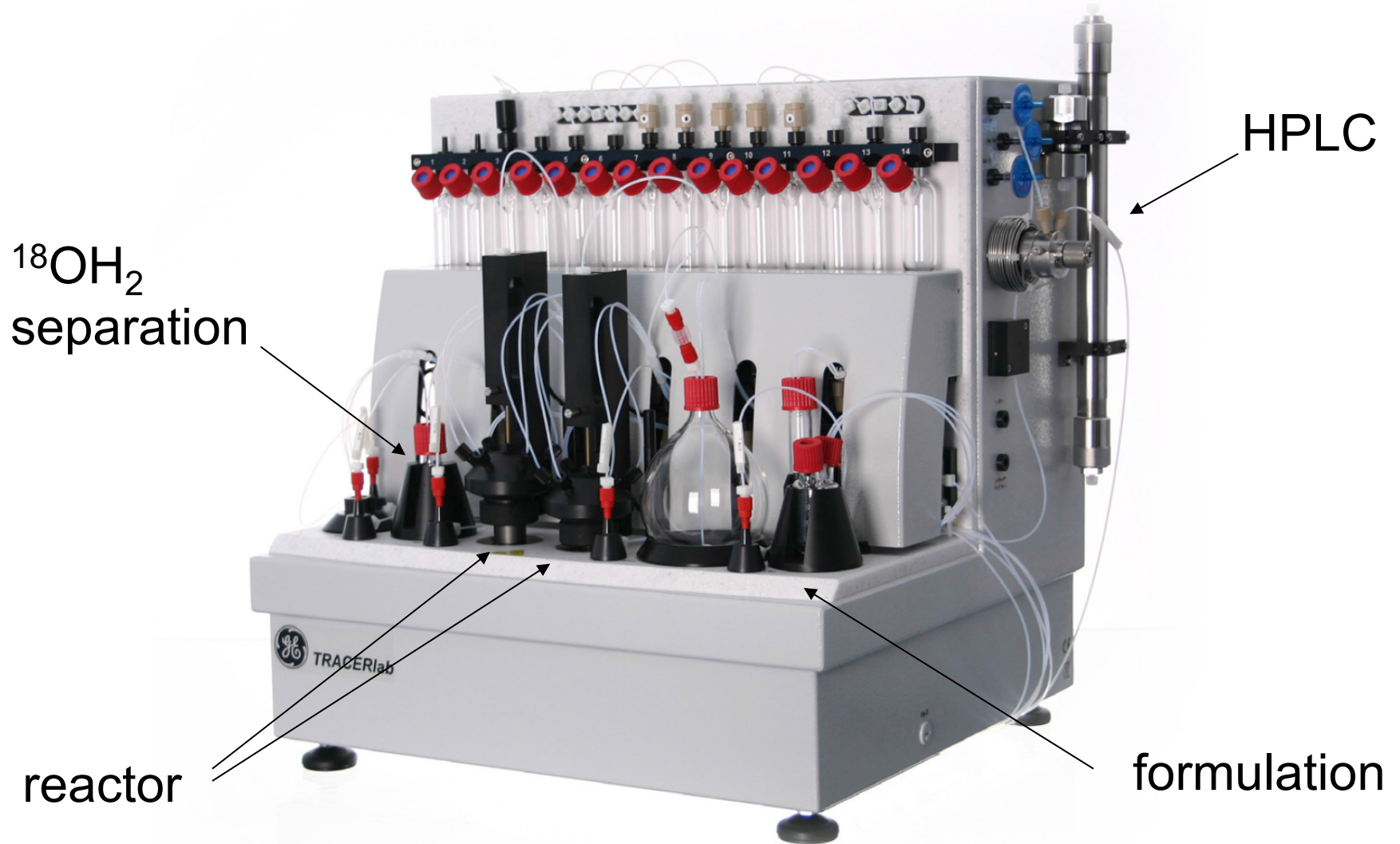


Flumazenil



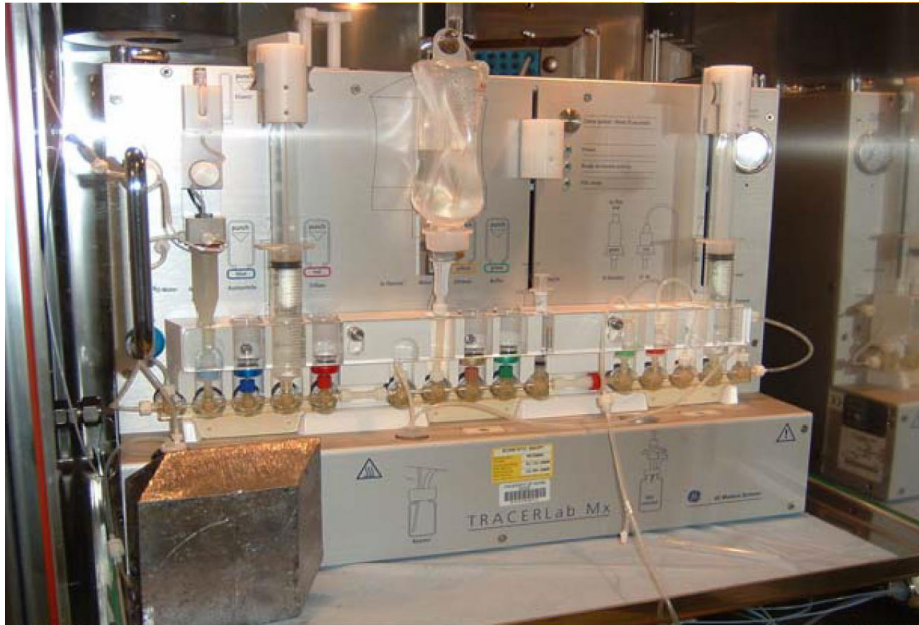
Flowchart GE Tracerlab Fx N Pro







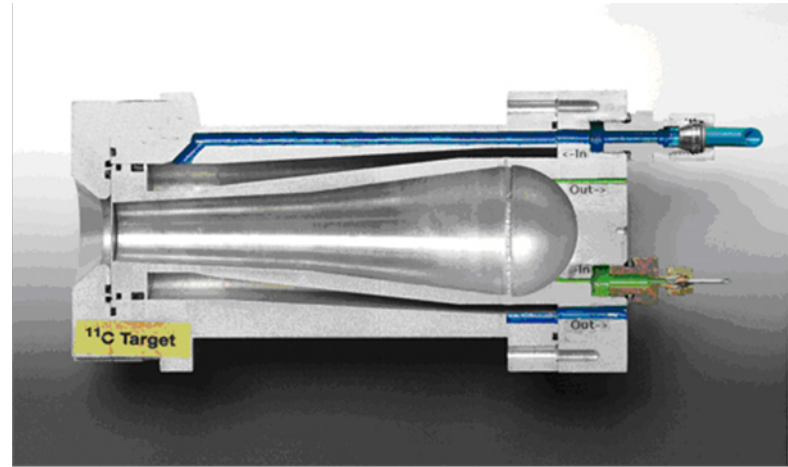
Synthesis of FDG: GE Tracerlab Mx (cartridge system)





Carbon-11 is a synthetic isotope which does typically not occur in nature.

Several nuclear reactions can be used to produce ^{11}C , but the most commonly used and convenient method is the application of a **nitrogen gas target** $^{14}\text{N}(\text{p}, \alpha)^{11}\text{C}$.

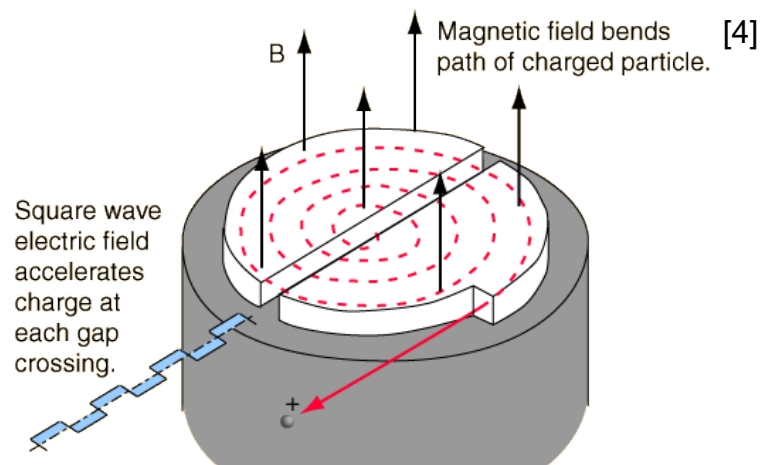
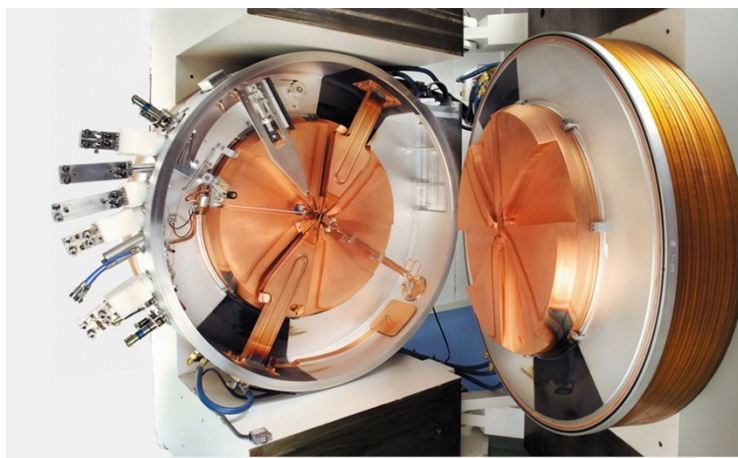
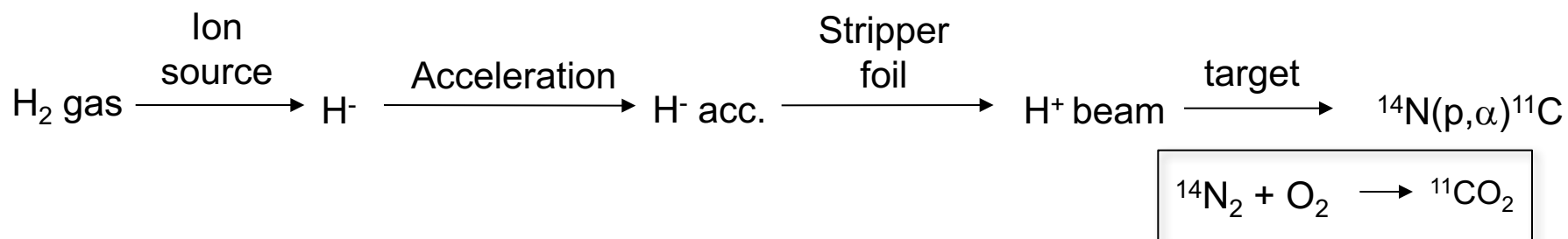


Half-life: 20.3 mins

Decay mode: 99.8% by positron emission

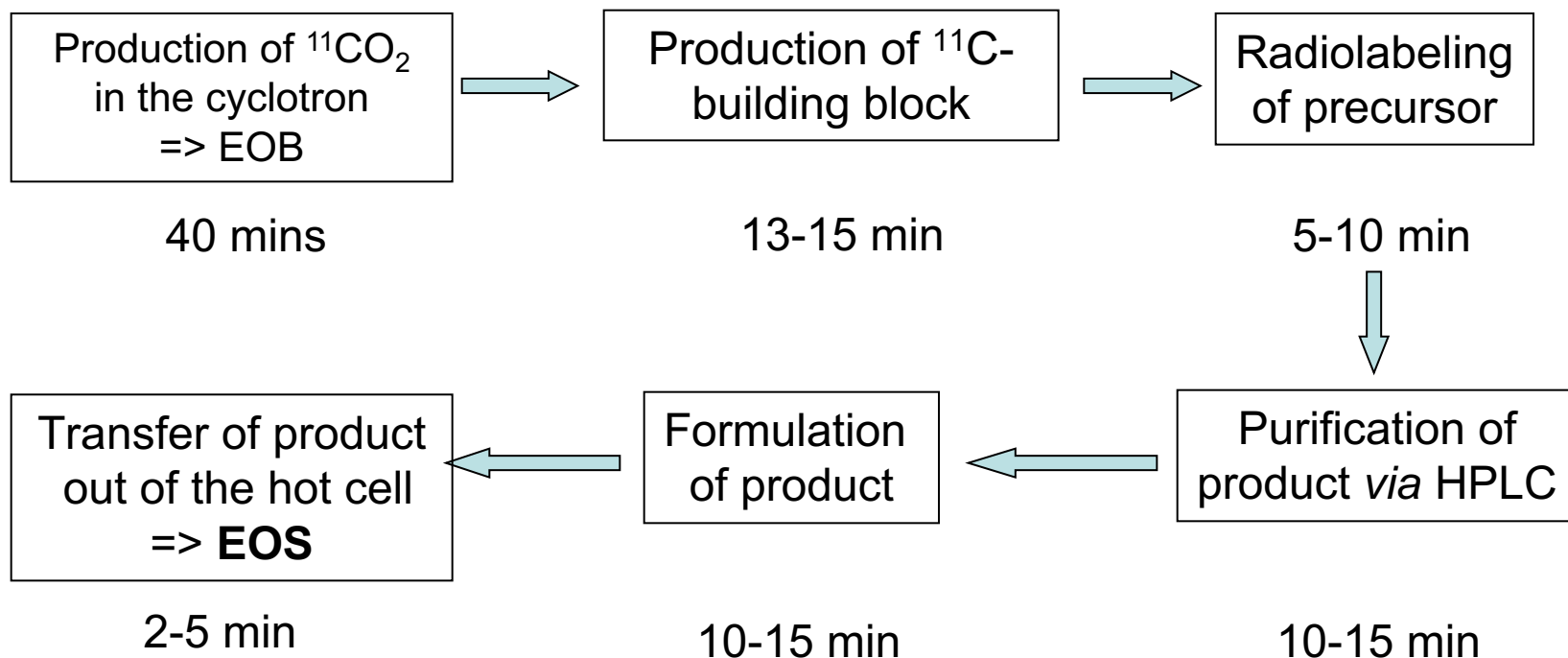
Maximum range (in water): 4.1 mm

Source of isotopes for PET radiochemistry is mostly a cyclotron. A cyclotron is a proton / deuteron accelerator, which accelerates protons / deuterons on a spiral trajectory.





Sequence of a ^{11}C -radiosynthesis



Minimum time for ^{11}C -radiosynthesis: ~30 min (without irradiation time)

Typical time for ^{11}C -radiosynthesis: ~60 min (without irradiation time)

Typical $^{11}\text{CO}_2$ activity after irradiation: ~ 200 GBq (EOB)

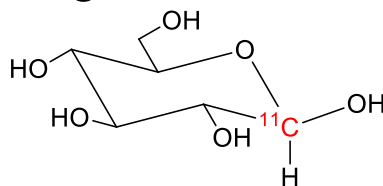


Organic Chemistry with ^{11}C

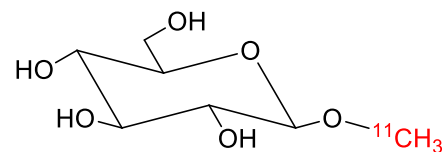
In principle, ^{11}C is a candidate for the isotopic or non-isotopic labeling of any organic compounds and is thus of major importance to PET.

Isotopic labeling: ^{11}C replaces stable $^{12}\text{C}/^{13}\text{C}$ in the molecule. The biological fate of the molecule is virtually unchanged.

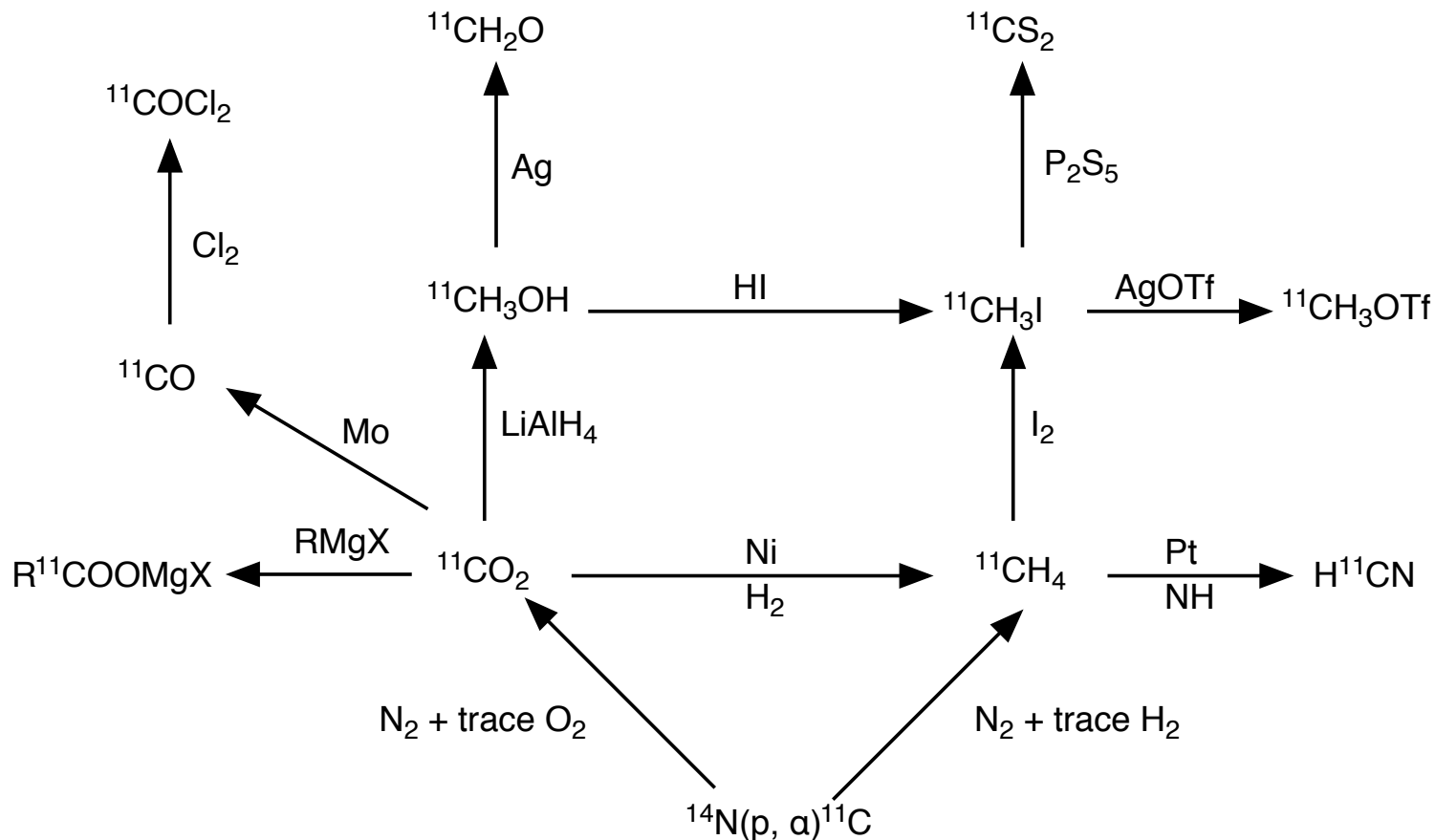
Non-isotopic labeling: a group containing ^{11}C is added to the molecule of interest, producing a new compound with different properties to the original.



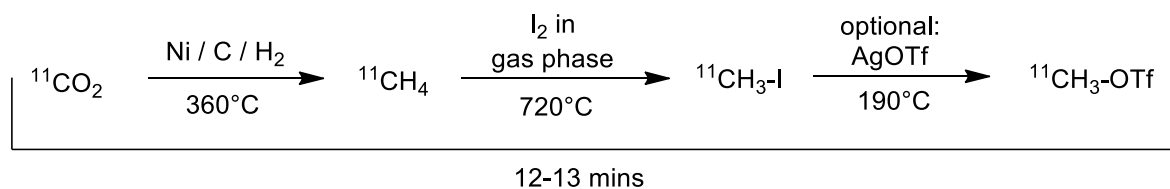
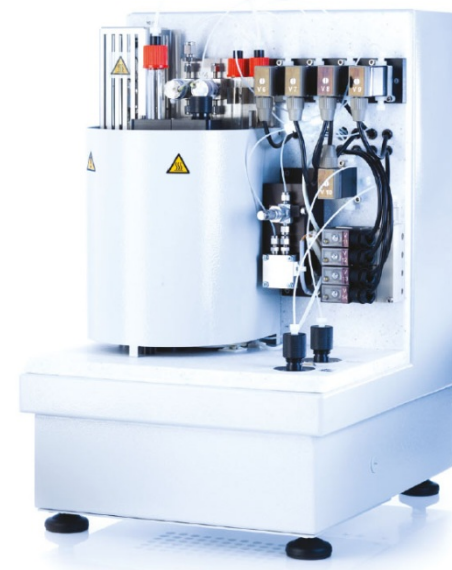
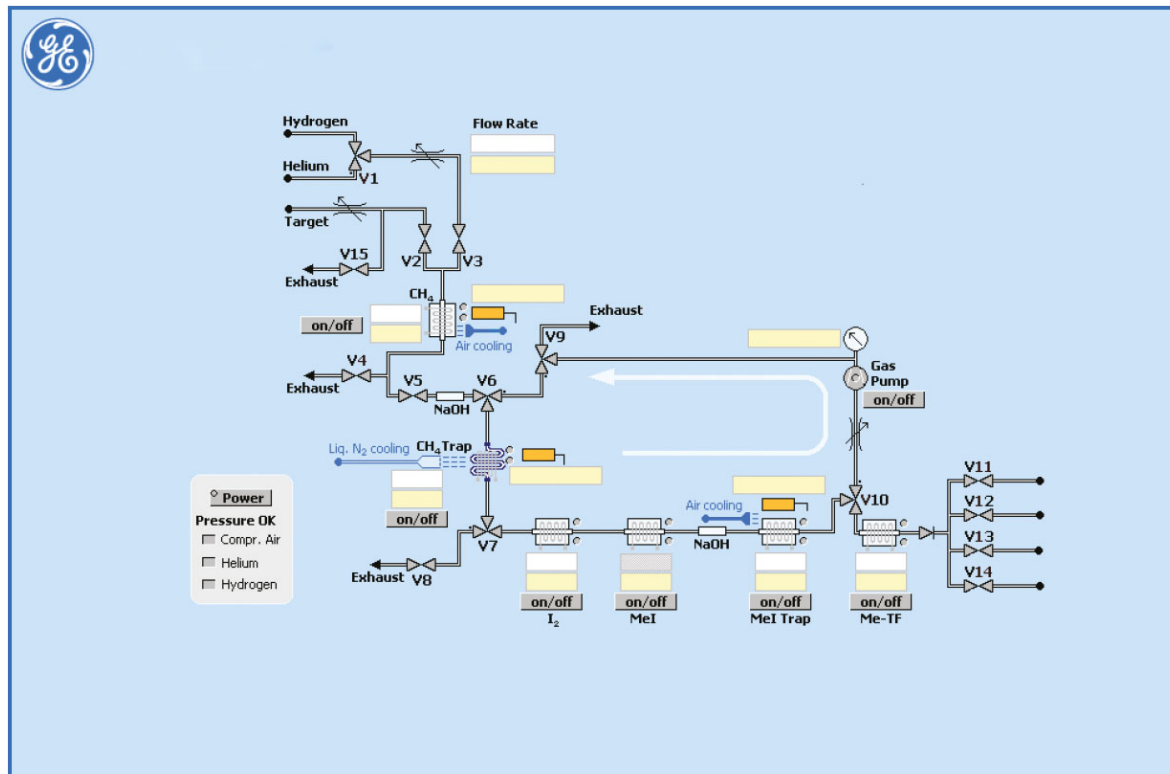
Isotopically-labeled
 ^{11}C -glucose
(substrate glucose-metabolism)



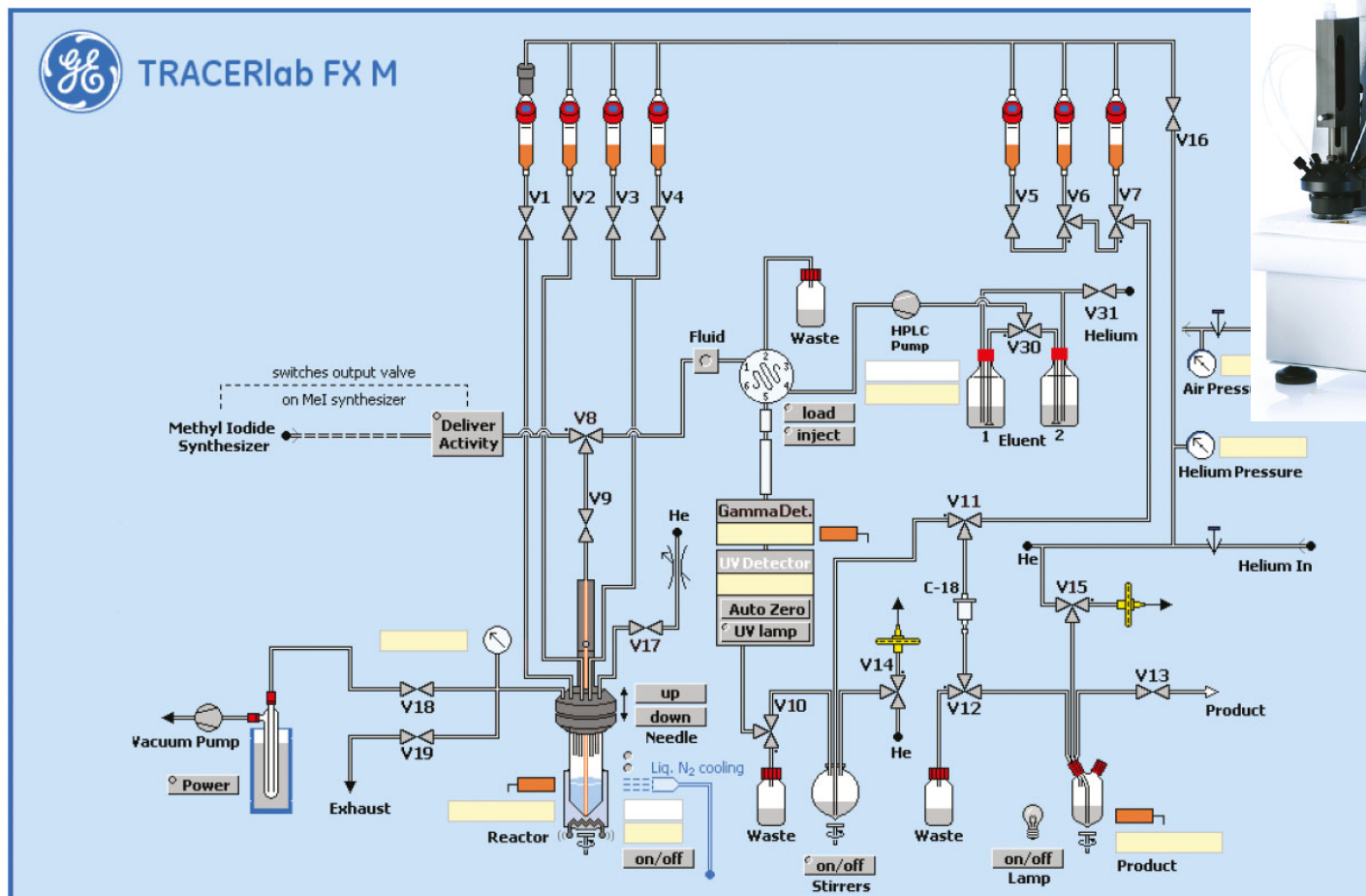
Non-isotopically-labeled
 ^{11}C -methyl-glucose
(tracer for SGLT1)

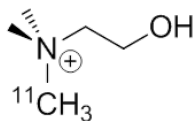


Synthesis of $[^{11}\text{C}]\text{CH}_3\text{I}$

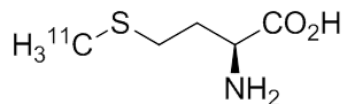


Flowchart of a ^{11}C -radiosynthesis

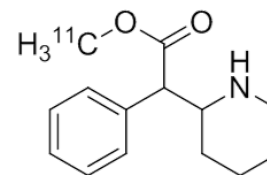




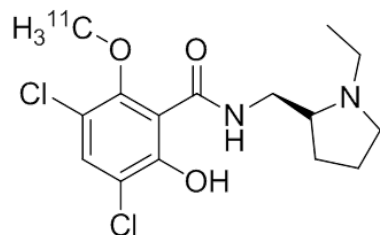
¹¹C-Choline
(=> neurotransmitter and
part of cell membranes)



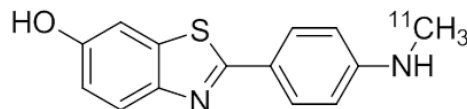
¹¹C-Methionine
(amino acid metabolism)



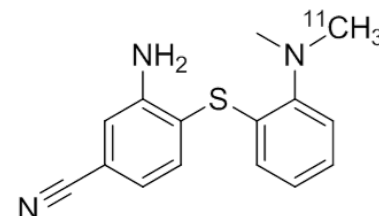
¹¹C-Methylphenidate
(Ritalin, Amphetamine)



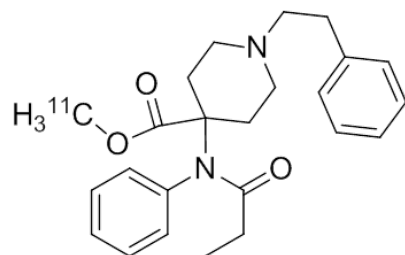
¹¹C-Raclopride
(antagonist for D2
Dopamine receptors)



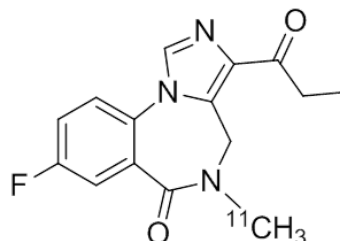
¹¹C-PIB
(binds to Aβ-
Alzheimer plaques)



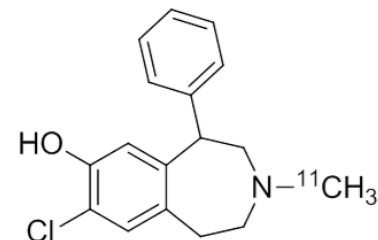
¹¹C-DASB
(binds to the Serotonin
transporter)



¹¹C-Carfentanil
(μ- or OP₃-receptor agonist)

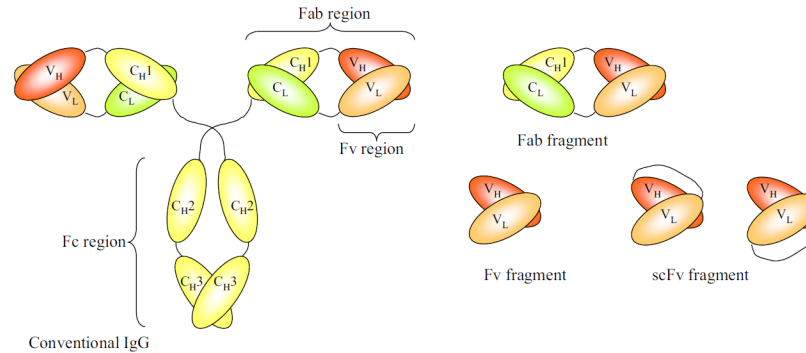


¹¹C-Flumazenil
(competitive GABA_A-receptor antagonist)

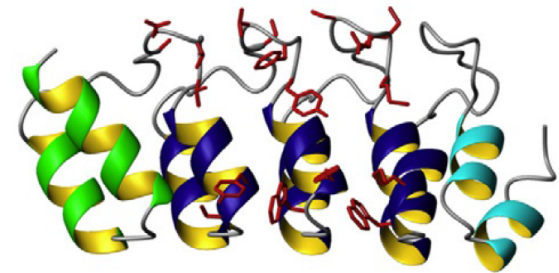


¹¹C-SCH23390
(D1 receptor antagonist)

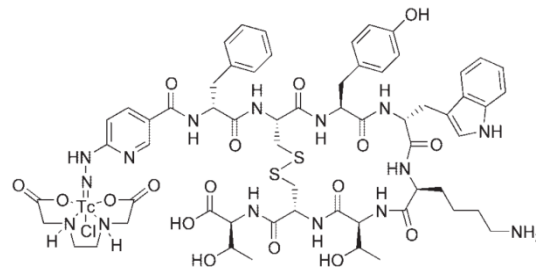
- Antibodies



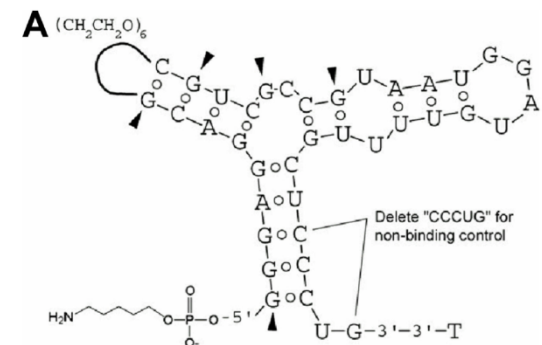
- Proteins



- Peptides



- DNA and RNA

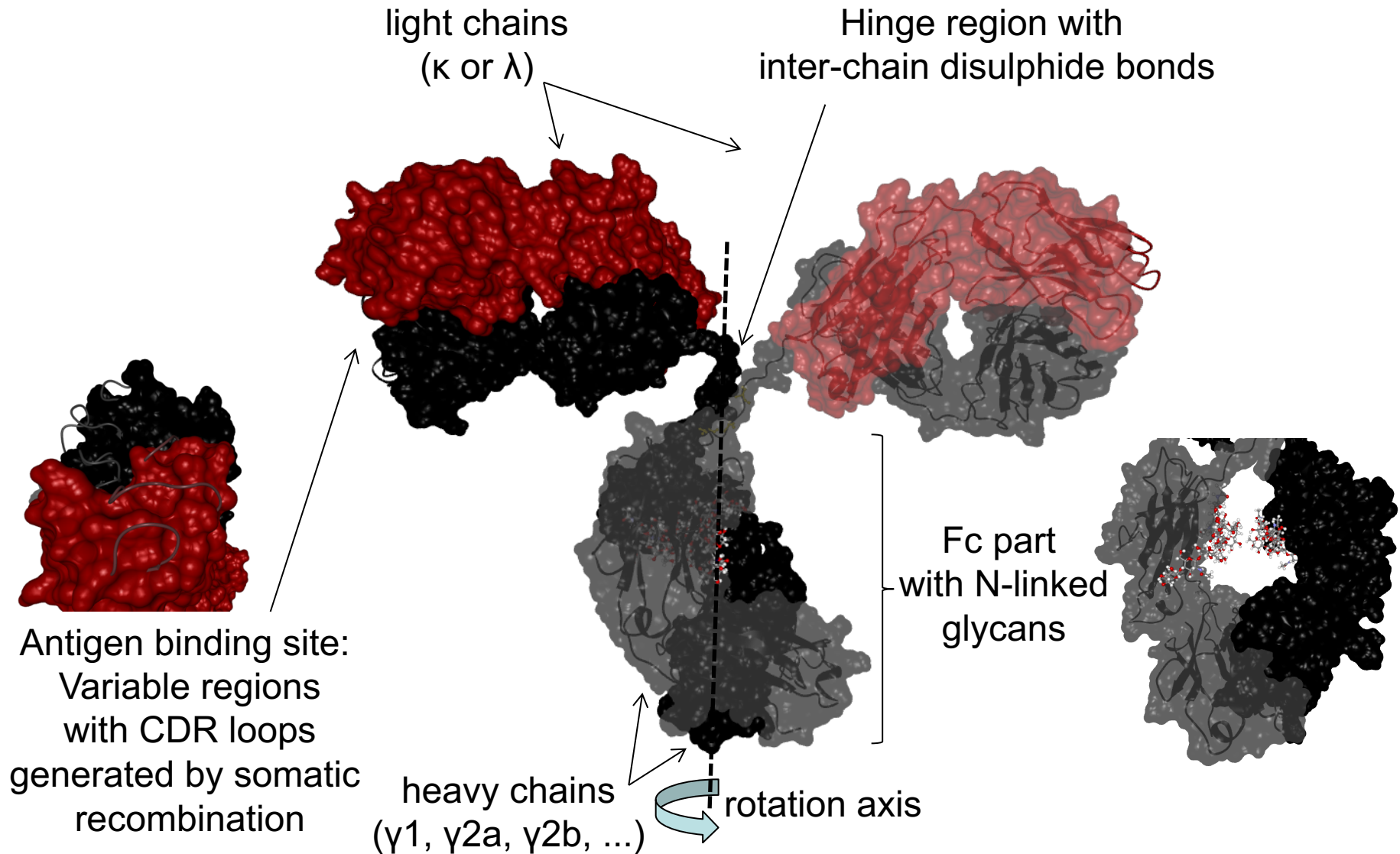


Advantages:

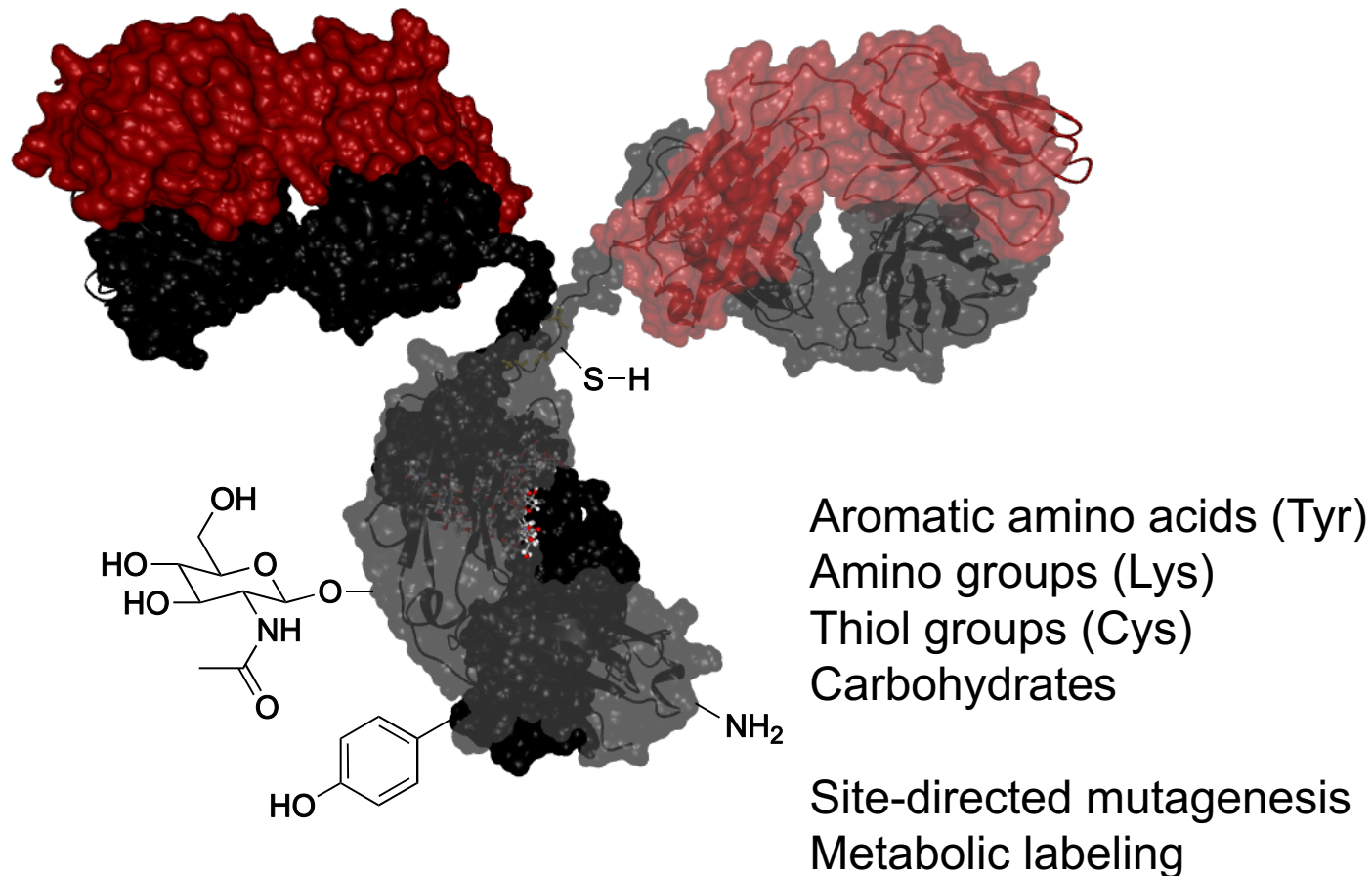
- Universal - possible for many proteins
- Easy - Often therapeutic antibodies available
- Specific - Selectivity between homologous proteins

Pitfalls:

- Only for extracellular proteins
- Large proteins - diffusion limits
- Species specific (Xenograft or transgenic models)



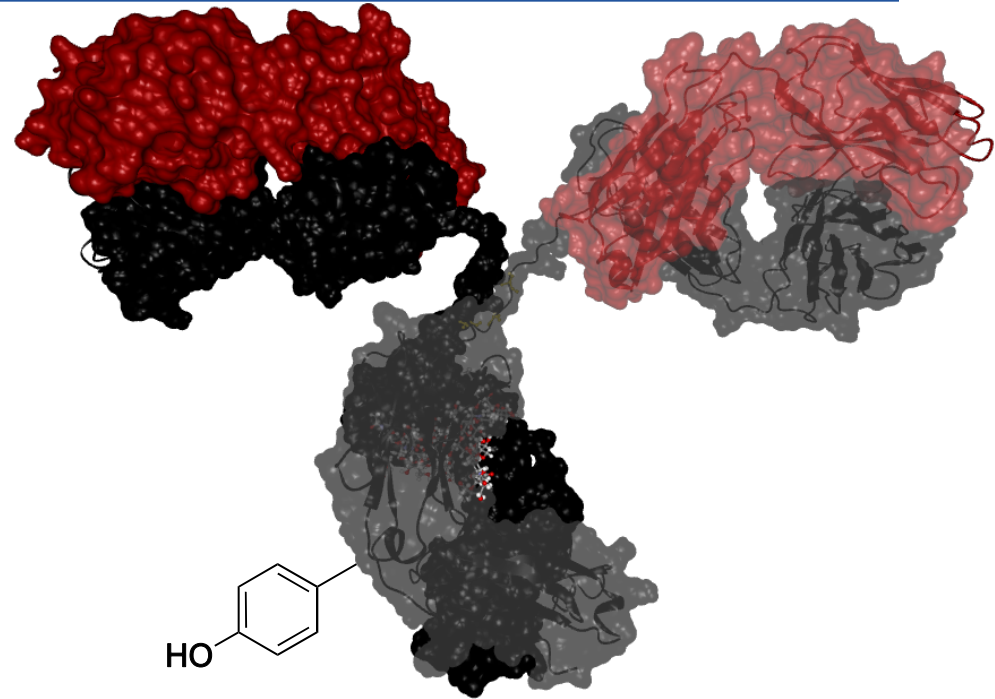
Important:
Retention of Immunoreactivity



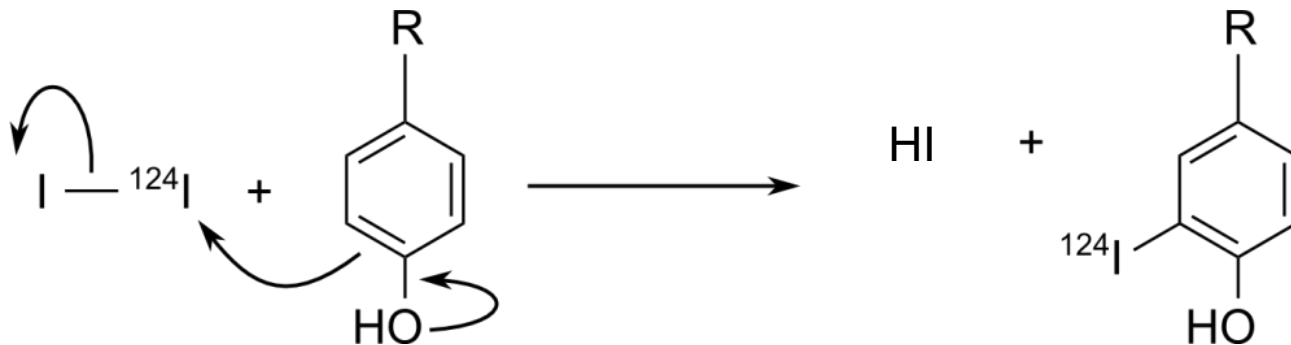
Labeling of Tyrosine Side Chains...



...with halogens:

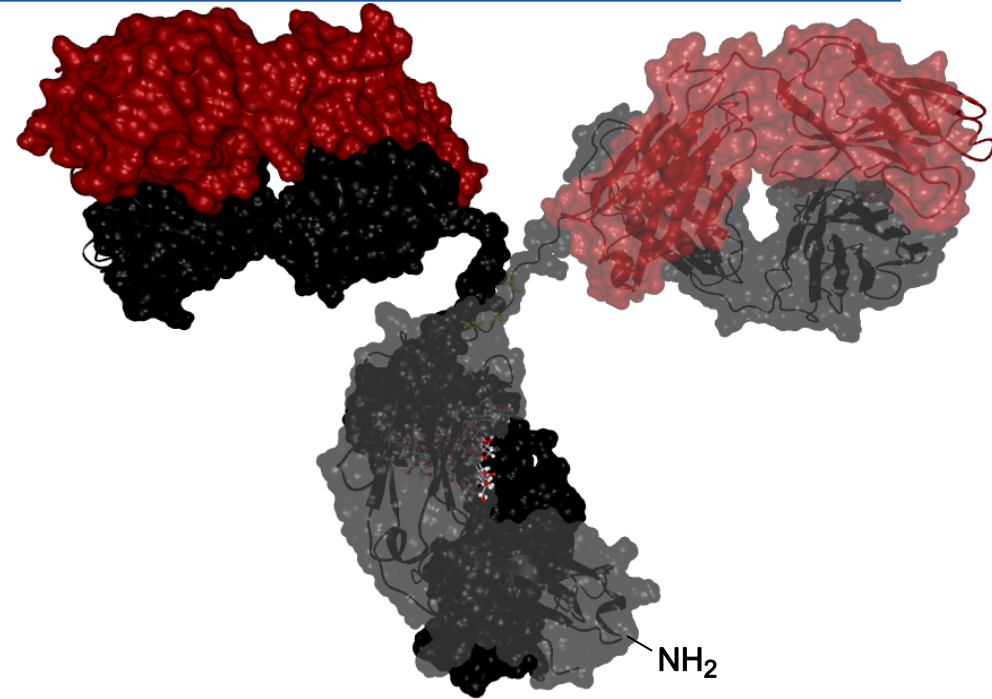


Electrophilic aromatic substitution:

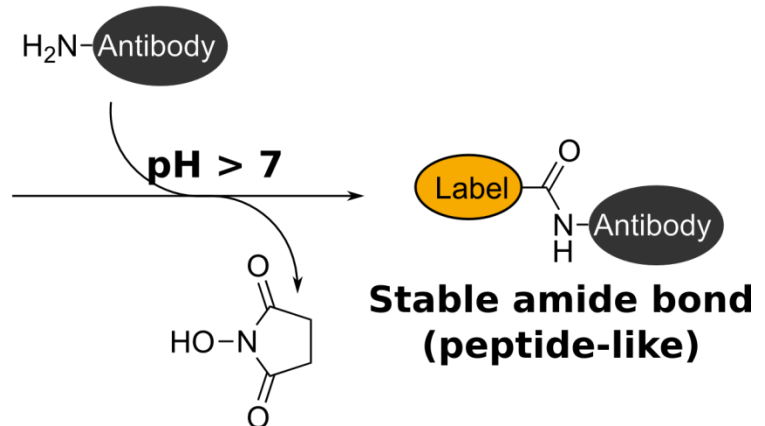
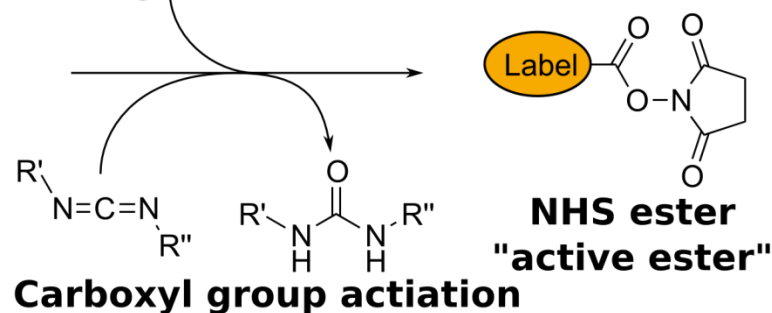
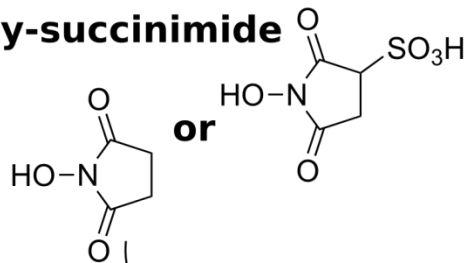


Labeling of Amino Groups...

...with carboxylic acids:



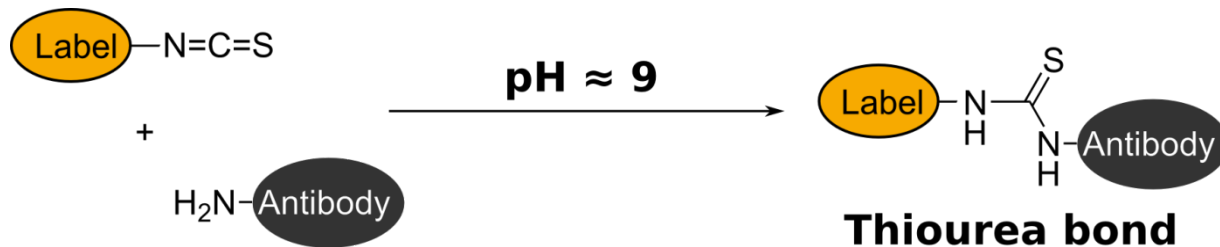
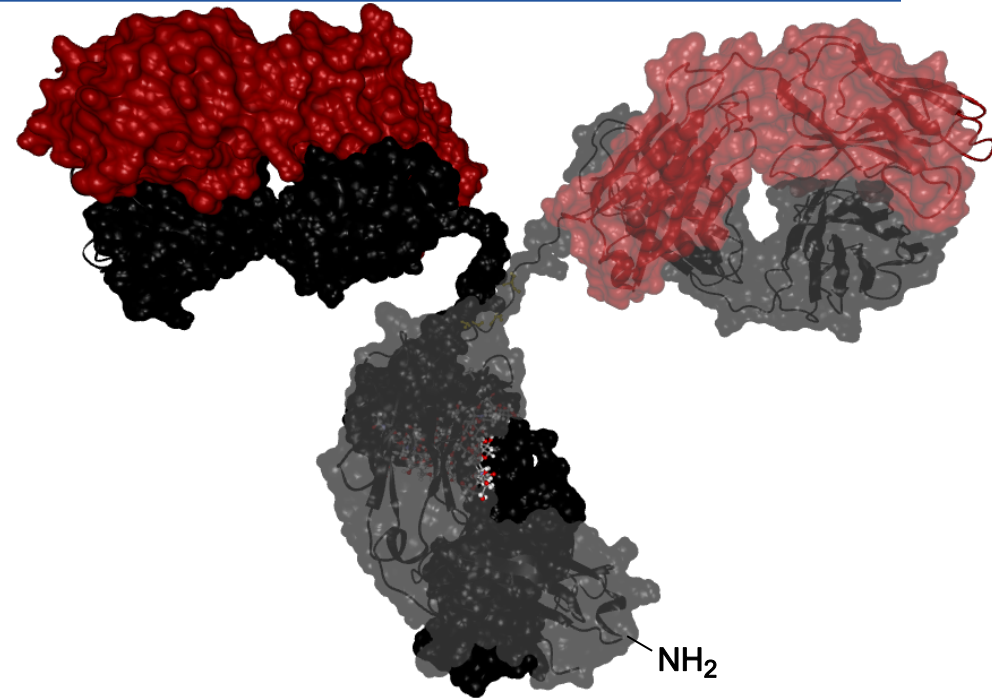
N-Hydroxy-succinimide



Labeling of Amino Groups...

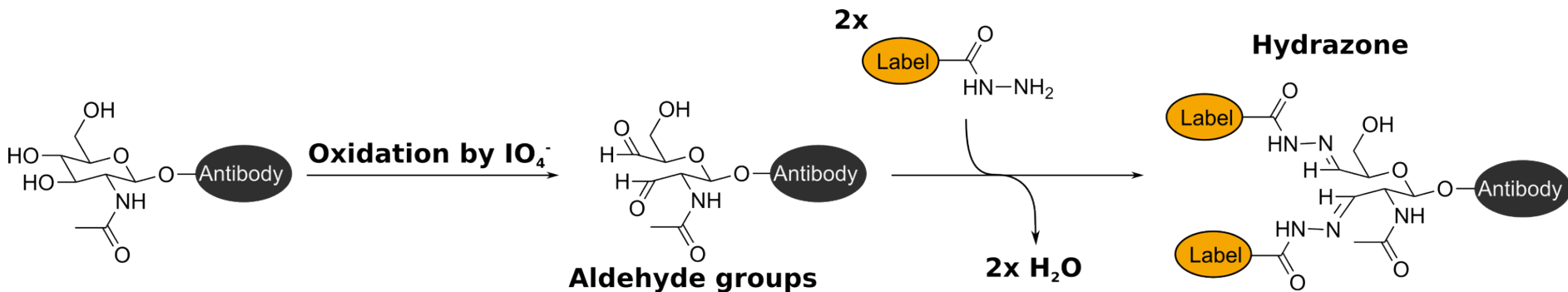
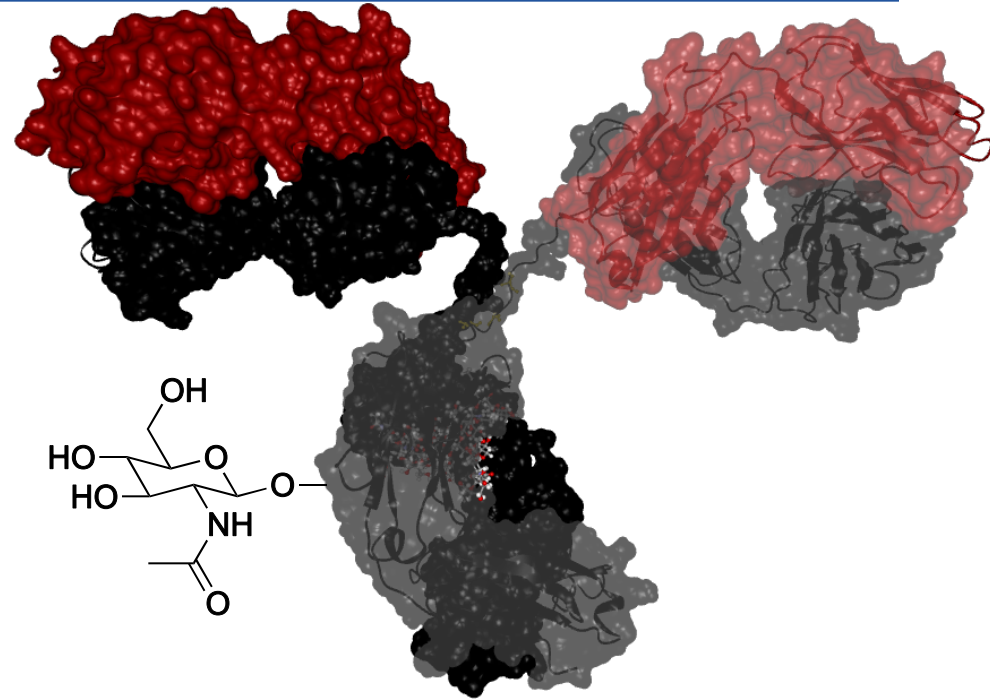


...with isothiocyanates:



Labeling of Carbohydrates...

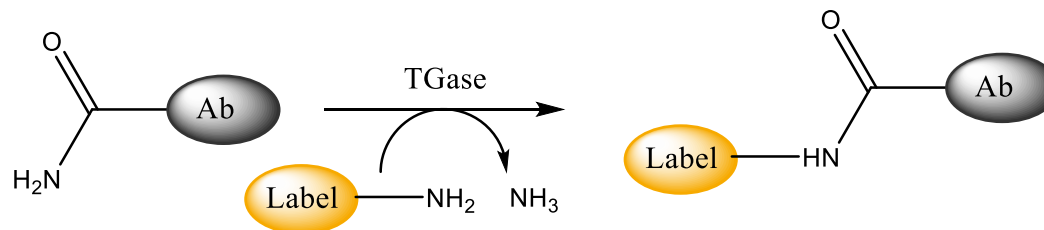
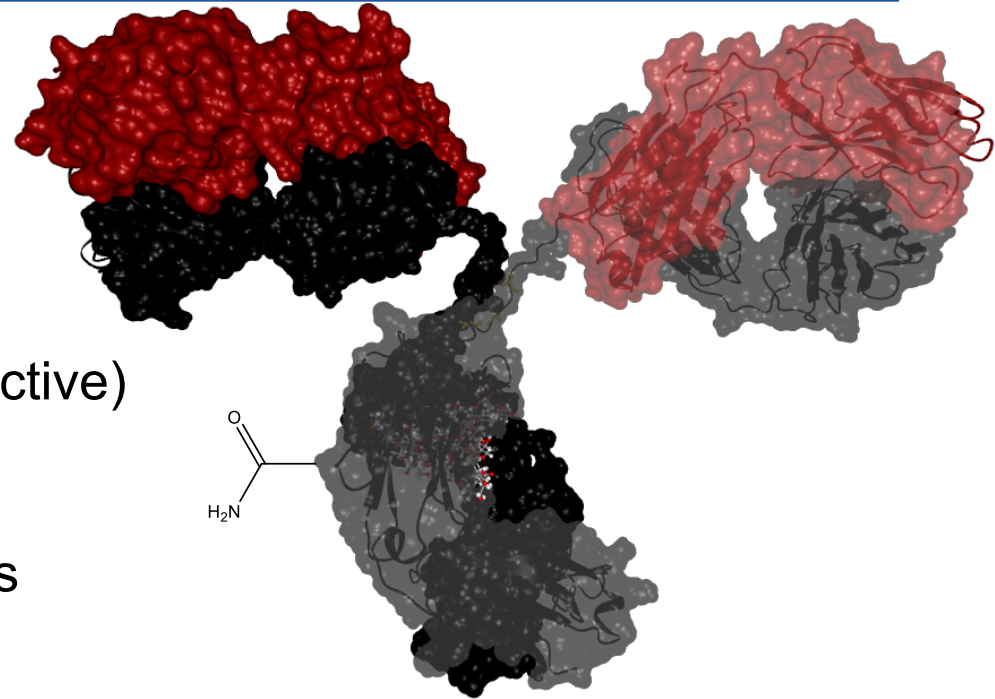
...with hydrazides:





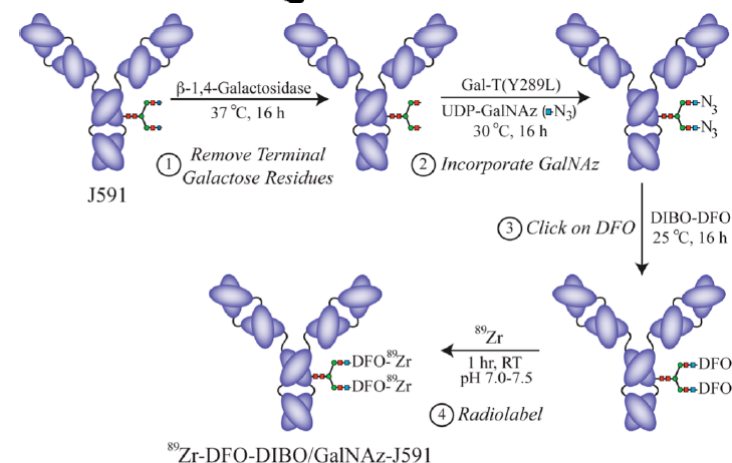
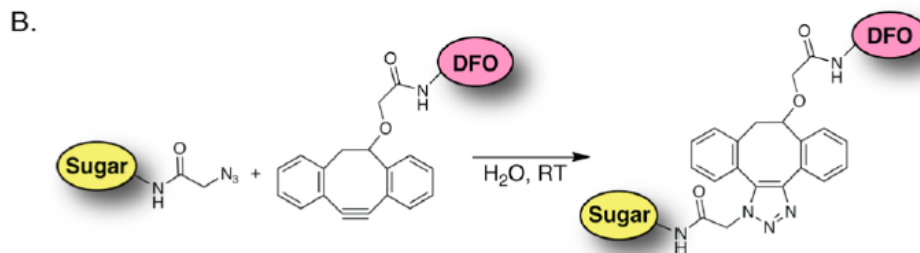
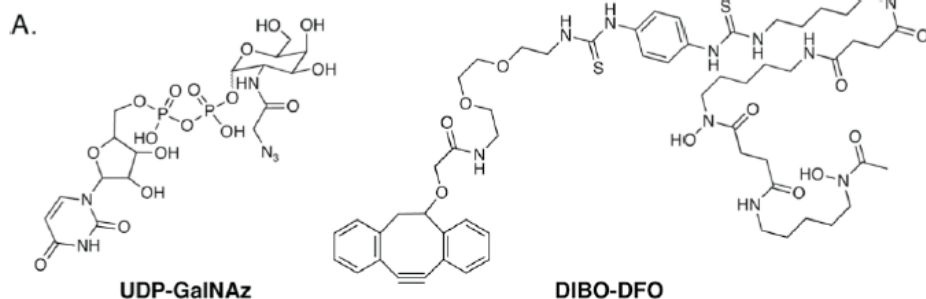
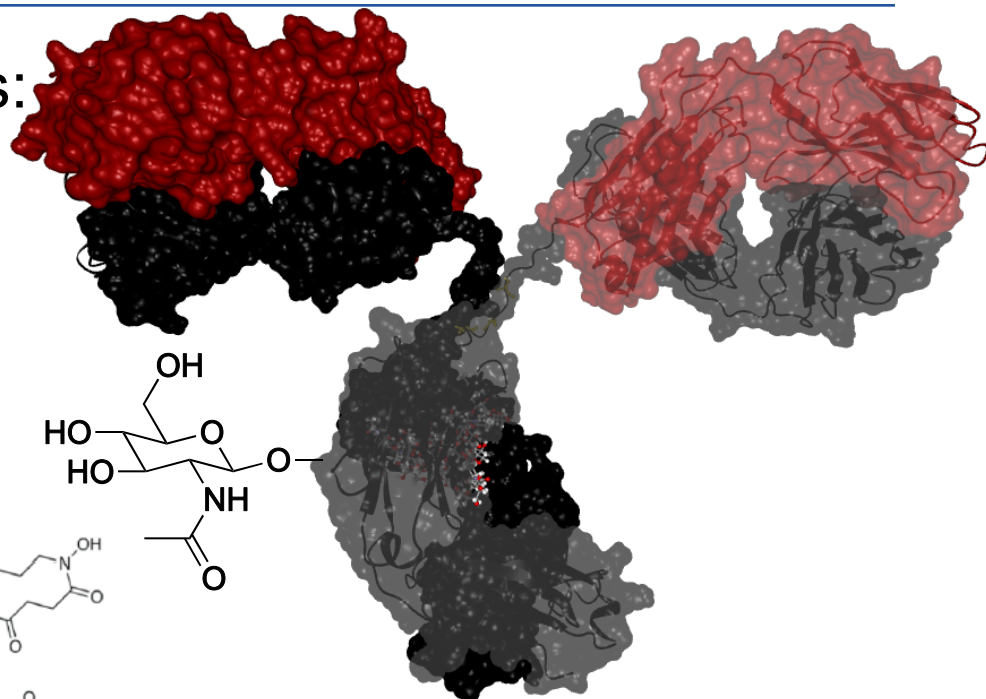
...using transglutaminase:

- Only at accessible sites (site-selective)
- Enzyme needed
- Reaction rather slow
- Enzyme prefers „small“ substrates

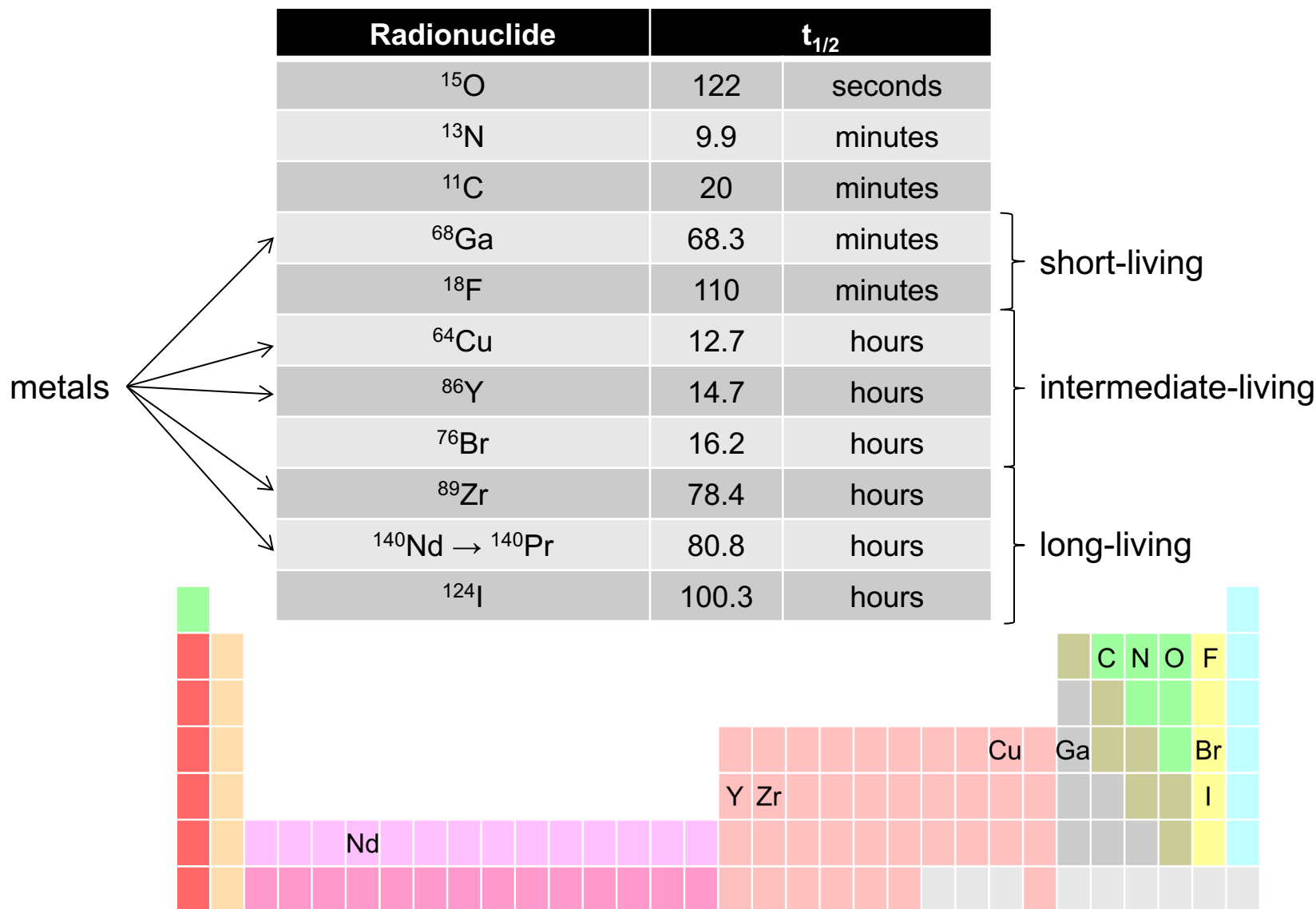


...using glycosyl transferases:

- Removal of terminal sugars
- Introduction of GalNAz
- Subsequent „click“ chemistry

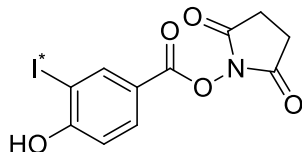


Isotopes for Antibody Imaging



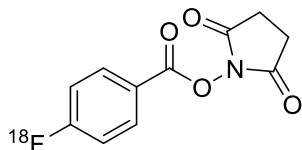
Prosthetic groups and chelators for introduction of radioisotopes:

I: electrophilic iodination (I_2)



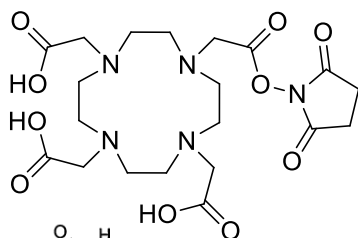
Bolton-Hunter-reagent

F:



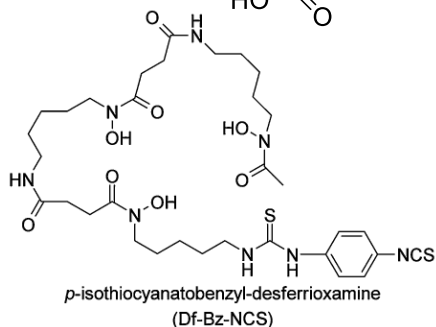
Succinimidofluorobenzoic acid (SFB)

Cu, Ga, Nd:



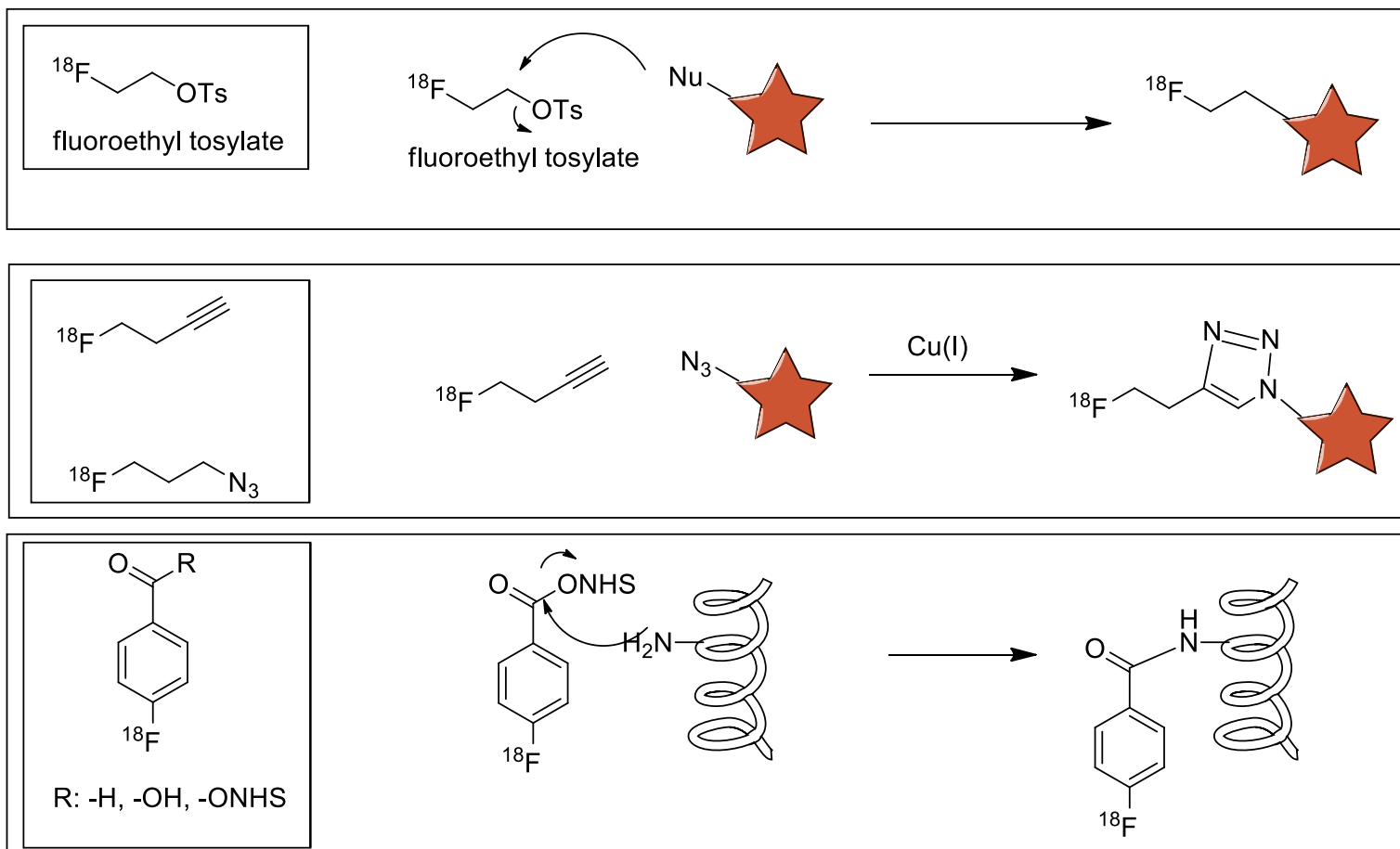
DOTA-NHS-ester
(suitable for ^{64}Cu , ^{68}Ga , ^{140}Nd)

Zr, In:

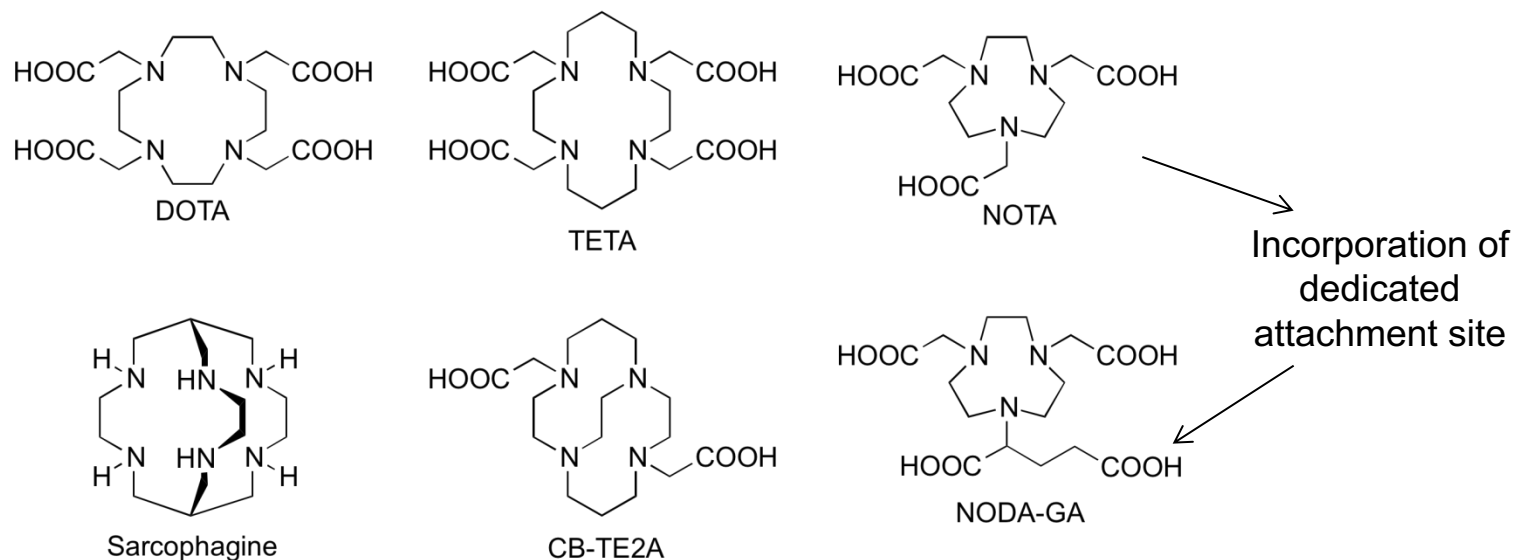


DFO-Bz-NCS
(for ^{89}Zr or ^{111}In labeling)

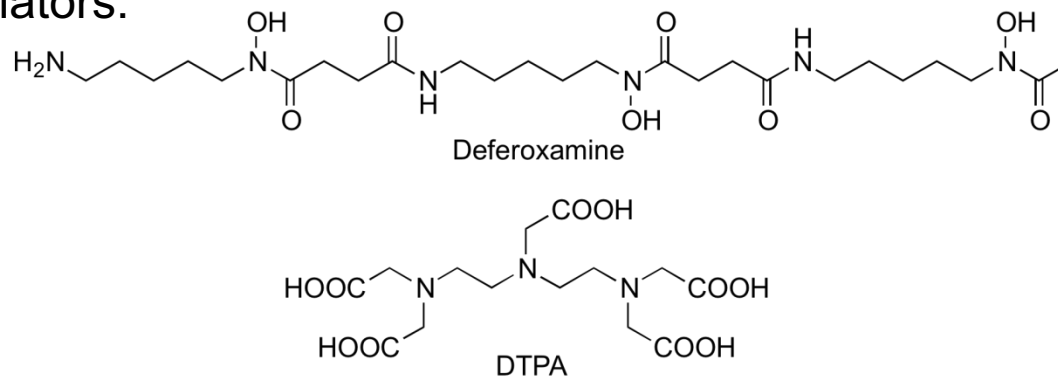
F-18 Prosthetic Groups



Macrocyclic chelators:

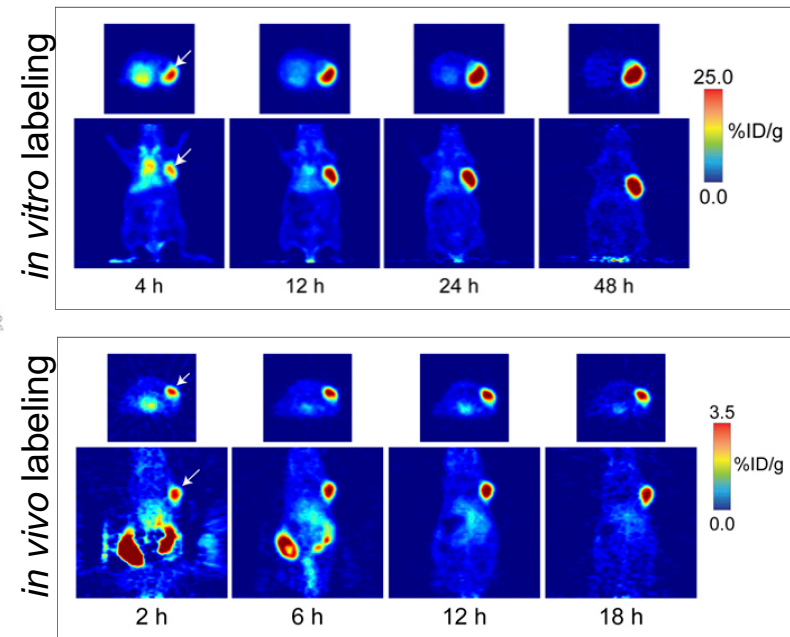
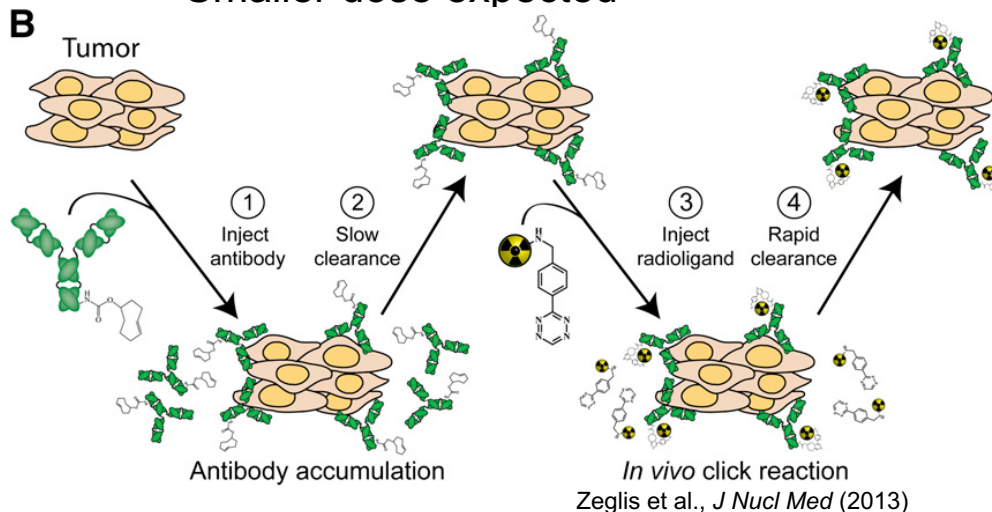
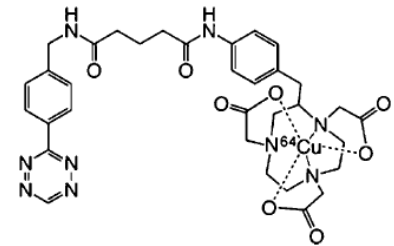


Non-cyclic chelators:





- Antibody half time can be problematic:
 - Good imaging only after >24 h of uptake time (slow clearance)
 - Requires „long“-lived isotopes
 - Leads to rather high doses
- Pretargeting might be a solution:
 - Injection of „cold“ alkyne-/alkene pretargeted antibody
 - Uptake time without radioactivity
 - Injection of radioisotope targeting the antibody (may be short-lived)
 - Click reaction happens *in vivo*
 - Rapid background clearance and imaging
 - Smaller dose expected



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