Historical Perspective - Radiotracing -

1943 Nobel Prize

1911, first radiotracer experiment:

One of the first radiotracer experiments was an experiment in gastronomy. George de Hevesy, one of the most significant figures in European nuclear medicine, left Berlin in 1911 to study under Rutherford in Manchester. He suspected that his landlady was recycling the remains of the Sunday meat pie to meals later in the week. To test this hypothesis he added a radioactive deposit of lead-212 to the freshly prepared pie and the following Wednesday, with the aid of an electroscope, demonstrated the presence of the activity in the souffle, proving beyond doubt there had been recycling.

Pb-212 (beta$^-$, $T_{1/2}$=10.62h)

Medical Imaging

- Structural imaging modalities
  - X-rays
  - CT / CAT (computerized tomography)

- Biochemical imaging modalities
  - SPE[C]T (**S**ingle**P**hoton**E**mission**C**omputerized**T**omography)
  - PET (**P**ositron**E**mission**T**omography)

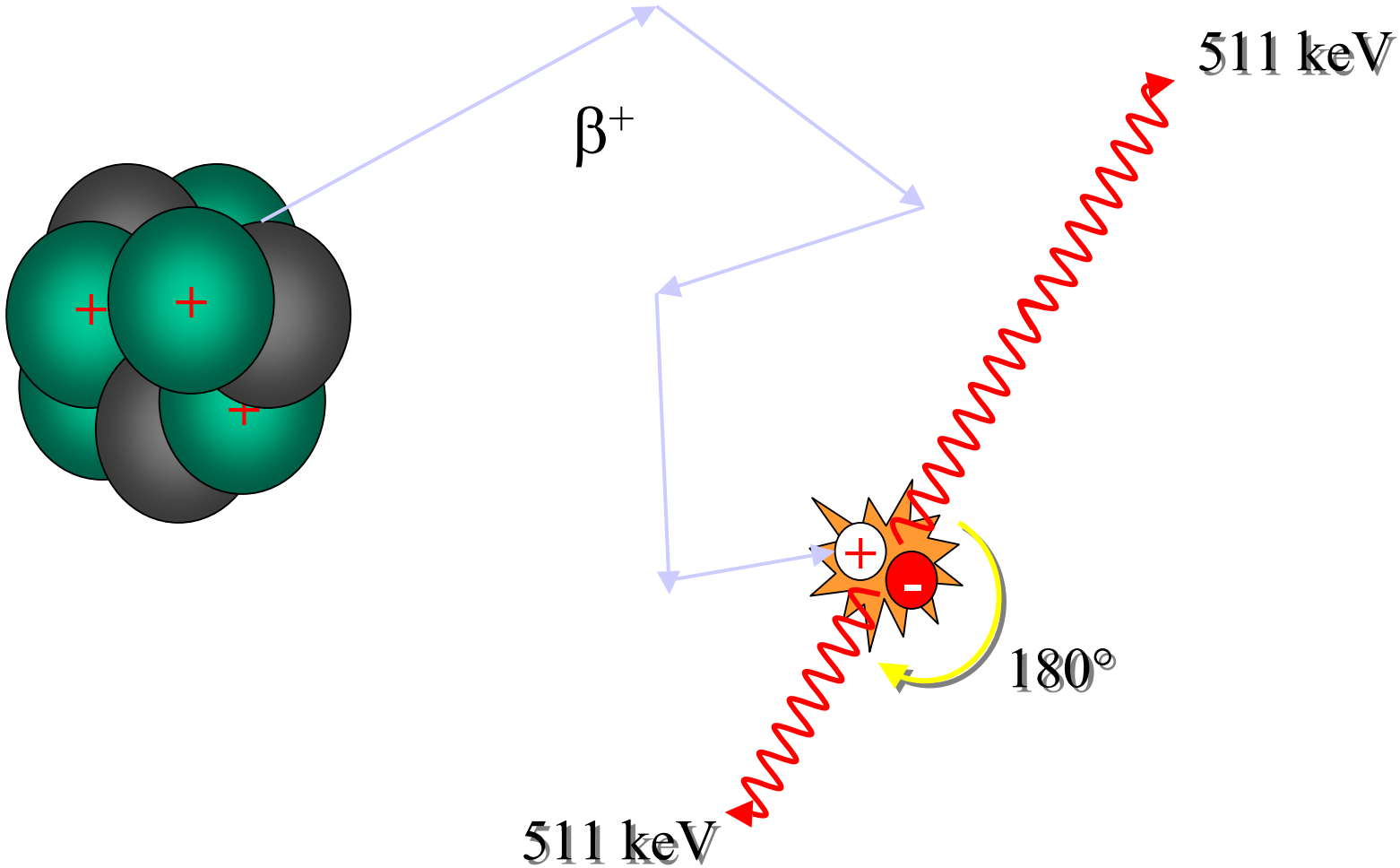
Positron (e^+) decay

Neutron deficient unstable atoms „decay“ by positron emission.
A proton (**P^+**) is transformed into a neutron (**n**) by emission of an electron antiparticle (e^+, i.e. a positron) and a neutrino (ν)

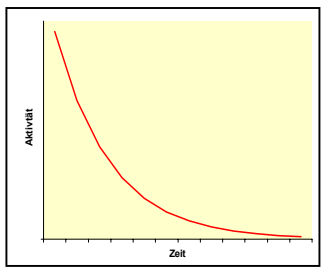
$$P^+ \longrightarrow n + e^+ + \nu + \text{energy}$$

The positron loses kinetic **energy** by collisions with atoms of the surrounding matter and comes to rest (travel distance ± 2.5 mm)
Combination with its antiparticle (an electron, e^-) leads to annihilation of both particles. Their mass is transformed into two 511 keV annihilation photons which leave the site of the annihilation in exact opposite directions (180° apart)

$$e^+ + e^- \longrightarrow \overset{511\ \text{keV}}{\underset{\gamma}{\longleftarrow}} + \overset{511\ \text{keV}}{\underset{\gamma}{\longrightarrow}}$$


β+
511 keV
180°
511 keV

Radionuclides



Decay: $N(t) = N(0)\, e^{-\lambda t}$

Half Life: $T_{1/2} = 0.693 / \lambda$

$$\lambda = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{t_{1/2}}$$

$N(T_{1/2}) = ½\ N(0)$

1 Curie (Ci): 3.7×10^{10} *desintegrations/s*

1 Bequerel (Bq):1 desintegration/s

Exponential reduction of the radionuclides.
N = nuclide; t = time; λ = decay constant; ln2 = 0.693

Radionuclides

$$N^* = \frac{m}{M} \cdot N_L \qquad N^* = \frac{A}{\lambda} = A \cdot \frac{t_{1/2}}{\ln 2}$$

$$A_s = \frac{A}{m} = \frac{\ln 2 \cdot N_L}{t_{1/2} \cdot M}$$

N^* = number of radioactive atoms
$N_L = 6.023 * 10^{23}$
A = activity
A_s = specific activity
λ= decay constant
ln2 = 0.693

Radiochemical / Radiopharmaceutical

= *radionuclide + chemical / pharmaceutical substance*

Radiochemical: for synthesis (precursor)

Radiopharmaceutical: radioactive substance for diagnosis and treatment of diseases
(ca. 95% of radiopharmaceuticals were used for diagnosis)

Radiopharmaceuticals
- laws and regulations -

Radiopharmaceuticals are drugs

- since 1992 radiopharmaceuticals need a licence in all countries of the European community
- there are special regulations for radiopharmaceuticals and patients in research

Pharmacopoeia (radioactive substance/preparation for diagnosis and treatment of diseases)

EURATOM (founded 1965; guidelines)

ICRP (international commission on radiation protection)

Radiopharmaceuticals
- quality control in the hot lab -

CRITERION:

You must be able to answer "***yes***" to the question:

"Would I inject this into my mother?"

Quality Control

→ drugs

→ + radionuclide purity: - other radionuclides? (spectroscopic methods)
e.g. I-124 in I-123 or Mo-99 in Tc-99
- during radionuclide production
- signed as % of the total activity:
e.g. 1% I-124 in I-123 means that at a certain time point 1% of all desintegrations is from I-124
- it is not constant!!

→ + radiochemical purity: determination of the activity of the drug formulation
radiochemical impurities = nuclide in another chemical formula
e.g. $^{99m}Tc^{-}$ and $^{99m}Tc(OH)_n$

Monographs/Drafts of PET-Radiopharmaceuticals (European Pharmacopoeia Commission)

1. ^{18}F-FDG: Fludeoxyglucose(^{18}F) Injection
2. General Monograph of Radiopharmaceuticals
3. ^{13}N-Ammonia: Ammonia (^{13}N) Injection
4. ^{15}O: Oxygen (^{15}O) inhalation gas
5. Carbon monoxide (^{15}O) inhalation gas
6. ^{15}O-Water: Water (^{15}O) Injection
7. ^{11}C-Methionine: L-((^{11}C)methyl)methionine Injection
8. ^{11}C-Raclopride
9. ^{11}C-Acetate
10. ^{11}C-Flumazenil
11. ^{18}F-Fluoride
12. ^{18}F-DOPA
13. ^{18}F-Uracil

Radionuclides in Nuclear Medicine: *criteria*

- half-life
- type of radiation emission
- high specific activity
- availability
- safety

Diagnostic:

– short half-life (min. – h)

– β^+ emitter (511 keV)

– gamma emitter (60-300 keV)

Therapy:

– half-life: h – d

– β^- emitter

– alpha emitter

– Auger electrons emitter

Positron**E**mission**T**omography (PET)

Single**P**hoton**E**mission**C**omputerized**T**omography (SPECT)

^{15}O	2.04	min
^{13}N	9.97	min
^{11}C	20.4	min
^{18}F	110	min
^{99m}Tc	6	h
^{123}I	13.2	h

Properties of the ideal diagnostic radiopharmaceutical

- pure gamma emitter
- gamma energy: 30 – 300 keV
- effective half-life = 1.5 x test duration
- high target : nontarget ratio
- minimal radiation dose to patient and nuclear medicine personal
- safety
- chemical reactivity
- availability

High target:nontarget ratio : e.g. bone imaging; bones should be visuable in soft tissue; metastases should be visuable against bones; ratios multiplicative: tumor:bones = 5:1 and bones:soft tissue = 5:1 then tumor:soft tissue=25:1

Properties of the ideal diagnostic radiopharmaceutical

short effective half-life (ca. 1.5 x test duration)

$\lambda_e = \lambda_p + \lambda_b$

$\lambda = 0.693/t_{1/2}$

$1/T_e = 1/T_p + 1/T_b$ or $T_e = \frac{T_p * T_b}{T_p + T_b}$

Example: ^{111}In-Verbindung

$T_p = 67$ h

$T_b = 1.5$ h

$T_e = \frac{T_p * T_b}{T_p + T_b}$

$= \frac{67 * 1.5}{67 + 1.5} = 1.47$ h

e = effective, p = physical, b = biological, λ = decay constant

Design of a diagnostic radiopharmaceutical

- *Tracer*
  - process to be measured
  - synthesis
  - radiation dose during synthesis
  - nuclide
  - side products (suitable position in the molecule, metabolism)
  - specific activity
- *Model* (pathways of the biochemical processes, compartments)
- *Quantification*
- *Validation*
- *Application* (normal or pathological situations)

Design of a diagnostic radiopharmaceutical

Biodistribution

distribution in the tissue	* experiments with animals
	* time course
	* radioactivity in different organs
	➔ imaging?
plasma clearance	* blood probes
	* time course
	* plot: activity versus time (half-time of clearance)
	➔ rate of localization/organ
secretion via urine…	
	➔ radiation dose
toxicity	

Design of a diagnostic radiopharmaceutical: *neuroreceptors*

- high extraction across BBB
- high specificity for the receptor
- rapid blood clearance
- rapid receptor-ligand association rate
- suitable metabolism
- rapid clearance from nonspecific sites
- high specific activities (> 1000 Ci/mmol)
- high affinity constant

Design of a diagnostic radiopharmaceutical: *neuroreceptors*

e.g. ^{11}C-labeled potential drug (tracer dose)

↓

- anatomical distribution
- receptor interaction
- metabolites

- non labeled drug (clinical dose)
- e.g. ^{11}C-labeled radiotracer

↓

- receptor occupation by the drug

PET radiopharmaceuticals as diagnostic tools

- contain a short-lived, positron emitting radionuclide
- are normally applied intraveneously (sterile and apyrogenic)
- in general have a high specific activity (A_s)
- injected mass dose is in the pico- to nanomolar range

Example

radioligand FW: 300 g/mol

A_s:1000 Ci / mmol = 1000 Ci / 300 mg, 1000 mCi / 300 µg

injected dose : 5 mCi

applied mass dose: $\frac{300}{1000} \times 5 =$ **1,5 µg (5 nmol)**

Radionuclide Production

I. Reactor nuclides

often neutron rich β^- emitter

e.g. (n,γ) reactions

II. Accelerator nuclides

often neutron rich β^+ or EC emitter

e.g. (p,n) reactions

most nuclides with short $T_{1/2}$

facility!!

III. Generator nuclides

$T_{1/2}$ (mother) > $T_{1/2}$ (daughter)

Cyclotron production

name	nucl. reaction	$t_{1/2}$	species	A_s (GBq/µmol)*
O-15	$^{14}N(d,n)^{15}O$	2 min	O_2	
N-13	$^{16}O(p,\alpha)^{13}N$	10 min	NO_x^-	
C-11	$^{14}N(p,\alpha)^{11}C$	20 min	CO_2	theor. $3.4 \cdot 10^5$, pract. 100
F-18	$^{18}O(p,n)^{18}F$	110 min	F^-	theor. $6.3 \cdot 10^4$, pract. 500

* refers to A_s @ end of synthesis

Comparison of Carbon-11 and Fluorine-18

CARBON-11

- authentic labelling
- demanding half-life (20 min)
  limited synth. time (± 60 min)
- allows repeated applications
- specific activity often problematic
- cyclotron proximity
  - on-site use only -
- good spatial resolution

FLUORINE-18

- analogue labelling (evaluation)
- long half-life (120 min)
  synth. time up to 120 min
- allows slow kinetics of ligand
- high specific activity
- can be distributed
  - „satellite concept“ -
- very good spatial resolution

The choice ot the radionuclide depends on the kind of information one wants to get

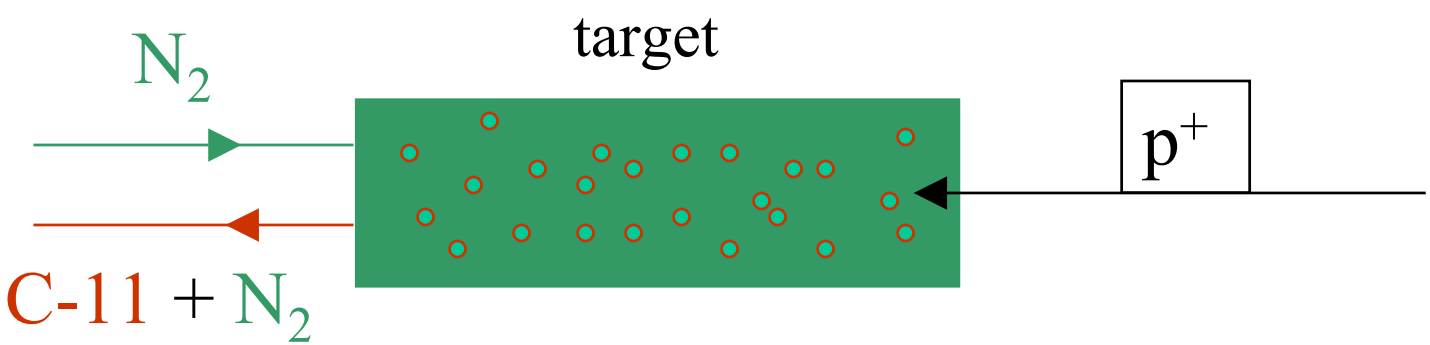
Carbon-11

C-11 $^{14}N(p,\alpha)^{11}C$

$t_{1/2}$ = 20.4 min; I_{b+} = 100%; E_{b+} = 0.96 MeV

gas target (N_2 + O_2)

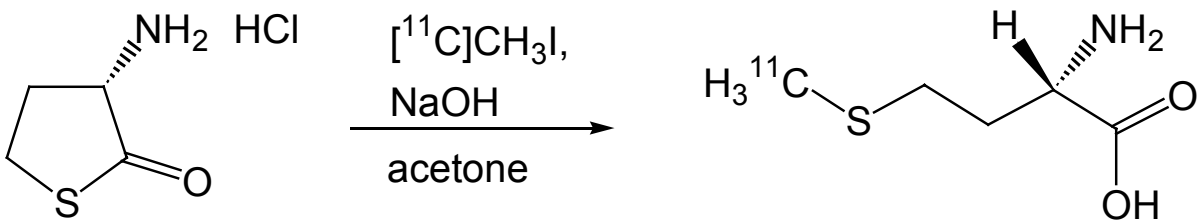
produced species: [^{11}C]carbon dioxide, [^{11}C]CO_2



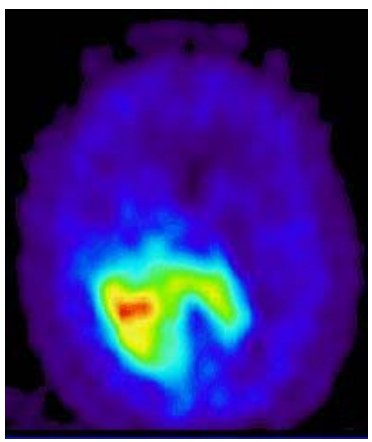
$$^{14}N + p \longrightarrow {}^{11}C + \alpha$$

$$^{14}N\ (p,\ \alpha)\ ^{11}C$$

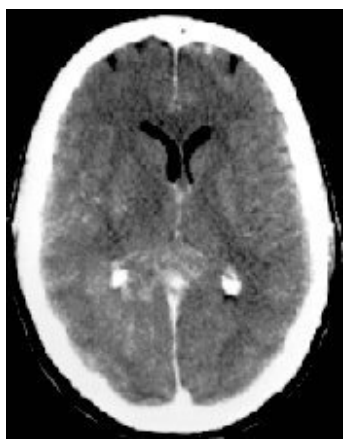
Radiosynthesis of [^{11}C]L-methionine



S-methylation



PET



CT with a contrast agent

Astrocytoma grade II

Langen *et al*, 1998

Fluorine-18

target material	*nuclear reaction*	*precursor*	*specific activity*
Ne (F_2)	$^{20}Ne(d,\alpha)^{18}F$	$[^{18}F]F_2$ (electrophilc)	~ 0.037 GBq / µmol
$H_2{}^{18}O$	$^{18}O(p,n)^{18}F$	$^{18}F^-_{aq}$ (nucleophilic)	< 740 GBq / µmol

$t_{1/2}$ = 109.6 min; I_{b+} = 97%; E_{b+} = 0.64 MeV

Radiolabelling with fluorine-18

principle:

substitution of H or OH by F

rationale:

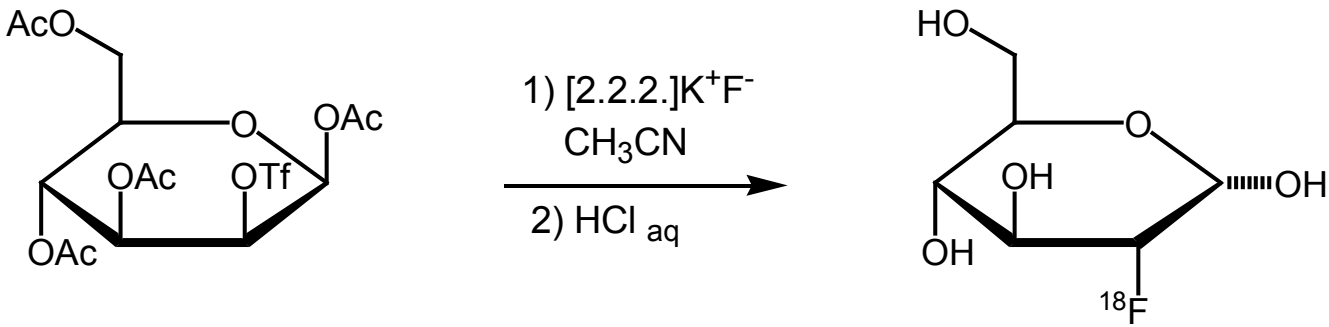
C-H and C-F bond sterically similar,
O and F form hydrogen bonds

but

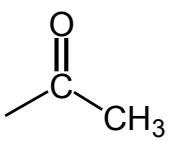
fluorine has a high electronegativity

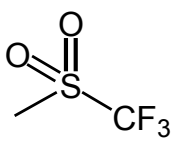
The analogue tracer approach requires a complete biological and pharmacological evaluation of the new fluorinated target compound !

Radiosynthesis of 2-[^{18}F]Fluoro-2-deoxy-D-glucose (FDG), „gold standard“ in PET



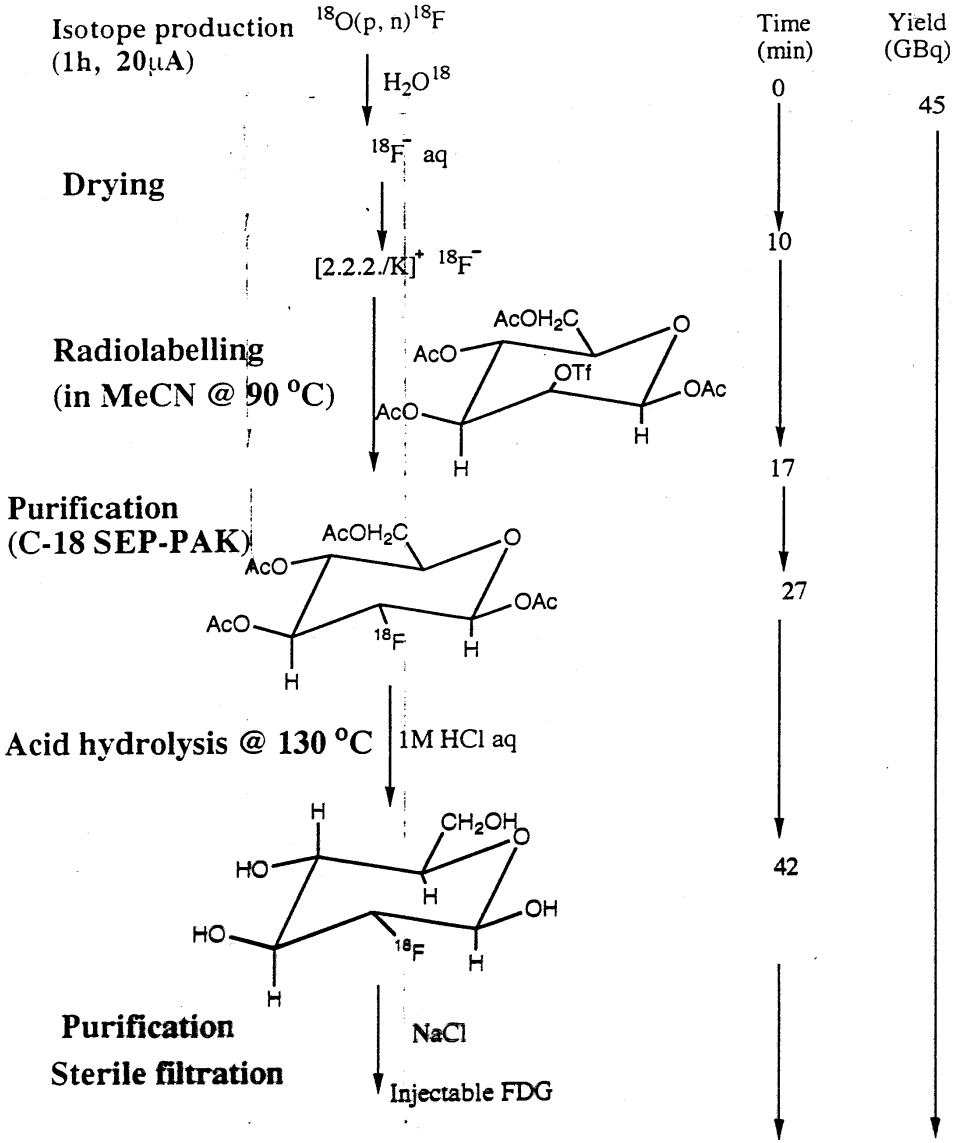
1,3,4,6-Tetraacetyl-β-D-mannopyranose-2-triflate

Ac: 

Tf: 

reaction temperature 85°C
synthesis time 55 min,
rcy 45 - 50%
A_s ± 5000 Ci / mmol

Radiosynthesis of 2-[^{18}F]Fluoro-2-deoxy-D-glucose (FDG), „gold standard“ in PET



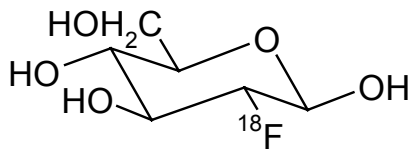
From:
Hamacher K, Coenen HH, Stocklin G.

J Nucl Med. 1986 Feb;27(2):235-8.

Design of a diagnostic radiopharmaceutical: *glucose metabolism*

[^{18}F]2-FDG (2-deoxy-2-fluor-D-glucose) method

- extended development of Sokoloff's method
- position of fluorine (hexokinase reaction)
  - 2-FDG and 2-FDM: substrates
  - 1-, 3-, and 4-FDG: bad substrates
  - 6-FDG: inhibitor



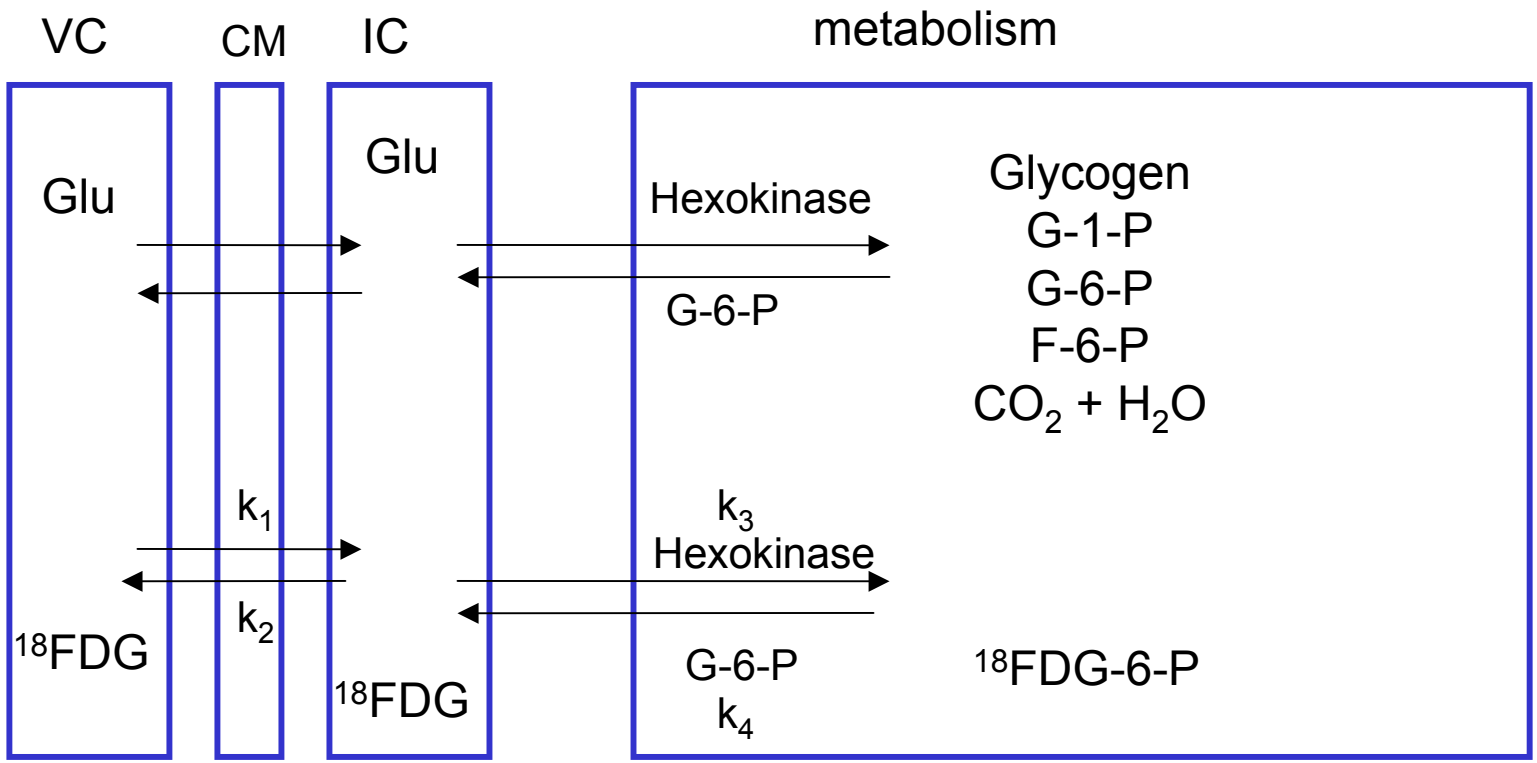
Fluorination of carbon-2 is successful for two reasons:

-it respects the chemical character of 2-DG without substantial distortion of geometry, which is a requirement for preservation of its needed activity with hexokinase

- 2-FDG-6-P, the product of the hexokinase phosphorylation of 2-FDG, will not be susceptible to further metabolism

Design of a diagnostic radiopharmaceutical:

[^{18}F]2-FDG method



VC = vascular compartment, CM = capillary membrane, IC = intracellular compartment

^{18}FDG-6-P remains in the cell. The back reaction is negligible if the experimental period is maintained within 45 min.