VU university medical center

Basics of cyclotron radioisotopes production

Bert Windhorst
radiopharmaceutical chemist

Outline

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- Cyclotron technique
- ^{18}F targetry production of fluoride and fluorine
- ^{11}C targetry and production
- ^{123}I targetry and production
- ^{124}I targetry and production

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Outline

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Cyclotron production

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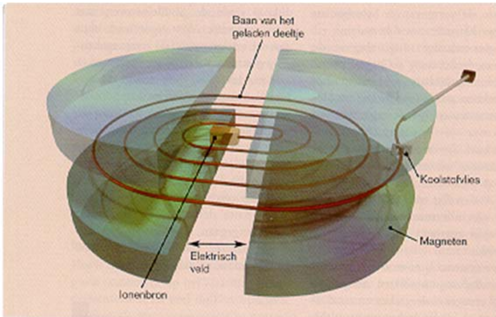

30.000 volt between D’s
300 circles, 600 accelerations of 30.000 volt = 18 MeV

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Cyclotron

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Cyclotron inside

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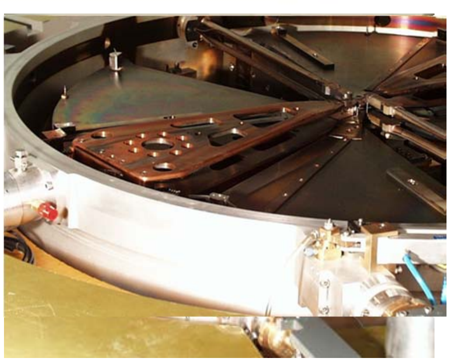

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IBA 18/9 cyclotron

^{18}F : 2,3 ml $H_2{}^{18}O$ in niobium
^{11}C : 60 ml N_2 + 0,5% O_2 in aluminum
^{13}N : 2,3 ml H_2O in niobium
^{15}O : 60 ml N_2 in aluminum

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Other cyclotrons, amongst others

GE

Siemens

Best

ACS

Sumitomo

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- ^{124}I targetry and production

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^{18}F Fluoride production

Nuclear reaction

$^{18}O(p,n)^{18}F$, obtained as Fluoride in water

Proton energy from 10 MeV

Side reaction

$^{16}O(p,\alpha)^{13}N$, obtained as nitrates in water

Side products

no nuclear side reactions

^{18}F Fluoride production

Several nuclear reactions possible

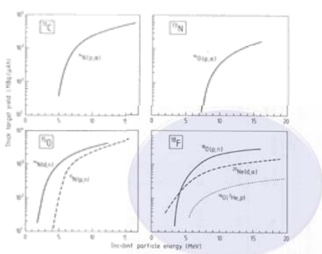

Figure 1. Integrated thick target yields of some commonly used positron-emitters expected from the most common production routes, plotted as a function of incident particle energy. Data were calculated using the measured excitation functions (for reference see text).

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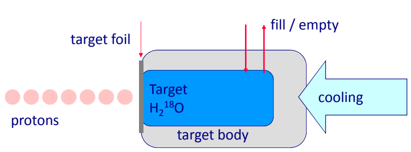
Kluwer Academic publishers, Dordrecht, 1993, isbn 0-7923-2340-8

^{18}F Fluoride targetry



Important characteristics for target body material:
- Heat capacity coefficient
  (limiting factor for high beam currents: high pressure in target)
- Radionuclidic side products
- Chemical purity of [^{18}F]Fluoride from target

Fluoride target on IBA 18/9

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Fluoride target on the bench

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^{18}F Fluoride target body material

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Silver

Advantage: - high heat capacity
- no long lived radio isotopes

Disadvantage: - Silver particles

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^{18}F Fluoride target body material

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Titanium

Advantage: - clean ^{18}F solution

Disadvantage: - lower heat capacity
- ^{48}V as side product

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Fluoride target holder

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Titanium	Silver
	
After several months in operation	After **2 weeks** in operation

Activation of Titanium

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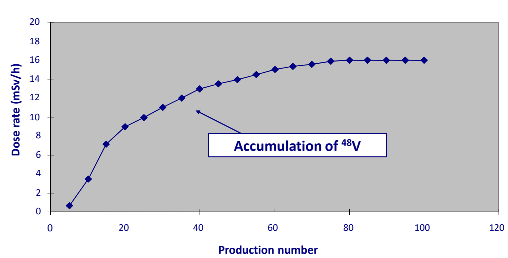

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^{18}F Fluoride target body material

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Niobium

Advantage:
- clean ^{18}F solution
- no long lived radio isotopes
- high heat capacity

Disadvantage: - ?

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Nuobium activation

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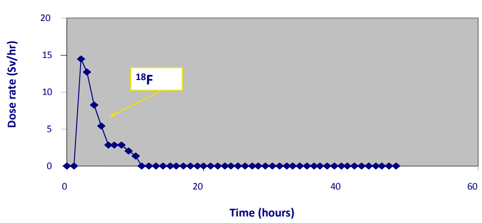

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Pressure in different materials

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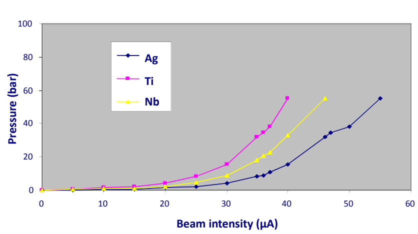

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Results different target materials

Summary of the results after 120 minutes irradiation

Target chamber material	Ag	Ti	Nb
Energy (MeV)	18	18	18
Beam intensity (µA)	40	30	35
Thick target yield (GBq/µA @ sat)	8.8	9.1	8.8
Yield obtained at EOB (GBq)	188	144	163

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Results at other centers

Table 3. Typical data for [^{18}F]fluorine produced at different centres from ^{18}O-enriched water targets (Data reproduced from Guillaume *et al.*, 1991, with permission).

Centre	St. Louis	Sendai	Villigen	Turku	Jülich	Hammersmith	Liège
Material insert	SS & Ti	Ti	Ag	Ag	Ti	SS316&Ti	Ni
Water width (mm)	3,5,7	3,4,5	5	1.5	3.5	3	3.4
Foils	Havar or Ti	Al/Ti & Ag	Ag	Ni	Ti	Al/Ti & SS316	Ti
Seal	O-ring	O-ring	Ag	Metal	Weld & Ag	Metal to metal	O-ring
Cooling (°C)	Water (10)	Coolant (0)	Water (30)	Coolant (10)	Water (10)	Water (10)	Water (10)
^{18}O-Enrichment of H_2O (%)	97	20	98	98	97	20	5
Volume (mL)	1.2, 2.0, 2.8	2.5	4.5	0.195	1.3	2.0	1.8
Pressure (atm)	1	Open or circulated (Pd)	Open	Open	15-25	2	2-3
E (MeV)	15	16	16	12	16.5	16	22.6
Irradiation (µA x min)	15-20x80	20x60	20x60	10x60	20-35x60	20x60	10x60
Yield (GBq/µAh at EOB)	2.22	0.33	2.07	1.11	2.41	0.407	0.11-0.12
(mCi/µAh at EOB)	ca 60	9	56	30	70	11	3-3.2
Sp. Act. (TBq/µmol EOB)	1.85	0.148	nca	5.18	7.4	11.1×10^{-3}	0.37
(Ci/µmol at EOB)	ca 50	4	nca	140	200	0.3	10
Reference	Kilbourn *et al.*, 1985	Iwata *et al.*, 1987	Huszar & Weinreich, 1985; Vogt *et al.*, 1986	Solin *et al.*, 1988	Qaim *et al.*, 1987; Nebeling *et al.*, 1990	Clark *et al.*, 1990	Guillaume *et al.*, 1990

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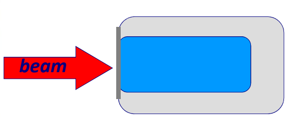
^{18}F Fluoride targetry



Target volume ± 2.4 ml
Target filling ± 2.4 ml
max 40 mA
p = 35 bar

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^{18}F Fluoride targetry

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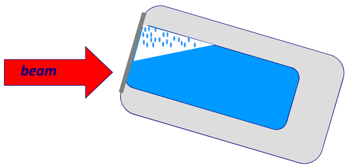

Target volume ± 4.5 ml
Target filling ± 3.3 ml
70 - 80 mA
p = 35 bar

XXXL : 150 mA

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^{18}F and [^{18}F]FDG yields 2004

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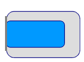
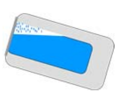


2 hr 40 μA

Start synthesis 166 GBq [^{18}F]Fluoride
End of synthesis 130 GBq [^{18}F]FDG



2 hr 70 μA

Start synthesis 315 GBq [^{18}F]Fluoride
End of synthesis 240 GBq [^{18}F]FDG

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^{18}F Fluorine production

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Nuclear reaction
- ^{20}Ne(d,α)^{18}F or ^{18}O(p,n)^{18}F
- deuterons from 7 MeV
- protons from 10 MeV

Side reaction
- -

Side products
- -

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^{18}F Fluoride production

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Several nuclear reactions possible

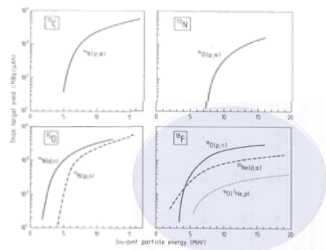

Figure 1. Integrated thick target yields of some commonly used positron-emitters expected from the most common production routes, plotted as a function of incident particle energy. Data were calculated using the measured excitation functions (for reference see text).

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^{18}F Fluorine targets

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Target material : Nickel or Monel

1st irradiation : ^{18}F fluorine deposit on target wall

Empty target, fill with Neon + 0.1-0.5% F_2

Irradiate

Yields $[^{18}F]F_2$ in Neon.

Alternative:
Have 0.1-0.5% F_2 present during first irradiation: one shot production

^{18}F Fluorine target Groningen

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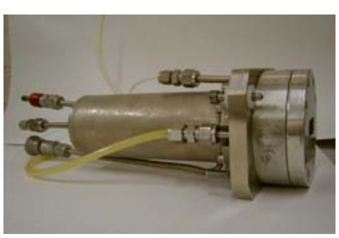

Installed in 1992

Design: Robert Dahl

Nickel / 153 ml

30 psi 1% F_2 / 100 psi Neon

Yield in 1992:

5 GBq / 50 µA / 1 hour

^{18}F Fluorine specific radioactivity

Addition of F_2 is essential,
but decreases specific radioactivity

Typically : less then 1 GBq/µmol

Gives problems for receptor studies

Production results

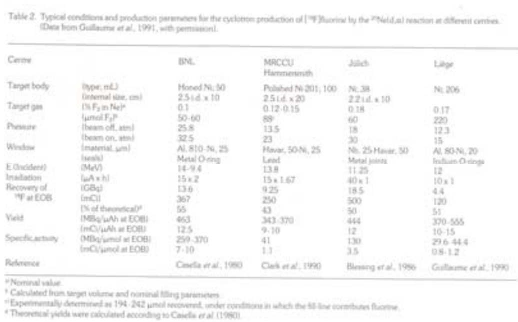

Table 2. Typical conditions and production parameters for the cyclotron production of [^{18}F]fluorine by the $^{20}Ne(d,\alpha)$ reaction at different centres. (Data from Guillaume et al., 1991, with permission).

Centre		BNL	MRCCU Hammersmith	Jülich	Liège
Target body	(type; mL)	Honed Ni; 50	Polished Ni 201; 100	Ni; 38	Ni; 206
	(internal size, cm)	2.5 i.d. x 10	2.5 i.d. x 20	2.2 i.d. x 10	
Target gas	(% F_2 in Ne)[a]	0.1	0.12-0.15	0.18	0.17
	(µmol F_2)[b]	50-60	88[c]	60	220
Pressure	(beam off, atm)	25.8	13.5	18	12.3
	(beam on, atm)	32.5	23	30	15
Window	(material, µm)	Al, 810-Ni, 25	Havar, 50-Ni, 25	Nb, 25-Havar, 50	Al, 80-Ni, 20
	(seals)	Metal O-ring	Lead	Metal joints	Indium O-rings
E (incident)	(MeV)	14-9.4	13.8	11.25	12
Irradiation	(µA x h)	15 x 2	15 x 1.67	40 x 1	10 x 1
Recovery of ^{18}F at EOB	(GBq)	13.6	9.25	18.5	4.4
	(mCi)	367	250	500	120
	(% of theoretical)[d]	55	43	50	51
Yield	(MBq/µAh at EOB)	463	343-370	444	370-555
	(mCi/µAh at EOB)	12.5	9-10	12	10-15
Specific activity	(MBq/µmol at EOB)	259-370	41	130	29.6-44.4
	(mCi/µmol at EOB)	7-10	1.1	3.5	0.8-1.2
Reference		Casella et al., 1980	Clark et al., 1990	Blessing et al., 1986	Guillaume et al., 1990

[a] Nominal value.
[b] Calculated from target volume and nominal filling parameters.
[c] Experimentally determined as 194-242 µmol recovered, under conditions in which the fill line contributes fluorine.
[d] Theoretical yields were calculated according to Casella et al. (1980).

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Production results Groningen

Radionuclide production:	1998 - 2004	2005
Target	SCX nickel plated / 150 ml Havar frontfoil (25 um)	SCX nickel plated / 150 ml Havar frontfoil (25 um)
Targetgas	0,44 % F2 in Neon / 75 psi	0,44 % F2 in Neon / 75 psi
Beamcurrent	15 uA	**25 uA**
Irradiation time	60-120 minutes	120 minutes
Preparation for the production	1x conditioning target and lines 1x 3 µAh irradiation to waste	1 x conditioning target and lines 1 x 3 µAh irradiation to waste
Yield [^{18}F]F_2	30-50 MBq/µAh at EOB 1.2 – 2.0 GBq at BOS	**70 - 80 MBq/µAh at EOB** **3.5 – 4.0 GBq at BOS**
Specific activity	4.4 ± 1.0 GBq/mmol	**10.7 ± 3.0 GBq/mmol**

Modern [^{18}F]Fluorine targets

Target holder material : Nickel, Monel or Aluminium

Load with >95% enriched [^{18}O]O_2 as target

1st irradiation: ^{18}O(p,n)^{18}F

^{18}F fluorine deposit on target wall

Empty target holder, recover [^{18}O]O_2 in cryogenic trap (liq N_2)

Fill target with Neon + 0.1-0.5% F_2

Irradiate again, eg 15 min, 15 mA: exchange of ^{18}F with ^{19}F

Yields [^{18}F]F_2 in Neon 40-60 GBq, specific activity 20-30 GBq/μmol

Outline

Cyclotron technique

^{18}F targetry production of fluoride and fluorine

^{11}C targetry and production

^{123}I targetry and production

^{124}I targetry and production

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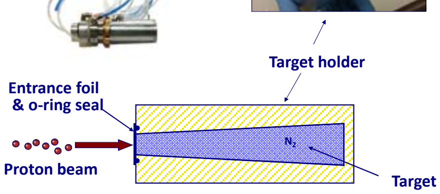
Carbon-11 production

^{11}C is produced by the ^{14}N(p, α)^{11}C nuclear reaction

Nitrogen gas is irradiated with high energy protons (16-18 MeV)

Oxygen is present to make [^{11}C]CO_2



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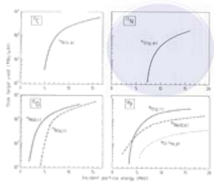
Carbon-11 production

Target pressure typically 25-35 bar: target foil important
> Aluminium disk, 0.5 mm thickness

Also reduces energy to about 15 MeV (starting form 18 MeV):
> optimal for carbon-11 production



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Carbon-11 production

Very important issue: specific activity

Labeled compound =
Mixture of compounds with stable isotopes and radioactive isotopes

Unit = GBq/µmol

Specific activity - 2

The theoretical specific activity of carbon-11 is 340918 GBq/µmol.

In practice 50-100 GBq/µmol at EOS is obtained

with 1 GBq of product this is 10-20 nmol

At 340918 GBq/µmol, this would be 0.23 nmol

Only a tiny fraction of the carbon is really carbon-11 labelled

^{11}C in ^{12}C = 1 – 2 %

EOS = End Of Synthesis

Specific activity - 3

Tracer principle: do not disturb the system by the measurement

Eg do not activate a receptor because of radiopharmaceutical

Then a high specific activity is required of >18.5 GBq/µmol

With decay the specific activity is reduced.
In practice often the specific activity determines the expiry time

EOS = End Of Synthesis

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Sources of isotopic dilution in $[^{11}C]CO_2$ production

Combustion of carbon containing materials inside target holder during irradiation

$$C_xH_yO_z \xrightarrow[\text{ionizing energy}]{O_2} CO_2 + H_2O$$

Migration and desorption of Carbon-12 carbon dioxide from the bulk metal of the target holder

$$CO_{2\,(ads)} \xrightarrow[\text{desorption}]{} CO_2$$

Impurities in the process gasses. Atmospheric leaks into the gas handling system, valves and tubing, etc.

Air contains 380 ppm carbon dioxide.

$[^{11}C]$Methane produced in target sometimes more beneficial
=> Not present in high amounts in the atmosphere nor in reagents used in further processing of the labelled tracer.

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Cyclotron technique

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^{123}I targetry and production

^{124}I targetry and production

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Iodine-123 production

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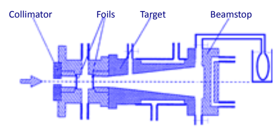
Nuclide production: $^{124}Xe(p,2n)^{123}Cs \rightarrow {}^{123}Xe$ (2 hr half life) $\rightarrow {}^{123}I$
Chemical form : $^{123}I^-$ in 0.01 M of NaOH

24 MeV protons required!

<u>Isolation of iodide-123</u>
- trap Iodine on anion-exchange column
- elute column with 1 % Na_2SO_4



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Outline

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Cyclotron technique

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^{11}C targetry and production

^{123}I targetry and production

^{124}I targetry and production

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Iodine-124 production

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Nuclide production : $^{124}Te(p,n)^{124}I$
Chemical form : $^{124}I^-$ in 0.01 M of NaOH

Up to 13 MeV protons required

<u>Isolation of iodide-124</u>
- dry distillation from Tellurium-124
- dissolve in 0.01 M of NaOH

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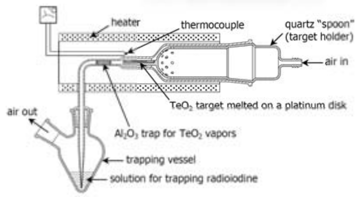
Iodine-124 work-up

- Beam current: up to 25 µA
- Average yield: 15 MBq/µAh
  -› typical bombardment yield ~2 GBq
- ~30% ^{123}I at EOB
- overall yield 90%
- <0.5% Te loss



Schematic view of TERIMO for thermo-chromatographic separation

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Further reading

Molecular Imaging: radiopharmaceuticals for PET and SPECT
by Shankar Vallabhajosula
Chapter 5

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Handbook of Radiopharmaceuticals :
Radiochemistry and applications
Ed MJ Welch, CS Redvanly
Wiley, Sussex, 2003, isbn 0-471-49560-3

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