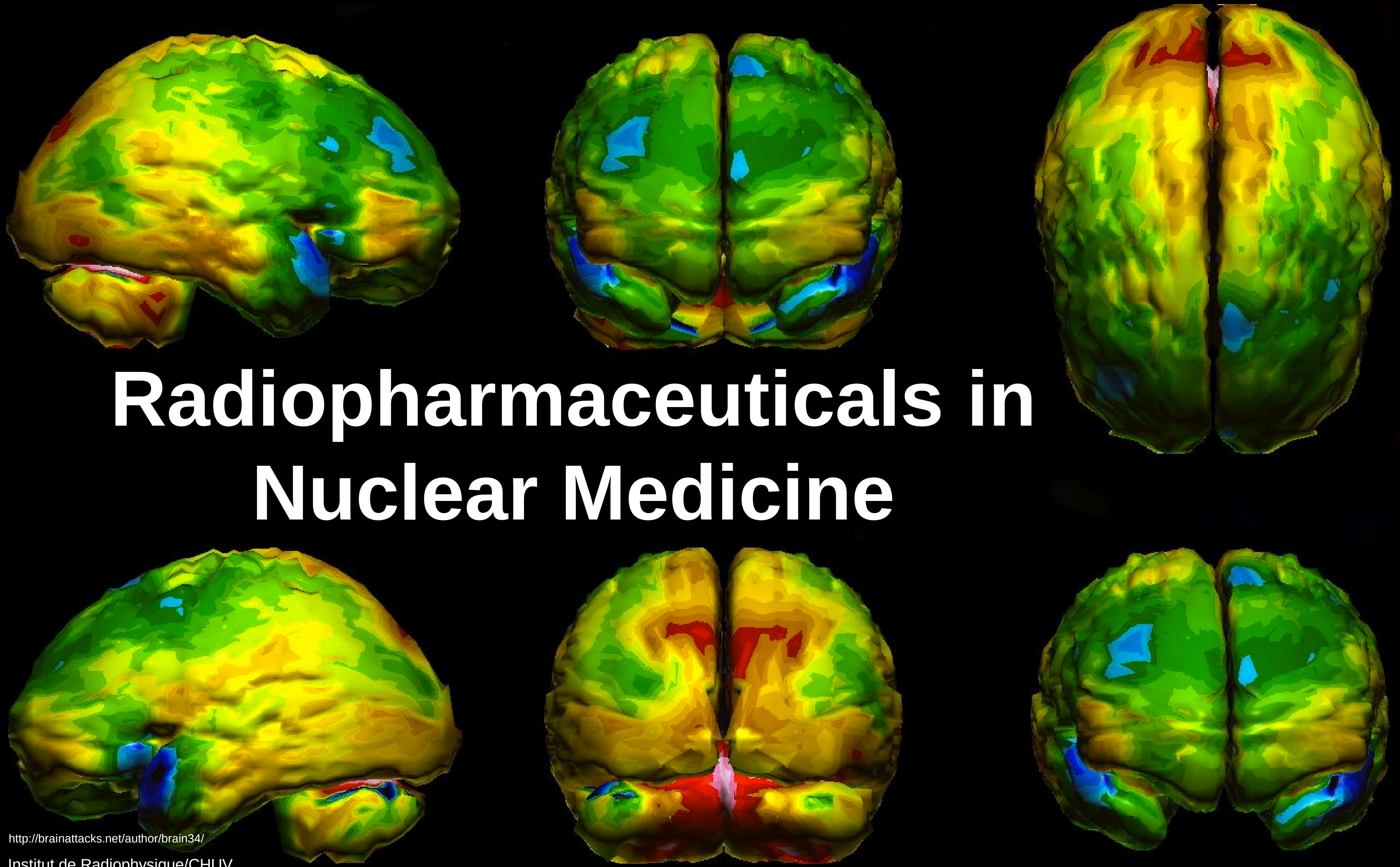
Radiopharmaceuticals in Nuclear Medicine



http://brainattacks.net/author/brain34/

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Program

Part I: Applications in Nuclear Medicine

Part II: Radionuclide Production

Part III: Radiopharmaceutical Products

Part IV: Facilities

Part V: Legislation for Radiopharmaceuticals

Part VI: Quality Control Methods

Part I: Applications in Nuclear Medicine

- PET Radionuclides
- SPECT Radionuclides
- Therapeutic Radionuclides
- Theranostics

What is a *radiopharmaceutical*?

A radioactive pharmaceutical compound used for the diagnosis and therapeutic treatment of human diseases.

Radionuclide + Pharmaceutical

Applications in Nuclear Medicine

- **Imaging**
  - Gamma or positron emitting isotopes
    - ^{99m}Tc (γ), ^{111}In (γ), ^{18}F(β^+), ^{11}C (β^+), ^{64}Cu (β^+)
  - Visualization of a biological process
    - Cancer, myocardial perfusion agents,…

- **Therapy**
  - Particle emitters
  - Alpha, beta, gamma
    - ^{188}Re, ^{89}Sr, ^{90}Y, ^{212}Bi, ^{225}Ac, ^{131}I, ^{177}Lu, ^{223}Ra…
  - Treatment of disease
    - Cancer, hyperthyroidism, …

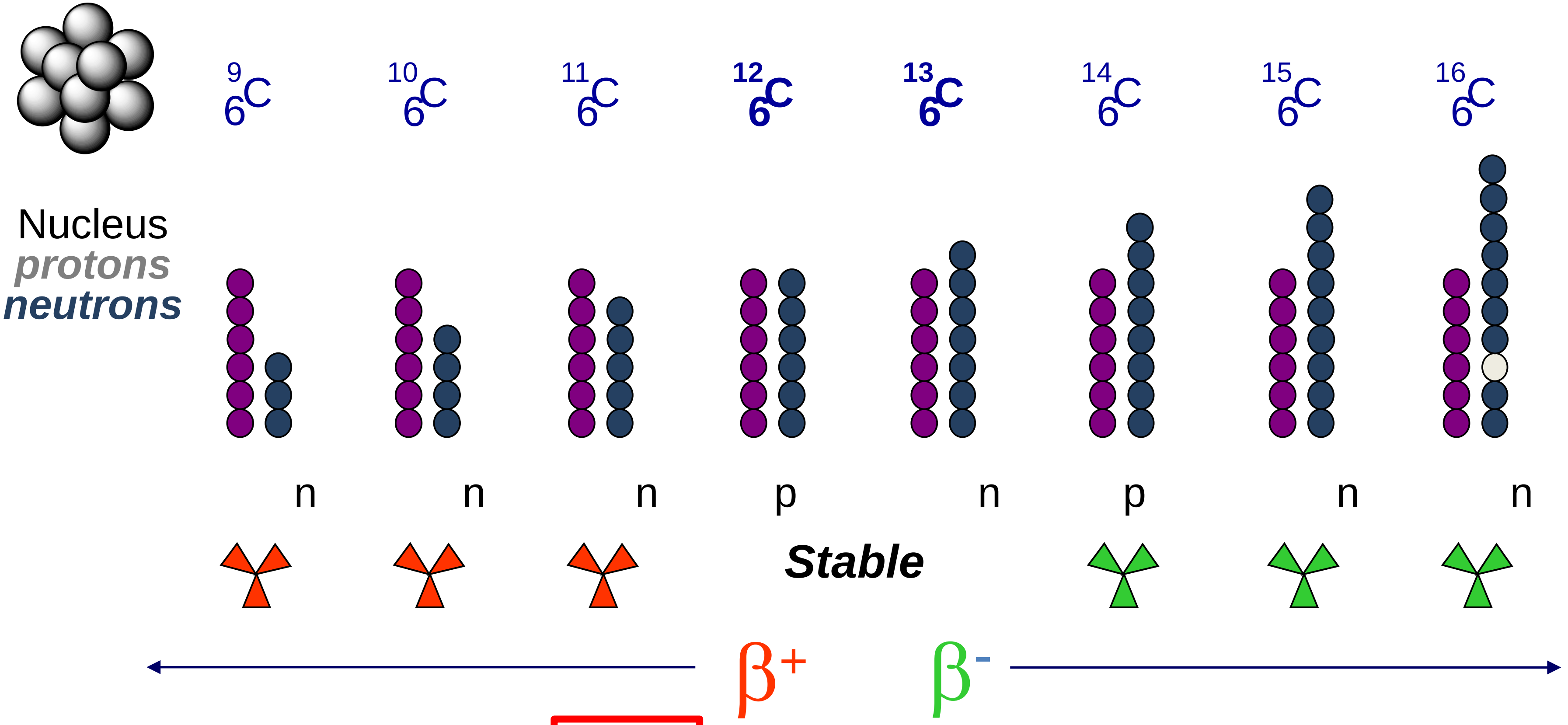
Criteria used to select radionuclides

- Physical half-life (should be in the range few minutes to several hours)
- Purity
- Nuclear Properties
- Wide Availability
- Effective Half life
- High target to non target ratio
- Simple preparation
- Biological stability
- Production costs

Ideal Nuclear Properties for imaging agents

- Reasonable energy emissions.
  - Radiation able to penetrate several layers of tissue (ideal: 120 – 150 keV)
- No particle (β, α) emission (gamma only)
- Short effective half life
- Cost effective

Example of carbon isotopes

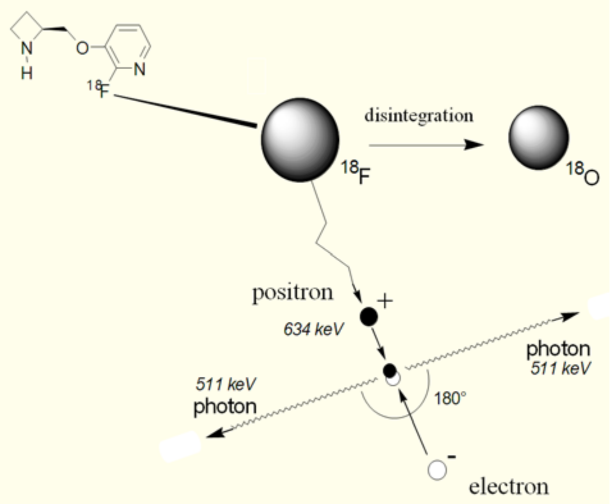


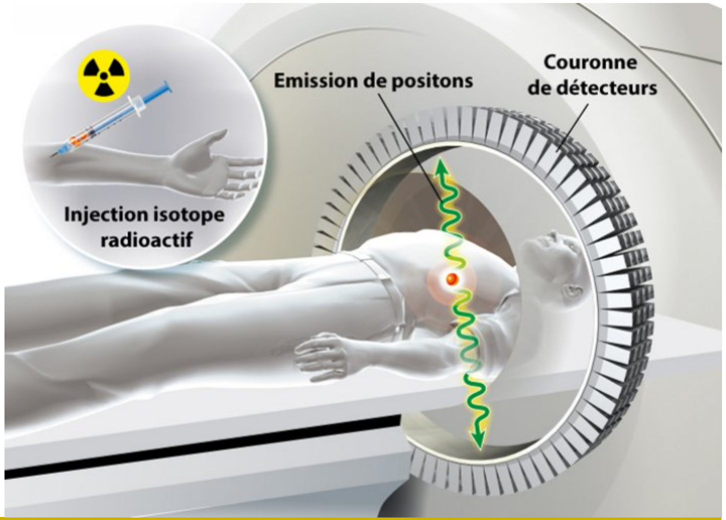
$T_{1/2}$	0.12 sec	19.2 sec	20.4 min	5730 year	2.45 sec	0.75 sec

Important PET radionuclides

Radionuclide	$T_{1/2}$	Mean β^+ energy (keV)	Resolution (mm)
^{11}C	20 min	386	1.1
^{15}O	2 min	735	1.5
^{18}F	110 min	250	0.7
^{64}Cu	12.7 h	278	0.7
^{68}Ga	1.1 h	830	2.4
^{76}Br	16.3 h	1180	3.2
^{124}I	4.17 d	820	2.3
^{89}Zr	3.27 d	396	1.1

Principle of PET (positron emission)



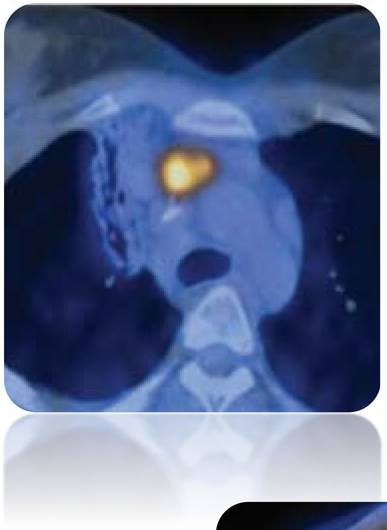


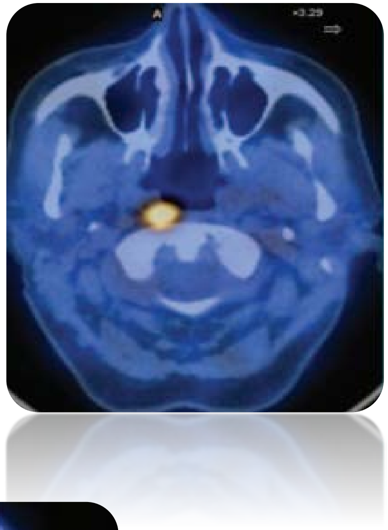
Radionuclide	Half-Life	β^+ fraction	Maximum β^+ Energy	How Produced
^{11}C	20.4 min	0.99	960 keV	Cyclotron
^{13}N	9.96 min	1.00	1.19 MeV	Cyclotron
^{15}O	123 sec	1.00	1.72 MeV	Cyclotron
^{18}F	110 min	0.97	635 keV	Cyclotron
^{62}Cu	9.74 min	0.98	2.94 MeV	Generator (from ^{62}Zn)
^{64}Cu	12.7 hr	0.19	580 keV	Cyclotron
^{68}Ga	68.3 min	0.88	1.9 MeV	Generator (from ^{68}Ge)
^{76}Br	16.1 hr	0.54	3.7 MeV	Cyclotron
^{82}Rb	78 sec	0.95	3.35 MeV	Generator (from ^{82}Sr)
^{124}I	4.18 days	0.22	1.5 MeV	Cyclotron

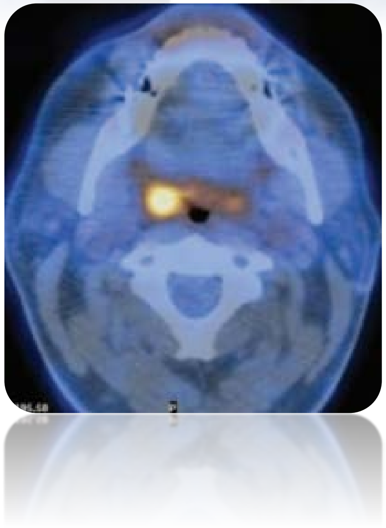
Most commonly used: ^{18}Fluorodeoxyglucose (FDG)

- β^+ emission
- PET scans
- Sugar metabolic pathway
- Rate dependence on cell type

- Brain, heart, tumor…
- Dementia, Alzheimer’s,
- Drug abuse…







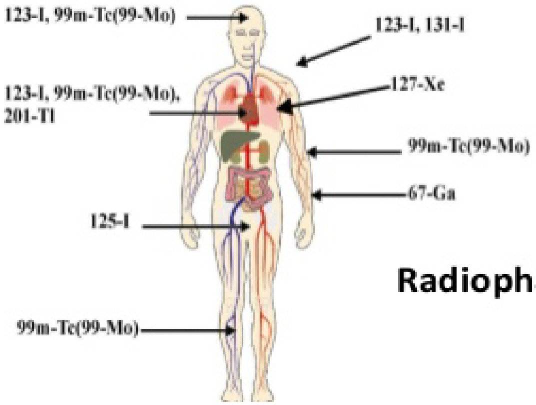
Important SPECT radionuclides (gamma)

Radionuclide	**$T_{1/2}$**	**gamma (%)**
Tc-99m	6.02 hr	140 KeV (89)
Tl-201	73 hr	167 KeV (9.4)
In-111	2.21 d	171(90), 245(94)
Ga-67	78 hr	93 (40), 184 (20), 300(17)
I-123	13.2 hr	159 (83)
I-131	8d	284(6), 364(81), 637(7)
Xe-133	5.3 d	81(37)

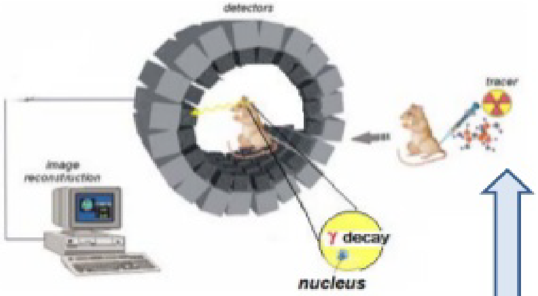
Principle of SPECT (gamma emitting radioisotopes)

Single Photon Emission Computerized Tomography

Radionuclides and tissues



Apparatus



Radiopharmaceuticals variable

- Generator methodology :
- no Mo-99 is injected, just Tc-99m

PET

PET tracers emit positrons that annihilate with electrons, causing two gamma photons:

- Biologically useful isotopes.

  (^{11}C, ^{13}N, ^{15}O, ^{18}F)

- Very short $T_{1/2}$
- Production on site (cyclotron)
- Very expensive

SPECT

Tracers used in SPECT emit gamma radiation that is measured directly:

- Complex and larger molecules.

  (^{99m}Tc, ^{123}I, ^{111}In, …)

- Longer half lives
- Available world wide (No special production equipment needed)
- Less expensive

Important radionuclides for therapy

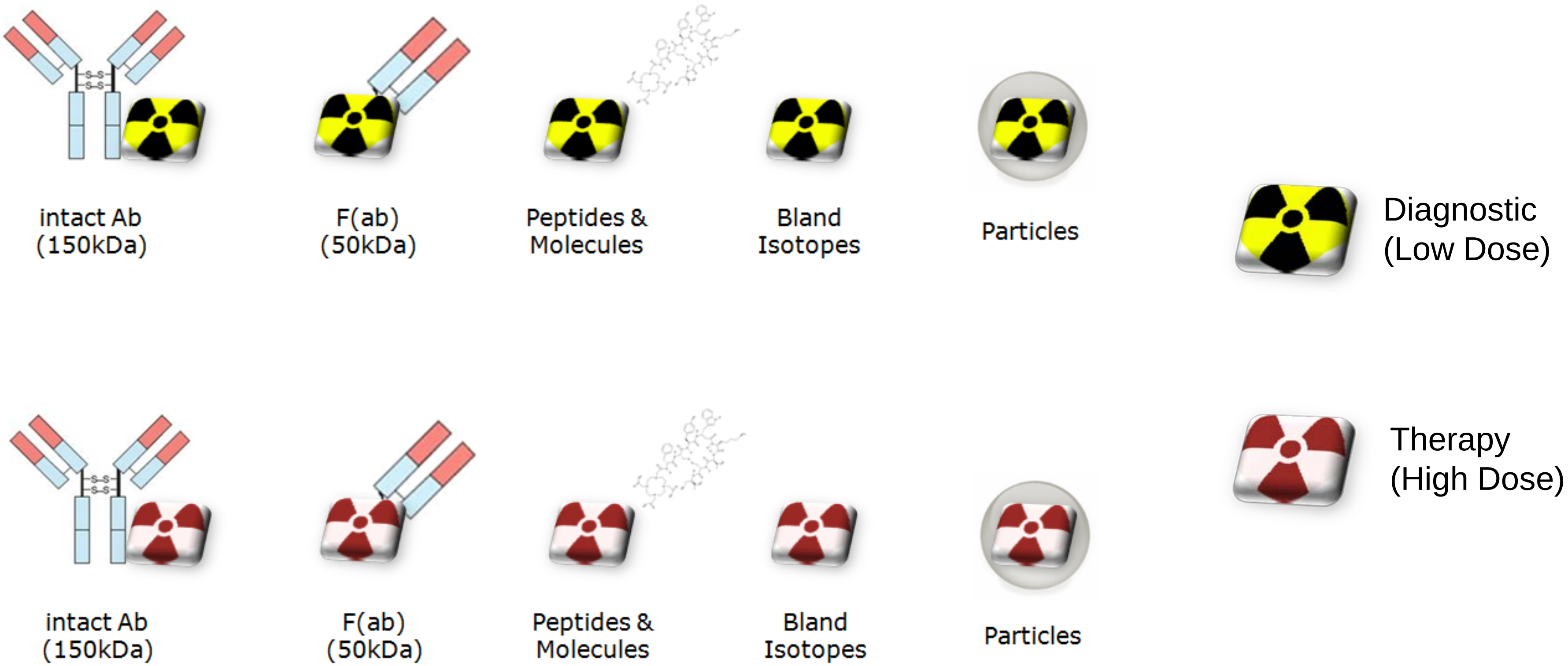
Radionuclide	**$T_{1/2}$**	**Particle (MeV)**
I-131(MIBG)	8 d	β^- (0.6) max
Sm-153	1.9 d	β^- (0.8) max
Re-186	3.8 d	β^- (1.1) max
Sr-89	50.6 d	β^- (1.5) max
P-32	14.3 d	β^- (1.7) max
Re-188	17 hrs	β^- (2.1) max
Y-90 (SIR-Spheres)	2.7 d	β^- (2.3) max
Lu-177 (Luthathera)	6.6 d	β^- (0.5) max
Bi-212	1 hr	α (6.05) max
Ra-223 (Xofigo)	11.4 d	α (5.78) max

Effective half life (radio and biological)

Rate of accumulation or elimination of the radioactive substance in the organism.

- Nuclear Decay ($T_{1/2}$)
  - Inherent statistical decay of the nuclide
- Biological $T_{1/2}$
  - Uptake/washout of the radiopharmaceutical
  - Equilibration
  - Decomposition

Evolution of Theragnostics



intact Ab
(150kDa)

F(ab)
(50kDa)

Peptides &
Molecules

Bland
Isotopes

Particles

Diagnostic
(Low Dose)

intact Ab
(150kDa)

F(ab)
(50kDa)

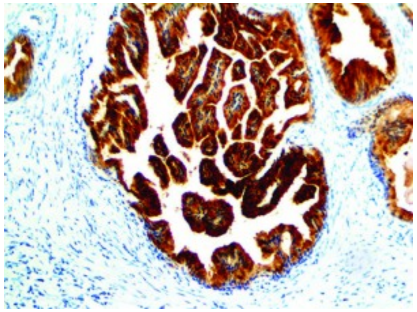
Peptides &
Molecules

Bland
Isotopes

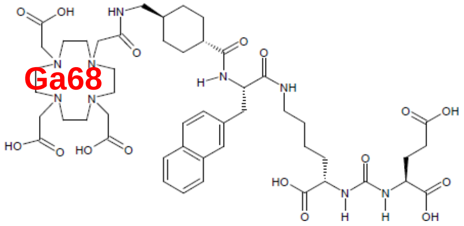
Particles

Therapy
(High Dose)

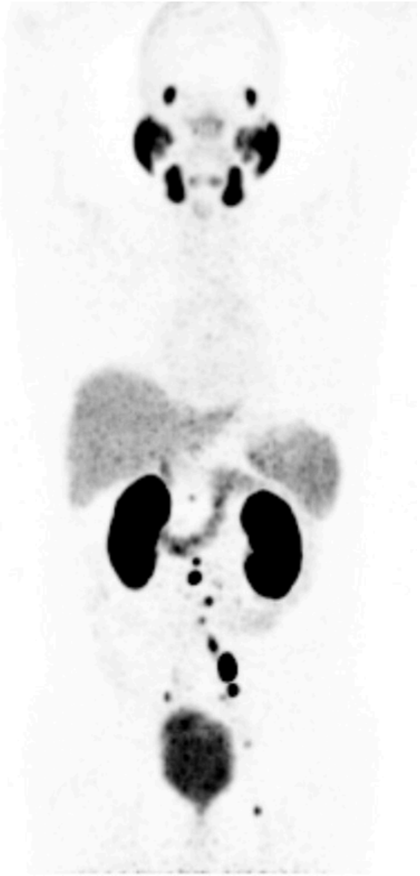
Prostate Cancer (Gallium 68 PSMA)



PSMA – R +++
Metastatic Prostate Cancer



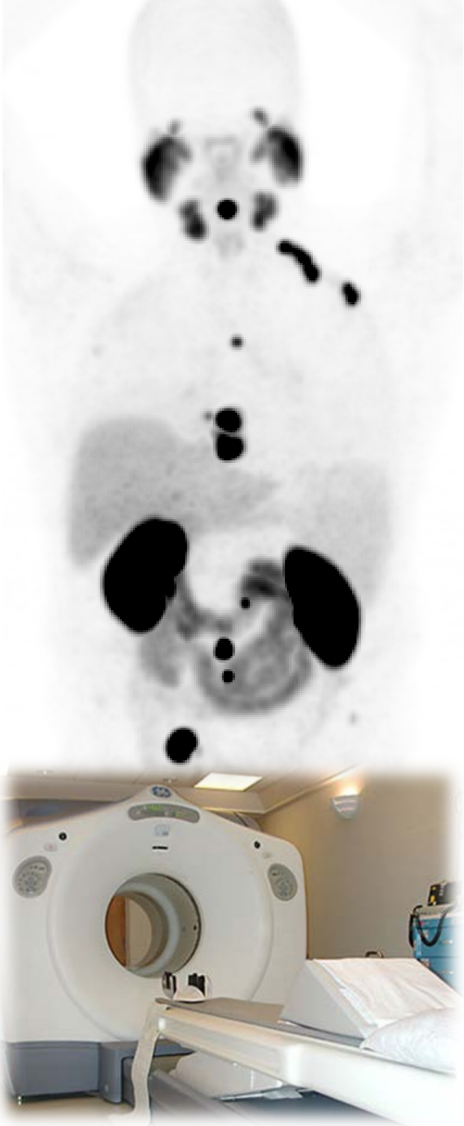
Ga68 PSMA-617



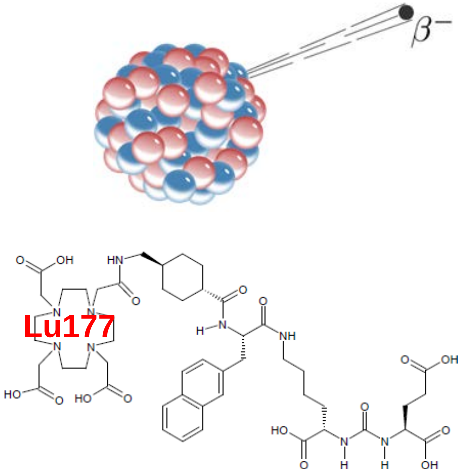
PET
Ga68 PSMA-617

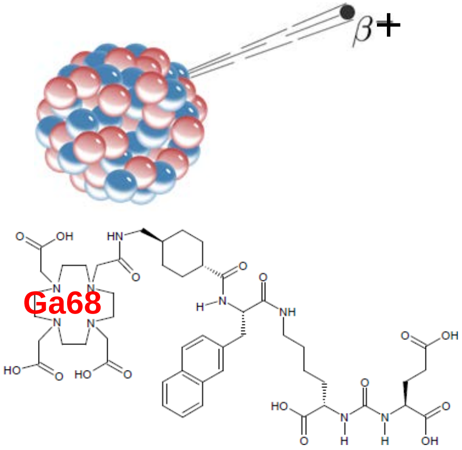
PET
18F CHOLIN (Standard)

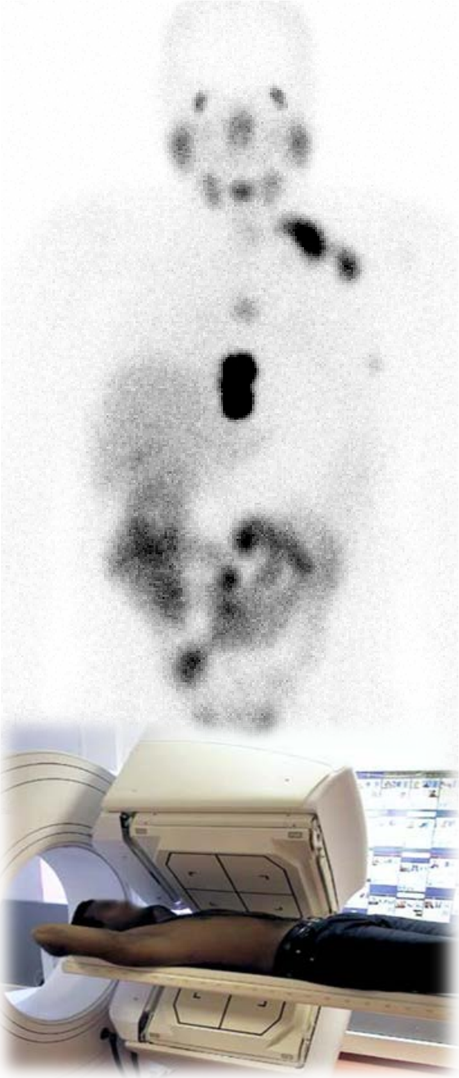
Ga68 / Lu177 PSMA



Ga68 PSMA-617







Lu 177 PSMA-617

Summary Part I

- Choice of nuclide depends on application (diagnostic or therapeutic)
- Ideally, short lived for diagnostics, longer lived for therapeutics
- New approaches in the fields of so called ‘theragnostics’:
    - Similar characteristics, same binding sites
    - Imaging and therapy combined

→ Focus on development in antibody and peptide labeled radiopharmaceuticals

Part II: Radionuclide Production

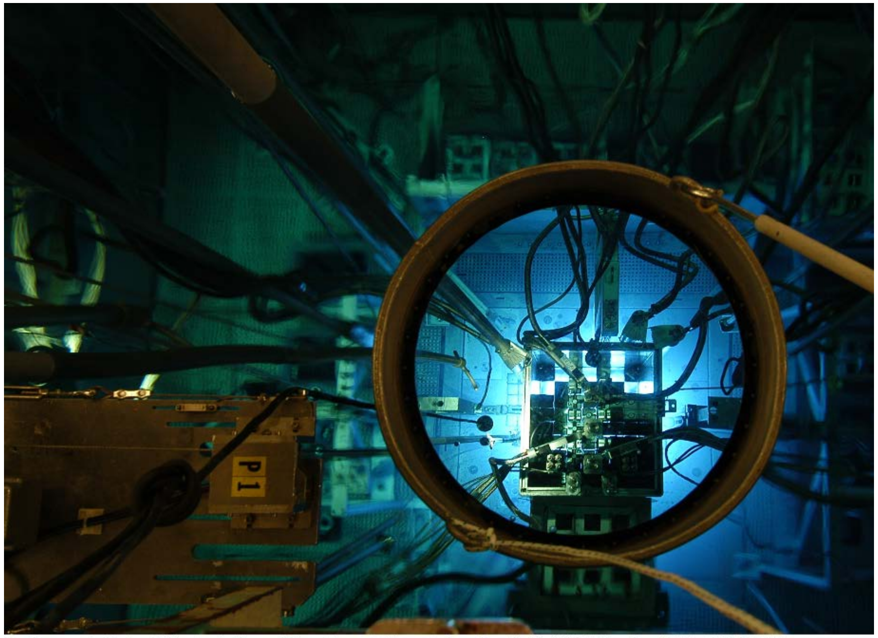
- Nuclear reactors, fission products
- Cyclotron Production (accelerators)
- Generators

Different modes of production

- Bombardment *using an electrically neutral particle*
- Bombardment *using particles electrically charged*
- Fission produced radio-nuclides
- Generators

Bombardment using an *electrically* ***neutral*** *particle*

- Type of particles: **neutrons**
- Source of particles: nuclear reactor
- Energy of the neutrons: 0,025 eV



Vue du coeur du réacteur Osiris. La réaction nucléaire est caractérisée par la lueur bleutée dûe à l'effet Cerenkov. Crédit : L.Godart/CEA

Main radionuclides via neutron bombardment

Radionuclide	Decay mode	Mode of production	Natural abundance in the target	Cross section (10^{-24} cm^2)
14C	β_	14N(n,p)14C	99,6	1,81
24Na	(β_,γ)	23Na(n,γ)24Na	100	0,53
32P	β_	31P(n,γ)32P	100	0,19
		32S(n,p)32P	95,0	--
35S	β_	35Cl(n,p)35S	75,5	--
42K	(β_,γ)	41K(n.γ)42K	6,8	1,2
51Cr	(EC,γ)	50Cr(n,γ)51Cr	4,3	17
59Fe	(β_,γ)	58Fe(n,γ)59Fe	0,3	1,1
75Se	(EC,γ)	74Se(n,γ)75Se	0,9	30
125I	(EC,γ)	124Xe(n,γ)125Xe125I	0,1	110
131I	(β_,γ)	130Te(n,γ)131Te131I	34,5	0,24

Bombardment using *particles* ***electrically charged***

- Particles are accelerated using magnetic fields (cyclotrons)
- Type of particles generally accelerated: H- and D-

- Different cyclotrons are used for the production of radionuclides:

  Medical cyclotrons (10 MeV-18MeV)

  Industrial cyclotrons (15 MeV to 70 MeV)

Small medical cyclotrons

GE PETtrace

p = 16.5 MeV
d = 8.4 MeV

I up to 100 μA

negative ion acceleration:
H^-, D^- !

IBA Cyclone 18/9

p = 18 MeV
d = 9 MeV

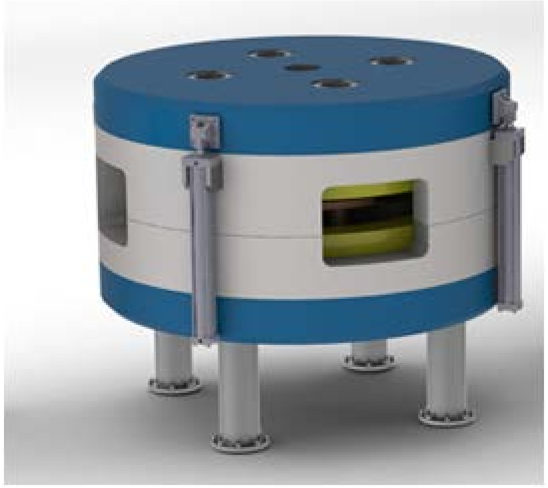
I up to 150 μA

- Main radionuclides produced : ^{11}C, ^{15}O, ^{13}N, ^{18}F

- Energy required : in the range of **10 MeV to 18 MeV**

- Size: “baby cyclotrons” easy to implant in hospitals

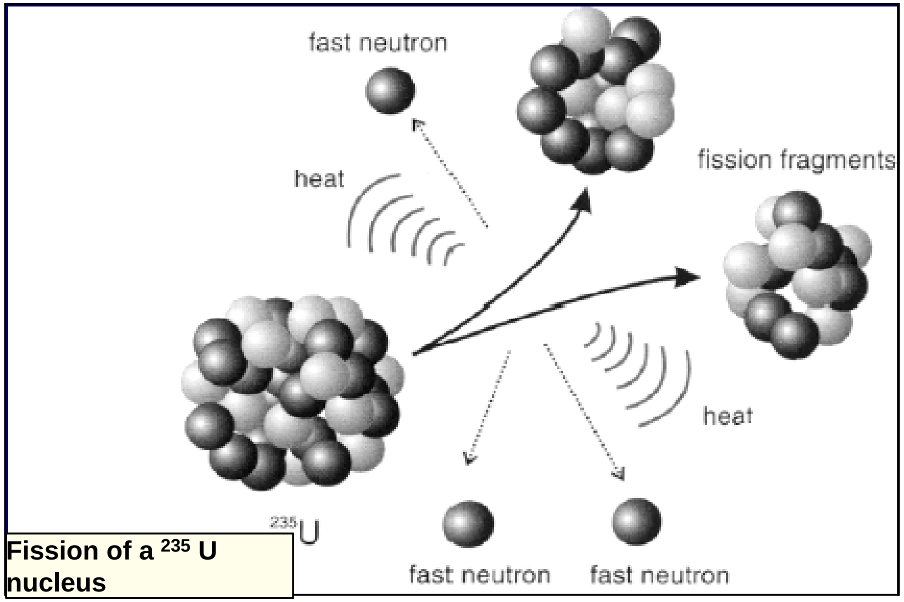
- Targets: mainly made of gas or liquid (very quick transfer from the irradiation site to the « hot » lab for the radioactive synthesis)



Fission reaction → ex. for generators (99mTc)

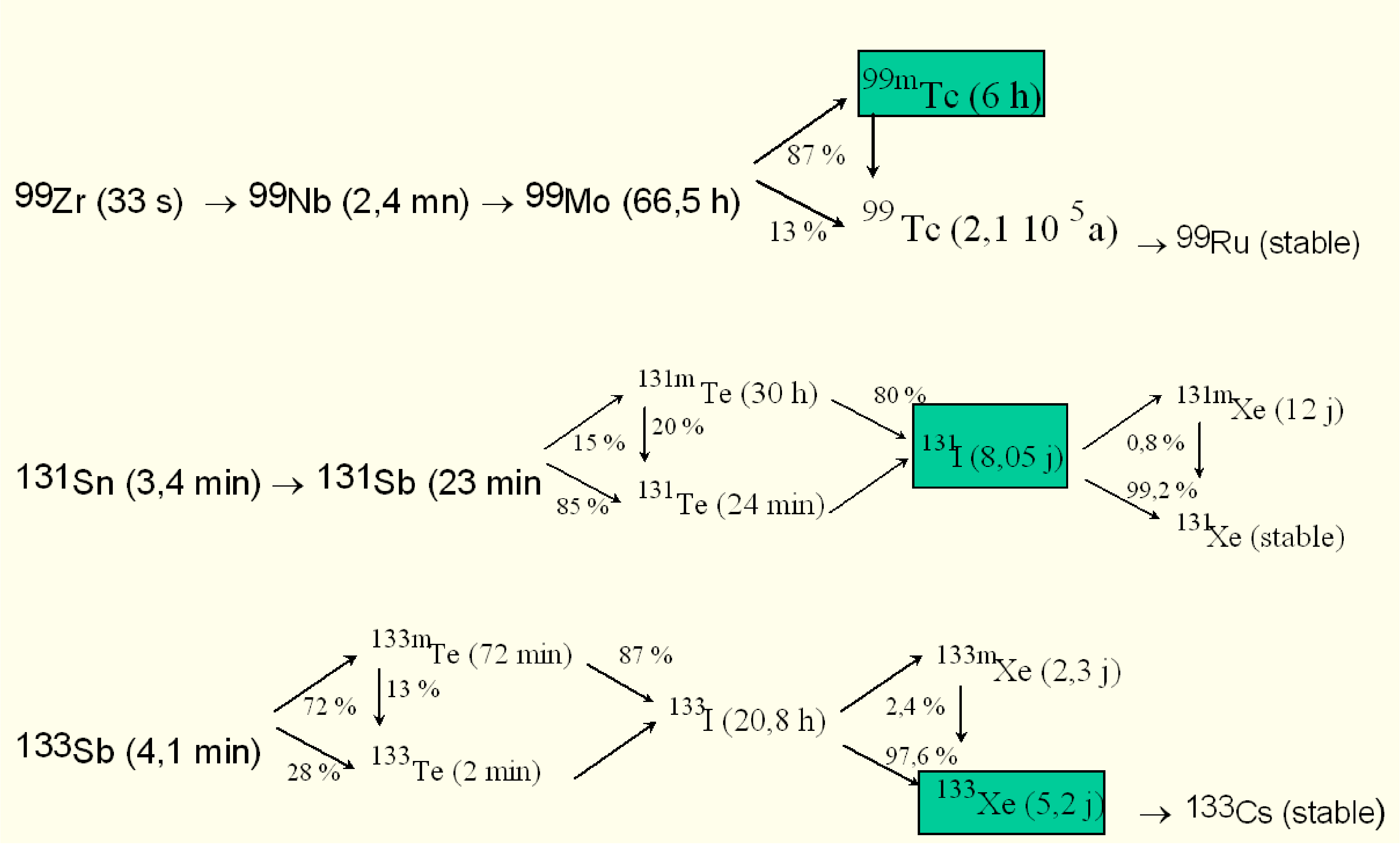
Nuclear fission is either a nuclear reaction or a radioactive decay process in which the nucleus of an atom splits into smaller parts (lighter nuclei). The fission process often produces free neutrons and gamma photons, and releases a very large amount of energy even by the energetic standards of radioactive decay.

Fission of ^{235}U induces the formation of about 200 different radionuclides



Fission of a ^{235} U nucleus

Radionuclides for diagnostic/therapeutic applications



^{99}Zr (33 s) → ^{99}Nb (2,4 mn) → ^{99}Mo (66,5 h)

87 %

^{99m}Tc (6 h)

13 %

^{99}Tc (2,1 10 ^{5} a) → ^{99}Ru (stable)

^{131}Sn (3,4 min) → ^{131}Sb (23 min

15 %

^{131m}Te (30 h)

20 %

85 %

^{131}Te (24 min)

80 %

^{131}I (8,05 j)

^{131m}Xe (12 j)

0,8 %

99,2 %

^{131}Xe (stable)

^{133}Sb (4,1 min)

72 %

^{133m}Te (72 min)

13 %

28 %

^{133}Te (2 min)

87 %

^{133}I (20,8 h)

^{133m}Xe (2,3 j)

2,4 %

97,6 %

^{133}Xe (5,2 j) → ^{133}Cs (stable)

Molybdenum Radionuclides, Iodine and Xenon Extracted from Fission Products

Molybdenum			**Iodine**			**Xenon**		
Atomic Mass	half-life	Fission yield %	Atomic Mass	half-life	Fission yield %	Atomic mass	Period	Fission yield %
95	Stable	6.27	127	stable	0.13	129	stable	0.8
97	Stable	6.09	129	1.7 x 10 y	0.8	131m	12 d	3.1
98	Stable	5.78	131	8.05 d	3.1	131	stable	3.1
99	66.5 h	6.06	132	2.30 h	4.7	132	stable	4.38
100	stable	6.30	133	20.8 h	6.62	133m	2.3 d	6.62
101	14.6 min.	5.0	134	52.5 min.	8.06	133	5.27 d	6.62
102	11.5 min.	4.3	135	6.70 h	6.3	134	stable	8.06
			136 to 139	a few sec. to a few min.		135	9.2 h	6.3
						136	stable	6.46
						137 to 140	a few sec. to a few min.	

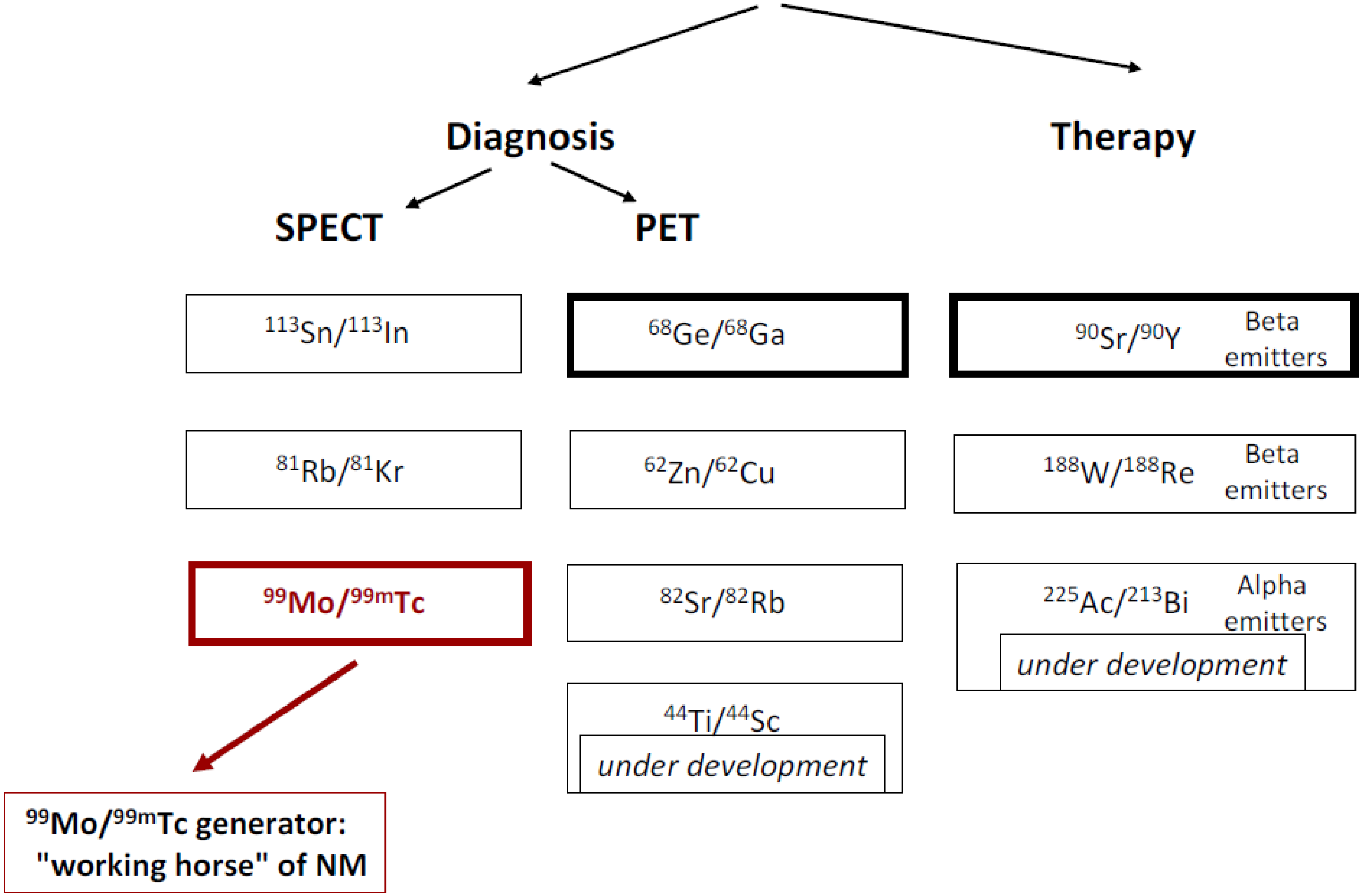
Radionuclide Generators

Permanent, convenient access to short or medium lived RNs:
A RADIONUCLIDE GENERATOR supplies a dedicated radionuclide for routine clinical practice

"isotope cow"

Failla

Important RN generators for medical application in nuclear medicine



Diagnosis

Therapy

SPECT

PET

^{113}Sn/^{113}In

^{81}Rb/^{81}Kr

^{99}Mo/^{99m}Tc

^{68}Ge/^{68}Ga

^{62}Zn/^{62}Cu

^{82}Sr/^{82}Rb

^{44}Ti/^{44}Sc

under development

^{90}Sr/^{90}Y Beta emitters

^{188}W/^{188}Re Beta emitters

^{225}Ac/^{213}Bi Alpha emitters

under development

^{99}Mo/^{99m}Tc generator: "working horse" of NM

Working principle of a generator

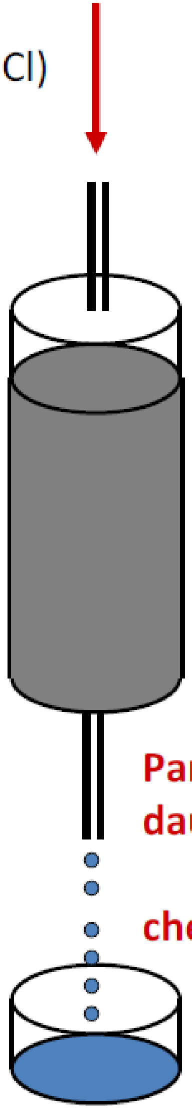
parent (mother) nuclide	**daughter nuclide**	**granddaughter nuclide**
- radioactive -	- radioactive -	- best case: non-radioactive -

$$\mathbf{A} \xrightarrow[T_{1/2}\ A]{\text{decay A}} \mathbf{B} \xrightarrow[\text{T1/2 B}]{\text{decay B}} \mathbf{C}$$

If $T_{1/2}$ A > $T_{1/2}$ B, C non-radioactive → best prerequisite for a generator system.

Further preconditions:

- Suitable nuclear properties of RN B ($T_{1/2}$, photon/particle energies ...)
- Half life of RN A – some days ... years
- Half life of RN B – some minutes to hours ... days
- Simple separation of RN B from RN A in
  - high yields
  - very low breakthrough of A → →high radionuclidic purity
  - one suitable chemical form
  - meet GMP - requirements



Eluent (e.g. 0.9% NaCl)

Column with
stationary phase
loaded with parent
RN A - chemically
stably absorbed
(RN B and RN C
formed by decay)

Parent RN A and daughter RN B: different chemical species!

Eluted RN B (RN C)
(e.g. in 0.9% NaCl)

General principle:

→ A long-lived parent RN A is sorbed on a stationary phase of a column

→ Long-lived parent RN A decays – generation of a daughter-RN B

→ Daughter-RN B is eluted – the parent RN A sticks on the column

→ use of RN B for (medical) application

Pro and Contra

Advantages:

- Radionuclide always available for use
- Easy delivery and operation of generator systems

Disadvantages:

- Eluate is not for all generator systems directly suitable for labelling reactions
- For long-lived generators: high elution volumes cause breakthrough
- For long-lived, high activity mother nuclides deterioration of the column material (radiolysis) is a serious problem!

→ breakthrough of the long-lived mother nuclide increases with each elution
→ shelf-life of the generator is short compared to actual half-life of the mother nuclide
→ clean-up procedures for the eluate are required, which require time and generate higher radiation exposure to personnel

Supply of mother radionuclides is for almost all generator systems critical!

The ^{99}Mo/^{99m}Tc Generator: Working horse of nuclear medicine

Walter Tucker and Margaret Greene developed first ^{99}Mo/^{99m}Tc-Generator

1957:
^{99}Mo/^{99m}Tc-generator

1961:

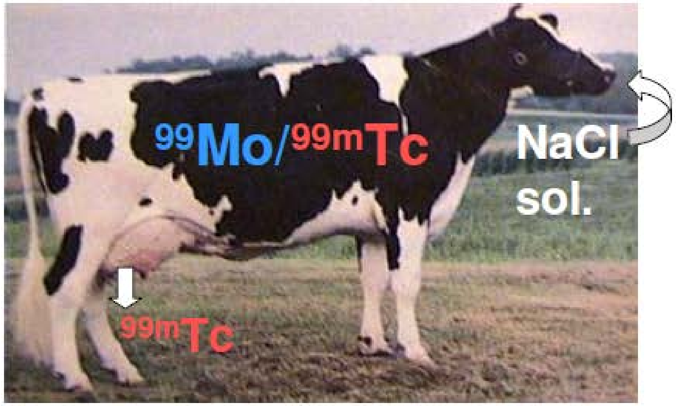
Clinical use

„Kit“

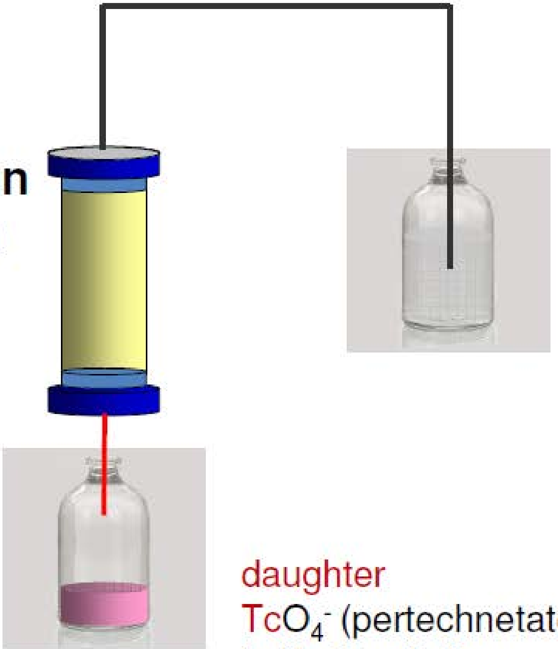
Basis of Nucl Med

Demonstration of eluting the ^{99m}Tc of ^{99}Mo (shielding is removed, Brookhaven NL, 1957)

Mother/Daughter Radionuclide Generator (Cow)



mother nuclide: ^{99}Mo
daughter nuclide: ^{99m}Tc

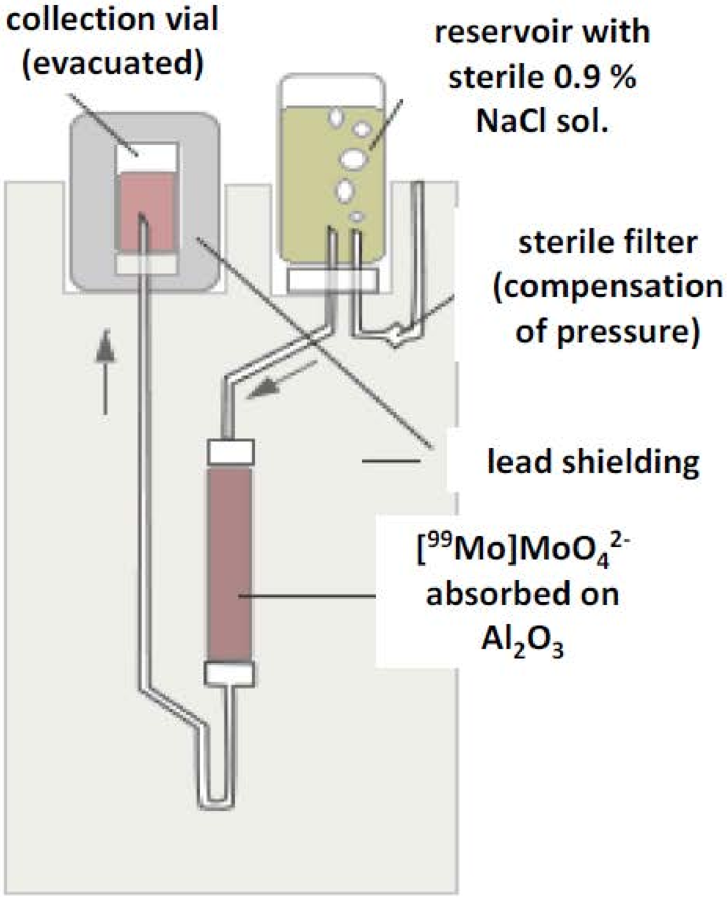


generator column

mother selective resin
MoO_4^{2-} (molybdate)
on Al_2O_3

strip solution
0.9% NaCl sol.

daughter
TcO_4^- (pertechnetate)
in NaCl solution



collection vial (evacuated)

reservoir with sterile 0.9 % NaCl sol.

sterile filter (compensation of pressure)

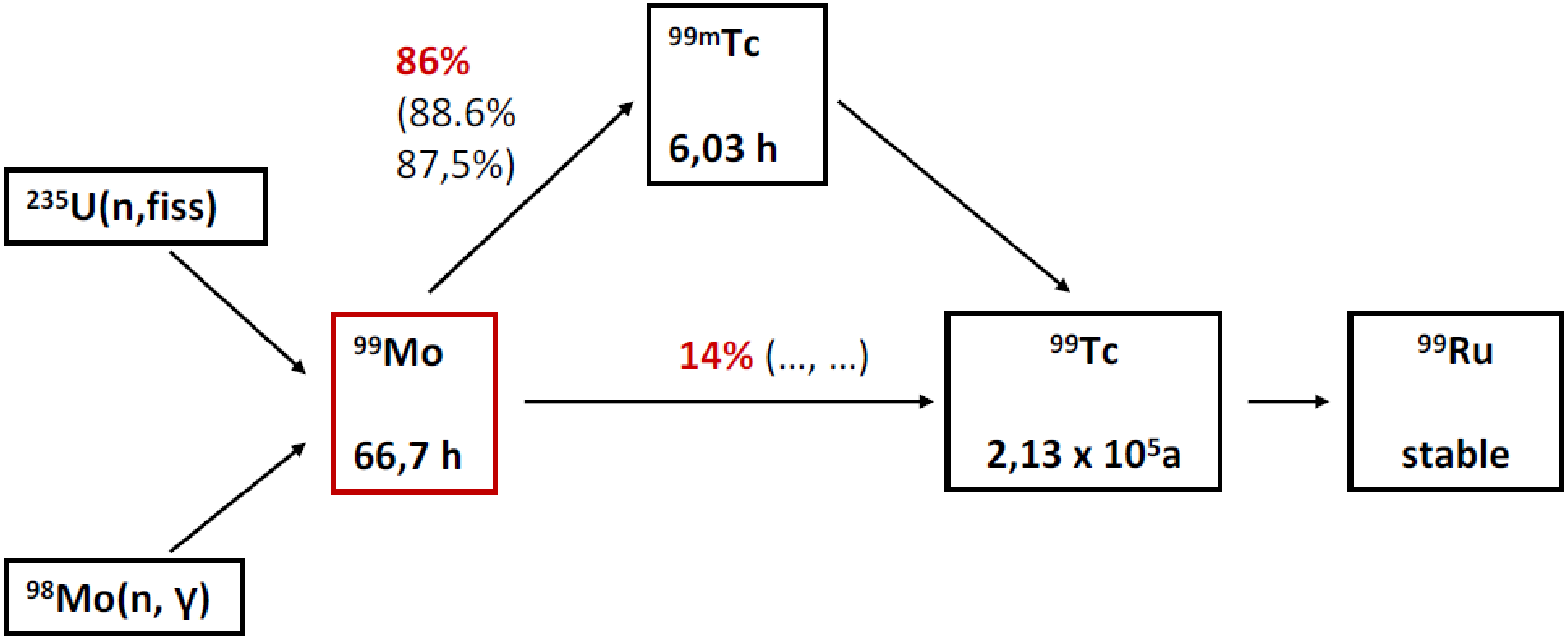
lead shielding

$[^{99}Mo]MoO_4^{2-}$ absorbed on Al_2O_3

Source: Mallinckrodt

$[^{99}Mo]MoO_4^{2-} \rightarrow$ absorbed on Al_2O_3

$[^{99m}Tc]TcO_4^{1-} \rightarrow$ eluted from Al_2O_3



$^{235}U(n,fiss)$

$^{98}Mo(n, \gamma)$

^{99}Mo 66,7 h

86% (88.6% 87,5%)

^{99m}Tc 6,03 h

14% (..., ...)

^{99}Tc 2,13 x 10^5a

^{99}Ru stable

- The ^{99m}Tc-generator provides n.c.a. ^{99m}Tc, chem. form: $[^{99m}Tc]TcO_4^-$
- A_s decreases depending on point in time of elution - "Generator history"
- 86% versus 14%: Difference in $A_{Mo\text{-}99}$ versus $A_{Tc\text{-}99m}$!!!

Remark: With growing yield A_s decreases ^{99m}Tc → ^{99}Tc

Pro and Contra ^{99m}Tc Generators

Advantages

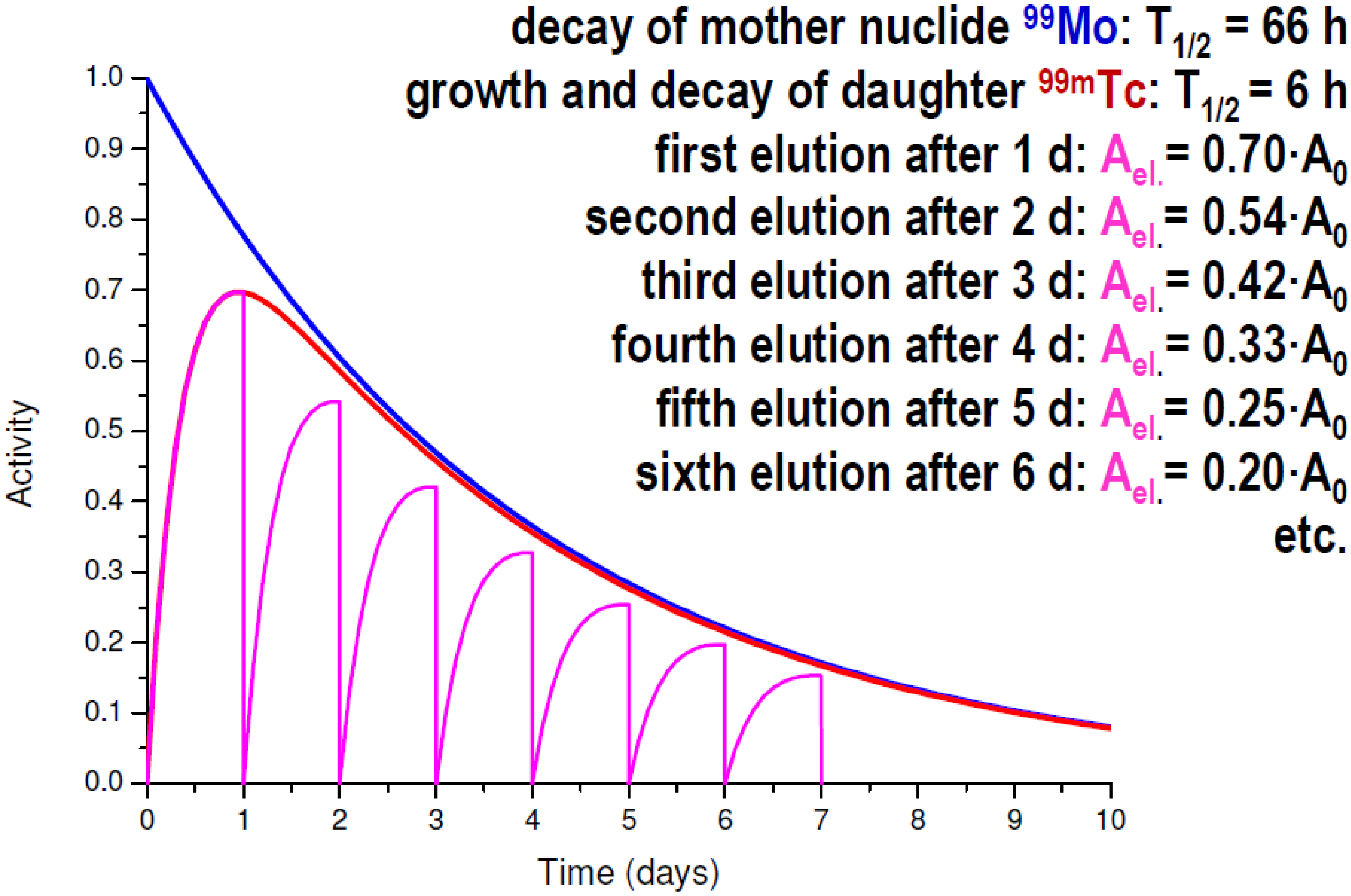
- Worldwide availibility and operation of the generator system.
- Simple operation of the generator system
- Eluate is directly suitable for labelling reactions (kit formulations)
- Eluate is sterile, pyrogen-free and as isotonic water solution ($Na^{188}TcO_4$)
- ^{99m}Tc is the most widely used radionuclide in nuclear medicine → numerous applications

Disadvantages

- ^{99}Mo/^{99m}Tc-Generator has a short shelf-life (usually 1 week).
- There has been a serious supply crisis for ^{99}Mo due to research) reactor shut-downs and generally old nuclear reactors suitable for ^{99}Mo production.

  → ongoing discussion, will be solved with new reactors
- Chemical isolation of ^{99}Mo from irradiated ^{235}U is highly demanding and expensive and generates lots of radioactive waste.

Activity calculations


decay of mother nuclide ^{99}Mo: $T_{1/2}$ = 66 h

growth and decay of daughter ^{99m}Tc: $T_{1/2}$ = 6 h

first elution after 1 d: $A_{el.} = 0.70 \cdot A_0$

second elution after 2 d: $A_{el.} = 0.54 \cdot A_0$

third elution after 3 d: $A_{el.} = 0.42 \cdot A_0$

fourth elution after 4 d: $A_{el.} = 0.33 \cdot A_0$

fifth elution after 5 d: $A_{el.} = 0.25 \cdot A_0$

sixth elution after 6 d: $A_{el.} = 0.20 \cdot A_0$

etc.

Other systems

Commercial realization by Eckert & Ziegler

Applied for licensing!

Problems may be:

- sterility after many elutions,
- breakthrough of ^{68}Ge after many elutions

Summary Part II

- Different productions modes of radiopharmaceuticals (Fission, Cyclotrons, Generators)
- Cyclotron production are challenging, market for ‘baby cyclotrons’ is increasing
- Generators are still most widely used, in combination with synthesis modules for radionuclides like Ga-68
- ‘Kit’ approach for radiopharmaceuticals is the easiest to use, market increasing (ex. PSMA-11, Dotatate, …)

Practical Exercise