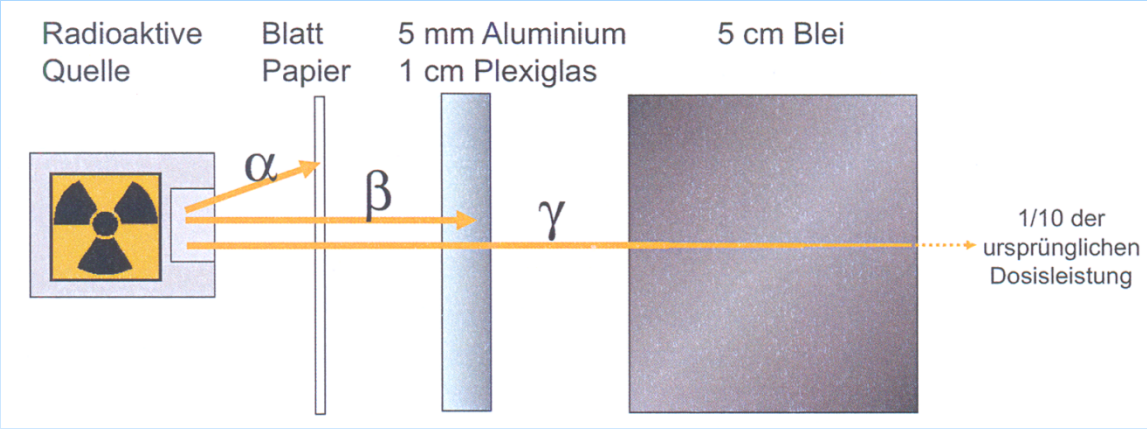
Radiation Protection

Shielding



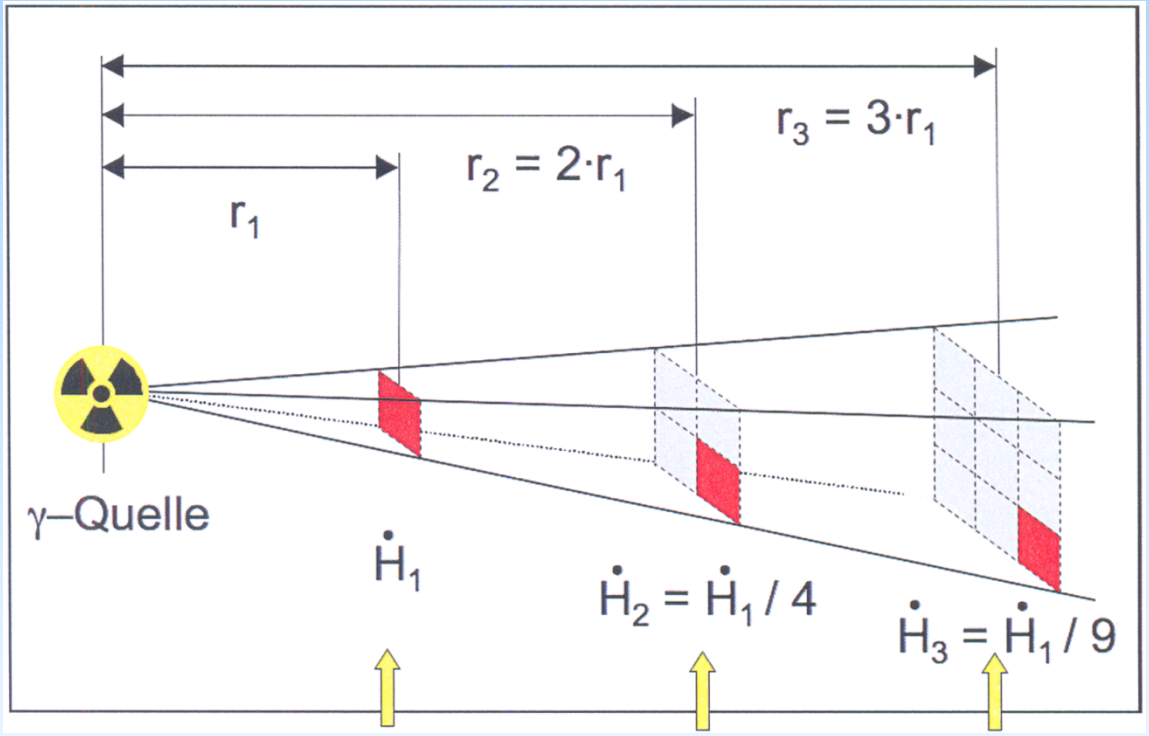
Lab coat → shields already approx. 80% of soft β-radiation

Neutrons → Moderation with materials that contain a lot of protons (e.g. water)

→ Absorption with B, Gd or Cd (leads to secondary γ-radiation)

Radiation Protection

The Square Root Law of Distance



$$\dot{H}_2 = \dot{H}_1 \cdot \left(\frac{r_1}{r_2} \right)^2$$

Radiation Protection

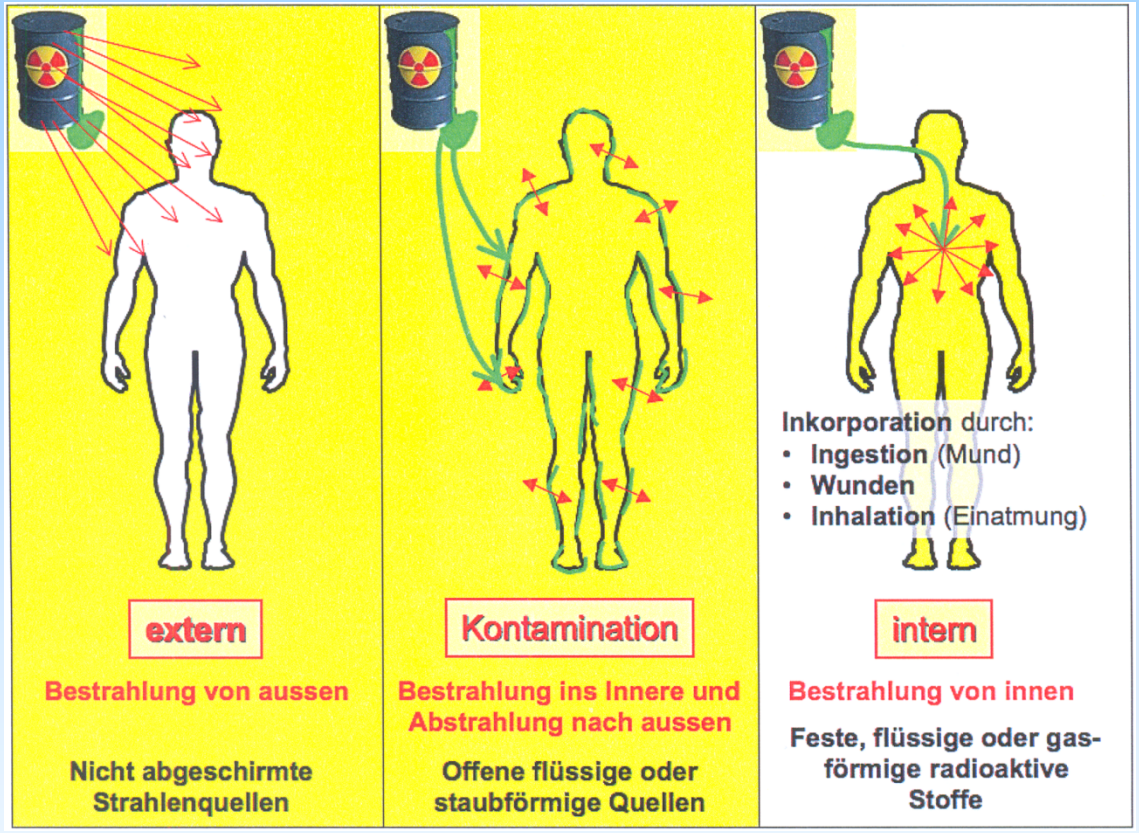
ALARA

As **L**ow **A**s **R**easonable **A**chievable

- Duration of stay (Aufenthaltszeit)
- Distance (Abstand)
- Shielding (Abschirmung)
- Activity
- Avoid contamination / incorporation

Radiation Protection

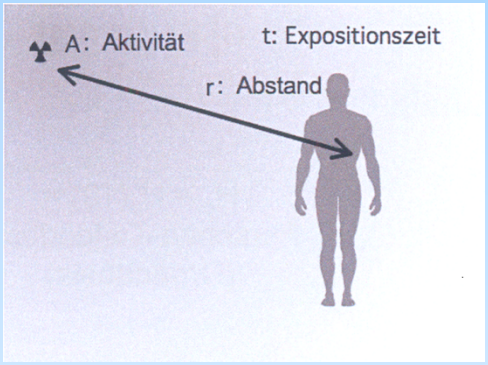
Dose Estimation



Radiation Protection

Dose Estimation

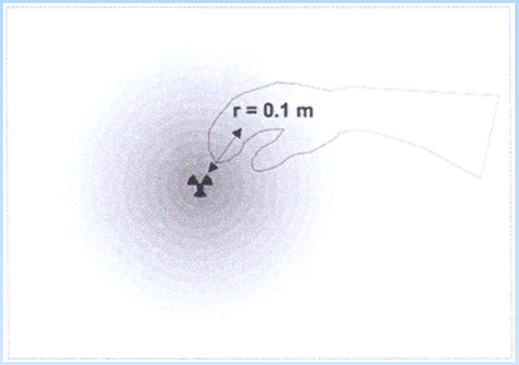
Organ Dose



$$H_p = A \cdot t \cdot h_{10} \cdot \left(\frac{1m}{r}\right)^2$$

h_{10}: Dose in mSv per GBq and per hour in 1 m distance to the source

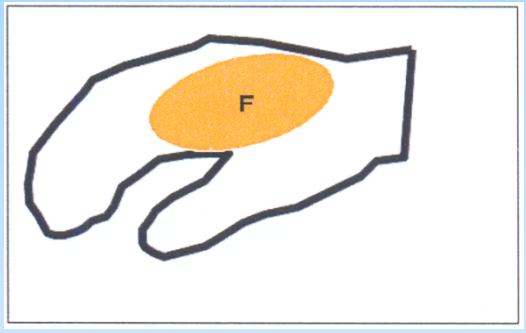
Skin Dose



$$H_S = A \cdot t \cdot h_{0.07}$$

$h_{0.07}$: Dose in mSv per GBq and per hour in 10 cm distance to the source

Skin Dose (Contamination)



$$H_S = \frac{A}{F} \cdot t \cdot h_{c0.07}$$

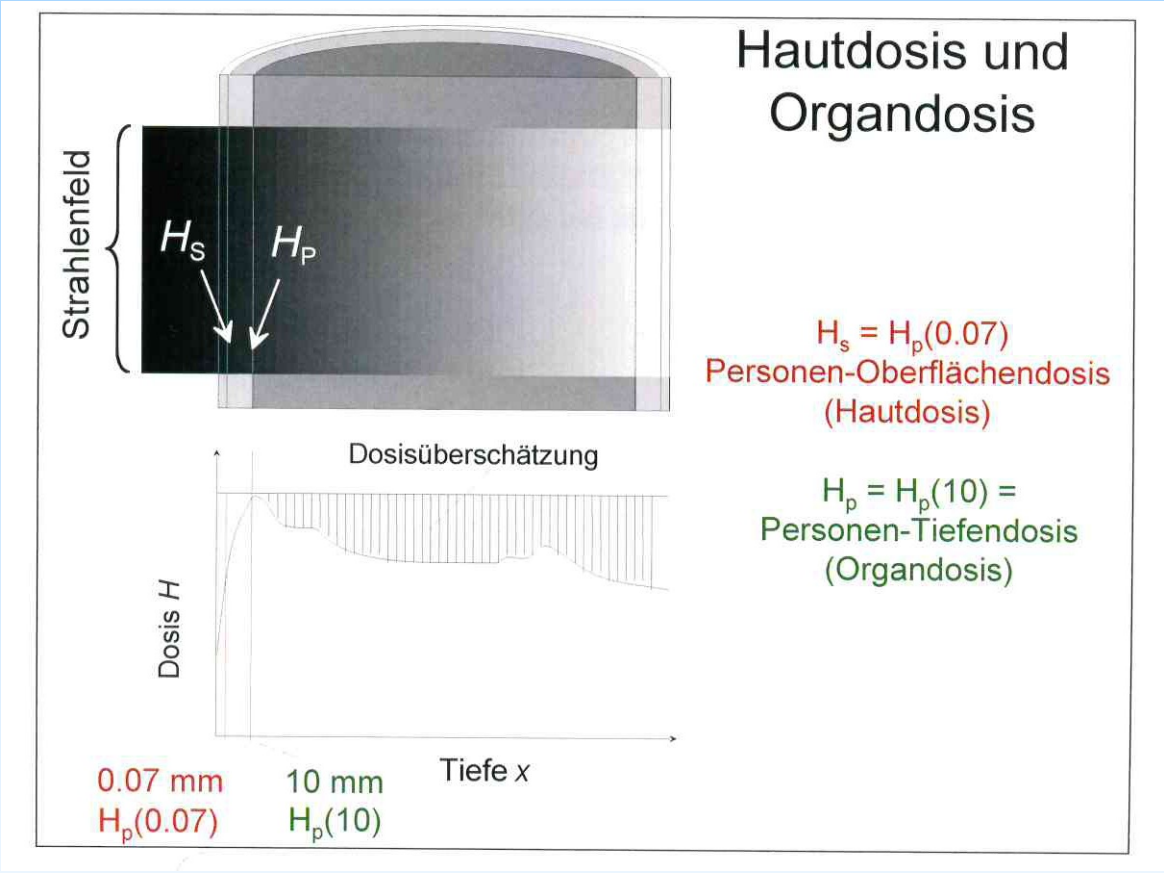
$h_{c0.07}$: Dose in mSv per kBq contamination and per hour on a surface of cm^2

Rule-of-thumb

1 GBq in 1 m distance during 1 h leads to a H_p of 1/3 mSv

Radiation Protection

Dose Estimation



Radiation Protection

Dose Estimation

Daten für den operationellen Strahlenschutz Organ-, Tiefendosis; Haut-, Oberflächendosis

Nuklid	Halbwerts-zeit	Zerfallsart/ Strahlenart	**einh** Sv/Bq	**eing** Sv/Bq	Beurteilungsgrössen **h10** (mSv/h)/ GBq in 1 m Abstand	Beurteilungsgrössen **h0,07** (mSv/h)/ GBq in 10 cm Abstand	Beurteilungsgrössen **hc0,07** (mSv/h)/ (kBq/cm²)	Freigrenze **LE** Bq/kg bzw. LE_{abs} Bq	Bewil-ligungs-grenze **LA** Bq	Richtwerte **CA** Bq/m³	Richtwerte **CS** Bq/cm²
1	2	3	4	5	6	7	8	9	10	11	12
H-3	12,35 a	β^-	4,1 E-11	4,2 E-11	<0,001	<1	<0,1	2 E+05	1 E+08	2 E+05	1000
H-3, HTO	12,35 a	β^-	1,8 E-11	1,8 E-11	<0,001	<1	<0,1	6 E+05	3 E+08	5 E+05	1000
H-3, Gas [7]	12,35 a	β^-	1,8 E-15		<0,001	<1	<0,1		3 E+12	5 E+09	
Be-7	53,3 d	ε, γ	4,6 E-11	2,8 E-11	0,008	<1	0,1	4 E+05	1 E+08	1 E+05	1000
Be-10	1,6 E6 a	β^-	1,9 E-08	1,1 E-09	<0,001	2000	1,6	9 E+03	3 E+05	9 E+01	3
⋮											
Tc-99m	6,02 h	γ	2,9 E-11	2,2 E-11	0,022	300	0,2	5 E+05	2 E+08	3 E+05	30
⋮											
I-123	13,2 h	ε, γ	1,1 E-10	2,1 E-10	0,043	400	0,3	5 E+04	5 E+07	8 E+04	10

Radiation Protection

Dose Estimation

A technician should work 3 h with 75 MBq I-125. The distance between the source and the body will be in average 0.5 m. What dose (Tiefenäquivalentdosis) will he accumulate?

$h_{10\ I\text{-}125}$ = 0.033(mSv/h)/GBq in 1 m distance

A technician works 20 min without any shielding with 200 MBq of C-14. What skin dose did he accumulated?

$h_{0.07\ C\text{-}14}$ = 200 (mSv/h)/GBq in 10 cm distance

After 2h, a skin contamination of 10 cm^2 with 1000 Bq Cs-137 has been detected and cleaned. What skin dose has been accumulated?

$hc_{0.07\ C\text{-}14}$ = 1.5 (mSv/h)/(kBq/cm^2)

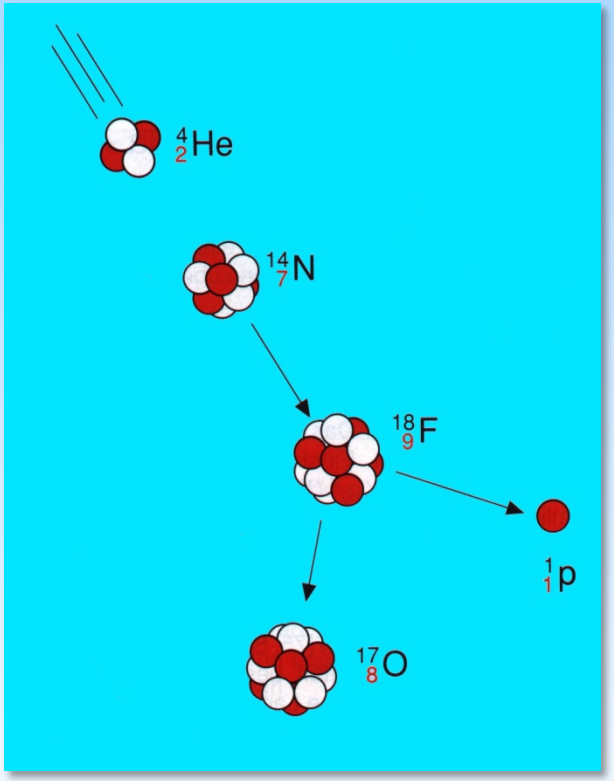
7. Production of radioisotopes

Historical

- first artificial nuclear reaction in 1919 (Curie)
- bombardment of nitrogen with α-particles
- transmutation of nitrogen into oxygen

$$^{14}_{7}N + ^{4}_{2}He \rightarrow ^{17}_{8}O + ^{1}_{1}H \qquad ^{14}N\,(\alpha,p)^{17}O$$

- all other particles are possible as projectiles (neutrons, protons, deuterons etc.)



Production of radioisotopes: Reactor

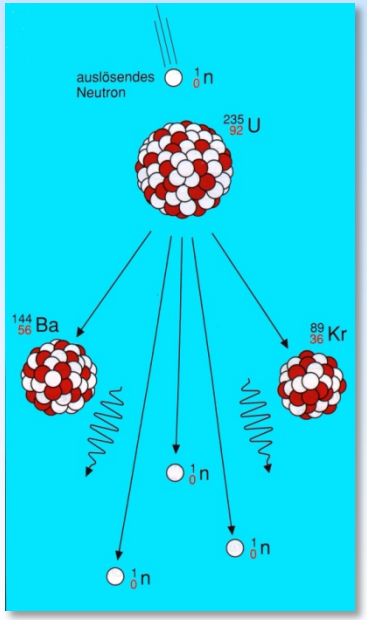
<u>Neutrons</u> as projectiles:

-neutral particles, no repulsion with the positively charged nucleus: important projectile

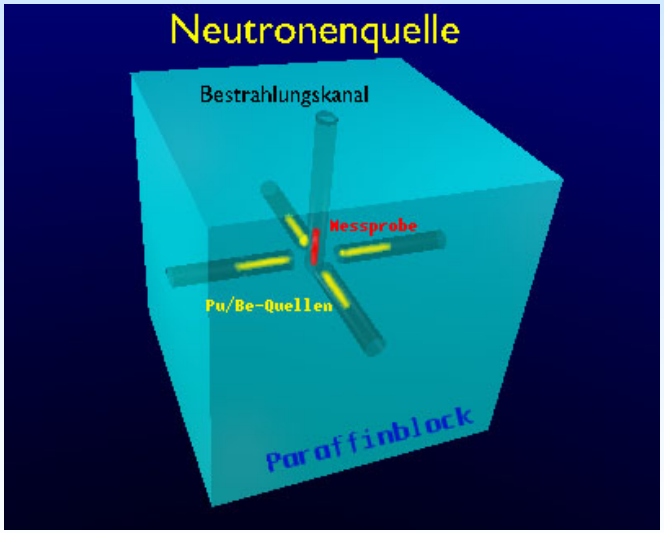
Origin of the neutrons:

Nuclear reactor: speed of the neutrons must be decreased (moderated)

moderators: water, hydrogen, deuterium



Neutron source

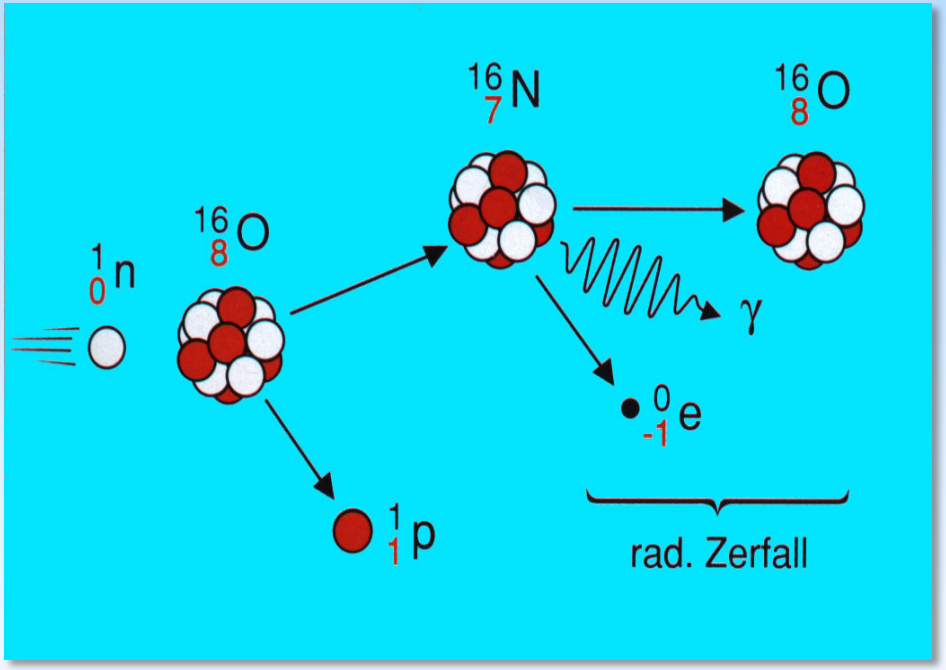


Production of radioisotopes: Reactor

Neutrons as projectiles:

-neutral particles, no repulsion with the positively charged nucleus: important projectile

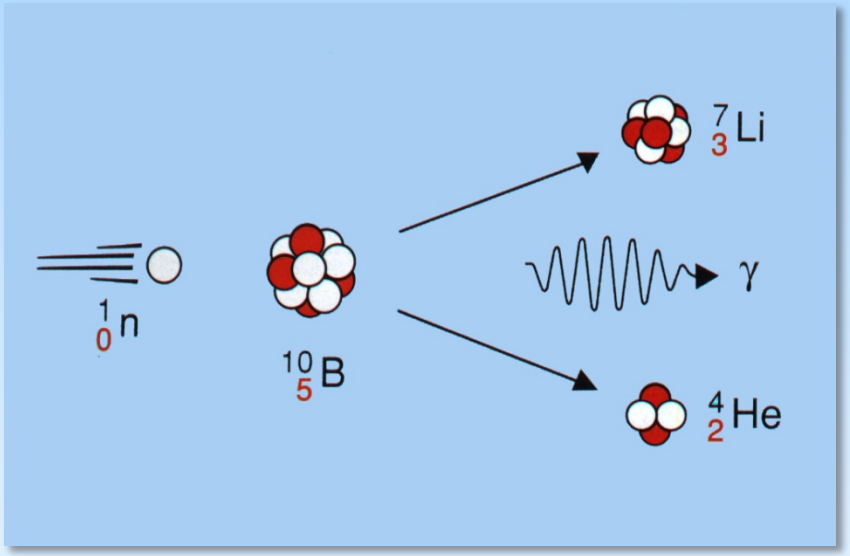
slow (moderated) neutrons react with many nuclei: ➡ neutron capturing (n,γ) reactions

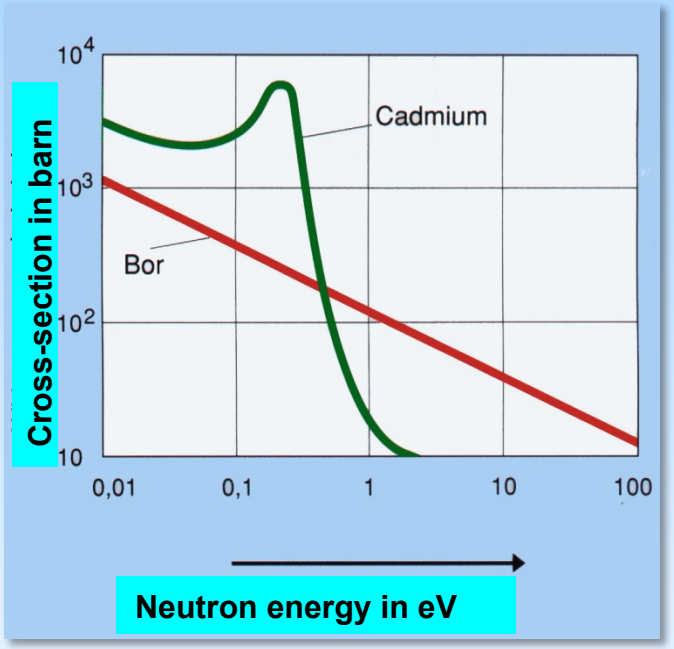


radioactive isotopes of almost all elements can be produced this way

Production of radioisotopes: Reactor

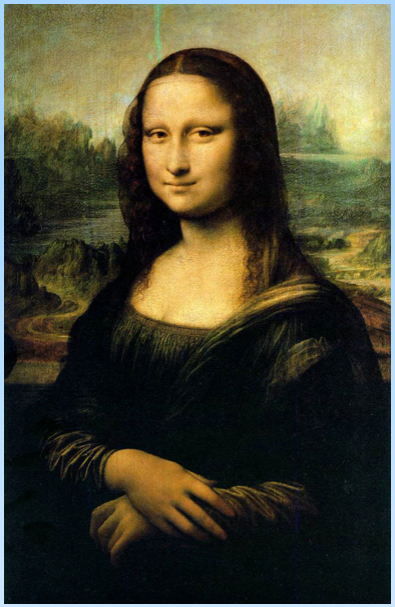
Neutrons as projectiles:





Cross section is a measure for the probability of a nuclear reaction (barn = $10^{-23}m^2$)

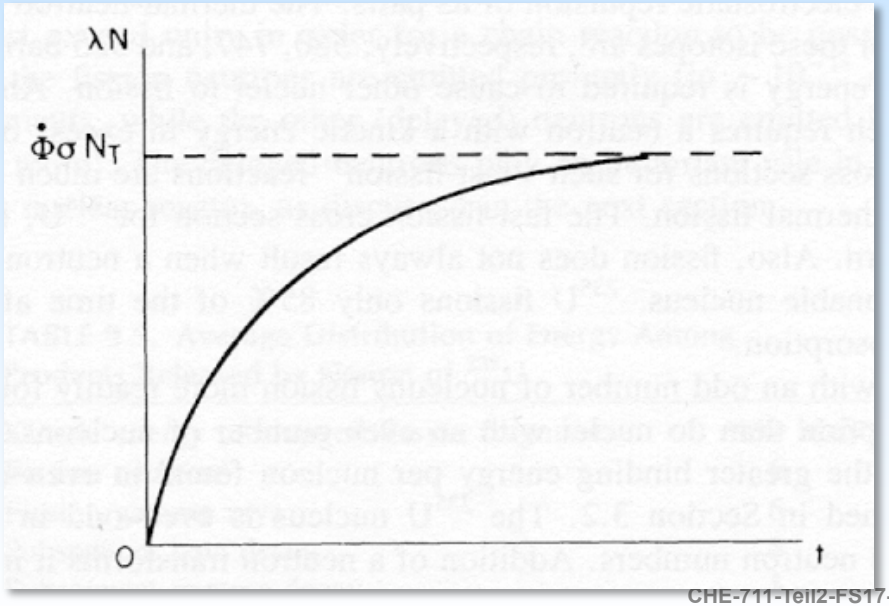
Neutron Activation Analysis



- Non-destructive analytical method for trace analysis
- Suitable for qualitative & quantitative analyses (internal standard)

$$\lambda \cdot N = \Phi \cdot \sigma \cdot N_T \cdot (1 - e^{-\lambda t})$$

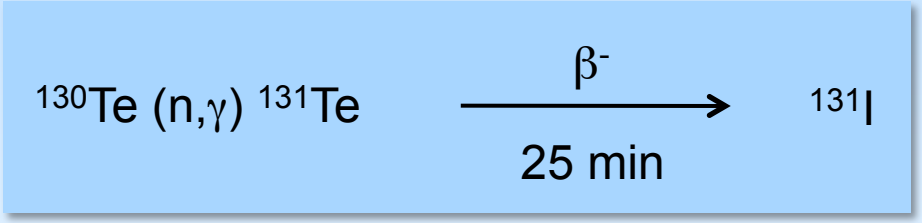
λ= decay constant of the daughter
N = number of daughter atoms
ϕ= fluence rate of neutrons
σ= cross section
N_T = number of target atoms



Production of radioisotopes: Reactor

<u>Neutrons</u> as projectiles:

- (n,γ) reactions do not produce carrier free isotopes (preferred for radio pharmaceutical applications)
- in most cases unstable nuclides are formed: secondary radioactive decay (e.g. ß- or γ-decay)

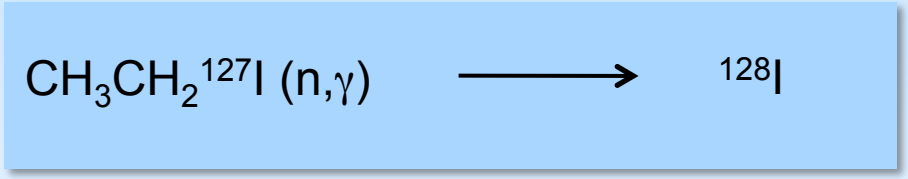


Szilard-Chalmers reactions

- The *Szilard-Chalmers*-effect is an other opportunity to produce carrier free isotopes

- If the recoil energy of a (n,γ) reaction is higher than the binding energy of a chemical bond the “naked” activated isotope can have different chemical properties

  → it can be isolated

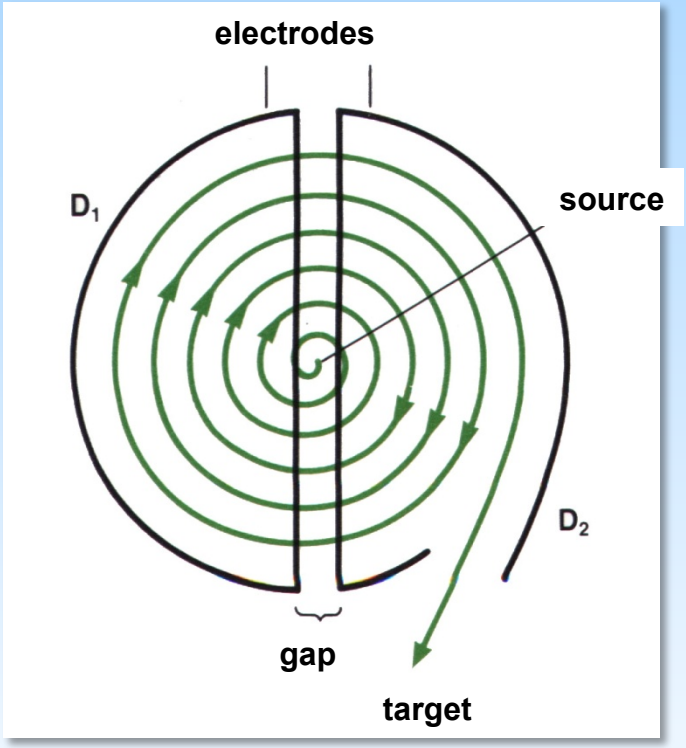


recoil energy: 300 eV
binding energy C-I: 1-6 eV

Production of radioisotopes: Cyclotron

Positively charged particles as projectiles:

Cyclotron



^{18}F production for PET

$$^{18}O + {}^{1}p \xrightarrow{(p,n)} {}^{18}F + {}^{1}n$$

Philips 140/IV
Particles and energies:
p = 4-30 MeV
d = 2-16 MeV
$^{3}He^{2+}$ = 6-42 MeV
$^{4}He^{2+}$ = 6-36 MeV

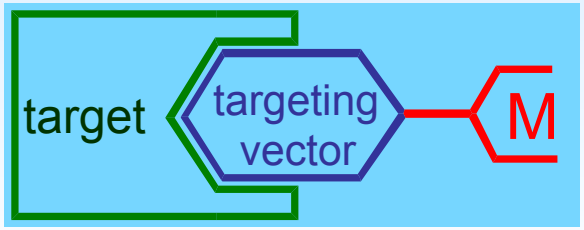
Universitätsklinikum Hamburg-Eppendorf

8. Application of Radionuclides in Radiopharmacy

<u>Non-invasively</u> visualizing a biological event or structure

Biological event: overexpression of certain types of cell-related receptors or transporters, e.g. somatostatin, RGB receptors, LAT1

Receptors:	cancer	peptides and proteins
	central nervous system	small lipophilic molecules
Metabolism:	glucose	^{18}FDG, ^{18}F labelled glucose
	amino acids	^{123}I labelled tyrosine
Enzymes:	thymidine kinase	thymidine / inhibitors
	carbonic anhydrase	sulfonamides



active metal-complex

What is Radiopharmacy

Radiopharmacy is a *diagnostic tool* in nuclear medicine

to visualize different forms of organic failures

- *enrichment* of a radionuclide in an organ
- *excretion* of a radionuclide from an organ
- metabolical turnovers

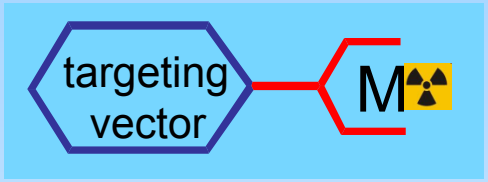
→ **Function**

- receptor densities
-pathological differences

→ **Anatomy**

What is Molecular Imaging

To <u>non-invasively</u> visualize a biological event on a molecular level



must specifically accumulate at the target site

high target / non-target ratio

must rapidly be excreted from the body

enables highly resolved images ➡ accurate diagnosis
minimizes the dose burden to the patient

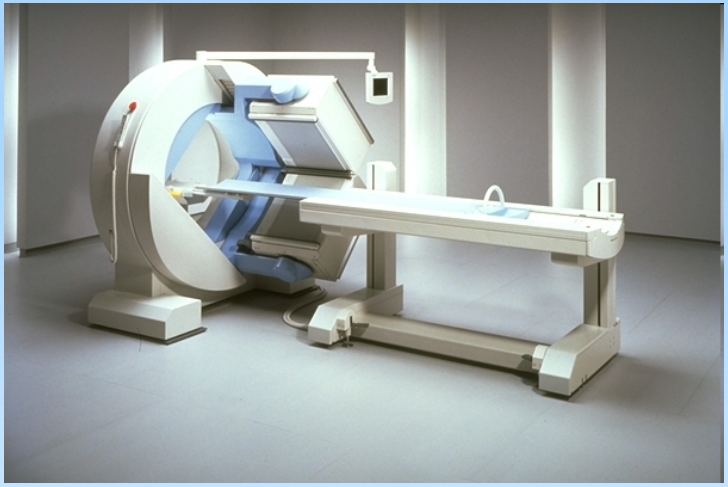
must retain biological activity and be stable under physiological conditions

comparison of „cold“ and „hot“ pharmaceutical

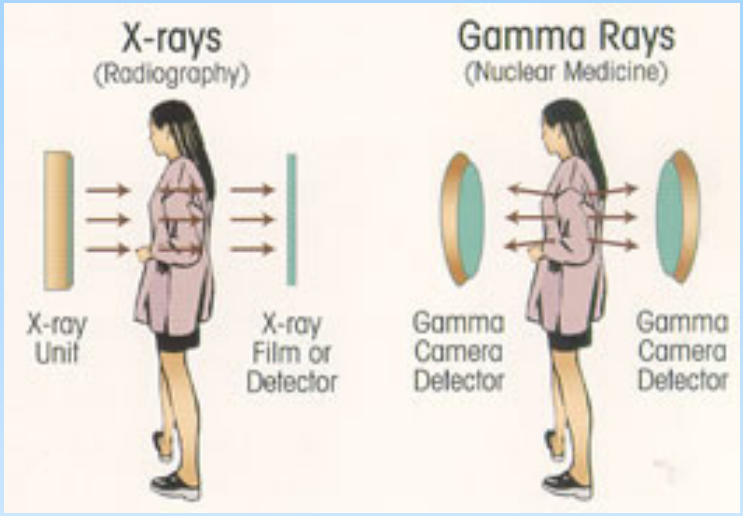
must be synthesized on site, in quantitative yield and in < 30 min

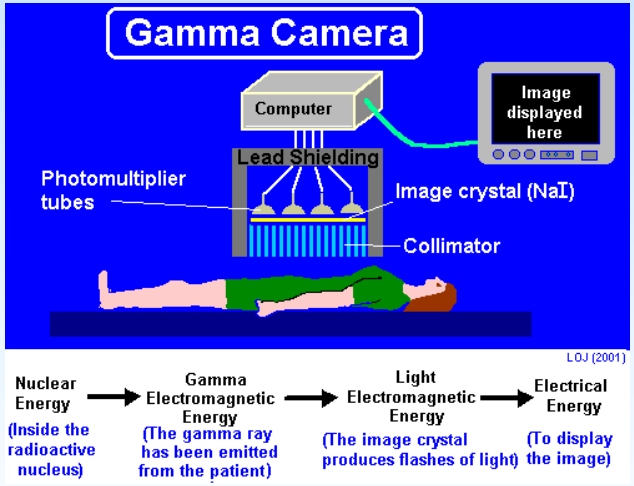
immediatly available whenever it‘s needed

What is Radiopharmacy

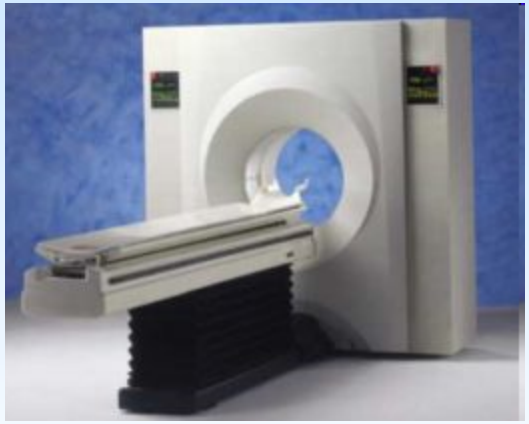


SPECT camera (γ-detection)



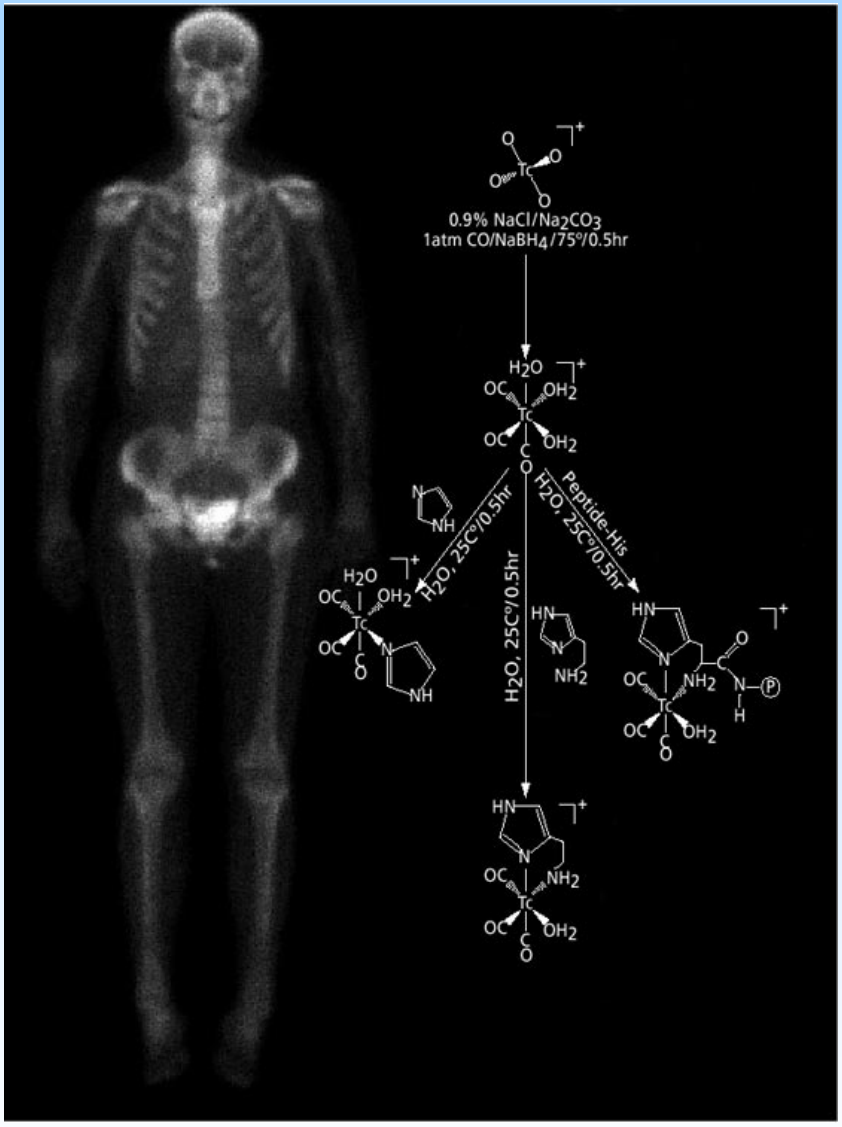


Principle of γ-cameras



PET camera (γ-detection, 511 keV)

What is Radiopharmacy



What is Radiopharmacy: Examples

Function

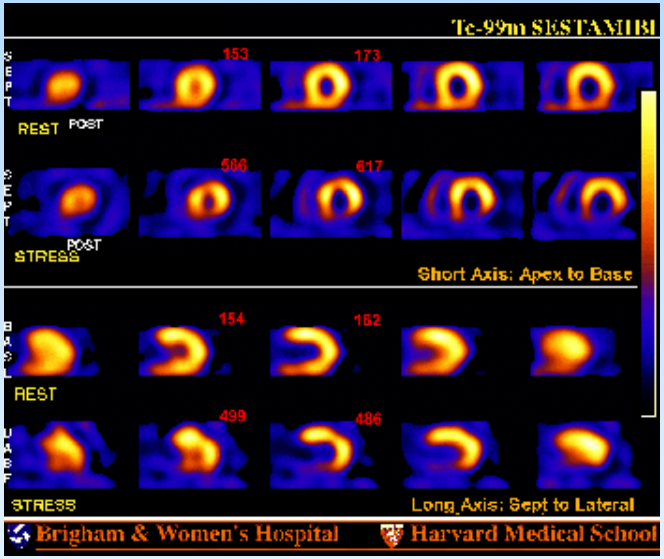
- *Metabolical function* in the brain visualized with radiolabelled glucose

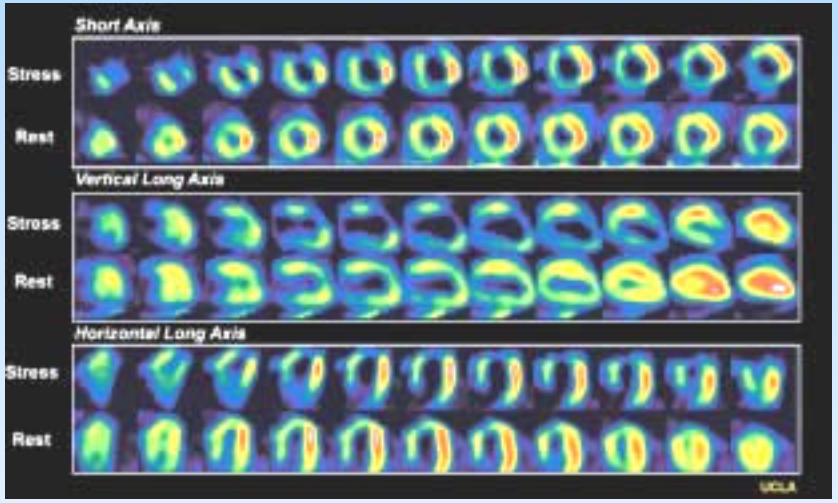
- Different types of behaviour reveal different types of metabolical action in the brain

What is Radiopharmacy: Examples

Function

Blood flow in the heart muscle at rest and during stress



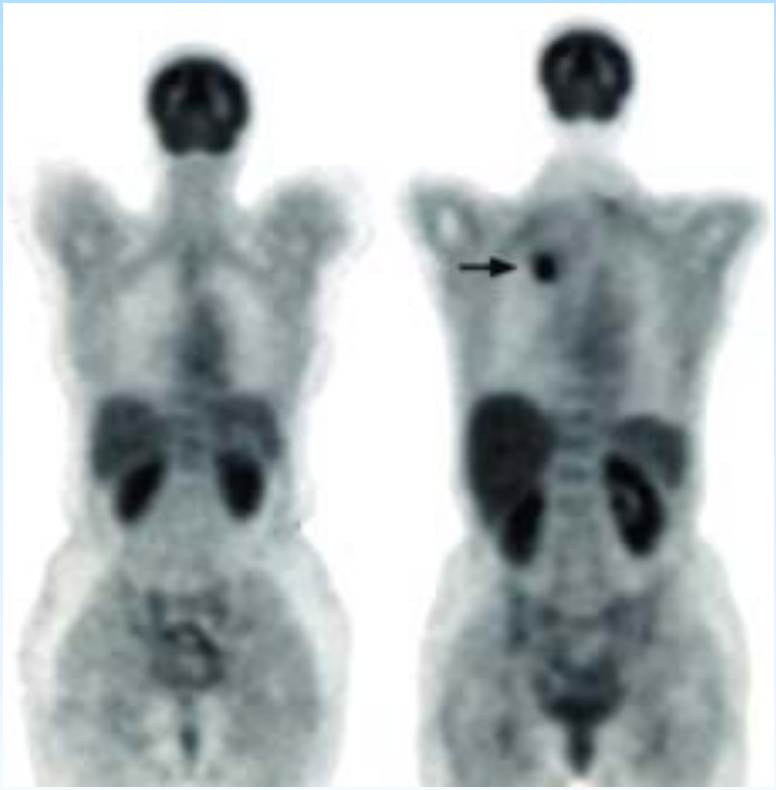


The heart scan, from a patient with coronary artery disease, shows where the heart muscle lacks adequate blood flow. The radiopharmaceutical Cardiolite (left), ^{201}Tl (right), mimics potassium and accumulates more in regions of normal blood flow.

What is Radiopharmacy: Examples

Function

enhanced (glucose) metabolism in tumor

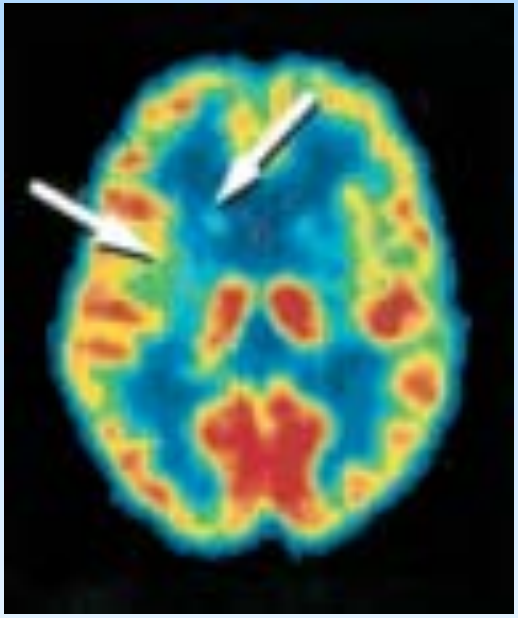


The left scan is normal; the right scan is from a patient with a *lung tumor* that spread from primary breast cancer. This scan shows increased ^{18}F FDG uptake in the tumor (arrow) because a growing tumor has a higher rate of sugar metabolism than the surrounding normal tissue.

What is Radiopharmacy: Examples

Function

Brain function: Lack of activity in certain regions



The brain scan shows reduced glucose metabolism in a pattern characteristic of *Huntington's disease*, evident years before the patient exhibited abnormal movements or other symptoms of this hereditary disease.

What is Radiopharmacy: Examples

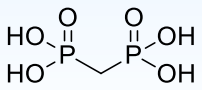
Function

Detection of small metastesis in i.e. bones

The bone scan is from a patient with prostate cancer that has spread to the spine and other bones.

The radiopharmaceutical, similar to the mineral in bone, accumulates at *bone tumors* (dark spots) because the diseased bone has faster mineral turnover.

[^{99m}Tc-mdp]: unknown structure



Medronic acid

What is Radiopharmacy: Examples

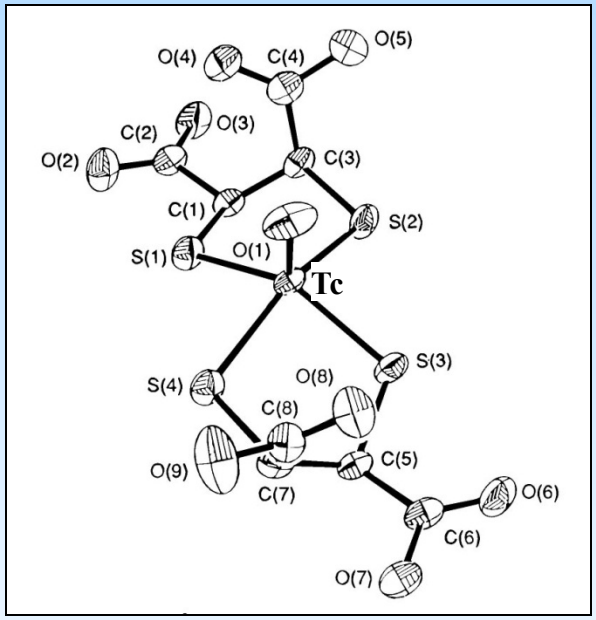
Function

Function: Detection of small metastasis in i.e. bones

Diagnosis

Injection

600 MBq



$[^{99m}TcO(dmsa)_2]^{(n-)}$

dmsa = dimer captosuccinic acid

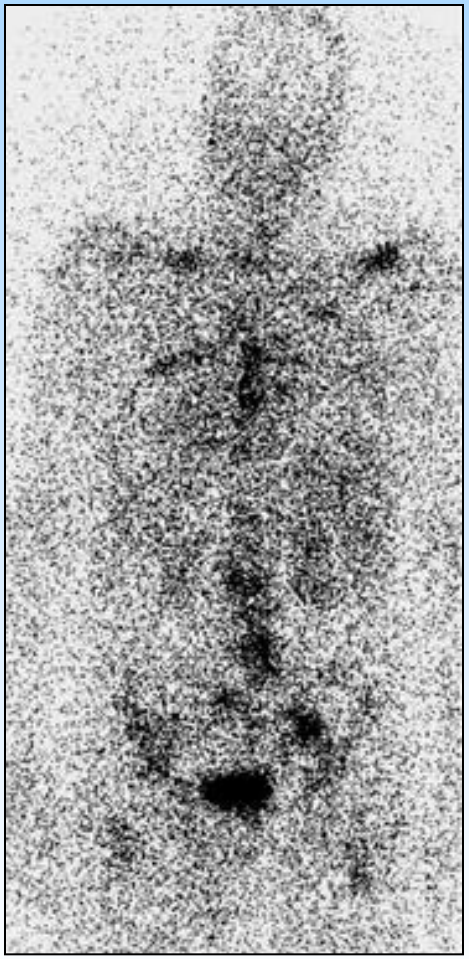
Blower, P. J.; et al *Eur. J. Nucl. Med.* **2000**, *27*, 1405-1409.

What is Radiopharmacy: Examples

Function

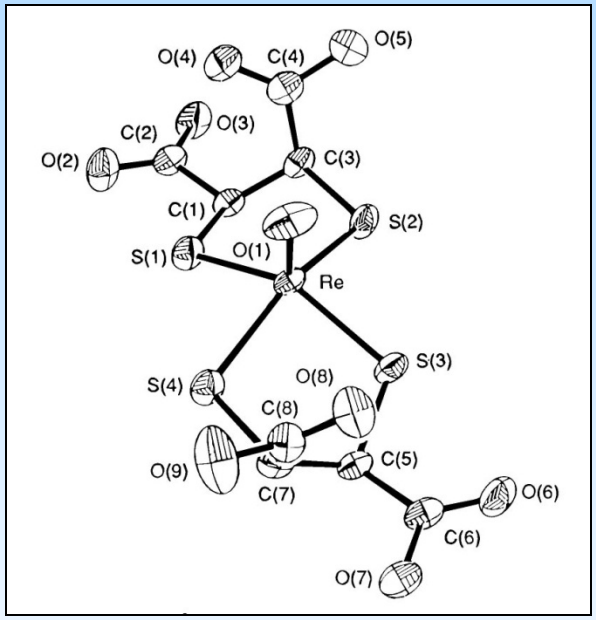
Function: Treatment of small metastasis in i.e. bones

Therapy



Injection

370 MBq



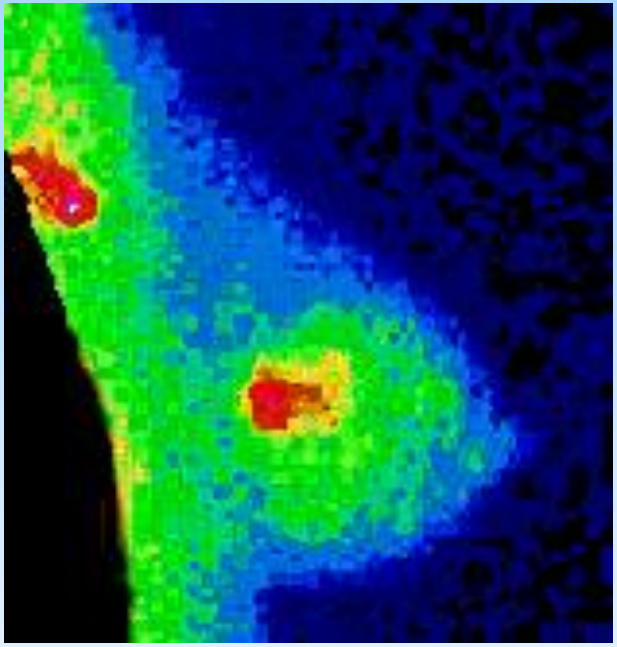
$[^{188}ReO(dmsa)_2]^{(n-)}$

β: 100%, 2.1 MeV
therapy by “cross fire effect”

What is Radiopharmacy: Examples

Function

Enhanced metabolic activity in the breast



The injected radiotracer shows high affinity for areas of high metabolism, as is commonly seen with tumor cells. In this example, the tracer is taken up in areas of increased metabolism in the breast and surrounding lymphatic areas. This is indicative of primary breast cancer, as well as the metastatic spread to the surrounding lymph nodes.

What is Radiopharmacy

Therapy

Radiopharmacy is a therapeutic tool in nuclear medicine

to visualize and treat different forms of organic diseases

- Small metastasis can be treated internally if sufficient

radioactivity is accumulated in the target cells

→ Difference to “knife and fire“

Tools of Radiopharmacy: Radiation

Quick repetition about the different types of decay and radiation

α-radiation

emitted particle: He^{2+}

energy in the MeV range

occurs mainly with nuclides of Z > 83

often accompanied by γ-emission

mass number → A
atomic number → Z

$$^{A}_{Z}M \longrightarrow {}^{A-4}_{Z-2}M + He^{2+}$$

Example: $^{225}_{89}Ac \xrightarrow{t_{1/2} = 10d} {}^{221}_{87}Fr + He^{2+}$

E_α = 5.83 MeV / 89 keV / μM

Tools of Radiopharmacy: Radiation

Quick repetition about the different types of decay and radiation

β^--radiation

emitted particle: electron e^-

energy in the keV - MeV range

occurs throughout the elements with excess of neutrons

mostly accompanied by γ-emission

mass number → A
atomic number → Z

$$^{A}_{Z}M \longrightarrow {}^{A}_{Z+1}M + e^- + \text{antineutrino}$$

Example: $^{188}_{75}Re \xrightarrow{t_{1/2} = 17\ h} {}^{188}_{76}Os + e^-$

E_β = 2.1 MeV / 0.22 keV / μM

Tools of Radiopharmacy: Radiation

Quick repetition about the different types of decay and radiation

β^+-radiation

emitted particle: positron e^+

energy in the keV - MeV range

occurs throughout the elements with excess of protons

mostly accompanied by γ-emission

mass number → A
atomic number → Z

$$^{A}_{Z}M \longrightarrow {}^{A}_{Z-1}M + e^+ + \text{neutrino}$$

Example: $^{68}_{31}Ga \xrightarrow{t_{1/2} = 68\ \text{min}} {}^{68}_{30}Os + e^+$

$E_{\beta+} = 1.9$ MeV

annihilation: $e^+ + e^- \longrightarrow 2\ \gamma$-quants (511 keV each)

Tools of Radiopharmacy: Radiation

Quick repetition about the different types of decay and radiation

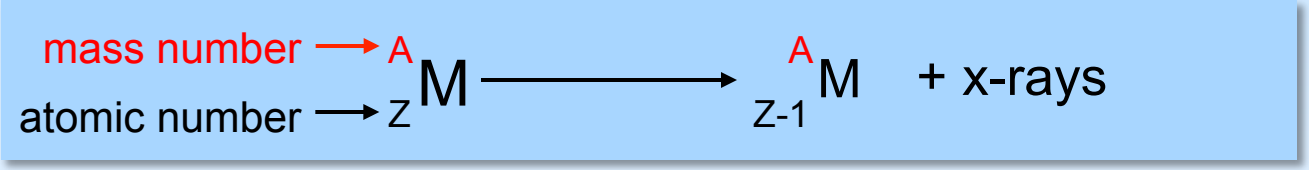
Electron capture EC

emitted particle: x-rays

energy in the low keV range

occurs throughout the elements with excess of protons

same product as with β^+



nuclide captures an electron from the shell (mostly K- or L-shell)

Tools of Radiopharmacy: Radiation

Quick repetition about the different types of decay and radiation

isomeric transitions (IT) and states

pure γ-emitter, not a radioactive decay

energy in the keV range

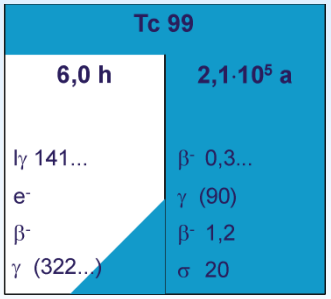
large change between nuclear spin state ➡ long $t_{½}$

compares with phosphorescence in the electron shell

mass number → Am

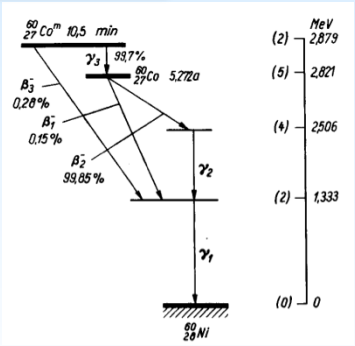
atomic number → z

$$^{Am}_{z}M \longrightarrow {}^{Ag}_{z}M + \text{x-rays}$$



Example: $^{99m}_{43}Tc \xrightarrow{t_{1/2} = 6\ h} {}^{99}_{43}Tc + \gamma$

$E_{\beta+} = 0.141$ MeV



Tools of Radiopharmacy: Radionuclides

Can we take any radionuclide for imaging or therapy ?

for uses in molecular imaging we need to consider :

- ➡ the radiation dose to the patient
- ➡ penetration of tissue ($E\gamma$ > 80 keV)
- ➡ efficiency of detection

the three most important properties of the radionuclide

- ➡ half-life
- ➡ type of radiation emitted
- ➡ energy of radiation emitted

Tools of Radiopharmacy: Radionuclides

Can we take any radionuclide for imaging or therapy ?

Half life should be

long enough to complete the scan

short enough so that after the scan the activity in the patient decreases rapidly

typically requires a half-life of a few hours

→ Hence, the dose might be kept at a reasonably low level

Tools of Radiopharmacy: Radionuclides

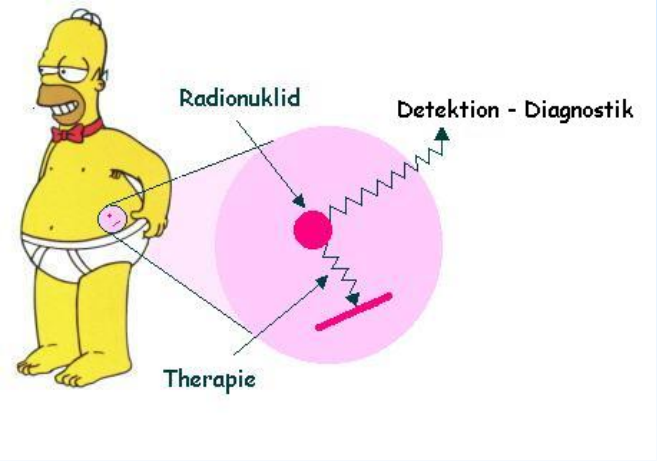
Can we take any radionuclide for imaging or therapy ?

Diagnosis

➡ pure gamma-ray emitting nuclides are preferred since

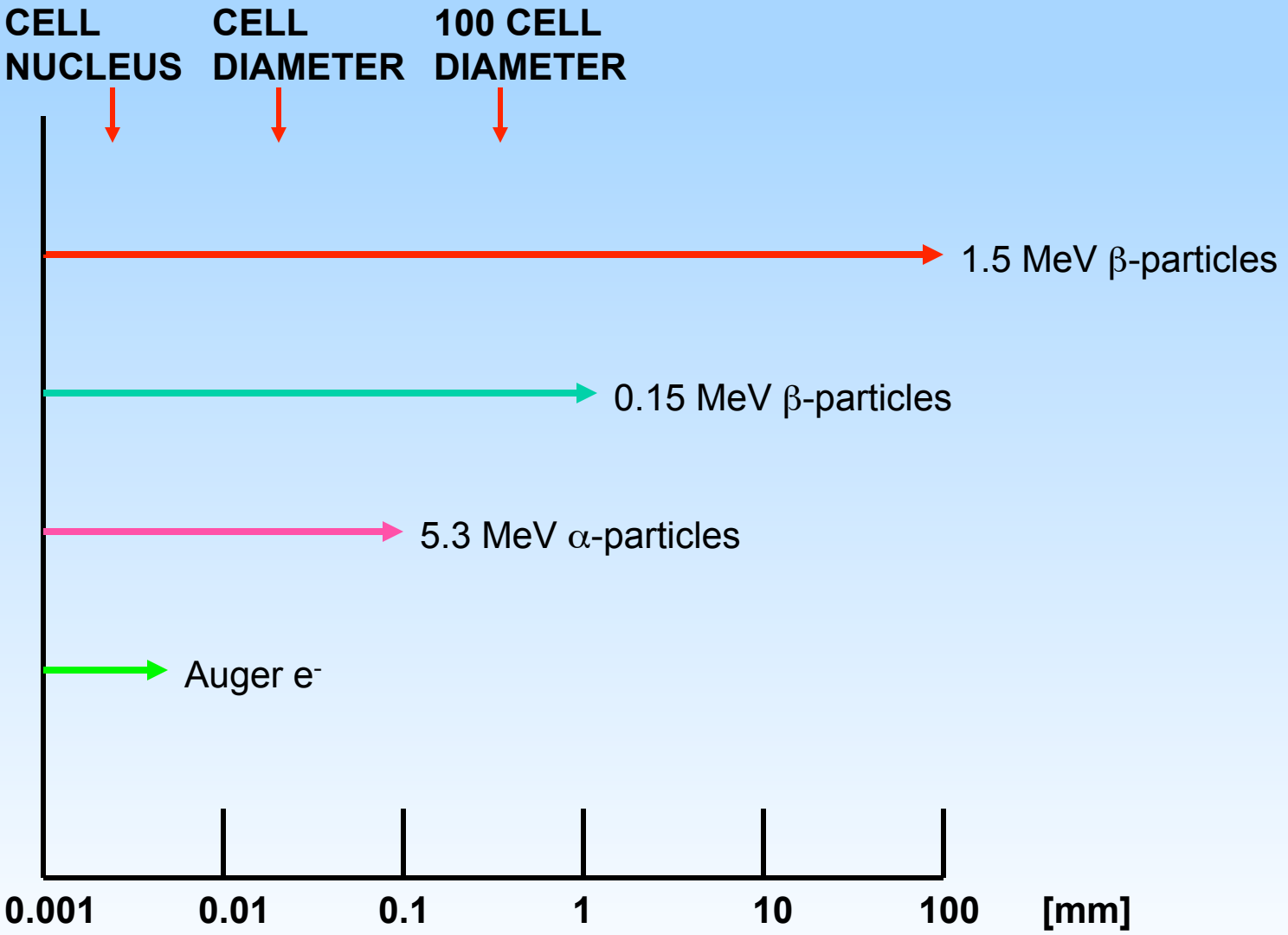
Therapy

particulate radiations (such as alphas or betas) *increase the dose* to the patient but are non-penetrating and therefore do not contribute to the image.



➡ particulate radiation and γ-ray emitters are preferred

Tools of Radiopharmacy: Radionuclides



Tools of Radiopharmacy: Radionuclides

Can we take any radionuclide for imaging or therapy ?

Energy of γ-emission should be ...

➡ greater than approx. 80 keV, the gamma-rays penetrate tissue

➡ less than approx. 300 keV, the gamma-rays can be detected and collimated

Specific activity should be ...

➡ *no carrier added* (*nca*): exclusively radioisotope is present

➡ *carrier*: any stable isotopes that “dilutes“ the radioisotope

Tools of Radiopharmacy: Radionuclides

Can we take any radionuclide for imaging or therapy ?

Specific activity

strict definition: Activity / weight of the radionuclide units in MBq/g .

but more usefully defined as:

the *activity/weight of the pharmaceutical* to which the nuclide is attached.

(units are MBq/g of pharmaceutical.)

Both should be high so that only trace amounts of pharmaceutical

(or stable element) need to be administered

Tools of Radiopharmacy: Radionuclides

Can we take any radionuclide for imaging or therapy ?

further considerations

- ⇨ non-toxic
- ⇨ availability
- ⇨ costs

Tools of Radiopharmacy: Radionuclides

The **physical and the biological half life time** are important

Physical half life time:

since $dN/dt = -\lambda N(t)$ then $\mathbf{N(t) = N_o e^{-\lambda t}}$

'exponential law' of radioactive decay

Biological half life time:

the biological excretion often approximates to an exponential

$\mathbf{e^{-\lambda_{biol}\, t}}$

Tools of Radiopharmacy: Radionuclides

The **physical and the biological half life time** are important

The combination of biological and physical half life time

when a radionuclide is administered to a patient the activity of the *nuclide* in the body will *decrease* due to both

physical [i.e. radioactive decay] and biological excretion

The activity remaining in the body is given by $A_o e^{-\lambda_{phys}\, t} \times e^{-\lambda_{biol}\, t}$

or $A = A_o\, e^{-(\lambda_p + \lambda_b)\, t}$ with $\lambda_p + \lambda_b = \lambda_E$

...which is the field of radiopharmacology and not interesting for us.

Tools of Radiopharmacy: Radionuclides

Just as an example for ^{99m}Tc and hypothetical $t_{1/2}$ (biol)

^{99m}Tc has a $t_{1/2}$ = 6 hours it follows $\lambda = 0.693 / t_{1/2}$

$$T_E = \frac{T_p \times T_b}{T_p + T_b}$$

t_p	t_b	t_{eff}
6 hr	***1 hr***	***0.86 hr***
6 hr	***6 hr***	***3 hr***
6 hr	***60 hr***	***5.5 hr***
6 hr	***600 hr***	***5.9 hr***

very important number for *dose calculation* and amount of activity

Tools of Radiopharmacy: Radionuclides

Example with radioisotopes of iodine

Iodide *vs*. iodinated hippuric acid

biological half life time iodide: 125 d; iodo-hippuric acid: 0.03 d

physical half life time ^{123}I:0.54 d; ^{131}I: 8.0 d

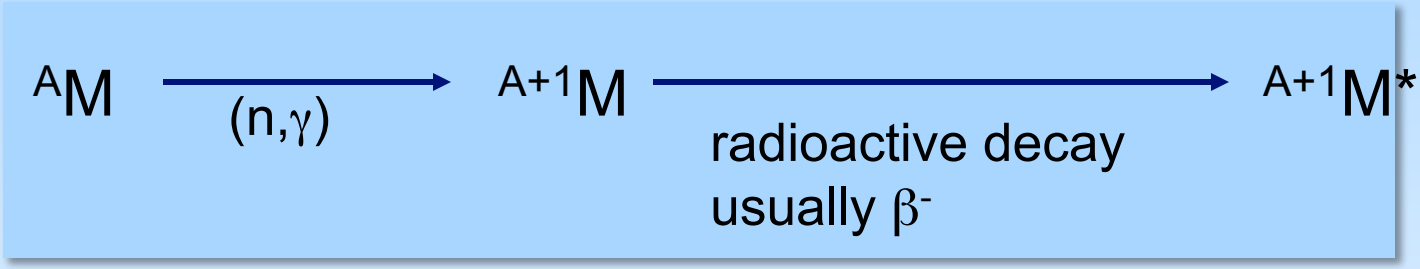
t_{eff}: Iodo-hippuric acid: ^{123}I: 0.028 d; ^{131}I: 0.03 d

t_{eff}: iodide: ^{123}I: 0.54 d; ^{131}I: 7.5 d

Tools of Radiopharmacy: Radionuclides

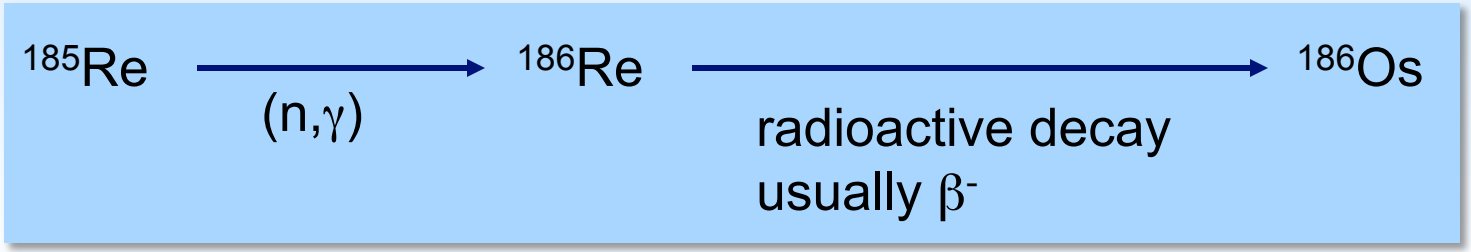
Radionuclide production

Important nuclides produced under neutron irradiation in a *fission reactor*



depending on the neutron cross section,

the process yields carrier added radionuclides



Tools of Radiopharmacy: Radionuclides

Some selected and medicinally important radionuclides

Molybdenum-99:
Used as the 'parent' in a generator to produce technetium-99m, the most widely used isotope in nuclear medicine.

Technetium-99m:
Used to image the skeleton and heart muscle in particular, but also for brain, thyroid, lungs (perfusion and ventilation), liver, spleen, kidney (structure and filtration rate), gall bladder, bone marrow, salivary and lacrimal glands, heart blood pool, infection and numerous specialized medical studies.

Copper-64:
Used to study genetic diseases affecting copper metabolism, such as Wilson's and Menke's diseases.

Iodine-125:
Used as an x-ray source for bone density measurements.

Tools of Radiopharmacy: Radionuclides

Some selected and medicinally important radionuclides

Iodine-131:
Widely used in functional imaging and therapeutic applications for the thyroid as in overactive and underactive thyroid, carcinomas and their secondaries

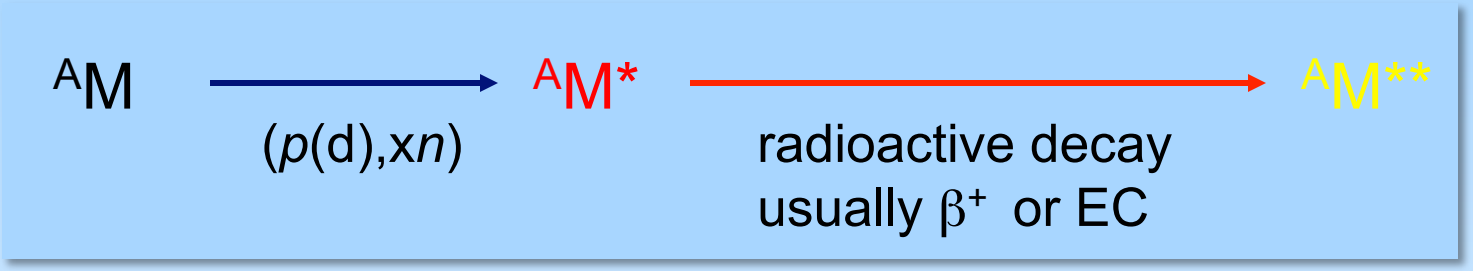
Rhenium-186/188:
Used in the treatment of cancer and for palliation therapy.

Strontium-89:
Used to relieve the pain of secondary cancers lodged in the bone.

Yttrium-90:
Used for cancer therapy and as silicate colloid for the treatment of arthritis in larger joints

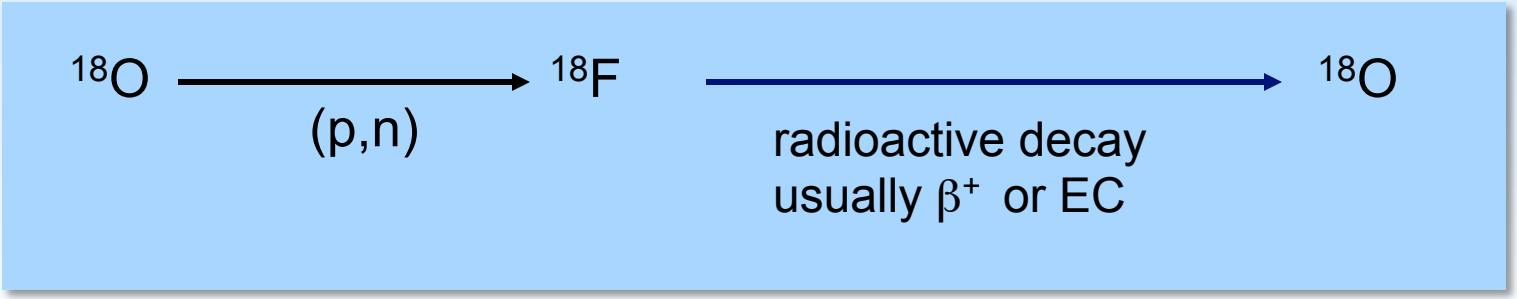
Tools of Radiopharmacy: Radionuclides

Radionuclides produced in a *cyclotron*



The product is a different element than the educt, can be separated

This nuclear reaction allows the preparation of **no carrier added** radioisotopes



Tools of Radiopharmacy: Radionuclides

Radionuclides produced in a *cyclotron*

Gallium-67:
Used for tumor imaging and localization of inflammatory lesions (infections).

Thallium-201:
Used for myocardial perfusion imaging for diagnosis and location of myocardial infarction (heart muscle death) and low-grade lymphomas.

Iodine-123:
Used for diagnosis of thyroid function and many others.

Indium-111: Used for peptide labelling, infection and colon transit studies.

Carbon-11, Nitrogen-13, Oxygen-15, Fluorine-18:
These are used in PET for studying brain physiology and pathology, for localizing epileptic focus, and in dementia, psychiatry and neuropharmacology studies. They also have a useful role in cardiology. F-18 in FDG has become very important in detection of cancers and the monitoring of progress in their treatment, using PET.

Tools of Radiopharmacy: Radionuclides

➡ Among the 1200 radionuclides present in the table of isotopes,

only *a very few* combine the properties outlined earlier.

The most important ones are:

^{11}C, ^{18}F, ^{67}Ga, ^{90}Y, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{131}I, ^{153}Sm, ^{177}Lu $^{188/186}Re$, ^{201}Tl ....

Cyclotron produced Reactor produced

Tools of Radiopharmacy: Summary

... for molecular imaging

1. pure gamma emitter

2. 80 keV < gamma energy < 250 keV.

3. Effective half-life = 1.5 X test duration.

4. High target:nontarget ratio.

5. Minimal radiation dose to patient and Nuclear Medicine personnel

6. Patient Safety

7. Chemical Reactivity

8. Inexpensive, readily available radiopharmaceutical.

Diagnostic: Summary

... for radionuclide therapy

1. essentially pure particle emitter (<10% γ-emitter).

2. medium/high energy (>1 MeV).

3. Effective half-life = moderately long, *e.g.*, days.

4. High target:nontarget ratio.

5. Minimal radiation dose to patient and Nuclear Medicine personnel

6. Patient Safety

7. Inexpensive, readily available radiopharmaceutical.

Tools of Radiopharmacy: Generators

Usually, nuclides produced by (n,γ) reactions are **not carrier free**

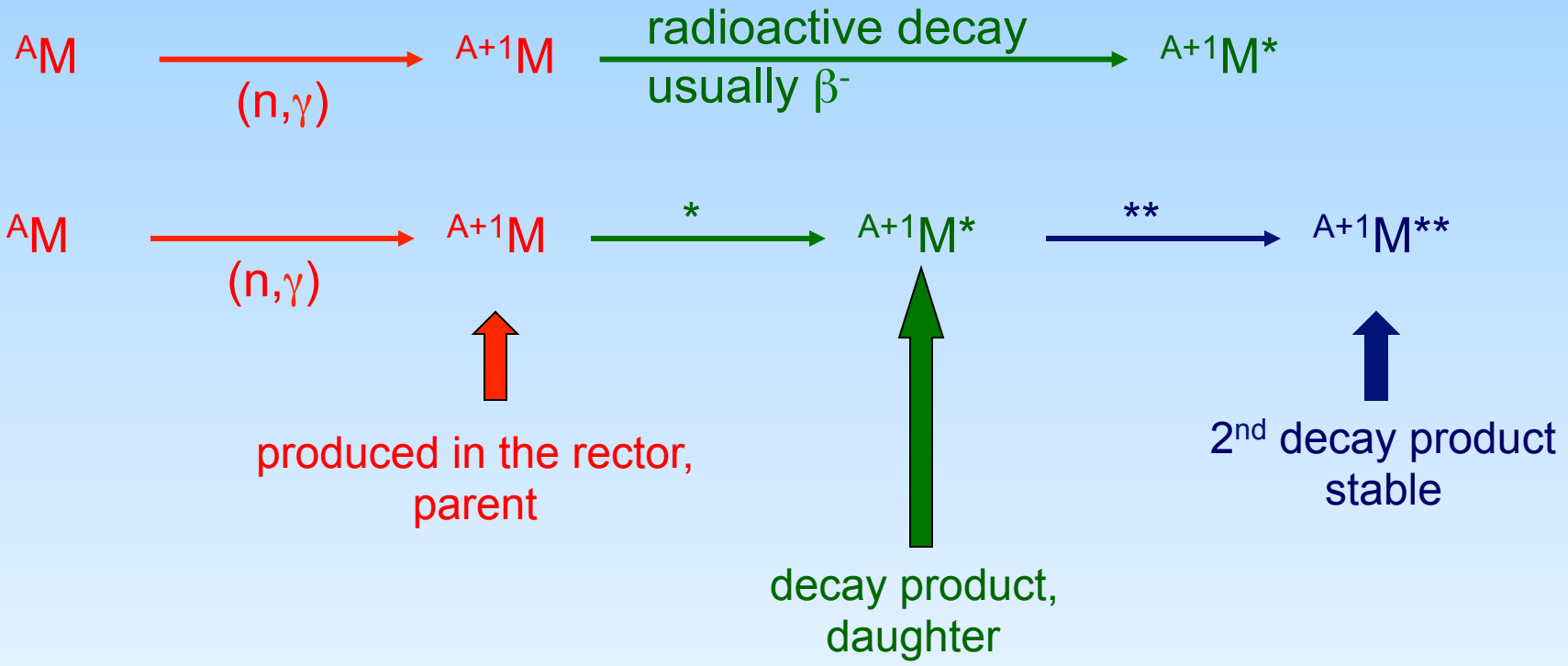
unless

the radionuclide is a *decay product* (daughter)

In that case *the daughter can be separated* chemically from the parent

since they belong to two different elements.

Tools of Radiopharmacy: Generators

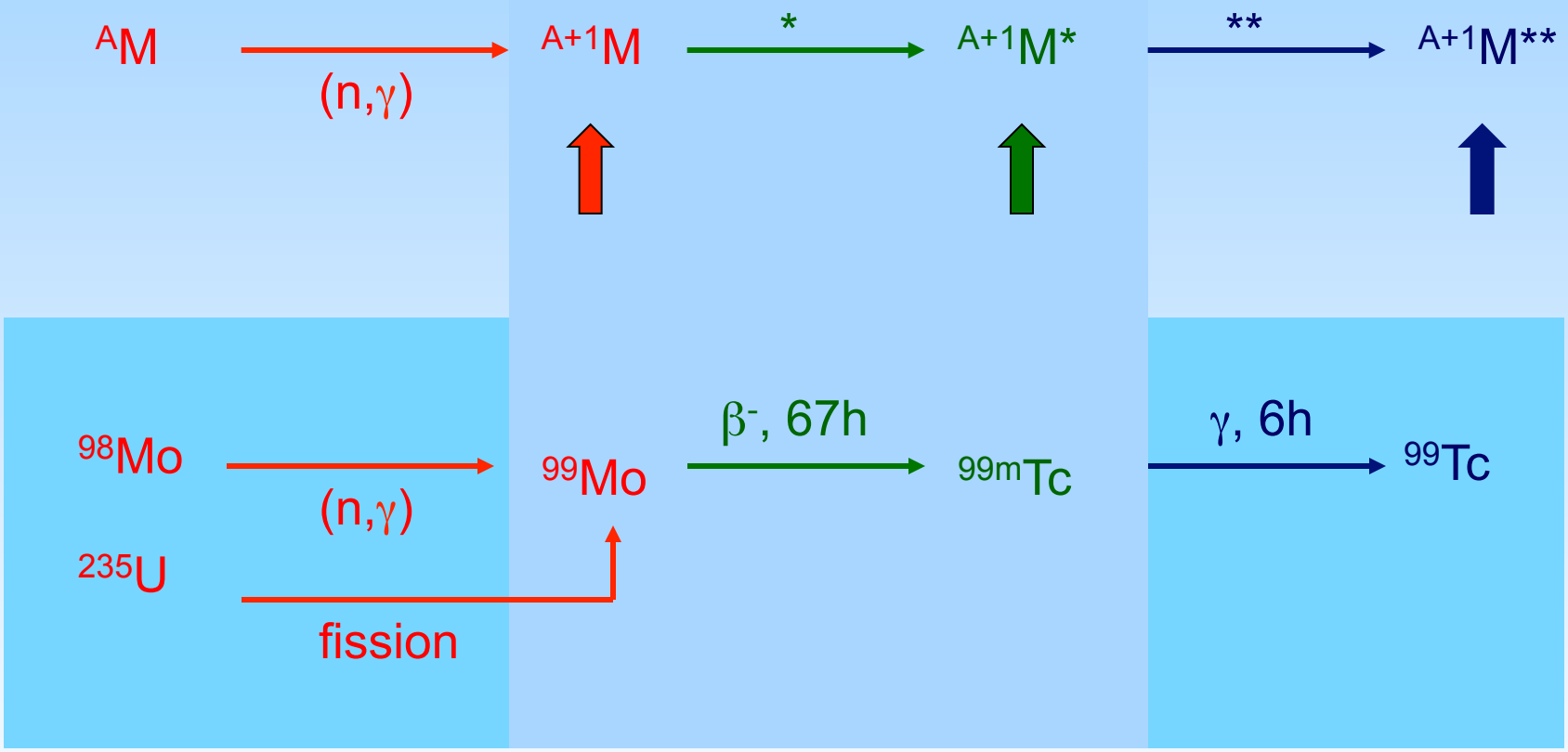


*radiation of interest particulate rad.

** radiation of interest

Tools of Radiopharmacy: Generators

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



** radiation of interest

Tools of Radiopharmacy: Generators

Since molybdenum and technetium are chemically different

they can be *separated* form each other.

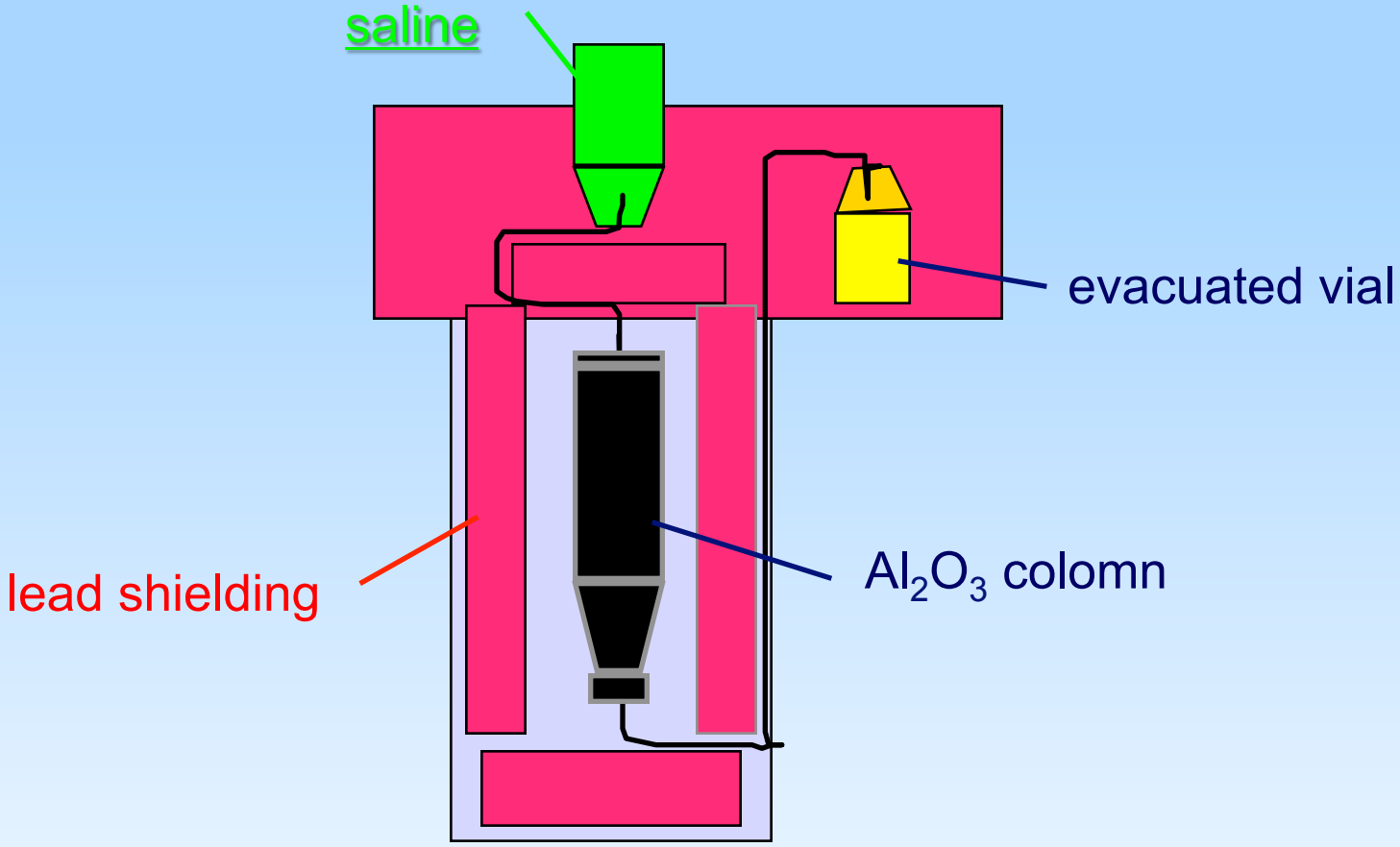
➡ If the separation can be performed *"on line"* then we get a so called

➡ **Generator System**

$[^{99}MoO_4]^{2-} \longrightarrow [^{99m}TcO_4]^-$

the "m" in ^{99m}Tc means metastable

Tools of Radiopharmacy: Generators

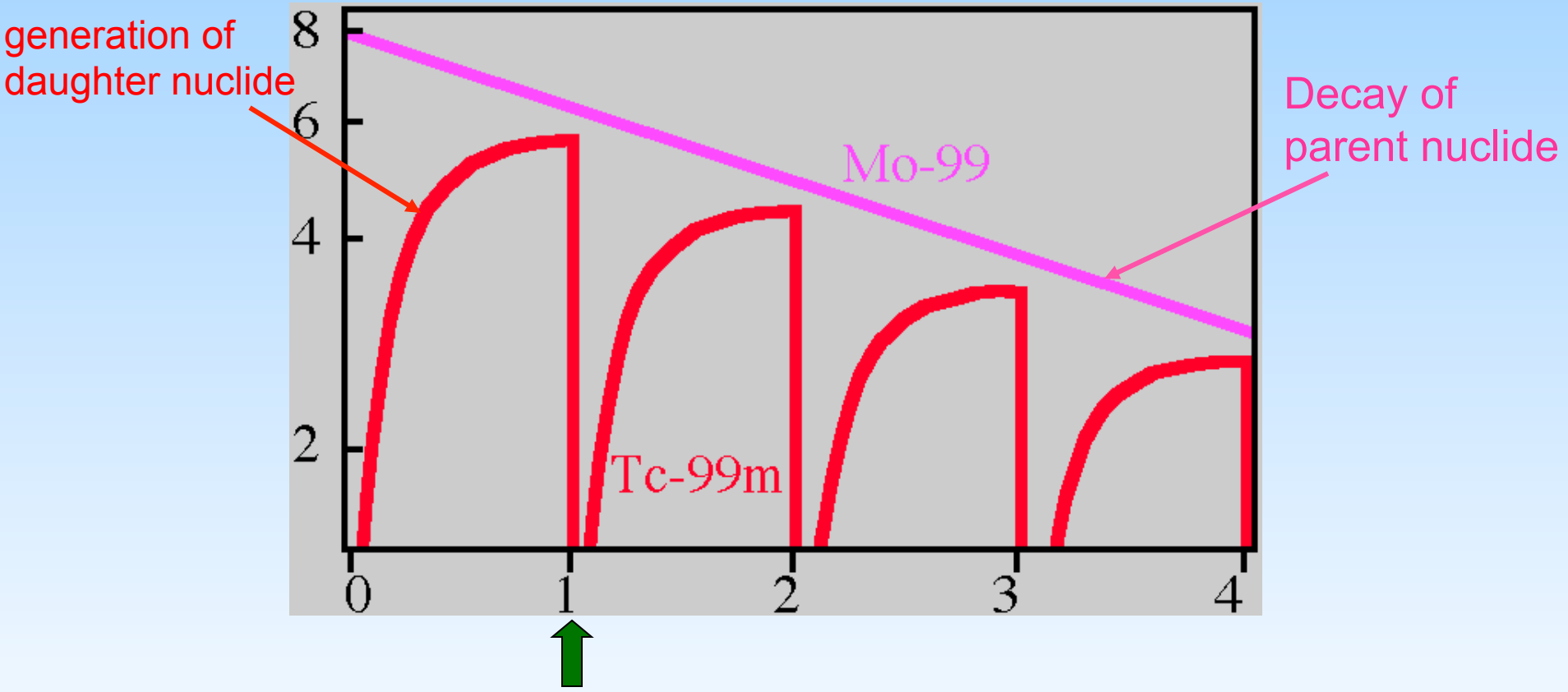


$[^{99}MoO_4]^{2-}$ is loaded on the Al_2O_3 colomn

$[^{99m}TcO_4]^{-}$ is eluted from the Al_2O_3 colomn

Tools of Radiopharmacy: Generators

Efficiency of a generator system



Tools of Radiopharmacy: Generators

^{99}Mo decays with *67 h* half life time

The activity of ^{99m}*Tc* that can be eluted at equilibrium is *equal* to the ^{99}*Mo* activity

The available activity decays according to

$$A = A_0 \bullet (2^n)$$

n = number of half life times

Tools of Radiopharmacy: Generators

Some specifications

Activity of ^{99}Mo in a typical hospital generator: 500 mCi (17.5 GBq)

Elution after:	^{99m}Tc [M]	^{99m}Tc	^{99}Tc	ratio	act.
4h:	$0.06\ 10^{-6}$	39 ng	47 ng	1.1	180
12h:	$0.13\ 10^{-6}$	79 ng	139 ng	1:2	400
24h:	$0.17\ 10^{-6}$	98 ng	288 ng	1:3	495

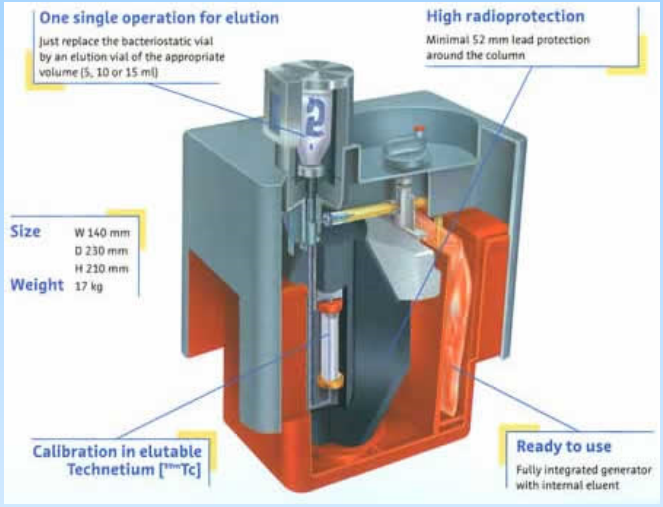
➡ These little amounts will have consequences for chemistry

Tools of Radiopharmacy: Generators

the *first generator*

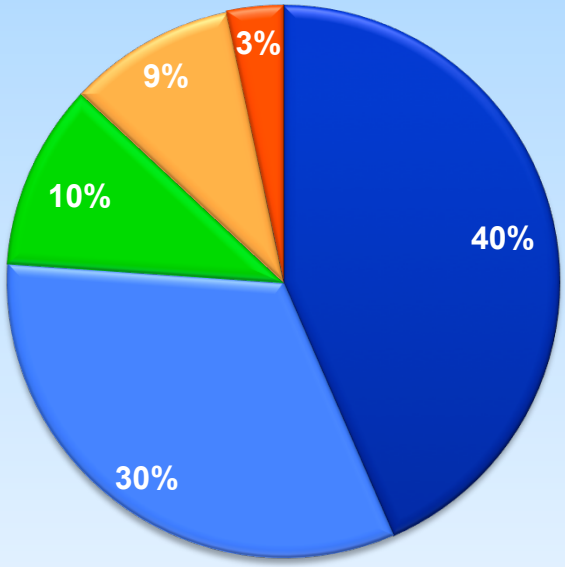
ever produced at Brookhaven Nat. Lab.

more modern designs



The “Technetium Issue” / ^{99}Mo shortage

Reactors used by large-scale producers of ^{99}Mo and % of worldwide production



- National Research Universal (NRU), Chalk River, Canada (1957, will be shut down in 2016)
- High Flux Reactor (HFR), Petten, Netherlands (1961)
- South Africa Fundamental Atomic Reactor Installation-1 (SAFARI-1), South Africa (1965)
- Belgium Reactor-2 (Br2), Belgium (1961)
- OSIRIS, France (1966)

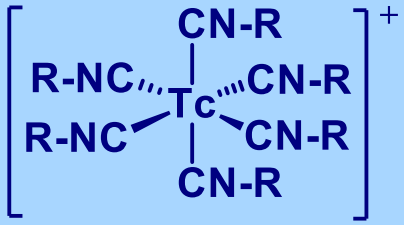
G. S. Thomas, J. Maddahi; *J. Nucl. Cardiol.*, **2010**, 17, 993.

Tools of Radiopharmacy: Radiopharmaceuticals

Type of radiopharmaceuticals

1st generation: *artificial molecules*

de novo radiopharmaceuticals



Cardiolite®

2nd generation: *natural (bio)molecules*

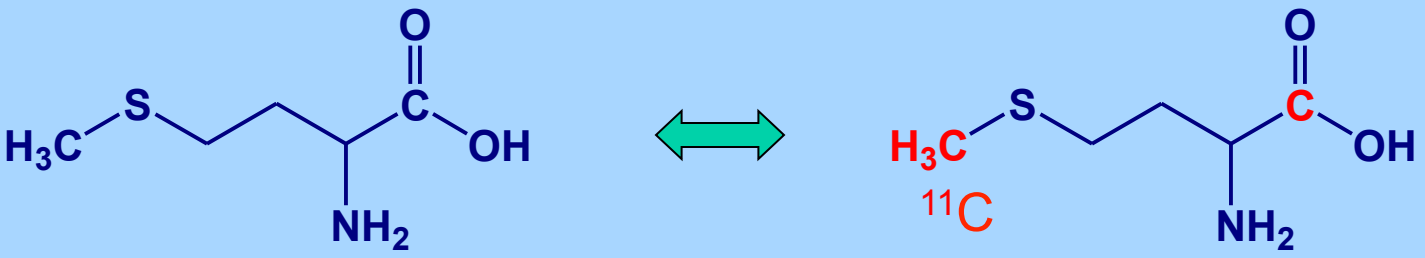
- „natural“ isotopes, ^{11}C, ^{15}O
- artificial isotopes ^{18}F, ^{99m}Tc

Tools of Radiopharmacy: Radiopharmaceuticals

Type of radiopharmaceuticals

➡ introduction of a radionuclide into a biologically active molecule

2nd generation: natural (bio)molecules with *natural* radioisotopes



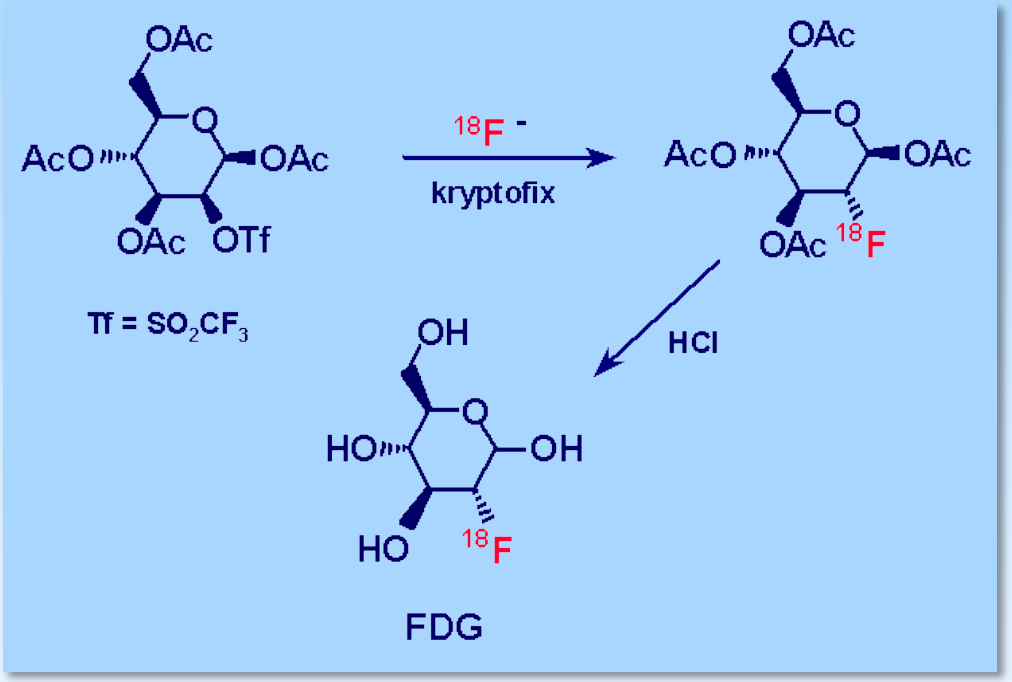
no chemical changes, same metabolical fate

introduction of ^{11}C demands *fast, sophisticated chemistry* (20min half life time)

Tools of Radiopharmacy: Radiopharmaceuticals

Type of radiopharmaceuticals

2nd generation: natural (bio)molecules with *non-natural* radioisotopes



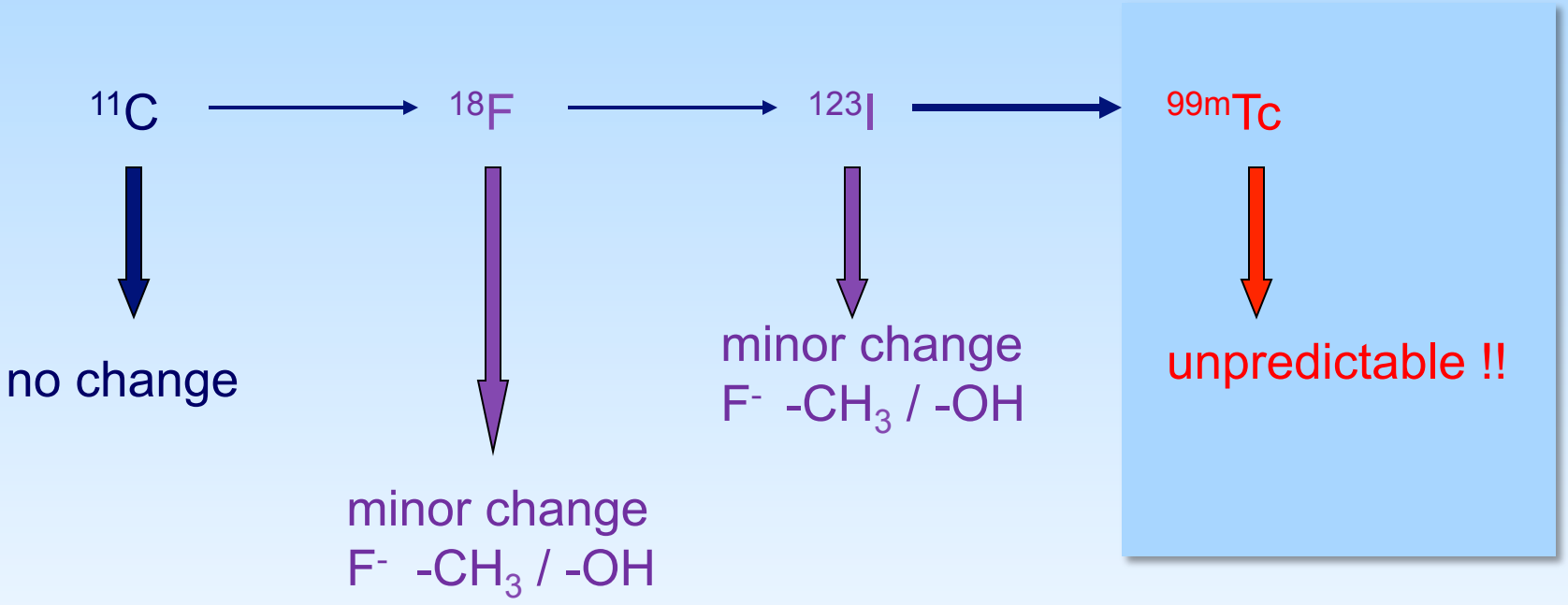
^{18}FDG

philosophy: F^- can substitute a $-CH_3$ or an -OH group without significantly affecting the bioactivity

Tools of Radiopharmacy: Radiopharmaceuticals

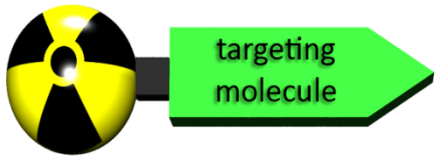
Type of radiopharmaceuticals

Extension: Problems related to the radiopharmaceuticals



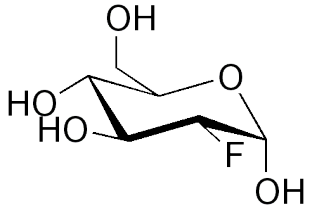
Labeling Strategies

Radiolabeling via covalent bonds:



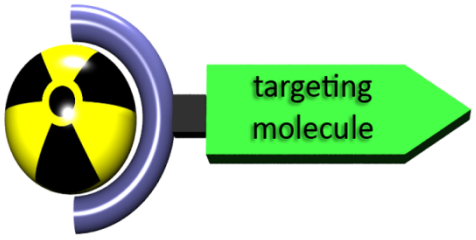
direct **radiolabeling**

«organic» or halogen radionuclides



Fludeoxyglucose ([^{18}F]FDG)

Radiolabeling via coordinative bonds:



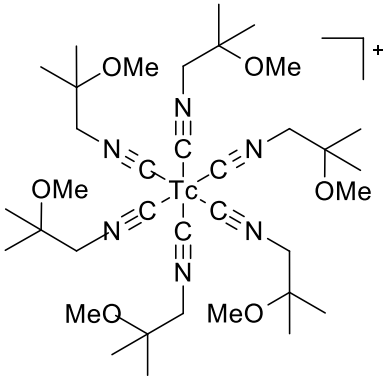
radiometals

indirect **radiolabeling**

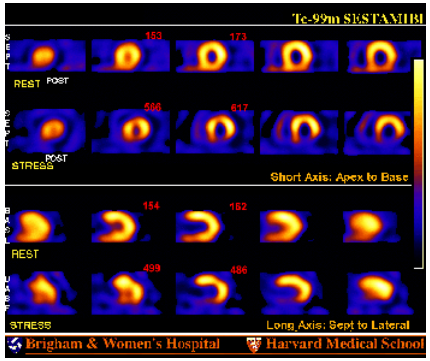
Labeling Strategies

Perfusion radiotracer (1. Generation):

Image the regional blood flow of major organs

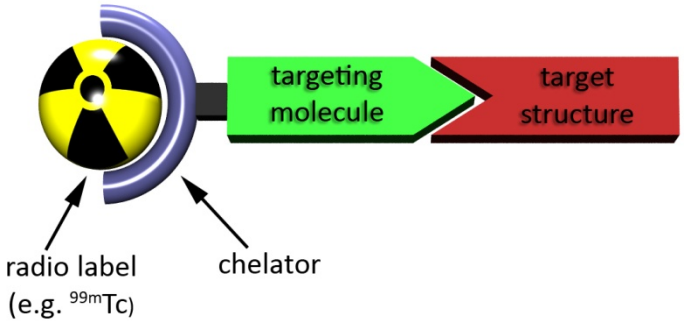


^{99m}Tc-Sestamibi
Cardiolite ®



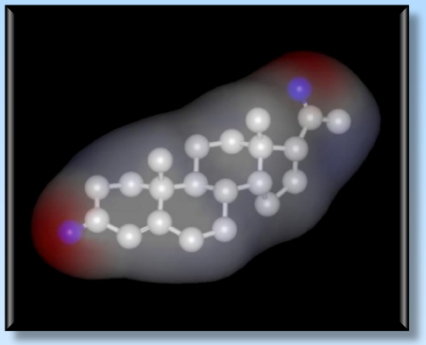
Target specific radio tracer (2. Generation):

Radioconjugates of a chemical inert metal complex and a target specific biomolecule

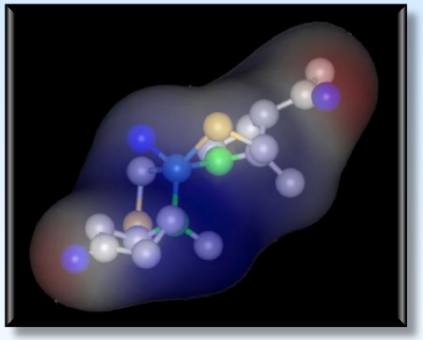


Labeling Strategies

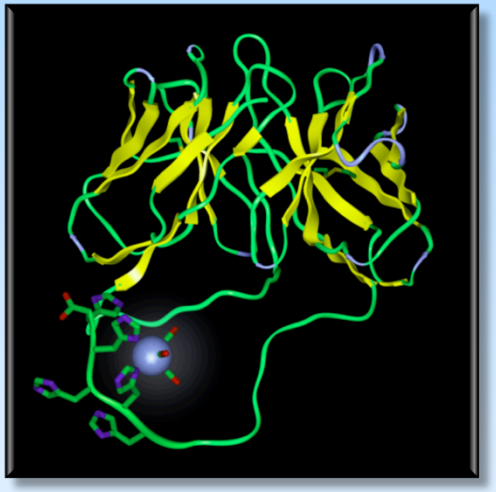
Biomimetic Approach

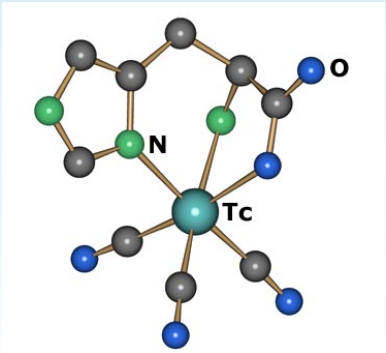


Progesteron

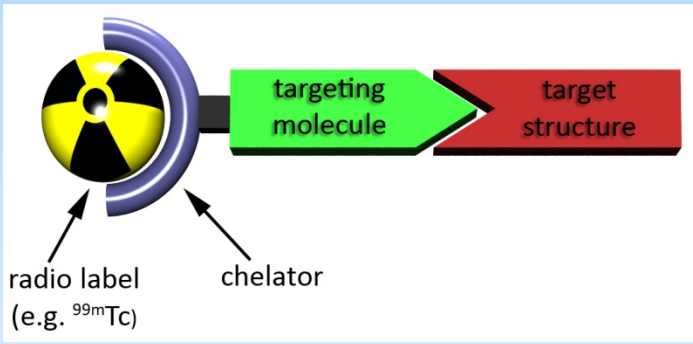


Direct Labeling



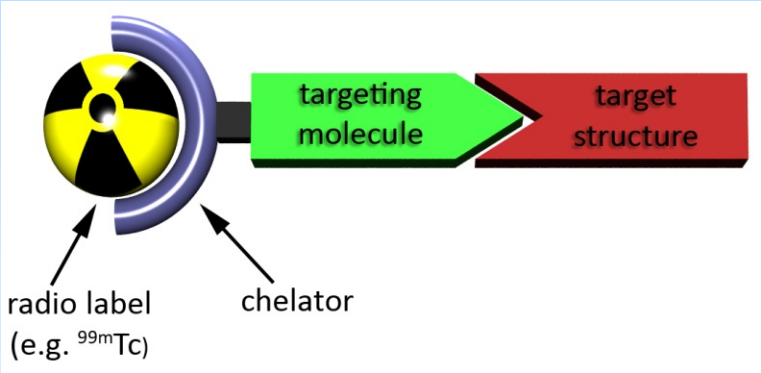


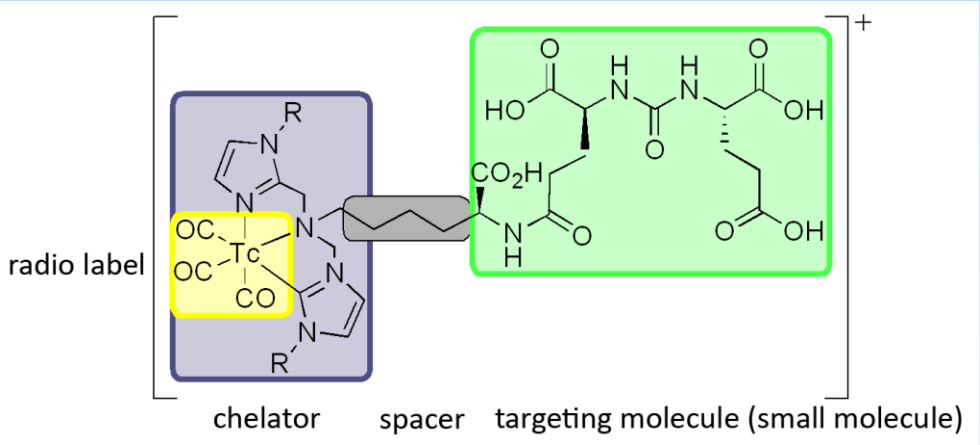
Bifunctional Chelator Concept



Labeling Strategies

Bifunctional Chelator Concept





A large diversity of bifunctional coupling agents for labeling of biomolecules have been developed

prostate-specific membrane antigene inhibitor (PSMA)

Zubieta et al., Nucl. Med. Biol., 2005, 32, 1.
Liu, Asv. Drug Delivery Rev. 2008, 60, 1347.

Babich et al., Bioorg. Med. Chem. Lett., 2013, 23, 1557.

Basics of Radiopharmacy: Summary

➡ Radiopharmacy needs radionuclides which are carried to particular places in an organism and underly a particular biological fate.

➡ Radiopharmaceuticals image in general functions but not structures

➡ Radiopharmacy means irradiation from inside

➡ Depending on the nuclide, radiopharmaceuticals can be *diagnostic*

no particulate emission

reasonable physical half life

adequate energy

Basics of Radiopharmacy: Summary

Depending on the nuclide, radiopharmaceuticals can be *therapeutic*

➡ particulate emission
➡ less than 10% γ-emission

No carrier added means only one isotope of the radionuclide is present

➡ specific activity is at its maximum

The physical and the biological half life are important for dose calc.

➡ effective decay constant

$$T_E = \frac{T_p \times T_b}{T_p + T_b}$$

Basics of Radiopharmacy: Summary

Production of radionuclides can be peformed in

- ➡ fission reactors (in general carrier added)
- ➡ cyclotrons (in general *n.c.a.*)

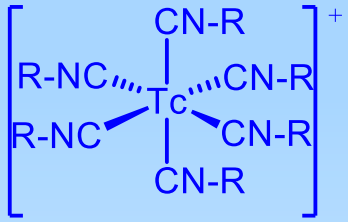
The most important radionuclides are:

^{11}C, ^{18}F, ^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{131}I, ^{153}Sm, $^{188/186}Re$, ^{201}Tl

Generators: The radionuclide of interest is a daughter which can be separated from the parent → yields *n.c.a.* radionuclides

Radiopharmaceutical chemistry

1st generation: artificial molecules



2nd generation: natural (bio)molecules targeting

- natural isotopes, ^{11}C, ^{15}O
- artificial isotopes ^{18}F, ^{99m}Tc

The most useful radionuclides *are not natural* and need to be combined with

- targeting molecule such as peptides or oligonucleotide or proteins ...
- or used as *de novo* radiopharmaceuticals

Radiopharmaceutical chemistry

de novo radiopharmaceuticals

Preparation: ➡

- procedure fully in aqueous solution
- yield > 98%, injectable
- time < 30 min
- high specific activity

Behaviour: ➡

- metabolically stable or controlled metabolism
- fast excretion from non-target organs
- organ specificity

This makes chemistry with transition metals difficult !!

Detectors for the measurement of ionizing radiation

For the measurement of radiation, the following reactions during the irradiation of matter are predominantly utilized:

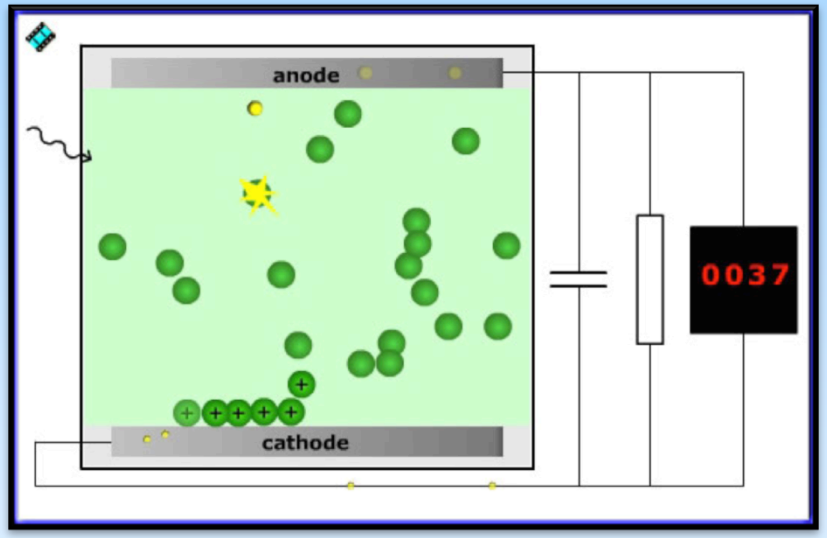
- Ionization in gases
  (Ionization chamber, proportional flow counter, release counter)

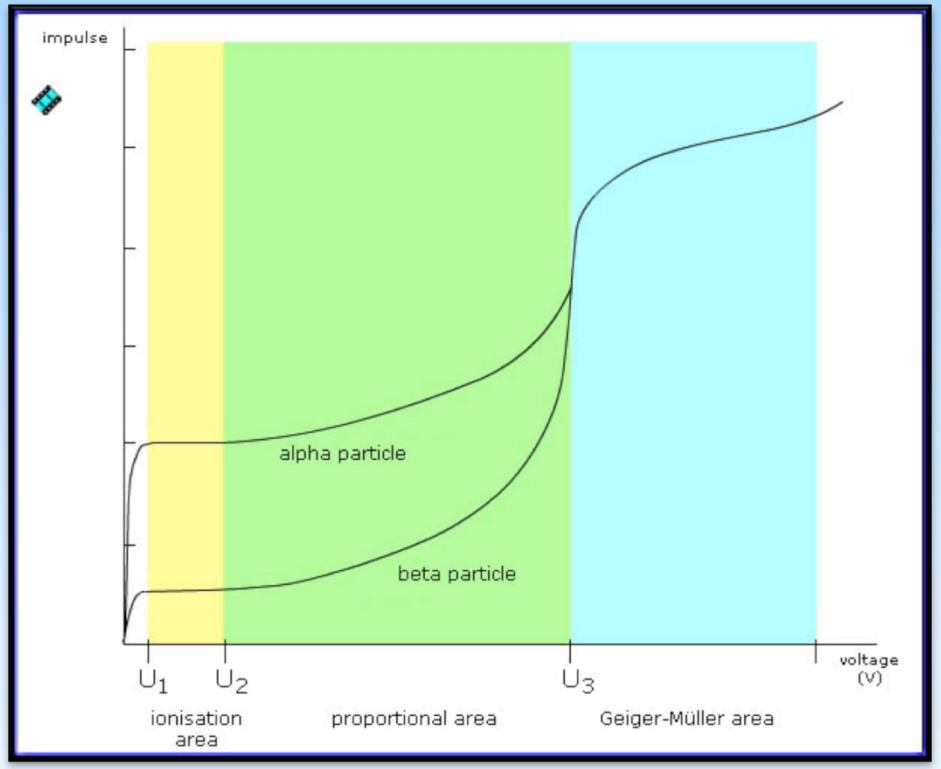
- Scintillation in solids and liquids
  (β- and γ- scintillation counters)

- Ionization in solids
  (semiconductor-detectors)

Detectors for the measurement of ionizing radiation

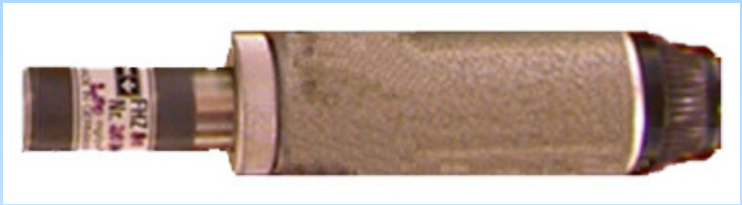
Ionization of gases (gas-filled detectors)

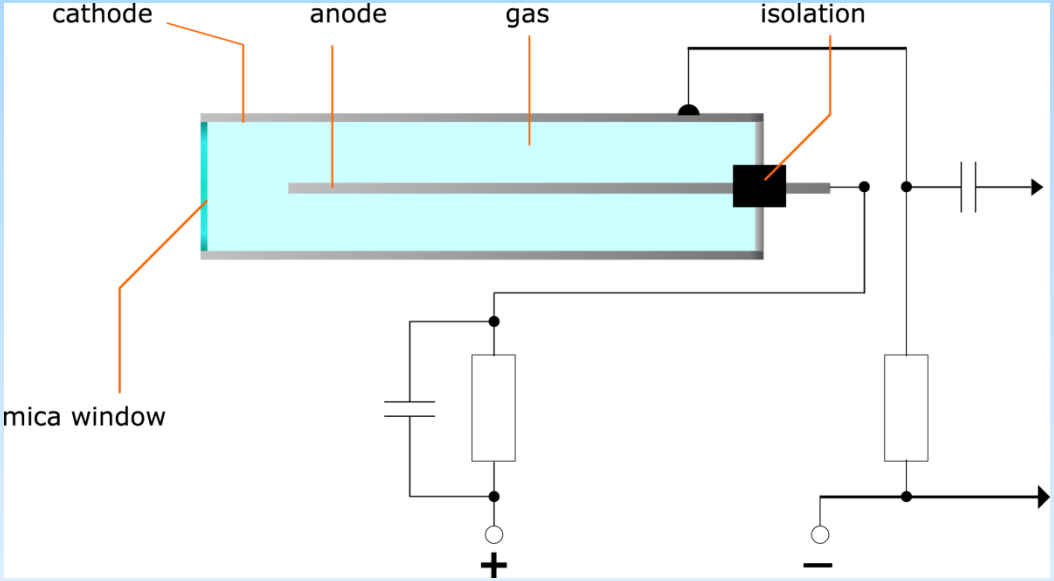




Detectors for the measurement of ionizing radiation

Geiger-Müller Counter

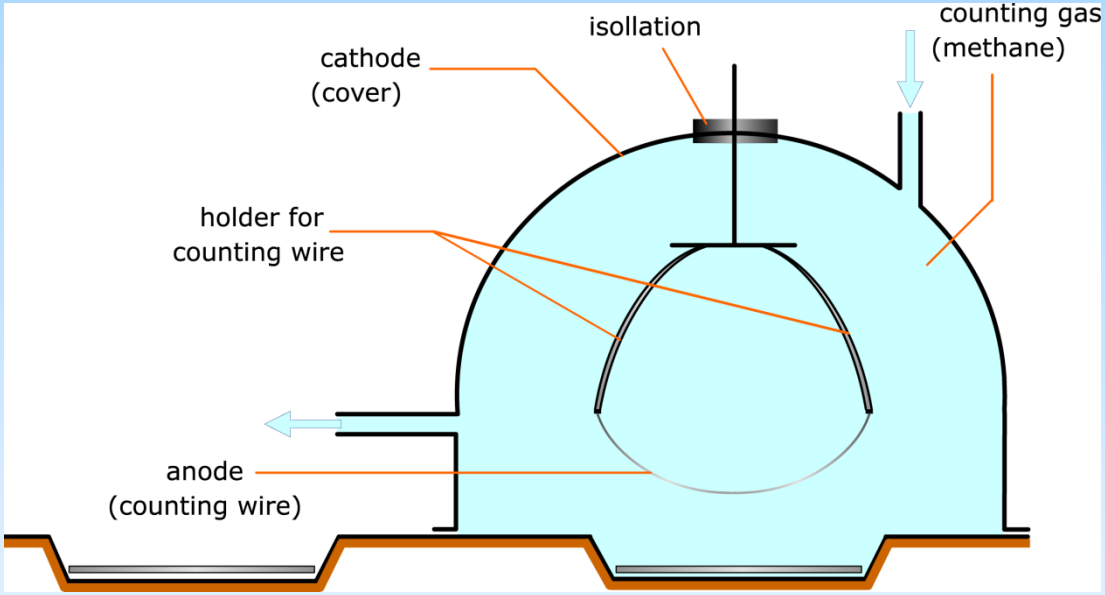




Geiger-Müller counters are most suitable for measuring high-energy β radiation (E_{max} > 1 MeV).

Detectors for the measurement of ionizing radiation

Proportional Flow Counter

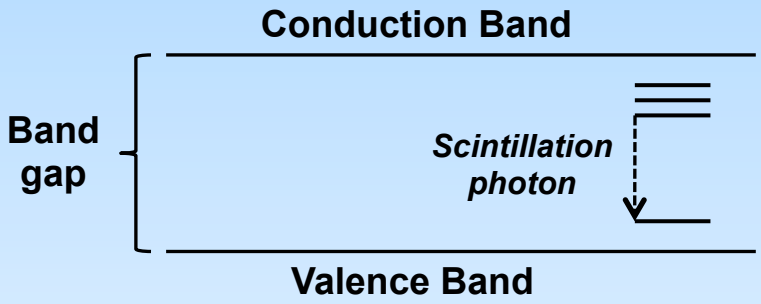


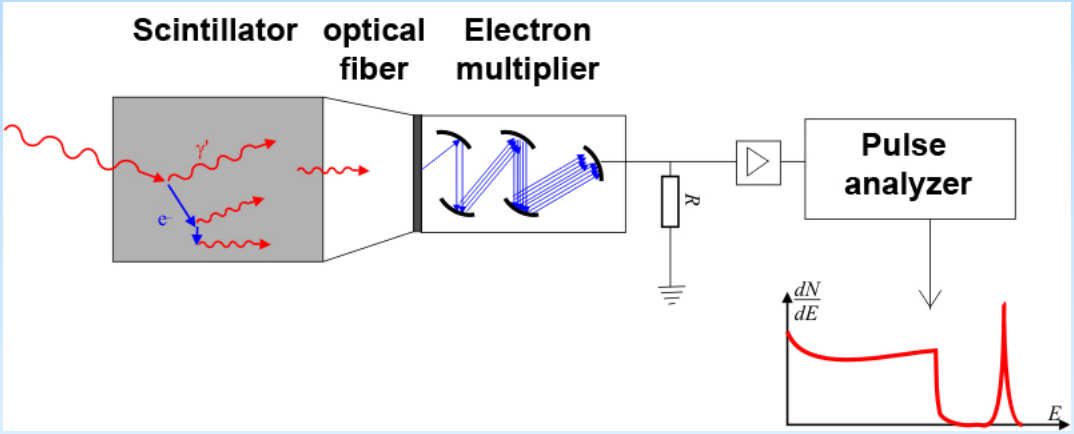
Especially suited for measuring α- and β-emitters.

Detectors for the measurement of ionizing radiation

Scintillation

Scintillation is the property of luminescence when exited by ionizing radiation.



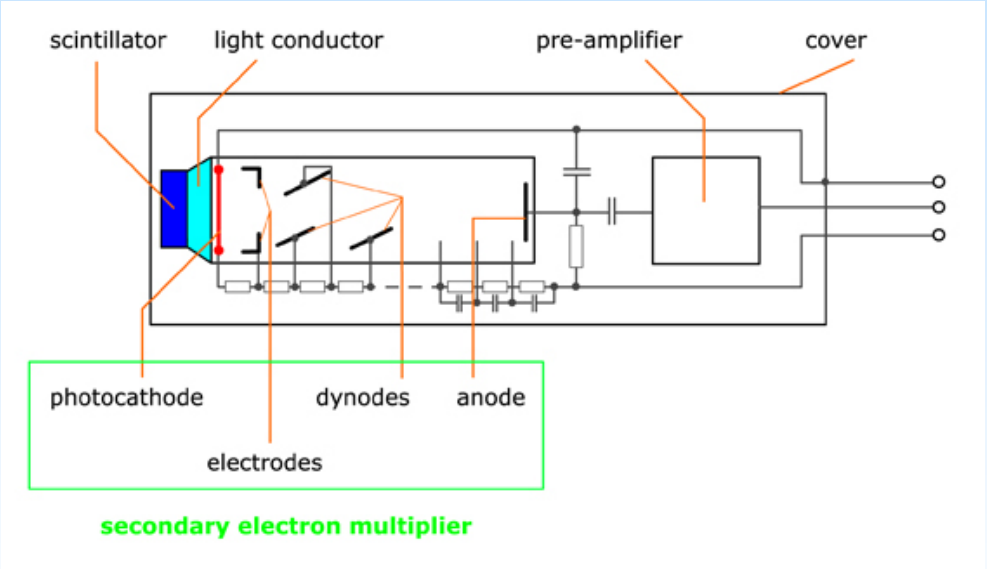


Detectors for the measurement of ionizing radiation

Solid Scintillation Detectors

In order to absorb the largest possible amount of the gamma radiation, thick crystals with large densities are used; e.g. sodium iodide crystals doped with thallium ($\rho = 3{,}67\ g \cdot cm^{-3}$).

By using organic crystals like anthracene, trans-stilbene or p-terphenyl, β radiation can be detected.



Detectors for the measurement of ionizing radiation

Scintillation / γ-scintillation counter (COBRA 5002)

Analytical Method: Quantitative

Detector: Thallium-activated sodium iodide crystal
(through-hole design)

Preset Nuclides:

I-125
I-131
Co-57
Co-60
Cr-51
Se-75
Fe-59
Na-22

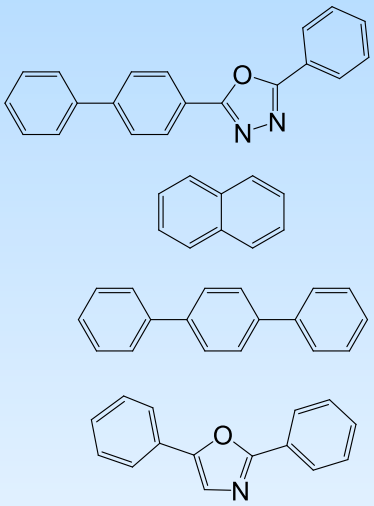
Manual Region: 15 – 2000 keV
(e.g. Tc-99m 140 keV)

Efficiency: >72% for I-125 (others have to be distinguished)

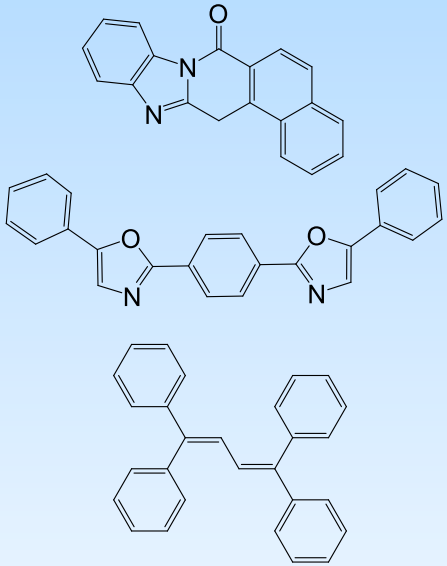
Detectors for the measurement of ionizing radiation

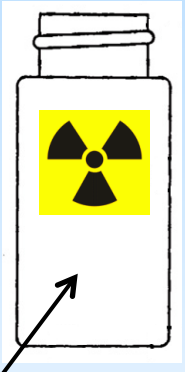
Liquid Scintillation Detectors

Primary
Scintillators:
320 – 360 nm

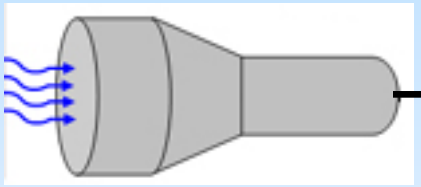


Secondary
Scintillators:
410 – 470 nm





PM Tube



Counter

Aromatic solvent in the scintillation cocktail:
Absorbs the kinetic energy from a charged particle and transfers the energy to the primary scintillator molecules.

Detectors for the measurement of ionizing radiation

Liquid Scintillation Detectors

The problem of quenching

Quenching is the loss of counts due to sample or cocktail characteristics

Chemical Quenching

Chemical quenchers absorb radioactive energy before it is converted to light.
Chemical quenchers reduce the number of photons generated by each β-particle.

Color Quenching

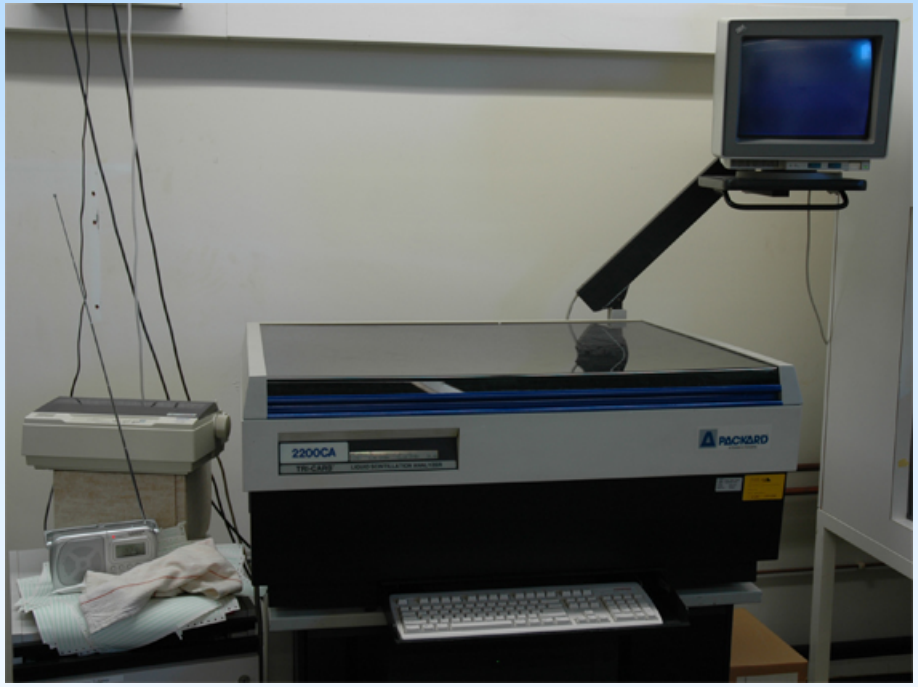
Color quenchers absorb light in the range of the wavelength emitted by the scintillator.
The number of photons emitted is not changed, but the number reaching the photomultiplier tube is reduced.

Detectors for the measurement of ionizing radiation

Scintillation / β-Liquid scintillation counter (TRI-CARB A2200)

Analytical Method: Quantitative / “Qualitative”

Scintillation Cocktail: ULTIMA Gold XR
Compatible with alkaline samples
High holding capacity (up to 50%)
High quench resistance
High counting efficiency
(up to 50% for H-3)



Preset Nuclides:

H-3
C-14
P-32
Ca-45
Tc-99

β-Spectra are recorded

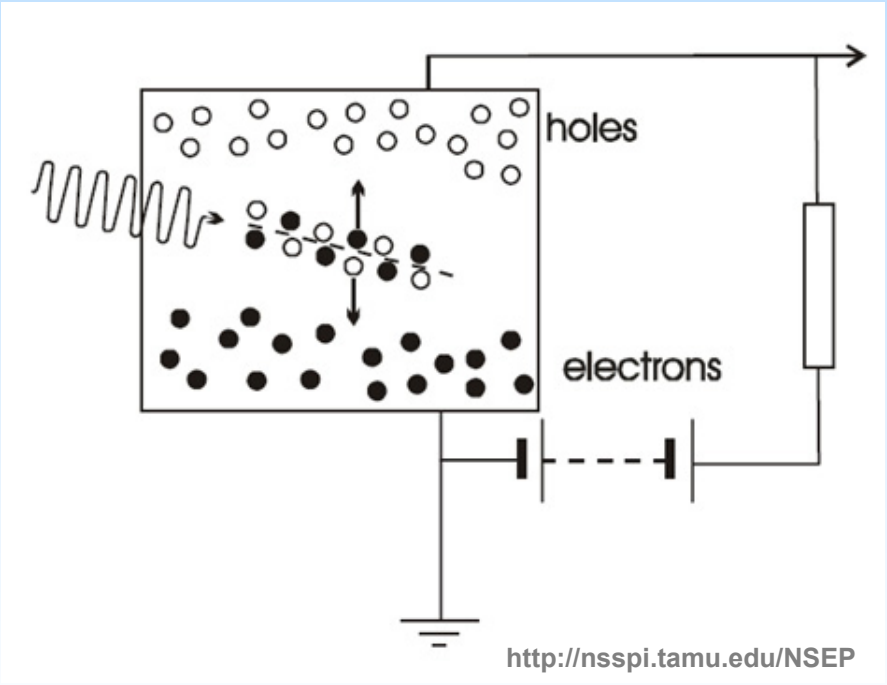
Detectors for the measurement of ionizing radiation

Semiconductor Detector

Ionizing radiation produces electron-hole pairs as it passes through a semiconductor detector

The number of electron-hole pairs is proportional to the energy transmitted by the radiation to the semiconductor

Measuring the number of electron-hole pairs (pulse height) allows the energy of the incident radiation to be found

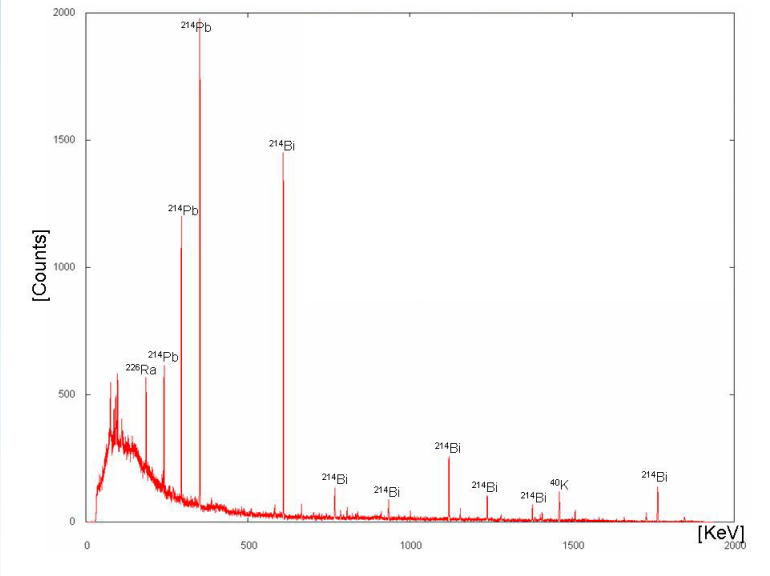


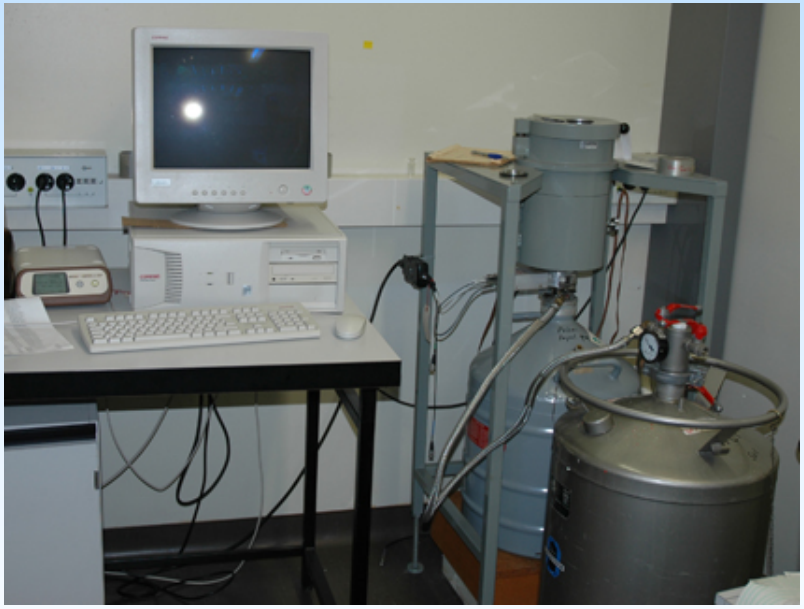
Detectors for the measurement of ionizing radiation

Semiconductor Detector / GeLi

⇒ Measurement of natural probes
(Elemental Analysis)

⇒ Measurement of probes
after neutron activation





Detectors for the measurement of ionizing radiation

The relationship between the activity and the counting rate

The net counting rate (R_N) is proportional to the activity (A) of the sample and the average number of the emitted quanta per decay (ν)

$$R_N = f \cdot A \cdot \nu$$

$$f = f_G \cdot f_A \cdot f_S \cdot f_R \cdot f_i$$

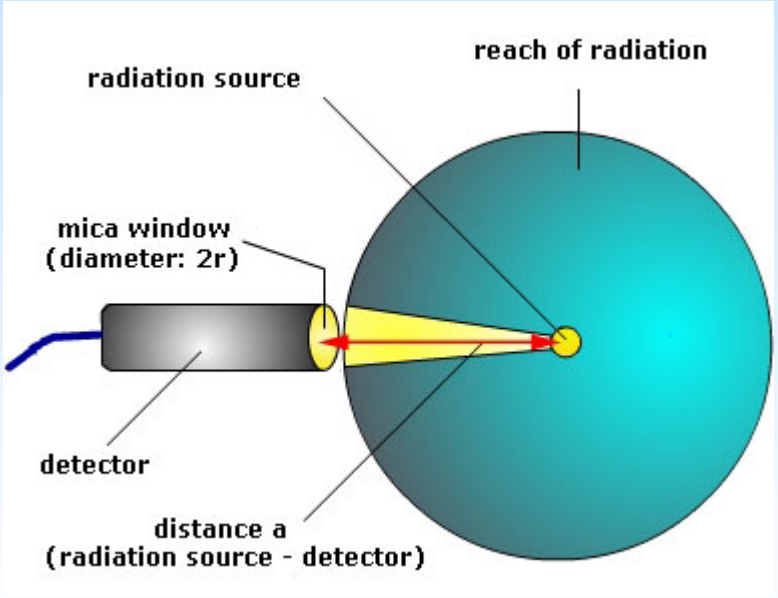
f_G: Geometric factor

f_A: Absorption factor

f_S: Self absorption factor

f_R: Backscattering factor

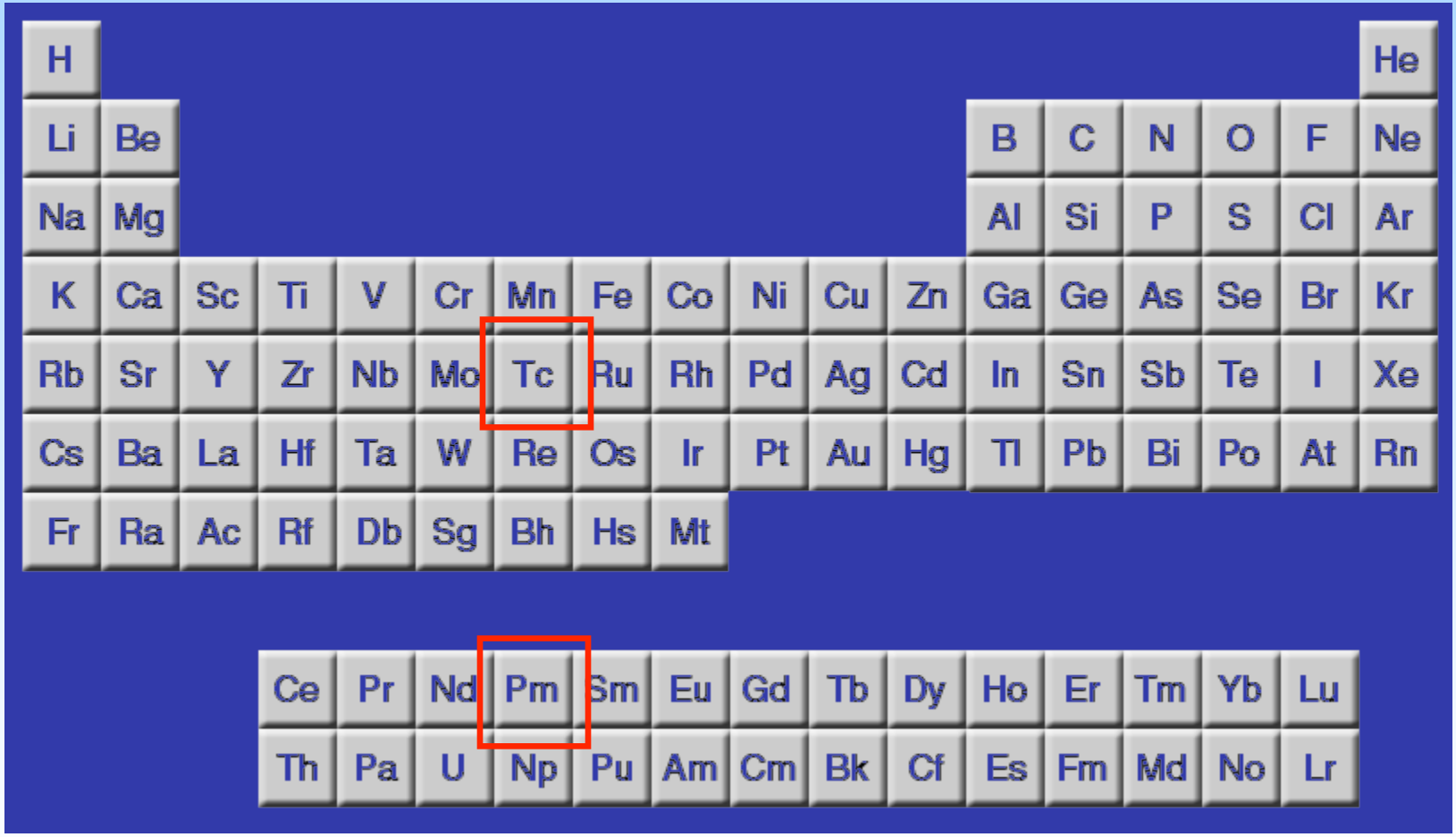
f_i: Response probability



9. Synthesis of Elements

Heaviest stable element is Bismuth

Holes in the periodic Table: Technetium, Promethium



Synthesis of Elements

Artificial elements

$^{96}_{42}Mo + ^{2}_{1}H \rightarrow ^{97}_{43}Tc + ^{1}_{0}n$ Molybdenum ➡ Technetium

$^{209}_{83}Bi + ^{4}_{2}He \rightarrow ^{211}_{85}At + 2^{1}_{0}n$ Bismuth ➡ Astatinium

$^{230}_{90}Th + ^{1}_{1}H \rightarrow ^{223}_{87}Fr + 2^{4}_{2}He$ Thorium ➡ Francium

The natural radioelements

Atomic number Z	Name of the element (Symbol)		Longest-lived nuclide (Half-life)		Discovery
84	Polonium	(PO)	^{209}PO	(102 y)	1898 P. and M. Curie
85	Astatine	(At)	^{210}At	(8.1 h)	1940 Corson, McKenzie and Segrè
86	Radon	(Rn)	^{222}Rn	(3.82 d)	1900 Rutherford and Soddy
87	Francium	(Fr)	^{223}Fr	(22 m)	1939 Perey
88	Radium	(Ra)	^{226}Ra	(1600 y)	1898 P. and M. Curie
89	Actinium	(Ac)	^{227}Ac	(21.6 y)	1899 Debierne
90	Thorium	(Th)	^{232}Th	($1.41 \cdot 10^{10}$ y)	1828 Berzelius
91	Protactinium	(Pa)	^{231}Pa	($3.28 \cdot 10^{4}$ y)	1917 Hahn and Meitner
92	Uranium	(U)	^{238}U	($4.47 \cdot 10^{9}$ y)	1789 Klaproth

Synthesis of Elements

Synthesis of Trans-Uranium Elements (history)

$^{238}U \xrightarrow{n,\gamma} {}^{239}U \xrightarrow{\beta^-} {}^{239}Np \longrightarrow$ McMillan 1940 (fission product)

$^{238}U \xrightarrow{n,2n} {}^{237}U \xrightarrow{\beta^-} {}^{237}Np$

$^{235}U \xrightarrow{n,\gamma \quad n,\gamma} {}^{237}U \xrightarrow{\beta^-} {}^{237}Np$

$^{238}U \xrightarrow{d,2n} {}^{238}Np \xrightarrow{\beta^-} {}^{238}Pu$ Seaborg 1940

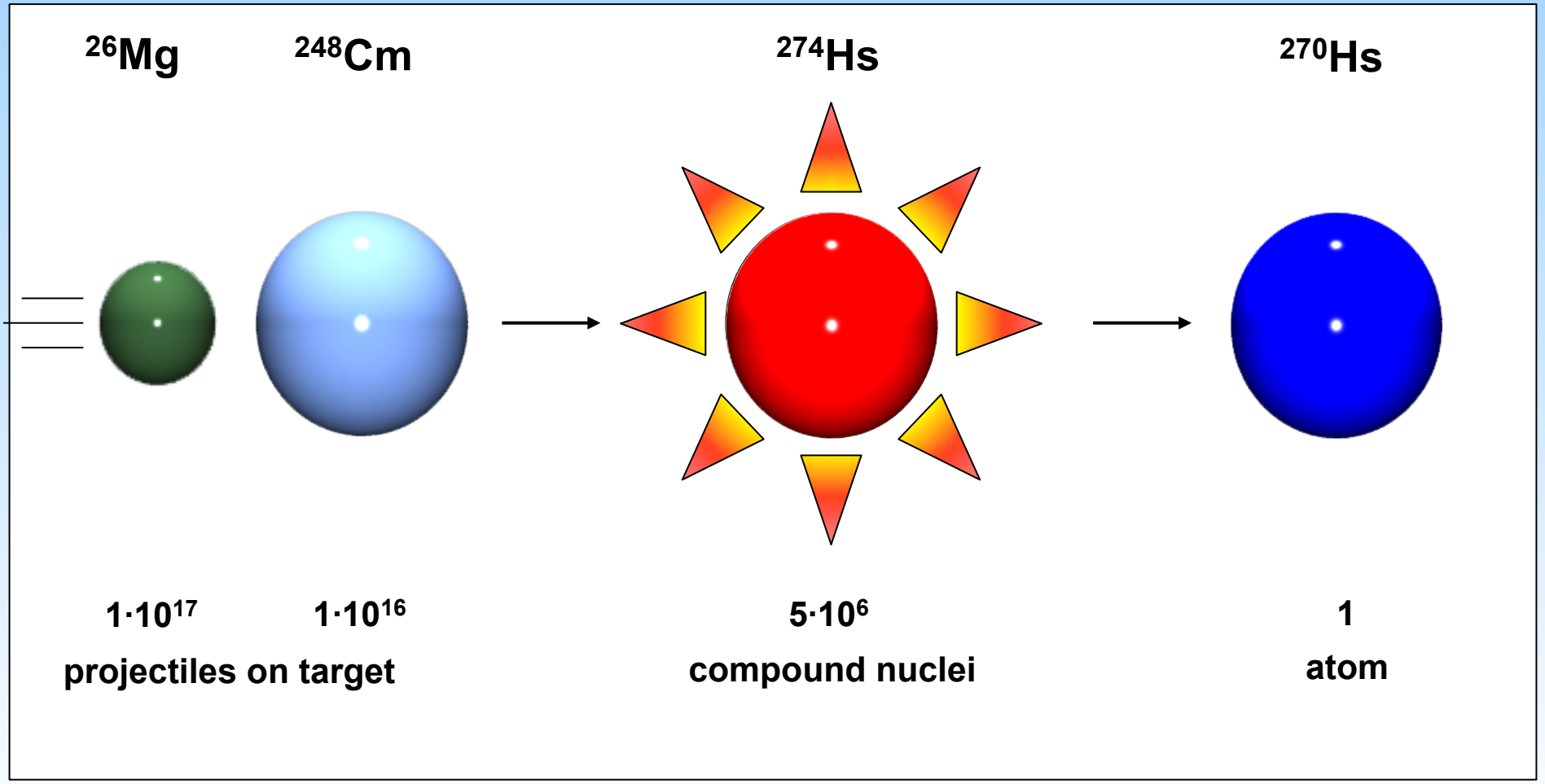
$^{239}Pu \xrightarrow{n,\gamma \quad n,\gamma} {}^{241}Pu \xrightarrow{\beta^-} {}^{241}Am$ Seaborg 1944

$^{241}Am \xrightarrow{n,\gamma} {}^{242}Am \xrightarrow{\beta^-} {}^{242}Cm$ Seaborg 1944

$^{242}Cm \xrightarrow{\alpha,n} {}^{245}Cf$ Thompson 1950

Synthesis of Elements

Synthesis of Trans-Uranium Elements



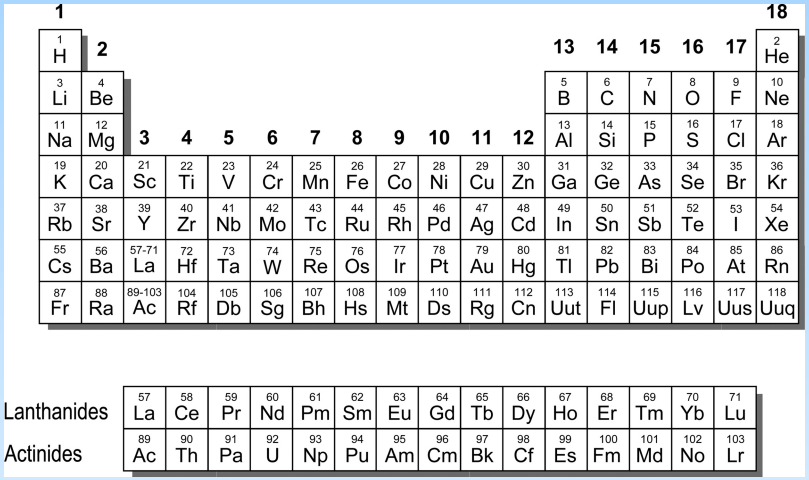
Synthesis of Elements

The artificial radioelements

Atomic number Z	Name of the element (Symbol)		Longest-lived nuclide (Half-life)		Discovery
43	Technetium	(Tc)	^{98}Tc	($4.2 \cdot 10^6$ y)	1937 Perrier and Segrè
61	Promethium	(Pm)	^{145}Pm	(17.7 y)	1947 Marinsky, Glendenin and Coryell
93	Neptunium	(Np)	^{237}Np	($2.14 \cdot 10^6$ y)	1940 McMillan and Abelson
94	Plutonium	(Pu)	^{244}Pu	($8.26 \cdot 10^7$ y)	1940 Seaborg et al.
95	Americium	(Am)	^{243}Am	(7380 y)	1944 Seaborg et al.
96	Curium	(Cm)	^{247}Cm	($1.6 \cdot 10^7$ y)	1944 Seaborg et al.
97	Berkelium	(Bk)	^{247}Bk	(1380 y)	1949 Thompson, Ghiorso et al.
98	Californium	(Cf)	^{251}Cf	(898 y)	1950 Thompson, Ghiorso et al.
99	Einsteinium	(Es)	^{252}Es	(350 d)	1952 Thompson, Ghiorso et al.
100	Fermium	(Fm)	^{257}Fm	(100.5 d)	1953 Thompson, Ghiorso et al.
101	Mendelevium	(Md)	^{258}Md	(55 d)	1955 Ghiorso et al.
102	Nobelium	(No)	^{259}No	(58 m)	1958 Ghiorso et al.
103	Lawrencium	(Lr)	^{262}Lr	(3.6 h)	1961 Ghiorso et al.
104	Rutherfordium	(Rf)	^{261}Rf	(65 s)	1969 Ghiorso et al.
105	Hahnium	(Ha)	^{262}Ha	(34 s)	1970 Ghiorso et al.
106	Seaborgium	(Sg)	^{266}Sg	(30 s)	1974 Ghiorso et al., Flerov et. al.
107	Nielsbohrium	(Ns)			1981 Münzenberg, Armbruster et al.
108	Hassium	(Hs)			1984 Münzenberg, Armbruster et al.
109	Meitnerium	(Mt)			1982 Münzenberg, Armbruster et al.

Synthesis of Elements

Synthesis of Trans-Uranium Elements



Current Periodic Table of the Elements with IUPAC approved numbering of groups and element symbols. The names for elements 114 (Flerovium, Fl) and 116 (Livermorium, Lv) suggested by the team of discoverers have recently been officially accepted by IUPAC.

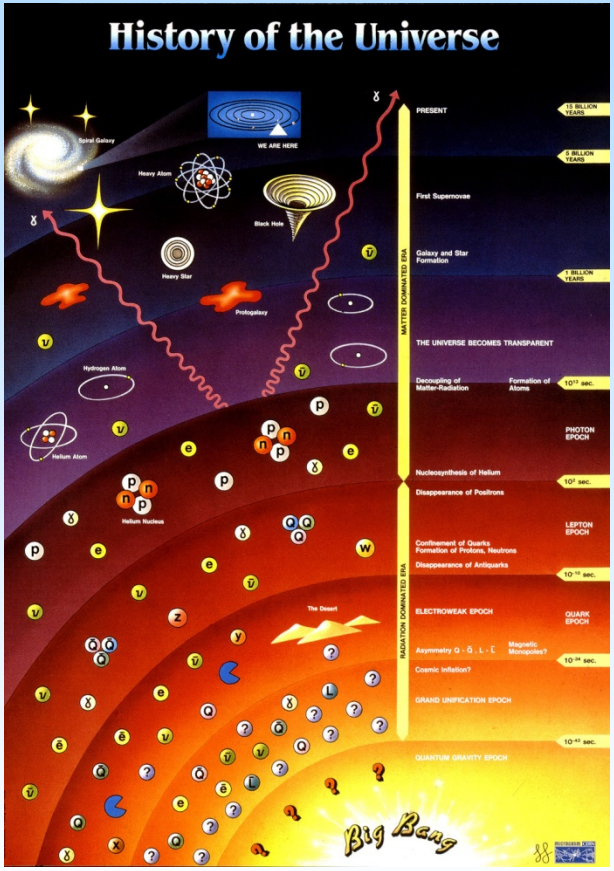
atomic no.	element name	symbol
101	mendelevium	Md
102	nobelium	No
103	lawrencium	Lr
104	rutherfordium	Rf
105	dubnium	Db
106	seaborgium	Sg
107	bohrium	Bh
108	hassium	Hs
109	meitnerium	Mt
110	darmstadtium	Ds
111	roentgenium	Rg
112	copernicium	Cn
113	ununtrium	Uut
114	flerovium	Fl
115	ununpentium	Uup
116	livermorium	Lv
117	ununseptium	Uus
118	ununoctium	Uuo

Andreas Türler; Valeria Pershina; *Chem. Rev.* 2013, 113, 1237-1312.

Synthesis of Elements: Nucleosynthesis

- Elements are remaining from the Big Bang

- Elements are continously synthesized in the stars

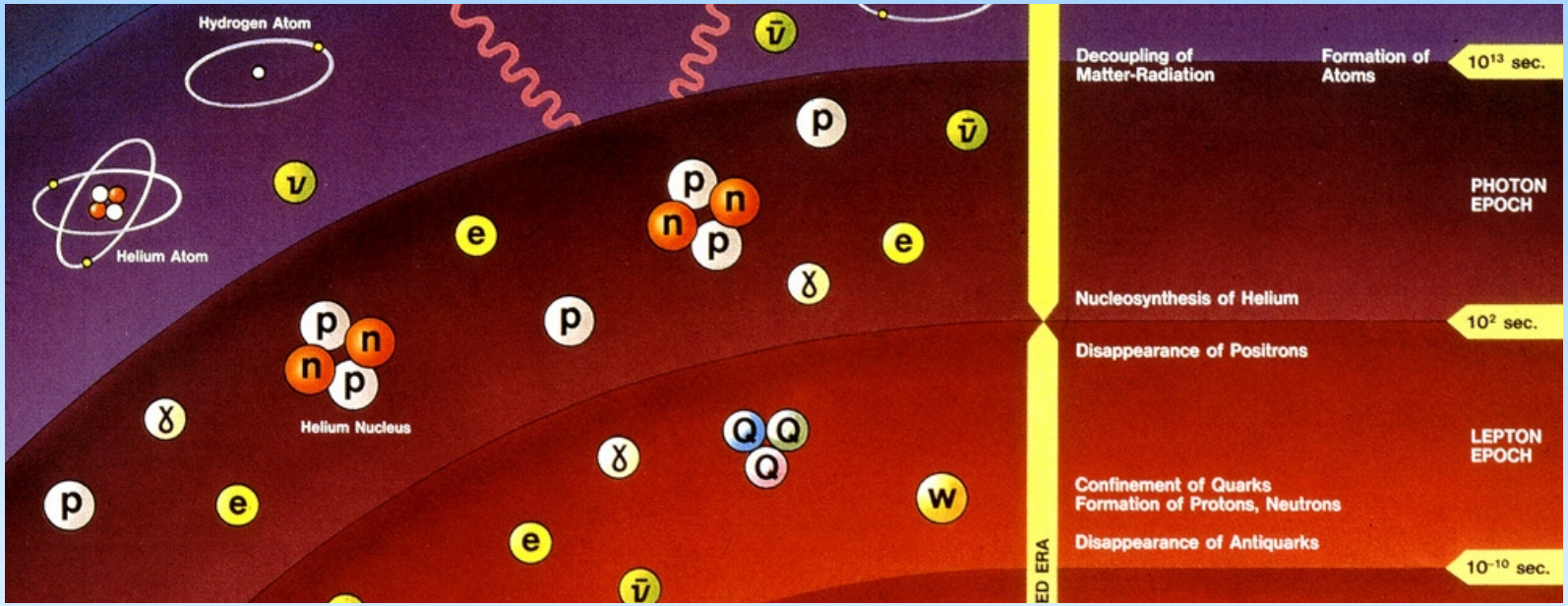


A short history of time

Zeit	T / ° K	E (eV)	Ereignis
~15 Gy	2.7	0.00023	Jetzt
~ 1 Gy	10	~0.001	Bildung erster Strukturen
~0.3 My	3000	0.26	Rekombination zu Atomen
			Universum wird transparent
~5×10^4 y	10'000	0.8	Equality Materie / Strahlung
3 min	7×10^8	6×10^4	**Nukleosynthese**
1 s	10^{10}	10^6	$e^+e^-\rightarrow\gamma\gamma$
4×10^{-6}s	5×10^{12}	4×10^8	QCD phase transition
< 4×10^{-6}s	>10^{13}	>10^9	**Baryogenese** ???

Synthesis of Elements: Nucleosynthesis

Elements are remaining from the Big Bang



- Nach etwa 1 Sekunde werden Protonen und Neutronen generiert.

- Heliumkerne bilden sich nach etwa 100 sec (E < 1 MeV).

- Verhältnis von He / H stimmt mit dem Big Bang Modell überein.

- Das Universum ist “milchig” da die Elektronen frei sind

Synthesis of Elements: Nucleosynthesis

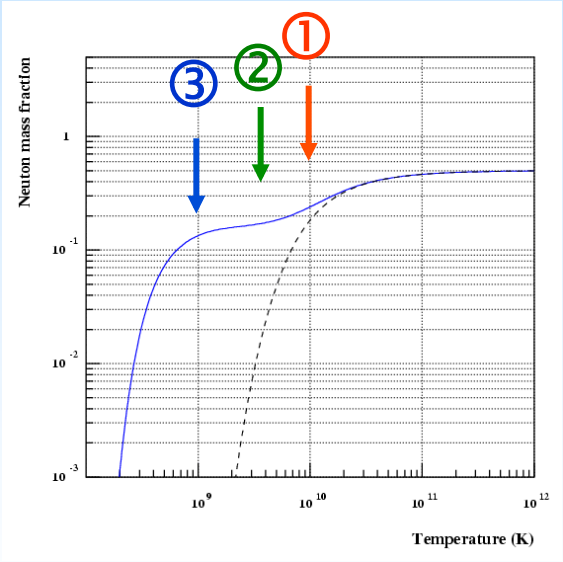
Primordiale Nucleosynthesis

Als die Temperatur für Nukleosynthese noch zu hoch war, zerfielen $n \Rightarrow p^+$

Andere Kernreaktionen für $T > 10^9$ K:

$$p^+ + e^- \rightleftharpoons n + \nu$$

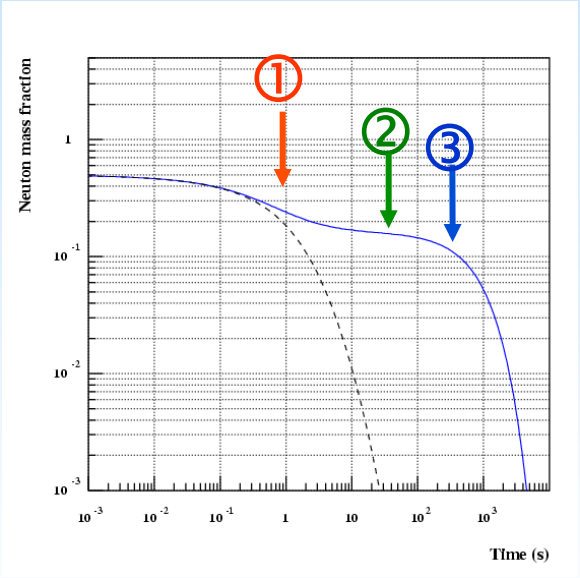
$$p^+ + \nu(\text{anti}) \rightleftharpoons n + e^+$$



① n,p entkoppelt

② n freier Zerfall

③ Beginn D Bildung



Synthesis of Elements: Nucleosynthesis

Primordiale Nucleosynthesis

Als die Temperatur T < 10^9 K setzt die D Synthese ein

$$n + p^+ \longrightarrow D + \gamma \quad \Delta E = +2.2 \text{ MeV}$$

weil die Deuterium Produktion schneller wird als die Photodesintegration (T > 10^9 K)

$$D + \gamma \longrightarrow n + p^+ \quad \Delta E = -2.2 \text{ MeV}$$

Unter diesen Bedingungen (T > 108 K) haben wir Gleichgewicht (Ggw)

Im Ggw hat die Systementropie ein Maximum erreicht (in einem isolierten System)

Ausdehnung bewirkt Abkühlung ➡ Bildung schwerer Kerne da exotherm

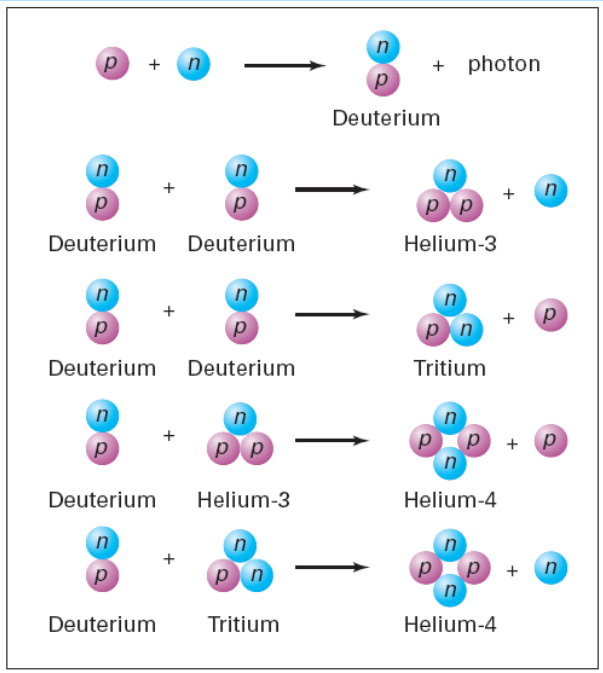
van‘t Hoff im Urknall oder in Sternen

Synthesis of Elements: Nucleosynthesis

Primordiale Nucleosynthesis

Die Nukleosynthese produziert jetzt im wesentlichen ^{4}He

zusammen mit Spuren von D, ^{3}He, ^{7}Li, ….



$^{4}He + T \longrightarrow {}^{7}Li$

- Ferner wurden in Spuren auch ^{7}Li, ^{9}Be, ^{10}B and ^{11}B gebildet (letztlich aus Photonen !!)

- Diese Elemente bildeten sich vor der Rekombination

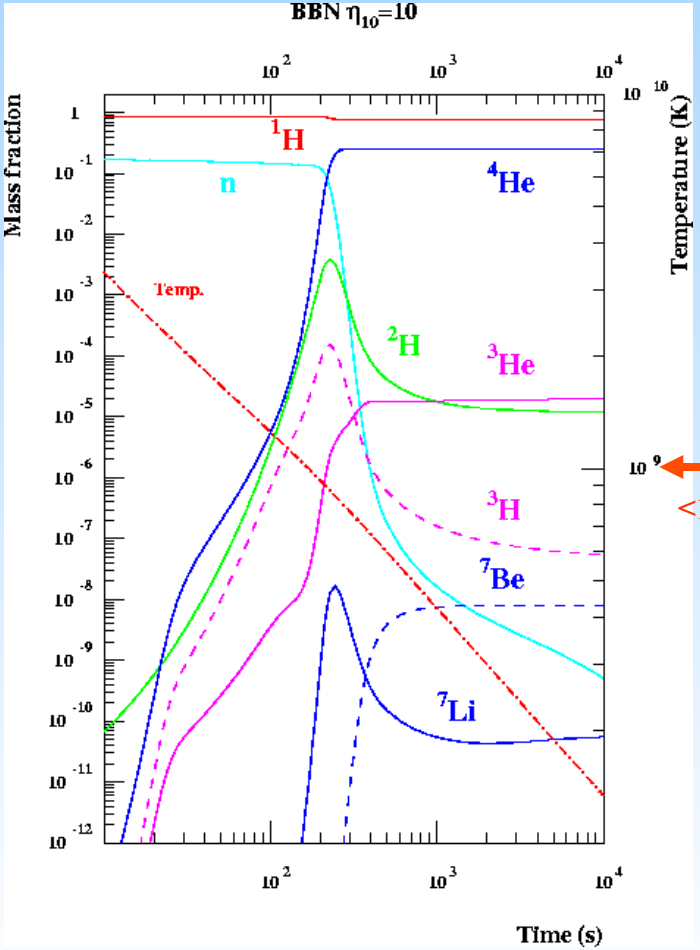
- Die relative Menge hängt vom Urzustand ab und wie schnell sich das Universium abkühlte

- die gefundenen Verhältnisse (75% H und 25% He) stimmen sehr gut mit dem Urknall Modell überein

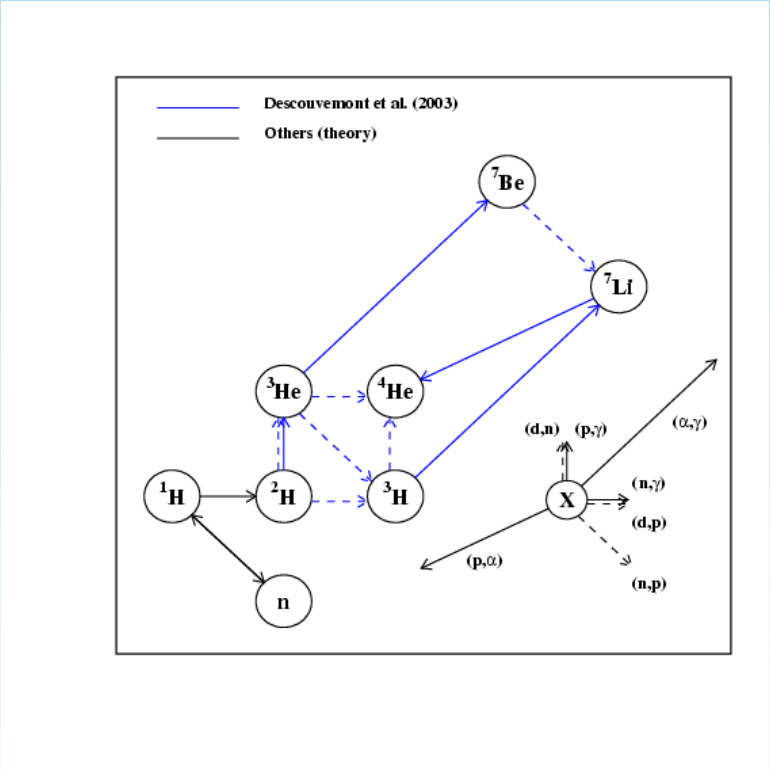
-^{4}He wird auch in Sternen produziert, aber viel zu wenig um den Gehalt im Universum zu erklären

Synthesis of Elements: Nucleosynthesis

Primordiale Nucleosynthesis



Die 12 wichtigsten Nukleosynthesen welche im Urknall abgelaufen sind



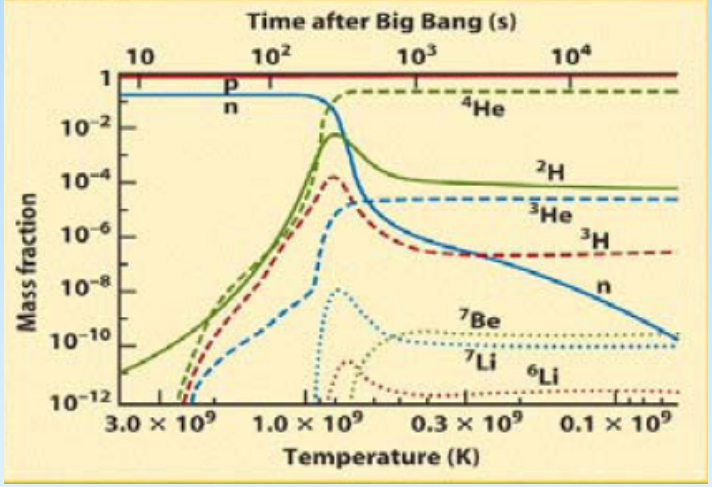
Es gibt keine bekannten Kerne mit A = 5 und A = 8 !

Synthesis of Elements: Nucleosynthesis

Primordiale Nucleosynthesis

Endzustand, vor der Bildung von Sternen

- primordiale Nukleosynthese nach ca. 30 min. beendet

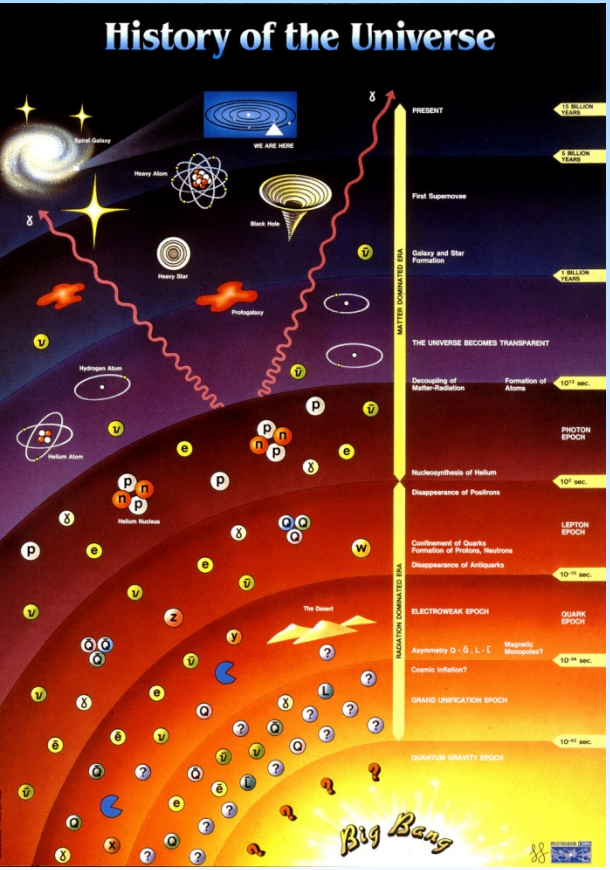


- Das Universum dehnt sich weiter aus, mit ρ_{rad} Energiedichte in Strahlung schneller abfallend als ρ_{mat} Energiedichte in Materie
- Nach ca 30,000 Jahren ist das Universum nicht mehr Strahlungs sondern durch Materie dominiert.

Synthesis of Elements: Nucleosynthesis

Primordiale Nucleosynthesis

und was geschah weiter ...



- Bei T = 3000 K nach t=400,000 Jahren sind Photonen nicht mehr energetisch genug um die Elektronen am Binden zu Kernen zu hindern

→ Atome entstehen

- Zeit der Rekombination": Plasma aus Elektronen und Protonen und einigen He Kernen kombinierten zu H und He.

- Die Wechselwirkung von Photonen mit gebundenen Elektronen ist schwächer als mit freien Elektronen.

→ Strahlung strömt ungehinderter

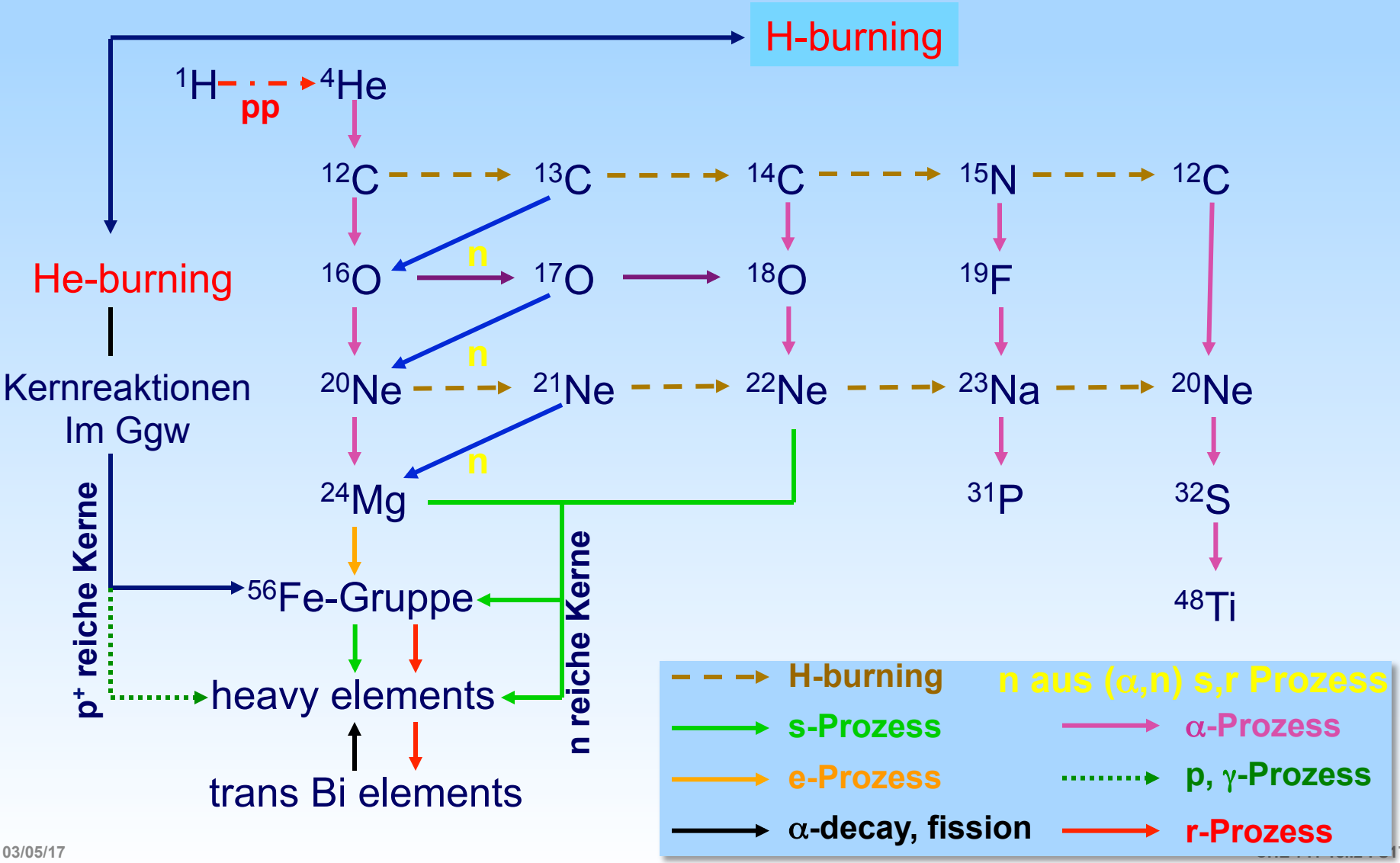
- Entkopplung von Materie und Strahlung, Materie begann ebenfalls sich frei zu bewegen,

→ Galaxien begannen sich zu bilden

Synthesis of Elements: Nucleosynthesis

Synthesis of Elements: Nucleosynthesis

Synthese der Elemente jenseits von H: insgesamt 8 Kernprozesse notwendig



Synthesis of Elements: Nucleosynthesis

Hydrogen-burning reaction sequences

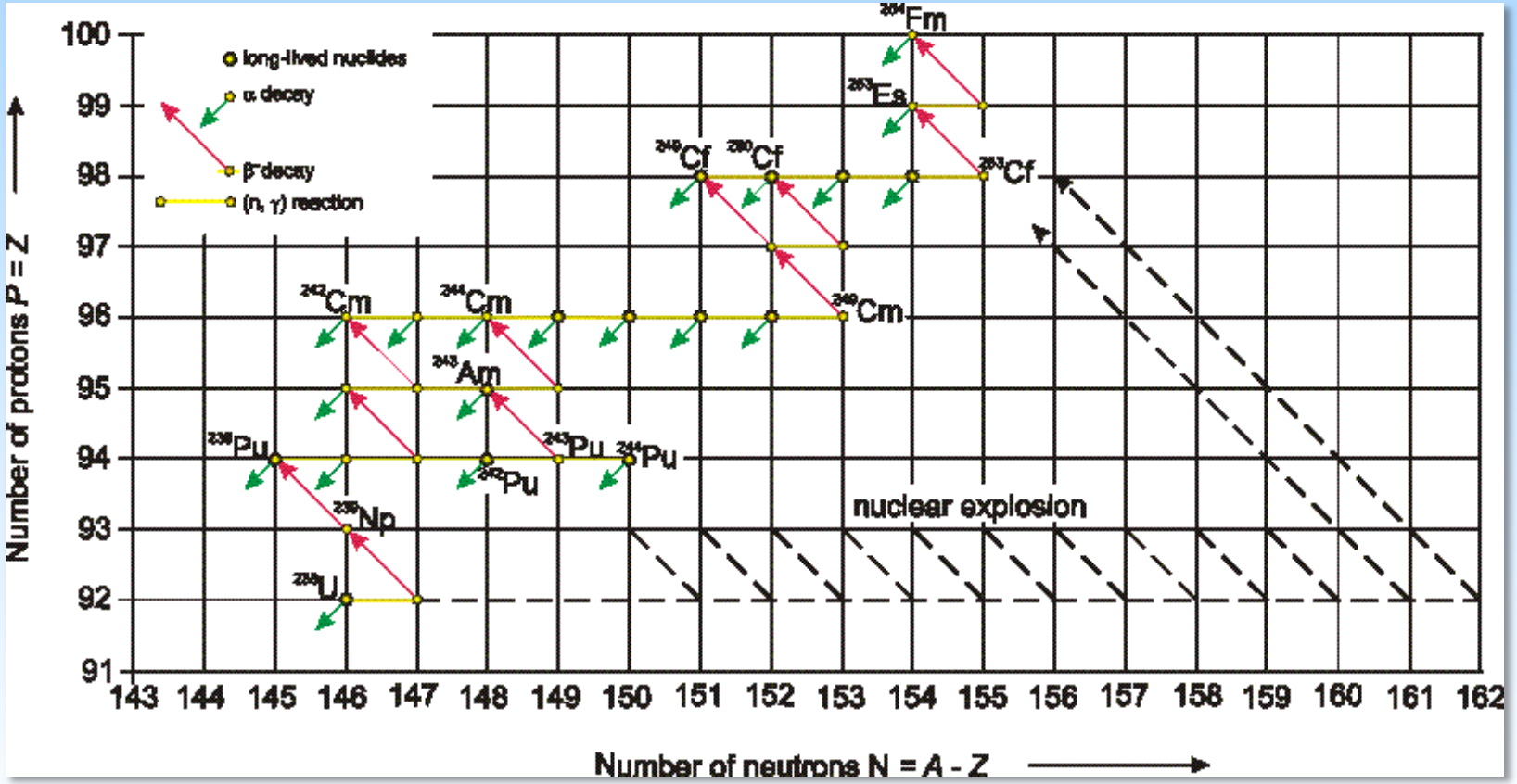
	Proton-proton chains	Carbon-nitrogen-oxigen cycles
PP I	$^{1}H + {}^{1}H \rightarrow {}^{2}D + e^{+} + \nu$	$^{12}C + {}^{1}H \rightarrow {}^{12}N + \gamma$
	$^{2}D + {}^{1}H \rightarrow {}^{3}He + \gamma$	$^{13}N \rightarrow {}^{13}C + e^{+} + \nu$
	$^{3}He + {}^{3}He \rightarrow {}^{4}He + 2{}^{1}H$	$^{13}C + {}^{1}H \rightarrow {}^{14}N + \gamma$
	or	$^{14}N + {}^{1}H \rightarrow {}^{15}O + \gamma$
	$^{3}He + {}^{4}He \rightarrow {}^{7}Be + \gamma$	$^{15}O \rightarrow {}^{15}N + e^{+} + \nu$
PP II	$^{7}Be + e- \rightarrow {}^{7}Li + \nu$	$^{15}N + {}^{1}H \rightarrow {}^{12}C + {}^{4}He$
	$^{7}Be + {}^{1}H \rightarrow {}^{8}Be \rightarrow 2{}^{4}He$	or
	or	$^{15}N + {}^{1}H \rightarrow {}^{16}O + \gamma$
	$^{7}Be + {}^{1}H \rightarrow {}^{8}B + \gamma$	$^{16}O + {}^{1}H \rightarrow {}^{17}F + \gamma$
PP III	$^{8}B \rightarrow {}^{8}Be + e^{+} + \nu$	$^{17}F \rightarrow {}^{17}O + e^{+} + \nu$
	$^{8}Be \rightarrow 2{}^{4}He$	$^{17}O + {}^{1}H \rightarrow {}^{14}N + {}^{4}He$

Synthesis of Elements: Nucleosynthesis

Helium and heavy-ion reactions

Helium-burning reactions	Carbon- and oxygen-burning reactions
$3\,^4He \rightarrow {}^{12}C + \gamma$	$^{12}C + {}^{12}C \rightarrow {}^{20}Ne + {}^4He$
$^{12}C + {}^4He \rightarrow {}^{16}O + \gamma$	$^{12}C + {}^{12}C \rightarrow {}^{23}Na + {}^1H$
$^{16}O + {}^4He \rightarrow {}^{20}Ne + \gamma$	$^{12}C + {}^{12}C \rightarrow {}^{23}Mg + n$
$^{20}Ne + {}^4He \rightarrow {}^{24}Mg + \gamma$	
also	
	$^{16}O + {}^{16}O \rightarrow {}^{28}Si + {}^4He$
$^{14}N + {}^4He \rightarrow {}^{17}F + \gamma$	$^{16}O + {}^{16}O \rightarrow {}^{31}P + {}^1H$
$^{18}F \rightarrow {}^{18}O + e^+ + \nu$	$^{16}O + {}^{16}O \rightarrow {}^{31}S + n$
$^{18}O + {}^4He \rightarrow {}^{22}Ne + \gamma$	
and	
$^{18}O + {}^4He \rightarrow {}^{21}Ne + n$	
$^{22}Ne + {}^4He \rightarrow {}^{25}Mg + n$	

$$^{1}H + {}^{1}H \rightarrow {}^{2}D + e^{+} + \nu$$


long-lived nuclides
α decay
β⁻ decay
(n, γ) reaction
Number of protons P = Z
Number of neutrons N = A - Z
nuclear explosion
100
99
98
97
96
95
94
93
92
91
143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162
254Fm
253Es
249Cf
250Cf
253Cf
249Cm
244Cm
242Cm
243Am
243Pu
244Pu
242Pu
238Pu
239Np
235U