QUALI-START-UP LECTURES 2019

Introduction in Radiopharmaceutical Chemistry

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JÜLICH
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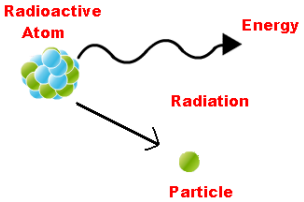
CONTENT

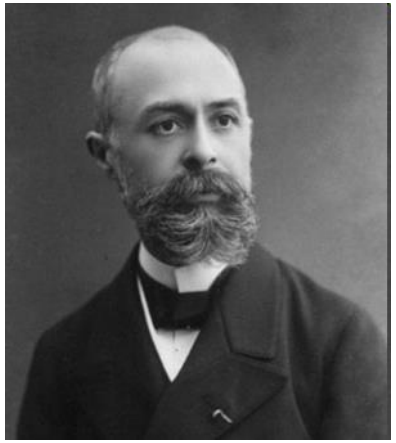
- Radioactivity
- Types of nuclides
- Radioactive decay
- Tracer concept
- Molecular Imaging
- Principles of SPECT & PET

RADIOACTIVITY

- Radioactive decay, also known as nuclear decay or radioactivity, is the process by which the nucleus of an unstable atom loses energy by emitting radiation.
- A material that spontaneously emits such radiation is considered radioactive.
- Radioactive decay is a stochastic (i.e. random) process at the level of single atoms, in that, according to quantum theory, it is impossible to predict when a particular atom will decay.

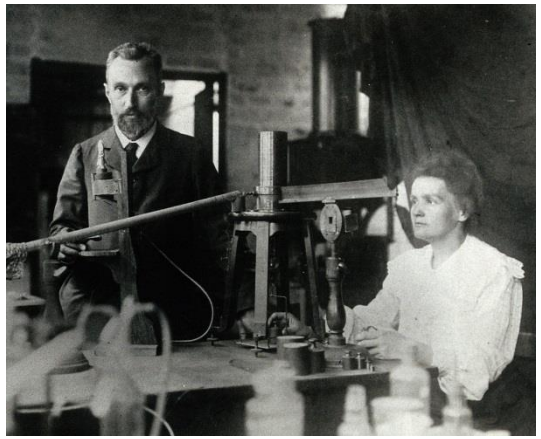


Antoine Henri Becquerel



Discoverer of radioactivity in 1896

Marie (born Maria Salomea Skłodowska) and Pierre Curie



Discoverer of polonium and radium 1896 & 1902

Nobel prize in physics: 1903

RADIOACTIVITY

The International System of Units (SI) unit of radioactive activity is Becquerel (Bq), named in honour of the scientist Henri Becquerel. One Bq is defined as one transformation (or decay or disintegration) per second.

Constant quantities:

- The half-life—$t_{1/2}$, is the time taken for the activity of a given amount of a radioactive substance to decay to half of its initial value
- The decay constant— λ, "lambda" the inverse of the mean lifetime, sometimes referred to as simply decay rate.

Although these are constants, they are associated with the statistical behaviour of populations of atoms. In consequence, predictions using these constants are less accurate for minuscule samples of atoms.

Time-variable quantities:

- Total activity— A, is the number of decays per unit time of a radioactive sample.
- Number of particles—N, is the total number of particles in the sample.

$$A = -\frac{dN(t)}{dt} = \lambda N(t) \qquad [Bq] \qquad T_{1/2} = \frac{\ln 2}{\lambda}$$

RADIOACTIVITY

Activity (radioactivity) A: $A = -\frac{dN}{dt}$

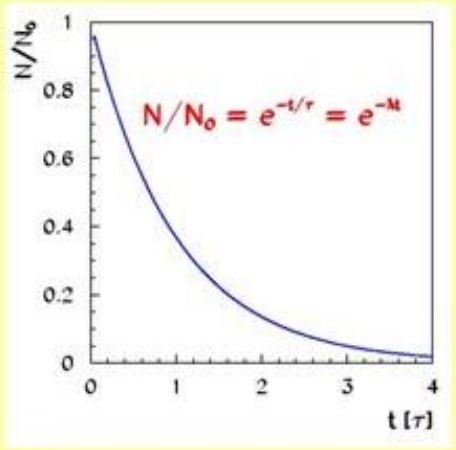
where N is number of nuclei at given time in sample [Bq = s^{-1}, Ci =$3.7 \cdot 10^{10}$Bq].

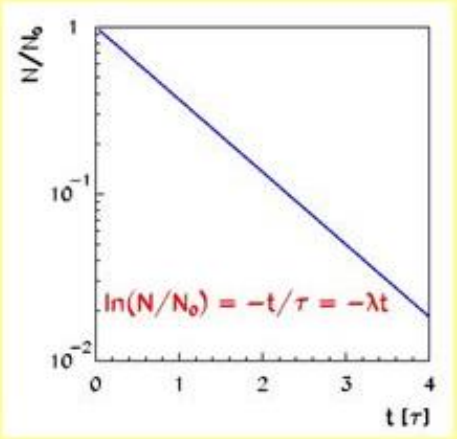
Constant probability λ of decay of each nucleus per time unit is assumed.
Number dN of nuclei decayed per time dt:

$$dN = -N\lambda dt \longrightarrow \frac{dN}{N} = -\lambda \cdot dt$$

Both sides are integrated: $\int_{N_0}^{N} \frac{dN}{N} = -\lambda \int_{0}^{t} dt$

$$\ln N - \ln N_0 = -\lambda t \longrightarrow N = N_0 e^{-\lambda t}$$





Then for radioactivity we obtain:

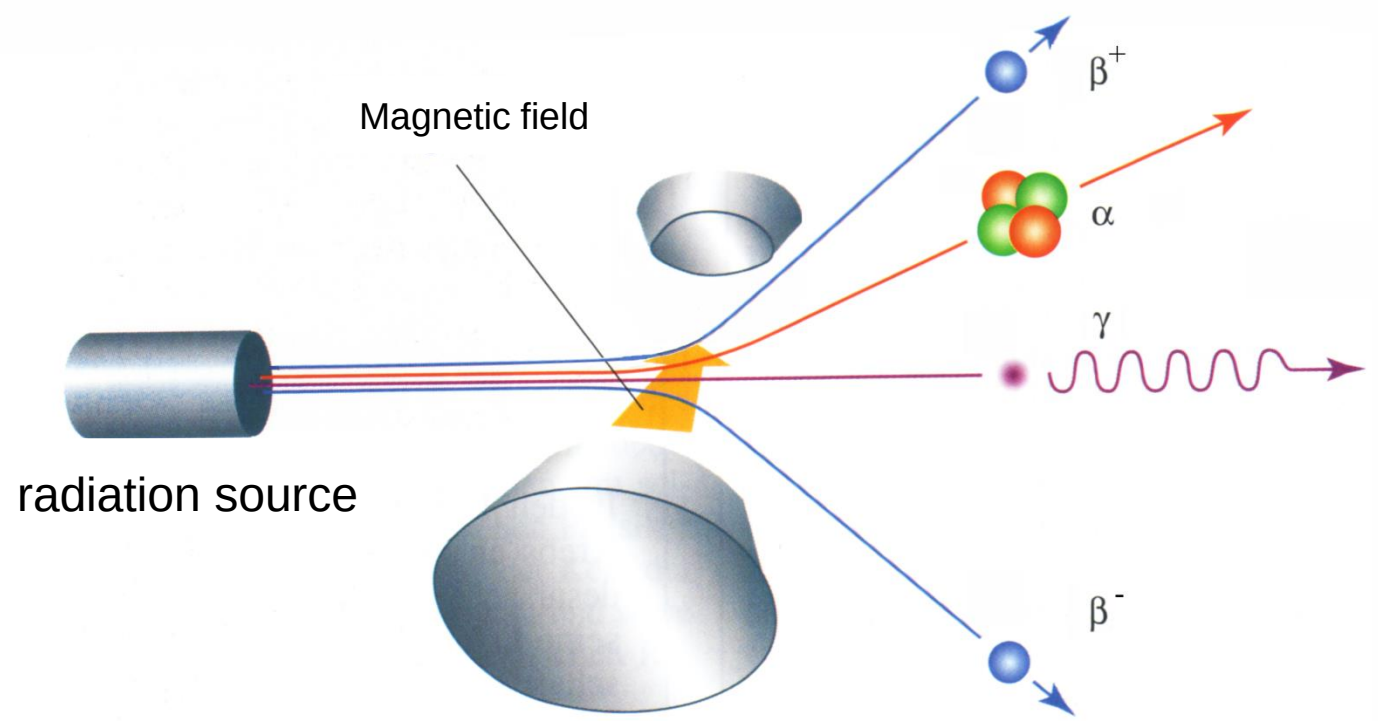
$$A = -\frac{dN}{dt} = \lambda N_0 e^{-\lambda \cdot t} = A_0 e^{-\lambda \cdot t} \quad \text{where} \quad A_0 \equiv -\lambda N_0$$

Probability of decay λ is named decay constant. Time of decreasing from N to N/2 is decay half-life $T_{1/2}$. We introduce $N = N_0/2$:

$$\frac{N_0}{2} = N_0 e^{-\lambda T_{1/2}} \longrightarrow T_{1/2} = \frac{\ln 2}{\lambda}$$

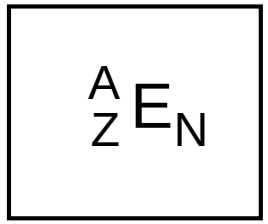
RADIOACTIVITY

Historically, the products of radioactivity were called alpha (α), beta (β), and gamma (γ) when it was found that they could be analysed into three distinct species by a magnetic field.



NUCLIDE

A nuclide (from nucleus) is an atomic species characterized by the specific constitution of its nucleus, i.e., by its number of protons Z, its number of neutrons N, and its nuclear energy state.



E element symbol
Z protons (= atomic number)
A mass number
N neutrons (N=A-Z)

IUPAC-rules allow:

$^{A}_{Z}\mathrm{El}_{N}$	$^{A}_{Z}\mathrm{El}$	$^{A}\mathrm{El}$	El-A
$^{238}_{92}\mathrm{U}_{146}$	$^{238}_{92}\mathrm{U}$	$^{238}\mathrm{U}$	U-238

NUCLIDE

Z = const. = Isotopes equal proton number	$^{24}_{12}Mg_{12}$	$^{25}_{12}Mg_{13}$	$^{26}_{12}Mg_{14}$
N = const. = Isotones equal neutron number	$^{24}_{12}Mg_{12}$	$^{23}_{11}Na_{12}$	$^{22}_{10}Ne_{12}$
A = N+Z = const. = Isobares equal mass number	$^{23}_{12}Mg_{11}$	$^{23}_{11}Na_{12}$	$^{23}_{10}Ne_{13}$
A – 2Z = N-Z = const. = Isodiaphers	$^{21}_{10}Ne_{11}$	$^{23}_{11}Na_{12}$	$^{25}_{12}Mg_{13}$

TABLE OF NUCLIDES

A table of nuclides is a two-dimensional graph in which one axis represents the number of neutrons and the other represents the number of protons in an atomic nucleus.

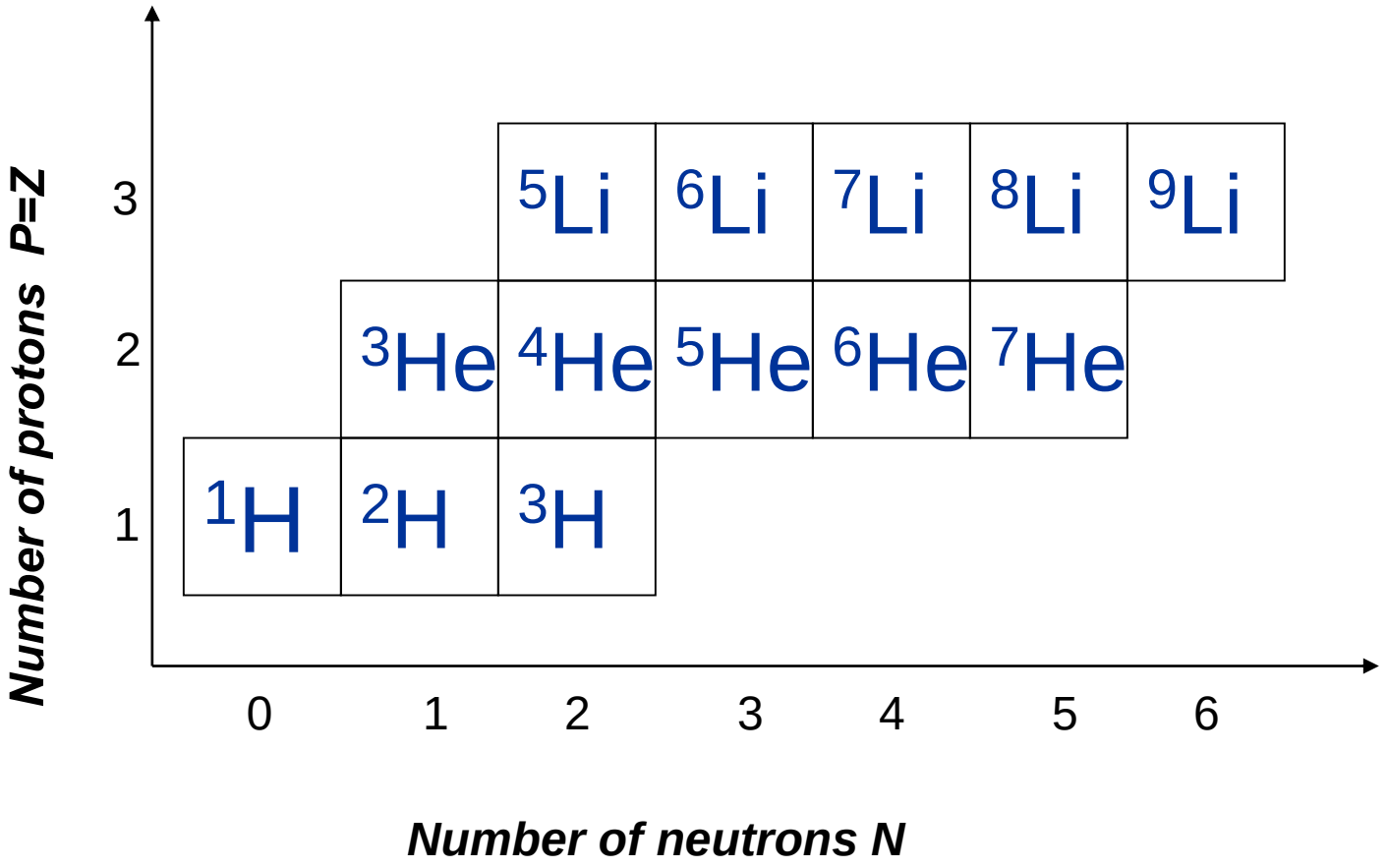


TABLE OF NUCLIDES

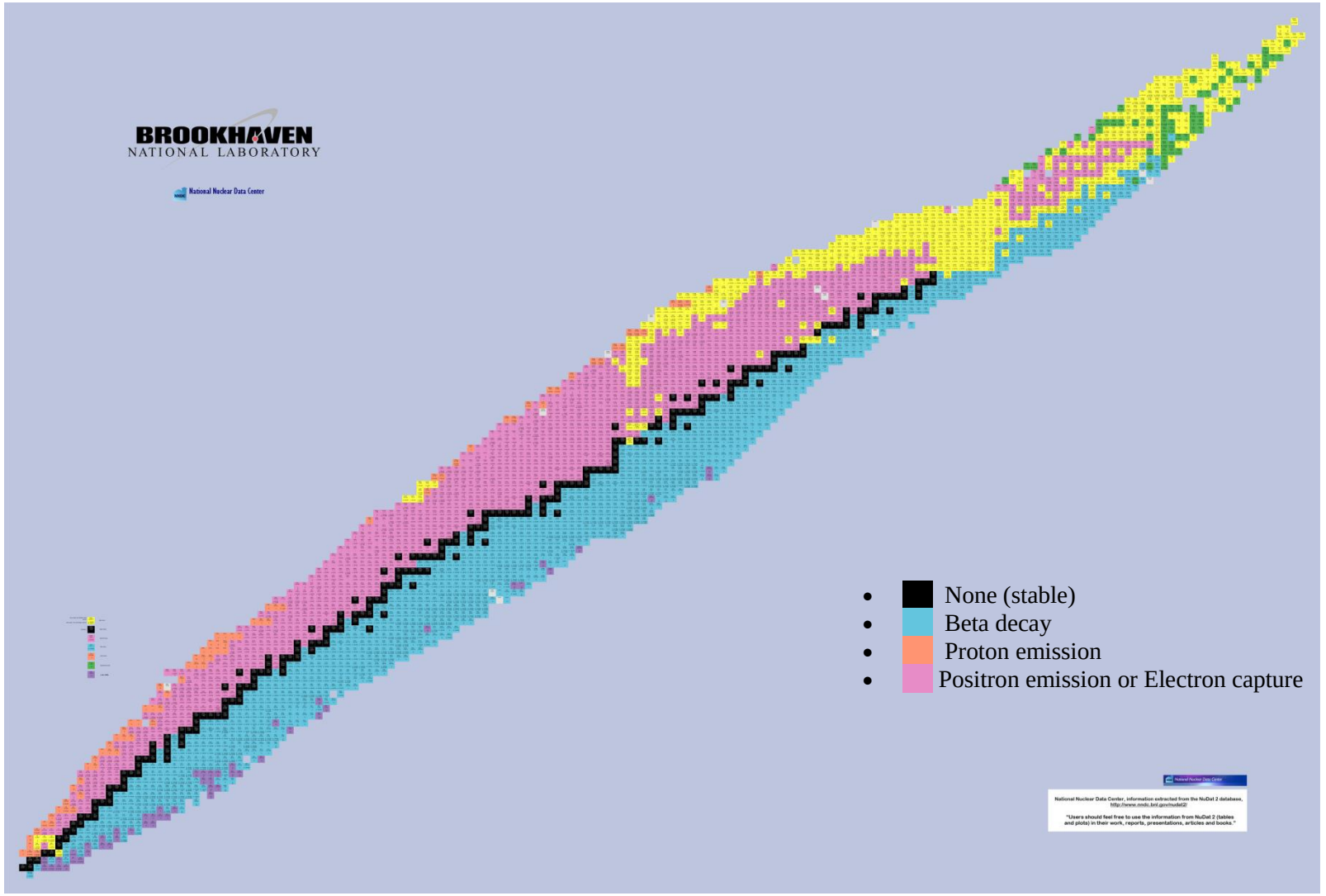


TABLE OF NUCLIDES

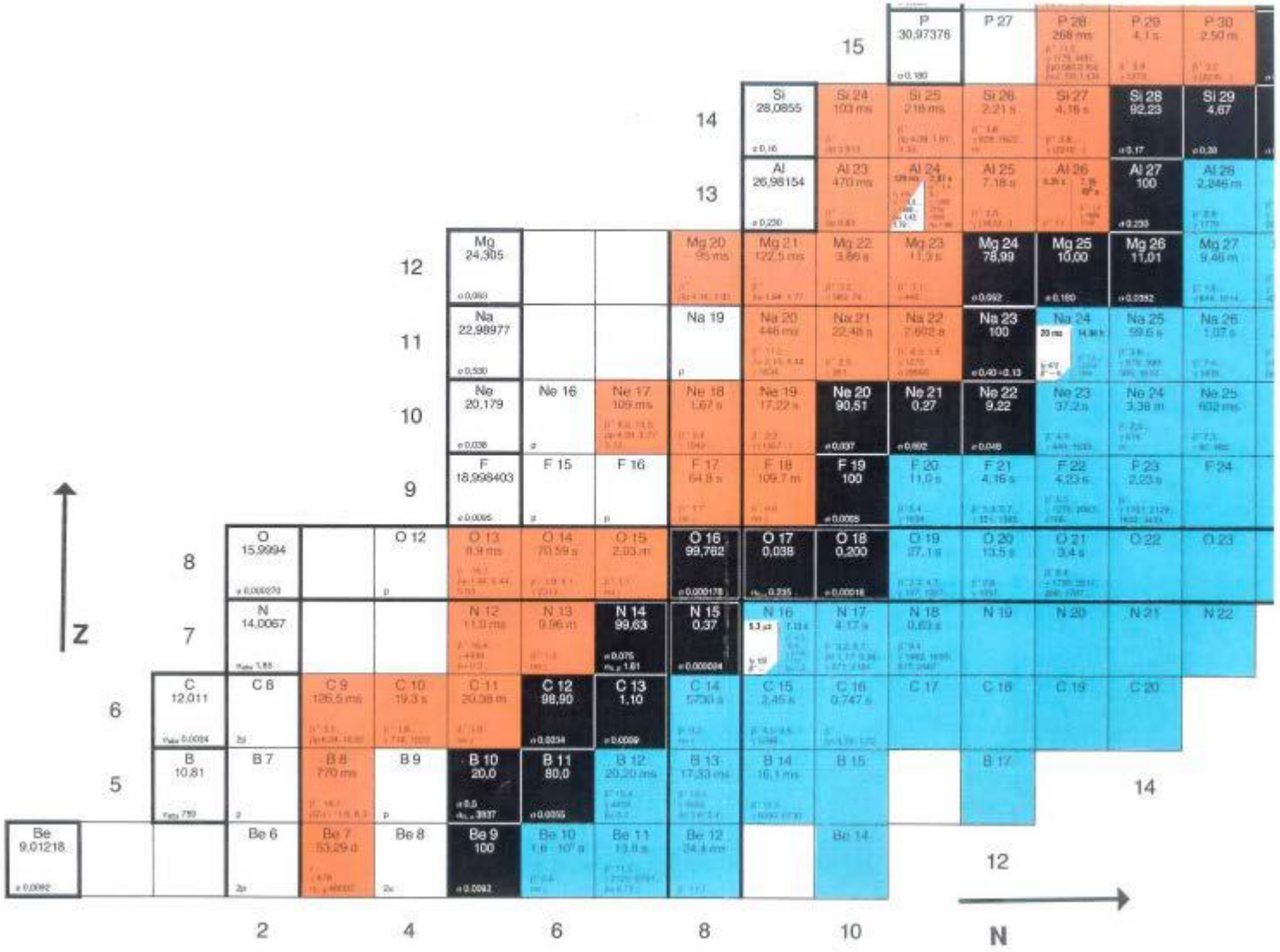
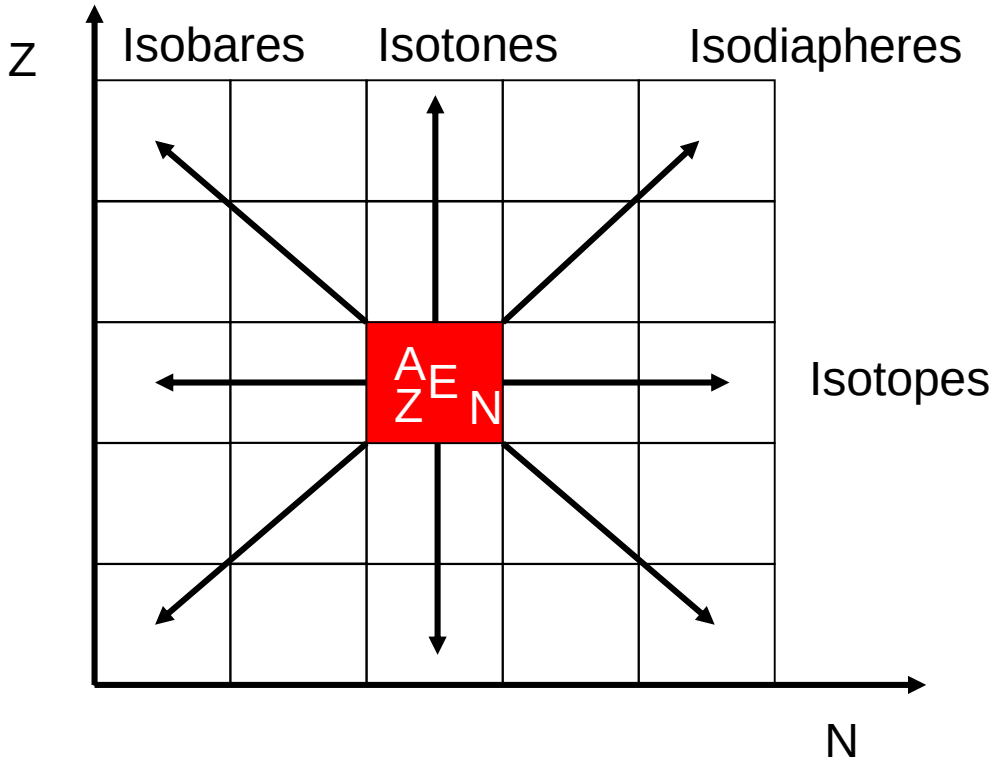
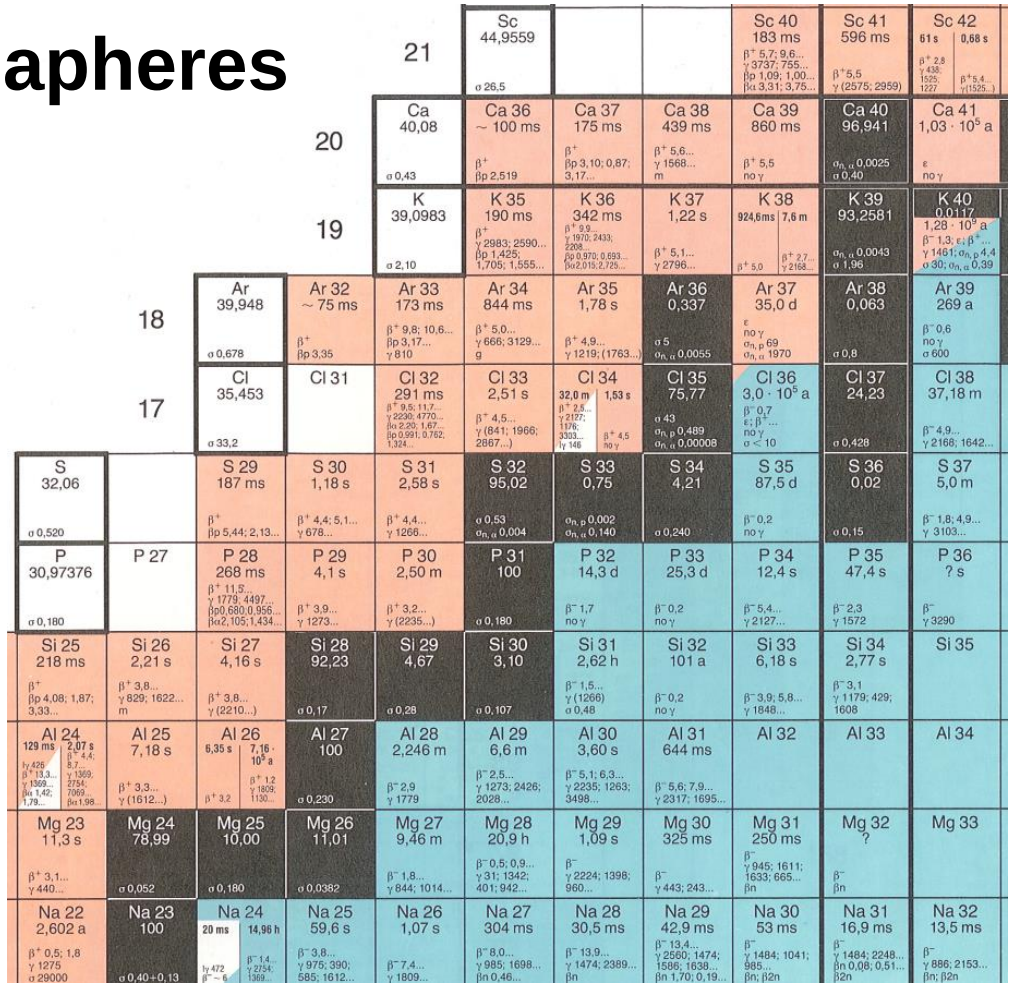


TABLE OF NUCLIDES

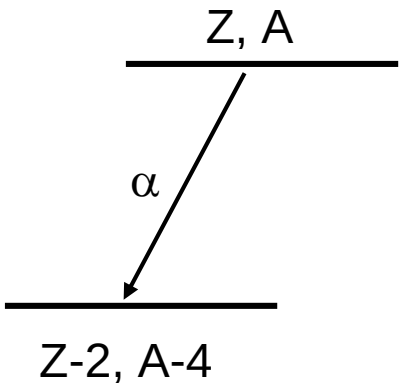
Isotopes, Isotones, Isobares, Isodiapheres

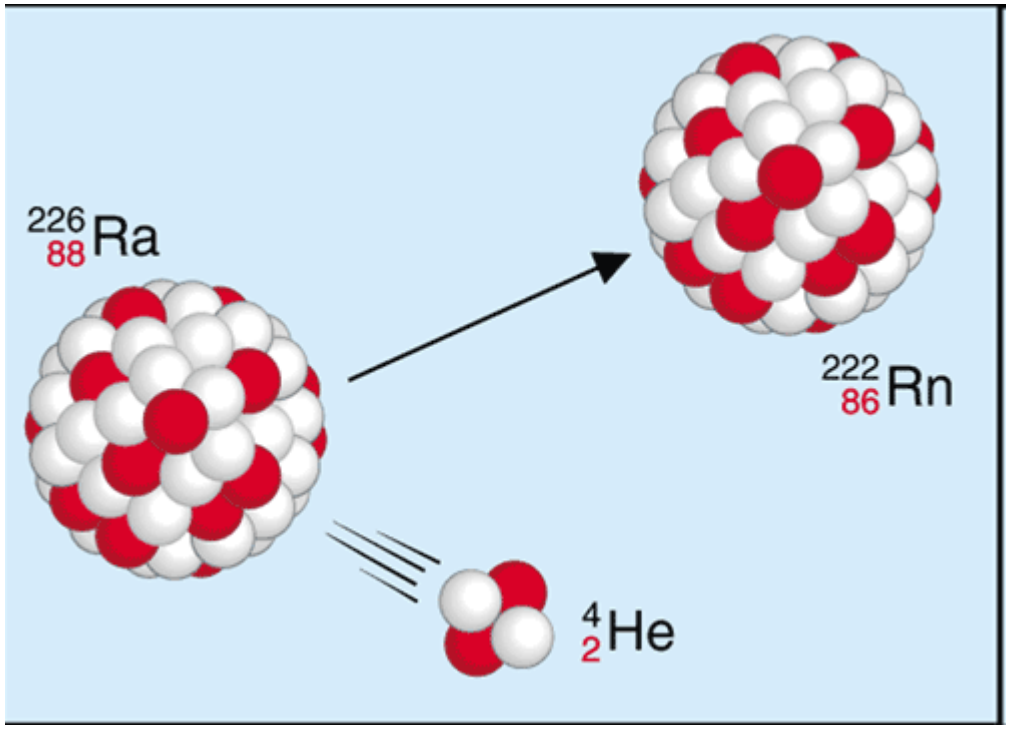




ALPHA-DECAY

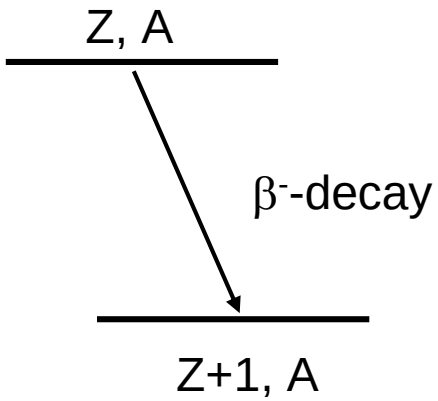
α-Decay

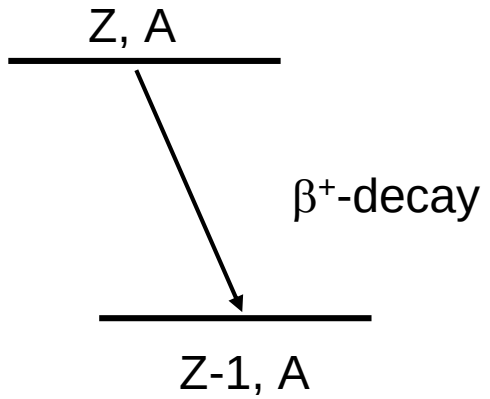




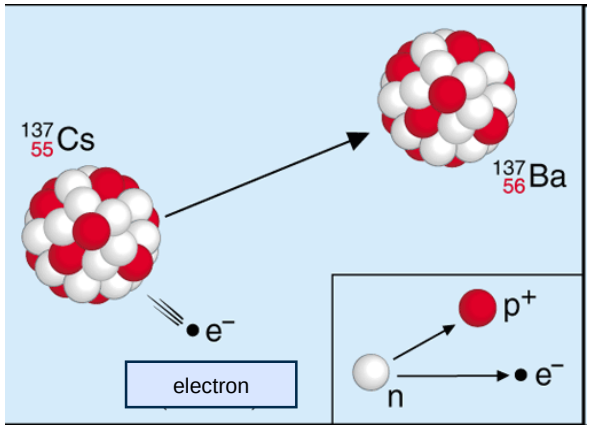
Emission of a doubly charged helium nucleus (2 protons + 2 neutrons, without electrons)
Usually subject to very heavy nuclei that decay

BETA-DECAY

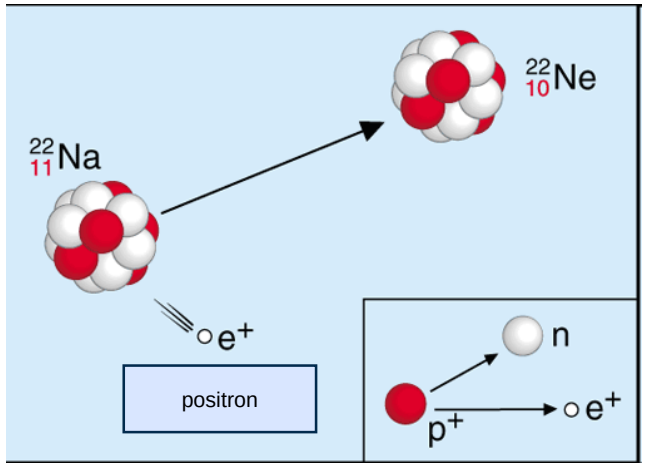




β^--decay: $n \rightarrow p + \beta^- + \bar{\nu}$ (+ antineutrino)



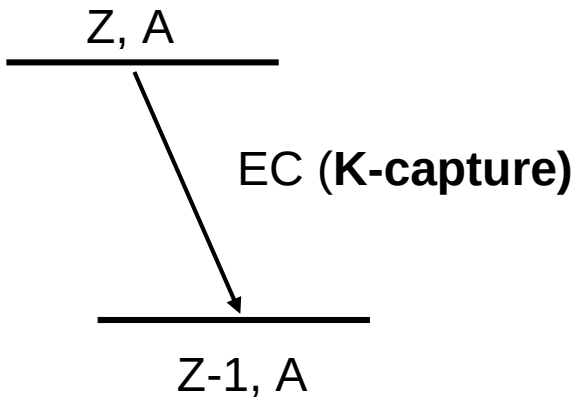
β^+-decay: $p \rightarrow n + \beta^+ + \nu$ (+ neutrino)



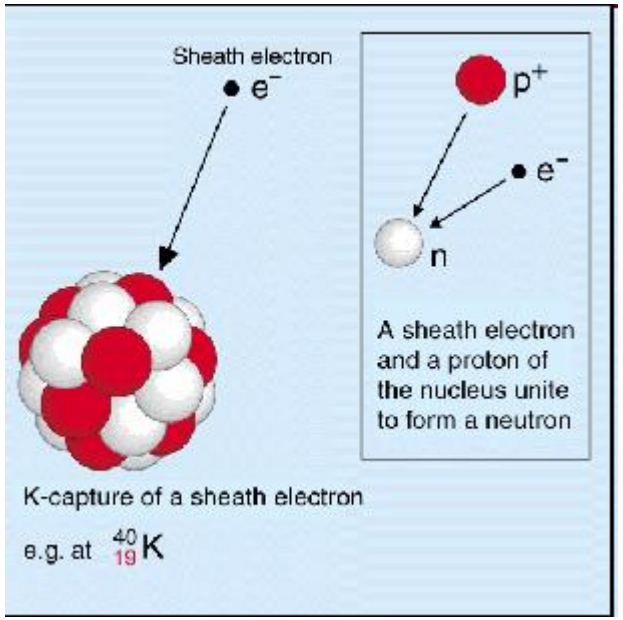
Die β^- radiation is electron radiation

The β^- particles possess variable energies (depending on the radionuclide)

ELECTRON CAPTURE (EC)



$p + e^- \rightarrow n$ (+ neutrino)



The daughter nuclide, if it is in an excited state, then transitions to its ground state.
EC occurs when the proton rich nucleus possesses not sufficient energy for formation of a positron (β+) (< 1022 keV) or if too much energy is released to the neutrinos.
During electron capture, one of the orbital electrons, usually from the K or L shell is captured by a proton in the nucleus, forming a neutron and a neutrino. While falling back to the ground state, the atom will emit an X-ray photon and/or Auger electrons. This happens in any higher shell.

AUGER ELECTRON

- Auger electrons are produced e.g. after an EC, when an outer shell electron receives sufficient kinetic energy (from X-rays) to fly away (internal photo effect).

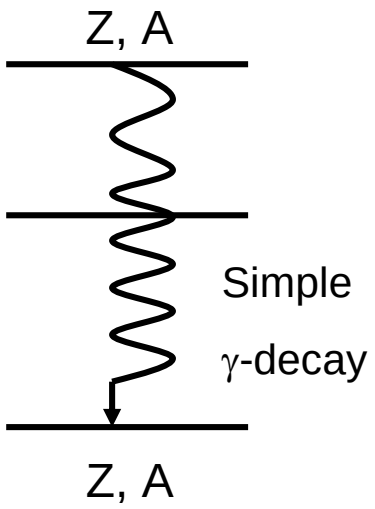
- These electrons have low energies (around 10 keV).

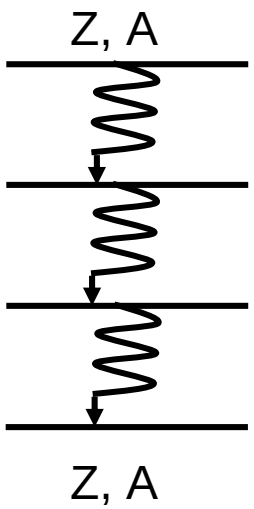
CONVERSION ELECTRONS (INTERNAL CONVERSION - IC)

- The existing energy of the nucleus can directly be transferred from the nucleus to an electron of the innermost shell. This electron then has sufficient energy to fly off at high speed (internal conversion (IC) instead of γ radiation).

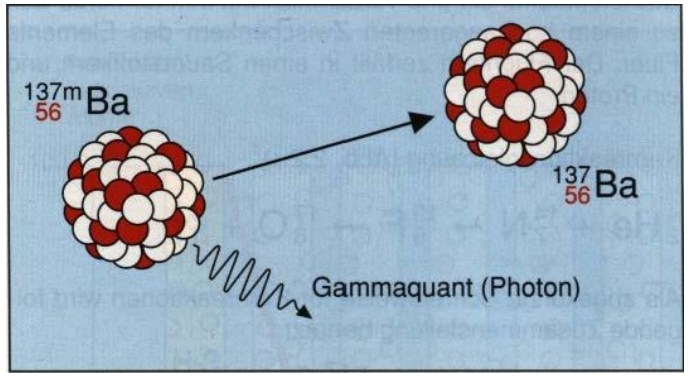
GAMMA-DECAY

γ-Decay





γ-cascade



Side effect: Internal conversion is a radioactive decay process wherein an excited nucleus interacts electromagnetically with one of the orbital electrons of the atom. This causes the electron to be emitted (ejected) from the atom with $E_{e^-}=E_\gamma-E_B$

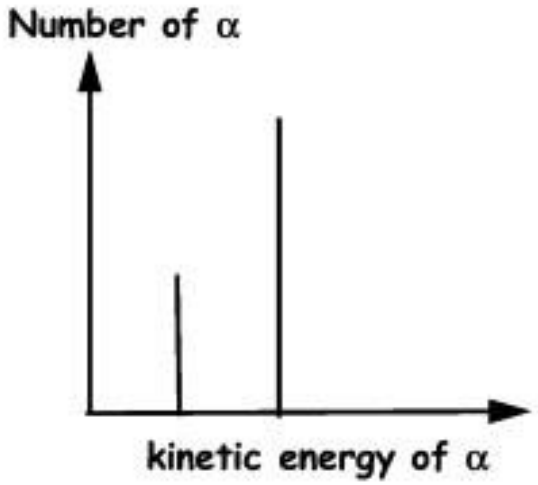
ISOMERIC TRANSITION

After a radioactive decay of the nucleus has sometimes still some residual energy in an excited metastable state. This energy can be released via γ-radiation

Technetium-99m is a metastable nuclear isomer of technetium-99 (itself an isotope of technetium), symbolized as ^{99m}Tc, that is used in tens of millions of medical diagnostic procedures annually, making it the most commonly used medical radioisotope.

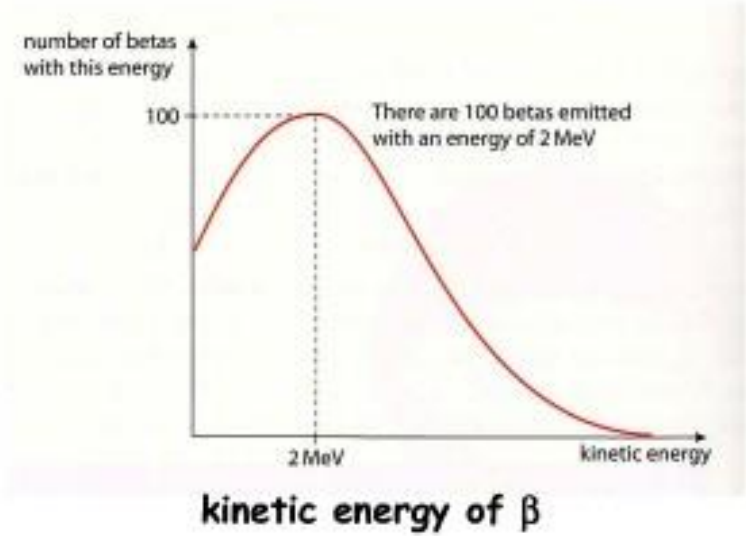
ENERGY DISTRIBUTION

α – radiation



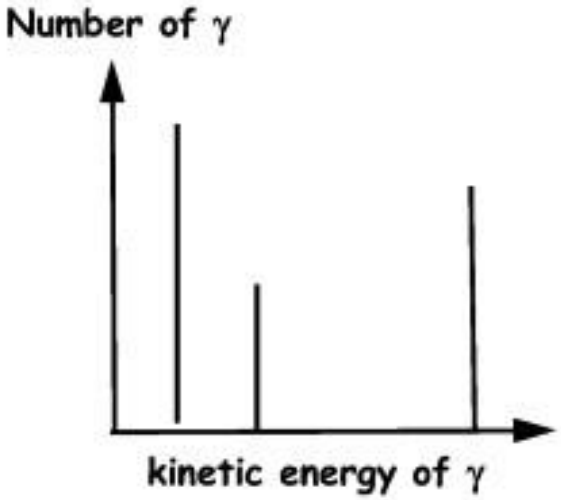
This radiation has constant energy values.

β – radiation



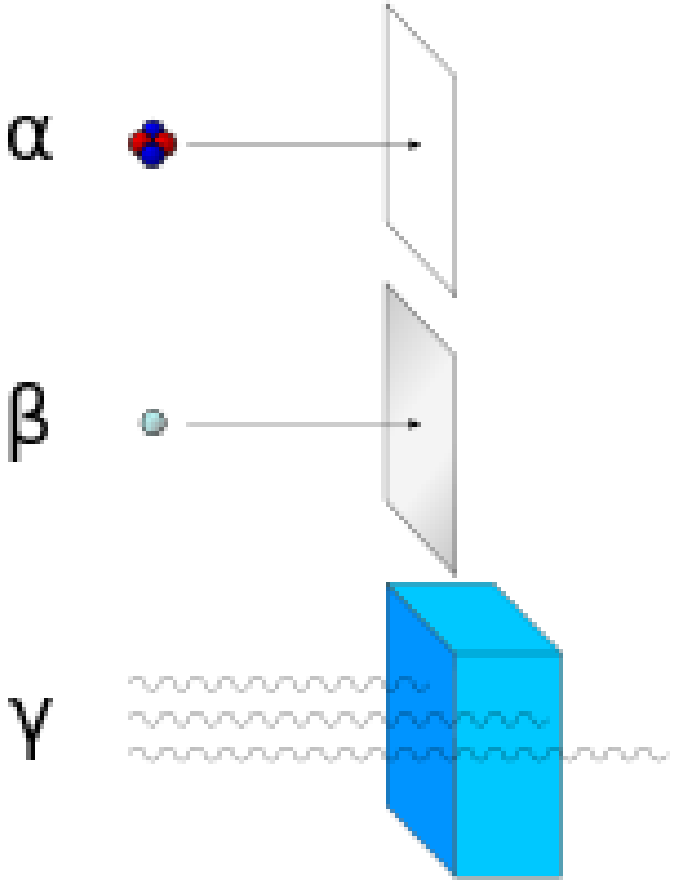
This radiation has not constant energy values because the kinetic energy is shared between the β and the ν.

γ – radiation



This radiation has constant energy values.

RADIOACTIVITY



Alpha particles may be completely stopped by a sheet of paper, beta particles by aluminium shielding. Gamma rays can only be reduced by much more substantial mass, such as a very thick layer of lead.

CHARGED PARTICLES

Charged Particles *continuously interact with electrons and protons in the nucleus via the long-range Coulomb force. Most interactions however are elastic (Rutherford) scattering with atomic electrons*

Charged particles lose kinetic energy via:

- *Excitation*
- *Ionization*
- *Bremsstrahlung*

~ 70% of charged particle energy deposition leads to non-ionizing excitation

LINEAR ENERGY TRANSFER (LET)

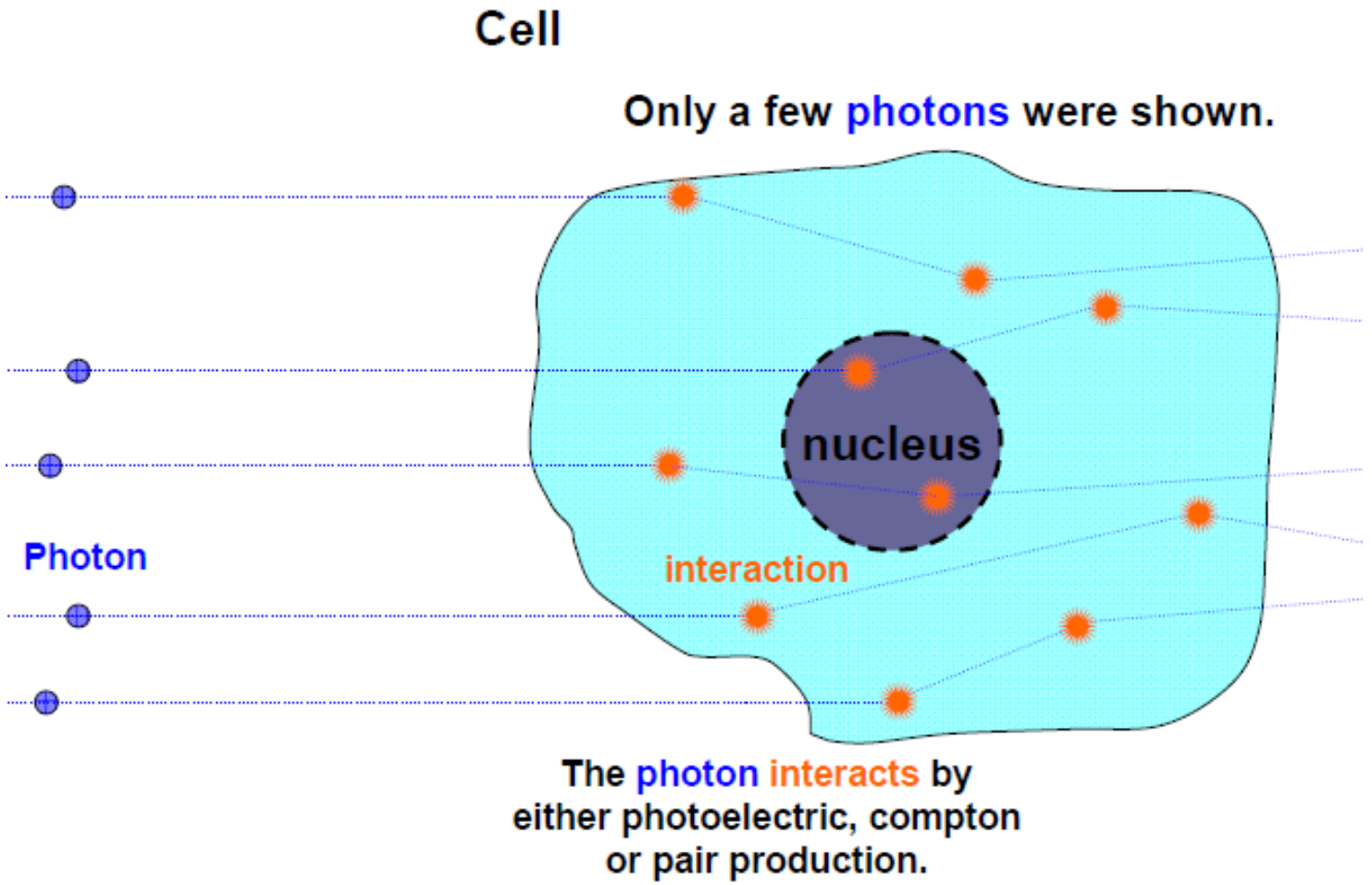
Linear energy transfer (LET) is a measure of the energy transfer for ionizing particles when traveling through matter

$$L_{\Delta} = \frac{dE_{\Delta}}{dx}$$

where dE_{Δ} is the energy loss of the charged particle due to electronic collisions while traversing a distance dx.

LINEAR ENERGY TRANSFER (LET)

Low **LET** radiation

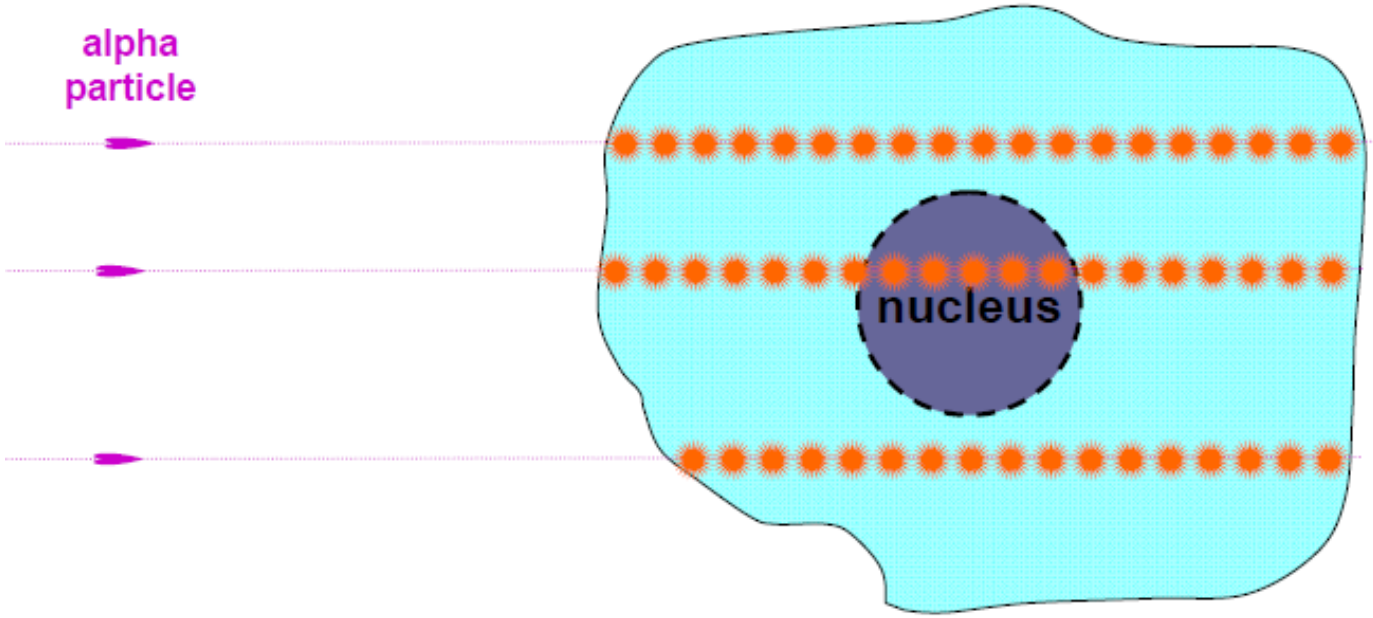


LINEAR ENERGY TRANSFER (LET)

High **LET** radiation

With high LET radiation the particles give rise to well-defined tracks of ionization which cause extensive damage along the path.

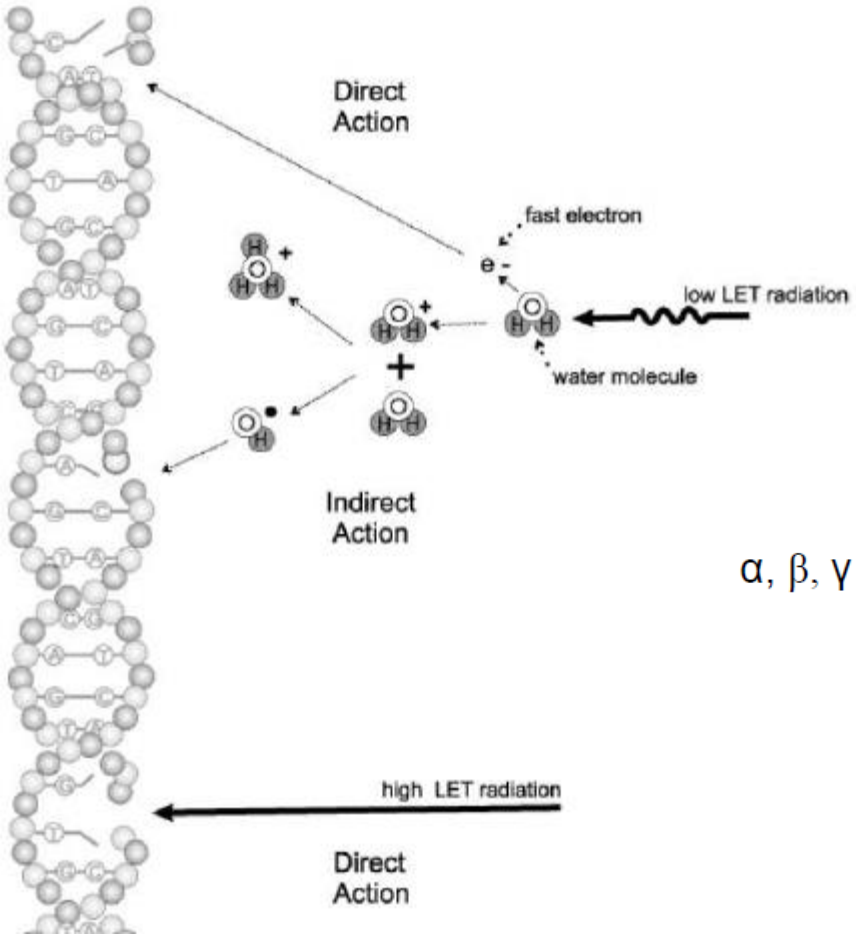
Therefore, it dose not take many high LET particles to kill a cell.

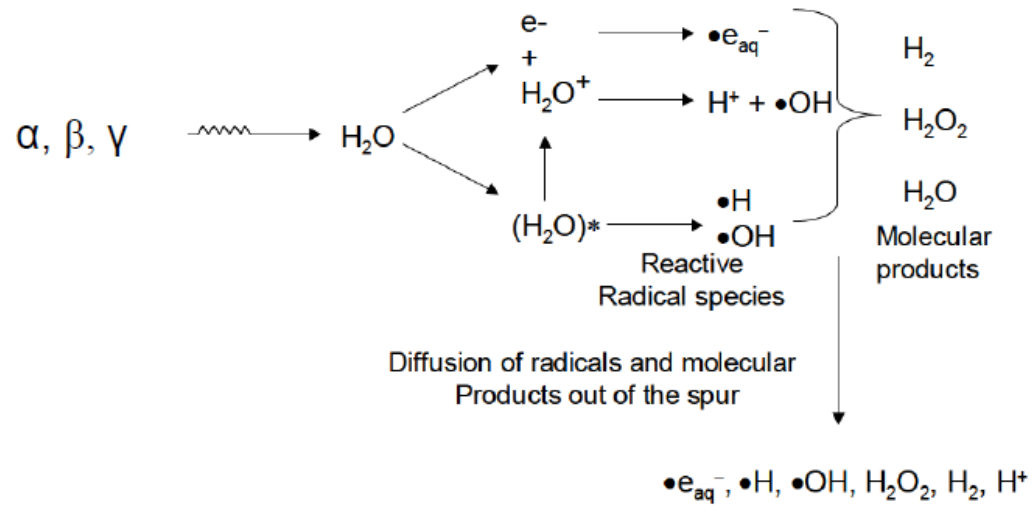


Thus the dose required to kill a cell is smaller as compared to low LET radiation.

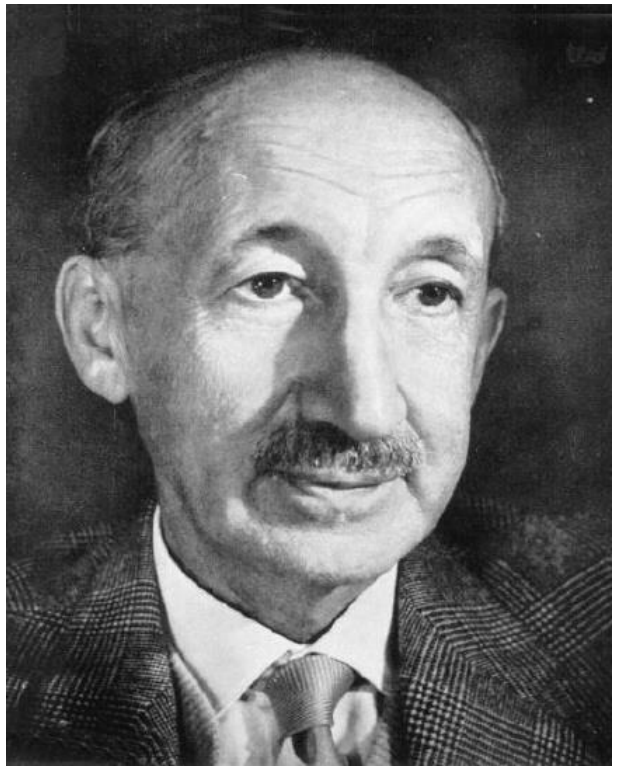
WHAT INDUCES IONIZING RADIATION *IN VIVO*?

1.) Predominantly radiolysis of water
2.) Direct interaction with DNA





RADIOTRACER METHOD



GEORGE DE HEVESY

Some applications of isotopic indicators

Nobel Lecture, December 12, 1944

Hevesy, György

01.08.1885 – 05.06.1966

Chemist

Nobel prize 1943

► **radiotracer principal**

"*Father of nuclear medicine*"

In 1923, he used 10.6 hour lead-212 to study the uptake of solutions in bean plants. He used small, non-toxic amounts of lead given the sensitivity of the radioactivity techniques.
His first experiment in animals used Bi-210 to label and follow the circulation of Bi-containing antisyphilitic drugs in rabbits.

RADIOTRACER METHOD

Radiotracer principal

A radioactive tracer is a chemical compound in which one or more atoms have been replaced by a radioisotope.
It is applied in minimal amounts, therefore, it has no pharmacologic effect in vivo. It can also be used to explore the mechanism of bio-/chemical reactions by tracing the path that the radioisotope follows from reactant to product.

SPECIFIC ACTIVITY

$$A = \lambda \cdot N$$

A = activity
λ = decay constant
N = number of atoms

$$n = \frac{N}{N_L}$$

$$A = \lambda \cdot n \cdot N_L \text{ (*)}$$

$$m = n \cdot M \qquad n = \frac{m}{M}$$

m = mass
M = molmass

add in *:

$$m = \frac{A \cdot M}{N_L \cdot \lambda}$$

$$m \propto \frac{1}{\lambda} \qquad m \propto t_{1/2}$$

Short half-life = low mass

Molar activity (IUPAC)
For a specified *isotope*, the *activity* of the compound divided by the amount of the material in moles: *A*m = *A*/*n*.

SPECIFIC ACTIVITY

Radiosyntheses can be classified as

• carrier-free (c.f.)

The absolute lack of a carrier is ideally only achieved when artificial radioelements (e.g. astatine) are used and the presence of longer-lived radioisotopes of the element can be excluded.

• no-carrier-added (n.c.a.)

When performing labelling reactions with cyclotron-produced radioisotopes of natural-occuring elements, traces of stable isotopes of these elements are omnipresent and act as isotopic carriers, provided that they are in the same chemical state. Possible sources of such contaminations are the air, target and reaction vessels, chemicals and solvents.

• carrier-added (c.a.)

Under several circumstances, weighable quantities of the natural-occuring element are added to the system in order to increase the radiochemical yield or even to make certain labelling methods possible.

DEFINITIONS

Def.: *in vivo* - in the living organism

In vivo means, literally, "in life"; a biologic or biochemical process occurring within a living organism.

Refers to biological processes that take place within a living organism or cell
Studies carried out in living organisms

Def.: *in vitro* - in an artificial environment outside the living organism

Studies performed outside a living organism such as in a laboratory.

STRENGTH OF RADIOTRACER METHOD

- wide range of application and easy handling.
- High detection sensitivity (amol = 10^{-18}).
- Absolute Quantification of the starting activity via several chemical transformations.
- Detection of secondary products (metabolites), which are not identified yet.

LOWER DETECTION LIMIT

Isotope	Detection limit [mol]	Number of atoms
^{14}C	40×10^{-12}	2×10^{13}
^{3}H	1×10^{-15}	6×10^{8}
^{35}S	18×10^{-18}	1×10^{7}
^{125}I	12×10^{-18}	7×10^{6}
^{32}P	3×10^{-18}	2×10^{6}
^{131}I	2×10^{-18}	1×10^{6}

Method	Detection limit [mol]	Number of atoms
chemiluminescence	0.5×10^{-18}	3×10^{5}
fluorescence	0.25×10^{-18}	1.5×10^{5}
Immuno PCR	1×10^{-21}	600
LCR-MS	8×10^{-14}	5×10^{10}

MEASUREMENT OF RADIOACTIVITY

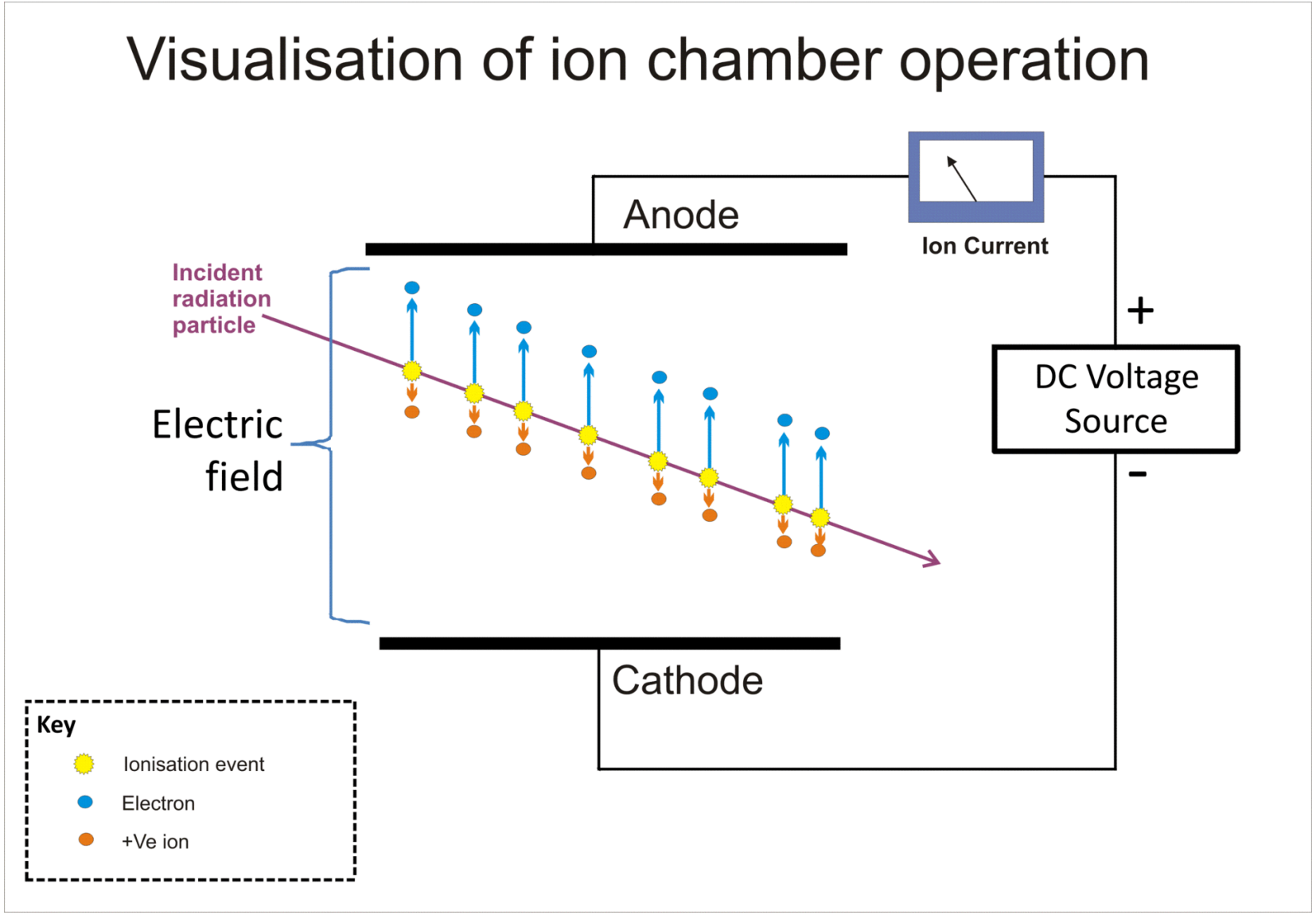
I. Ionisation chamber
(Gas-filled tube counters e.g. the Geiger Müller Counter)

II. Scintillation counter
a) anorganic Szintillation counter NaI(Tl)
b) organic Szintillation counter (liquid, solid)

III. Semi-conductor Detectors

IV. Film, Phosphor Screen

IONISATION CHAMBER

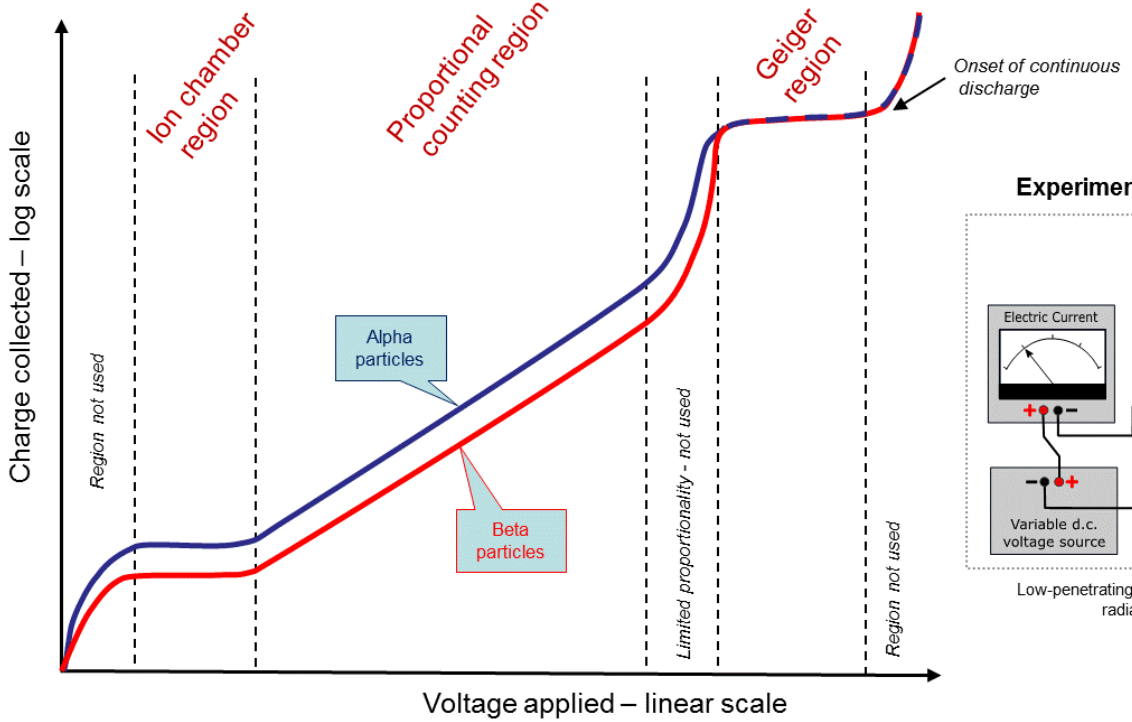


IONISATION CHAMBER

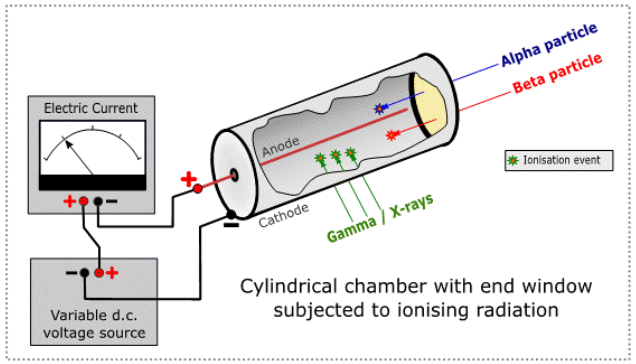
Practical Gaseous Ionisation Detection Regions

This diagram shows the relationship of the gaseous detection regions, using an experimental concept of applying a varying voltage to a cylindrical chamber which is subjected to ionising radiation. Alpha and beta particles are plotted to demonstrate the effect of different ionising energies, but the same principle extends to all forms of ionising radiation.
The ion chamber and proportional regions can operate at atmospheric pressure, and their output varies with radiation energy. However, in practice the Geiger region is operated at a reduced pressure (about 1/10th of an atmosphere) to allow operation at much lower voltages; otherwise impractically high voltages would be required. The Geiger region output does not differentiate between radiation energies.

Variation of ion pair charge with applied voltage



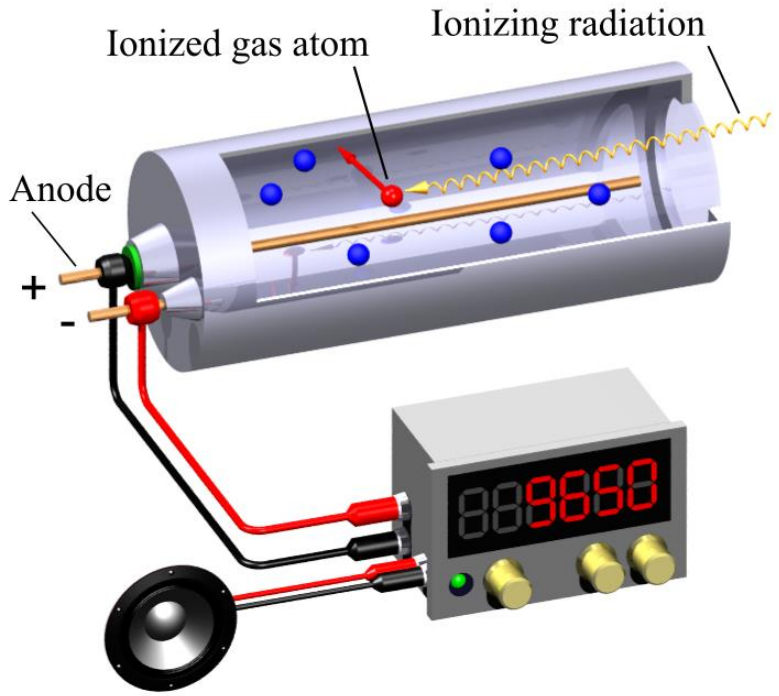
Experimental set-up of a cylindrical chamber



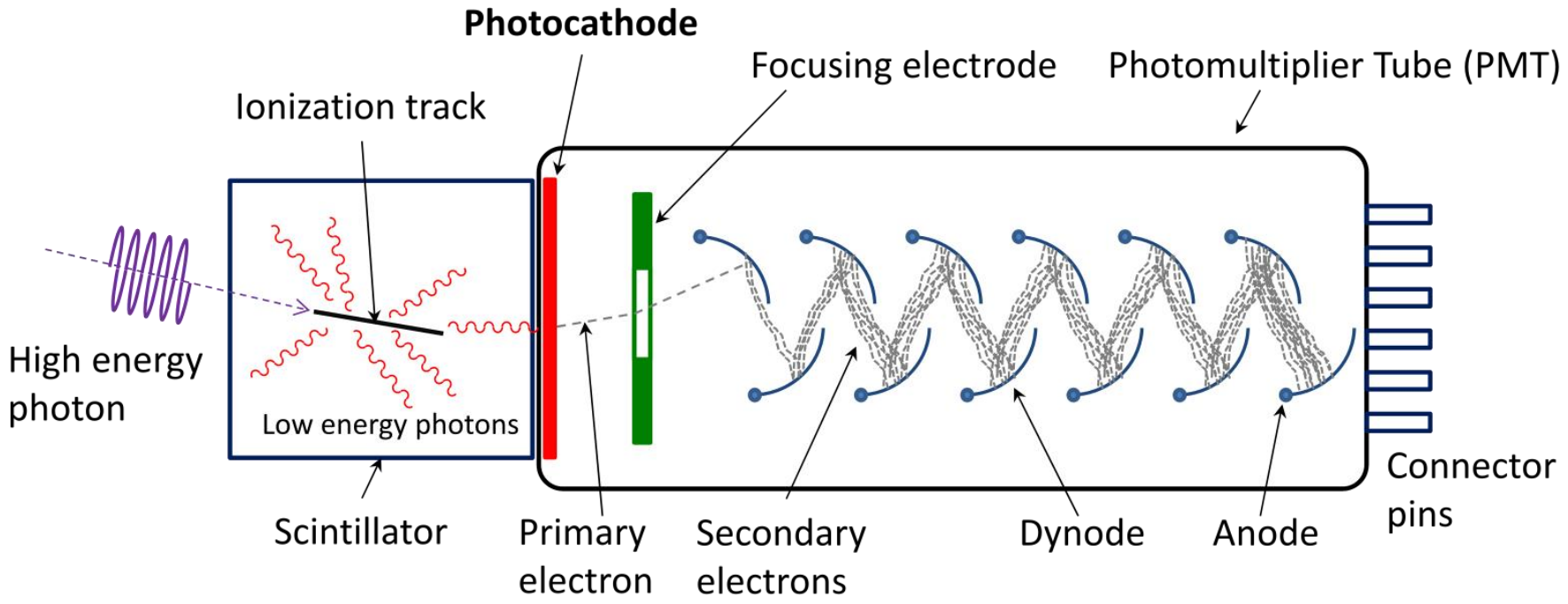
Low-penetrating radiation enters via an end window, but high-penetrating radiation can also enter via the cylinder side wall.

IONISATION CHAMBER

The Geiger Müller Counter:
A potential difference just below that required to produce a discharge is applied to the tube (1000 V).
Any atoms of the gas struck by the γ-rays entering the tube are ionized, causing a discharge.
Discharges are monitored and counted by electronic circuitry.



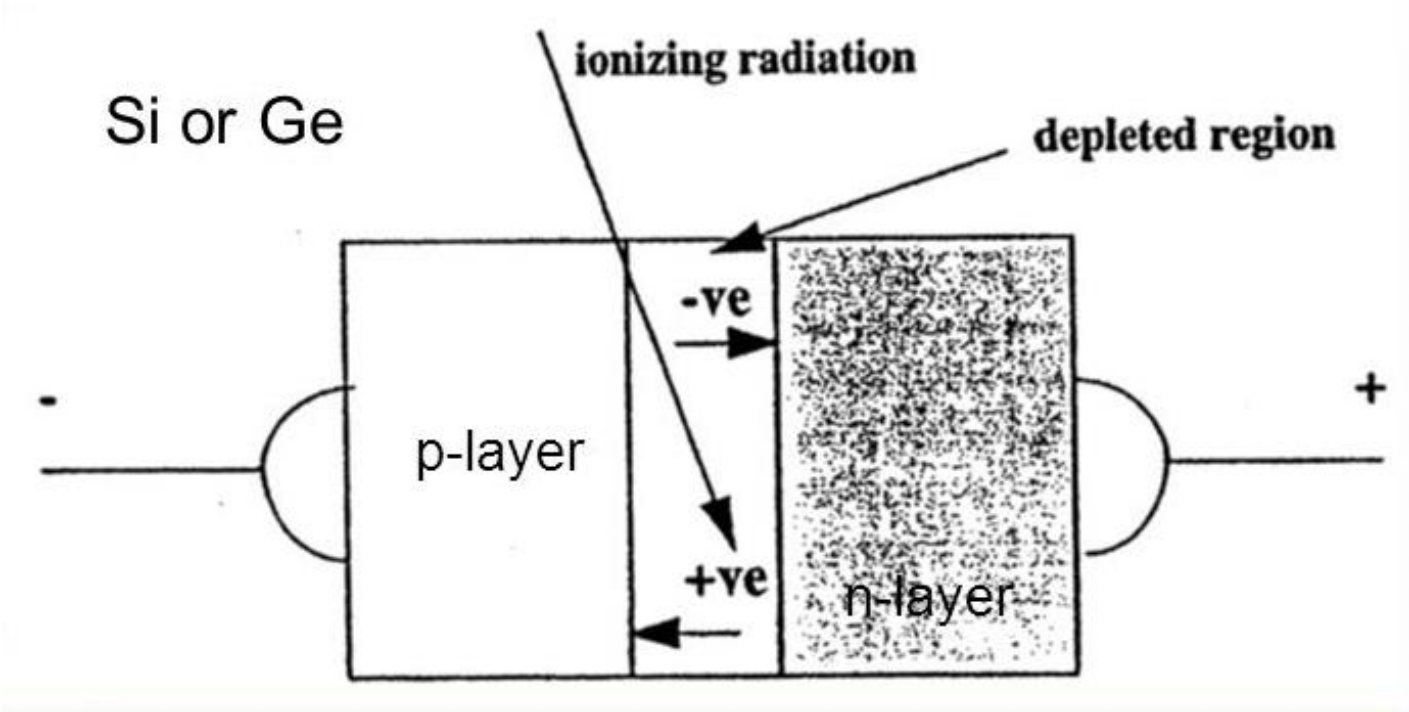
SCINTILLATION COUNTER



Crystals of certain substances e.g. caesium fluoride, cadmium tungstate, anthracene and sodium iodide emit small flashes of light when bombarded by γ-rays. The most commonly used phosphor in scintillation counters is NaI with a minute quantity of thallium added. In the instrument, the crystal is positioned against a photocell which in turn is linked to a recording unit. The number of flashes produced per unit time is proportional to the intensity of radiation.

SEMI-CONDUCTOR DETECTORS

A semi-conductor is a substance whose electrical conductivity is between that of a metal and an insulator. It is noted that Ge(Li) semi-conductors ate excellent detectors of γ-rays with a resolution ten times higher than NaI (Th) scintillometers. The main disadvantage of these is a lower efficiency for higher energy x-rays. Besides, Ge(Li) semi-conductors need to be cooled by liquid nitrogen and are hence cumbersome and not suitable as field instruments.



DEFINITIONS

Molecular imaging is a discipline at the intersection of molecular biology and *in vivo* imaging. It enables the visualization of the cellular function and the follow-up of the molecular process in living organisms while minimally perturbing them (non-invasive imaging). It is recognized as one of the important technologies in the drug development process and personalized medicine in the future.

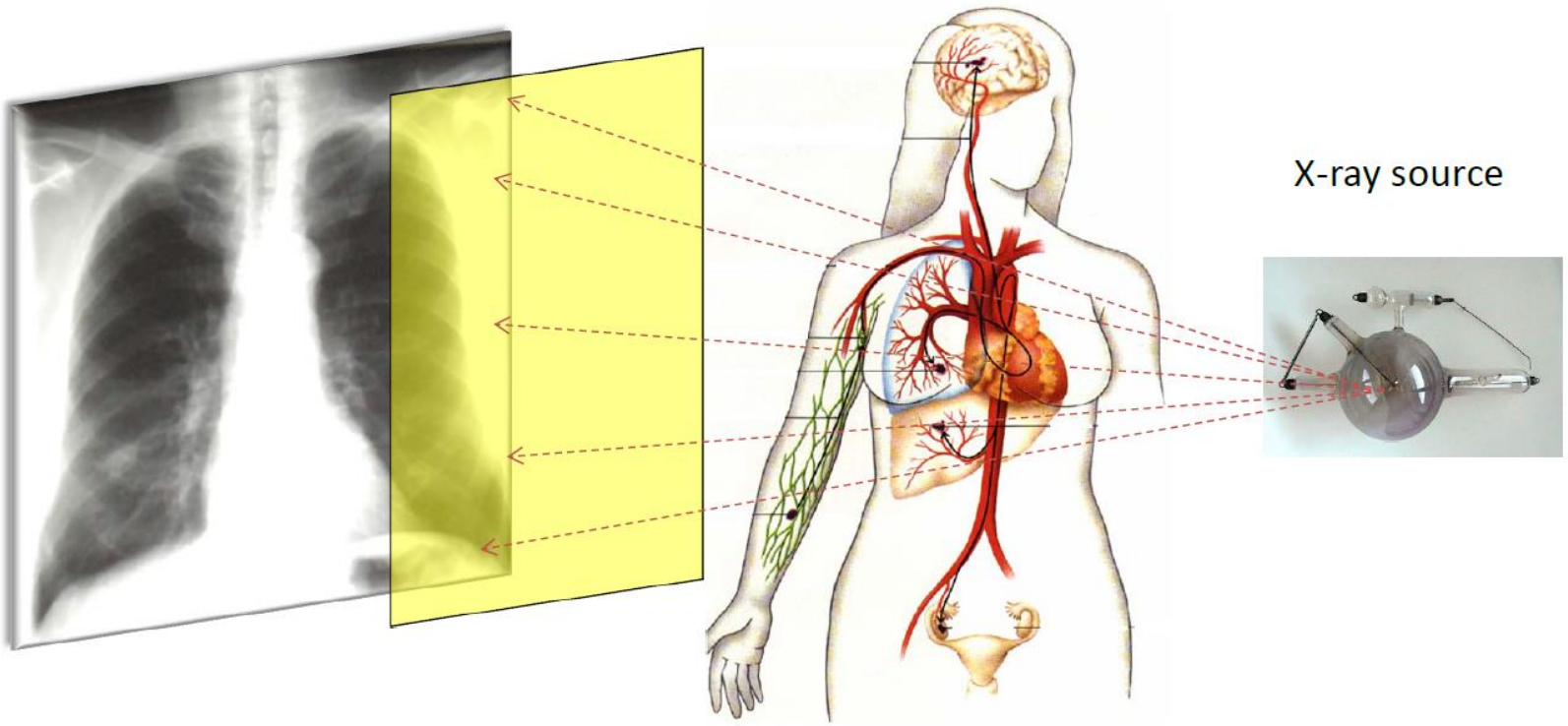
A radiopharmaceutical is a radioactive compound used for the diagnosis and/or therapeutic treatment of human diseases.

Diagnostic radiopharmaceuticals allow to non-invasive understanding of the fundamental molecular events inside an organism

Therapeutic radiopharmaceuticals allow the destruction of (cancer) cell inside an organism

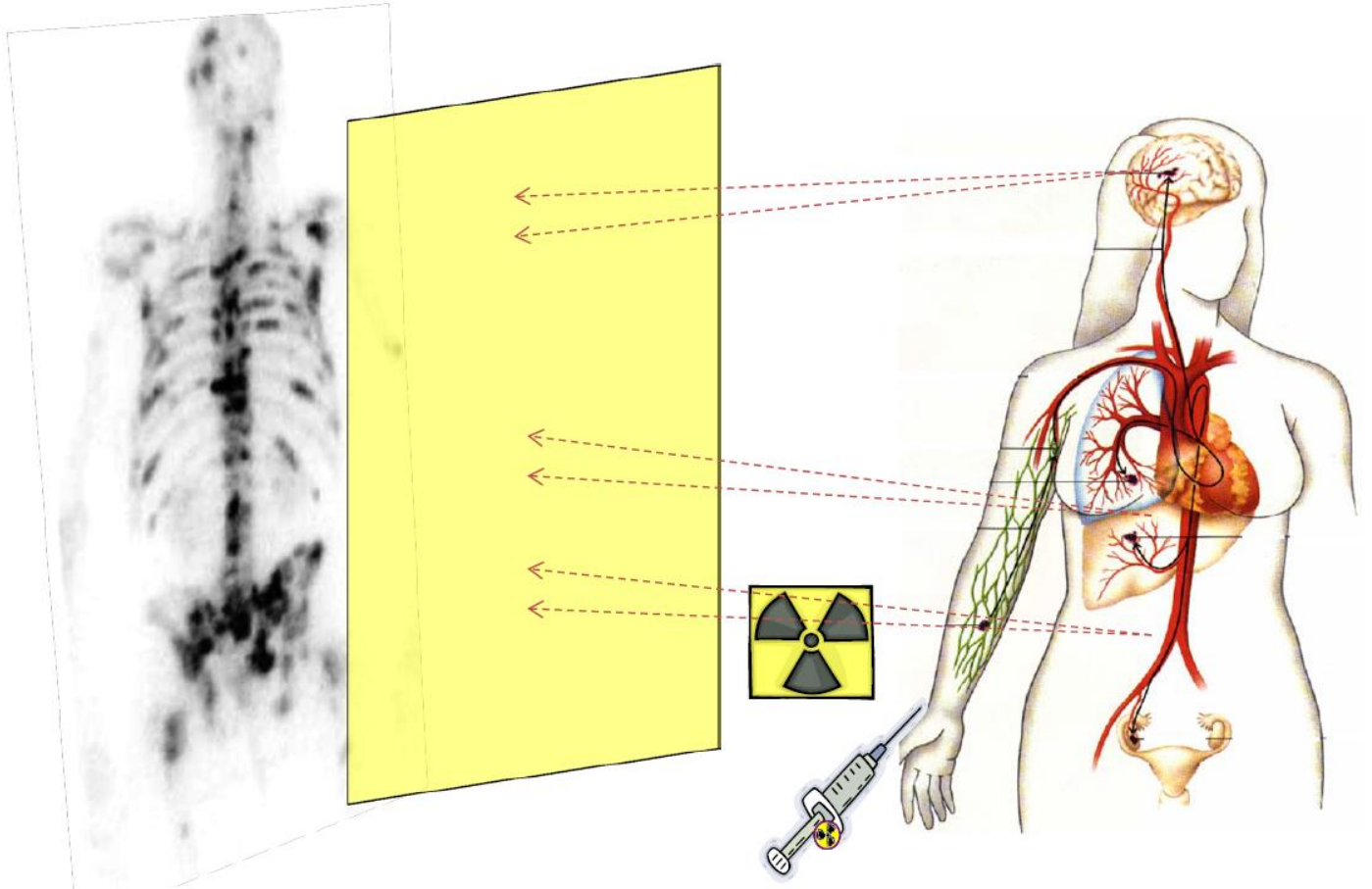
~95 % of radiophamaceuticals are used for diagnostic purposes

PRINCIPLE OF X-RAY & CT



Courtesy of R. Schibli, ETH Zürich

PRINCIPLE OF SCINTIGRAPHY



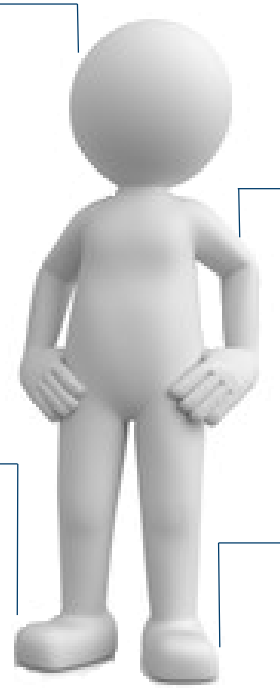
Courtesy of R. Schibli, ETH Zürich

MOLECULAR IMAGING - WHY?

AIM:

Non-invasive elucidation of disease specific biochemical-, molecular-, physiological- and pathological processes

Evaluation of molecular response



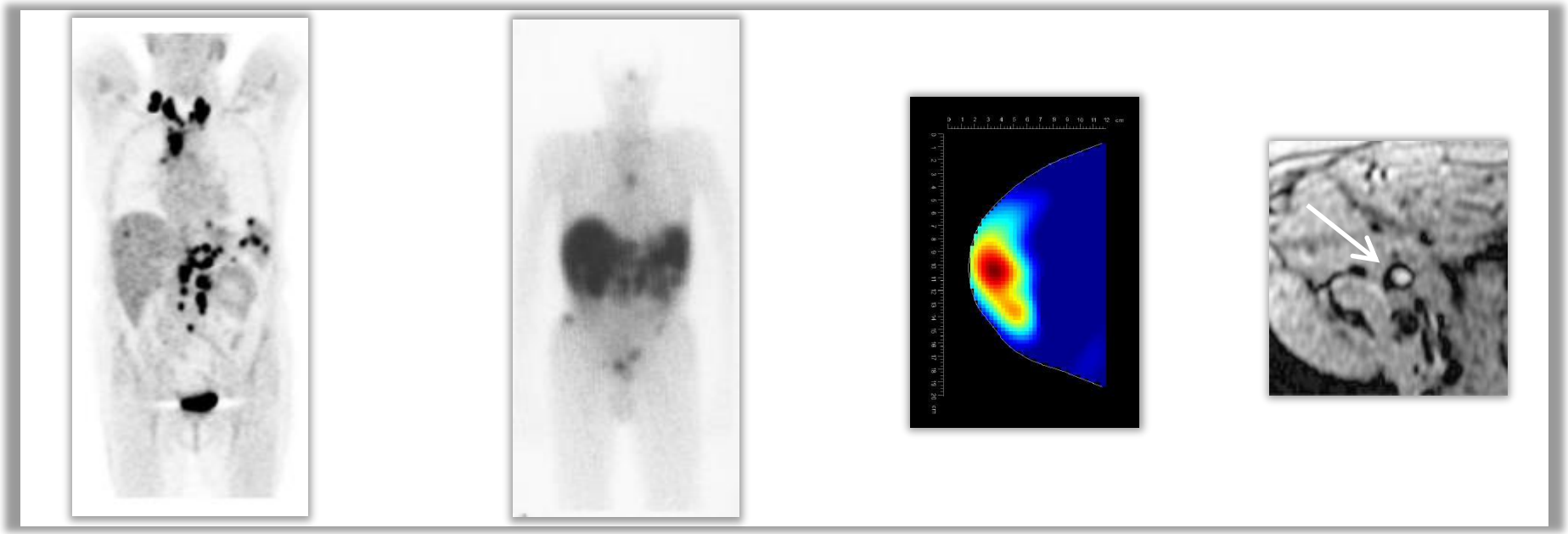
Disease detection as early as possible

Patient stratification – optimal and individual therapy for each patient

Monitoring of therapy efficacy

MOLECULAR IMAGING: DEFINITION AND EXAMPLES

„*In-vivo*-characterization of biological processes at the molecular level“



PET
Positron **E**mission **T**omography
(NHL;[^{18}F]FDG)

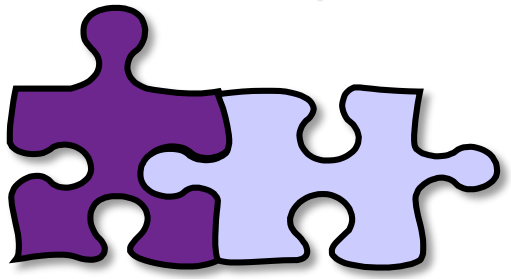
SPECT
Single **P**hoton **E**mission **C**omputed **T**omography
(NET; ^{111}In-DTPA-Octreotid)

Softscan
NIR Fluorescence Imager
(Breast cancer; DeoxyHb)

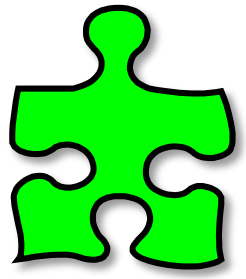
MR
Magnetic **R**esonance
(PCa, lymph node metastasis; Sinerem NT)

PRINCIPLE OF MOLECULAR IMAGING

Targeting molecule
(Vehicle)



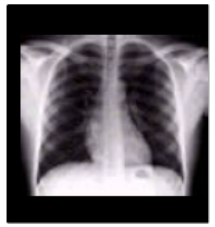
Reporter
(Radionuclide,
fluorescent dye or
magnetic label)



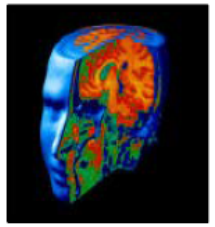
Biological targets

PRINCIPLE OF SCINTIGRAPHY

Imaging Method	Spatial resolution	Sensitivity
Ultrasound	50 µm	10^{-3} Mol
CT	50 µm	10^{-3} Mol
MRI	100 µm	10^{-5} Mol
Bioluminescent	1-3 mm (depth!)	10^{-8} Mol
Nuclear*	***~ 1mm***	***10^{-9}-10^{-12} Mol***



Morphology



Function

Positron **E**mission **T**omography - ***PET***

Single **P**hoton **E**mission **T**omography - ***SPET*** (3D); Scintigraphy (2D)

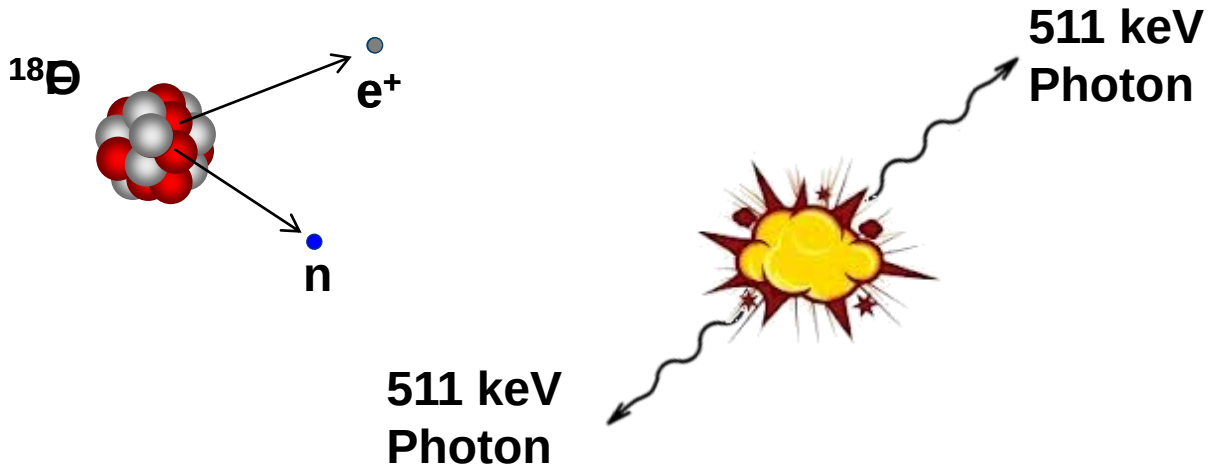
Courtesy of R. Schibli, ETH Zürich

WHAT IS SPECT?

- Single-photon emission computed tomography (SPECT, or less commonly, SPET) is a nuclear medicine tomographic imaging technique using gamma rays.
- It is very similar to conventional nuclear medicine planar imaging using a gamma camera. However, it is able to provide true 3D information.

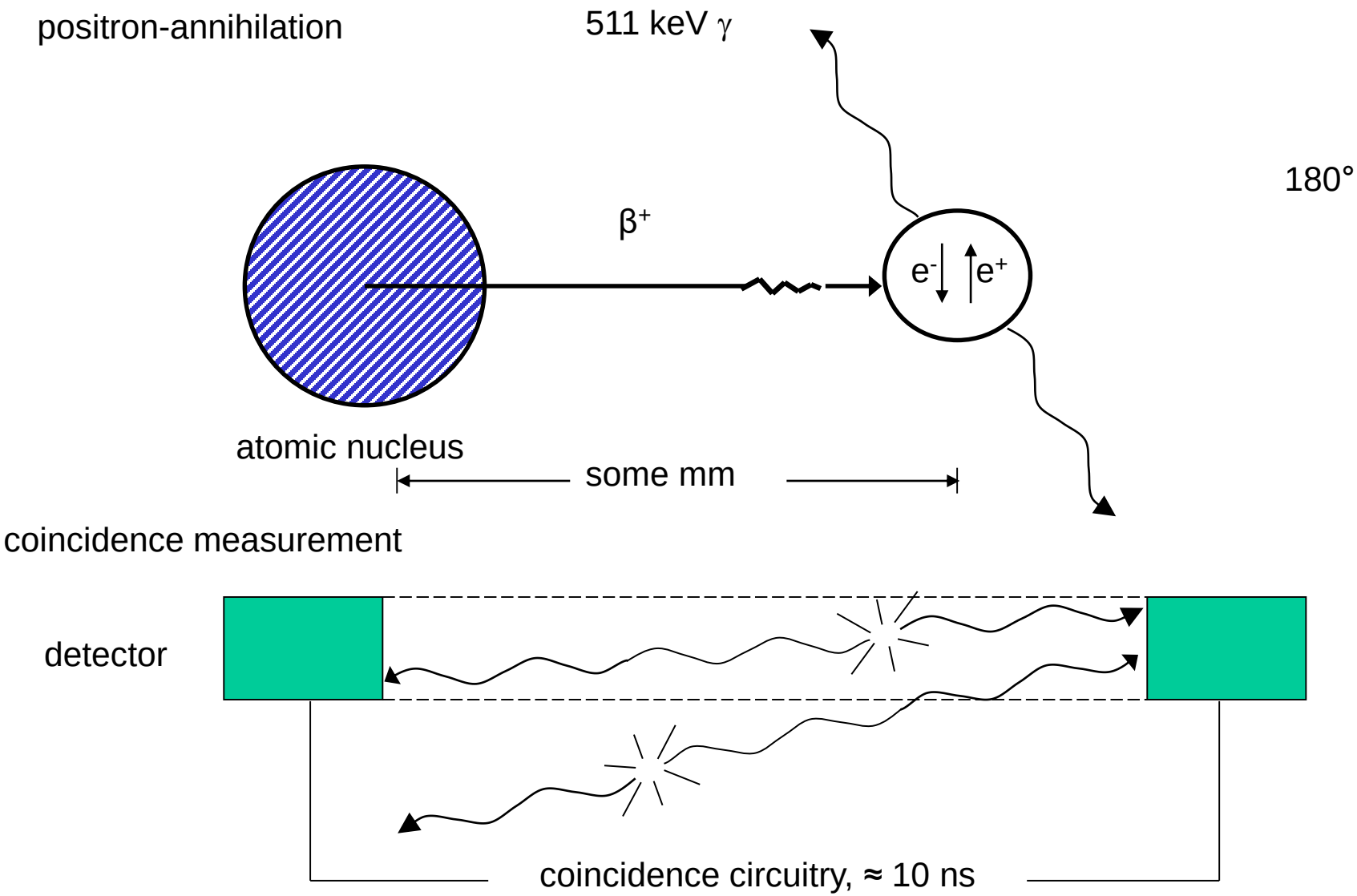
PET: PHYSICAL BACKGROUND

POSITRON DECAY AND POSITRON-ELECTRON-ANNIHILATION (E.G. FOR ^{18}F)



- Emission of an positron as a result of β^+ decay
- Positron is thermalized and undergoes recombination with electron
- Conversion of mass into energy by $E = m \cdot c^2$
- Emission of two annihilation photons in opposite directions (180°)

POSITRON EMISSION TOMOGRAPHY (PET)



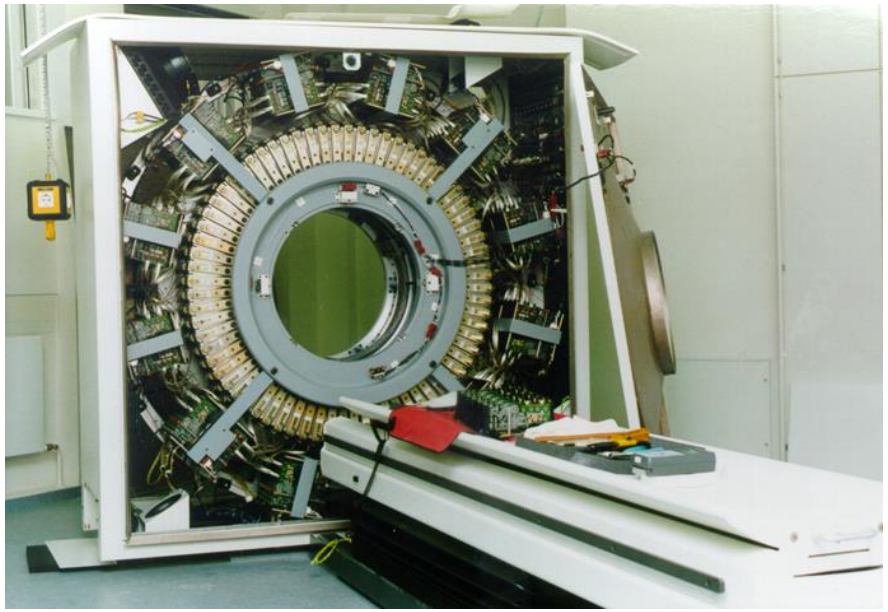
POSITRON EMISSION TOMOGRAPHY (PET)

- imaging on the molecular level without pharmacodynamic interference
- quantitation of concentrations and metabolic rates

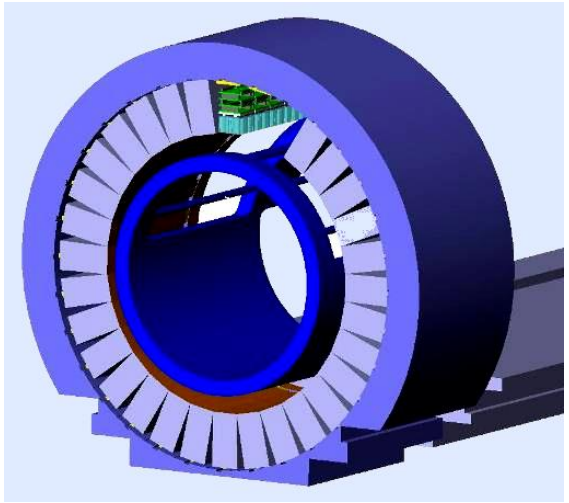
  (bio-mathemathical model)
- resolution
    - temporal: seconds to minutes
    - spatial: 5 mm (standard)

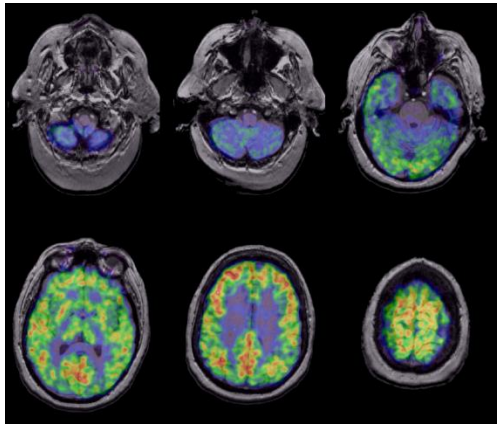
POSITRON EMISSION TOMOGRAPHY (PET)

After injecting the radiopharmaceutical, the patient is placed on a special moveable bed, which slides by remote control into the circular opening of the scanner (called **gantry**). Placed around this opening, and inside the gantry, there are several rings of **radiation detectors**. Each crystal detector emits a brief pulse of light every time it is struck with a gamma ray coming from the radioisotope within the patient's body. The pulse of light is amplified (increased in intensity), by a **photomultiplier**, and the information is sent to the computer which controls the apparatus. The whole process is called **scintigraphy** (from scintillation, which is the pulse of light).



MR-PET HYBRID SYSTEM - SIEMENS-3T-TRIO





Use of photo diodes
instead of photomultipliers

SPECT OR PET?

	SPECT	PET
Resolution	Lower resolution with clinical SPECT camera (10–15 mm)	Good resolution with clinical PET camera (5–7 mm)
Sensitivity	Lower-sensitivity detection	Higher-sensitivity detection
Quantification	Not allowed	Allowed
Half-life	Some SPECT-nuclides (e.g., ^{99m}Tc and 6 h) have a very practical half-life for a wide range of applications	Most of the PET-nuclides have (very) short half-lives, these allows only for investigations of biological processes on the order of minutes or a few hours
Production	The routinely applied SPECT nuclide is a generator nuclide (^{99}Mo/^{99m}Tc Generator)	The routinely applied PET nuclide ^{18}F has to be produced by a clinical cyclotron
Costs	Relatively low (e.g., bone scan with ^{99m}Tc, ~ $3 per procedure)	Relatively high (e.g. [^{18}F]FDG scan, ~ $300 per procedure)

R. Alberto, H. Braband, in *Comprehensive Inorganic Chemistry II (Second Edition): From Elements to Applications, Vol. 3, 2013, pp. 785.*

CONTENT

- Radionuclides for Nuclear Medicine
- Sources of radionuclides
- Development of Radionuclide production
- Nuclear Data

RADIONUCLIDES FOR NUCLEAR MEDICINE

Diagnostic Radionuclides

For SPECT

γ-emitters (100 – 250 keV)

^{99m}Tc, ^{123}I, ^{201}Tl

- **For PET**

  β^+ emitters

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

  ^{68}Ga, ^{82}Rb

Therapeutic Radionuclides (*in vivo*)

- β^--emitters (^{67}Cu, ^{90}Y, ^{131}I, ^{153}Sm, ^{177}Lu)
- α-emitters (^{211}At, ^{223}Ra, ^{225}Ac, etc.)
- Auger electron emitters (^{51}Cr, ^{75}Se, ^{77}Br, ^{125}I, ^{193m}Pt)

CRITERIA FOR *IN VIVO* APPLICATION OF RADIOTRACERS

Diagnostics:

- no α- or β^--emitters (γ- or β^+-emitter)
- suitable half-life
- suitable detection

Therapeutics

- α-emitter
- β^--emitter
- Auger emitter

CRITERIA FOR *IN VIVO* APPLICATION OF RADIOTRACERS

The choice of the appropriate radioisotope for nuclear imaging is dictated by the physical characteristics of the radioisotope:

- a suitable physical half-life; long enough for monitoring the physiological organ functions to be studied, but not too long to avoid long term radiation effects

- decay via photo emission (X-ray or γ-ray) to minimize absorption effects in body tissue

- photon must have sufficient energy to penetrate body tissue with minimal attenuation

- but photon must have sufficiently low energy to be registered efficiently in detector and to allow the efficient use of lead collimator systems (must be absorbed in lead)

- decay product (daughter) should have minimal short-lived activity

CYCLOTRON PRODUCED „ORGANIC“ POSITRON EMITTING NUCLIDES

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

*refers to molar activity at the end of synthesis

ADVANTAGES OF SHORT-LIVED RADIONUCLIDES

short half-life = small mass

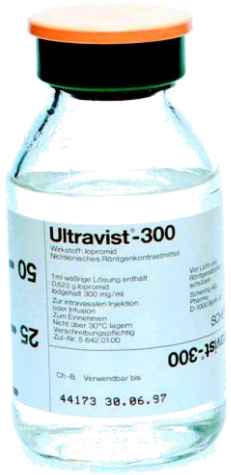
$$N^* = A / \lambda = A \cdot T_{1/2} / \ln 2$$

	molar activity (GBq / µmol)	
	theor.	**prac.**
^{15}O ($t_{1/2}$ = 2.1 min)	3.4×10^6	-
^{11}C ($t_{1/2}$ = 20.4 min)	3.4×10^5	100
^{18}F ($t_{1/2}$ = 109.7 min)	6.3×10^4	150

carbon-11
- short study intervals possible
- authentic labelling

fluorine-18
- extended syntheses and studies
- monovalent, covalent chemistry

PET- TRACERS NEED VERY VERY LOW MASS DOSES...



X-ray CM (Ultravist)
100 ml (77 g Iopromide)
77 000 000 µg

MRI (Magnevist)
10 ml (4.7 g Gd-DTPA)
4 700 000 µg

FDG-PET

0.08 µg

Courtesy of M. Bräutigam, Schering AG

SOURCES OF RADIONUCLIDES

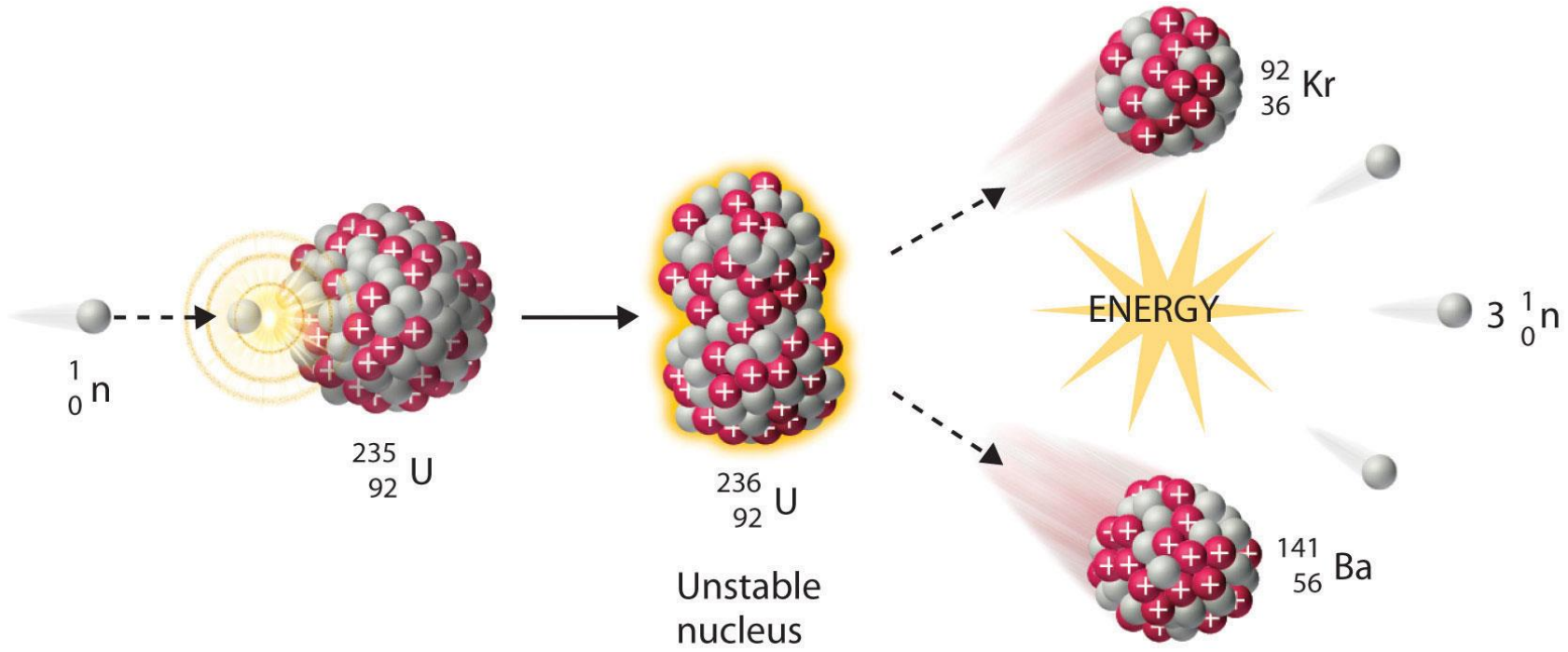
- nuclear fission (nuclear reactor)
- neutron activation processes
- charged particle induced reactions (cyclotron)
- radionuclide generator (chemical method)

Each method provides useful isotopes with differing characteristics for nuclear imaging.

The production of radioisotopes is expensive!

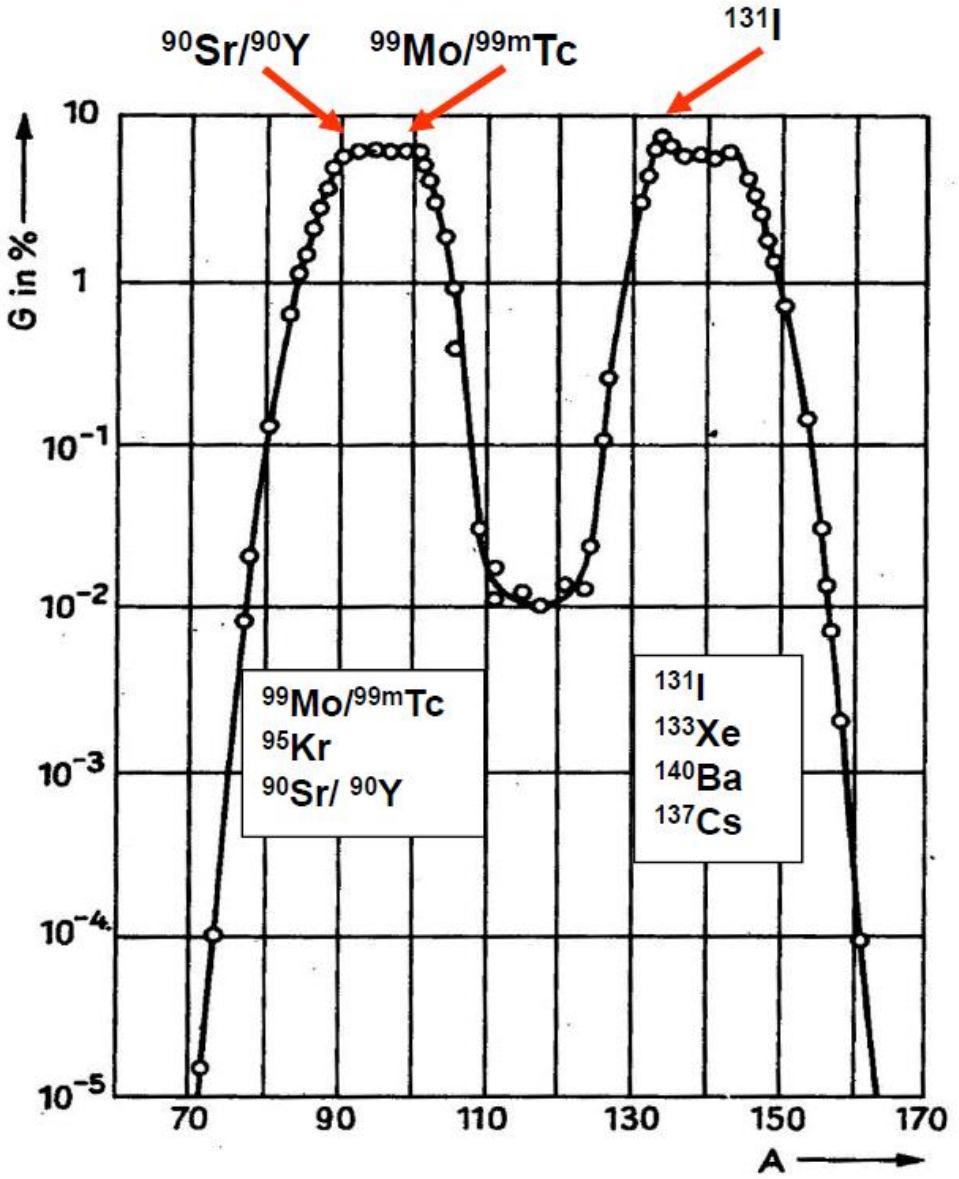
NUCLEAR FISSION

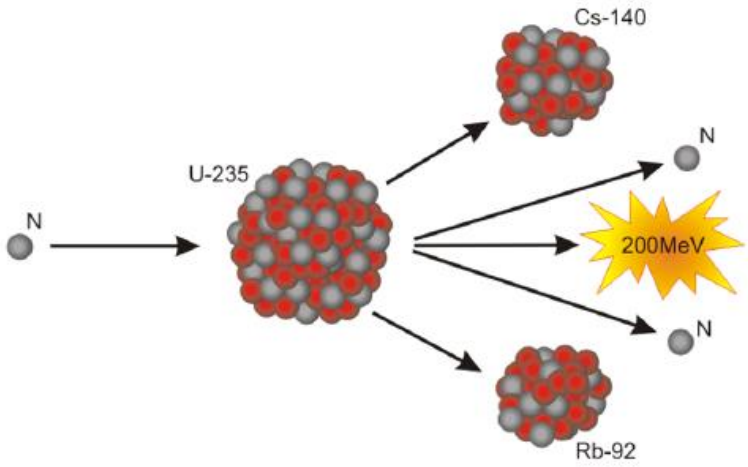
Nuclear fission is a nuclear reaction in which the nucleus of an atom splits into smaller parts (lighter nuclei). The fission process often produces free neutrons and gamma photons, and releases a very large amount of energy even by the energetic standards of radioactive decay.



The most common radioisotopes produced by fission (with subsequent isotope separation based on different physical and chemical methods) are ^{99}Mo (which decays to ^{99m}Tc) and ^{131}I!

NUCLEAR FISSION





Fission yield of ^{235}U bombarded with thermal neutrons → base for production of n-rich RNs

NEUTRON ACTIVATION

Neutron Activation is based on capture reactions of thermal neutrons (produced in the reactor as consequence of the fission process) on stable isotopes which are positioned near the reactor core.

Examples for radioisotope production via neutron capture are:

- $^{98}Mo + n \rightarrow {}^{99}Mo + \gamma$
- $^{50}Cr + n \rightarrow {}^{51}Cr + \gamma$
- $^{31}P + n \rightarrow {}^{32}P + \gamma$
- $^{32}S + n \rightarrow {}^{32}P + p$

Disadvantage is that the produced radioisotope is typically an isotope of the target element, therefore chemical separation is not possible. This means that the (n,γ) produced radionuclide are not carrier-free.

PRINCIPLES OF A GENERATOR

- A generator is constructed on the principle of the decay-growth relationship between a long-lived parent radionuclide and its short-lived daughter radionuclide.
- The chemical property of the daughter nuclide must be distinctly different from that of the parent nuclide so that the former can be readily separated
- In a generator, basically a long-lived parent nuclide is allowed to decay to its short-lived daughter nuclide and the latter is then chemically separated.

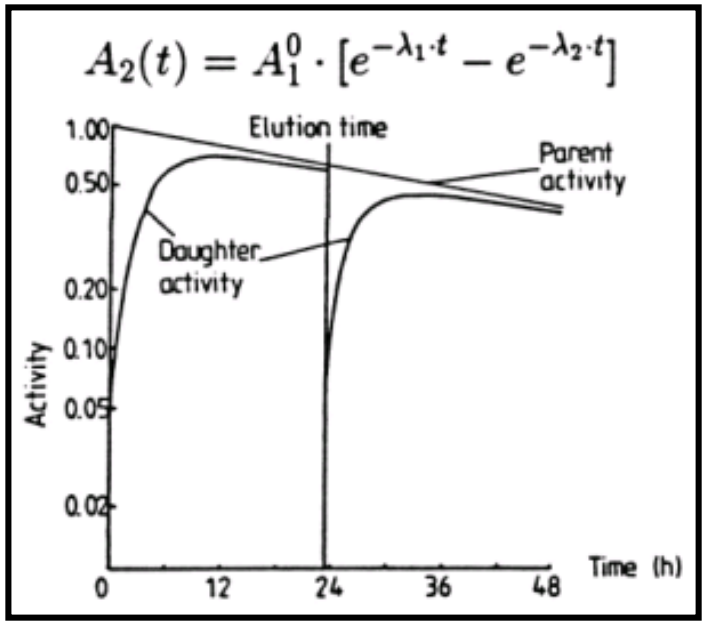
Advantages

1. Easily transportable
2. Serve as sources of short-lived radionuclides in institutions far from the site of a cyclotron or reactor facility

PRINCIPLES OF A GENERATOR

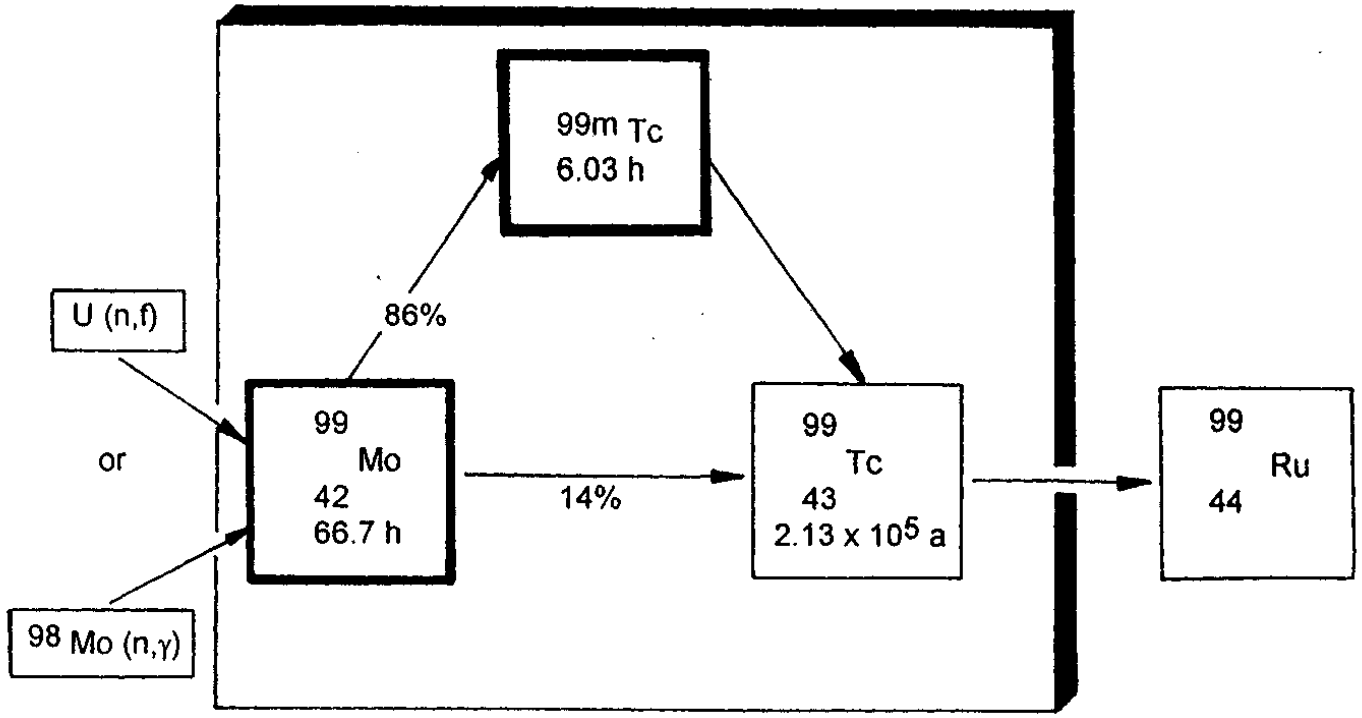
This method is in particular applied for the separation of the rather short-lived ^{99m}Tc ($T_{1/2}$=6 h) from the long lived ^{99}Mo ($T_{1/2}$=2.7 d).

Applying the radioactive decay law the growth of activity of the daughter nuclei A_2 with respect of the initial activity of the mother nucleus A_1^0 can be expressed in terms of their respective decay constants λ_2 and λ_2 with $\lambda_2 >> \lambda_1$:



Milking cow analogy

TECHNETIUM-99m



TECHNETIUM-99m

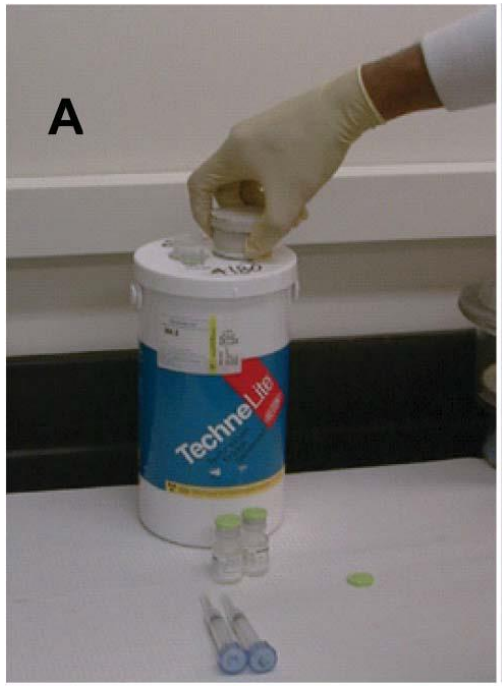
A technetium generator comprises a lead pot enclosing a glass tube containing the radioisotopes. The glass tube contains molybdenum-99 that decays to technetium-99 (half-life of 6 hours). The Tc-99 is washed out of the lead pot (A) by saline solution when it is required (B).

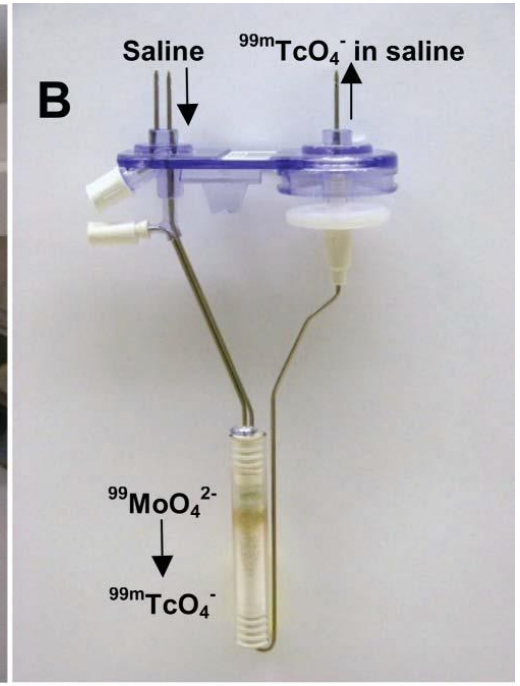
The process by which a radionuclide is washed out of a radionuclide generator is called **elution**. Typically, a solvent-filled vial is connected to one side of the generator and an evacuated vial is connected to the other side. The solvent is then pulled through the generator into the evacuated vial, taking along with it the dissolved radioactive substance to be eluted. The resulting solution is called the **eluate**.

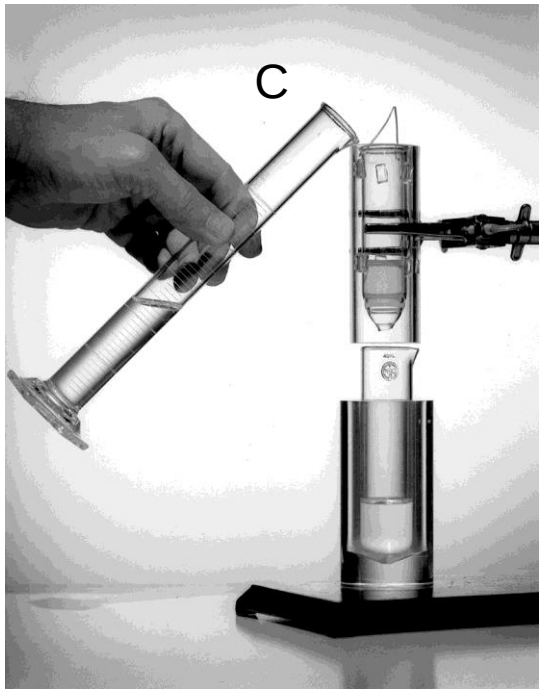
In a Mo-99/Tc-99m generator, in which the half-life of the parent nuclide is significantly longer than that of the daughter nuclide, removing the daughter nuclide from the generator ("milking" the generator) is done every 6 or more hours, though at most twice daily. After 1-2 weeks, the generator is returned to the reactor site for “recharging”.

The first technetium-99m generator was developed in 1958 at Brookhaven National Laboratory, USA (C).

TECHNETIUM-99m







$^{68}Ge/^{68}Ga$-GENERATOR

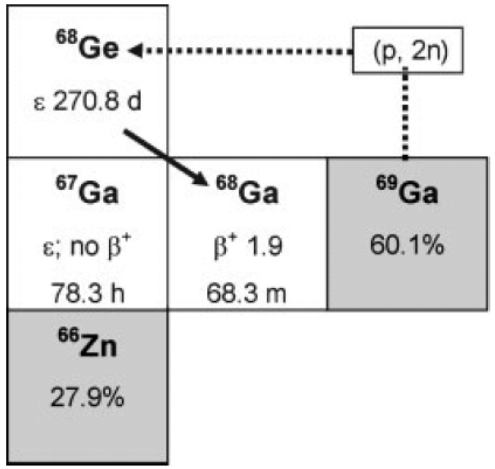


Figure 1. Production of ^{68}Ge by the (p, 2n) reaction of ^{69}Ga.

$^{68}_{32}Ge$ 271 d

↓

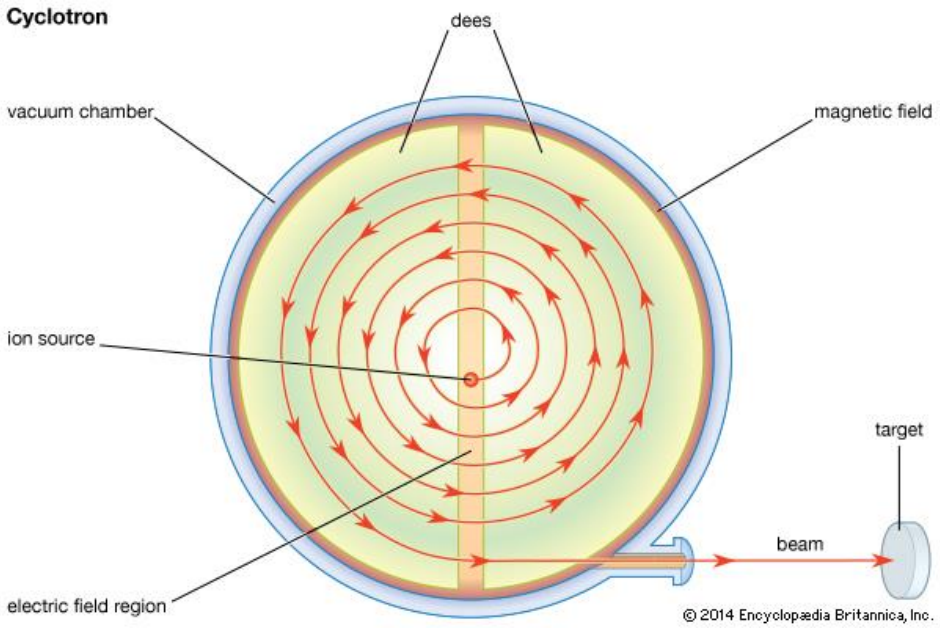
$^{68}_{31}Ga$ **68 min**

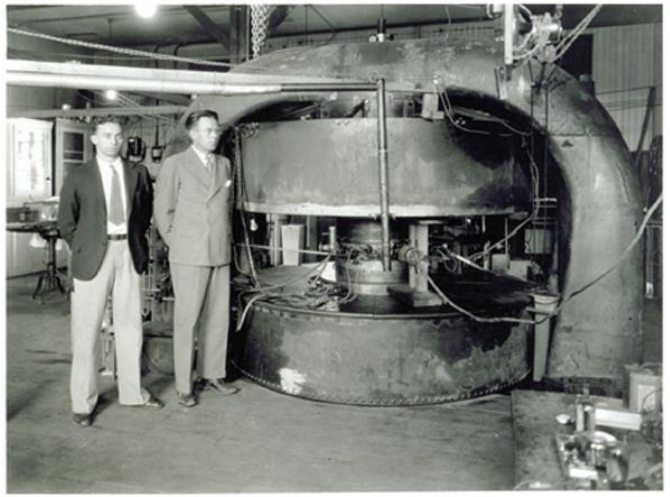
↓

$^{68}_{30}Zn$ stable

PRODUCTION OF RADIONUCLIDES AT A CYCLOTRON

A cyclotron is a type of particle accelerator in which charged particles accelerate outwards from the centre along a spiral path.
The particles are held to a spiral trajectory by a static magnetic field and accelerated by a rapidly varying (radio frequency) electric field.

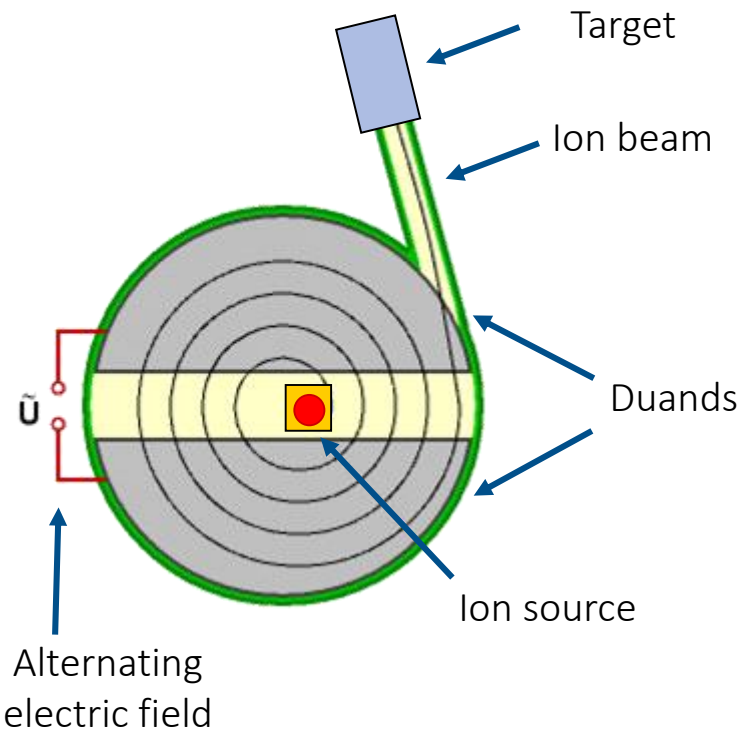


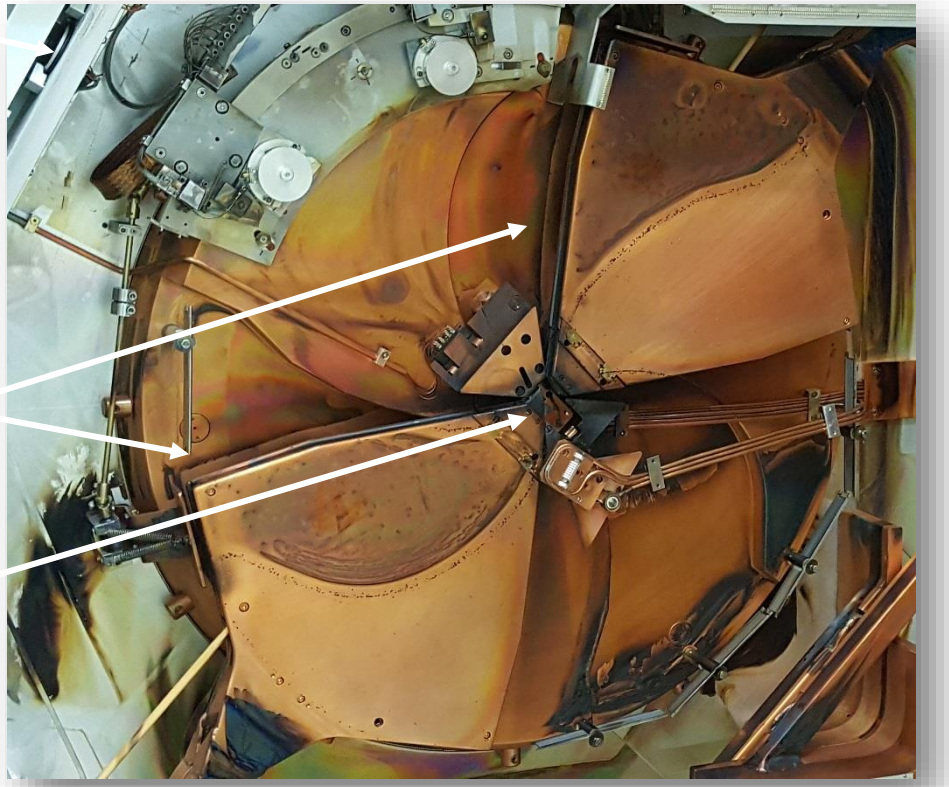


M. S. Livingston and E. O. Lawrence **1932**

Nobel prize in physics: 1939

PRODUCTION OF RADIONUCLIDES AT A CYCLOTRON

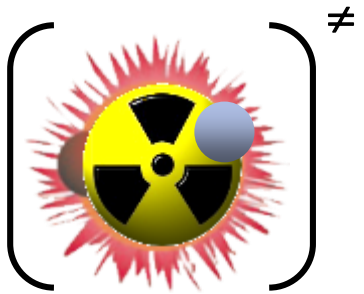




CYCLOTRON-PRODUCED RADIONUCLIDE [^{18}F]FLUORIDE

proton

^{18}Oxygen



neutron

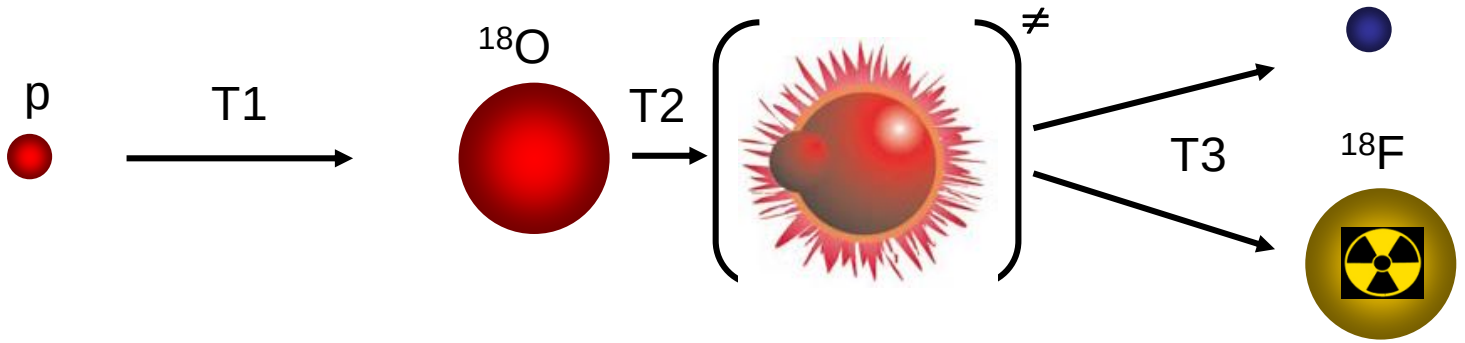
^{18}Fluoride

Compound nucleus [^{19}F]*

Reaction: ^{18}O(p,n)^{18}F

^{18}F half life: 110 min

CYCLOTRON-PRODUCED RADIONUCLIDE [^{18}F]FLUORIDE



Compound nucleus

T1 Projectile + Target

T2 Reaction

T3 Ejectile + emitted particle

Target + Projectile → Ejectile + emitted particle

Target (Projectile, emitted particle) Ejectile

^{18}O(p,n)^{18}F

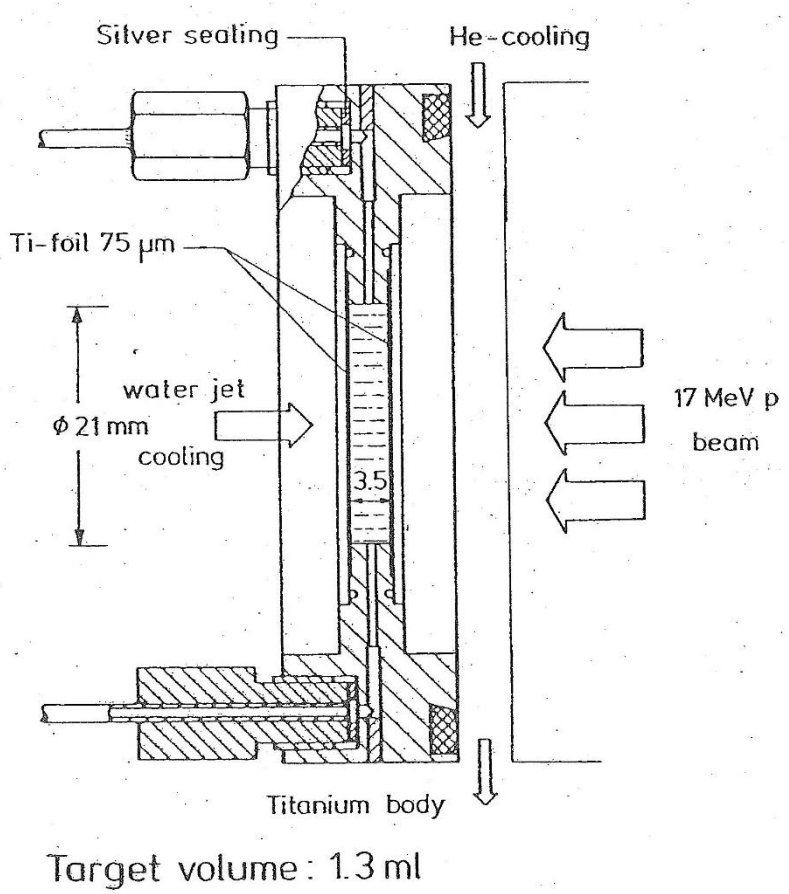
$H_2{}^{18}O$-TARGET FOR $^{18}F^-_{aq}$ PRODUCTION

Nuclear reaction: $^{18}O(p,n)^{18}F$

Production yield of $^{18}F^-_{aq}$: 74 GBq (2 Ci)

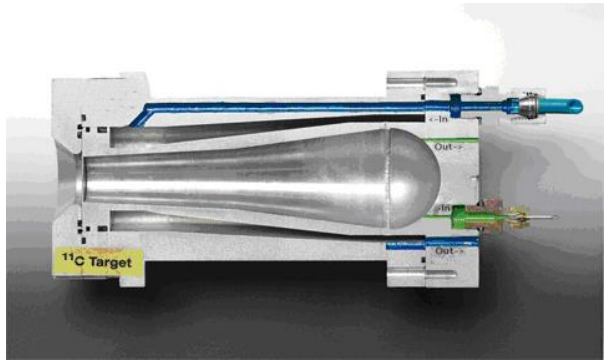
Recycling of ^{18}O-Water: Adsorption of $^{18}F^-$ on anion exchange column (AG 1x8 or QMA)

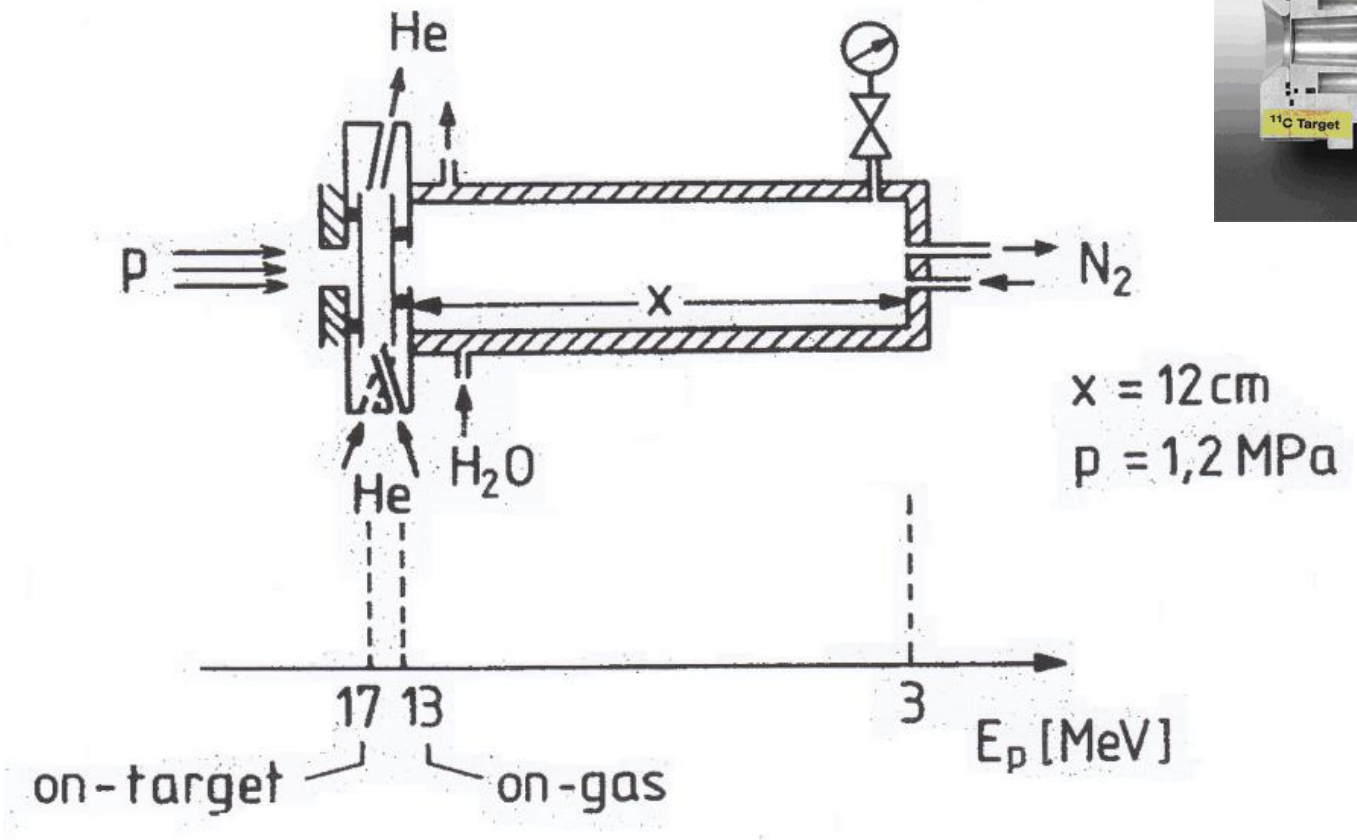
Desorption with aqueous K_2CO_3 solution



^{14}N-TARGET FOR ^{11}C PRODUCTION

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



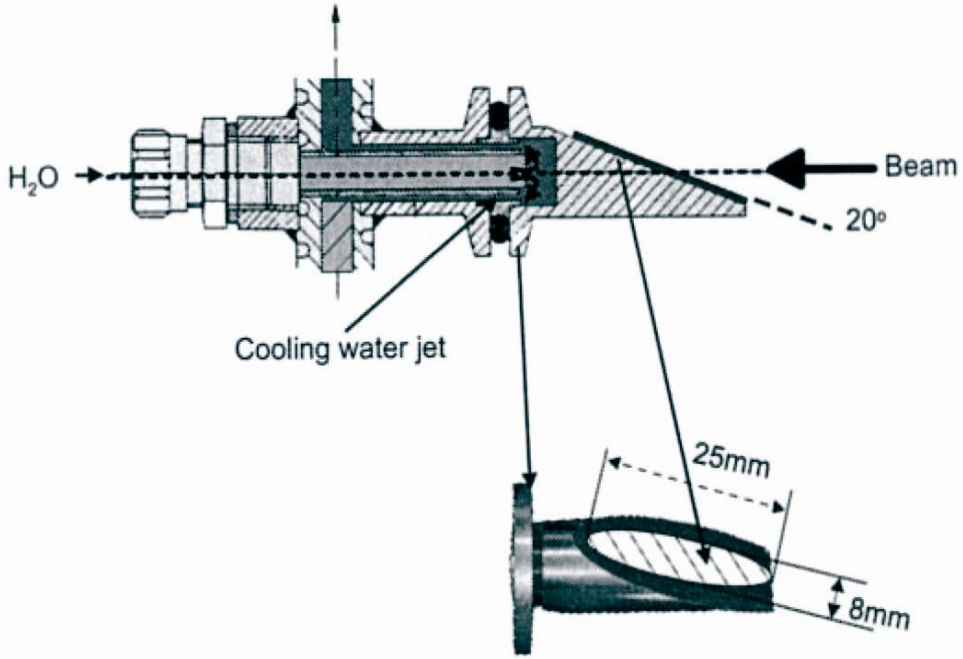


SOLID TARGETRY

Sample preparation: electrolysis, alloy formation, pellet

Heat dissipation: 2π or 4π cooling, slanting beam

Example: Use of slanting beam



- Standard technology used in production of radionuclides (^{55}Co, ^{64}Cu, ^{124}I, etc.)

Spellerberg et al., ARI **49**, 1519 (1998).

DEVELOPMENT OF RADIONUCLIDE PRODUCTION

Steps involved

- Nuclear data
  (knowledge of decay and nuclear reaction data)
- Irradiation technology
- Chemical processing
- Quality control
- Suitability tests

COMMONLY USED PHOTON EMITTERS

Radionuclide	$T_{½}$	Main γ-ray energy in keV (%)	Production route	Energy range (MeV)
^{67}Ga	3.26 d	93 (37) 185 (20)	^{68}Zn(p,2n)	26 → 18
^{99}Mo ↓ (generator)	2.75 d	181 (6) 740 (12)	^{235}U(n,f) ^{98}Mo(n,γ)	
^{99m}Tc	6.0 h	141 (87)		
^{111}In	2.8 d	173 (91) 247 (94)	^{112}Cd(p,2n)	25 → 18
^{123}I	13.2 h	159 (83)	^{123}Te(p,n) ^{124}Te(p,2n) ^{127}I(p,5n)^{123}Xe[a)] ^{124}Xe(p,x)^{123}Xe[a)]	14 → 10 26 → 23 65 → 45 29 → 23
^{201}Tl	3.06 d	69 – 82 (X-rays) 166 (10.2)	^{203}Tl(p,3n)^{201}Pb[b)]	28 → 20

a) ^{123}Xe decays by EC (87%) and β^+ emission (13%) to ^{123}I
b) ^{201}Pb decays by EC to ^{201}Tl

COMMONLY USED POSITRON EMITTERS

^{11}C	($T_{½}$ = 20.0 min)	^{14}N(p,α)
^{13}N	($T_{½}$ = 10.0 min)	^{16}O(p,α)
^{15}O	($T_{½}$ = 2.0 min)	^{14}N(d,n)
^{18}F	($T_{½}$ =110.0 min)	^{18}O(p,n)

} (produced at small-sized cyclotrons)

^{68}Ga ($T_{½}$ = 68 min) ^{68}Ge (270 d) – ^{68}Ga Generator

^{82}Rb ($T_{½}$ = 1.3 min) ^{82}Sr (25.5 d) – ^{82}Rb Generator

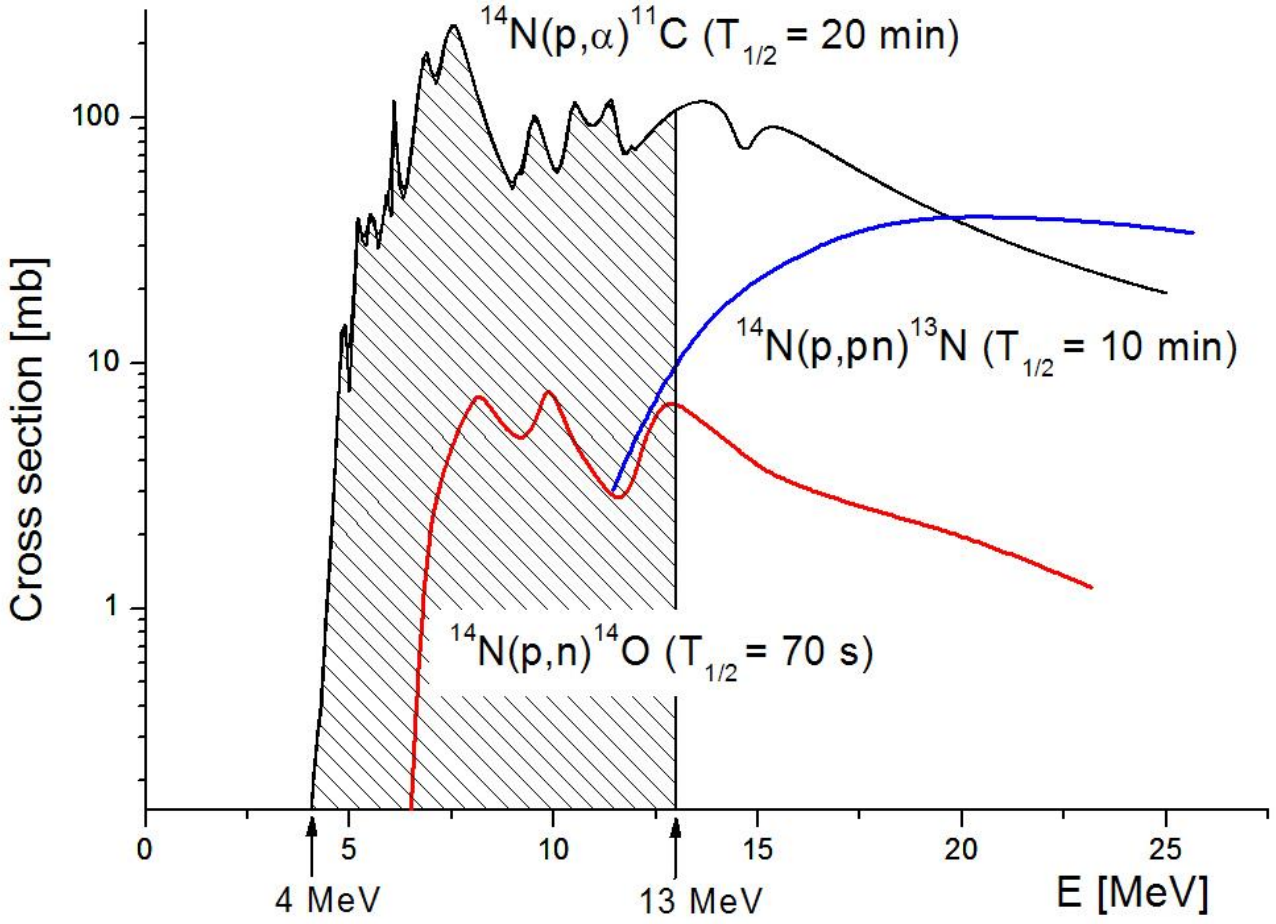
(produced via spallation and intermediate energy reactions)

SOME COMMONLY USED THERAPEUTIC RADIONUCLIDES

Radionuclide	$T_{½}$	E_{β^-} in MeV	$E\gamma$ in keV (%)	Production route
^{32}P	14.3 d	1.7		^{32}S(n,p)
^{89}Sr	50.5 d	1.5		^{89}Y(n,p)
^{90}Y	2.7 d	2.3		^{90}Sr/^{90}Y Generator
^{125}I	60.2 d	Auger electrons	35 (7)	^{124}Xe(n,γ)^{125}Xe → ^{125}I
^{131}I	8.0 d	0.6	364 (81)	^{130}Te(n,γ)^{131}Te → ^{131}I ^{235}U(n,f)
^{153}Sm	1.9 d	0.8	103 (30)	^{152}Sm(n,γ)
^{177}Lu	6.7 d	0.5	208 (11)	^{176}Lu(n,γ) ^{176}Yb(n,γ)^{177}Yb → ^{177}Lu
^{188}Re	17 h	2.0	155 (15)	^{188}W/^{188}Re Generator
^{192}Ir	73.8 d	0.7	317 (83)	^{191}Ir(n,γ)

- Production carried out mostly using nuclear reactors

EXCITATION FUNCTIONS OF PROTON-INDUCED NUCLEAR REACTION ON NITROGEN-14



- **Optimal energy range**
  E_P = 13 ➞ 3 MeV
- **^{11}C-yield (EOB):**
  103 mCi/mAh
- **^{13}N-impurities (EOB):**
  ca. 5%
- **^{14}O-impurities (EOB):**
  ca. 20%

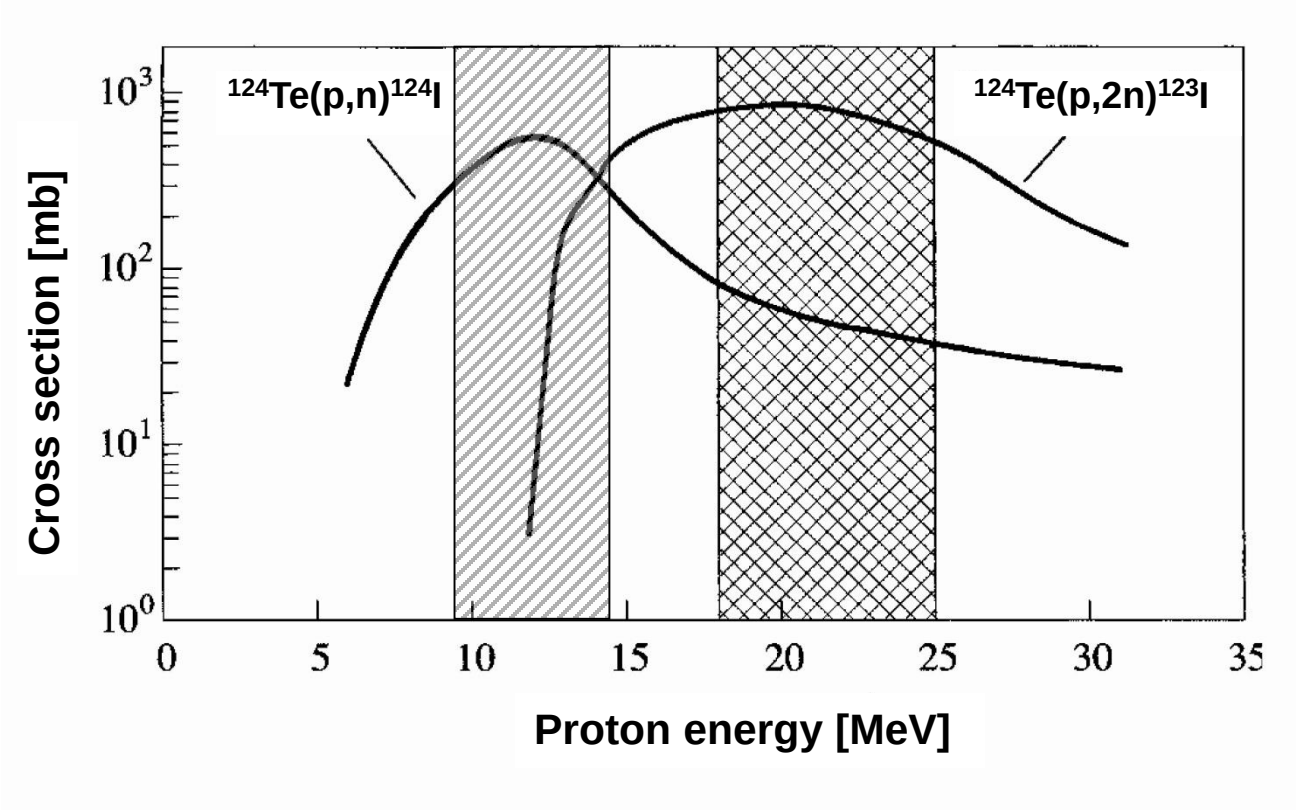
ROLE OF NUCLEAR DATA IN OPTIMISATION OF A PRODUCTION ROUTE USING CHARGED PARTICLES

Example:

Excitation functions of ^{124}Te(p,xn)^{123,124}I reactions

(Jülich-Debrecen)

Scholten et al.,
ARI **46**, 255 (1995).



Production of ^{124}I	**Production of ^{123}I**
E_p: 14 → 9 MeV	E_p: 25 → 18 MeV
(^{125}I impurity < 0.1%)	(^{124}I impurity < 1%)

CHEMICAL PROCESSING

Aims

- Isolation of the desired radionuclide in a pure form
- Recovery of the enriched target material for reuse

Methods

- Distillation
- Thermochromatography
- Ion-exchange chromatography
- Solvent extraction

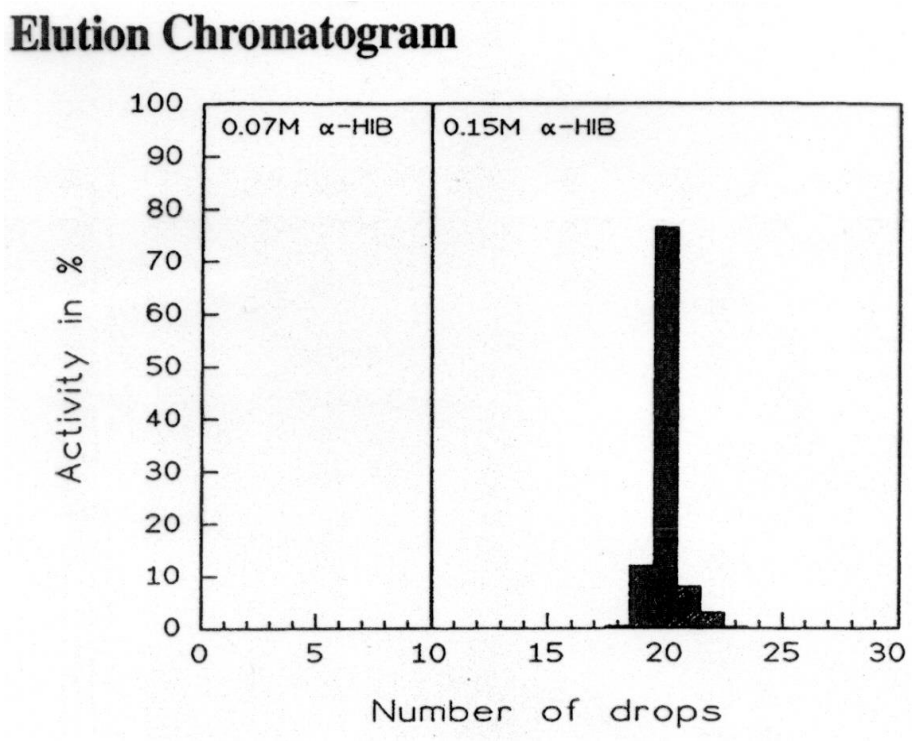
All separations to be done without addition of inactive carrier material!

RADIOCHEMICAL SEPARATION OF ^{86}Y ($T_{½}$ = 14.7 h) PRODUCED VIA $^{86}Sr(p,n)$-PROCESS

Target : 96.3 % $^{86}SrCO_3$ pellet ***Irradiation*** : 16 MeV p, 4µA, 5h

Separation :
Co-precipitation and ion-exchange chromatography

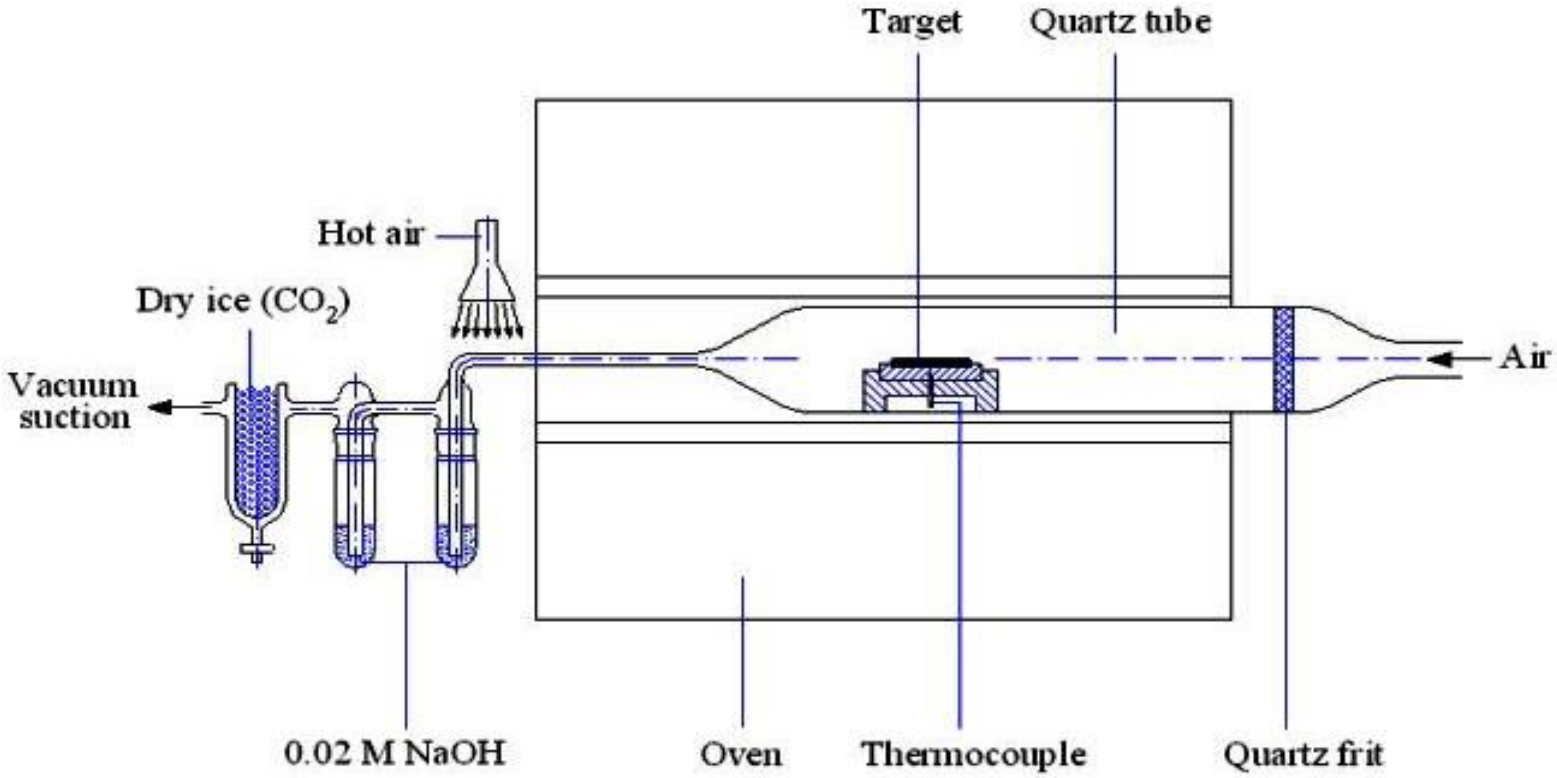
- Dissolution of $^{86}SrCO_3$ in conc. HCl
- Addition of 2 mg La^{3+} carrier
- Precipitation as $La(OH)_3$ (carrying ^{86}Y)
- Dissolution of ppt. in HCl
- Transfer to Aminex A5
- Elution with α-HIB
  (separation of ^{86}Y from La)



^{86}Y activity (3 GBq) collected in 3 drops

Rösch et al.,
ARI **44**, 677 (1993).

DISTILLATION OF RADIOIODINE



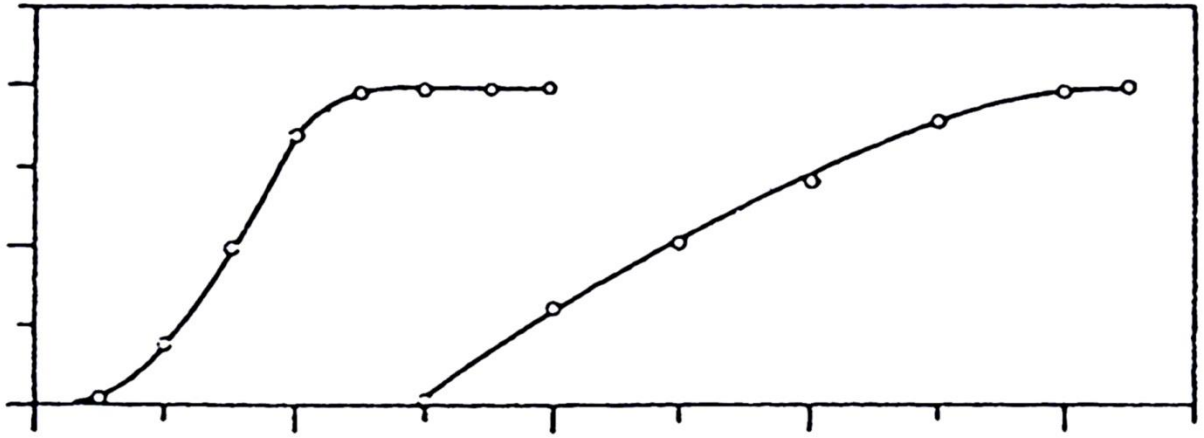
Distillation at 750 °C for 15 min

Batch yield :	480 MBq ^{124}I
Radionuclidic purity (%):	^{124}I (99), ^{123}I (<1), ^{125}I (0.1)
Radiochemical purity:	> 98 % iodide
Radiochemical impurity:	Te (<1µg)

SEPARATION OF RADIOSELENIUM

Thermochromatography

- Irradiated Cu_3As target heated in O_2 stream
- Fractionated removal of As and radioselenium



Two step thermochromatography essential

Purification of radioselenium via extraction in benzene

Batch yield: 6 GBq ^{73}Se (2 h, 20 µA)

^{72,75}Se impurity: < 0.05 %

QUALITY ASSURANCE OF THE PRODUCT

Measurement of radioactivity and determination of radionuclidic purity

- High resolution γ-ray spectrometry (^{67}Ga, ^{123}I)
- X-ray spectrometry (^{82}Sr, ^{103}Pd, ^{125}I)
- Liquid scintillation counting in case of soft β^- and Auger electrons (^{125}I, ^{140}Nd)

Radiochemical purity

- TLC, HPLC ($^{124}I^-$, $^{124}IO_3^-$)
- GC (inert constituents $[^{18}F]CF_4$, $[^{18}F]NF_3$ in $[^{18}F]F_2$)

Chemical purity

- UV-spectrophotometry
- ICP-OES (“inductively coupled plasma optical emission spectrometry“)
- NAA (neutron activation analysis)

Specific activity

- Determination of radioactivity via radiation detector
- Determination of mass via UV, refractive index or thermal conductivity detector

EVALUATION OF SUITABILITY OF NOVEL RADIONUCLIDES FOR PET

Major Considerations

- Positron energy (end point energy and mean energy)
- Positron emission intensity
- Energies and intensities of emitted photons (especially near the annihilation peak)

Interferences in Imaging

- image distortion
- low resolution
- faulty quantification
- non-reproducibility

Evaluation studies at individual positron tomographs essential; new analytical algorithms need to be developed

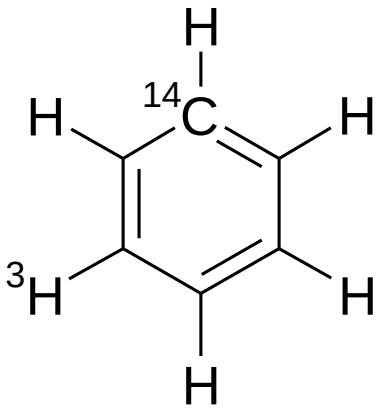
METHODS OF RADIOLABELLING

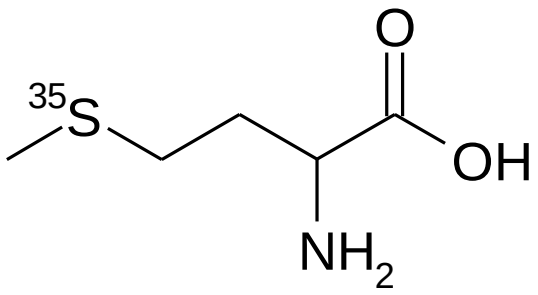
- Isotope exchange
- Introduction of a foreign label
- Labelling with bifunctional chelating agent
- (Biosynthesis)
- (Recoil labelling)
- (Excitation labelling)

ISOTOPE EXCHANGE REACTIONS

In isotope exchange reactions, one or more atoms in a molecule are replaced by isotopes of the same element having different mass numbers. Since the radiolabelled and parent molecules are identical except for the isotope effect, they are expected to have the same biologic and chemical properties.

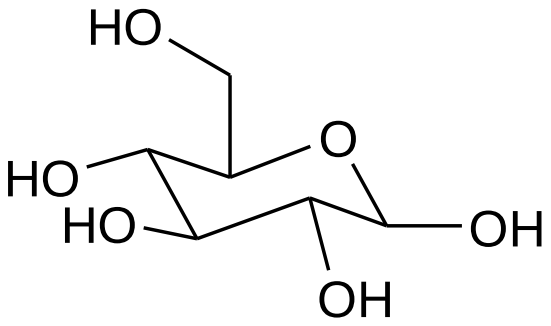
Examples: ^{14}C, ^{35}S- and ^{3}H-labelled compounds



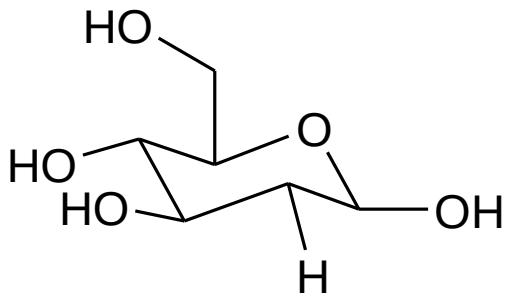


INTRODUCTION OF A FOREIGN LABEL

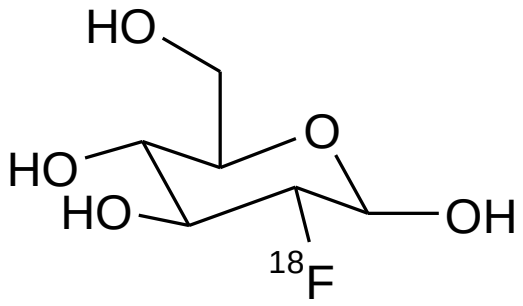
In this type of labelling, a radionuclide is incorporated into a molecule that has a known biologic role, primarily by the formation of covalent or co-ordinate covalent bond. The tagging radionuclide is foreign to the molecule and does not label it by the exchange of one its isotopes.



glucose



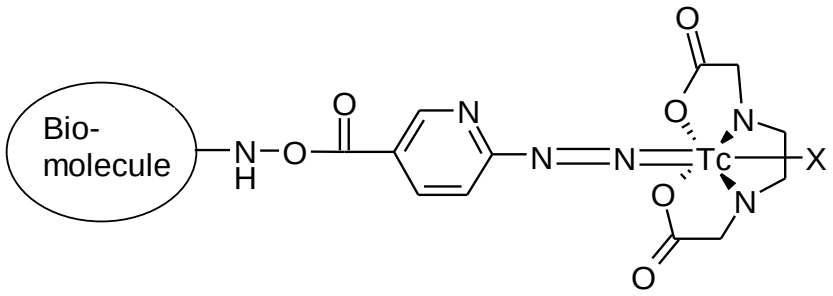
deoxyglucose



[^{18}F]fluorodeoxyglucose

LABELLING WITH BIFUNCTIONAL CHELATING AGENTS

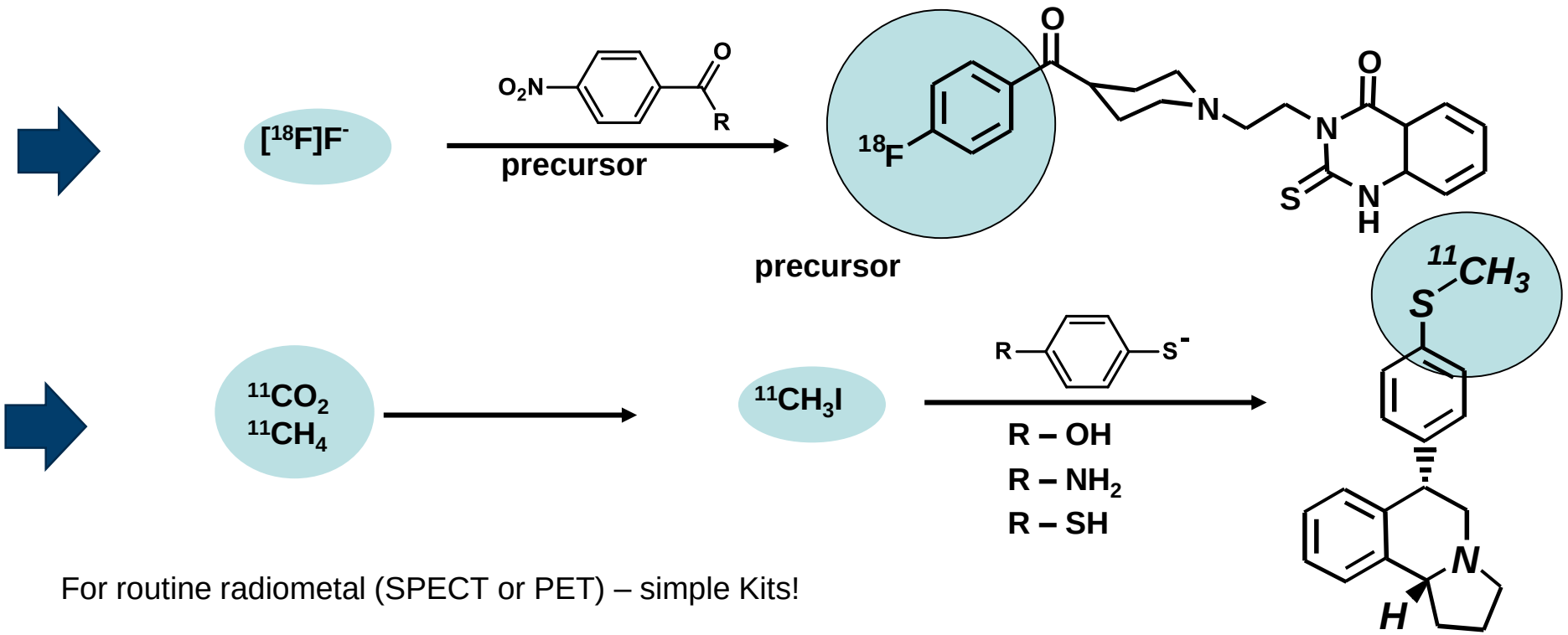
In this approach, a bifunctional chelating agent is conjugated to a macromolecule (e.g. protein, antibody) on one side and to a metal ion (e.g. Tc) by chelating on the the other side. Examples of bifunctional chelating agents are DTPA (diethylenetriamine pentaacetic acid), diamide dimercaptide, and dithiosemicarbazone.



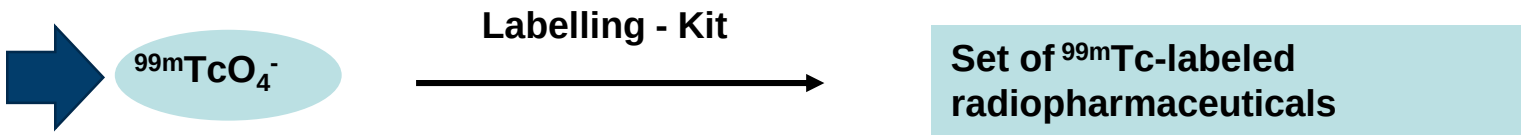
^{99m}Tc HYNIC (hydrazinonicotinyl)

DAILY ROUTINE: RELIABILITY OF PRIME IMPORTANCE!

For routine PET with standard positron emitters – simple processes!



For routine radiometal (SPECT or PET) – simple Kits!



<u>Simple (one step) and efficient labelling methods</u>
Others: Only few applications - often of "scientific interest"

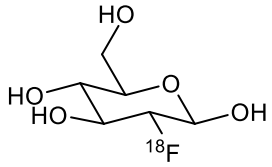
PRINCIPLES OF LABELLING - EXAMPLES

Direct labelling:

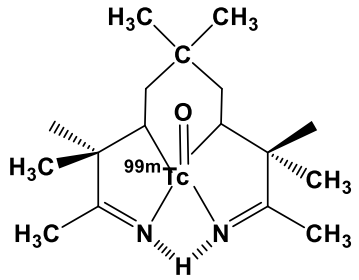
introduction of the label directly into a precursor to the final compound

Examples:

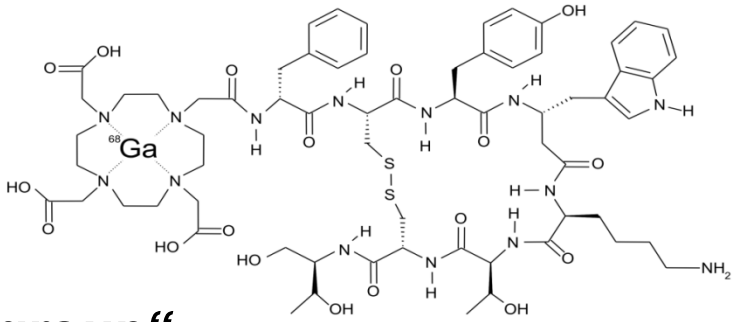
- **[^{18}F]FDG**



- **[^{99m}Tc]TcHMPAO**



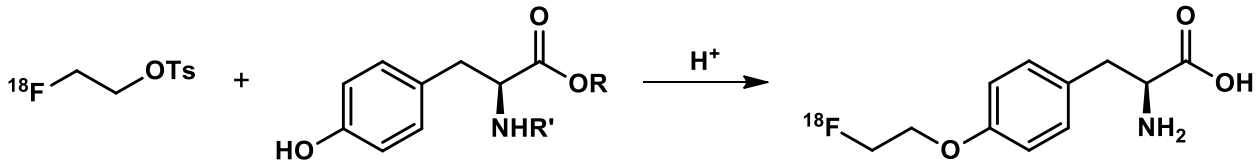
- **[^{68}Ga]Ga-DOTATOC**



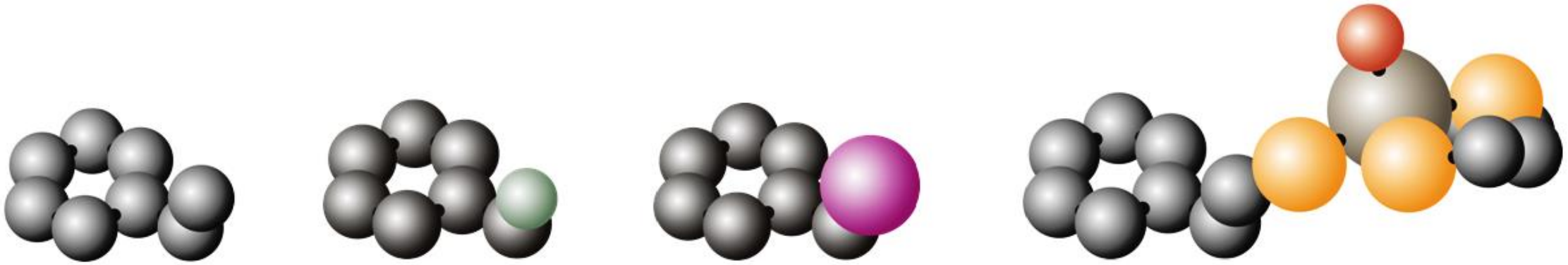
Indirect labelling:

via labelled precursors - ***„prosthetic group“***

[^{18}F]FET



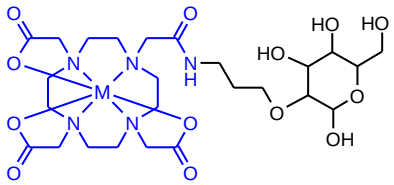
“ALIENATION“ CAUSED BY RADIOACTIVE LABELLING

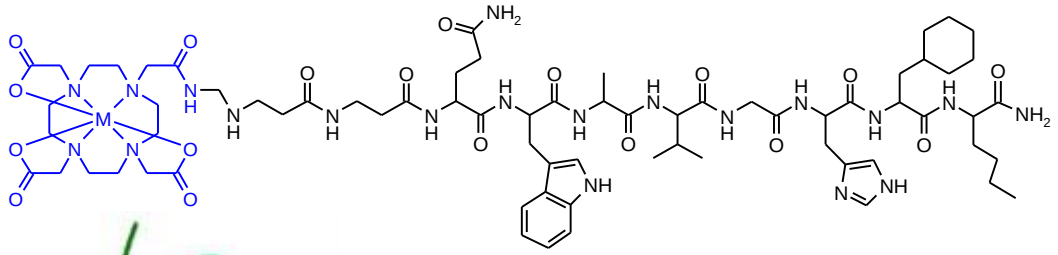


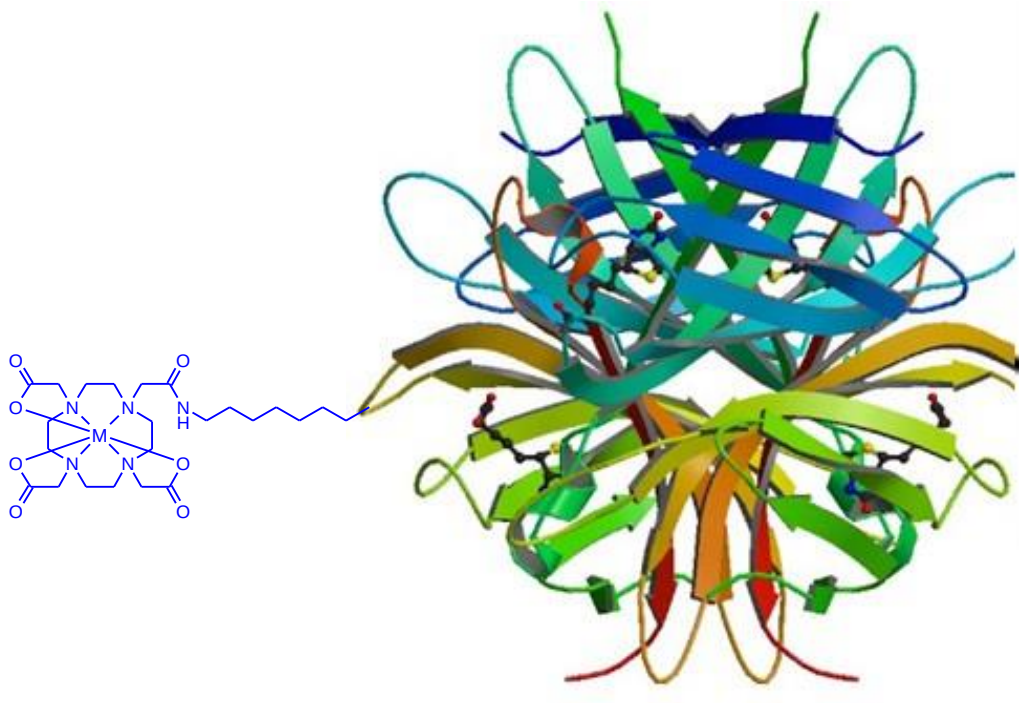
C-11	F-18	I-123	radiometal (e.g. Tc-99m, Cu-64)
native substrate	F for -H,-OH	I für -H,-OH,-CH_3	drastic alterations

increasing physiological alterations (not predictable !)

“ALIENATION“ CAUSED BY RADIOACTIVE LABELLING







STEPS OF DEVELOPMENT OF *IN VIVO* RADIOTRACERS

Radionuclides	nuclear data, nuclear reactions, target construction
Labelling methods	no-carrier-added radiosyntheses, radioanalytics
Radiotracers	organic syntheses, radiosyntheses, *in vitro* and *in vivo* evaluation

Clinical research demands routine production of:

Radiopharmaceuticals	internal and external service, GMP-conformity

ADVANTAGES OF TRACERS LABELLED WITH SHORT-LIVED POSITRON-EMITTERS FOR *IN VIVO* APPLICATION

^{11}C ($t_{1/2}$=20 min), ^{18}F ($t_{1/2}$=110 min)

molar activity > 10^{11} Bq/µmol

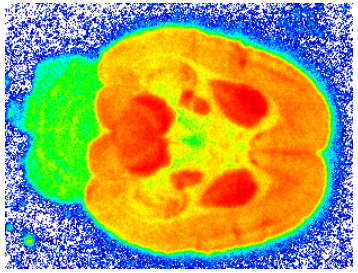
⟹ minute amount of mass applied (<1 µg)

⟹ small radiation doses (<10 mSv)

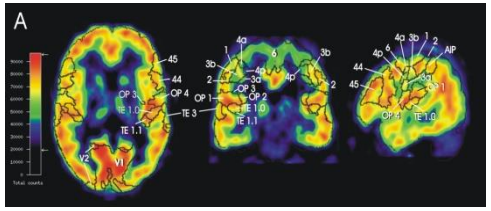
⟹ quantitative imaging with PET
(high spatial and temporal resolution)

RADIOTRACER DEVELOPMENT: FROM BENCH TO BEDSIDE

Cyclotron



In vitro autoradiography



PET-scan

Radionuclide production

↓

Radiotracer development and synthesis

↓

Biological evaluation

↓

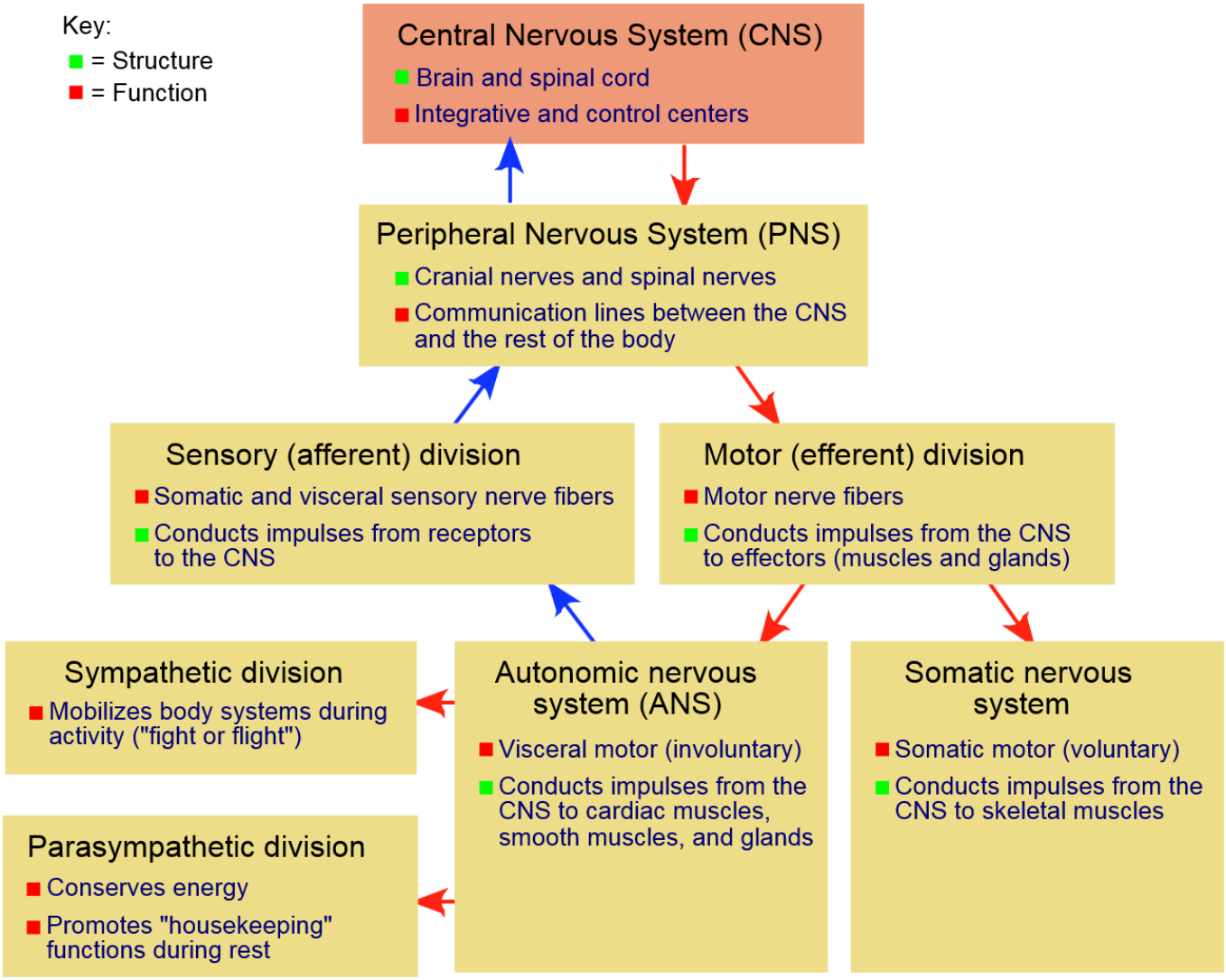
Clinical studies / basic brain research

↓

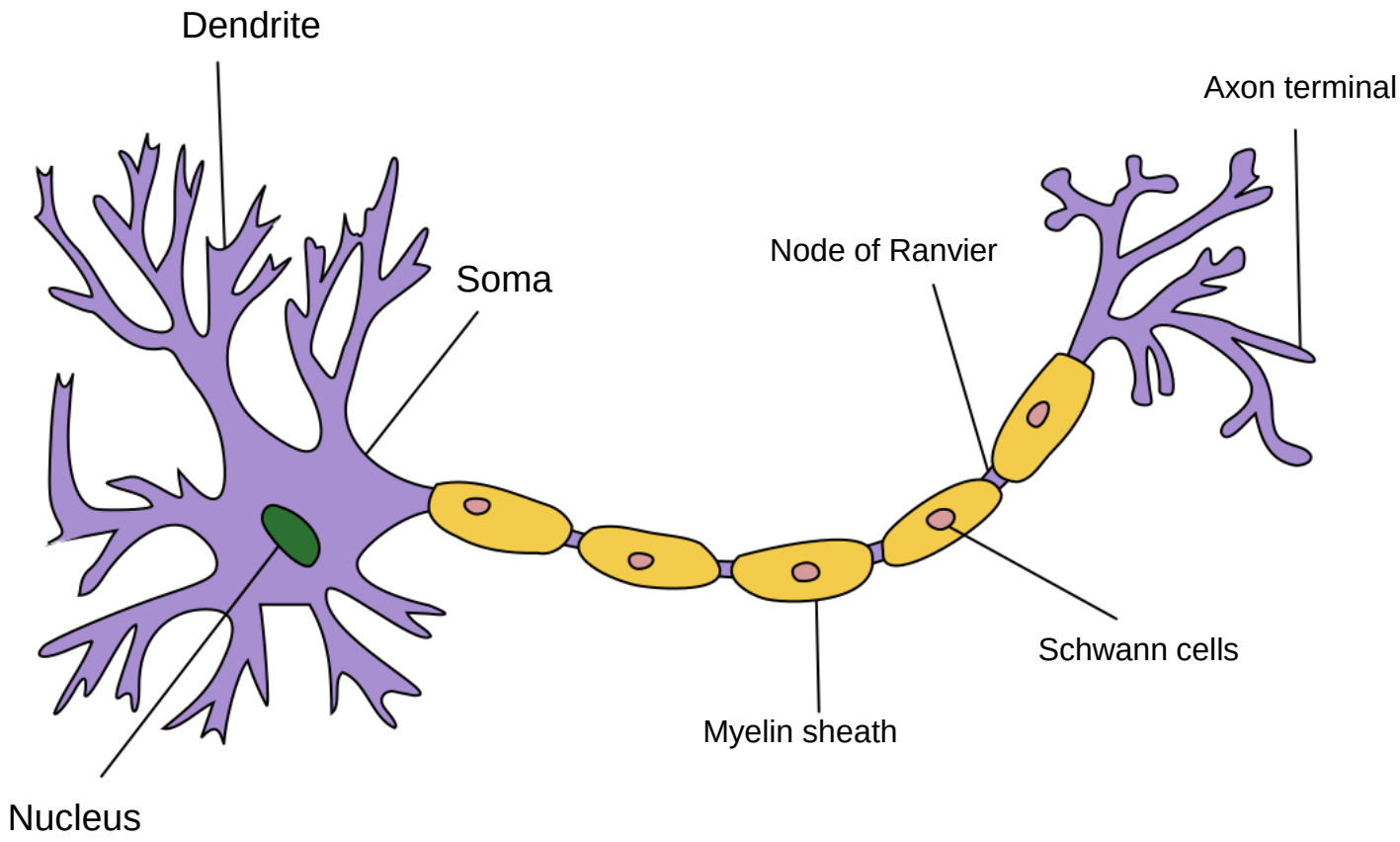
Implementation into clincial daily routine

Synthesis module

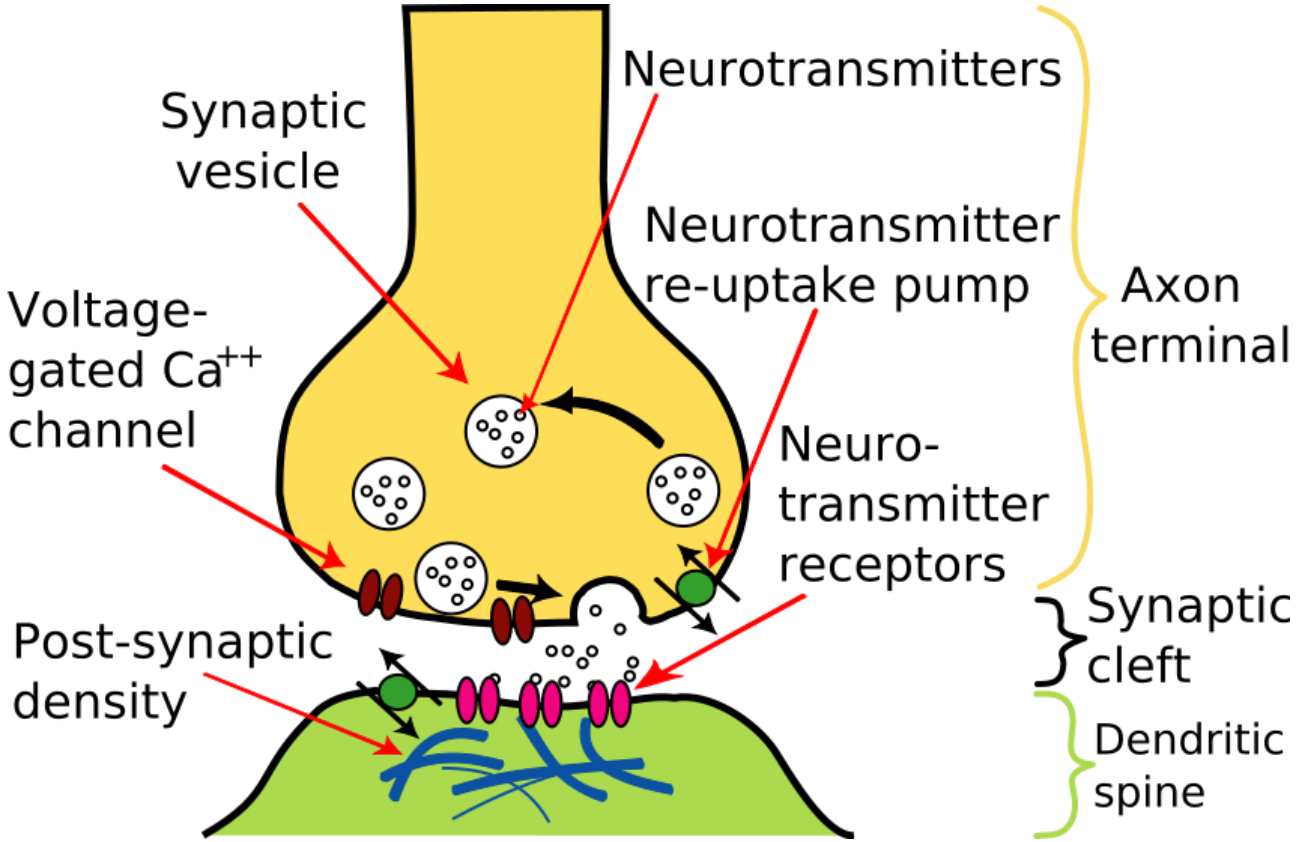
NERVE SYSTEM



NERVE SYSTEM



NERVE IMPULSE RELEASE

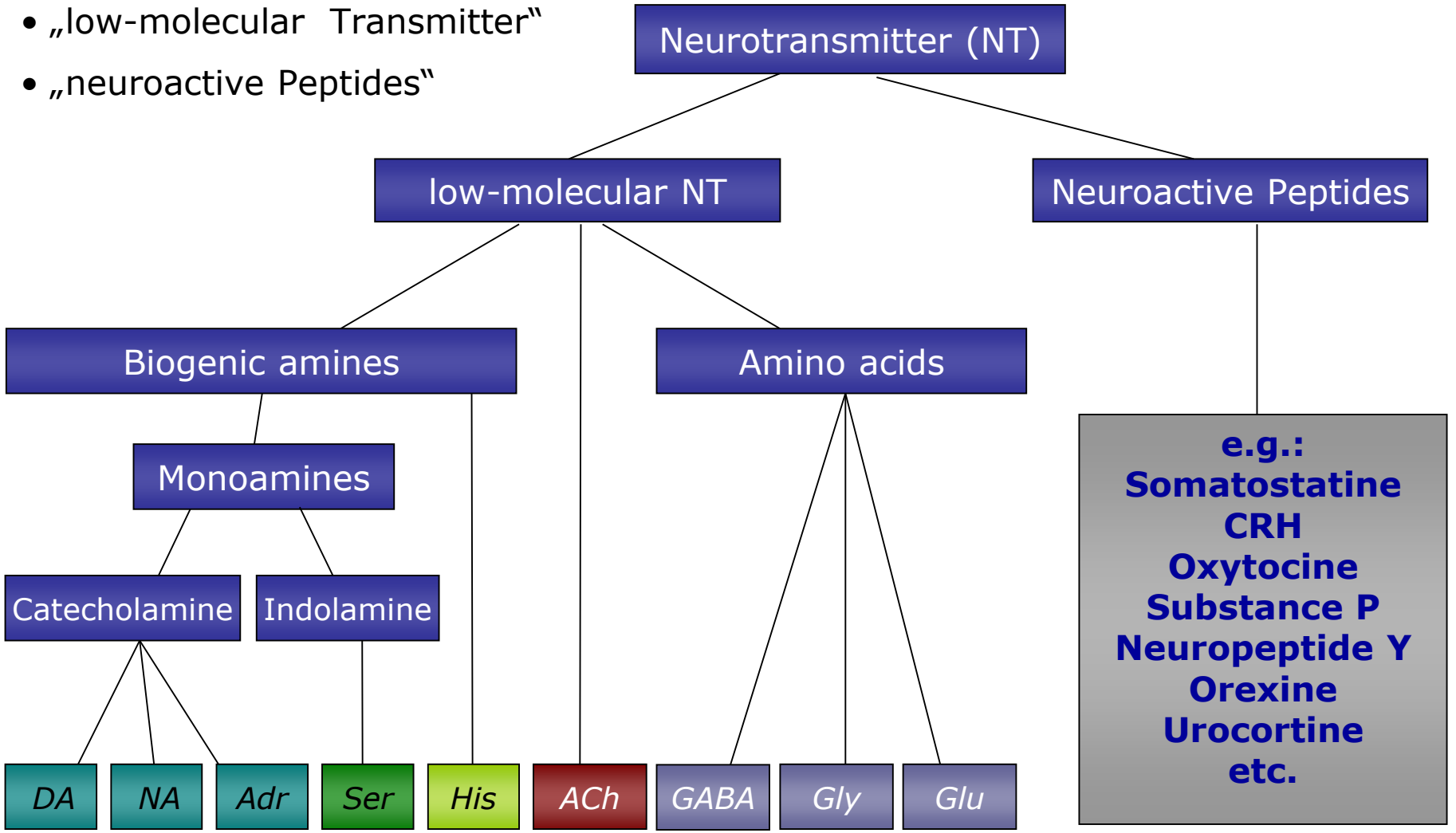


When an action potential arrives at the end of the pre-synaptic axon (yellow), it causes the release of neurotransmitter molecules that open ion channels in the post-synaptic neuron (green). The combined potentials of the inputs can begin a new action potential in the post-synaptic neuron.

NEUROTRANSMITTERS

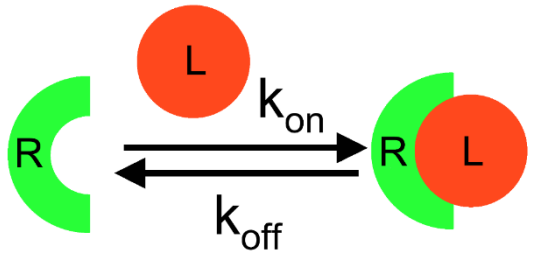
Two main class of transmitters:

- „low-molecular Transmitter"
- „neuroactive Peptides"



SATURATION STUDIES

K_D = Dissociation constant: specific type of equilibrium constant that measures the propensity of a larger object to separate (dissociate) reversibly into smaller components



$$L + R \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} B \qquad v_{on} = L \cdot R \cdot k_{on} \qquad v_{off} = B \cdot k_{off}$$

At equilibrium $v_{on} = v_{off}$

$$L \cdot R \cdot k_{on} = B \cdot k_{off} \qquad \frac{L \cdot R}{B} = \frac{k_{off}}{k_{on}} = K_D$$

Determination of affinity (K_D) of a ligand :

- kinetically
- at equilibrium

SATURATION STUDIES

$$L + R \underset{k_{off}}{\overset{k_{on}}{\rightleftarrows}} B$$

The concentration of free receptors is experimentally not directly accessible, but of interest :

$B_{max} = R + B$

$$K_D = \frac{1}{K_A} = \frac{L \cdot R}{B}$$

?: B=f(L):

$$K_D = \frac{(B_{max} - B) \cdot L}{B}$$

$$K_D = \frac{B_{max} \cdot L - B \cdot L}{B}$$

$$\frac{B_{max} \cdot L}{B} - L = K_D$$

$$\frac{B_{max} \cdot L}{B} = K_D + L$$

$$B = \frac{B_{max} \cdot L}{K_D + L}$$

SATURATION STUDIES

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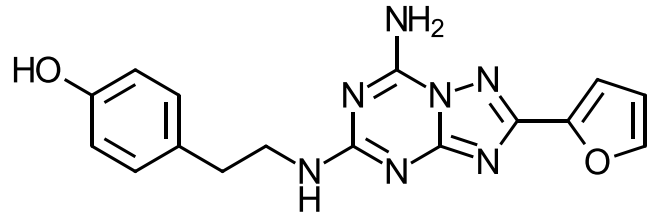
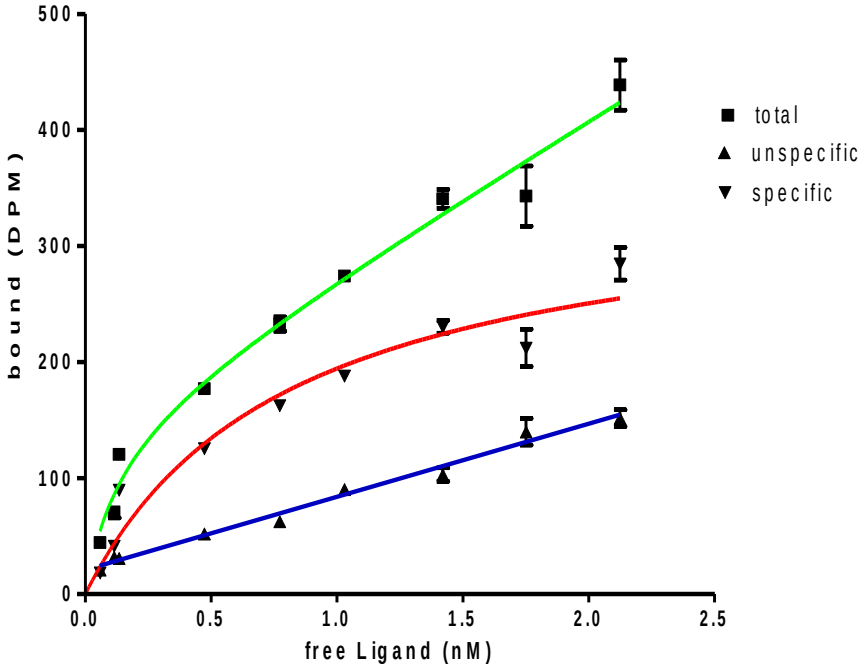
SATURATION STUDIES

K_D of [^{3}H]ZM 241385



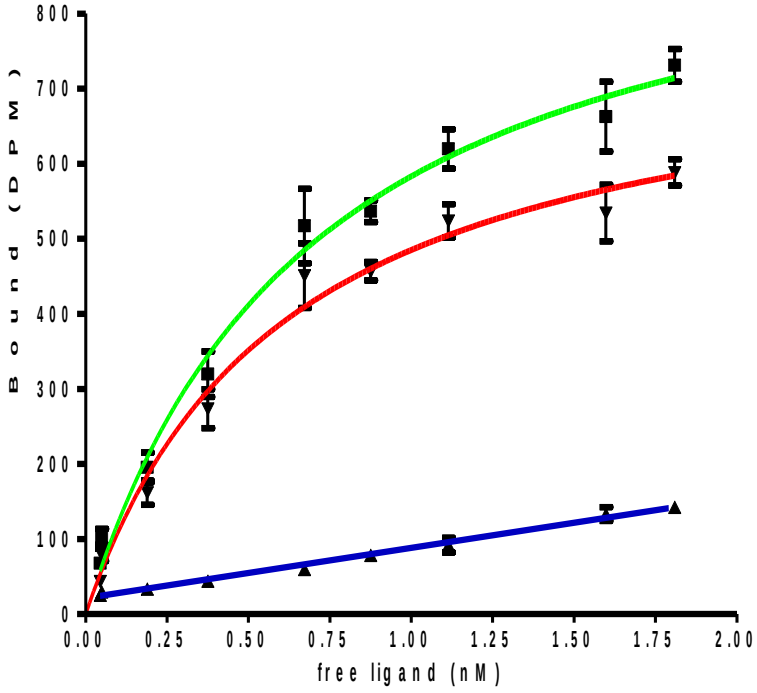
CHO K1 Cells Homogenate

CHO K1 cells stably expressing the human A_{2A} adenosine receptor
(Gene Bank Accession Number: ADORA2)



K_D 1.4 +/- 0.8 nM (n=15)

Rat striata homogenates



K_D 0.8 +/- 0.3 nM n=6

K_D = Dissociation constant: specific type of equilibrium constant that measures the propensity of a larger object to separate (dissociate) reversibly into smaller components

SATURATION STUDIES

Linearization (determine K_D using linear regression)

$$K_D = \frac{(B_{max} - B) \cdot L}{B}$$

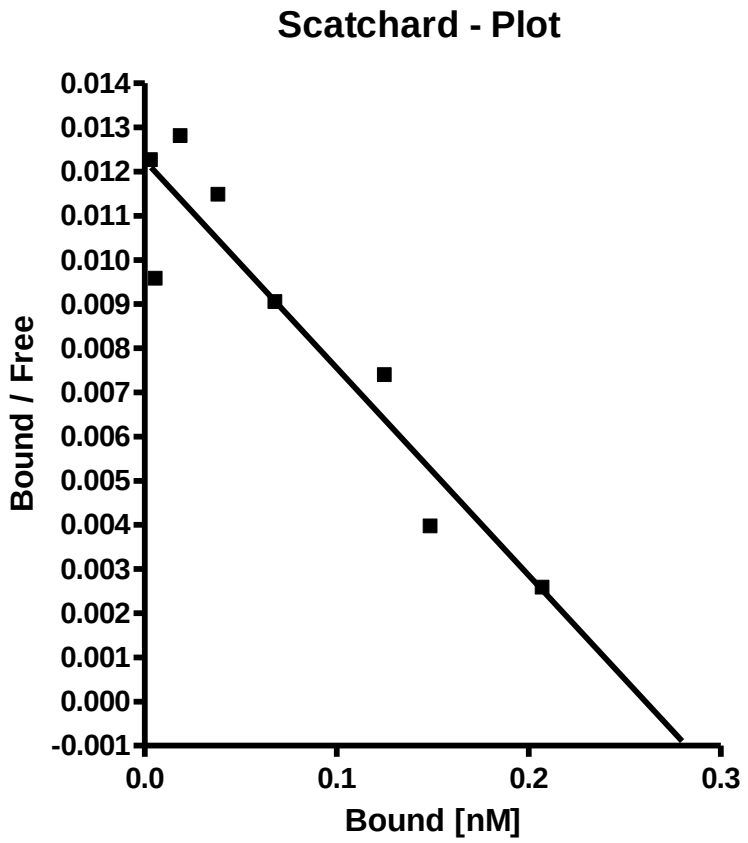
$$K_D \cdot B = (B_{max} - B) \cdot L \qquad \frac{B}{L} = \frac{(B_{max} - B)}{K_D}$$

$$\frac{B}{L} = -\frac{1}{K_D} \cdot B + \frac{B_{max}}{K_D}$$

y=mx+b (linear equation)

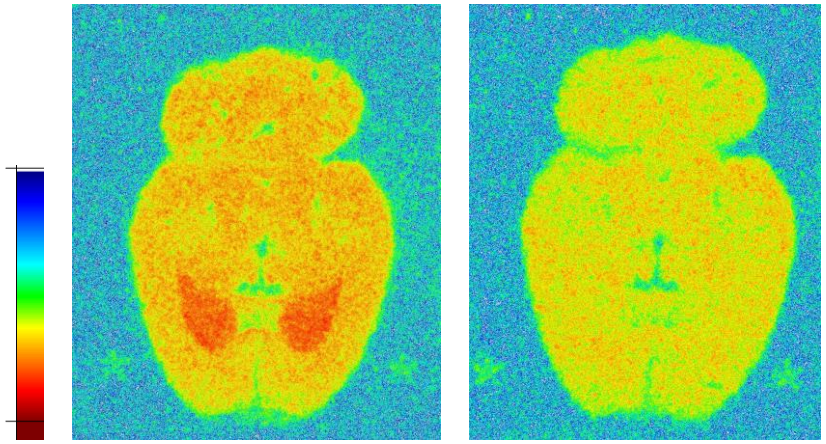
y= B/L x=B

y-axis intercept (x=0) $\Rightarrow$ B_{max} / K_D
x-axis intercept (y=0) $\Rightarrow$ B_{max}
slope: - 1/ K_D



AUTORADIOGRAPHY

[^{18}F]JL 192



total binding
<< 1 nM

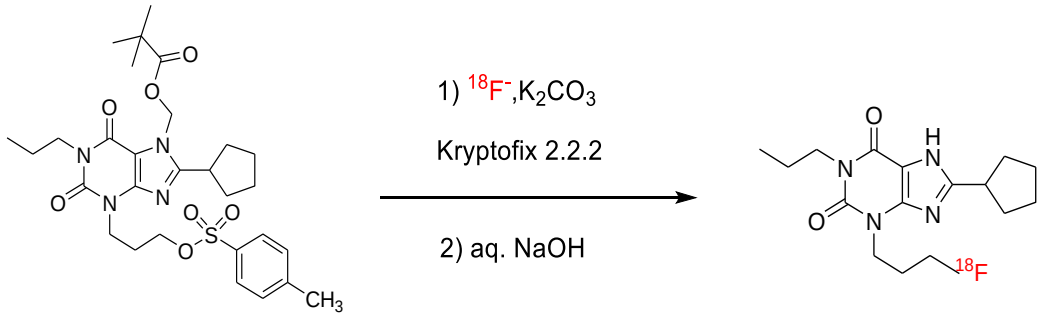
unspecific binding
(+ 1 µM ZM 241385)

[^{3}H]ZM 241385

total binding
≈ 1 nM

unspecific binding
(+ 1 µM ZM 241385)

IN VITRO EVALUATION



[^{18}F]CPFPX
(< 1 nM)

[^{3}H]CPFPX
(≈ 10 nM)