Therapeutic and diagnostic radiopharmaceuticals

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<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1895</td>
<td>X-rays (W.C. Röntgen)</td>
<td>1951</td>
<td>Nal crystals for positron detection (W. Sweet, G. Brownell)</td>
</tr>
<tr>
<td>1896</td>
<td>Radioactivity</td>
<td>1953</td>
<td>Cerebral blood flow with Kr-81m (N. Lassen)</td>
</tr>
<tr>
<td>1898</td>
<td>Po, Ra, Th (M. S. Curie)</td>
<td>1958</td>
<td>Anger gamma camera (H. O. Anger)</td>
</tr>
<tr>
<td>1923</td>
<td>Tracer principle (Gy. Hevesy)</td>
<td>1959</td>
<td>Radioimmunoassay (R. S. Yalow, S. Berson)</td>
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<tr>
<td>1928</td>
<td>Gas filled counter (J. W. Geiger, W. Müller)</td>
<td>1962</td>
<td>Tc-99m generator (P. Harper, K. Lathrope)</td>
</tr>
<tr>
<td>1932</td>
<td>Cyclotron (E. O. Lawrence)</td>
<td>1962</td>
<td>SPET (D. Kuhl)</td>
</tr>
<tr>
<td>1934</td>
<td>I-128 (E. Fermi)</td>
<td>1973</td>
<td>Description of the CT scanner (G. H. Hounsfield)</td>
</tr>
<tr>
<td>1936</td>
<td>Tc-99m (E. G. Segre)</td>
<td>1973</td>
<td>First PET tomograph (M. Ter-Pogossian, M. Phelps)</td>
</tr>
<tr>
<td>1936</td>
<td>Therapeutic use of P-32 (J. H. Lawrence)</td>
<td>1978</td>
<td>$[^{18}\text{F}]$FDG (T. Ido)</td>
</tr>
<tr>
<td>1938</td>
<td>I-131 (G. Seaborg)</td>
<td>1997</td>
<td>FDA approves $[^{18}\text{F}]$FDG as radiopharmaceutical</td>
</tr>
<tr>
<td>1946</td>
<td>Thyroid cancer therapy (S. M. Seidlin, L. D. Marinelli)</td>
<td>1998</td>
<td>PET/CT prototype (D. Townsend, R. Nutt)</td>
</tr>
<tr>
<td>1949</td>
<td>Thyroid carcinoma therapy in Europe (C. Winkler, E. E. Pochin)</td>
<td>2000s</td>
<td>Revolution of hybrid tomographic imaging (PET/CT and SPECT/CT); end of 2D planar imaging</td>
</tr>
<tr>
<td>1951</td>
<td>Rectilinear scanner (B. Cassen)</td>
<td>2010s</td>
<td>Quantitative 3D imaging on hybrid devices, beginning of targeted therapies</td>
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</tbody>
</table>
• p⁺ and n⁰ are composite particles:

• e⁻ is a fundamental particle

**NUCLIDE REPRESENTATION:** A Z X

A - mass number (= number of protons + number of neutrons)
Z - atomic number (= number of protons = number of electrons)

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**ISOTOPES:**
Number of neutrons are different
e.g. 6 protons ⇒ CARBON

+ 5 neutrons ⇒ ¹¹C
+ 6 neutrons ⇒ ¹²C
+ 7 neutrons ⇒ ¹³C
+ 8 neutrons ⇒ ¹⁴C

artificial
99%
1%
1.2 10⁻¹⁰ %

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**Chemical properties of the isotopes are identical:**
Radioactive decay is a way for unstable nuclides to achieve a more stable nuclear state

Binding energy per nucleon as a function of mass number
1. **Alpha decay** (elements above Pb in the periodic table, e.g. decay series)

\[
^{226}_{88}\text{Ra} \xrightarrow{\alpha} ^{222}_{86}\text{Rn} + ^4_2\text{He} \\
^{222}_{86}\text{Rn} \xrightarrow{\alpha} ^{218}_{84}\text{Po} + ^4_2\text{He}
\]

2. **Beta decay**

a) Isotopes with an excess of neutrons: emit \(\beta^-\) particles (electrons)

\[
n \xrightarrow{\beta^-} p^+ + e^- + \bar{\nu} \\
^{32}_{15}\text{P} \xrightarrow{\beta^-} ^{32}_{16}\text{S} + e^- + \bar{\nu}
\]

b) Isotopes with a deficiency of neutrons: emit \(\beta^+\) particles (positrons = anti-electrons)

\[
p^+ \xrightarrow{\beta^+} n + e^+ + \nu \\
^{18}_{9}\text{F} \xrightarrow{\beta^+} ^{18}_{8}\text{O} + e^+ + \nu
\]

OR their nucleus captures an electron:

c). Electron capture

\[
p^+ + e^- \xrightarrow{\text{EC}} n + \nu \\
^{111}_{49}\text{In} \xrightarrow{\text{EC}} ^{111}_{48}\text{Cd} + E(\nu, \gamma, \text{X-rays, Auger-}e^-)
\]

The nucleus captures an electron from an orbital shell, then an electron from a higher energy level fill the vacancy resulting in *characteristic X-ray* photons or Auger electrons.
complex decay of I-125

$^{125}_{53} \text{I} \rightarrow ^{125}_{52}\text{Te} + \nu$

IT:
7% $\gamma$
93% IC ($e^- + X\text{ray}$)

$^{125}_{52}\text{Te} + \gamma$

EC:

$^{125}_{53}\text{I} \rightarrow ^{125}_{52}\text{Te} + \nu$

X-ray
Auger $e^-$$

$^{125}_{53}\text{I}$

EC:

Auger $e^-$$

L_2
L_1
K

OR
characteristic X ray

$\gamma$ – IC competition:

$^{125}_{52}\text{Te}$

IT:

$\gamma$
conversion $e^-$

characteristic X ray

$\gamma$ radiation
The radioactive decay is random:

\[
\begin{align*}
32^P_{15} & \rightarrow 32^S_{16} + \beta^- + \bar{\nu}
\end{align*}
\]
Description of the radioactive decay

Radioactivity is the decay rate of a radioactive substance:

\[ A = - \frac{dN}{dt} \]

The decay rate is proportional to the number of radionuclides, \( N \). If \( N \) and the decay rate are great enough:

\[ -\frac{dN}{dt} = \lambda N \]

1000 unstable atoms decay 10 times faster than 100 unstable atoms of the same isotope

If the original number of nuclei at \( t = 0 \) s is \( N_0 \), then integration yields:

\[ N = N_0 e^{-\lambda t} \]

Substitution with \( A/\lambda \) for \( N \) and \( A_0/\lambda \) for \( N_0 \) results in the practical expression:

\[ A = A_0 e^{-\lambda t} \quad \text{and} \quad \lambda = \frac{\ln 2}{t_{1/2}} \]
For a given radioactive isotope, the time taken for any number of atoms to decay to half, the **HALF-LIFE**, is a unique number. The half life can be used to qualitatively **identify a specific isotope**.

**half-life values range** from $10^{15}$ y to $10^{-18}$ s

![Graph showing radioactive decay curves for different isotopes](image)
Absolute activity: A
The definition of activity: the number of disintegrations per unit time.
disintegrations per second, or dps (1 dps = 1 Bq (SI unit))

Historical: 1 Ci is the activity of 1 g of radium

1 Bq = 1 dps = $2.7 \times 10^{-11}$ Ci
1 Ci = $3.7 \times 10^{10}$ dps = 37 GBq (exactly)

1 Ci of pure $^{60}$Co ($t_{1/2} = 5.27$ y) $\Rightarrow$ 0.9 mg
1 Ci of natural $^{238}$U ($t_{1/2} = 4.5 \times 10^9$ y) $\Rightarrow$ over 2 t

**SPECIFIC ACTIVITY**
activity per unit mass of a radioactive substance
e.g. Ci/g or Bq/g

molar activity (e.g. TBq/mmol), and Bq/cm$^3$ are also called specific activity

\[ a = \lambda \cdot N_A = \frac{\ln 2}{t_{1/2}} \cdot 6.023 \times 10^{23} \text{ [Bq/mol]} \]

**ACTIVITY CONCENTRATION**
e.g. MBq/mL
**Interaction of the radiation with matter**

**α-particles**: short, straight path
- Lose their energy by ionization and excitation

\[\alpha \rightarrow \text{ionization and excitation} \]

**β-particles**: longer, random path

\[\beta \rightarrow \text{random path} \]

**γ-rays**: long range, 3 major routes
- **Photoelectron**:\( \gamma \) photons collide with and eject an \( e^- \)

\[ \text{hv} \rightarrow e^- \]

- **Compton-electron**:\( \gamma \) photons collide with and eject an \( e^- \), and are scattered with reduced energy

\[ \text{hv} \rightarrow e^- + e^- \]

- **γ photons (> 1.02 MeV) are completely absorbed with the formation of an \( e^- \) and \( e^+ \) pair**

\[ \text{hv} \rightarrow e^- + e^+ \]
Measurement of radioactivity

Based on the radiation – matter interactions (mainly ionization and excitation)

GAS IONIZATION DETECTORS
  e.g. Geiger-Müller ionization chamber proportional counter

SCINTILLATION COUNTERS
  Liquid scintillation analysis Čerenkov counting

SEMICONDUCTOR DETECTORS
Measurement of radioactivity

Schematic representation of gas ionization detectors:

Characteristics of gas ionization detectors:

Three main types of gas ionization detectors:
- ion chamber (all the primary ions are collected)
- proportional counter (the number of additional ions is proportional to the number of primary ions)
- Geiger-Müller counter (the total number of ions is independent of the number of primary ions)
Measurement of radioactivity

Liquid scintillation process:
Energy conversion → formation of fluorescence photons
Detection of FL photons with PMTs
Measurement of radioactivity

Chemical, photon and color quench during liquid scintillation
Solid scintillation detectors: count also fluorescence photons

Fluorescence photons generate photoelectrons at the photocathode, followed by secunder electron emissions in the dinode system.

SPECT camera: the NaI(Tl) detector rotates around the patient

Kowalsky, R.J., Falen S.W.(2011)
Radiopharmaceuticals in nuclear Pharmacy and nuclear medicine
Measurement of radioactivity

Detection of annihilation photons in PET

PET detector scintillators: BGO (Bi_4Ge_3O_{12}), LSO (Lu_2SiO_5(Ce)) and GSO (Gd_2SiO_5(Ce))

A PET/CT instrument
Production of medical radioisotopes

1. Neutron activation in nuclear reactors:

\[ ^{152}\text{Sm}(n,\gamma)^{153}\text{Sm} \]
\[ ^{50}\text{Cr}(n,\gamma)^{51}\text{Cr} \]
\[ ^{130}\text{Te}(n,\gamma)^{131}\text{Te} (\beta^-) \rightarrow ^{131}\text{I} \]

\[ t_{1/2}(\text{Te-131})= 25 \text{ min}, \quad t_{1/2}(\text{I-131})= 8 \text{ d} \]

2. Isolation among the fission products of U-235:

Xe-133, I-131, Mo-99

3. Cyclotron production:

\[ ^{111}\text{Cd}(p,n)^{111}\text{In} \]
\[ ^{18}\text{O}(p,n)^{18}\text{F} \]
### Radionuclide generators

Common radionuclide pairs in radionuclide generators:

<table>
<thead>
<tr>
<th>Parent ($t_{1/2}$)</th>
<th>Decay</th>
<th>Daughter ($t_{1/2}$)</th>
<th>Decay</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ge-68 (270 d)</td>
<td>EC</td>
<td>Ga-68 (68 min)</td>
<td>$\beta^+$ (1.9 MeV), EC</td>
<td>PET</td>
</tr>
<tr>
<td>Rb-81 (4.5 h)</td>
<td>EC</td>
<td>Kr-81m (13 s)</td>
<td>IT (191 keV $\gamma$)</td>
<td>imaging</td>
</tr>
<tr>
<td>Sr-82 (25 d)</td>
<td>EC</td>
<td>Rb-82 (75 s)</td>
<td>$\beta^+$ (3.18 MeV)</td>
<td>PET</td>
</tr>
<tr>
<td>Sr-90 (28.8 y)</td>
<td>$\beta^-$</td>
<td>Y-90 (64 h)</td>
<td>$\beta^-$ (2.28 MeV)</td>
<td>therapy</td>
</tr>
<tr>
<td>Mo-99 (66 h)</td>
<td>$\beta^-$</td>
<td>Tc-99m (6 h)</td>
<td>IT (140 keV $\gamma$)</td>
<td>imaging</td>
</tr>
<tr>
<td>Sn-113 (115 d)</td>
<td>EC</td>
<td>In-113m (1.7 h)</td>
<td>IT (393 keV $\gamma$)</td>
<td>imaging</td>
</tr>
</tbody>
</table>

Relative activity of Mo-99 and Tc-99m in the generator:
**Linear energy transfer (LET):** transferred energy on the unit length of the particle path

<table>
<thead>
<tr>
<th>LET (keV/μm)</th>
<th>Co-60 γ</th>
<th>0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 kV X-ray</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>β</td>
<td>- 10</td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>50 - 70</td>
<td></td>
</tr>
</tbody>
</table>

\[
LET = \frac{\Delta E}{l} \quad \left[ \frac{keV}{\mu m} \right]
\]

This energy transfer responsible for the biological effects:
Direct and indirect effects of the ionizing radiation

\[ \text{H}_2\text{O} \rightarrow \text{e}^{\text{aq}}^- + \text{H}_3\text{O}^+ \]

\[ \ddot{\text{OH}} + \text{H}^+ \]

indirect energy transfer

direct energy transfer
**Dosimetry**

**ABSORBED DOSE (D):**

\[ D = \frac{d\epsilon}{dm} \quad \text{J/kg} = \text{Gy (gray)} \]

**EQUIVALENT DOSE (H_{T,R}):**

\[ H_{T,R} = w_R \cdot D_{T,R} \]

\[ 1 \text{ J/kg} = 1 \text{ Sv (sievert)} \]

For a tissue

\[ w_R = \text{radiation weighting factor, proportional to LET} \]

**EFFECTIVE DOSE (E):**

\[ E = \sum_{T} w_T \cdot H_T \]

\[ 1 \text{ J/kg} = 1 \text{ Sv (sievert)} \]

For the whole body

\[ w_R = \text{tissue weighting factor} \]

**COMMITTED DOSES:**

After incorporation
**Deterministic and stochastic effects**

**Deterministic effects:**
- at low dose: successful repairs
- threshold dose depends on the sensitivity of the tissue
- above t.d. the effect appears for everybody (eg. $D_0 = 2$ Gy for skin reddening)

**Stochastic effects:**
- only for population level not for individuals
# Effective dose values of different procedures

<table>
<thead>
<tr>
<th>Source of radiation exposure</th>
<th>Effective dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation sickness</td>
<td>&gt; 1 Sv immediately</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>16 mSv</td>
</tr>
<tr>
<td>$[^{67}\text{Ga}]\text{Ga}$-citrate (4 mCi) body scan</td>
<td>15 mSv</td>
</tr>
<tr>
<td>$[^{18}\text{F}]\text{FDG}$ (20 mCi) brain PET scan</td>
<td>14 mSv</td>
</tr>
<tr>
<td>Mammography (X-ray)</td>
<td>4 mSv</td>
</tr>
<tr>
<td>Natural background radiation (worldwide average)</td>
<td>2.4 mSv/y</td>
</tr>
<tr>
<td>Head CT</td>
<td>2 mSv</td>
</tr>
<tr>
<td>$[^{123}\text{I}]\text{NaI}$ (0.25 mCi) thyroid scan</td>
<td>1.9 mSv</td>
</tr>
<tr>
<td>$[^{111}\text{In}]\text{pentetreotide}$ (6 mCi) body scan</td>
<td>1.2 mSv</td>
</tr>
<tr>
<td>Dose limit for the general public</td>
<td>1 mSv/y</td>
</tr>
<tr>
<td>$[^{133}\text{Xe}]\text{Xe}$ (20 mCi) lung ventilation</td>
<td>0.5 mSv</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>0.1 mSv</td>
</tr>
<tr>
<td>Exemption levels of radioactive substances</td>
<td>&lt; 10 mSv/y</td>
</tr>
</tbody>
</table>
Currently, the major problem in radionuclide therapy is that there is no accepted standard method for calculating the absorbed dose from internal radionuclides.

The **European Association of Nuclear Medicine (EANM)** has recently issued a guidance document on **“Good Practice of Dosimetry Reporting”**.

Definitions issued by the committee:

**-Medical internal radiation dose (MIRD):** Calculation of the average tumor-absorbed dose at macroscopic level. This calculated dose assumes a homogenous distribution of radionuclide in organs. It does not calculate with intra-tumoral heterogenic distribution of the radionuclides.

**-Equivalent uniform biologically effective dose (EUBED):** A uniform value of the biologically effective dose that gives the same surviving fraction as the non-uniform distribution.

Aim: To avoid unwanted irreversible isotope exchange, non-targeted tissue deposition and to improve tissue distribution and biological elimination rate.

Formulation strategies:

1. Peptide and protein-based carriers: a chelator is linked to the carrier that is responsible for the highly specific interaction with membrane-bound receptors, cytoplasmic proteins or DNA of tumor cells.

   e.g. Ga-68, Tc-99m, Sr-89, Y-90, In-111, Lu-177, At-211, Ac-225

W.A. Volkert, Chem. Rev. 1999
Formulation strategies:

2. Nano-assemblies: Inorganic multivalent nanoparticles that dispose of optical (e.g. gold nanoparticles, carbon nanotubes, silica nanoparticles) or magnetic (e.g. iron oxide) properties, can be exploited for thermal-ablation therapy of malignant tumors or molecular imaging. Other types of radiolabeled nanoparticles, composed of self-organizing materials (e.g. dendrimers, micelles, liposomes), have proven to be promising tools as imaging agents in the diagnosis and therapy of malignant processes.

Mode of action: Passive accumulation through an enhanced perfusion/retention effect, which likely occurs in tumors with disorganised vasculature.

Y. Xing, Theranostics 2014
PET provides high resolution functional information on the target organ or its metabolic activity, still before the anatomical signs of the disease are observed.

**Radiodiagnostic agents:** $^{18}$F or $^{11}$C-containing organic compounds, e.g.:

**Clinical diagnostic use:** Brain and cardiovascular diseases.

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Gamma-emitting radiopharmaceuticals are exploited to visualize tumors and to investigate energy imbalances and cardiovascular deficiencies by SPECT system.

**Radiodiagnostic agents:** Tc-99m or I-123 containing organic compounds

- $[^{99m}\text{Tc}]$sestamibi (breast imaging)
- $[^{99m}\text{Tc}]$tetrofosmin (heart imaging)
- $[^{99m}\text{Tc}]$medronate (bone imaging)
- $[^{99m}\text{Tc}]$bicisate (localization of stroke)
- $[^{99m}\text{Tc}]$pentetate and gluceptate (brain and kidney imaging)
- $[^{99m}\text{Tc}]$mebrofenin and disofenin (hepatobiliary imaging)
- $[^{99m}\text{Tc}]$exametazime (detection of altered cerebral perfusion in stroke)
- $[^{123}\text{I}]$MIBG (or iobenguane sulfate) (localization of neuroblastomas, pheochromocytomas)

**Advantage:** no on site cyclotron is required

**Disadvantage:** lower resolution than that of PET
Combination of different modalities such as nuclear medicine and radiology.

In synchronous multimodality imaging, morphological and functional information are merged and processed in time and space.

**Advantages:** fast and accurate diagnosis (more precise localization, extent and metabolic activity of the target tissue).

**Multimodality technologies:** SPECT-CT, PET-CT, PET-MRI, fMRI-NIRS, MRI-MEG, MRI-EEG

**Clinical application:** measurement of ischemic conditions (heart and brain diseases)
Therapeutic radiopharmaceuticals are designed to deliver therapeutic doses to cancerous tumors with high tissue specificity and with appropriate clearance from nontargeted tissues.

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Clinical use</th>
<th>References</th>
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<tbody>
<tr>
<td><strong>β-particle emitters:</strong></td>
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<td></td>
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<tr>
<td><strong>α-particle emitters:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Auger-electron emitters:</strong></td>
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</tbody>
</table>
**Aims:** To improve biodistribution of radiopharmaceuticals, and to enhance tumor uptake and faster blood clearance.

The most well-known strategy is the avidin/streptavidine biotin system.

**Steps:**
1. Pre-sensitization of the target cancer cells with a long-lived, high affinity and specificity circulating non-radiolabeled monoclonal antibody (MAb).
2. Elimination of the unbound MAb construct from the blood and other non-target tissues with a “chase molecule”.
3. Administration of the radiolabeled (usually $^{90}$Y, $^{131}$I, $^{188}$Re or $^{67}$Cu) hapten or biotin conjugate.

R. Schoffelen, Br. J. Cancer 2013
Thank you for your attention!

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