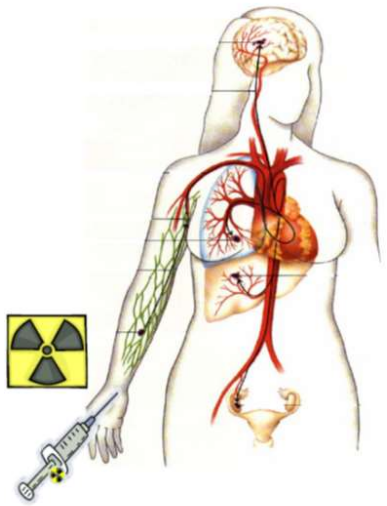
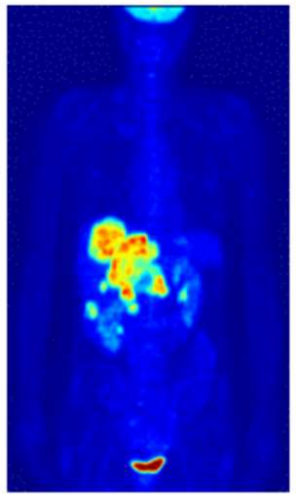
The Radiopharmacy and Radiopharmaceuticals

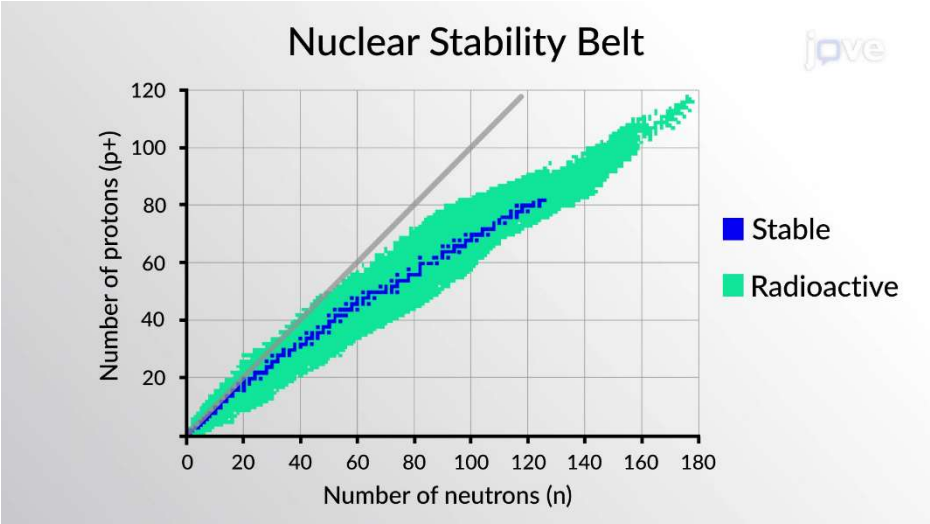
Nuclear medicine and radiotracer

- Nuclear medicine, in the simplest terms, is the medical specialty based on examining the regional chemistry of the living human body.
- In the 1920s, Georg De Hevesy coined the term “radioindicator” (radiotracer) and introduced the “tracer principle” to the biomedical sciences.
- One of the most important characteristics of a true tracer is the ability to study the components of a homeostatic system without disturbing their function.





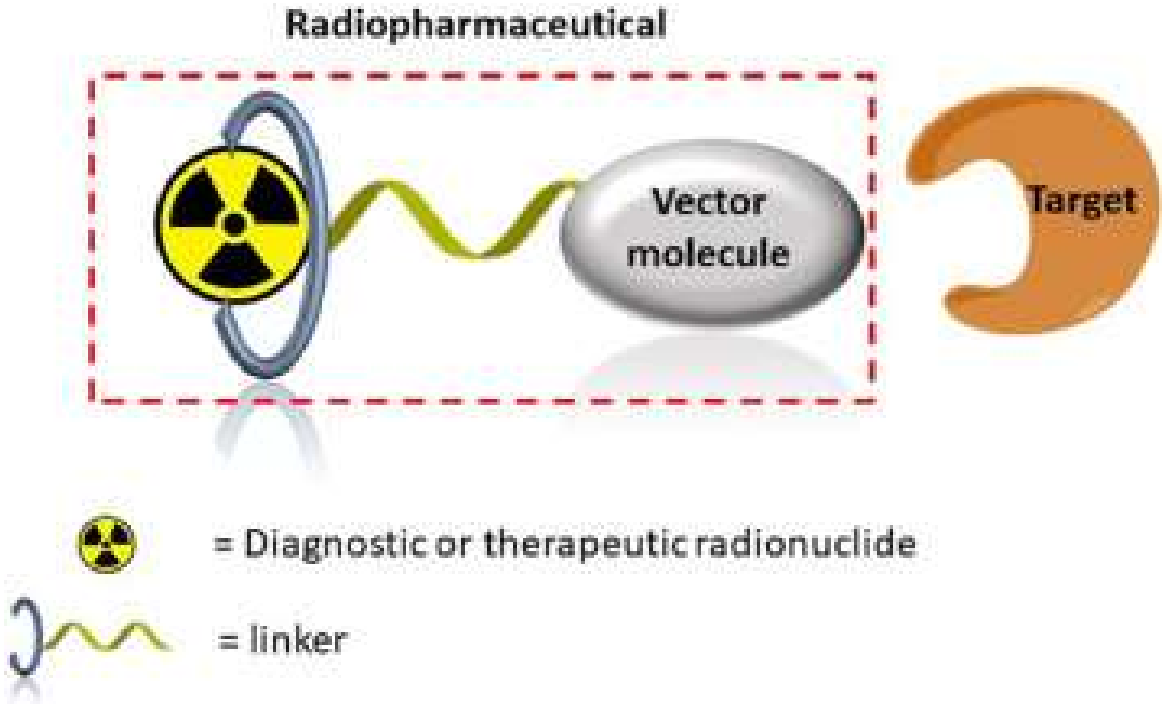
- **Radioactivity** is a property of atomic nuclei and may be defined as the spontaneous transformation of a structurally unstable nucleus to a structurally more stable nucleus, with the emission of energy in the form of ionizing radiation.
- A nucleus not in its stable state will adjust itself until it is stable either by ejecting portions of its nucleus or by emitting energy in the form of photons (gamma rays). This process is referred to as radioactive decay.
- Two features largely determine the structural stability of a nucleus: **the size** (i.e., atomic number, Z) and **the neutron-to-proton** (N-to-Z) **ratio**.



Definition of a Radiopharmaceutical

A radiopharmaceutical is a radioactive drug used for diagnosis or therapy in a tracer quantity, masses so small that they do not produce pharmacologic effects,

It is composed of two parts : a radionuclide and a pharmaceutical



Definition of a Radiopharmaceutical

- The usefulness of a radiopharmaceutical depends on characteristics of radionuclide and ligand (vector molecule)
- Ligand: The properties are primarily responsible for dictating how the product will behave in the body. Ligand is chosen on the basis of its preferential localization in a given organ or its participation in the physiologic function of the organ.

Ideal Properties of Diagnostic Radiopharmaceutical

- **Decay mode:** Electron capture or isomeric transition from metastable states; gamma emission , without particulate radiation;
- **Photon energy:** 100 - 200 keV is ideal.
- **Short Effective Half-Life:** Effective Half-Life (Te) in any biologic system, the loss of a radiopharmaceutical is due to both the physical decay of the radionuclide and the biologic elimination of the radiopharmaceutical. The physical half-life (**Tp**) is independent of any physicochemical condition and is characteristic for a given radionuclide.
- Biologic half-life (**Tb**): Radiopharmaceuticals administered to humans disappear from the biological system through fecal or urinary excretion, perspiration, or other mechanisms. Thus, every radiopharmaceutical has a biologic half-life.
- **1/TE = 1/TB + 1/TP or TE =(TB TP)/ (TB + TP)**

Ideal Properties of Diagnostic Radiopharmaceutical

Easy Availability: The radiopharmaceutical should be easily produced, inexpensive, and readily available in any nuclear medicine facility

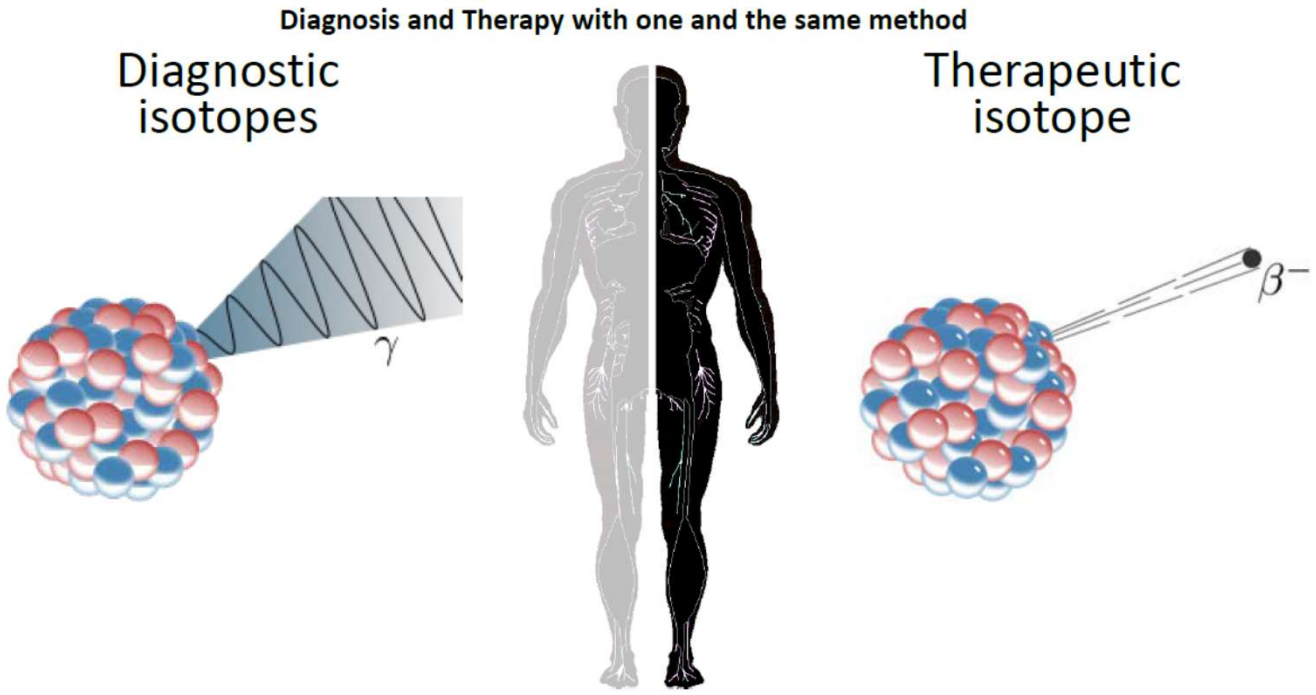
Chemical properties: Can be compounded into different chemical forms.

High Target-to-Non-target Activity Ratio: it is desirable that the radiopharmaceutical be localized preferentially in the organ under study, while maintaining minimum uptake in the normal tissue

The stability of a labeled compound is one of the major concerns in labeling chemistry. It must be stable both in vitro and in vivo.

- *An ideal radiopharmaceutical should have all the above characteristics to provide maximum efficacy in the diagnosis of diseases and a minimum radiation dose to the patient.*
- *However, it is difficult for a given radiopharmaceutical to meet all these criteria and the one of choice is the best of many compromises.*

Diagnostic vs. therapeutic isotope



In nuclear medicine nearly 95% of the radiopharmaceuticals are used for diagnostic purposes, while the rest are used for therapeutic treatment.

Factors Influencing the Distribution and Localization of Radiopharmaceuticals

Size of the Molecule

- The molecular size of a radiopharmaceutical is an important determinant in its absorption in the biologic system. Larger molecules (mol. wt. >~60, 000) are not filtered by the glomeruli in the kidney.

Protein Binding

- Protein binding is greatly influenced by a number of factors, such as the charge on the radiopharmaceutical molecule, the pH, the nature of protein, and the concentration of anions in plasma
- Protein binding affects the tissue distribution and plasma clearance of a radiopharmaceutical and its uptake by the organ of interest

Factors Influencing the Distribution and Localization of Radiopharmaceuticals

Solubility

- the cell membrane is primarily composed of phospholipids, and unless the RF is lipid soluble, it will hardly diffuse through the cell membrane.
- Protein binding reduces the lipid solubility of a radiopharmaceutical. Ionized drugs are less lipid soluble, whereas nonpolar drugs are highly soluble in lipids and hence easily diffuse through cell membranes.

Ideal Therapeutic Radiopharmaceuticals

Particulate emission: α, β– or Auger electron emitters with a physical half-life in the range of several hours to about 10 days, a small amount of accompanying γ -emission is advantageous to determine the radioactivity distribution in the body and for dosimetry.

Energy: medium/high (>1 MeV)

Effective Half-life: 5-20 days

The higher the linear energy transfer (LET) of the emitter, the higher will be the effect on the targeted tissue per decay

Target-to-Non target Ratio

Easy Availability

Production Modes

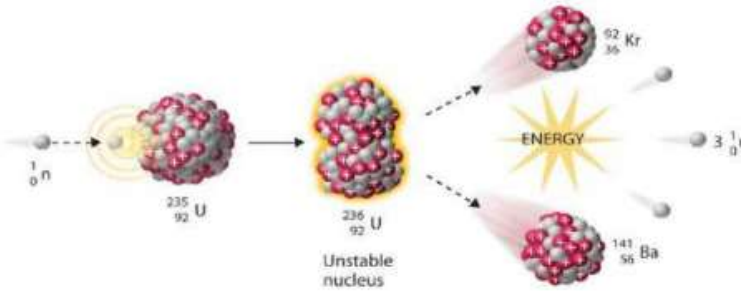
- According to their production modes, radionuclides can be divided into three groups:

- Reactor - produced radionuclides

  Fission or (n,f) Reaction

$$^{235}_{92}U + ^{1}_{0}n \rightarrow ^{236}_{92}U \rightarrow ^{92}_{36}Kr + ^{141}_{56}Ba + 3\,^{1}_{0}n$$

$$\rightarrow ^{131}_{53}I + ^{102}_{39}Y + 3\,^{1}n$$

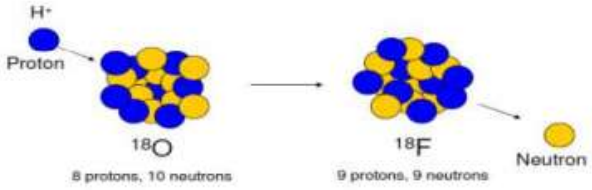


  Neutron Capture or (n, γ) Reaction

$$^{98}Mo(n,\gamma)^{99}MO \;、\; ^{196}Hg\ (n,\gamma)^{197}Hg$$

- Cyclotron - produced radionuclides

$$^{18}O(p,n)^{18}F \;、\; ^{14}C(p,\alpha)^{11}C \;、\; ^{66}Zn(d,n)^{67}Ga$$

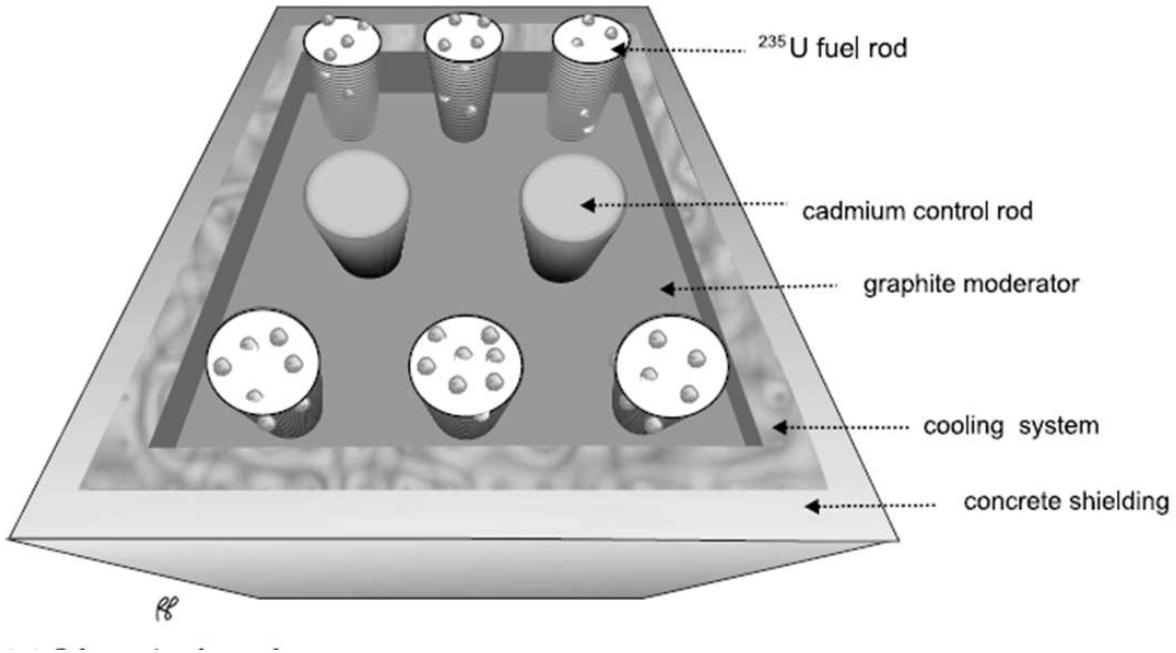


- Generator - produced radionuclides

$$^{99}Mo/^{99m}Tc \;、\; ^{68}Ge/^{68}Ga \;、\; ^{113}Sn/^{113m}In$$

Reactors

- Radionuclides for nuclear medicine are also produced in nuclear reactors. Some examples include ^{131}I, ^{133}Xe, and ^{99}Mo.
- It is composed of fuel rods that contain large atoms (typically uranium- 235, uranium-238, or plutonium-239) that are inherently unstable. These atoms undergo fission. Two or three neutrons and approximately 200MeV of heat energy are emitted during fission.



- If this chain reaction were to grow unchecked, the mass would explode.
- To maintain control, cadmium control rods are inserted to absorb the neutrons in the reactor.

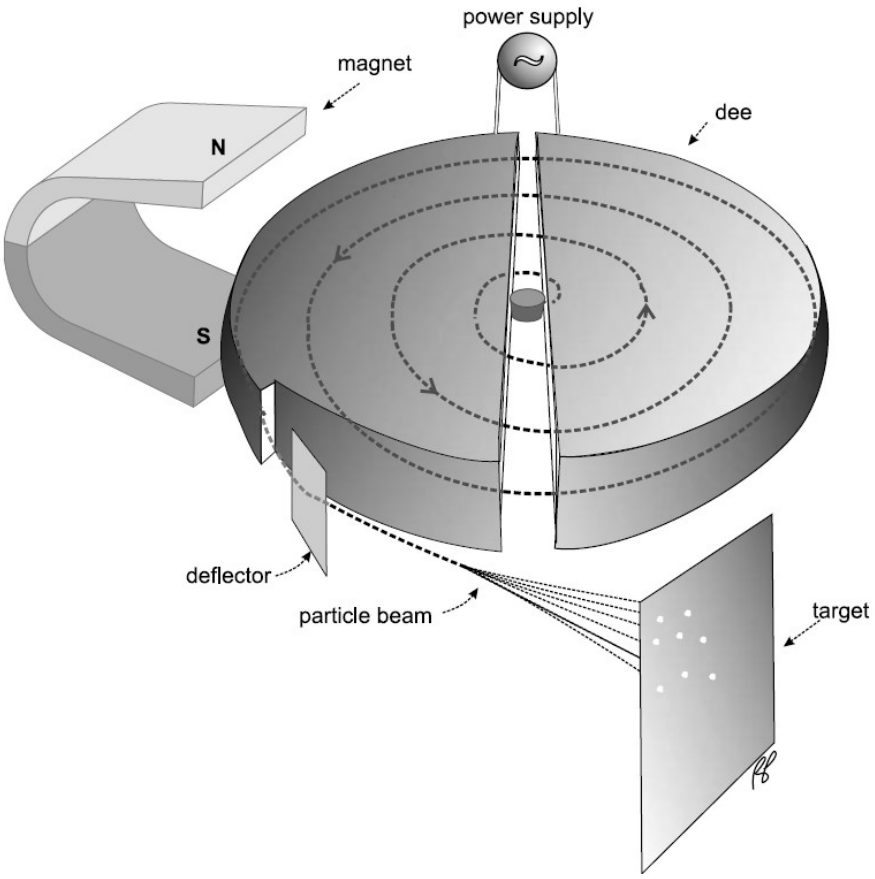
Reactor Nuclides

- **(n, γ) reaction** produce neutron-rich isotopes, thermal neutrons will react with stable isotopes deposited inside a reaction chamber in defined areas of the nuclear reactor. This will preferably lead to β –- emitters. Isotopes produced like this are of relatively low specific activity, as the produced isotope is of the same element as the target. Thus the produced isotope cannot be chemically separated from the target isotope.
- (**n, p) reaction:** may occur in regions of the nuclear reactor where fast neutrons dominate. In this case, the mass of the produced isotope will not change. However, by eliminating a proton from the target isotope a change in the element (one unit lower) will occur.

Cyclotron Nuclides

- Since a high energy beam of positively charged particles is required to produce proton rich radionuclides, accelerators have been developed to generate a well defined, high energy beam of charged particles with high beam intensity.
- Because acceleratable particles are of a charged nature, typical cyclotron produced isotopes are neutron deficient. They are produced by irradiation of stable target compounds with charged particles like protons (p), deuterons (d) or helium nuclei.
- Because of the neutron deficient nature of the produced isotopes, they tend to stabilize by electron capture (EC) or by positron emission (β +). These decay modes are particularly useful for nuclear medicine purposes and they are thus useful diagnostic isotopes.

Cyclotron Nuclides



The cyclotron consists of three major components:

- an electromagnet with a field strength of 1.5–2.0 tesla,
- a pair of semicircular hollow copper electrodes, called “dees” located between the poles of the magnet,
- ion source capable of generating high intensity negative ions.

The entire structure of the cyclotron is kept under high vacuum.

Cyclotron Nuclides

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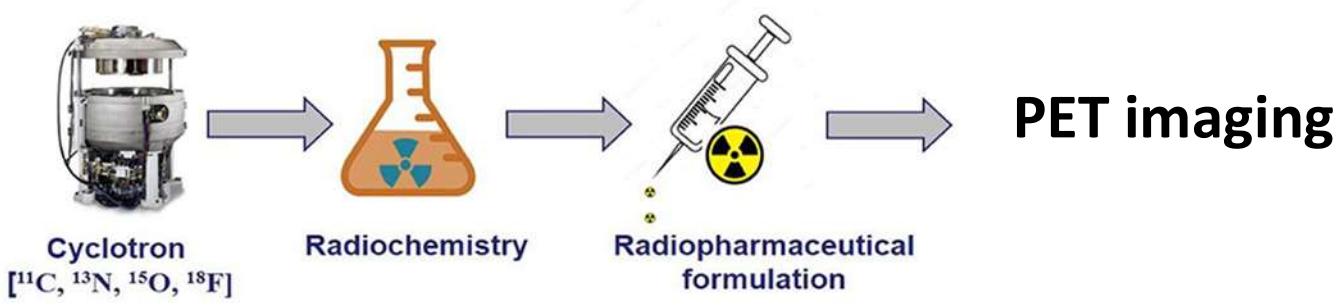
PET Radionuclides

- the organic positron emitters such as ^{11}C,^{13}N, ^{15}O and ^{18}F.
- The physical half-life of most of these positron emitters is relatively short (<2 h) and as a result the theoretical specific activity (SA) is very high.
- The basic principle of PET imaging technique is based on the coincident detection of annihilation photons produced by the interaction of positron with an electron.



PET Radiopharmaceuticals: Mechanisms of Cellular Uptake and Localization

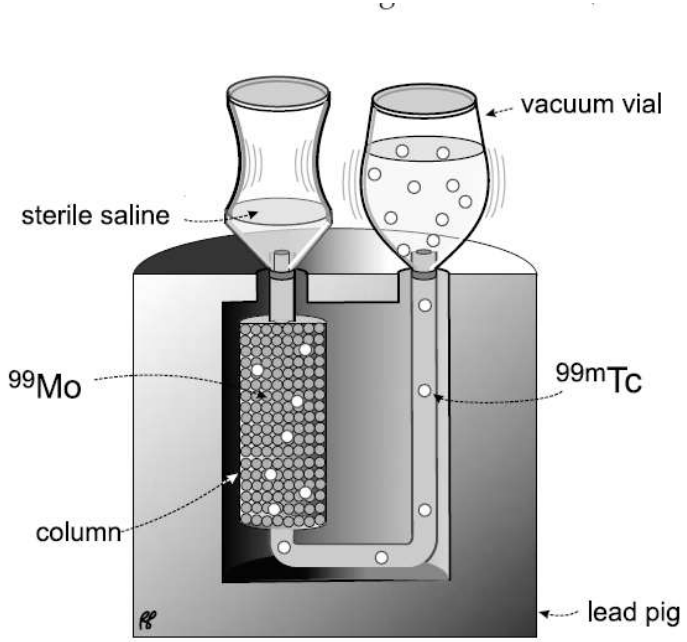
- Compared to SPECT, the PET technique has the unique advantage of developing radiopharmaceuticals as diagnostic radiotracers or molecular imaging probes to detect and quantitate the function of an organ or a unique biochemical process in a specific tissue.
- PET radiopharmaceuticals can be **generally classified based on their ability to image a specific biochemical process** or based on **their unique mechanism of localization in a specific organ/tissue** of interest .

Molybdenum/Technetium Generators

•All radionuclide generators work on the principle that a relatively long-lived “parent” radionuclide decays to produce a “daughter” radionuclide, where the chemical nature of parent and daughter are quite different. This difference allows separation of the daughter from the parent.

•The $^{99}Mo/^{99m}Tc$ generator consists of ^{99}Mo absorbed onto an alumina filled column. The ^{99}Mo decays to its daughter radionuclide ^{99m}Tc

- ^{99m}Tc is removed from the column as sodium pertechnetate, $Na^{99m}TcO4$, by drawing a solution of sodium chloride (NaCl) 0.9% through the column. This process is known as eluting the generator and gives a sterile solution of sodium pertechnetate (the eluate)



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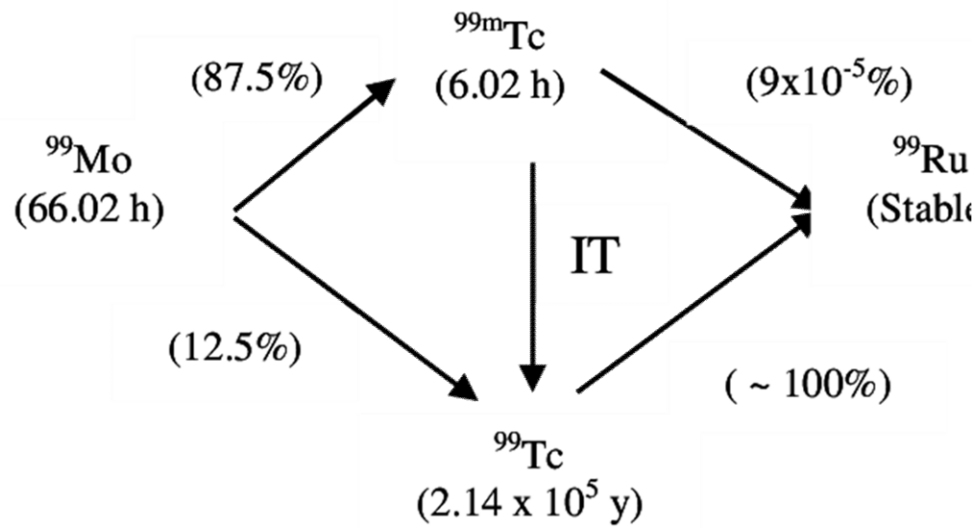
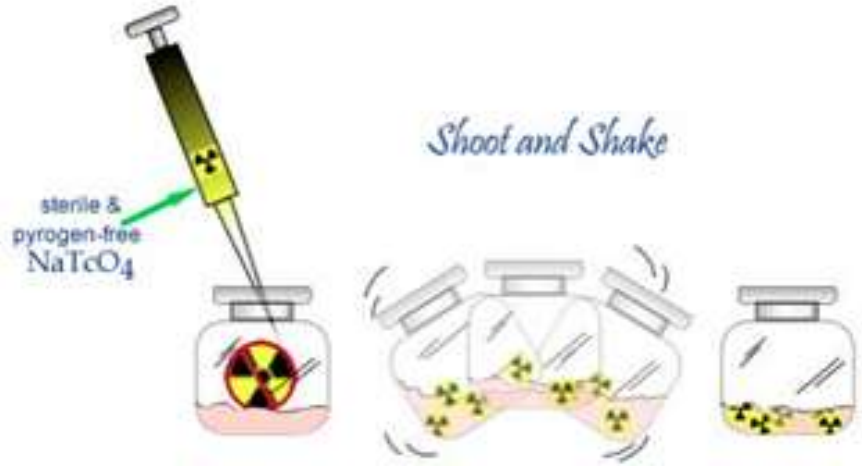
Technetium-99m

- decays with a half-life of 6.0 h by isomeric transition to 99mTc, emitting a single photon with an energy of 141 keV.
- The rich complex chemistry of technetium allows incorporation of the radioisotope into a wide variety of ligands stabilizing the radionuclide at different oxidation states.
- In order to form Tc-99m-labeled organic molecules it is necessary to reduce the pertechnetate anion to a lower oxidation state. A variety of reducing agents might be used; however, stannous(II) ions are used in most cases.



Preparation of a Technetium-99m labeled radiopharmaceutical

- Tc-99m as sodium Pertechnetate is added to the reaction vial
- Tc-99m radiopharmaceutical is ready for dispensing
- The patient dose is withdrawn from the vial
- Each dose is measured in the dose calibrator before it dispensed



Characteristics of Commonly Used Generators

$$^{68}\mathrm{Ge} \xrightarrow[275\ \mathrm{d}]{\varepsilon} {}^{68}\mathrm{Ga} \xrightarrow[1.14\ \mathrm{hr}]{\beta^+,\ \varepsilon,\ \gamma} {}^{68}\mathrm{Zn}$$

$$^{81}\mathrm{Rb} \xrightarrow[4.7\ \mathrm{hr}]{\beta^+,\ \varepsilon} {}^{81\mathrm{m}}\mathrm{Kr} \xrightarrow[13\ \mathrm{sec}]{\gamma} {}^{81}\mathrm{Kr}$$

$$^{82}\mathrm{Sr} \xrightarrow[25\mathrm{d}]{\varepsilon} {}^{82}\mathrm{Rb} \xrightarrow[75\ \mathrm{sec}]{\beta^+,\ \varepsilon,\ \gamma} {}^{82}\mathrm{Kr}$$

$$^{99}\mathrm{Mo} \xrightarrow[67\ \mathrm{hr}]{\beta^-,\ \gamma} {}^{99\mathrm{m}}\mathrm{Tc} \xrightarrow[6\ \mathrm{hr}]{\gamma} {}^{99}\mathrm{Tc}$$

$$^{113}\mathrm{Sn} \xrightarrow[118\ \mathrm{d}]{\varepsilon} {}^{113\mathrm{m}}\mathrm{In} \xrightarrow[1.7\ \mathrm{hr}]{\gamma} {}^{113}\mathrm{In}$$

Radiopharmaceuticals classification on their ability to image a specific biochemical process

- Perfusion Agents (Myocardial, Brain , Lung Perfusion)
- Lung Ventilation Imaging Agents
- Metabolism Agents (Glucose, Amino Acid, Nucleosides Metabolism, Hypoxia Imaging)
- Peptides and Proteins (Somatostatin Receptor Tracers, Annexin V)
- Monoclonal Antibodies
- Neurotransmitter Receptor and Transporter Tracers (Benzodiazepine, Serotonergic (5-HT), Dopaminergic Receptor Tracers, Dopamine Transporter (DAT), Norepinephrine Transporter (NET)
- Amyloid Imaging
- Cell Labeling

IDEAL GENERATOR SYSTEMS

1. If intended for clinical use, the output of the generator must be sterile and pyrogen-free.

2. The chemical properties of the daughter must be different than those of the parent to permit separation of daughter from parent.

3. Generator should be eluted with 0.9% saline solution and should involve no violent chemical reactions. Human intervention should be minimal to minimize radiation dose.

4. Daughter isotope should be short-lived gamma-emitting nuclide (physical half-life = hrs-days)

5. Physical half-life of parent should be short enough so daughter regrowth after elution is rapid, but long enough for practicality.

6. Daughter chemistry should be suitable for preparation of a wide variety of compounds

7. Inexpensive, effective shielding of generator, minimizing radiation dose to those using it.

Radiopharmaceutical agents exhibit a huge range of physical and chemical properties and may be classified into eight different categories	
Radiolabeled particles	99mTc-MAA
Radiolabeled gases	133Xe, 127Xe, 81mKr 99mTc-Technegas
Radiolabeled chelates	99mTc-MDP, HDP 99mTc-DTPA 99mTc-MAG3
Radiotracers as ions	99mTc-pertechnetate (TcO-4)
Radiolabeled cells	99mTC-RBC, 111In-WBC
Receptor binding radiotracers	111In-pentetreotide, Octreoscan
Radiolabeled monoclonal antibodies	111In-antimyosin 111In-Prostascint
Radiolabeled metabolic substrates	18F-Fluorodeoxyglucose, 11C-choline

- The pharmacokinetics, biodistribution, and metabolism of the radiopharmaceutical are very important to understanding
- the mechanisms of radiopharmaceutical localization in the organ or tissue of interest.
- The mechanisms of radiopharmaceutical localization may be **substrate-nonspecific** (not participating in any specific biochemical reaction) or **substrate specific** (participating in a specific biochemical reaction), depending upon the chemistry of the molecule. Many radiopharmaceuticals were designed to take advantage of the pathophysiology in order to increase the specificity of the nuclear medicine imaging techniques.

Mechanisms of Radiopharmaceutical Localization

- Isotope Dilution (51Cr-RBCs, 125I-HSA)
- Physicochemical Adsorption (99mTc-labeled phosphonates)
- Capillary Blockade (99mTc-MAA)
- Cellular Migration and Sequestration (111In-oxine- or 99mTc-HMPAO- leukocytes)
- Simple Diffusion (133Xe, 127Xe, 81mKr) inert lipophilic gases,
- Diffusion and Intracellular Metabolism/Binding (99mTc-HMPAO, 99mTc-ECD)
- Diffusion and Mitochondrial Binding –(99mTc-sestamibi)
- Facilitated Diffusion-18F-fluorodeoxyglucose (FDG)
- Active Transport-Radioiodide and 99mTc-Pertechnetate Anions.
- Phagocytosis-99mTc-sulfur colloid

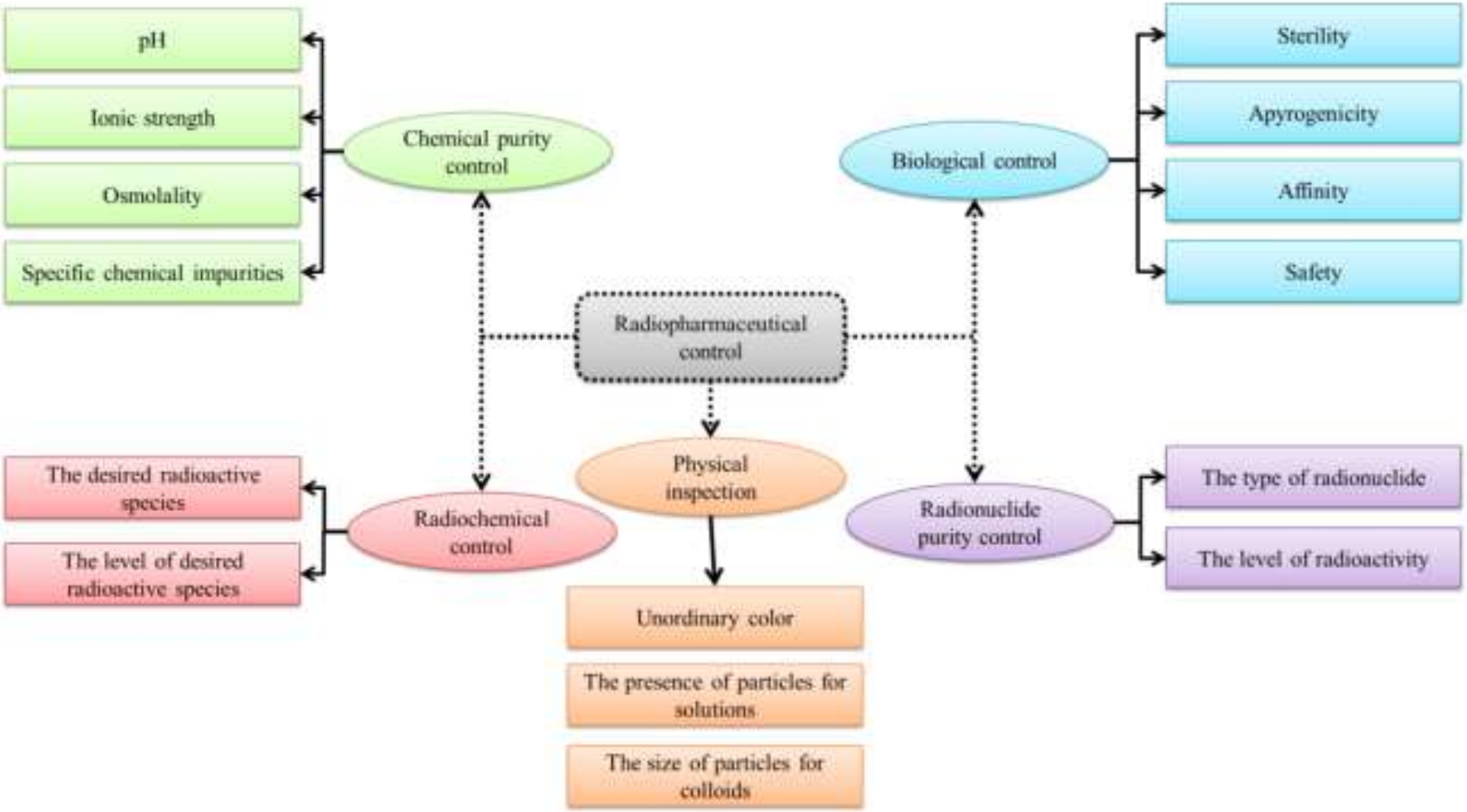
What happens when 99mTcO4- is administered IV?

- when 99mTcO4- is administered IV 100% of the dose immediately enters the blood stream. Once in the vascular compartment, 99mTcO4- level begin to drop. Physiologically 70 to 80% of the initial dose is partially bound to the RBC. Free 99mTcO4- passes into the interstitial space.
- As the rate of free Tech drops, the partially bound 99mTcO4- breaks away from the RBC, becomes free, and then it might enter the interstitial space.
- Pertechnetate will also concentrate in the following organs: stomach, salivary glands, thyroid, bowel, mucous membranes, choroids plexus.

Quality Assurance of Radiopharmaceuticals

- The radiopharmaceuticals are formulated as sterile, apyrogenic injections and are intended for administration to patients for a diagnostic or therapeutic purpose. These injections have to comply with the same standards of safety and efficacy as conventional pharmaceuticals.
- Analytical tests to check radionuclidic, radiochemical, and chemical purity must be carried out routinely. For injection, the radiopharmaceutical should be in aqueous solution at a pH compatible with blood pH (7.4). The ionic strength and osmolality of the agent should also be appropriate for blood.

Quality Assurance of Radiopharmaceuticals



Quality Assurance of Radiopharmaceuticals

1. Physicochemical Tests

✓*Physical characteristics*-inspect the color, size and state of radiopharmaceutical

Colloidal or aggregated RF: size checked with hemocytometer under a light microscope

99mTc-labeled colloid: for visualization of the reticuloendothelial system： 10nm -1 μm

^{99m}Tc-MAA, ^{99m}Tc-label albumin microsphere： 10 -90μm (>150 μm → pulmonary arterial blockade → embolism; smaller than 10 μm → localize in the reticuloendothelial system)

✓*pH:* Ideal pH radiopharmaceutical should be7.4 (pH of the blood). However, radiopharmaceutical can vary between 2-9 because of high buffer capacity of blood.

✓*Radionuclidic purity, Radiochemical purity*

2.Biological Tests (Sterility test, Apyrogenicity test)

Radionuclidic Purity

- the ratio, expressed as a percentage, of the radioactivity of the radionuclide concerned to the total radioactivity of the source. Radionuclides used medicinally are of a high radionuclidic purity (>95%).
- **^{99}Mo-^{99m}Tc generator**: There is the possibility of accidental elution of the parent ^{99}Mo during elution of the generator and a limit test for the ^{99}Mo should be performed. Acceptable limits of contaminants is less than 0.15 µCi per 1 mCi of 99mTc
- Radionuclidic purity is determined by measuring the half-live and characteristic radiation emitted by individual radionuclides.

Radiochemical Purity

- Radiochemical purity (RCP) may be defined as "the proportion of the total radioactivity in the sample which is present as the desired radiolabelled species“.
- For example free ^{99m}TcO4 and hydrolyzed ^{99m}Tc in ^{99m}Tc labeled complexes are the main radiochemical impurities for ^{99m}Tc-based radiopharmaceuticals
- For ^{99m}Tc radiopharmaceuticals, RCP may be measured by chromatographic means, for example using planar chromatography, electrophoresis, and high performance liquid chromatography (HPLC).

Chemical Purity

- for sodium pertechnetate (^{99m}Tc) injection - a limit test for the aluminum ($Al^{3+)}$ content of ^{99m}Tc eluates. Al^{3+} may originate from the generator column, being produced during the absorption process of the ^{99}Mo onto the alumina column. It is important to perform this test since Al^{3+} can affect the stability of some colloidal radiopharmaceuticals.

Sterility Assurance, Pyrogen Testing

- All preparations intended for parenteral administration must be tested to ensure that they comply with the test for sterility. There are problems, however, in applying this test to 99mTc-RF. Because of their short shelf-life, preparations have to be released prior to the results of the sterility test being known.
- Radioactive injections have been shown to support microbial growth, but are far from ideal growth media for long-term microbiological survival.
- Even in the absence of radioactivity, generator eluates and reconstituted kits have been shown not to support long-term microbiological growth.
- Pyrogens are non-volatile, water-soluble substances that, when injected into the body, cause a rise in temperature

THANK YOU FOR YOUR ATTENTION!

QUESTIONS