

Review About Role of Radiopharmaceuticals Application in Diagnosis and Therapy

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ABSTRACT

A class of radioactive substances used for medicinal or diagnostic purposes is known as radiopharmaceuticals. The biomolecular characteristics of radiopharmaceuticals, i.e., the regions of the bright signal seen on positron emission tomography (PET) or single photon emission computed tomography (SPECT) scans that indicate a high metabolic requirement for tissue, make them prone to localize to certain tissues, even if their administration is frequently systemic. Radiopharmaceuticals also act as radioactive tracers among patients via gamma-ray emissions. As a result, patients may get radiopharmaceuticals as diagnostic tools to look for any anomalies related to biochemistry, molecular biology, physiology, or anatomy. Internal administration of therapeutic radiopharmaceuticals can be used to treat certain abnormal cells or organs by means of a selective impact.

Keywords: Radiopharmaceutical, Positron emission tomography, Single photon emission computed tomography.

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INTRODUCTION

Radiopharmaceuticals, already credited to as drugs in 1960, are radiolabelled molecules designed for in vivo application.¹ Nuclear physics, medicine, and chemistry come together to form the important field of radiopharmaceuticals, which are essential to targeted therapies and diagnostic imaging,² Radioactive versions of chemical elements, known as radioisotopes, It is described as an unstable nuclide that spontaneously decays by releasing photons (gamma rays) or particles (alpha or beta particles).³ These radioisotopes can be used to diagnose or treat a variety of medical diseases, depending on the kind of radiation they produce. Their applications include the treatment of cancer and hyperthyroidism as well as the examination of numerous organs such as the kidney, brain, heart, and metabolism of bone.⁴

Radiopharmaceuticals are administered to patients via injection (into the patient's vein), oral administration (in pill form), or interstitially (inside a bodily cavity). The method is selected based on the targeted organ or system, and they can be monitored and studied using external medical devices and testing. Most countries have specialized safety measures in place to protect patients and health workers from the potential harmful effects of these pharmaceuticals.

Radioactive medications, or radiopharmaceuticals, are created by mixing a radioactive chemical that emits radiation,

a customized targeting molecule that varies to target various organs or tissues, and a linker that provides stable attachment. This radiation could be gamma photons for diagnostic purposes, or alpha or beta particles for therapy. Radiopharmaceuticals are divided into two categories: radionuclides with half-lives (radiative decay periods) shorter than two hours and those with half-lives longer than two hours.

Chemicals that emit beta particles (positrons or electrons) or gamma rays are often utilized for diagnostic reasons, whereas chemicals that produce Auger electrons or alpha particles (helium nuclei) are frequently used for therapeutic treatments.⁵ A radioactive chemical that emits radiation, a customized targeting molecule that changes to target particular organs or tissues, and a linker that assures stable attachment can be used to create radioactive medications, often known as radiopharmaceuticals. This radiation may consist of beta or alpha particles for therapeutic purposes or gamma photons for diagnostic purposes, as depicted in Figure 1.⁴

Molecular Imaging Technology

Molecular imaging is a new tool for viewing particular molecular alterations in illnesses in live organisms. It is noninvasive and very safe. Molecular imaging technology has numerous applications, including drug development, clinical research, and diagnostic procedures. Molecular imaging

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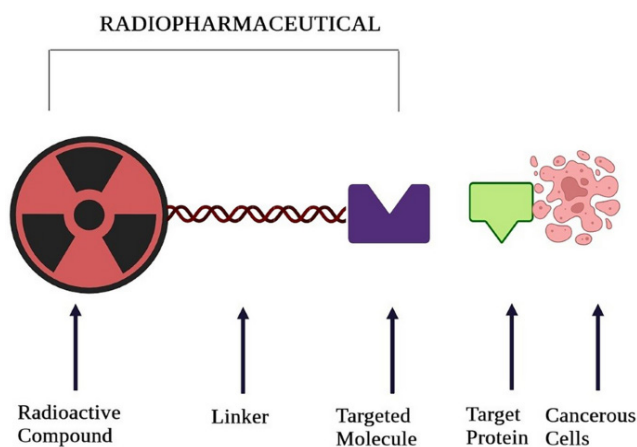


Figure 1: Radiopharmaceutical consist of a radioactive molecule, a targeting molecule, and a linker that joins the two⁶

Table 1: Common radionuclides used for diagnosis

<i>Technetium-99m (Tc 99m)</i> ⁹	<i>Iodine-131 (I-131)</i> ¹⁵
Thallium-201 (Tl-201) ¹⁰	Nitrogen-13 (N-13) ¹⁶
Floro-18 (F-18) ¹¹	Rubidium-82 (Rb-82) ¹⁷
Galium-67 (Ga-67) ¹²	Indium-111 (In-11) ¹⁸
Galium-68 (Ga-68) ¹³	Oxygen-15 (O-15) ¹⁹
Iodine-123 (I-123) ¹⁴	Carbon-11 (C-11) ²⁰

approaches rely on molecular mechanisms that operate in vivo. This imaging technology allows for the viewing, characterization, and quantification of biological processes in humans and other living things at the molecular and cellular levels.

This method employs radiopharmaceuticals designed for human use, which must be sterile, pyrogen-free, safe, and effective for certain indications.⁷ Nuclear medicine techniques include Single Photon Emission Computerized Tomography (SPECT), Positron Emission Tomography (PET), computed tomography-PET (PET-CT) (for better anatomical visualization), and micro-computerized axial tomography (micro-CAT), micro-PET (with ultra-high resolution).⁸ Unlike anatomical imaging, nuclear medicine techniques can give physiological imaging with great sensitivity and specificity at sub-millimolar levels.⁷ The commonly used Radiopharmaceutical used for diagnosis in PET and SPECT are tabulated in Table 1.

Nuclear Medicine Techniques

Diagnostic procedures in nuclear medicine use radioactive tracers that release gamma radiation into the body. The locations where radiation is released are combined by the camera to form a picture. To observe the anomalies, this image is enlarged on a computer and displayed.²¹

Single-photon Emission Computed Tomography (SPECT)

Nuclear imaging techniques like single-photon emission computed tomography (SPECT) are widely employed in

diagnostic medicine.²² A number of neurological diseases are frequently diagnosed and evaluated clinically using perfusion SPECT. Research using neuroreceptor SPECT imaging has proven helpful in determining the chemical state of various neuropsychiatric disorders, including alcoholism, bipolar disorder, Alzheimer's disease, cocaine addiction, major depression, Parkinson's disease, schizophrenia, and tobacco dependence. These disorders are caused by an imbalance of chemicals in the brain.²³ The detection of gamma ray photons from radioisotopes that decay in the patient's tissue is the fundamental component of imaging technology in nuclear medicine departments.²⁴ The resolution and sensitivity of SPECT imaging systems have increased recently due to advancements in collimator design and novel solid-state crystals of zinc telluride (CZT) and cadmium telluride (CdT). While SPECT radiopharmaceuticals are based on gamma-emitting radioisotopes, including 99mTc, 123I, 131I, 111In, 67Ga, 201Tl, 81mKr, and 133Xe, their design issues are similar to those for PET. PET has more sensitivity and resolution, while SPECT is more affordable and widely available.²⁵ Radiopharmaceuticals used for imaging are described in Table 2.

PET

PET, or Positron Emission Tomography, is a potent imaging modality that can be used to get quantitative data regarding the distribution of radiopharmaceuticals tagged with positron emitters in the body. Positively charged beta particles are known as positrons (β^+). When an atom is enriched in protons, they are released.²⁶ After passing through the surrounding tissue for a few millimeters, the positrons released by radioisotopes rapidly lose their kinetic energy. Afterward, they move slowly and combine with electrons to produce two 511 keV γ -rays, sometimes referred to as annihilation radiation, that travel in almost opposite directions.²⁷ Targeting a wide range of disorders, several PET radiopharmaceuticals have been tried and assessed in clinical studies. Although the vehicle molecules (or ligands) of each of these PET compounds vary, they all need to meet the same standards in order to be used as imaging agents: high specificity, high binding affinity, low toxicity, stability (e.g., against various enzymes in plasma), quick clearance from non-targeted tissue, affordability, and authorization for clinical use.²⁸ The biological tracers are four positron-emitting radioisotopes: carbon-11, nitrogen-13, oxygen-15, and fluorine-18. The fundamentals of life are 11C (t/2 20.4 min), 15O (t/2 2.1 min), and 13N (t/2 10 min).²⁶ Radiopharmaceutical has used the image in pet is described in Table 2.

Radiopharmaceutical Therapy (RPT)

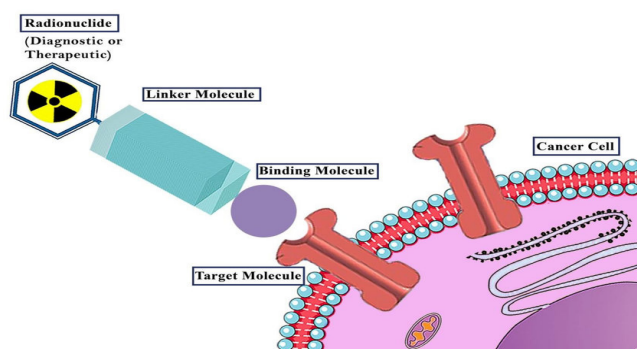
Many of us believe the roots of nuclear medicine are as much therapeutic as diagnostic. Theranostics is a revolutionary medical technique that combines imaging and treatment in one step. Therapy aims to diagnose and treat damaged tissues and cells accurately. RPT enables quicker, safer, and more reliable treatment for major aspects of healthcare, including

Table 2: Radiopharmaceutical used for imaging brain, heart, liver and kidney

Radiopharmaceutical	Application
^{99m}Tc exametazine (HMPAO) ²⁹	Cerebral Perfusion scintigraphy
^{99m}Tc bisicate (ECD) ³⁰	Perfusion scintigraphy
$^{111}\text{In}^{31}$	Brain studies
$^{122}\text{I}^{32}$	Blood flow
$^{42}\text{K}^{33}$	Coronary blood flow
N-13 ammonia ³⁴	Myocardial blood flow
$^{191\text{m}}\text{Ir}^{35}$	Cardiovascular angiography
$^{103}\text{Ru}^{36}$	Myocardial blood flow
$^{99m}\text{Tc}^{37}$	MAA -intra-arterial perfusion
^{99m}Tc colloidal sulphur ³⁸	Liver, Spleen Scintigraphy
^{99m}Tc - diethylenetriamine acid (DTPA) and mercaptoacetyltriglycine(MAG ₃) ³⁹	Renal dynamic scintigraphy

diagnosis and therapy.⁴⁰ Radioactive atoms are delivered to targets linked with tumors in radiopharmaceutical treatment (RPT). RPT is a cutting-edge therapeutic method that offers a number of benefits over current therapeutic modalities in the treatment of cancer. Radiation is delivered using radionuclides with varying emission characteristics, mainly β -particles or extremely powerful α -particles.⁴¹ But radiation and RPT are not the same, and it's critical to comprehend how those differences affect treatment.⁴² Creating RPTs requires a multidisciplinary process involving knowledge of radiochemistry, radiobiology, pharmacology, oncology, medical physics, radionuclide imaging, and dosimetry. The majority of pharmaceutical companies and the oncology community are ignorant about the use of radiation and radionuclide therapies in combination with RPT medications. A binding molecule, or targeting vector, is coupled with a radionuclide. The radionuclide selection determines the radiopharmaceutical's goal. While β - and α -emitters are utilized in treatment, γ - or β + -emitters are used for diagnostics. The radiopharmaceutical is guided to its specified target (such as receptors) via the targeting vector. Depending on the kind of radionuclide (metal or non-metal), connecting structures (linker molecules) are often required to unite the radionuclide with a target vector without decreasing its affinity to its target, as depicted in Figure 2.⁴³

Delivering extremely powerful radiation straight to tumor cells is one of RPT's distinguishing features. Understanding RPT requires an awareness of three distinct forms of radiation: α -particles, electrons, and photons.⁴⁴ Photons come in two varieties: γ -rays and X-rays. The former come from orbital electron transitions and are typically lower energy than γ -rays. Although the dispersion of the RPT may be visualized using radionuclide photon emissions, they cannot be employed to locally deliver fatal radiation.⁴⁵ While all nuclear medicine imaging cameras (γ -cameras and single-photon emission computed tomography (SPECT) cameras) work best with photon emission energies between 100 and 200 keV, a broad range of photon energies (70–400 keV) can be observed.

**Figure 2:** General concept of theranostic radiopharmaceutical⁴³

Positron emission tomography (PET) cameras detect the emission of 511-keV photons, which are produced by a variety of radionuclides as well.

Electron emissions are categorized based on both the kind of decay and their energy. RPT is related to auger electrons, β -particles, and monoenergetic electrons. Suborbital transitions produce auger electrons. Generally speaking, their emissions have a very short wavelength—between 1 and 1000 nm, depending on the emission energy. The RPT medication may be extremely cytotoxic if it localizes into the cell nucleus.⁴⁵⁻⁵⁰ However, Auger electron-emitter RPT has not gained widespread acceptance. Despite the significant therapeutic efficacy demonstrated by preclinical research, the limited number of human trials did not result in clinical.⁵¹⁻⁵⁴ Additionally, emitters including iodine-123, iodine-125, indium-111, and bromine-77 are being studied.^{55,56}

Electrons released from the nucleus are known as β -Particles. With a typical range of 1-4 mm in tissue, they are the most often used emission type for RPT medicines. This is partly because there are a lot of radionuclides that produce β -particles, and many of them also emit photons in an energy range that is easy to photograph. Over the past forty years, the β -particle emitters lutetium-177, yttrium-90, samarium-153, and I-131 have been introduced and widely employed. Iodine-131 is the most well-known and widely utilized of them, and it is used to treat thyroid cancer.⁵⁷⁻⁶¹ However, preclinical and clinical research with at least eight additional beta-emitting radionuclides—lutetium-177, holmium-166, rhenium-186, rhenium-188, copper-67, promethium-149, gold-199, and rhodium-105—is being conducted in the area of medicine.⁶² The radiopharmaceutical commonly used for the therapy is mentioned in Table 3.

α -RPT, or alpha-particle emitter radiopharmaceutical therapy, is a novel and exciting approach to treating cancer that differs greatly from all existing cancer treatments. Helium nuclei from radioactive atoms, or radionuclides, are released as α -particles. They move 50–90 μm through the tissue, depending on the energy that the radionuclide emits.^{80,81} The particles show strong LET (60-230 keV/ μm) over their range, with a peak at three times the beginning value at the end of the route (the Bragg peak). Most alpha particles also release⁸²⁻⁸⁴ Gamma-rays. Furthermore, the intracellular accumulation

Table 3: Commonly used radiopharmaceutical for RPT

RPT agent	Emission	Indication	Properties	References
Radium -223 chloride	α	Bone metastasis	Calcium analogue	63,64
^{131}I radioiodine	β	Thyroid cancer Hyperthyroid, Radioimmunotherapy (RIT) for NHL and neuroblastoma	Na-I symporter-mediated active uptaking and follicular cell storage	65-68
$^{153}\text{[Sm]}$ lexidronam	β	Cancer bone pain	Binding to hydroxyapatite matrix	69-71
^{131}I -labelled aCD45	β	Bone marrow transplant preparation	antibody based on ^{131}I that targets CD45+ cells to ablate bone marrow prior to transplantation	72,6
^{211}At	α	RIT leukemia, brain tumor, RLT prostate cancer	–	73-75
^{213}Bi	α	RIT leukemia, brain tumor	–	74,75
^{90}Y	β	Liver metastasis, hepatocellular carcinoma, neuroendocrine tumor	Radioembolization of liver microvasculature	65,73-77
^{169}Er	β	Synovitis	–	73,74
^{227}Th -labeled MSLN- TTC ^a	α	Mesothelin ⁺ tumours	Anti-mesothelin- -emitter immunoconjugate	78,79

of α particles effectively causes many clusters of DSBs and DNA double-strand breaks (DSBs) in target cells, obstructing cellular repair systems.^{85,84,86} Furthermore, the α particles' short travel distance lessens the harm they cause to the nearby healthy tissue.^{87,88} Biological molecules tagged with alpha particles, such as monoclonal antibodies (mAb), enable precise radiation targeting and deliver intense radiation only to the target with minimal harm to healthy organs.⁷⁰ As of right now, the following primary emitters have been found for TAT usage, either directly or via generator: $^{223,224}\text{Ra}$, $^{225}\text{Ac}/^{213}\text{Bi}$, $^{212}\text{Pb}/^{212}\text{Bi}$, $^{227,226}\text{Th}$, ^{211}At .^{89,90}

Mechanism and Biological Effects

The death of cells brought on by radiation is the mechanism of action of RPT. Radiation's impact on tissues and tumors were first studied not long after radiation and radioactivity were discovered. RPT benefits from the extensive body of knowledge that is radiation.⁹¹ The rate at which a dose is administered determines the biological impacts of that dose on a tumor.⁹²⁻⁹⁴ The difference in biological outcomes will be determined by the tumor's biological healing and radiosensitivity. Dose-rate concerns apply to normal organs.⁴⁵ It is more likely that all of the target cells will be destroyed during radiotherapy if there are fewer target cells to kill for a given radiation-absorbed dosage. This is due to the fact that when the number of target cells decreases, the likelihood of eliminating every cell increases. By contrast, with RPT, fewer cells do not necessarily equate to a higher chance of tumor control. This occurs as a result of uneven radiation delivery

to each cell. A lesser portion of the radiation is deposited into the targeted cells when there are fewer cells present if a radionuclide on the surface of tumor cells is the source of the radiation.⁹⁵

CONCLUSION

Radionuclides find extensive usage in several nuclear energy-related fields. A unique combination of science and innovation, radiopharmaceuticals are bringing in a new era of medical innovation. Around the world, radionuclides are becoming increasingly essential for diagnosis and treatment. In the field of imaging and theranostic, radiopharmaceutical is set to wield enhanced diagnostic and therapeutic potential and improve patient outcomes. For a long time, the two most popular nuclear medicine procedures were SPECT and PET. However, more precise methods are currently being developed, such as X-ray computed tomography (which produces three-dimensional pictures). For the focused treatment of several cancer types, radiopharmaceutical therapy can be a safe and successful method. In comparison to alternative systemic cancer therapy techniques, RPT has exhibited notable efficacy while maintaining minimal toxicity.

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