RADIOPHARMACEUTICALS

Abstract

Radiopharmaceuticals (RPs) have revolutionized the fields of nuclear medicine, diagnostic imaging, and targeted therapy. The chapter begins by elucidating the brief explanation of production and design of RPs. This chapter focuses on newly produced diagnostic & therapeutic radiopharmaceuticals that are being employed in normal clinical settings as well as innovative, exciting technologies and agents for the treatment of cancer and other chronic diseases. In this chapter, we delve into the introduction and key applications of therapeutic RPs, with a focus on radio immunotherapy (RIT) and targeted radionuclide therapy (TRT). Subsequently, the chapter delves into the diverse imaging modalities where RPs play a pivotal role including SPECT (Single-Photon Emission Computed Tomography) and PET (Positron Emission Tomography), where radiopharmaceuticals are crucial. It draws attention to the developments in molecular imaging that have made it possible to diagnose diseases early, stage them accurately, and track treatment outcomes. Moreover, this chapter also addresses the concept of personalized medicine as the potential of RPs to target specific molecular pathways in the treatment of various disease such as cancer, cardiac and neurodegenerative disorders also highlights the most recent developments in neuroimaging and examine their possible effects on the detection of various neurodenegenerative disorders. The most significant RPs pharmaceutical elements are discussed in this chapter.

Keywords: Radiopharmaceuticals (RPs), nuclear medicine, diagnostic, therapy.

Authors

Vipasha Sharma
Department of Pharmacy
Panipat Institute of Engineering and Technology (PIET) Samalkha
Panipat, Haryana, India.

Suman Khurana
Department of Pharmacy
Panipat Institute of Engineering and Technology (PIET) Samalkha
Panipat, Haryana, India.

Mukesh Rani
Department of Pharmacy
Panipat Institute of Engineering and Technology (PIET) Samalkha
Panipat, Haryana, India.

Arun Mittal
SRM IST Delhi-NCR
Campus
Modinagar, Uttar Pradesh, India

Parveen Kumar Goyal
Department of Pharmacy
Panipat Institute of Engineering and Technology (PIET) Samalkha
Panipat, Haryana, India

I. INTRODUCTION

The radioactive substances employed in nuclear medicine are called radiopharmaceuticals (RPs). It aids in the detection and treatment of several disorders in nuclear medicine. RPs must display high and precise localization of radioactivity inside target tissue [1]. RPs contain radionuclides, or radioactive isotopes which are created in cyclotrons or nuclear reactors [2]. RPs represent a remarkable intersection of nuclear medicine and pharmaceutical sciences, offering a unique and powerful approach to diagnose and treat disease at a molecular level [3].Due to its efficacy, the current healthcare system cannot function perfectly without radiation. RPs are a fairly safe class of medications with very few side effects and unexpected biodistributions [4]. RPs generally has two components i.e.a radionuclidethat permits external scanning is connected to a nonradioactive element and a biologically active chemical, medication, or cell that acts as a carrier or ligand that carries the radionuclide to a specific organ [5]. The molecular target type and location, the intended application, and the time constraints imposed by the radionuclide's short half-life must all be taken into account when choosing adequate radionuclide which combine with a suitable vector molecule for the reaction [6].

Several RPs are employed for diagnostic and therapeutic purposes, including C-14, Cr-51, Co-57 or I-131 etc. for the treatment of various diseases, especially malignant neoplasms [7]. Because of their nuclear physical properties and ubiquitous availability, radiometals like ^{99m}Tc and ^{111}In have drawn a lot of interest among radionuclides used in radiopharmaceuticals [8].These specialised substances have transformed medical imaging and therapy, allowing doctors to learn crucial information about the inner workings of the human body and provide specialised medicines. In this chapter, we explore the world of radiopharmaceuticals, their essential characteristics, and their profound impact on healthcare [9]. MI makes it possible to characterise, visualizeand quantify biological processes at the cellular and subcellular levels in live organisms, including patients. Optical imaging, ultrasound, MRI, MRS, nuclear medicine (PET and SPECT), radiotracer imaging, and other modalities may be used in MI [10]. This chapter gives in-depth information on therapeutic and diagnostic radiopharmaceuticals and a new era for the use of radiopharmaceuticals has been sparked by recent developments in molecular biology, radiopharmaceutical chemistry, and radioisotope production [11].

II. PRODUCTION OF RADIOPHARMACEUTICALS

RPs consist of three components, a radionuclide for permitting external scans, a vector for acting as a carrier for conducting the radionuclide to the particular organs, linker for making a stable connection between radionuclide and vector. Radionuclides are unstable and contain excess energy because of heavy nuclei or an imbalance in the ratio of proton and neutron. The electromagnetic radiations (gamma rays) or particles (alpha and beta particles) are released due to excess energy in radionuclides. These can be produced artificially or spontaneously via cyclotrons, particle accelerators, or radioactive decay of additional radionuclides. RPs production involves three procedures: radionuclide production, selection of vector, and reaction of the radionuclide with the vector [12].

1. **Radionuclide production:** Radionuclides are produced in a nuclear reactor or in a cyclotron depending on the target material and the energy of the bombarding particles. In

this procedure, high-energy particles are bombarded on the target nuclei to convert into the radionuclide [12].

- **Radionuclides production in the reactor**: The Production of radionuclides in a reactor depends on two types of reaction i.e. neutron capture and fission of heavy elements. In neutron capture, an isotope of the same element as the target nuclides is created, and the target nucleus absorbs a thermal neutron and emits gamma radiation. This type of reaction can result in the production of radionuclides like ^{131}Te, ^{51}Cr, ^{197}Hg, ^{99}Mo, ^{59}Fe, etc. in the fission of heavy elements, the heavy nucleus is split into two having equal mass, and neutrons are emitted. The elements such as ^{235}U, ^{239}Pu, ^{237}Np, ^{233}U, and ^{232}To are used as heavy elements to produce radionuclides. The fission of ^{235}U yields a variety of clinically valuable radionuclides, including ^{131}I, ^{99}Mo, ^{133}Xe, and ^{137}Cs [12].

- **Production of radionuclides in the cyclotron:** In a cyclotron,Radionuclides are produced with the help of electron capture or positron emission. Cyclotron was created by E.O. Lawrence and M.S. Livingston in 1934 to produce high quantities of kinetic energy with the help of accelerating particles. In a cyclotron, there are charges particle accelerators that use electromagnetic fields to accelerate particles in a circular orbit that will collide with a target element, and a radionuclide is produced. Radionuclides such as ^{18}F, ^{13}N, ^{15}O, ^{68}Ga, ^{44}Sc, and ^{89}Zr are produced in cyclotron [12].

2. **Vector:** Vector is the main component as it is responsible for targeting the tissues for maintaining a higher concentration of radionuclide. As a result, therapeutic radiopharmaceuticals can selectively irradiate the target cells while providing the picture contrast necessary for diagnostic imaging.Small molecules, peptides, proteins, and cells are used as vectors that are explained further.For intracellular targets, small molecules are used as vectors because of having specific characteristics such as membrane permeability and designing molecules within the cytoplasm and nucleus. They can cross the blood-brain barrier (BBB). Small molecules including biochemical such as fatty acids, amino acids, nucleosides, and xenobiotic are used as vectors. Peptides are used as vectors because many peptides are present in tumour tissues as compared to normal tissue. Peptides contain less than 50 amino acids and diffusion is higher into the target tissues and long retention period in tumour cells. Peptides are synthesized easily and have favourable pharmacokinetic characteristics such as fast clearance from the blood pool and non-targeted tissues, and high concentration in the target tissue [6].

3. **Linker:** The linker is used to form a chemical connection between the radionuclide and the vector molecule that will make the radiopharmaceutical stable [6].

III. DESIGN OF RADIOPHARMACEUTICALS

As we have studied the components of RPs, for designing, it requires specific characteristics in their production to successfully diagnose and treat health problems. Half-life time, specific activity, gamma ray particles, localization, stability, and the design and care preparations all play imperative roles in RPs compound creation and composition [13].

1. **Half-life:** Half-life should be depending on the type of RPs i.e. diagnostic and therapeutic. The diagnostic RPs should have a short half-life to limit radiation dose and it should decay immediately after the diagnostic image. Therapeutic RPs should have a long life so that they can have a better therapeutic effect.

2. **Type of radiations:** For diagnostic purposes, gamma rays or beta particles are used. SPECT (Single photo emission computed photography) scans use gamma rays for diagnosis and PET (Positron emission tomography) uses positrons that are developed after the decay of radionuclides. Positrons interact with electrons in the body to create photons that can be measured and used to create images of internal organs. Therapeutic radionuclides use auger electrons or alpha particles for therapeutic efficacy. These alpha particles are emitted to local tissue for destroying harmful tissues without affecting healthy tissues.

3. **Specific Activity:** Specific activity means the amount of radioactivity per unit mass of radionuclide. It should be high in the case of locally used RPs.

4. **Localize largely and quickly:** RPs should localize largely and quickly around the receptor site. This will help in providing specialized treatment to the affected part without affecting the healthy tissues with harmful radioactivity.

5. **Stability:** Particularly in diagnostic imaging, RPs stability is crucial. Light, temperature, and pH balances can all affect the stability of radioisotopes. Metabolically-decomposed RPs used in diagnostic imaging can lead to the undesired distribution of radioactivity and poor image quality if these effects are not taken into account during the production and storage of compounds, making diagnosis challenging.

6. **Cost, Availability, and Care:** The development of RPs substances requires specific design features. The simplicity, accessibility, and cost of manufacture are other significant considerations even if the traits previously mentioned heavily influence a compound's design. The accessibility and cost of manufacture play a significant role in developing useful RPs, just like in any clinical trial or treatment. Pharmaceutical manufacturing firms must take into account the cost of manufacture as well as the widespread availability of necessary components, such as the right nuclide for a given treatment or diagnosis. Additionally, adequate storage must be taken into consideration. In order to reduce potential exposure to the lowest and safest levels, RPs must be able to be stored in a specific location, such as a sealed container.

7. **Safety:** Like any pharmaceutical manufacturer, the production of RPs can be hazardous, however, there are regulations and procedures in place to handle the creation of compounds. To handle pharmaceutical chemicals securely, GMPs must be adhered to, including thorough sanitization and labelling of items. This idea necessitates that radiation exposure be kept to a minimum, that the radiation source be properly shielded, and that the workers are kept as far away from the radiation source as practicable.

IV. THERAPEUTIC RADIOPHARMACEUTICALS

RPshave extended their reach beyond diagnostic imaging and have emerged as powerful tools in the realm of targeted therapy. A number of RPs have been developed for the internal treatment of inflammatory lesions, malignant and various other chronic disease [14, 15].Therapeutic RPs have the potential to provide precise and efficacious therapeutic treatments by fusing the special characteristics of radioisotopes with selective targeting agents. Radionuclides with high linear energy transfer (LET), such as beta, alpha, Auger or low energy conversion electron emitters, are required to eliminate the diseased tissues [15]. Metalloid radionuclide-labeled substances including ^{67}Cu, $^{186,188}Re$, $^{89,90}Sr$, and ^{90}Y have drawn interest as potential therapeutic agents.These metallic radionuclides have drawn the greatest interest because of their intrinsic ability to coordinate with a wide range of ligands as well as their nuclear physical properties. The high and precise localisation of radiometallic compounds in a target tissue is made possible by this tremendous adaptability [9]. Coadministration of radioprotective regimens, such as the use of lysine-arginine infusions with radiopeptide treatment, may be necessary for therapeutic radiopharmaceuticals [4]. Alpha particle range is limited to a few cell diameters. They are therefore successful in treating micrometastases and circulating malignant cells. More than 0.1 micro metres is the range of Auger and conversion electrons. When they get through the cell membrane and enter the nucleus to damage DNA, they are particularly effective in killing cells [15]. Additionally, radiation oncology uses reusable sealed sources for brachytherapy, while nuclear medicine uses unsealed radioactive sources (RPs) for patient administration [16].Direct localised delivery of the radiopharmaceutical can improve therapeutic efficacy [15].Therapeutic RPs aim to minimize collateral damage by specifically targeting disease sites. By exploiting the ability of radiation to disrupt cellular processes, these treatments offer the potential for enhanced efficacy and reduced systemic toxicity [17,18].

1. **Therapeutic RPs for Cancer Therapy or Radioimmunotherapy (RIT):** Numerous people lose their lives to cancer each year. RIT is one difficult new technique that has been developed to treat cancer. In RIT, a therapeutic radionuclide is coupled with anticancer monoclonal antibodies (mAbs) (including those fragments) or peptides [19,20]. RIT is a novel method for the treatment of small or large tumour [21].This therapy is an excellent and acceptable way to treat haematological cancers.The FDA has only approved two RIT treatments for non-Hodgkin lymphomas (NHLs), [^{131}I]I-tositumomab (Bexxar) and [^{90}Y]Y-ibritumomabtiuxetan (Zevalin) both of which are anti-CD20 monoclonal antibodies effective for follicular lymphoma patients, particularly during recurrence [22]. Solid tumours tend to be radioresistant, necessitating higher doses of radiation and more radiation energy to completely eradicate them. Pretargeted RIT (PRIT) is one of several strategies for usage in solid tumours that raises or amplifies the therapeutic index [20]. Furthermore, preclinical research on solid tumours needs some encouraging findings [19].Numerous preclinical studies have demonstrated that RIT procedures have therapeutic value in mouse models.Thus, 92 clinical trials were reported. Among these, 30 deal with solid tumours and 62 deal with the treatment of haematological malignanciesFurthermore, neither the FDA nor the EMA have as of yet validated a RIT for solid tumours. Metuximab was just approved by the FDA (China) in 2005, and the results of the clinical trials are fairly underwhelming.The wide range of recently identified targets and antibodies, along with the use of strong alpha-emitters, point to new and exciting possibilities for RIT in solid tumours, particularly for metastatic

cancers. Additionally, new developments in pretargeted approaches and small mAb fragment bioconjugation indicate advantages for enhancing effectiveness and extending RIT for solid tumours in the upcoming ten years [22]. Until now, RIT has looked into a variety of biological, chemical, and treatment procedure enhancements to decrease needless exposure and increase therapeutic efficacy [19].

- **Principles of RIT:** The monoclonal antibody specificity serves as the cornerstone of RIT. These mAbs are made with the intention of identifying and attaching to certain antigens or proteins which are present on the surface of cancer cells. After being given to the patient, the radiolabeled monoclonal antibodies seek for and bind to the cancer cells, serving as a carrier for the radioactive isotopes (radionuclides) they are connected [23]. The radiation (beta particles) emitted by the radioisotopes employed in RIT has a limited range of penetration, often in the region of a few millimetres. This makes it possible to administer radiation locally, concentrating on the cancer cells of interest while sparing surrounding healthy tissues [24].

- **Advantages of RIT in Cancer Treatment**: In comparison to other cancer therapies, RIT has a number of advantages:
  ➢ Targeted Therapy: RIT targets cancer cells that express certain antigens with precision, minimising side effects and harm to healthy organs.
  ➢ Systemic Treatment: RIT can deliver radiation to cancer cells everywhere in the body, including those that have spread to distant or difficult-to-reach areas.
  ➢ Reduced Resistance: Traditional medicines can cause cancer cells to become resistant, while RIT focuses on specific antigens, perhaps bypassing resistance mechanisms.
  ➢ Combination Potential: To improve therapeutic outcomes, RIT can be used in conjunction with other treatment techniques like chemotherapy or immunotherapy [25-27].

2. **Targeted Radionuclide Therapy (TRT) for Specific Diseases:** The use of radionuclides for disease-specific targeted therapy has a long history in the field of nuclear medicine. TRT is a rapidly advancing and specialized form of the treatment that uses radiolabeled molecules to deliver radiation directly to specific cells or tissues expressing particular targets [28].TRT's main objective is to be able to deliver cytotoxic radiation to cancer cells with a low level of toxicity to the healthy tissues around them by using specially designed targeting vehicles (such as small organic molecules, peptides, and proteins) that deliver beta or alpha emitting radionuclides into the tumour cells [29]. Significant promise has been demonstrated by this therapeutic strategy in the treatment of a number of illnesses, including cancer and a few non-malignant ailments [30]. In the 1940s, iodine-131 was first used frequently to treat thyroid conditions.The ability to precisely bind proteins which are overexpressed on the surface of tumour cellswas first demonstrated in the 1990s by antibodies and peptides. For RIT, a few of these antibodies were radiolabeled with iodine-131 such as I^{131}-meta-iodobenzylguanidine (I^{131}-MIBG) and I^{131}-tositumomab whereasa small number of peptides were radiolabeled for peptide receptor radionuclide therapy (PRRT) using radiometals such yttrium-90 and lutetium-177 [28, 31].PRRT is a specialised type of targeted radionuclide treatment that delivers radiation to certain cells expressing peptide receptors using radiolabeled peptides. Results from this therapy strategy have been encouraging, especially when used to treat neuroendocrine tumours (NETs) [32].

- **Principles of TRT:** TRT is based on the concept of selective targeting. MAbs, peptides, and other radiolabeled compounds are made to bind to and recognise certain receptors, proteins, or antigens which are present on the surface of target cells. The linked radioactive isotopes (radionuclides) are transported by these radiolabeled molecules to the desired cells. The DNA and internal cell structures are harmed by the radionuclide's radiation, which causes cell death or function impairment [33, 34].

- **Advantages of TRT:** TRT has a number of important advantages that make it a valuable and prospective therapeutic option for a variety of disorders are as following:

  - **Selective Targeting:** In TRT, radiolabeled molecules bind only to certain receptors, proteins, or antigens which are present on the surface of target cells. In contrast to conventional therapies, this enables the precise and targeted delivery of radiation to the sick cells while preserving healthy tissues, lowering collateral damage, and minimising adverse effects [33].
  - **Better Tumour Control:** TRT provides targeted radiation to the tumour location, resulting in a greater radiation dosage inside the target, which can improve tumour control and raise the likelihood that the tumour will shrink or disappear [35].
  - **Personalised Medicine:** Based on the illness features, receptor expression, and general health condition of the patient, TRT has the ability to produce personalised therapy recommendations. Individualised treatment plans can maximise therapeutic effect and enhance patient outcomes [36].
  - **Reduced Resistance:** Cancer cells can become resistant to standard treatments, however targeted radionuclide therapy can get around this by concentrating on a few key biochemical pathways [35].
  - **Non-invasive:** Since many targeted radionuclide treatments may be given intravenously, they are less disruptive to patients and non-invasive [36].
  - **Systemic Reach:** TRT can target sick tissues or cancer cells throughout the body, even metastatic lesions that may be difficult to treat with localised therapy [37].
  - **Combination Therapy:** Combining TRT with other therapeutic modalities, such as chemotherapy, immunotherapy, or external beam radiation, might have synergistic effects and could improve the effectiveness of treatment [37].

3. **Clinical Applications of Therapeutic Radiopharmaceuticals: Some of the key applications of RIT and TRT are as follows:**
   - **Non-Hodgkin Lymphoma (NHL):** To treat CD20-positive B-cell NHL, the anti-CD20 monoclonal antibody rituximab has been radiolabeled with the radioisotopes yttrium-90 (^{90}Y) or iodine-131 (^{131}I). In relapsed or refractory NHL, RIT has shown to be highly effective in inducing remission or decreasing tumour burden [29,38].
   - **Leukemia:** Radioisotopes like iodine-131 or bismuth-213, has been used for specific kinds of leukaemia, including acute lymphoblastic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL) [39].
   - **Metastatic Castration-Resistant Prostate Cancer (mCRPC):** For patients with mCRPC, RIT using radiolabeled prostate-specific membrane antigen (PSMA) targeting mAbs, such as ^{177}Lu-PSMA, has shown as a promising treatment [40].
   - **Consolidation Therapy for Lymphoma:** After initial chemotherapy, RIT has been utilised in a few cases of NHL and Hodgkin lymphoma to further boost remission rates and lengthen survival [38, 39].

- **Solid Tumors:** Although haematological malignancies have seen the majority of RIT's clinical success, research is underway to examine the possibility of RIT in solid tumours by focusing on certain antigens or proteins expressed on cancer cells [38].
- **Palliative Care for Bone Metastases:** RIT can be used to provide targeted radiation to bone metastases in patients with advanced cancer, reducing discomfort and controlling tumour growth. Patients with bone metastases from different malignancies can receive palliative treatment from radioisotopes like strontium-89 and samarium-153 [29].
- **Neuroendocrine Tumors (NETs):** PRRT targets the somatostatin receptors found on NETs such as bronchial and gastroenteropancreatic NETs (GEP-NETs). Patients with inoperable or metastatic NETs have seen considerable tumour control and symptom improvement with PRRT [41].
- **Thyroid Diseases:** Iodine-131 (^{131}I) therapy is frequently used to treat differentiated thyroid tumours, such as papillary and follicular thyroid tumours, as well as hyperthyroidism (overactive thyroid) [41].
- **Rheumatoid Arthritis:** Radiosynoviorthesis uses radiopharmaceuticals injected directly into the joint to treat inflammatory joint diseases including rheumatoid arthritis [41].
- **TRT for Bone Metastases:** Radium-223 (^{223}Ra), a radioisotope, specifically accumulates in bone metastases from prostate cancer and can be used locally to alleviate pain and tumour management [41].
- **Radioembolization:** Yttrium-90 microspheres are used to deliver targeted radiation to liver tumors in hepatocellular carcinoma and metastatic liver tumors [41, 42].
- **Pheochromocytoma and Paraganglioma:** MIBG (metaiodobenzylguanidine) treatment is used to treat tumours that develop from the paraganglia or adrenal glands [41].

V. DIAGNOSTIC RADIOPHARMACEUTICALS

Medical doctors and chemists have identified a large number of chemicals that are absorbed by specific organs. The thyroid, for example, absorbs iodine while the brain absorbs glucose. It is important to remember that radionuclides are administered in such dosages for research and diagnostics that there are no detectable biological side effects [43].To visualize the activities of many organs, including the kidney, lung, thyroid, and heart, as well as bone metabolism and blood circulation, RPs are administered orally, intravenously, or by inhalation in the imaging modality [44]. Although the applications of integrated diagnostic systems have expanded to include cardiology, neurology, and the imaging of inflammatory diseases, they have demonstrated their clinical worth most prominently in the field of oncology [45]. Some diagnostic RPsare given in table 1 along with their function in particular organ [46].

Table 1: Clinical Applications of Diagnostic RPs

S No.	Organs	Radiopharmaceuticals	Function
1	Brain	11C, 13N,15O 13F-FDG 111In 122I	Physiology and pathology Glucose metabolism Brain studies Blood flow

2	Thyroid	13F-FDG 123I	For cancer detection Function
3	Pulmonary perfusion	133Xe	Lung ventilation
4	Stomach	58Co	Gastrointestinal absorption
5	Intestines	51Cr 58Co 141Ce	Human serum albumin Gastrointestinal absorption Gastrointestinal tract Diagnosis
6	Skeleton	41Ca 100Eu	Bone metabolism Colloid sulfur-bone marrow scintigraphy
7	Soft tissues	57Ga citrate, 18F-FDG	
8	Kidneys	99mTc-DTPA	Renal dynamic
9	Liver	99mTc-MAA 99mTc	Intra-arterial perfusion Colloid sulfur-bone marrow scintigraphy
10	Heart	42K 103Ru	Coronary blood flow Myocardial blood flow
11	Salivary glands	99mTc-Pertechnetate	
12	Lacrimal glands	99mTc-DTPA	Inflammation

VI. RPS IN NUCLEAR CARDIOLOGY

Nuclear cardiology is a specialized area of nuclear medicine that focuses on employing radioactive tracers to diagnose and treat a variety of heart diseases. Nearly a century ago, in 1927, the first use of radioisotopes to examine human blood circulation (pulmonary circulation time) was described. In 1949, measured cardiac output and blood volumes using sodium iodide probes and radiolabeled albumin. These significant early studies laid the foundation for nuclear cardiology, which has since expanded its applications to include non-invasive imaging using a variety of radiotracers [47]. These tracers are typically administered to patients either intravenously or orally and emit gamma rays, which can be detected by gamma cameras [48]. Recently, a number of radiopharmaceutical tracers that target myocardial perfusion Imaging , Cardiac metabolism, cardiac innervation, Atherosclerosis, Inflammation and Infiltrative Disease have been created to assess CVD [49]. In cardiac disease, radiotracers are primarily employed for the following evaluation criteria.

1. **Myocardial Perfusion Imaging (MPI):** For MPI, which evaluates blood flow to the heart muscle, RPsare frequently utilized. The assessment of myocardial perfusion and function has been improved with to developments in SPECT and PET, which allow for non-invasive imaging [49]. The FDA has previously authorised 4 SPECT radiotracers for clinical use includes [201]Th, ^{99m}Tc-Sestamibi, ^{99m}Tc-Tetrofosmin, and ^{99m}Tc-Teboroxime, as well as 2 PET agents i.e. Rb-82 and N-13 Ammonia. Due to the proportionate uptake of these tracers by cardiac muscle cells in relation to blood flow, it is possible to identify locations with insufficient or inadequate blood supply. When diagnosing diseases like

coronary artery disease (CAD) and determining the degree of ischemia or restricted blood flow, this information is essential [47].The development of 18F-labeled PET radiotracers may really open the door to a comprehensive evaluation of the heart's present metabolic and functional condition, such as following an acute MI or for advanced heart failure [50]. Currently being investigated for perfusion imaging of the heart tissue include ^{123}I-rotenone, ^{18}F-fluorpiridaz, ^{18}F-labeled p-uorobenzyltriphenylphosphoniumcation, ^{3} NH$_3$, and ^{82}Rb^{+} salts [51].

2. **Cardiac Metabolism:** Radiotracers play a crucial role in studying cardiac metabolism because they provide valuable insight on how the heart makes use of various nutrients and energy sources to satisfy its energy requirements. ATP is produced by a number of metabolic reactions that take place inside the heart muscle cells (cardiomyocytes). These reactions are referred to as cardiac metabolism. Understanding normal heart function as well as various cardiovascular disorders requires an understanding of cardiac metabolism. Radiotracers are used with nuclear medicine imaging methods to study heart metabolism [52]. It is feasible to investigate cardiac metabolism using various sources since the heart receives its energy from a number of sources, including free fatty acids, glucose, lactate, and ketone bodies. SPECT radiotracers include ^{123}I-BMIPP (beta-methyl-p-iodophenylpentadecanoic acid) and ^{123}I-IPPA (iodophenylpentadecanoic acid), whereas PET tracers include ^{18}F-FDG (fluorodeoxyglucose), ^{11}C-Palmitate, ^{18}F-FTHA (fluoro-6-thia-heptadecanoic acid), and ^{11}C-Acetate [47, 53]. In order to better understand cardiac metabolism, some radiotracers play the following crucial roles:

- **Evaluation of Glucose Metabolism:** ^{18}F-FDG, a glucose analogue, is one of the primary radiotracers used to evaluate heart metabolism. Similar to how cells absorb glucose, FDG is not further metabolised, causing it to accumulate inside cardiomyocytes. The distribution and absorption of FDG in the heart may be seen by FDG PET imaging, which can reveal details about how glucose is used in different parts of the myocardial. Metabolic diseases, ischemia, inflammation, and other illnesses can all be identified by abnormalities in glucose metabolism [53].

- **Assessment of Fatty Acid Metabolism:** The metabolism of fatty acids in the heart is studied with radiotracers like ^{11}C-Palmitate and Iodine-123-labeled fatty acids i.e ^{123}I-BMIPP & ^{123}I-IPPA.Cardiomyocytes absorb these radiotracers and integrate them into the fatty acid oxidation pathway [54].

- **Evaluation of Oxidative metabolism:** ^{11}C-Acetate is the widely used radiotracer for the evaluation of myocardial oxygen consumption or MVO$_2$ because of the strong relationship between the tricarboxylic acid cycle and oxidative phosphorylation. Acetate undergoes fast acetyl-CoA synthesis and tricarboxylic acid cycle (TCA) metabolism as its main metabolic fate [54].

3. **Cardiac Innervation:** The investigation of cardiac innervation—the heart's nerve supply—involves radiotracers significantly. The heart's contractility, rhythm, and rate are all under the direction of the autonomic nervous system (ANS), which also balances the heart's sympathetic and parasympathetic (rest and digest) inputs [47, 55]. Different cardiovascular illnesses may result from cardiac innervation dysfunction or imbalance. When combined with nuclear medicine imaging methods, radiotracers aid in the

evaluation of cardiac innervation and offer important insights into the neurological control of the heart. SPECT radiotracers includesnorepinephrine analogue 123I–meta-iodobenzylguanidine (123I–MIBG) and PET radiotracers includes 11C-labeled & 18F-labeled targeting SNS [56, 57].

- **^{123}I-MIBG:** The FDA authorised ^{23}I-MIBG in 2013, and it is currently the primary drug used in clinical practise. Cardiovascular imaging with ^{123}I-MIBG has been found to be extremely helpful in evaluating patients post-cardiac transplant, diabetes mellitus, myocardial ischemia, primary arrhythmic diseases and the monitoring of chemotherapy toxic effects [47, 57, 58].

- **^{11}C-labeled tracers:** To measure myocardial SNS, a number of ^{11}C-labeled catecholamine analogue radiotracers have been studied.These three radiotracers—^{11}C-hydroxyephedrine (^{11}C-HED), ^{11}C-epinephrine, and ^{11}C-phenylepinephrine—are the most frequently utilised radiotracers. The kinetic characteristics of these carbon-11 compounds all vary, including their vulnerability to degrading enzymes like monoamine oxidase (MAO) and catechol-O-methyltransferase as well as their affinity for neuronal uptake-1. Consequently, combining many PET radiotracers with such pronounced variances in their characteristics may provide a more thorough understanding of cardiac SNS in the failing heart [57, 59, 60].

- **^{18}F-labeled tracers:** The half-life of radiotracers labelled with ^{18}F is much longer (110 min) & less expensive than ^{11}C (20 min). Several ^{18}F- labelled tracers includes ^{18}F-Fluoro-Hydroxyphenethylguanidines [^{18}F-fluoro-3-hydroxyphenethylguanidine (^{18}F-4F-MPHG) and its structural isomer 3-^{18}F-fluoro-4-hydroxyphenethylguanidine (^{18}F-3F-PHPG)] [55-57].

4. **Atherosclerosis, Inflammation and Infiltrative Disease:** With the development of novel and focused molecular imaging techniques over the past ten years, nuclear cardiac imaging has advanced dramatically, particularly in the assessment of infiltrative and inflammatory heart disorders [47]**.

- **Atherosclerosis:** The disease known as atherosclerosis is characterised by the accumulation of plaque inside arteries, which can restrict blood flow and cause cardiovascular problems. There are numerous approaches to research atherosclerosis with radiotracers:

  ➢ **Lipid Imaging:** Inflamed atherosclerotic plaques can be identified using radiolabeled substances like Fluorine-18 FDG. By highlighting regions of elevated metabolic activity, which are a sign of inflammation inside the plaque, FDG PET imaging can assist determine the fragility of the plaque [47, 61].
  ➢ **Thrombus Imaging:** Activated platelets, which are important in the development of thrombus, can be targeted by radiotracers such medicines labelled with technetium-99m. These radiotracers help detect and treat issues including deep vein thrombosis (DVT) and pulmonary embolism (PE) by imaging thrombi [61-63].

- **Inflammation:** In order to evaluate different inflammatory states including infections and autoimmune illnesses, radiotracers are extremely important [47].

- **Infection Imaging:** Sites of infection or inflammation can be localised using radiotracers like Technetium-99m-labeled white blood cells or Gallium-67 citrate. These tools aid in identifying inflammatory foci that could otherwise be difficult to find, evaluating therapy outcomes, and diagnosing infections [47, 63, 64].
- **Infiltrative Diseases:** Radiotracers are used to identify and assess diseases in which aberrant substances invade tissues or organs.
  - ➢ **CardiacAmyloidosis:** Radiotracers can build up in amyloid deposits in disorders like cardiac amyloidosis, allowing for non-invasive imaging and diagnosis. These radiotracers include ^{99m}Tc PYP (Pyrophosphate), ^{123}I-MIBG, ^{18}F-NaF, and amyloid binding radiotracers such as ^{99m}Tc-aprotinin, ^{123}I-Serum amyloid P component or SAP [47, 63].

VII. RPS IN NEUROIMAGING

Accurate diagnosis is essential for developing possible medicines to treat neurodegenerative diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) or to prevent their progression. The creation of RPs is an essential initial step in nuclear imaging. Researchers and medical professionals use imaging technology known as "neuroimaging" to visualize the structure and function of the brain in order to study neurological disorders, brain function, and the impact of various medications [65]. Specific probes with the required pharmacological qualities that can pass the blood-brain barrier can be used to identify neurodegenerative disorders. The ability to recognize and measure a variety of physiological processes occurring inside the brain is made feasible by the use of radioactive tracers.A rising range of brain receptors, transporters, enzymes, and other molecular targets may now be seen and examined using radiotracers [66]. One of the primary methods for diagnosing these disorders by nuclear imaging, includes PET and SPECT [67]. The imaging of brain metabolism, measurement of receptors and transporters, and imaging of neurodegenerative, neuroinflammatory, and neurooncologic processes are now the key contributions of PET and SPET radiotracers [66]. Imaging neurotransmitter systems is a powerful technique used in neuroimaging to examine the location, density, and operation of numerous neurotransmitter receptors and transporters in the brain [68]. Imaging neurotransmitter systems is crucial for comprehending brain function and disease pathophysiology since abnormalities in neurotransmitter systems have been linked to a variety of neurological and psychiatric illnesses [69]. Neuroimaging has also potential applications for psychiatric disorders includes depression, schizophrenia, anxiety or addiction.

1. **PET and SPECT tracers for Neurodenerative Diseases:** The study of neurodegenerative illnesses has made substantial use of PET and SPECT tracers to help with early diagnosis, differential diagnosis, disease staging, and disease progression monitoring. These tracers target certain neurochemical or pathophysiological abnormalities linked to various neurodegenerative diseases [70]. The most common PET radionuclides are C^{11} ($t_{½}$, 20 min.) , Ga^{68} ($t_{½}$, 68 min.) and F^{18} ($t_{½}$, 110 min.), while SPECT includes Tc^{99m} ($t_{½}$, 6 hours) and I^{123} ($t_{½}$, 13 hours) [65]. Various neurodegenerative disorders are treated with PET and SPECT tracers, as seen in the following examples:

- **Alzheimer's Disease (AD):** One of the most common neurodegenerative diseases, AD, is characterized by buildup of tau tangles and amyloid plaques in the brain. The

creation of numerous probes able to detect Aβ deposits, tau protein buildup, microglia activation, and neuroinflammation is the result of intense efforts in radiopharmaceuticals research [71, 72].

- ➢ **Amyloid β (Aβ) Imaging:** A developing field in radiopharmaceutical design is the creation of SPECT and PET tracers for Aβ imaging. There have been a lot of promising Aβ imaging radioligands created and tested in-vitro. They are either derived from histopathological stains like Congo red (CR), chrysamine-G (CG), and Thioflavin T (TT), or they are monoclonal antibodies to Aβ and radiolabeled Aβ peptides [71].PET tracers like PiB (Pittsburgh compound B), florbetapir (Amyvid), florbetaben (Neuraceq), and flutemetamol (Vizamyl) target Aβ plaques, which are one of the characteristic pathological features of AD. These tracers make amyloid plaques in the brain visible and quantifiable, aiding in the diagnosis and staging of AD [74-76].

- ➢ **Tau Imaging:** Novel PET tracers have been created to identify and quantify neurofibrillary tangles, which are made up of aberrant tau protein, including AV-1451 (F^{18}-Flortaucipir), THK5317, PBB3, and MK-6240. Tau imaging is useful for monitoring the development of AD pathology [76-78].

- • **Parkinson's Disease:** PET and SPECT are sensitive methods for measuring the loss of nigrostriatal dopaminergic fibres in Parkinson's disease and for identifying the presence of dopaminergic dysfunction in asymptomatic at-risk family members and patients with isolated tremor [79]**.** Tools like [11C] raclopride PET and [123I] IBF SPECT were promise for determining the state of D2 receptors in people [80]. PET and SPECT tracers for imaging the dopamine system, such as [^{18}F]-FDOPA &[^{123}I]β-CIT SPECT, can help assess the integrity of dopaminergic neurons in the brain. Dopamine agonists may have a minor neuroprotective impact and may reduce the illness's course, according to preliminary findings from PET and SPECT investigations in people with early PD [81].
  - ➢ **Dopamine Transporter (DaT) Imaging:**
  - ➢ **[^{123}I]-FP-CIT (loflupane)/ [^{123}I]-loflupane (DaTSCAN):** This is a SPECT tracer that binds to the DaT in the striatum. The striatum is a brain region rich in dopaminergic neurons, and its degeneration is characteristic of Parkinson's disease. The diagnosis of PD and its distinction from other parkinsonian syndromes are supported by decreased binding of [^{123}I]-FP-CIT in the striatum, which denotes a loss of dopaminergic neurons [82-85].
  - ➢ **[18F]- labelledradioligands:** A newer PET tracer for DaT imaging that offers higher resolution, higher sensitivity and better quantitative accuracy than SPECT and has shown comparable results to [123I]-FP-CIT SPECT. The 18F-labeled radioligands [^{18}F]FP-CIT, [^{18}F]LBT-999, and [^{18}F]FE-PE2I are only a few of the DAT radioligands for PET that are available. [18F]FE-PE2I can now be regarded as the most accurate choice due to its strong selectivity to DAT and its advantageous pharmacokinetic characteristics [83].
  - ➢ **Dopamine D2 Receptor Imaging:** Carbon-11 and fluorine-18 labelled radiotracers including [^{11}C]raclopride, [^{11}C]fallypride, [^{18}F]fallypride, and [^{11}C]FLB 457 have been used in PET imaging investigations [86]. Butthe most often utilised PET tracer for studying the availability of the D2 receptor in vivo was ^{11}C-raclopride. 11 C-

raclopride is a selective marker for D2/D3 receptors and binds to D2 receptors on the cell surface because of its low lipophilicity. The availability of D2 receptors has been investigated using ^{11}C-raclopride PET in patients with PD. In PD, there is a reduction in dopamine release due to dopaminergic neuron loss, leading to upregulation of D2 receptors. [^{11}C]-raclopride can help visualize these changes in D2 receptor binding in the striatum [87, 88].

2. **Potential Applications of Neuroimaging in Psychiatric disorders:** The development of new psychiatric medications and the diagnosis of mental disorders are both aided by neuroimaging. It is used to separate depression from brain tumours or neurodegenerative disorders and to identify structural flaws that lead to psychosis. If a patient has mental symptoms, neuroimaging may help determine the proper diagnosis [89, 90]. They can, however, be studied using modern neuroimaging techniques, particularly quantitative structural imaging, as demonstrated by voxel-based morphometry, and functional neuroimaging, which makes use of MRI, PET, and SPECT scans [91].

- **Depression:** The frontal and limbic areas of the brain, were shown to have potential biomarkers by PET and SPECT in depression. However, PET and SPECT results also revealed additional abnormalities in the brainstem and midbrain .PET imaging of serotonin transporter (SERT) binding has been utilized to investigate alterations in serotoninergic systems in individuals with depression [92].

- **Schizophrenia:** A direct method of examining the pathophysiology of schizophrenia in vivo is using functional neuroimaging. Molecular imaging methods including PET, SPET, and MRS can be used to evaluate the function of neurotransmitters involved in schizophrenia, such as dopamine and glutamate [93]. PET studies have explored dopamine D2 receptor binding in the striatum of individuals with schizophrenia, offering insights into the dopamine hypothesis of this disorder [94].

- **Addiction:** Drug intoxication, yearning, bingeing, and withdrawal are common patterns of subjective experiences that may be used to describe the phenomenology of drug addiction. The cycle ends with a continuous obsession with getting, using, and recovering from the substance. Imaging research on drug addiction over the past 20 years has shown that reward and impulsivity-related brain circuits are impaired [95]. Imaging studies with radiotracers targeting dopamine and opioid receptors have helped elucidate the neural pathways involved in addiction and substance abuse [96].

- **Anxiety Disorders:** Recently, neuroimaging methods have made significant contributions to understanding the structural and functional neuroanatomy of anxiety disorders consistently pointed to the "fear network," which consists of the amygdala, insula, and anterior cingulate cortex, as playing a critical role in the onset and maintenance of anxiety disorders. The identification of structural and functional characteristics underlying mental disorders has been greatly aided by the development of neuroimaging techniques such as MRI, fMRI, PET, and SPECT [97-99].

VIII. CONCLUSION

In conclusion, the book chapter on RPs has provided a comprehensive overview of the essential aspects that shape this dynamic field. The foundation of contemporary medicine, RPs haverevolutionized both focused therapeutic and diagnostic imaging. The promise for personalized medicine has been highlighted as we have examined their crucial role in nuclear medicine and molecular imaging throughout the chapter.The chapter commenced by discussing the production and design behind RPs. The different imaging techniques, such as SPECT and PET, which employ radiopharmaceuticals to facilitate precise disease identification, staging, and treatment response tracking, were then covered in detail. Significant highlight of this chapter is showcasing the seamless integration of diagnostics and therapeutics RPs.

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