CHEMICAL REVIEWS

Review

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Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications

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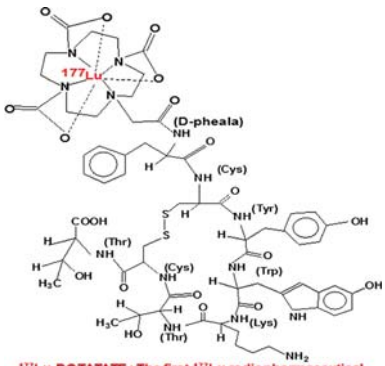

^{177}Lu-DOTATATE : The first ^{177}Lu radiopharmaceutical approved for clinical use.

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1. INTRODUCTION

Interest in the use of radionuclides for treatment of various diseases has a long history and parallels the isolation of radium by Marie and Pierre Curie in the early part of the 20th Century. The availability of radium generated widespread enthusiasm and was considered as a potential medicine for many incurable diseases. Success evaded such attempts until radioactive phosphorus (^{32}P) prepared at the University of California Berkeley cyclotron was found to be effective for treating polycythemia rubra vera, a myeloproliferative disease characterized by overproduction of red blood cells. The introduction of iodine-131 (^{131}I) as a radioactive medicine for treatment of thyroid cancer in 1946 saw the successful application of radionuclides in medicine. The clinical use of radioiodine (^{131}I) therapy is a key example of molecular nuclear medicine, and this therapeutic radionuclide continues to be used in many technologies focused on cancer treatment where no competing replacement is envisaged in the near future.

Several radionuclides which decay by emission of beta particles (β^-), alpha particles (α), or Auger (AE) and conversion electrons (CE) are under both radiopharmaceutical development and clinical evaluation as potential therapeutic radionuclides. Among the radionuclides suggested for targeted therapy, research with ^{177}Lu-based radiopharmaceuticals has demonstrated spectacular growth in recent years. Less than 10 papers were published on the development of lutetium-177 (^{177}Lu)-labeled radiopharmaceuticals in the last century, whereas more than 500 publications have appeared in the last 14 years, demonstrating the increasing interest in the use of this therapeutic radionuclide. Monoclonal antibodies, peptides, phosphonate ligands, particulates, steroids, and other small molecules have been radiolabeled with ^{177}Lu for the development of a wide variety of therapeutic radiopharmaceuticals. The success of treating patients suffering from neuroendocrine tumors with ^{177}Lu-labeled DOTA-Tyr^3-octreotate (DOTA-TATE), a somatostatin analogue peptide, is the single most important example that has contributed to the worldwide interest and growth of ^{177}Lu as a therapeutic radionuclide.[1]

Although decay properties are an important consideration for selection of a therapeutic radionuclide, the success of using any radioisotope as an integral part of a radiopharmaceutical depends on the feasibility for production in high activity levels with acceptable quality and the ability for transportation to nuclear medicine facilities, which are generally distant from production centers. As discussed later in this review, ^{177}Lu has many advantages compared to other therapeutic radionuclides for the potential treatment of several types of cancers. Radionuclidic characteristics of ^{177}Lu such as the energies and abundance of the emitted β^- particles and gamma photons and its half-life make it suitable for use as a therapeutic radionuclide for targeting small primary tumors and metastatic sites.

Although the clinical efficacy of several ^{177}Lu radiopharmaceuticals has been demonstrated using "in-house" formulations, at present there are no ^{177}Lu-labeled radiopharmaceuticals with regulatory approval for routine clinical use. A number of clinical trials using ^{177}Lu radiopharmaceuticals are also in progress in many countries; however, it is expected that approved ^{177}Lu radiopharmaceuticals will be commercially available in the near future.

This paper is the first published review on ^{177}Lu radiopharmaceuticals and summarizes the developments in this emerging important field. This comprehensive review on ^{177}Lu radiopharmaceuticals covers research from 1960 and begins with an introduction on radiopharmaceuticals used in nuclear medicine with a goal to orient the reader to the importance of this field. Lutetium is the last member of the lanthanide family, and its chemistry plays an important role in the preparation of radiopharmaceuticals that are stable in vivo. Various bifunctional chelating agents (BFCA) that are used for tagging ^{177}Lu with carrier vectors are discussed. The review also covers the production aspects of ^{177}Lu in detail and its different production methods. The comparative advantages and disadvantages of the two major reactor production routes are elaborated. Research which led to the development of different ^{177}Lu radiotracers is provided, and this review also describes the results of promising clinical studies that have been conducted with ^{177}Lu radiopharmaceuticals.

1.1. Radiopharmaceutical Overview

Radioactive drugs (radiopharmaceuticals) used in nuclear medicine, oncology, interventional radiology/cardiology, and related specialties involve the use of unsealed radioactive sources—as opposed to the use of sealed radioactive sources in radiation oncology. Radiopharmaceuticals are radiolabeled molecules designed to target tissues and processes in vivo and are used in either diagnostic or therapeutic applications. Unlike the well-established applications of nonradioactive drugs, diagnostic radiopharmaceuticals contain very small doses of the active ingredients and are not pharmacologically active. On the other hand, therapeutic radiopharmaceuticals generally possess a significant concentration of active ingredient which can induce pharmacological changes. Radiopharmaceuticals are designed to measure a physiological event (imaging) or for the treatment of a malady (therapy). In the case of therapeutic applications, such as

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the use of ^{177}Lu-labeled pharmaceuticals discussed in this review, the therapeutic effects results from the radiotoxicity induced by the emission of particulate radiations. Radiopharmaceuticals are manufactured under current Good Manufacturing Practices (cGMP) with specific regulations and must be of adequate purity for human administration.

The major tools employed for diagnosis are imaging modalities, which include both planar and tomographic imaging technologies such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Radionuclides that primarily emit gamma photons or positrons that can have a high abundance of photon emissions are used in diagnostic nuclear medicine. Radiopharmaceuticals used for therapeutic applications, in contrast, contain radionuclides that decay by particulate emission (alpha, beta, or Auger electrons), and the decay energy is deposited at the target sites to kill cancerous or other diseased cells.[2,3] The design of radiopharmaceuticals involves radionuclide attachment to the targeting molecule either directly or via the use of a bifunctional chelating agent (BFCA). An example of a direct radiolabeling is the radioiodination of the phenolic group of the amino acid tyrosine in a biological vector. In the case of radiolabeling through a chelator, a radionuclide is complexed with the donor atoms of a BFCA. These targeting molecules are often peptides, antibodies, antibody fragments, or small molecules that are receptor specific and peptidomimetics or nonpeptide receptor ligands. Often a proven conventional drug is selected as a lead molecule to be developed into a radiopharmaceutical by incorporating an appropriate radionuclide useful for diagnosis or therapy. An important challenge is to maintain the molecular targeting characteristics of the modified molecule, since even subtle structural changes in molecules that act as the vector can often result in loss of targeting properties. The design of a radiopharmaceutical for a specific application therefore must take into consideration the properties of both the targeting carrier molecule as well as the radionuclide.

1.2. Role of Molecular Nuclear Medicine

The distinct advantage of nuclear medicine is its application using novel biomarkers for the study of biochemical processes at the cellular level. These techniques can delineate changes in cellular function at a stage much earlier than the manifestation of anatomical changes or the onset of clinical symptoms. This unique and important strength is referred to as molecular nuclear medicine.[4] Many nuclear medicine imaging techniques measure flow, but localization of the radiopharmaceutical can also provide information to visualize and map the biological processes, such as cell growth or cell destruction leading to biochemical changes occurring in living systems. An example is the widespread use of ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG or simply FDG) where a glucose analogue radiolabeled with ^{18}F, a positron-emitting radionuclide, is injected into a patient followed by imaging with positron emission tomography (PET) instrumentation. The images obtained permit the visualization of abnormal cellular metabolism and proliferation as glucose, and thereby FDG is taken up by diseased cells more than in normal cells. The clinical introduction of dual imaging modalities such as PET/CT (computed tomography) and more recently PET/MRI (magnetic resonance imaging) permits simultaneous measurement of both cellular metabolic processes as well as anatomical details. The increasing availability of these technologies has led to a new era of accurate mapping of cellular processes occurring in cancer and other diseases, which range from detection, staging, treatment planning, and finally disease management. These studies not only aid in assessing treatment response for the use of chemotherapeutic agents but also help in distinguishing cells which are proliferating owing to angiogenesis from normal cells.

Molecular nuclear medicine has thus attained the present status due to a gradual evolutionary process which includes the unique capability for noninvasive assessment of physiological processes occurring in vivo by following radiopharmaceutical metabolism. The advances in imaging techniques have expanded opportunities, paving the way for nuclear medicine investigators to obtain two-dimensional images of the whole body. Subsequent improvements brought about by the introduction of new and improved radiotracers as well as new imaging techniques have enabled the acquisition of tomographic (i.e., three-dimensional) images of coronary blood flow and related tissue function.

Understanding changes at the molecular and cellular level provides vital clues for evaluating the effectiveness of a clinical treatment strategy. This information, in turn, has a major impact on understanding disease and its detection and progression, deciding individualized treatment, and consequently developing suitable drugs. The concept of molecular nuclear medicine provides a "window" to visualize the biochemical processes occurring in vivo.[5] Functional radionuclide imaging helps in following the pathology in individual patients and provides a means to tailor clinical management, contributing to the conceptualization of the new era of "personalized medicine". The relatively well-established, unique advantages of molecular nuclear medicine over conventional techniques such as ultrasound (US), CT, and MRI are the opportunities to provide unique physiological and molecular information in the fields of oncology, cardiology, and neurology.

2. TARGETED THERAPY

In contrast to the use of diagnostic applications in nuclear medicine, radiopharmaceuticals designed for therapy are agents which deliver therapeutic doses of particulate and ionizing radiation to the diseased sites.[2,3,6] As the term implies, targeted therapy is a treatment modality using agents which act as molecular vectors for transporting/targeting radionuclides to specific biological sites. Agents intended for use in targeted therapy are endowed with target specificity due to the presence of the carrier molecule with specific affinity for targeted sites. Examples include monoclonal antibodies which target specific antigens or peptides which target specific receptors that are overexpressed on cancerous tissues. Therapeutic efficacy is accomplished by inducing cytotoxicity to the tumor cells to arrest further proliferation. The most desirable features of a therapeutic radiopharmaceutical are the ability to deliver sufficient radiation dose to the target, to retain the radiopharmaceutical or the metabolite carrying the radionuclide at the site of interest, and to ensure rapid clearance of radioactivity from nontargeted tissues and organs. Target specificity is ensured by identifying a suitable target-seeking molecule and radiolabeling it with the radionuclide without compromising biological targeting.

There are several challenges involved in the development of therapeutic radiopharmaceuticals which arise from the required balance between specific in vivo targeting properties to the sites of interest with simultaneously less accumulation and more rapid clearance of radioactivity from nontarget sites. The possibilities of designing new radiopharmaceuticals arise from the evaluation of a large number of therapeutic radionuclides with widely

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different radionuclidic characteristics and also the availability of a large library of molecular targeting vectors.

2.1. Therapeutic Radionuclides

While designing a radiopharmaceutical for a particular therapeutic application, the choice of the appropriate radionuclide constitutes a prime determinant.[2,3,7−9] The major criteria for choice of a radionuclide for therapeutic use include the radionuclidic half-life, the type, energy, and branching ratio of particulate radiation, as well as photon abundance and energies. It is important to match the physical half-life of the radionuclide with the biological half-life of the carrier molecule used. Other important considerations include the availability of convenient and high-yield chemical strategies for stable attachment of the radionuclide to the carrier molecule, specific activity (activity/mass), radionuclidic and chemical purity, production feasibility, and cost. There are a large number of radionuclides which show potential use for the development of therapeutic radiopharmaceuticals. While it is difficult to select any one radionuclide as ideal or the best suited for therapy, a few will have more desirable properties than others for a desired application. A summary of key radionuclides which exhibit nuclear decay characteristics of interest for various in vivo therapeutic applications is given in Table 1.[10]

On the basis of the nature of the emitted radiation, radionuclides can be classified as α-particle emitters, β^--particle emitters, conversion electron (CE) emitters, or Auger electron emitters (AE). Auger electrons are emitted by radionuclides that decay by electron capture (EC) or internal conversion (IC). The decay creates a vacancy in an inner atomic shell which is filled by electrons cascading down from higher shells leading to a cascade of electron transitions with the emission of characteristic X-ray photons or Auger, Coster−Kronig, or super Coster−Kronig monoenergetic electrons. These electrons are distinguished on the basis of the shells involved with the transition and are often collectively referred to as Auger electrons.

Many of the radionuclides also emit γ rays after emission of either α or β^- particles, and some metastable radionuclides emit only γ photons. Each type of particle emission used for targeted therapy with unsealed sources has different linear energy transfer (LET) values and different ranges in soft tissue (Figure 1). LET is the measure of the energy transferred to the medium as an ionizing radiation passes through it and is used to quantify the effect of ionizing radiation on the medium such as a biological specimen. The LET values depend on both the nature of the radiation as well as on the material through which the particulate radiation passes. Particulate emissions such as α and β^- particles have high LET, whereas gamma and X-rays have low LET. High LET results in higher radiation damage to the biological systems and is quantified by the term "relative biological effect" (RBE). The RBE is the ratio of biological effectiveness of one type of ionizing radiation relative to another, given the same amount of absorbed energy. Among nuclear radiation, the RBE of alpha particles is the highest, followed by β^- particles and γ rays. The higher the RBE, the more damaging the radiation for the same absorbed energy. Radiations having higher LET, and hence high RBE, are necessary for inducing therapeutic effects. Pure gamma emitters are hence not useful for therapeutic applications in nuclear medicine, whereas high intensity γ radiation is used in sealed sources. Among the three other particulate emissions, α particles have the highest LET and are hence capable of producing the maximum RBE.[11] Radionuclides which emit α particles are effective where it is advantageous to use particulate radiation with a range of only a few cell diameters, such as the use of ^{213}Bi for therapy of leukemia cancer cells in the vascular system.[12] An emerging clinical application of an alpha emitter (^{223}Ra), such as Alpharadin, is for the treatment of cancer metastases in the skeleton.[13] Alpha particles deposit their energy over a short range (40−100 μm) and produce high-density ionizations along the tracks they traverse.[14] As a result, α particles are capable of producing significant cellular damage by inducing double-stranded DNA breakage while delivering minimum radiation damage to nontargeted tissues. For oncologic applications, α-particle emitters are more compatible for use in the treatment by rapid localization in blood-borne cancers and tumors with small diameters and where their localization within the tumor is homogeneous and crossfire to surrounding cells is not an issue.[15] One of the challenges for broader use of α-particle therapy is the lack of large-scale availability of suitable radionuclides. In addition, the short tissue range and short

Table 1. Summary of Key Therapeutic Radionuclides of Current Interest[10]

radionuclide	half-life	particulate energy in keV	principal γ energy in keV (% abundance)
β^--particle emitters			
^{111}Ag	7.450 days	1036	342 (6.7)
^{77}As	38.83 h	682	239 (1.6)
^{198}Au	2.695 days	1372	411 (95.5)
^{199}Au	3.139 days	452	158 (36.9)
^{67}Cu	61.83 h	577	184 (48.7)
^{165}Dy	2.33 h	1286	94 (3.6)
^{169}Er	9.400 days	351	nil
^{159}Gd	18.48 h	970	58 (26.2)
^{166}Ho	26.83 h	1854	80 (6.2)
^{131}I	8.020 days	970	364 (81.2)
^{177}Lu	6.734 days	498	208 (11.0)
^{32}P	14.26 days	1710	nil
^{109}Pd	13.70 h	1115	88 (3.6)
^{149}*Pm*	53.08 h	1071	285 (2.8)
^{142}Pr	19.13 h	2162	nil
^{186}Re	90.64 h	1069	137 (8.6)
^{188}Re	16.98 h	2120	155 (14.9)
^{105}Rh	35.36 h	567	318 (19.2)
^{47}Sc	3.345 days	600	159 (68.0)
^{153}Sm	46.27 h	808	103 (28.3)
^{89}Sr	50.53 days	1496	nil
^{161}Tb	6.88 days	518	74 (10.2)
^{90}Y	64.10 h	2282	nil
^{175}Yb	4.185 days	470	396 (6.5)
α-particle emitters			
^{225}Ac	10.0 days	5935	99 (3.5)
^{211}At	7.21 h	5982	687 (0.25)
^{212}Bi	60.55 min	6207	727 (11.8)
^{213}Bi	45.59 min	5982	439 (27.3)
Auger electron emitters			
^{125}I	59.40 days	12.24	35 (6.68)
^{111}In	2.80 days	6.75	245 (94)
^{67}Ga	3.26 days	6.26	93 (39.21)
conversion electron emitter			
^{117}Sn	13.6 days	127, 129	159 (86)

[a]For β^- particles the maximum β^- energy is mentioned. Auger electron energy is the average kinetic energy of Auger and Coster−Kronig electrons emitted per decay.

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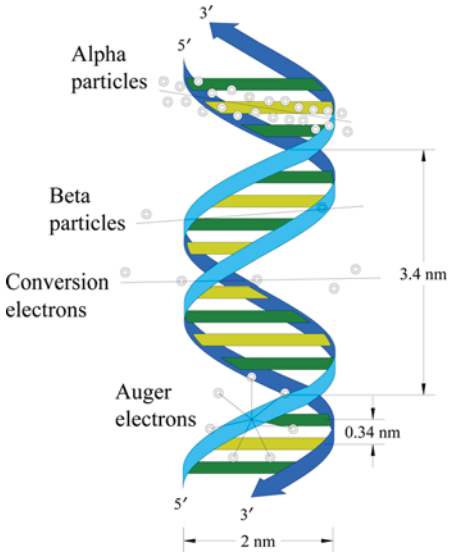

Figure 1. Cartoon illustration showing the interaction of different types of particulate radiation with DNA. Path ranges in the figure are not drawn to scale.

half-life generally require rapid targeting. The ranges of the different ionizing radiations along the tracks as they pass through the biological system are α = 50−100 μM, β^- = 0.2−15 mm, Auger electrons = a few nanometers, γ = several centimeters. The ionization densities (mean energy deposition/path length (keV/μm) are α = 80−300, β^- = 0.2, and AE = 4−26.[3]

Radionuclides that decay by emission of β^- particles and conversion electrons have been most extensively used for a broad series of radiotherapeutic applications because of their availability and suitability to treating large tumor volumes. These applications include cancer therapy, treatment of rheumatoid arthritis (synovectomy), arterial restenosis therapy, nonmelanoma skin cancer, etc.[2,3] β-Particle emitters produce a nearly homogeneous radiation dose distribution even though generally their deposition is heterogeneously distributed in target tissues.[16] As an example, most neoplasia consist of a heterogeneous distribution of stromal (structural), normal parenchymal (functional) cells, and tumor cells. Although the tumor cells may express a specific receptor, due to differential blood flow and other barriers, all cells will not be accessible by the targeting agent and hence will not receive the tracer. This makes the "cross-fire" effect particularly important for larger tumors.

Auger electrons are monoenergetic, low-energy electrons emitted during the decay of certain radionuclides by internal conversion (IC) or electron capture (EC) processes. Auger electrons have very short range in soft tissues and deposit their energy over subcellular dimensions. If targeted to the cell nucleus, high radiotoxicity is exhibited in the immediate vicinity of the DNA decay site.[17,18] Although Auger electrons actually have very low energy (20−500 eV), a high LET-like response is achieved due to their short range (1−10 nm).[19] However, Auger electron emitters must generally be targeted into the cell nucleus. The cytotoxicity, and hence the therapeutic efficacy, will be much less even when these radionuclides are present in the cytoplasm or on the surface of the target cells. Early studies have indicated that ^{111}In−Octreotide, an Auger-electron-emitting radiopharmaceutical, has low therapeutic efficacy where the tumor size becomes an important factor for the success of such therapy.[20] The disadvantage of the peptides radiolabeled with hard beta emitters such as ^{90}Y is the dose-limiting toxicity to the kidneys. While efforts with promising Auger electron emitters are currently being focused on the design of therapeutic radiopharmaceuticals, the design of agents which demonstrate the high targeting required for effective in vivo therapy remains a challenge.

2.2. Theranostics: Use of Diagnostic/Therapeutic Radionuclide Pairs

The term "theranostics" was coined to describe the combined use of a diagnostic tool that assists in the selection of the most appropriate therapeutic tool for treatment of a specific disease.[21,22] The concept of theranostics, also known as "theranosis", is utilized to tailor the therapy in a specific patient following the complete diagnosis of the disease, thus introducing the concept of personalized medicine. Nuclear medicine offers an ideal opportunity for theranostics since the dose of a diagnostic agent can be augmented to obtain a therapeutic effect. The advantage of this modality is the ability to perform imaging using SPECT/CT or PET/CT to provide the necessary pretherapy information on biopharmacokinetics and to guide the dosimetry focused on limiting dose to a critical organ or tissue.[23] The information thus obtained is used for defining the maximum tolerated dose (MTD). If the imaging results then warrant it, it is generally considered safe and appropriate to follow up with dose-ranging experiments to allow targeted molecular therapy using a higher dose of the same radiopharmaceutical. These factors are especially important for being able to perform individualized imaging as well as therapy with the same radiopharmaceutical, in the same patient.

A typical example of a theranostic radionuclide which emits both gamma photons as well as particulate radiation is ^{131}I, which has been used for many years in low doses for the diagnosis and staging of thyroid cancer using gamma imaging.[24] Subsequently, large doses of ^{131}I are administered for thyroid ablation therapy. Examples of radionuclides which have theranostic potential are given in Table 2.

3. EVOLUTION OF ^{177}Lu RADIOPHARMACEUTICALS

The first clinical use of ^{177}Lu was reported by Anderson et al. in 1960 when three patients suffering from myelomatosis were treated by intravenous injection of ^{177}Lu as lutetium chloride and/or citrate.[25] Results of these clinical studies were not promising since the patients did not show long-term survival but reported mild pain relief. No subsequent publication on ^{177}Lu appeared until Keeling et al. in 1988 reported a study on the uptake of ^{177}Lu hydroxyapatite (HA) particles to investigate the mechanism of uptake on bone minerals by in vitro techniques.[26] Schlom et al. in 1991 reported ^{177}Lu radiolabeling of the CC49 murine monoclonal antibody that recognizes the tumor-associated glycoprotein 72 (TAG-72).[27] Ando et al. reported the preparation and biological evaluation of ^{177}Lu−EDTMP (EDTMP = ethylenediaminetetramethylene phosphonic acid) as a bone palliating agent which was followed by another independent report by Solla et al., who applied this agent in patients.[28,29] The broader potential use of ^{177}Lu as a therapeutic radionuclide was, however, established with the use of ^{177}Lu−DOTATATE (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; TATE = tyrosine-3-octreotate), a radiopharmaceutical which targets neuroendocrine tumors.[1,30] Radiolabeling of several lead molecules has been more recently reported, and the potential application of ^{177}Lu as a therapeutic radionuclide is expanding, as seen from the increase of publications since the beginning of the past decade (Figure 2).

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