A Review on Technetium and Rhenium Based Radiopharmaceuticals for Diagnostic Imaging and Therapeutic Nuclear Medicine

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Abstract: Radionuclides (radioisotopes) are radioactive atoms with specific nuclear properties that have found an application in medical diagnostic imaging and radiotherapy in the form of various radiopharmaceuticals. Rhenium (Re) and technetium (Tc) have shown significant potential in nuclear medicine due to the prospective applications of rhenium radionuclides 186Re and 188Re in therapeutic nuclear medicine and technetium radionuclide 99mTc in medical diagnostic imaging. 186Re and 188Re radionuclides are both γ and β-emitting agents, while 99mTc radionuclide is only a γ-emitting agent; they exhibit favorable nuclear properties for medical imaging and therapy. Rhenium and technetium based radiopharmaceuticals are discussed in this review as they are widely applied in medical diagnostic imaging and therapeutic nuclear medicine in Europe and other parts of the world. Rhenium radionuclide agents are not yet approved for use in the United States. The nuclear properties of medical 186Re, 188Re and 99mTc radionuclides and their production and incorporation into radiopharmaceuticals are discussed. Stabilization and biodistribution (pharmacokinetics) of rhenium and technetium based radiopharmaceuticals from the administered site to the targeted organ during imaging and therapy are also clarified. Finally the classification of rhenium- and technetium-based radiopharmaceuticals, and their most common uses in nuclear medicine are discussed.

Key words (MeSH): Rhenium; Technetium; Radiopharmaceuticals; Nuclear medicine

INTRODUCTION

Nuclear medicine is an independent medical specialty that involves administration of radioactive drugs (radiopharmaceuticals) for the purpose of medical imaging and therapy [1]. In terms of nuclear chemistry, the radiopharmaceuticals contain radioactive elements (radionuclides) that emit particular types of nuclear radiation (α, β, γ) over a particular duration of time (half-life) and with a specific energy level and length of body tissue penetration [2]. The potential use of radionuclides in medical diagnostic imaging and therapeutic nuclear medicine has been recognized for many decades [3]. Current research shows that approximately over 10,000 medical facilities worldwide use radionuclides in medical diagnostic imaging and therapy [1, 2].

Radiopharmaceuticals target certain organs and physiologic processes. Special cameras (gamma cameras) are designed to track and monitor both pharmacokinetic and pharmacodynamic behaviors of radiopharmaceutical from the administered site to the targeted organ [5]. The selection of a particular radiopharmaceutical depends on the clinical question and organ or pathology of concern. Choice of the radiopharmaceutical to apply in diagnostic imaging and therapeutic nuclear medicine is typically based on the availability at the hospital, side effects, and its pharmacokinetic and pharmacodynamic properties [4]. However, the nuclear characteristics of radiopharmaceutical, particularly its mode of decay, half-life, energy level, and tissue penetration ability are also taken into consideration [4].

Introduction of nuclear medicine began in the early 1950's with an endocrine emphasis, initially applying γ-ray emitter iodine-131 (131I) for diagnostic imaging of the thyroid gland and therapeutic treatment of patients with hyperthyroidism [1, 5]. Since then the field of nuclear medicine has expanded to include a large array of radiopharmaceuticals based on various radioactive elements. Nearly every organ of the body and many kinds of tumors can be assessed with nuclear imaging. Some radionuclides have also displayed success as therapeutic treatment [1, 2].

Cancerous and benign tumors have received considerable attention due to severity and increasing death rates. Similarly, rhenium (Re) and technetium (Tc) have been researched due to potential therapeutic nuclear medicine application of rhenium radionuclides 186Re and 188Re, but also the potential application of technetium radionuclide 99mTc in medical diagnostic imaging [6, 7].

Rhenium based radiopharmaceuticals involve both 186Re and 188Re radionuclides and they are both γ and β-emitting agents. Due to their favorable nuclear properties, minimized side effects, and favorable pharmacokinetic and pharmacodynamic properties, they are widely applied in therapeutic nuclear medicine for different disease treatment in which both cancerous and benign tumors are emphasized [8]. In addition, the 188Re radionuclides based radiopharmaceuticals have shown value for a variety of applications in oncology, rheumatology and

interventional radiology/cardiology [8]. Technetium based radiopharmaceuticals involve a 99mTc radionuclide, which is a γ-emitter and finds applications in nuclear medicine, specifically in medical diagnostic imaging [6]. The use of 99mTc radionuclide in medical diagnostic imaging began in 1961, with the thyroid being the first imaged organ [6].

This review discusses and reports on the findings of technetium and rhenium based radiopharmaceuticals as applied in medical diagnostic imaging of different organs and therapeutic treatment of diseased organs.

General Chemistry of Rhenium and Technetium

The chemistry of rhenium and technetium (Tc) are similar to each other. Hence, the chemistry of rhenium can successfully be used for modeling the technetium chemistry and vice versa [9]. Similar physical properties of rhenium and technetium, particularly displaying the same photo-emission energy, are of interest in nuclear medicine. These enable monitoring of biodistribution of radiopharmaceuticals based on these metals using the same γ-ray camera [2, 10]. Another advantage is that the analogous rhenium and technetium radiopharmaceuticals are expected to share the same biodistribution pattern in the patient [2, 11].

Rhenium (Re) and technetium are located in Group VII on the Periodic Table with the atomic numbers 43 (technetium) and 75 (rhenium) and are perhaps the most versatile of all the transition metals [12]. Due to their location in the middle of the d-block of transition metals, they exhibit the properties of both early and later transition metals. Consequently, they display a variety of coordination compounds in all oxidation states from -1 to +7 [12]. Rhenium and technetium compounds in the +2 and +6 oxidation states show instability and consequently, are rare in literature [2, 13]. Rhenium and technetium based radiopharmaceuticals are typically in +5 and +1 oxidation states due to considerable stability [2, 13]. In addition, technetium and rhenium based radiopharmaceuticals in +1 and +5 oxidation states have shown respectable biodistribution (pharmacokinetics) in medical imaging and therapeutic nuclear medicine compared to other oxidation states [14-16].

Production and Nuclear Properties of Medical Rhenium and Technetium Radionuclides

Radionuclides applied in therapeutic nuclear medicine are those emitting particles, such as gamma (γ) and beta (β), which have a high linear energy transfer [17, 18]. Beta particles exhibit fewer ionization events per unit of distance traveled than gamma particles, allowing them to penetrate deeper in the concerned tissue or organ for therapeutic treatment [17, 18]. Gamma particles show more ionization events per unit of distance traveled which results in more cellular damage over a shorter range [19, 20]. Gamma particles are detected by γ-cameras, for imaging, biodistribution, or absorbed radiation dose studies [20]. ^{186}Re and ^{188}Re radionuclides are γ and β-emitting agents, and are consequently applied in therapeutic nuclear medicine [2].

^{186}Re is produced in nuclear reactors by irradiation of natural or enriched ^{185}Re by neutrons (n) in the nuclear reactor [21]:

186Re has 90.64 hours half-life, and emits β particles of 1.07 Mev energy and γ particles of 137 Kev energy. It is noted that the specificity of 186Re produced in this manner is limited by neutron flux in the reactor [21]. The longer half-life of 90.64 hours for ^{186}Re radionuclide is advantageous due to the prolonged therapeutic treatment of the targeted organ [20]. ^{186}Re has disadvantage of showing a low specificity activity in therapeutic treatment due to its production via neutron (n) irradiation of 185Re [19, 20]. Due to its favorable mode of decay and its potentiality in therapeutic treatment, the methods for producing high specific activity ^{186}Re are being explored [18, 20].

^{188}Re radionuclide is obtained in high specific activity from a commercially available tungsten-188 / Rhenium-188 (188W / ^{188}Re) generator system, and has 17 hours half-life, and emits β particles of 2.12 Mev energy and γ particles of 155 Kev energy [19]. As result, ^{188}Re radionuclide is produced from a generator with the parent radioisotope 188W (W = Tungsten) which originates in a nuclear reactor by double neutron capture of 186W to produce 188W [22]. The production of ^{188}Re radionuclide applies beta (β) decay of 188W radionuclide generator and the reaction has half lif of 69.4 days. The production of ^{188}Re radionuclide is shown in the following nuclear reaction scheme [21]:

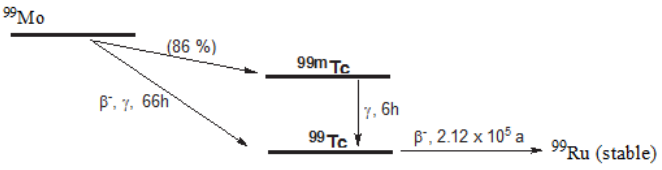
$$^{186}\mathrm{W} \xrightarrow{n,\gamma} {}^{187}\mathrm{W} \xrightarrow{n,\gamma} {}^{188}\mathrm{W} \xrightarrow{t_{1/2}\,=\,69.4d} {}^{188}\mathrm{Re}$$

The separation of ^{188}Re from unreacted 188W is performed in generators by column chromatography, extraction or gel technology [22]. However, the most accurate results are obtained using chromatographic technique in which 188W is adsorbed on aluminum and ^{188}Re is eluted in a saline solution [22]. The ^{188}Re yield after elution are generally 75 % to 80 % of the available ^{188}Re at the hospitals with a nuclear medicine department [8].

Radionuclides emitting gamma particles (γ) are successfully used in medical diagnostic imaging [18]. The emitted γ radiation interacts minimally with the low atomic weight elements found in the body, allowing it to escape the patient for detection by γ-cameras [18]. Technetium-m99 (^{99m}Tc) radionuclide is γ-emitter and it is applied in medical diagnostic imaging. It was isolated in 1938 after studying molybdenum-99 (^{99}Mo) deflectors, which had been irradiated with deuterons [23]. Although discovered in 1938, ^{99m}Tc did not become medically applied until the 1960 after a generator system was developed to easily separate ^{99m}Tc from its parent 99Mo [24].

Technetium radionuclide ^{99m}Tc is then produced from a molybdenum radionuclide (^{99}Mo) [25]. During that process, the long half-life of 99Mo (66 hours) in the form of a molybdate ion, 99MoO42,- is introduced to the reactor, and the short half-life of 99mTc (6.02 hours) is progressively produced from the decay of the parent ^{99}Mo

and it is formed as pertechnetate ion, $^{99m}TcO4^-$, with β and γ ray emissions [6, 26].



Scheme 1: Production of ^{99m}Tc radionuclide

^{99m}Tc has 6.02 hours of half-life and emits γ particles of 140.5Kev energy, and its shorter half life is of interest in medical imaging [26]. The production of ^{99m}Tc radionuclides occur in the molybdenum-technetium (^{99}Mo-^{99m}Tc) generator system; it is based on the principle that the short-lived radioactive daughter, 99mTc, is easily and repeatedly isolated from the long-lived parent radionuclide, ^{99}Mo [26, 27].

The separation of ^{99m}Tc from the mother radionuclide, ^{99}Mo, in the molybdenum-technetium generator is also facilitated by the difference in physical and chemical properties of technetium radionuclide, ^{99m}Tc, and molybdenum radionuclide, ^{99}Mo [26, 27].

Both radionuclides, ^{186}Re and ^{188}Re, are radiochemically active and are γ and β-emitting agents [28], while ^{99m}Tc is only a γ-emitting agent [2, 27]. The suitability of radionuclides

^{186}Re and ^{188}Re in therapeutic nuclear medicine and 99mTc in diagnostic imaging are related to their favorable nuclear properties summarized in Table 1 [26, 29, 30].
Table 1: Nuclear characteristics of medical ^{186}Re, ^{188}Re and ^{99m}Tc radionuclides

Characteristics	^{186}Re	^{188}Re	^{99m}Tc
Mode of decay	γ, β	γ, β	γ
Half-life	90.64 h	17 h	6.02 h
Energy (E_{max})	$_{\gamma}$=137 Kev, β=1.07 Mev	$_{\gamma}$=155 Kev, β= 2.12 Mev	140.5 Kev
Soft tissue penetration	1.6 mm	3.9 mm	No limit

Rhenium and Technetium Based Radiopharmaceuticals

Radiopharmaceuticals are used in nuclear medicine for diagnostic imaging of different organs and radiotherapy for various diseases [4]. The potential application of radioisotopes in diagnostic imaging or therapeutic nuclear medicine is related to their nuclear characteristics such as chemical properties, mode of decay, half-life, daughter product(s), side effects and tissue penetration ability [4, 31]. However, radionuclide production techniques and purity are also taken into consideration [31].

Rhenium based radiopharmaceuticals involve both ^{186}Re and ^{188}Re radionuclides and are widely used in therapeutic nuclear medicine for treatment of various diseases, particularly destroying or weakening cancerous and benign tumors and malfunctioning cells located in different organs [2]. The favorable nuclear properties of medicinal ^{186}Re and ^{188}Re radionuclides for therapeutic nuclear medicine are tissue penetration abilities, which are suitable for treatment of small and large tumors, their relative half-lives, which are long enough to prolong the treatment period and their β-particle emission energies, which are high enough to deliver the radiation dose (see Table 1) [2, 11]. Rhenium based radiopharmaceuticals are the most popular radiopharmaceuticals in therapeutic nuclear medicine due to their favorable nuclear properties, minimized side effects, availability in the majority of hospitals due to cost-effectiveness, easy forms of biodistribution in patient's and reduced toxicity risks of metal rhenium [8].

Technetium based radiopharmaceuticals involve ^{99m}Tc radionuclides and are widely applied in nuclear medicine, specifically for medical imaging [2]. The chemistry of rhenium and technetium are similar to each other and consequently, the preparation of therapeutic rhenium based radiopharmaceuticals may be successfully used for preparing homologous diagnostic imaging technetium based radiopharmaceuticals [32]. Technetium radionuclide ^{99m}Tc is used worldwide in 80% of diagnostic imaging procedures [33]. The use of technetium radionuclides, ^{99m}Tc, in medical diagnostic imaging is related to its favorable nuclear characteristics. It has a short half-life ($t_{1/2}$ = 6.02 h, see Table 1) which is a major benefit since the radionuclide decays very quickly, causing minimal damage to the patient's tissues and allowing rapid scans and diagnosis [33]. The γ-ray emissions from ^{99m}Tc have an energy of 140 keV [34], this energy is efficient enough to penetrate the imaged organ since the defined optimum energy range for successful medical imaging facilities currently presented in various hospitals is 100-200 keV [34, 35]. The low γ-ray energy of 140 keV from ^{99m}Tc easily escapes the human body, are successively detected by gamma cameras and cause very little damage to the patient's imaged organ [35]. In addition, ^{99m}Tc radionuclides may be prepared in different forms and travel to different organs, allowing specific diagnostics with minimized side effects [34]. The ^{99m}Tc radionuclide in its various formulations is currently used in scanning to locate and diagnose conditions in the heart, kidneys, lungs, brain, thyroid, bones, stomach and liver [34, 36]. The typical example is the image shown below (Figure 1) which represents the ^{99m}Tc normal brain scan image (a) and 99mTc tumor positive brain scan image (b, arrow) [37].

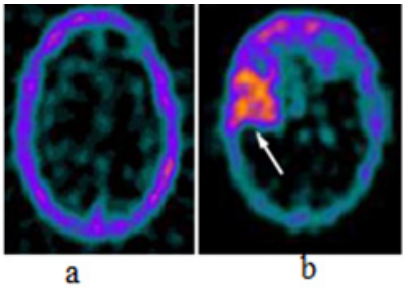


Figure 1: Representative of 99mTc normal brain scan image (a) and 99mTc tumor positive brain scan image (b, arrow)

^{99m}Tc based radiopharmaceuticals have the potential advantages in medical imaging due to the fact that they provide (in some clinical cases) the detailed insight into a living system in a way that classical imaging techniques, such as magnetic resonance imaging (MRI) and X-ray, typically cannot [37]. The typical example is the brain tumors which mostly represent the clinical problem in oncology due to their increasing incidence, difficulties in treatment and high rates of recurrence [18, 37]. Today, there is a potential challenge to evaluate the post treatment of diseases status because differentiation of recurrence from treatment-induced changes is not possible with the use magnetic resonance imaging (MRI) or X-ray [37]. ^{99m}Tc has been used in this regard as imaging methods, and has shown the successful differentiation of recurrence from treatment-induced changes (see Figure 2) leading to the successfully brain tumors treatment [37].

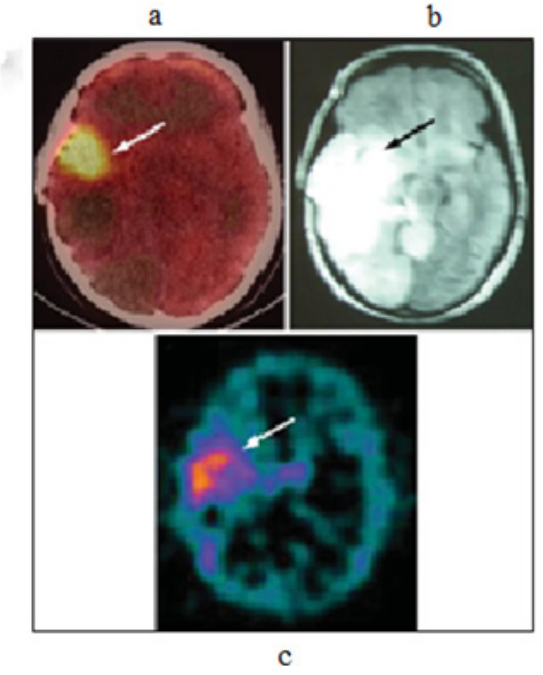


Figure 2: Presentation of 18F scan (a, arrow), MRI scan (b, arrow) and 99mTc scan (c, arrow) for patient with temporal glioma post surgery and radiotherapy with clinically suspected recurrence

According to the Figure 2, it is clear that the patient was positive for recurrence on 18-fluoride (18F) scan (a, arrow), magnetic resonance imaging (MRI) scan (b, arrow) and ^{99m}Tc scan (c, arrow). However, the lesion on MRI (b) covered both viable tumor and radionecrotic area. ^{99m}Tc scan image (c, arrow) showed only tracer uptake at viable tumor area, well correlated with the positive tumor area delineated by 18F scan (a, arrow).

Preparation of Rhenium and Technetium Based Radiopharmaceuticals

Typical preparation of rhenium and technetium-based radiopharmaceuticals starts from the perrhenate ion, $^{186/188}$ReO4−, and pertechnetate ion, ^{99m}TcO4−, respectively obtained from different radionuclide generators [6, 34]. During the preparation, metal ions have to be reduced by appropriate reducing agents (mostly a Sn(II) salt), and coordinated by suitable chelating ligand which will stabilize the low oxidation state of the Lewis acidic metal center, and determine the biodistribution of radiopharmaceutical in the patient [6, 34].

In addition, the physiological buffer solution for adjusting the pH to the physiological pH is added to the reaction [34]. Such procedures commonly occur in so-called "instant kits" (Figure 3) [6] and the reaction must be optimized since the expected purity and yield of the products should be reproducible at 95% [2, 6]. After performing their chromatographic quality control, the produced radiopharmaceuticals should be ready for injection without further purification [2, 6].

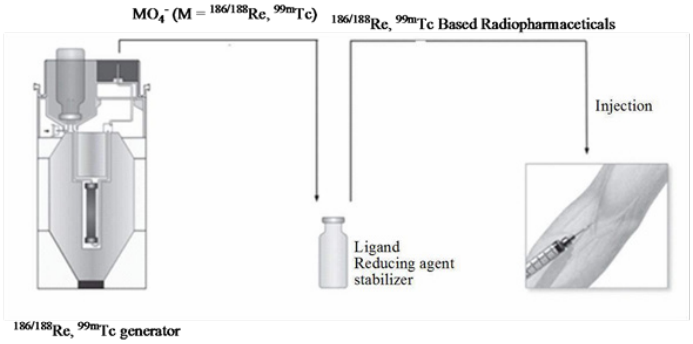


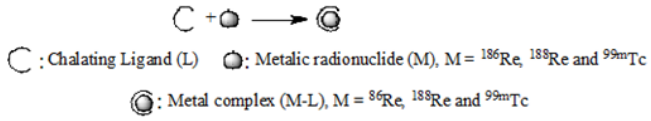
Figure 3: Instant kit reconstitution for preparing rhenium and technetium based radiopharmaceuticals

Stabilization of Rhenium and Technetium Based Radiopharmaceuticals

As for other metal-based radiopharmaceuticals, the major objective to be taken into consideration during the designing of rhenium and technetium based radiopharmaceuticals is to assure that they accumulate in and are eliminated from the targeted organ / tissue, blood and the entire body [17]. The scientific approaches are used when attempting to shuttle rhenium and technetium based radiopharmaceuticals to specific areas in body. In most of cases the metal rhenium and technetium must be coordinated to a specific chelating ligand in order to keep the metal away from becoming a free agent in the body, and in some cases to help stabilize its oxidation state [18]. Consequently, before being administered as radiopharmaceuticals, ^{186}Re, ^{188}Re and ^{99m}Tc radionuclides must be stabilized by the appropriate chelating ligands (L) to help maintain their composition in physiologic conditions. Without stabilizing measures, alteration of radiopharmaceutical chemical properties in the human body (e.g. changing oxidation state etc) could alter the biodistribution, leading to unsuccessful therapeutic treatment or diagnostic imaging [28, 38, 39]. Stabilization of radiopharmaceuticals before administration is therefore an important step in achieving diagnostic quality imaging

studies and successful radiotherapy in nuclear medicine [28, 38-40].

The chelating ligand (L) for stabilizing ^{186}R, ^{188}Re and ^{99m}Tc radionuclides are usually those with multiple heteroatom donor sites such as nitrogen (N), sulfur (S), oxygen (O) and phosphorous (P), and coordinate to rhenium and technetium centre resulting in M–L complex (M = ^{186}R, ^{188}Re and ^{99m}Tc) (Scheme 2) with a particular stability [28, 39].



Scheme 2: Stabilization of rhenium and technetium radionuclides (M) by chelating ligand (L) resulting in stable M-L complex (M)

Biodistribution of radiopharmaceuticals is therefore determined by the properties of the total M–L complex, leading to an essential rhenium and technetium based radiopharmaceuticals with accurate diagnostic imaging and therapeutic properties [8, 38].

Administration and Biodistribution of Rhenium and Technetium-Based Radiopharmaceuticals in Patients

The administration mode of radiopharmaceuticals and timing of imaging depends on the disease process being studied. The amount of radiopharmaceutical given to the patient should be kept to the minimum amount (nano- to picomolar quantity) necessary to achieve high quality imaging or effective therapy [18]. Once this minimum quantity is respected, radiopharmaceuticals will rarely cause the physiological effects and will offer a way to monitor their pharmacokinetics and pharmacodynamic behavior with a minimum disruption to the system [18]. In nuclear medicine, radiopharmaceuticals are administered to a patient through intravenous injection, oral ingestion, inhalation or direct injection or instillation into the concerned organ [30, 38].

Biodistribution of radiopharmaceuticals describes how they are biologically distributed (pharmacokinetic) and transported through the body from the administered site to the targeted organ during medical imaging or radiotherapy. For intravascular administered radiopharmaceuticals biodistribution is facilitated by blood flow or binding to biological molecules such as proteins and enzymes on targeted organ [39]. Other modes of administration such as inhalation or ingestion rely on the physiology of lung and GI tract.

Biodistribution of rhenium and technetium-based radiopharmaceuticals in the body is commonly determined by different factors such as physico-chemical properties of radiopharmaceutical, stability of radiolabel, purity of radiopharmaceutical, pathophysiologic state of the patient and the presence or absence of interfering drugs [38]. Consequently, the availability, shape, size and solubility of biological molecules, which control the biodistribution and transport of rhenium and technetium based radiopharmaceuticals to the targeted organ, are important factors to consider for successful medical imaging and therapy in nuclear medicine [38, 39]. There are two main methods in which rhenium and technetium based radiopharmaceuticals are biodistributed and transported to the targeted organ for therapeutic or medical imaging purpose [35, 39]:

Biodistribution by Blood Flow and Perfusion

Radiopharmaceuticals whose biological distribution is strictly determined by blood flow and perfusion are named perfusion agents. This biodistribution mode often occurs when the targeted sites are urinary, mononuclear phagocyte and bone systems as well as hepatocyte tissue [39, 41].

Biodistribution by Specific Interactions

Rhenium and technetium based radiopharmaceuticals which are biodistributed by specific interactions are called second-generation agents or target-specific radiopharmaceuticals. In this case, radiopharmaceutical biodistribution is determined by specific interactions such as receptor binding, transporting or enzymatic interactions; thus targeting low capacity sites [39, 41].

Classification of Rhenium and Technetium Based Radiopharmaceuticals

Rhenium and technetium based radiopharmaceuticals are divided into three generations according to their biodistribution modes or respective synthetic approach [34].

First Generation Rhenium and Technetium Based Radiopharmaceuticals

The first generation of radiopharmaceuticals are those with a biological distribution strictly determined by blood flow and perfusion. They can be classified as perfusion agents since they do not display any targeting functions in the body [2, 34]. The nuclear medicine application of these radiopharmaceuticals primarily depends on their physiochemical properties including hydrophilicity, charge and size of the 186/188Re–L complex. These properties have also been proven to determine biological distribution of radiopharmaceutical between tissues [34]. Most commercially available technetium-based radiopharmaceuticals for medical imaging are first generation [6].

The first generation radiopharmaceuticals are often applied when the targeted sites are urinary, mononuclear phagocyte and bone systems as well as hepatocyte tissue [2, 35]. For, example, 99mTc–Gla and 99mTc–Glh complexes in which gluconic acid and glucoheptonic acid, Gla and Glh (Figure 4) respectively, have been introduced for renal imaging [2, 42].

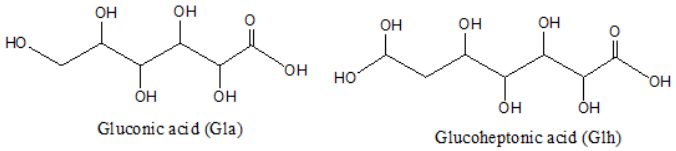


Figure4: Structure of gluconic acid (Gla) and glucoheptonic acid (Glh)

Another example of first generation rhenium and technetium radiopharmaceuticals utilizes

$^{186/188}$Re–HEDP and ^{99m}Tc–HEDP, in which HEDP is 1-hydroxyethylidene-1,1- diphosphonate (Figure 5). The $^{186/188}$Re–HEDP complex has been successfully used for palliation of pain relief from metastatic bone cancer [2, 36]. The ^{99m}Tc–HEDP complex is widely used for skeletal imaging [2, 43].

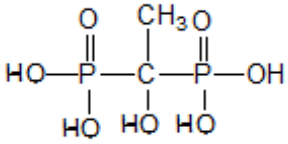


Figure5: Structure of 1-hydroxyethylidene-1,1-diphosphonate (HEDP)

Second Generation Rhenium and Technetium Based Radiopharmaceuticals

Second generation rhenium based radiopharmaceuticals target specific biological molecule receptors and bind for transport to the targeted organ. Hence, the radiopharmaceutical distribution to the specific site in the body is facilitated by such biological molecule receptors [2, 6, 34]. The ligands (L) coordinated to the second generation $^{186/188}$Re and ^{99m}Tc radiopharmaceuticals must be bifunctional in order to stabilize the metal ion in a particular oxidation state through coordination and covalently link the radiopharmaceutical to the biovector [2]. Possible biological molecule receptors are peptides, antibodies, proteins and pharmacophores [34].

The connecting functionality of the radiopharmaceutical to the biovector commonly occurs through carboxylate (COO-) or amine groups (NH2, NH and N), which can be conveniently activated with standard strategies from organic chemistry such as carbon-hydrogen (C-H) nitrogen-hydrogen (N-H), nitrogen-carbon (N-C) and carbon-oxygen (C-O) bonding modes [4, 34]. Consequently, the carboxylate and/or amine functions of polyaminopolycarboxylic acids have been applied as stabilizing ligands (L) of $^{186/188}$Re and ^{99m}Tc radionuclides in preparation of second generation rhenium and technetium based radiopharmaceuticals [2, 34].

Examples include $^{186/188}$Re–DTPA and ^{99m}Tc–DTPA, $^{186/188}$Re–DOTA and ^{99m}Tc–DOTA radiopharmaceuticals in which DTPA is diethylenetriaminepentaacetic acid and DOTA is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Figure 6) [2, 34].

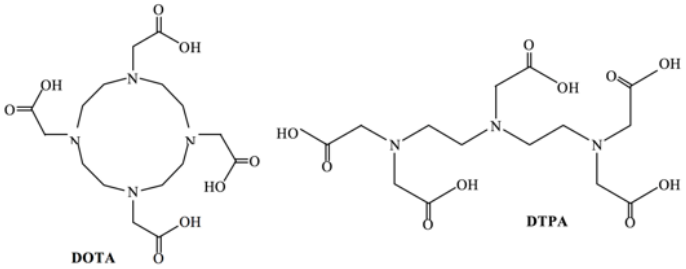


Figure 6: Structure of diethylenetriaminepentaacetic acid (DTPA) and 1,4,7,10- tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)

The $^{186/188}$Re–DTPA is used as a potential radiopharmaceutical for intravascular radiation therapy while ^{99m}Tc–DTPA complex is used for kidney and brain scintigraphy [44]. The $^{186/188}$Re–DOTA-chelated compounds are potential radiopharmaceutical targeted therapeutic treatment of various types of tumors. ^{99m}Tc-DOTA-chelated compounds can be used for diagnostic imaging in the kidney, lung and liver imaging [45–47].

DMSA is "dimercaptosuccinic acid" (Figure 7) and it is a thiol (-SH) and carboxylate (-OOC) functionalized ligand.

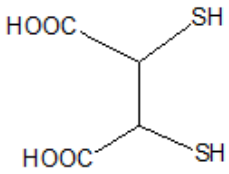


Figure 7: Structure of dimercaptosuccinic acid (DMSA)

The $^{186/188}$Re(V)–DMSA complex is a second-generation radiopharmaceutical and is suggested as an agent for therapeutic treatment of medullar carcinoma [48]. The homologous ^{99m}Tc(V)–DMSA complex is widely used as a radiopharmaceutical for diagnostic imaging of medullar thyroid carcinoma [48]. The $^{186/188}$Re–DMSA complex has shown selective uptake in tumor tissue analogous to that of its technetium counterpart and offers the possibility of therapeutic treatment of this disease [49, 50].

Mercaptoacetyltriglycine (MAG3) is a triamide, ester and thiol functionalized ligand (Figure 8) that efficiently stabilizes rhenium radionuclides. The $^{186/188}$Re(V)–MAG3 system is a second-generation radiopharmaceutical which forms a square pyramidal oxo complex and is commonly used as a radiation source in liquid-filled balloons for therapeutic prevention of restenosis [2, 51]

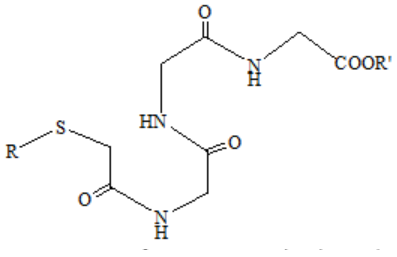


Figure 8: Structure of mercaptoacetyltriglycine (MAG3)

The analogous technetium complex ^{99m}Tc(V)−MAG3 is commonly used as a diagnostic imaging agent for renal function [39, 52]. In both cases, the system has been adapted by the attachment of an activated ester group via an amide group to permit conjugation to antibodies.

Third Generation Rhenium and Technetium Based Radiopharmaceuticals

In this case, the essential parts of biological molecules (mostly hormones) are mimicked and the radiopharmaceutical complex $^{186/188}$Re−L is incorporated into the carbon skeleton [2, 38]. The radionuclides of rhenium or technetium are incorporated into the carbon skeleton by coordination to carboxylate or aminothiol groups. The radioactive metal center and its ligands are insulated by metal-oxygen double bonds to mimic the electronic structure of the respective hormone [2, 34]. Hormones such as progesterone and testosterone have been synthesized and tested for this application [47].

An example is the oxorhenium(V) radiopharmaceutical ($^{186/18}$8ReO3+), synthesized from radionuclides rhenium and tetradentate chelating ligand (ligand with four coordination sites for bonding to rhenium) with amino (-NH2), amido (O=C-NH-), thioether (R-S-R) and thiol (R-SH) groups which incorporated into the chelating ligand [2, 34]. This oxorhenium(V) complex is known to be incorporated in the female hormone, estradiol, replacing the C and D rings as shown in Figure 9 [2, 34].

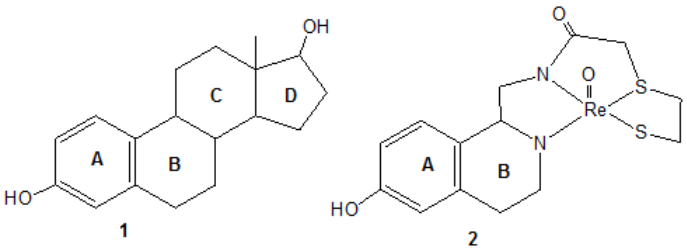


Figure 9: Structure of estradiol hormone (1) and rhenium-estradiol template (2)

CONCLUSION

Radionuclides $^{186/188}$Re and ^{99m}T play a considerable role in the development of new target-specific medical imaging and therapeutic radiopharmaceuticals. Medical imaging radiopharmaceuticals should be those with short half-life and emit gamma (γ) particles since they are detected by γ-camera leading to the successful organ imaging. γ-emitter ^{99m}Tc has short half-life and maps the physiological function giving more specific information about the organ function and dysfunction, and in some clinical cases, 99mTc shows the better diagnostic imaging performance than other medical imaging techniques.

Therapeutic radionuclides should emit γ and β particles with a high linear energy transfer and long half-life for prolonging therapeutic treatment.$^{186/188}$Re are γ and β-emitters and have the longer half-life, and higher linear energy transfer making them to be efficient in therapeutic treatment. The similarity between rhenium and technetium chemistry, particularly emitting γ-particles enable the monitoring of the biodistribution of radiopharmaceuticals based on these metals using the same γ-ray camera. In addition, analogous rhenium and technetium based radiopharmaceuticals are expected to have the similar pharmacokiteic properties.

Rhenium and technetium based radiopharmaceuticals have been potentially and worldly applied in medical imaging and therapeutic treatment of benign and cancerous tumors. For fighting against benign and cancerous tumors, there is a need of exploring the chemistry of rhenium and technetium for designing the new radiopharmaceuticals based on these metals.

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REFERENCES:

1. World Nuclear Medicine Association. Radioisotopes in Medicine, November, 2016.

2. Mukiza J. Rhenium complexes with potentially multidentate ligands containing the amino, imino, hydroxyl and thiol groups. PhD Thesis. Nelson Mandela Metropolitan University, April, 2016.

3. Yeong C-H, Cheng M-H, Ng K-H. Therapeutic radionuclides in nuclear medicine: Current and future prospects. J. Zhejiang Univ. Sci. B.2014; 15:845-863.

4. Nerves M, Kling A, Lambrecht RM. Radionuclide production for therapeutic radiopharmaceuticals. Appl. Rad. Isotop.2002; 57:657−664.

5. Kahn J. From Radioisotopes to Medical imaging, History of Nuclear Medicine. Berkeley, September 1996.

6. Abram U, Alberto R. Technetium and Rhenium, Coordination Chemistry and Nuclear Medical Application. J. Braz. Chem. Soc. 2006; 17:1486−1500.

7. Gerber TIA, Luzipo D, Mayer P. A monooxorhenium(V) complex with an unusually long Re=O bond: the structure of [ReOI2(ame)(PPh3)] (Hame=2-(2-aminophenyl)ethanol)molecules. J. Coord. Chem. 2004; 57:1345−1349.

8. Argyrou M, Valassi A, Andreou M et al. Rhenium-188 Production in Hospitals by W-188 / Re-188 Generator for Easy Use in Radionuclide Therapy. Int. J. Mol. Imaging. 2013; 2013:1−7.

9. Kukushki VY. Metal-ion mediated deoxygenation of sulfoxides. Coord. Chem. Rev. 1995; 139:375−407.

10. Booysen IN. Rhenium(I) and (V) Complexes with Potentially Multidentate Ligands Containing the Amino Group. PhD Thesis. Nelson Mandela Metropolitan University, 2009.

11. Yumata NC. Reactivity of Rhenium(III) and Rhenium(V) with Multidentate NN- and NO-Donor Ligands. MSc Dissertation. Nelson Mandela Metropolitan University, 2009.

12. Mukiza J, Gerber TIA, Hosten E et al. A (μ-O)(μ-Br)ReIV2 metal-metal triple bond complex with a bridging tridentate ligand. Synthesis, structure and DFT study. Inorg. Chem. Commun. 2014; 49:5–7.

13. Mukiza J, Gerber TIA, Hosten E et al. Trans, trans [ReO2I2 (PPh3)2] , a rare Rhenium(VI) complex. Synthesis and DFT study. Inorg. Chem. Commun. 2015; 51:83–86.

14. Balch AL, R.H. Holm RH. Complete electron-transfer series of the [M-N4] type. J. Am. Chem. Soc. 1966; 88:5201-5209.

15. Mukiza J, Gerber TIA, Hosten E. Coordination of Bidentate Aroylhydrazone-Based N,N-Donor ligands to the fac-[Re(CO)3]+ Core. J. Chem. Crystallogr. 2014; 44:368–378.

16. Carl R, Watkins S, Hamphrey SM, Bulman PCP et al. Rhenium(I) phenanthrolines bearing electron withdrawing CF3 substituents: synthesis, characterization and biological evaluation. RSC Adv. 2013; 3:23963–23966.

17. Azuwuike O, Mohan P, Samy S. Designing of Radiopharmaceuticals. In: The Handbook of Radiopharmaceuticals, 1995; Springer, Boston, MA.

18. Lauren Radford L. Technetium and Rhenium (I and V) Complexes for Radiopharmaceutical Applications. PhD Thesis, University of Missouri, 2016.

19. Fassbender ME, Ballard B et Al. Proton irradiation parameters and chemical separation procedure for the bulk production of high-specific-activity 188Re using WO3 targets. Radiochim. Acta, 2013; 101:339–346.

20. Matthew DG, Connor RH et Al. Accelerator-based production of the 99mTc- 186Re Diagnostic-therapeutic pair using metal disulfide targets (MoS2, WS2, OsS2). Appl. Radiat. Isot. 2016; 114:159–166.

21. Alberto R, Schibli R, Egli A. Technetium and Rhenium: Coordination Chemistry and nuclear medical applications. Coord. Chem. Rev. 1999; 901:190–192.

22. Vucina J, Han R. Production and therapeutic use of rhenium-186,188-the future of radionuclides. Med. Pregl. 2003; 56:362–365.

23. Segre´ and E, Seaborg GT. Nuclear isomerism in element 43. Phys. Rev. 1938; 54:772–772.

24. Richards P. Technetium-99m: The early days. Conference paper, 1989.

25. H. Christopher HG Green. Technetium-99m production issues in the United Kingdom. J. Med. Phys. 2012; 37:66–71.

26. Targholizadeh H, Raisali G, Jalilian AR et al. Cyclotron production of technetium radionuclides using a natural metallic molybdenum thick kit target and consequence preparation of [Tc]-BRIDA as a radio-labelled kit sample. Nucleonika. 2010; 55:113–118.

27. Takacs S, Szucs Z, Tarkanyi F et al. Evaluation of proton induced reactions on 100Mo new cross sections for production of 99mTc and 99Mo. J. Radioanal. Nucl. Chem. 2003; 257:195–201.

28. Jalil ZM, Qassim MM, Hamed HM. Preparation of new ligands containing nitrogen and spectrophotometric study with Rhenium complexes. Magazine of Al-Kufa University for Biology. 2013; 5:130–140.

29. Iznaga-Escobar N. Direct radiolabeling of monoclonal antibodies with rhenium-188 for radioimmunotherapy of solid tumors-a review of radiolabeling characteristics, quality control and in vitro stability study. Appl. Rad. Isotop. 2001; 54:399–403.

30. Ting G, Chang C-H, Wang H-L et al. Nanotargeted Radionuclides for Cancer Nuclear Imaging and Internal Radiotherapy. J. Biomed. Biotechnol. 2010; 2010:1–17.

31. Santos I, Paulo A, Correia JDG. Rhenium and technetium complexes anchored by phosphines and scorpionates for radiopharmaceutical applications. Top. Curr. Chem. 2005; 252:45–84.

32. Potgieter KC. Complexes of the ReO3+ / Re(CO)3+ cores with multidentates N,O-donor chelates. MSc Dissertation. Nelson Mandela Metropolitan University, 2009.

33. World Nuclear Association. Radioisotopes in Medicine, October, 2012 <http://www.world-nuclear.org/info/inf55.html>.

34. Sophie J, Herrmann WA, Fritz KE. Rhenium and Technetium based Radiopharmaceuticals: Development and Recent advances. J. Orgnomet. Chem. 2014; 751:83–89.

35. Mukiza J, Gerber TIA, Hosten E. Dimeric Rhenium(IV) and Monomeric Rhenium (I) and V) Complexes of Orotic Acid. Polyhedron. 2015; 98:251–258.

36. Office of Science of the U.S. Department of Energy. The Tc-99m Generator. October 2012. <http://www.bnl.gov/bnlweb/history/tc-99m.asp>.

37. Amburanjan S, Rakesh K. Use of 99m-technetium-glucoheptonate as a tracer for brain tumor imaging. An overview of its strengths and pitfalls. Indian J. Nucl. Med. 2014, 30:1-8.

38. Ronald J, Chilton M, Ponto JA et al. Procedure Guideline for the Use of radiopharmaceuticals. J. Nucl. Med. Technol. 2007; 35:272–275.

39. Mukiza J. Rhenium (I) and (V) Complexes with Biologically Active NN- and NS-Donor Ligands. MSc Dissertation. Nelson Mandela Metropolitan University, 2013.

40. Vites JC, Lynam MM. Rhenium 1992. Coord. Chem. Rev.1995; 142:1-20.

41. Sousa SCA, Fernandes CA. Highly efficient and chemoselective reduction of sulfoxides using the system silane/oxo-rhenium complexes. Tetrahedron Lett.2009; 50:6872–6876.

42. Abrams MJ, Larsen SK, Zubieta J. Investigations of the technetium-hydrazido core. The synthesis and structural characterization of [TBA][Tc2(NNPh2)2(C6Cl4O2)4]•CH2Cl2•2C2H5 OH, a Tc(V)/Tc(VI) complex with the hydrazido ligands adopting the unused η1 bridging modes. Inorg. Chem. 1991; 30: 2031−2035.

43. Brenner W, Kampen W, Forstner CV et al. Skeletal Uptake and Soft Tissue Retention of 186Re-HEDP and 153Sm-EDTMP in Patients with Metastatic Bones Diseases. J. Nucl. Med. 2001; 42:1545−1550.

44. Hsieh BT, Hsieh JF, Tsai SC et al. Rhenium-188-Labeled DTPA: a new radiopharmaceutical for intravascular radiation therapy. Nucl. Med. Biol. 1999; 26:967−972.

45. Varshney R, Hazari PP, Uppal JK et al. Solid phase synthesis, radiolabeling and biological evaluation of a 99mTc-labeled αVβ3 tripeptide (RGD) conjugated to DOTA as a tumor imaging agent. Cancer Biol. Ther. 2011; 11:893−901.

46. Volkert WA, Hoffman TJ. Therapeutic Radiopharmaceuticals. Chem. Rev. 1999; 99: 2269−2292.

47. a) Chen J, Cheng Z, Hoffman TG et al. Melanoma-targeting properties of (99m)technetium- labeled cyclic alpha-melanocyte-stimulating hormone peptide analogues. Cancer Res. 2000; 60:5649−5658,

b) Puja P, Normando I-E et al. Radiolabeling and biological evaluation of DOTA-Ph-Al derivative conjugated to anti-EGFR antibody ior egf/r3 for targeted tumor imaging and therapy. Cancer Biol.Ther. 2005; 4:854-860.
48. Kothari K, Pillai MRA, Unni PR et al. Preparation of [186Re]Re-DMSA and its bio-distribution studies. Appl. Rad. Isotop. 1999; 51: 43−49.

49. Blower JP, Singh J, Bisundan MM et al. The chemical identity of pentavalent technetium-99m-dimercaptosuccinic acid (DMSA). J. Nucl. Med. 1990; 31:768−770.

50. Mayer P, Yumata NC, Gerber TIA et al. Coordination of the Bidentate Ligands 2,2′-Dypyridylamine,1-phenyl-1,3-butadione and N′-(Propan-2-ylidene)benzohydrazide to Rhenium(III). S. Afr. J. Chem. 2010; 63:180−185.

51. Dilworth JR, Parrot SJ. The biomedical chemistry of technetium and rhenium. Chem. Soc. Rev. 1998; 27:43−55.

52. Helberg LE, Orth SD. Coordination Chemistry of Low-Valent Rhenium Polypyridyl Complexes: Synthesis, Reactivity, and Electrochemistry. Inorg. Chem. 1996; 35:5584−5594.