CRITICAL REVIEW

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The role of coordination chemistry in the development of target-specific radiopharmaceuticals

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Received 5th April 2004
First published as an Advance Article on the web 16th August 2004

There is a great current interest in developing target-specific radiopharmaceuticals for early detection of diseases and radiotherapy of cancers. This *critical review* will focus on the role of coordination chemistry in the development of target-specific radiopharmaceuticals. It will also discuss the recent development in technetium, copper, gallium, indium, yttrium and lanthanide chemistry, as well as analytical tools for quality control and characterization of radiolabeled small biomolecules (159 references).

Introduction

Radiopharmaceuticals

Radiopharmaceuticals are drugs containing a radionuclide, and are used routinely in nuclear medicine for the diagnosis or therapy of various diseases. Almost all radiopharmaceuticals are administered *via* intravenous injection. They are mostly small organic or inorganic compounds with definite composition. They can also be macromolecules such as monoclonal antibodies and antibody fragments that are not stoichiometrically labeled with a radionuclide. Depending on their medical applications, radiopharmaceuticals can be divided into two primary classes: diagnostics and therapeutics. They can also be classified according to their biodistribution characteristics: those whose biodistribution is determined exclusively by their chemical and physical properties; and those whose ultimate distribution is determined by their receptor binding or other biological interactions. The latter class is often called target-specific radiopharmaceuticals.

Diagnostic radiopharmaceuticals are molecules labeled with gamma-emitting isotopes for single photon emission computed tomography (SPECT) or positron-emitting isotopes for positron emission tomography (PET). In general, diagnostic radiopharmaceuticals are used at very low concentrations, in the range of 10^{-6} to 10^{-8} M, and are not intended to have any pharmacological effect. The aim of the diagnostic application is the detailed description of the morphologic structure of organs or tissues and above all the testing of their physiological function through accumulation of the radiotracer. Diagnostic radiopharmaceuticals are predominantly metal complexes with an organic chelator for metal-essential agents or a chelator–biomolecule conjugate for target-specific radiopharmaceuticals. Diagnostic radiopharmaceuticals provide a non-invasive method of assessing the disease or disease states and monitoring the effect of treatment.

Therapeutic radiopharmaceuticals are molecules designed to deliver therapeutic doses of ionizing radiation to specific diseased sites. Radiotherapy has been around for over four decades starting with the use of radioiodine for the treatment of thyroid disorders. The main obstacles to radiotherapy assuming a wider role in clinical practice are the availability of therapeutic isotopes and techniques for their specific localization in diseased tissues, such as tumors. Therapeutic doses of radiation can be delivered to sites of disease in three ways: external beam irradiation, implantable "seeds" or systemic administration. Brachytherapy involves the use of "seeds", which are physically placed at the tumor site and will remain there unless they are surgically removed. Brachytherapy plays a vital role in the care of prostate cancer patients. It is only useful for the treatment of accessible tumor mass. The systemic administration of radiopharmaceuticals that are designed for specific localization at tumor sites provides opportunities for treatment of the disseminated metastatic tumors. Ideally, therapeutic radiopharmaceuticals should localize at the diseased site in sufficient concentration to deliver a cytotoxic radiation dose to the tumor cells, and clear rapidly from the blood and other normal organs to minimize radiation damage to normal tissues.

Metal complexes as radiopharmaceuticals

Throughout history, metals and metal compounds have been used for treatment of various diseases, such as arthritis and

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DOI: 10.1039/b309961j

Table 1 Selected small complex radiopharmaceuticals for diagnosis or treatment of diseases

Radiopharmaceutical	Trade name	Primary uses
Indium-111 pentetate	Indium-111 DTPA®	Imaging of CSF kinetics
Indium-111 oxyquinoline	Indium-111 oxine®	Labeling leukocytes and platelets
Samarium-153 EDTMP	Quadramet®	Palliative treatment of bone pain
Tc-99m Bicisate (ECD)	Neurolite®	Cerebral perfusion imaging
Tc-99m Disofenin (DISIDA)	Hepatolite®	Hepatobiliary imaging
Tc-99m Exametazine (HMPAO)	Ceretec®	Cerebral perfusion imaging
Tc-99m Gluceptate	Glucoscan®	Renal imaging
Tc-99m Lidofenin (HIDA)	Technescan® HIDA	Hepatobiliary imaging
Tc-99m Mertiatide	Technescan® MAG3	Renal imaging
Tc-99m Oxidronate (HDP)	Osteoscan® HDP	Bone imaging
Tc-99m Pentetate (DTPA)	Techneplex®, Technescan®	Renal imaging and function studies
Tc-99m Sestamibi	Cardiolite®	Myocardial perfusion imaging
	Miraluma®	Breast tumor imaging
Tc-99m Succimer (DMSA)	DMSA	Renal imaging
Tc-99m Teboroxime	Cardiotec®	Myocardial perfusion imaging
Tc-99m Tetrofosmin	Myoview®	Myocardial perfusion imaging

cancer. However, the use of radiometal complexes as radiopharmaceuticals for medical imaging and radiotherapy is a relatively new area. Metallic radionuclides are of particular interest for the development of radiopharmaceuticals due to their wider range of nuclear properties (type of radiation, gamma ray or beta particle energy, and half-life), and their rich coordination chemistry. Table 1 lists selected examples of commercial radiopharmaceuticals based on small radiometal complexes, along with their medical applications. ^{99m}Tc radiopharmaceuticals are most widely used for diagnostic nuclear medicine.

In 1959, Brookheaven National Laboratory developed the first ^{99}Mo/^{99m}Tc generator, which marks a significant milestone for subsequent development of small ^{99m}Tc complex radiopharmaceuticals.[1] The first application of ^{99m}Tc for medical imaging involved the use of $^{99m}TcO_4^-$ for diagnosis of thyroid disease on the assumption that the $^{99m}TcO4^-$ would behave similarly to iodide, known to be taken up by thyroid. Since then, many ^{99m}Tc complexes have been synthesized and studied as imaging agents. This led to the successful development of a number of first-generation ^{99m}Tc complex radiopharmaceuticals,[1,2] which are often called ''technetium essential agents'' (Fig. 1). During this period of time, the coordination chemistry of technetium played a significant role. The successful development of ^{99m}Tc imaging agents was totally dependent on the design of technetium complexes since the biodistribution and targeting capability depend exclusively on their lipophilicity, size and charge.

Target-specific radiopharmaceuticals

For the last decade, the direction of research in this area has been shifted towards developing target-specific radiopharmaceuticals based on receptor binding of a radiolabeled receptor ligand in the diseased tissue. A receptor ligand is often termed as ''targeting biomolecule'' (BM), which serves as the ''vehicle'' to carry the radionuclide to the diseased tissue, which is known to contain a substantial concentration of the target receptor. Accumulation of the radiotracer at diseased tissues relies on the localization of the radiolabeled receptor ligand that binds to receptors with high affinity and specificity. The high specificity of receptor binding results in selective uptake and distribution of the radiolabeled receptor ligand at diseased tissues. It is this high receptor binding affinity and specificity that makes receptor imaging (often called ''molecular imaging'') advantageous over traditional scintigraphic imaging using simple Tc complex radiopharmaceuticals or other imaging modalities such as X-ray computed tomography (CT), ultrasound (US), and nuclear magnetic resonance imaging (MRI).

Many biomolecules, including monoclonal antibodies, antibody fragments and small peptides, have been studied for as ''carriers'' for radionuclides. Due to these intensive efforts, several radiolabeled monoclonal antibodies and peptides (Fig. 2) have been approved by FDA (Food and Drug Administration) for diagnosis or treatment of various diseases. Table 2 lists selected commercial target-specific radiopharmaceuticals and their medical applications. The approval of the

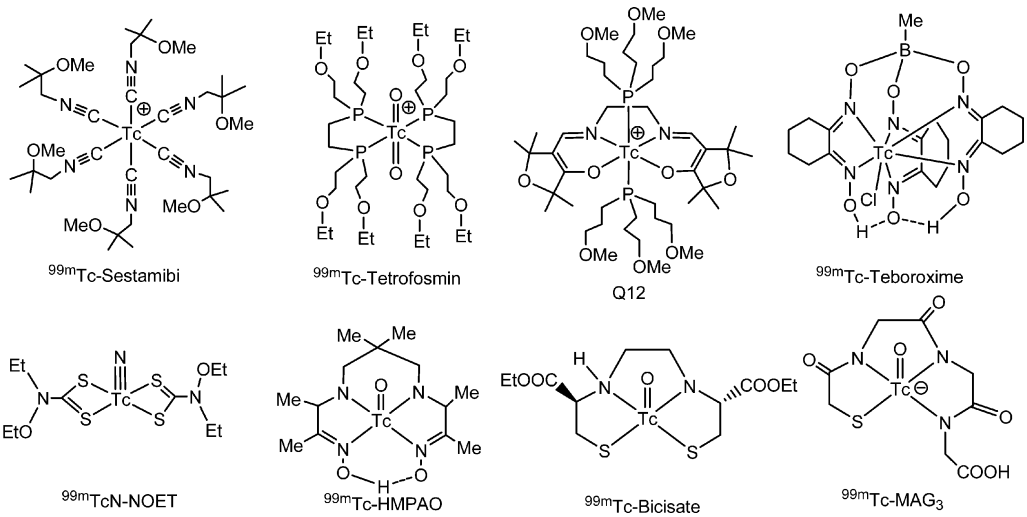


Fig. 1 Structures of selected radiopharmaceuticals based on small metal complexes. It is important to note that the name of each radiopharmaceutical is different from that of the commercial kit.

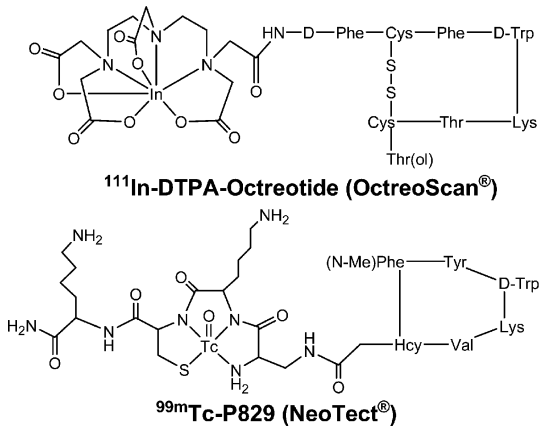


Fig. 2 Structures of selected target-specific radiopharmaceuticals. The name in brackets indicates the commercial kit preparation of the corresponding radiopharmaceutical.

^{90}Y-labeled anti-CD20 monoclonal antibody (Zevalin®, IDEC Pharmaceuticals Corp.) for treatment of non-Hodgkin's lymphoma represents the most significant milestone in the use of radiolabeled MoAbs for radioimmunotherapy (RAIT) of cancers.[6–9]

Coordination chemistry and nuclear medicine

Radiopharmaceuticals are the blood stream of nuclear medicine. In the 1980s, radiopharmaceutical research was focused mainly on development of perfusion radiotracers, the biodistribution of which reflects the regional blood flow to the areas of major organs such as the heart and brain. For example, ^{99m}Tc complex cations, such as ^{99m}Tc-sestamibi $[^{99m}Tc(MIBI)_6]^+$ (MIBI = 2-methoxy-2-methylpropylisonitrile) and ^{99m}Tc-Tetrofosmin $[^{99m}TcO_2(Tetrofosmin)_2]^+$ (Tetrofosmin = 1,2-bis[bis(2-ethoxyethyl)phosphino]ethane), are still widely used as myocardial perfusion imaging agents while neutral ^{99m}Tc complexes, such as ^{99m}Tc-Bicisate $[^{99m}TcO(ECD)]$ (ECD = L,L-ethylenedicysteine diethyl ester), are available for measuring cerebral blood flow. As we march into the new century, discovery research in the radiopharmaceutical industry has been more focused on the use of radiolabeled receptor ligands as target-specific radiopharmaceuticals for diagnosis or therapy of various diseases. Inorganic chemists and radiochemists are often facing some critical questions. What is the role of coordination chemistry in developing target-specific radiopharmaceuticals? Do we still lack the fundamentals of coordination chemistry of radiometals? How can we contribute to the radiopharmaceutical development process?

Several excellent reviews have appeared recently covering a broad range of topics related to metal complexes as diagnostic tools,[3] bifunctional chelators (BFCs) for radiolabeling of small biomolecules,[4,5] including monoclonal antibodies[6–11] and small peptides[12–29] as diagnostic and therapeutic radiopharmaceuticals. This review will focus on the role of coordination chemistry in the development of target-specific radiopharmaceuticals. It will also discuss the most recent development in technetium, copper, gallium, indium, yttrium and lanthanide chemistry, as well as analytical tools for quality control and characterization of radiolabeled small biomolecules. While it is impossible to cover all aspects related to the application of coordination chemistry in the development of target-specific radiopharmaceuticals, the author would apologize to those whose work has not been presented in detail in this critical review.

Coordination chemistry and radiopharmaceutical design

Although the focus of radiopharmaceutical research has shifted towards biological characterization of radiolabeled receptor ligands in the last several years, coordination chemistry still plays a significant role in the design and development of new target-specific radiopharmaceuticals. Fig. 3 shows three general strategies of radiopharmaceutical design. In all three cases, inorganic chemistry is the "centerpiece" of the radiopharmaceutical design. The radiometal is the radiation source for imaging or therapy. It is the radiometal that distinguishes radiopharmaceuticals from traditional therapeutic pharmaceuticals.

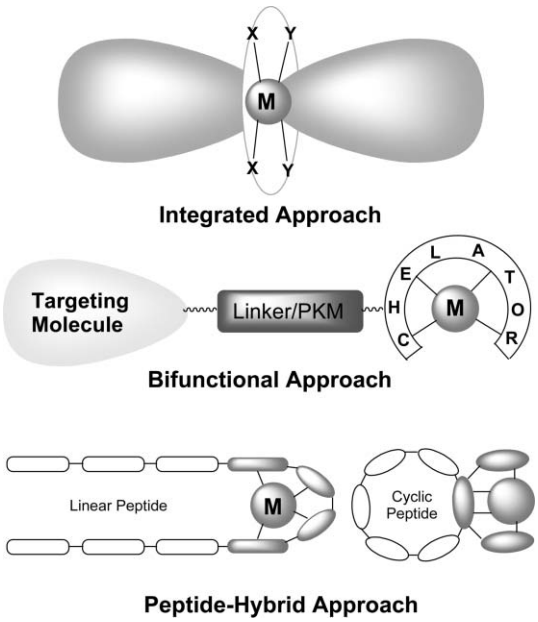


Fig. 3 Schematic representation of three approaches in radiopharmaceutical design.

Integrated approach

The integrated approach involves replacement of part of a known high affinity receptor ligand with an "unnatural" metal chelate in such a way that there are minimal changes in size,

Table 2 Selected target-specific diagnostic and therapeutic radiopharmaceuticals

Radiopharmaceutical	Trade name	Primary uses
Indium-111 capromab pendetide	ProstaScint®	Imaging of prostate cancer
Indium-111 pentetreotide	Octreoscan®	Imaging of neuroendocrine tumors
Indium-111 satumomab pendetide	OncoScint®	Imaging of metastatic disease associated with colorectal and ovarian cancer
Tc-99m Apcitide	AcuTect®	Synthetic peptide for imaging DVT (deep vein thrombosis)
Tc-99m Arcitumomab	CEA-Scan®	Monoclonal antibody for colorectal cancer
Tc-99m Depreotide	Neotect®	Somatostatin receptor-bearing pulmonary masses
Y-90 Ibitumomab tiuxetan	Zevalin®	Treatment of non-Hodgkin's lymphoma
I-131 Tositumomab	Bexxar®	Treatment of non-Hodgkin's lymphoma

conformation, and receptor binding affinity. The radiometal chelate is a vital part of the receptor binding motif. In this approach, individual parts are not active in receptor binding. Through metal chelation, all parts are arranged in such a way that the whole metal complex becomes a high affinity receptor ligand. Unfortunately, this approach often results in more synthetically challenging target molecules with relatively low receptor binding affinity.[30] Apparently, replacement of the C–C or C–heteroatom bonds with M–N or M–O or M–S bonds has significant impact on the size and conformation of the receptor ligand, which are critical for the receptor binding. Introduction of the metal core can also change the lipophilicity of the receptor ligand.

Bifunctional approach

The bifunctional approach uses a high affinity receptor ligand as the targeting biomolecule, a BFC for conjugation of the receptor ligand and chelation of the radiometal (*e.g.* ^{67}Cu, ^{90}Y, ^{99m}Tc, ^{111}In, ^{177}Lu, ^{186}Re, and ^{188}Re), and a linker for pharmacokinetic modification. Biomolecules can be monoclonal antibodies, small peptides, peptidomimetics, or non-peptide receptor ligands. The choice of BFC is largely determined by the nature and oxidation state of the radiometal. The radiometal chelate is often kept away from the receptor-binding motif to minimize possible interference with receptor binding by the radiometal chelate. This is the more popular approach for development of target-specific radiopharmaceuticals, in part, due to the likelihood of retaining the receptor binding affinity with a careful selection of the BFC for radiolabeling. This approach has been used for the development of a number of target-specific radiopharmaceuticals, either commercially available (Fig. 2) or under clinical trials. The main advantage of this approach is that the receptor binding affinity could be retained by a careful design and attachment of the radiometal chelate.

Hybrid approach

In the hybrid approach, the radiometal (^{99m}Tc or ^{188}Re) is chelated by a tripeptide sequence (such as Gly-Gly-Gly, Cys-Gly-Gly, or Cys-Gly-Cys) containing an N_4, N_3S, or N_2S_2 donor set. In this approach, the tripeptide sequence can be part of either a long linear polypeptide or a cyclic peptide backbone. The radiometal can also be incorporated as part of a macrocyclic peptide framework. The unchelated linear peptide has a relatively low binding affinity for the intended receptor, and the chelation of radiometal results in a constrained macrocyclic metallopeptide with increased receptor binding affinity. A major advantage of this approach is that the bonding of radiometal increases the receptor binding affinity of the polypeptide. This approach has been successfully used to prepare ^{99m}Tc- and ^{188}Re-labeled α-melanocyte-stimulating hormone peptide analogues.[31–33] However, the potential of this approach for commercial product development remains to be seen.

Coordination chemistry and pharmacokinetics

Pharmacokinetics

Pharmacokinetics is a term used conventionally to refer to the movement of a drug in the body, including absorption, distribution, metabolism, and elimination. When it is used in the context of radiopharmaceuticals, it often refers to the distribution and elimination of the radionuclide following administration of the radiopharmaceutical. At this moment, one may ask how the coordination chemistry contributes to pharmacokinetics of the target-specific radiopharmaceuticals.

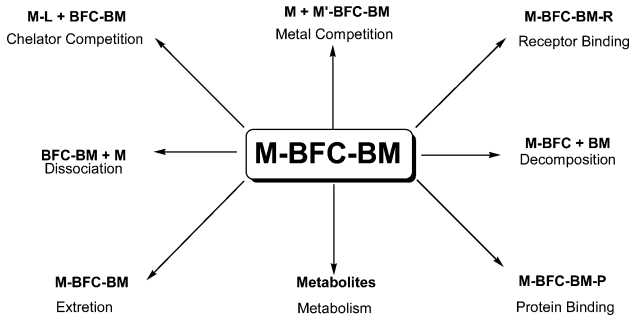


Fig. 4 Distribution and elimination of a radiopharmaceutical following administration (M–BFC–BM: M = radionuclide; M′ = metal ion in the blood stream; BFC = bifunctional chelator; BM = biomolecule; L = competing chelator).

Biological interactions

Fig. 4 shows possible biological interactions of a radiopharmaceutical in the blood circulation. Biological interactions include receptor binding, protein binding, and chemical reactions between the radiopharmaceutical and metal ions or "native" chelators. While receptor binding is necessary, protein bonding is often detrimental, and will have dramatic impact on the blood retention time of the radiopharmaceutical and target-to-background ratios. The *in vivo* chemical reactions are the main source of radiation toxicity, particularly for a ^{90}Y and lanthanide therapeutic radiopharmaceutical. For example, the reaction between the ^{90}Y chelate with other biologically important metal ions, such as Ca^{2+} and Fe^{3+}, will produce free ^{90}Y, which will localize in the bone and cause bone marrow toxicity. The competition between the BFC and native chelators, such as amino acids and transferrin, may also result in early release of ^{90}Y from the ^{90}Y-labeled BFC–BM conjugate.

Pharmacokinetic considerations

The main pharmacokinetic consideration for a diagnostic radiopharmaceutical is that the radiolabeled biomolecule is able to have highest target-to-background ratio in a short period of time. To achieve this goal, the radiolabeled biomolecule should have a short blood residence time. The fast blood clearance is necessary to minimize non-target radioactivity. The blood retention time should also be long enough to allow the radiolabeled biomolecule to reach the receptor sites and achieve adequate accumulation at the targeted tissue. The time to reach the target should also be short; otherwise, it will take a long time to get diagnostically useful images. One of many challenges associated with radiolabeled antibodies for imaging is their slow kinetics to reach the targeted tissue and to clear from blood circulation. The receptor binding rate of the radiolabeled biomolecule should be fast. In this way, the radioactivity accumulation at the targeted tissue can be maximized. Finally, the new radiopharmaceutical should have a rapid renal clearance to avoid accumulation of activity in the gastrointestinal tract, which may obscure visualization of abdominal targets. For therapeutic radiopharmaceuticals, this is particularly important because excretion *via* the hepatobiliary system often leads to accumulation of activity in the gastrointestinal tract, which creates a tremendous radiation burden on normal organs such as the liver.

Modification of pharmacokinetics

There are several ways to modify pharmacokinetics of radiopharmaceuticals. These include chemical modification of the biomolecule, chemical modification of the metal chelate, the use of a PKM linker, and the choice of coligands for radiometal chelation (Fig. 5). Chemical modification of the biomolecule

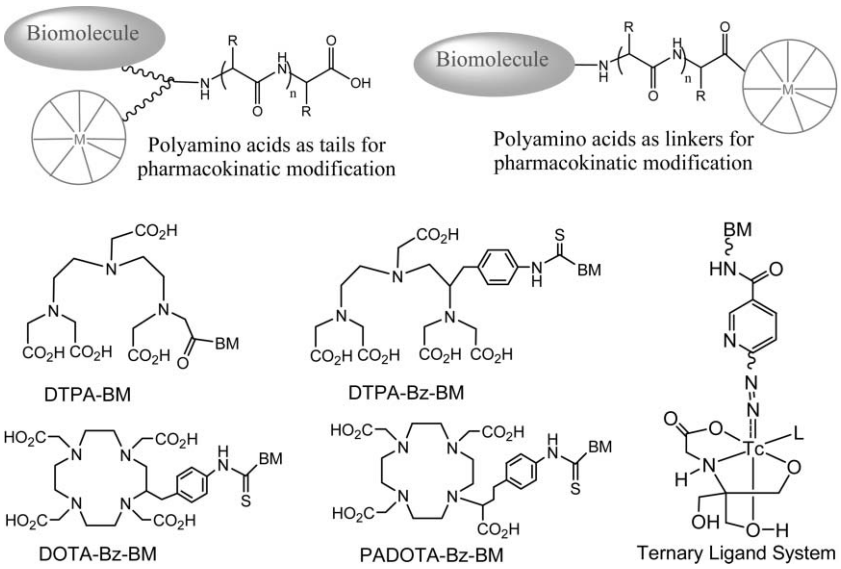


Fig. 5 Modification of pharmacokinetics by using polyamino acid linkers or by the choice of chelating systems. Chemical modification of the metal chelate can be achieved either using BFCs with different charge and hydrophilicity or the choice of coligands.

can be achieved by introducing various hydrophilic groups, such as poly aspartic acid. Chemical modification of the metal chelate can be achieved using BFCs with different charge and hydrophilicity. For metal chelates containing two or more ligands, the choice of coligands may also be used for modification and improvement of pharmacokinetics of the radiopharmaceutical.

Radiometals for diagnostic and therapeutic radiopharmaceuticals

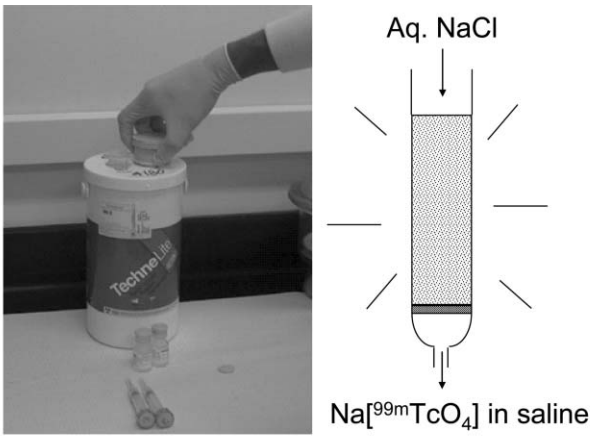
The use of radiometals offers many opportunities for designing new radiopharmaceuticals by modifying the coordination environment with various chelators. The coordination chemistry of the radiometal will determine the geometry and solution stability of the radiometal chelate. Different radiometals have different coordination chemistries, and require BFCs with different donor atoms and chelator frameworks. Since the radiometal chelate can have a significant impact on biological properties, the biodistribution of a target-specific radiopharmaceutical can be systematically changed by either modifying the coordination environment around the radiometal with a variety of chelators or by the use of various coligands, if it is needed.

Radiometals for SPECT

The radiometal for a diagnostic radiopharmaceutical is often a gamma-emitting isotope for SPECT or PET. The choice of the radiometal depends largely on physical and nuclear properties, availability, and cost. In general, generator-produced radiometals are considered ideal, since the generator system consists of a long-lived parent isotope that decays to a short-lived daughter isotope, and a daughter radionuclide that can be easily separated from the parent by either ion-exchange chromatography or solvent extraction. Among various radiometals, ^{99m}Tc remains the most widely used for diagnostic nuclear medicine mainly due to its optimal nuclear properties, easy availability, and low cost. ^{111}In is also useful for scintigraphic imaging. ^{111}In-labeled BFC–BM conjugates are often used as imaging surrogates for dosimetry determination of their corresponding therapeutic ^{90}Y–BFC–BM analogs since ^{90}Y is a pure beta emitter.

^{99m}Tc is produced from a parent radionuclide, ^{99}Mo (Fig. 6), a fission product with a half-life of 2.78 days. In a ^{99}Mo–^{99m}Tc generator, $^{99}MoO_4^{2-}$ is absorbed to an alumina column and ^{99m}Tc is formed by decay of ^{99}Mo. $^{99m}TcO_4^-$ is eluted from the column with saline. The ^{99m}Tc produced by the generator is never carrier-free because thirteen percent of ^{99}Mo decays directly to the long-lived isotope ^{99}Tc ($t_{1/2} = 2.13 \times 10^5$ y). The specific activity of eluted ^{99m}Tc is dependent upon the prior-elution time. In general, the total concentration of technetium (^{99m}Tc and ^{99m}Tc) in the ^{99}Mo–^{99m}Tc generator eluant is in the range of 10^{-7} to 10^{-6} M.

^{111}In is a cyclotron-produced radionuclide, generally by the ^{111}Cd(p, n)–^{111}In nuclear reaction, and has a half-life of 67.9 h



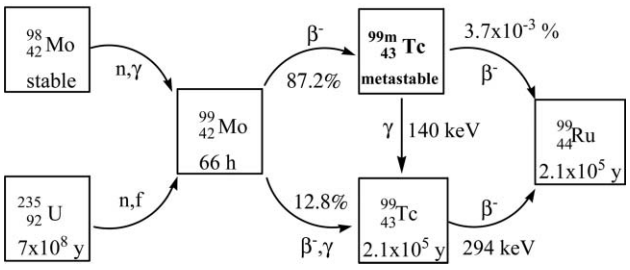


Fig. 6 The ^{99}Mo–^{99m}Tc generator for production ^{99m}Tc. The ^{99}Mo produced by neutron capture is of little medical value due to low specific activity. All ^{99}Mo–^{99m}Tc generators are made using the ^{99}Mo produced by fission reaction, and must be stored inside a lead shield to minimize the radiation dose to workers.

(2.83 days). The ^{111}In is separated from the cadmium using solvent extraction, ion exchange, or both, even though co-precipitation with ferric hydroxide has also been used. ^{111}In decays by electron capture with emission of gamma photon of 173 and 247 keV (89% and 95% abundance, respectively) and is widely used in gamma scintigraphy.

Radiometals for PET

There are several radiometals useful for PET imaging. In general, it is highly desirable the isotope does not have radiation decays other than 511 keV positron emission. This will minimize the impairment of the spatial resolution due to high β^+ energy and reduce the radiation burden to the patient. A generator-based isotope is needed to achieve the high specific activity for receptor-based radiopharmaceuticals. It is also much easier for transportation, delivery, and quality control using a generator produced isotope. The half-life of the parent isotope should be long while the half-life of the corresponding daughter isotope should be short. Radiolabeling should be easy to complete, preferably over 10–30 min. In addition, the cost for the production of the parent isotope and availability of the enriched source (for the production of the parent isotope) should also be considered.

^{62}Zn–^{62}Cu generator

Zinc-62 has a half-life of 9.3 h, and the daughter isotope ^{62}Cu has a half-life of 9.7 min. ^{62}Cu decays by positron emission 511 keV (190% abundance). The short half-life of ^{62}Cu allows repeated doses without imposing a significant radiation burden on the patient. The generator is made up of a Dowex ion exchange column. Carrier-free ^{62}Cu is eluted from the column with 2 N HCl. The ^{62}Zn–^{62}Cu generator only lasts for 1–2 days due to the short half-life of ^{62}Zn. This makes PET imaging with ^{62}Cu very expensive. However, the cost of the ^{62}Zn–^{62}Cu generator may be reduced significantly as their usage increases.[34]

^{68}Ge–^{68}Ga generator

Germanium-68 has a half-life of 271 days, and ^{68}Ga, with a half-life of 68 min, decays by positron emission and hence 511 keV annihilation radiation. The photon abundance is 178%. The generator is commercially available. The generator is made up of alumina loaded in a plastic or glass column. Carrier free ^{68}Ge in HCl is neutralized in EDTA solution and absorbed on the column. Then ^{68}Ga is eluted from the column with 0.05 M EDTA solution. Alternatively, ^{68}Ge is absorbed on a stannous dioxide column and ^{68}Ga is eluted with 1 N HCl. This generator can be eluted quite frequently because the maximum yield is obtained in a few hours. The ^{68}Ge–^{68}Ga generator is fairly expensive. Due to the long half-life of ^{68}Ge, the ^{68}Ge–^{68}Ga generator can be used for almost a year, allowing PET imaging at facilities without an on-site cyclotron. Additionally, the $t_{1/2}$ of ^{68}Ga is long enough to permit multiple-step syntheses of the appropriate radiotracer, and data acquisition over longer periods. Therefore, cameras with the highest sensitivity are not prerequisite for obtaining high quality images. With properly designed radiopharmaceuticals, ^{68}Ga could be as useful for PET as ^{99m}Tc for SPECT. However, there is a shortage of ^{68}Ge for the development of ^{68}Ga-based radiopharmaceuticals mainly due to the lack of efficient production methods of ^{68}Ge and its widespread application in transmission source for PET scanners. As a result, ^{68}Ga is often considered the most cost-prohibitive radionuclide for PET imaging.[34]

Copper-61 and copper-64

^{61}Cu has a relatively high β^+ emission rate (61%) with maximum β^+ energy of 1.2 MeV and a half-life of 3.4 h. It also has two gamma rays with $E_\gamma = 283$ (13%) and 656 keV (11%). Several nuclear reactions can be used for the production of ^{61}Cu. These include nuclear reactions [^{59}Co(α, 2n)^{61}Cu] (40 MeV), [^{nat}Ni(α, p)^{61}Cu] (21 MeV), and [^{61}Ni(p, n)^{61}Cu]. The latter methods are often free from ^{64}Cu radio-impurity. Although the physical properties are attractive for PET imaging, ^{61}Cu has not been used to the same extent as ^{64}Cu, which has a low β^+ emission rate (18%) with maximum β^+ energy of 0.66 MeV and a half-life of 12.7 h. The longer half-life of ^{64}Cu is much more feasible for the radiolabeling of small biomolecules. ^{64}Cu can be produced by proton irradiation of ^{nat}Ni or enriched ^{68}Zn. Both methods suffer from low yield and co-production of ^{61}Cu and ^{67}Cu radioimpurities.[34]

Technetium-94m

^{94m}Tc is a cyclotron-produced radionuclide. It has a half-life of 52 min and a β^+ energy of 2.47 MeV (72%). It can be obtained from a number of production methods, including ^{94}Mo(p, n)/^{94m}Tc (13.5–11 MeV), ^{nat}Nb(^{3}He, 2n)/^{94m}Tc (18–10 MeV), ^{92}Mo(α, pn)/^{94m}Tc (26–18 MeV). To obtain sufficient yield with small cyclotrons, the reaction ^{94}Mo(p, n)/^{94m}Tc is the production method of choice. Access to this isotope makes it possible to use PET to solve problems with estimating the uptake of ^{99m}Tc radiopharmaceuticals. The quantitative superiority of PET permits modeling of radiotracer kinetics and dosimetry measurements. The successful preparation of ^{94m}Tc in the pertechnetate form allows the use of the same commercially available kit for ^{99m}Tc radiopharmaceuticals (such as ^{99m}Tc-Sestamibi, ^{99m}Tc-Tetrofosmin, and ^{99m}Tc-P829) to prepare the corresponding ^{94m}Tc analogs. The use of dual isotopes ^{99m}Tc/^{94m}Tc (SPECT/PET) may provide much better imaging quality of diseased tissue. The integration of PET and SPECT radiotracers would pave the way for better exploitation of the current strengths of the two imaging modalities.

Radiometals for therapeutic radiopharmaceuticals

An inherent determinant in developing therapeutic radiopharmaceuticals is the selection of appropriate radionuclides,[5,35–39] and requires weighing a variety of factors. These include tumor uptake and tumor retention, blood clearance, rate of radiation delivery, half-life and specific activity of the radionuclide, and the feasibility of large-scale production of the radionuclide in an economical fashion. The key point for a receptor-based therapeutic radiopharmaceutical is to deliver a tumorcidal dose of radiation to the tumor cells while not causing unmanageable side-effects.

Among various radionuclides, ^{90}Y and lanthanide radiometals are of particular interest. There are several lanthanide isotopes to choose, including low energy β-emitter ^{177}Lu, medium energy β-emitters, ^{149}Pm and ^{153}Sm, and high-energy β-emitters, ^{166}Ho and ^{90}Y. Yttrium and lanthanide metals share similar coordination chemistry. Bifunctional chelators and their coordination chemistry with yttrium and lanthanide metals are well developed and understood. In addition, β-emitters have relatively long penetration range (2–12 mm in the tissue), which is particularly important for solid tumors with high heterogeneity. The β-particle emitters yield a more homogeneous dose distribution even when they are heterogeneously distributed within the target tissue.

Yttrium-90

For systemic cancer radiotherapy, ^{90}Y is of particular interest due to its high-energy pure β-particle emission. ^{90}Y is a generator-produced radionuclide, resulting from the decay of

^{90}Sr, and decays with the high energy β-particle to form ^{90}Zr. ^{90}Y has a half-life of 2.7 days, which is short enough to achieve a critical dose rate and at the same time is long enough to allow the radiopharmaceutical to be manufactured and delivered for clinic use. The specific activity for ^{90}Y is high, and is well suited for receptor-based therapeutic radiopharmaceuticals. For quantitative imaging, the ^{111}In-labeled BFC–BM conjugate is often used as a surrogate to determine the biodistribution and dosimetry of the ^{90}Y-labeled BFC–BM conjugate.

Samarium-153

^{153}Sm has three β-emissions (30% 0.64 MeV, 50% 0.71 MeV, and 20% 0.81 MeV) and a γ-emission (28% 103 keV) with a half-life of 1.95 days. It can be produced in large amounts with high specific activity by neutron activation of enriched ^{152}Sm. The short half-life of ^{153}Sm allows for the delivery of fractionated dose regimes while the 103 keV gamma ray is useful for the determination of biodistribution of the therapeutic radiopharmaceutical *via* gamma camera.

Holmium-166

^{166}Ho is an excellent radionuclide for radiotherapy since ^{166}Ho emits a beta particle with maximum energy of 1.85 MeV (maximum penetration range ~9 mm) and a small portion of gamma rays (80.6 keV at 6.6% and 1.38 MeV at 0.9%), which are useful for the determination of biodistribution of the therapeutic radiopharmaceutical *via* gamma camera. It has a half-life of 26.78 h. ^{16}Ho is produced with relatively high specific activity by neutron capture reaction [^{165}Ho(n, γ)^{166}Ho].

Lutetium-177

^{177}Lu is a reactor-produced radionuclide. It has three β-emissions (12% 0.176 MeV, 9% 0.384 MeV, and 79% 0.497 MeV) and two γ-emissions (6.4% 113 keV and 11% 208 keV) with a half-life of 6.75 days. One method for the production of ^{177}Lu involves irradiation of enriched ^{176}Lu in a reactor. By this method, ^{177}Lu can be prepared in high yield and medium high specific activity at low cost. The specific activity of ^{177}Lu from University of Missouri Research Reactor is routinely more than 20 Ci mg^{-1}.

Rhenium-186/188

Rhenium has two isotopes (^{186}Re and ^{188}Re). ^{186}Re has a half-life of 3.68 days with a β-emission (E_{max} = 1.07 MeV, 91% abundance) and a gamma-photon (E = 137 keV, 9% abundance) which should allow imaging during therapy. ^{186}Re is a reactor-produced radionuclide. There is only one possibility to produce ^{186}Re by the irradiation of ^{185}Re with neutrons (^{185}Re(n, γ)^{186}Re). The yield of ^{186}Re depends on the amount of Re in the target, the energy of the neutrons available, and the neutron reflux. The specific activity is from low to medium, but a carrier-free product is not possible. ^{188}Re has a half-life of 16.98 h with a high-energy β-emission (E_{max} = 2.12 MeV, 85% abundance) and 155 keV gamma photons (15% abundance). ^{188}Re can be prepared either from the nuclear reaction (^{187}Re(n, γ)^{188}Re) or from the ^{188}W–^{186}Re generator. The generator-produced ^{188}Re is carrier-free and has very high specific activity. The major advantage of using ^{188}Re in therapeutic nuclear medicine is the inexpensive and readily available ^{188}W–^{186}Re generator, which has a very long useful shelf-life.

Coordination chemistry of technetium and ^{99m}Tc radiopharmaceuticals

Nearly 80% of all radiopharmaceuticals used in diagnostic nuclear medicine are ^{99m}Tc-labeled compounds. The 6 h half-life is long enough to allow a radiopharmacist to prepare the radiopharmaceutical dose and for nuclear medicine practitioners to collect useful images. At the same time, it is short enough to permit administration of millicurie amounts of ^{99m}Tc without causing a significant radiation dose to the patient. The monochromatic 140 keV photons are readily collimated to give images of high spatial resolution. Furthermore, ^{99m}Tc is readily available from the ^{99}Mo–^{99m}Tc generators at low cost.

^{99m}Tc-based radiopharmaceuticals are used in very low concentrations (10^{-8} to 10^{-6} M). Therefore, the radiolabeling kinetics must be taken into consideration in the development of ^{99m}Tc radiopharmaceuticals. ^{99m}Tc is obtained from the ^{99}Mo–^{99m}Tc generator as $^{99m}TcO_4^-$ in saline. This requires that all the radiolabeling reactions be performed in an aqueous solution. Due to its short half-life (~6 h), the radiochemical synthesis has to be completed within 30 min. The yield of the radiopharmaceutical must be greater than 90% since the injection of a mixture of different ^{99m}Tc-containing species will decrease organ specificity, and needlessly increases the radiation dose to patients. Since almost all ^{99m}Tc radiopharmaceuticals are administered by intravenous injection, the radiochemical synthesis has to be conducted under sterile, pyrogen free conditions. This requirement virtually eliminates any sort of chromatographic purification of the desired ^{99m}Tc radiopharmaceutical. Each of these constraints provides a unique challenge for inorganic chemistry. Fortunately, most of these challenges have been successfully met with the development of coordination chemistry of technetium and new ^{99m}Tc-labeling techniques.

Diverse redox chemistry

One of the characteristics of technetium is its rich and diverse redox chemistry. Since there is no effective chemistry that can be used to attach the $^{99m}TcO_4^-$ anion to biomolecules, the Tc(VII) in $^{99m}TcO_4^-$ has to be reduced to a lower oxidation state. When $^{99m}TcO_4^-$ is reduced, the oxidation state of Tc depends upon the reducing agent, chelator, and reaction conditions. The rich and diverse redox chemistry makes it difficult to control the oxidation state and stability of Tc complexes. At the same time, it also provides opportunities to modify structures and properties of Tc complexes by the choice of chelators, through the use of donor atoms, as well as the introduction of non-donating functional groups. Technetium chemistry and ^{99m}Tc-labeling of biomolecules have been reviewed recently.[4,13]

Isomerism

Another aspect of technetium chemistry is isomerism, including geometric isomers, epimers, enantiomers, and diastereomers.[40] Fig. 7 shows selected examples of isomerism in technetium chelates. Epimers are often found in square pyramidal or octahedral oxotechnetium complexes containing chelating ligands with substituents on the ligand backbone or a tertiary amine-N donor atom. Formation of epimers is due to the relative orientation (*anti* and *syn*) of substituents to the $[Tc{=}O]^{3+}$ core. Enantiomers are often found in Tc(V)–oxo complexes, such as $[TcO(MAG_3)]^-$, due to asymmetrical bonding of chelator to the $[Tc{=}O]^{3+}$ core even though the free chelator does not have a chiral center. Enantiomers are also formed when the Tc chelate contains a pro-chiral chelator, such as tricine in ternary ligand Tc complexes (Fig. 7). Enantiomers are indistinguishable by NMR; but they are

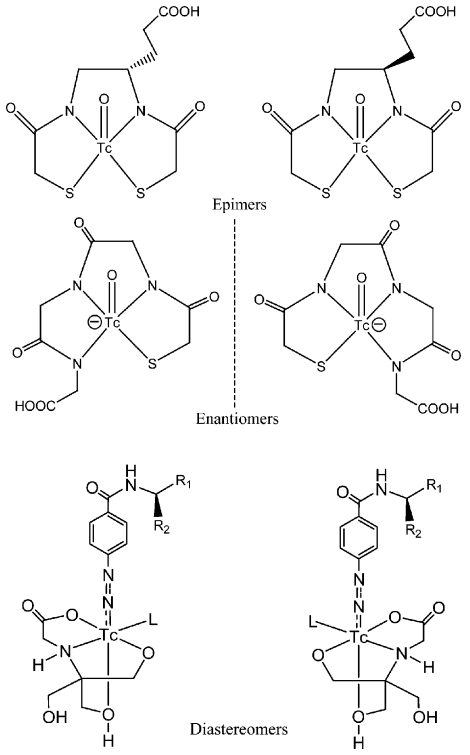


Fig. 7 Examples of isomerism in technetium complexes.

separable under chiral chromatographic conditions (chiral solid phase or chiral mobile phase) by HPLC. If a Tc complex contains two or more chiral centers, diastereomers may be formed, and are often separated by reversed phase HPLC methods. Isomers often have different lipophilicity and biodistribution patterns. This is particularly true for small Tc complex radiopharmaceuticals as their biological properties are determined exclusively by the physical and chemical characteristics of the Tc complex.[4,13,40] For example, the complex $[TcO(map)]^-$ (map = 2,3-bis(mercaptoacetamido)-propanoate), has two epimers (*anti* and *syn*) due to the disposition of the COOH group on the chelate ring relative to the Tc=O moiety. It was reported that in humans 58% of *syn* isomer was excreted at 30 min as compared to only 19% of *anti* isomer.[41,42] For receptor-based radiopharmaceuticals, the target uptake is largely dependent on the receptor binding affinity of the radiolabeled receptor ligand, receptor population and the blood clearance, which is determined by the physical properties of both the targeting biomolecule and the Tc chelate. Therefore, the formation of isomers for the Tc chelate may have significant impact on the biological properties of a radiopharmaceutical. The choice of BFC should be those which form technetium complexes with minimal isomerism.

Technetium cores and bifunctional chelators

Fig. 8 shows selected Tc cores, which have been used for ^{99m}Tc-labeling of biomolecules, including antibodies, small peptides, peptidomimetics, and non-peptide receptor ligands. Since Tc chemistry and Tc cores have been reviewed in detail recently,[4,13] we will focus on the most recent development of Tc cores and related coordination chemistry. Since the classical nitrogen/sulfur/phosphorus-based chelating systems and their related coordination chemistry with the $[Tc=O]^{3+}$ core have been optimized in the last two decades, it is unlikely that significant improvements in the ^{99m}Tc-labeling of biomolecules can be expected with these chelating systems.[43] Further advances are more likely achieved in bifunctional chelating

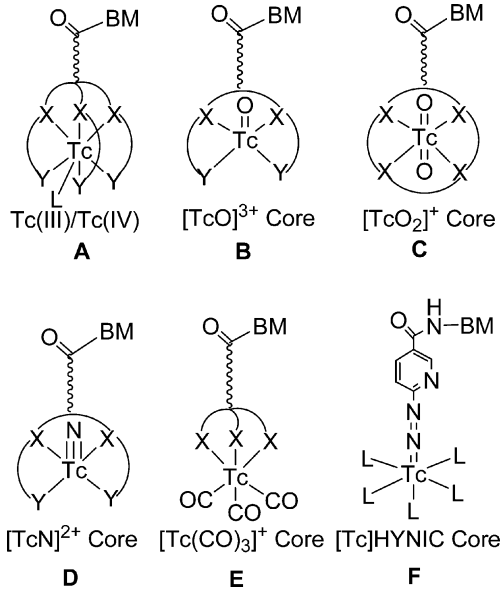
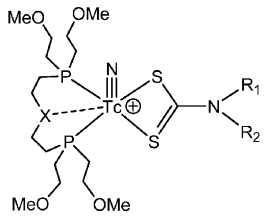


Fig. 8 Technetium cores useful for the ^{99m}Tc-labeling of biomolecules.

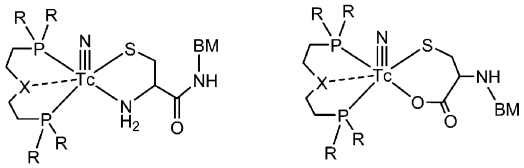
systems which coordinate strongly to $[Tc{\equiv}N]^{2+}$, $[Tc(CO)_3]^+$ and [Tc]HYNIC cores.

The $[Tc{\equiv}N]^{2+}$ core is isoelectronic with $[Tc=O]^{3+}$. The nitrido ligand is a powerful π-electron donor and shows a high capacity to stabilize the Tc(v) oxidation state. The $[Tc{\equiv}N]^{2+}$ core forms Tc(v)-nitrido complexes with various chelators.[44–47] Many Tc-nitrido complexes of N-substituted dithiocarbamates have been studied as heart and brain imaging agents. As a result, [^{99m}TcN(noet)$_2$] (noet = *N*-ethyl-*N*-ethoxydithiocarbamato) is under development as a new myocardial perfusion imaging agent.[46]

Duatti and coworkers recently reported a new class of asymmetric cationic ^{99m}Tc-nitrido complexes (Fig. 9),[48,49]



X = O or NR; R = CH_2CH_2OMe and CH_2CH_2OEt;
R_2 and R_2 = Me, Et, MeO, EtO, CH_2CH_2OMe, CH_2CH_2OEt



BM = RGD-containing peptide or benzodiazepine

Fig. 9 Examples of cationic ^{99m}Tc–nitrido complexes for myocardial imaging and the ^{99m}Tc–nitrido core for the labeling of biomolecules.

which contain the $[^{99m}Tc{\equiv}N]^{2+}$ core, a tridentate bisphosphine, and a dithiocarbamate, and their use as radiopharmaceuticals for heart imaging.[49,50] It has been elegantly demonstrated that the heteroatom in the tridentate PXP (Fig. 9: X = O and NR) bisphosphine ligand is required for stable ^{99m}Tc-nitrido complexes with the heteroatom invariably *trans* to the Tc≡N triple bond.[51,52] The metal–heteroatom distances are quite long; but this weak interaction seems play a significant role in providing

a stabilization for the ^{99m}Tc–nitrido core and in preventing formation of neutral bis(dithiacarbamato) ^{99m}Tc–nitrido complexes. Biodistribution studies showed that these cationic ^{99m}Tc–nitrido complexes are rapidly extracted by the myocardium of rats, and retained in the heart for a long time.[49,50] The lung uptake became negligible at 5 min post-injection. The heart/liver ratios were increased exponentially with time, and liver activity was almost completely eliminated into the intestine at 60 min post-injection. The heart/liver ratios were 10 times higher than those of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin at 60 min post-injection in the same animal model.[49,50] These results clearly demonstrated that it is possible to design simple ^{99m}Tc complex radiopharmaceuticals with better heart uptake and faster liver/lung washout than those of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin by controlling their physical and chemical characteristics.

The $[^{99m}Tc{\equiv}N]^{2+}$ core has also been used for ^{99m}Tc-labeling of small peptides and the benzodiazepine receptor ligands.[53–55] The PXP bisphosphine ligands (Fig. 9: X = O and NR) are used as coligands to stabilize the $[^{99m}Tc{\equiv}N]^{2+}$ core, and the bifunctional chelators containing thiolate-S, amine-N or carboxylate-O donors are attached to the peptide or benzodiazepine receptor ligands. It has been demonstrated that the $[^{99m}TcN(PXP)]^{2+}$ fragment reacts with the cysteine residue to form asymmetrical ^{99m}Tc–nitrido complexes in very high specific activity. However, biodistribution studies of the ^{99m}Tc-labeled benzodiazepine conjugate in rats showed very little uptake in the brain. *In vitro* binding studies with the corresponding ^{99}Tc-analog, on isolated membranes, showed that the complex lost the affinity for benzodiazepine receptors as compared to the starting benzodiazepine receptor ligand.[48,54,55]

Alberto and coworkers first reported the one-step synthesis of Tc(I) and Re(I) complexes $[M(H_2O)_3(CO)_3]^+$ (M = ^{99m}Tc and ^{188}Re) by direct reduction of [^{99m}Tc]pertechnetate or [^{188}Re]perrhenate with sodium borohydride in aqueous solution in the presence of carbon monoxide.[56] The yield of the ^{99m}Tc complex was >95%. $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was not designed as a "stand-alone" radiopharmaceutical, but as a precursor for the radiolabeling of biomolecules. In $[^{99m}Tc(H_2O)_3(CO)_3]^+$, all three water molecules are very labile with respect to substitution. Therefore, a variety of chelators can be used as BFCs for the ^{99m}Tc-labeling of biomolecules.[57–68]

Fig. 10 shows bidentate and tridentate chelators containing N-heterocycles, such as imidazoles, pyridines and pyrazoles, amides, amines, carboxylic acids and combination thereof.

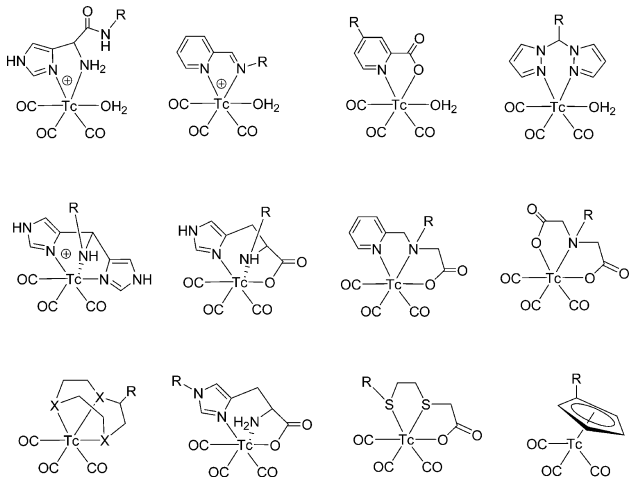


Fig. 10 Examples of bidentate and tridentate bifunctional chelating systems for ^{99m}Tc- and $^{186/188}$Re-labeling of biomolecules. The R group may be a biomolecule or a linker attached to the biomolecule.

Since imidazole is part of the side-chain, histidine is of particular interest as the BFC for the ^{99m}Tc-labeling of monoclonal antibodies and small peptides.[57–68] The diverse coordination chemistry of the $[^{99m}Tc(CO)_3]^+$ core offers a tremendous opportunity for the development of new BFCs. However, monodentate and bidentate chelators often form ^{99m}Tc(I)-tricarbonyl complexes with low solution stability, which results in high protein binding and high background activity in the blood stream.[43] In contrast, tridentate chelators form ^{99m}Tc(I)-tricarbonyl complexes with high stability and rapid clearance from blood and other major organs. Schibli and coworkers reviewed organometallic radiopharmaceuticals recently.[43] Apparently, the $[^{99m}Tc(CO)_3]^+$ core is an extremely valuable alternative to the state of the art ^{99m}Tc-labeling techniques.

Since Abrams and coworkers first reported the use of [Tc]HYNIC core for ^{99m}Tc-labeling of polyclonal IgG,[69,70] HYNIC has been used as a BFC for ^{99m}Tc-labeling of proteins[71,72] and small biomolecules, including chemotactic peptides,[73–75] somatostatin analogs,[76–81] liposomes,[82] antisense oligonucleotides,[83,84] a folate receptor ligand,[85] and polypeptides.[86,87] Since HYNIC can only occupy one or two coordination sites, a coligand such as tricine is needed to complete the coordination sphere of technetium. The advantage of using HYNIC as the BFC is its high labeling efficiency and the choice of coligands such as tricine and glucoheptonate, which allows easy modification of the hydrophilicity and pharmacokinetics of the ^{99m}Tc-labeled biomolecules. However, the use of tricine or glucoheptonate as coligands suffers two major drawbacks: (1) the solution instability of binary ligand complexes $[^{99m}Tc(HYNIC–BM)(L)_2]$ (Fig. 11: BM = biomolecule;

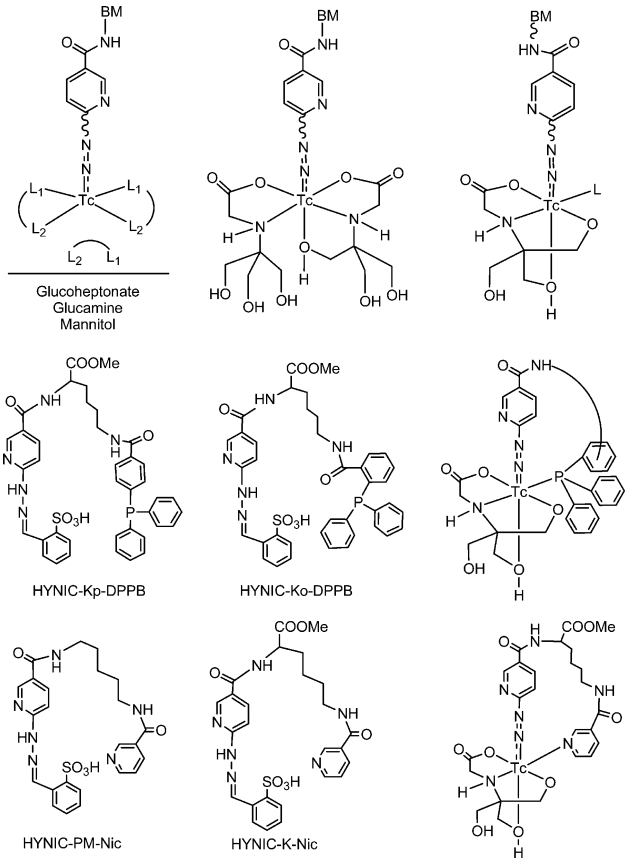


Fig. 11 Technetium complexes of HYNIC-containing chelating systems.

L = tricine and glucoheptonate), and (2) presence of multiple species for binary ligand complexes $[^{99m}Tc(HYNIC–BM)(L)_2]$ in solution due to different bonding modalities of the HYNIC and the tricine or glucoheptonate coligands.[88]

For the last several years, Liu and coworkers have been using a ternary ligand system (Fig. 11: HYNIC, tricine and TPPTS) for ^{99m}Tc-labeling of a variety of small biomolecules, including a chemotactic peptide,[88] LTB_4 receptor antagonists,[89] vitronectin receptor antagonists,[90] and a GPIIb/IIIa receptor antagonist.[91–95] It is amazing that three different ligands combine with Tc to form ternary ligand complexes, [^{99m}Tc(HYNIC–BM)(tricine)(phosphine)], in high yield and high specific activity. These complexes have extremely high solution stability, and often show two isomeric forms if the BM contains one or more chiral centers. Like water-soluble phosphines, pyridine analogs were also used as coligands for ^{99m}Tc-labeling of the HYNIC–BM.[96] The presence of two peaks is due to the resolution of two diastereomers resulting from the chiral centers on the peptide backbone and the chiral technetium chelate.[93,96] The 1 : 1 : 1 : 1 composition for Tc : HYNIC : L : tricine (L = phosphine or pyridine analog) was determined through a series of mixed ligand experiments,[93,96] and has been confirmed by the FAB-MS and LC-MS spectral data for technetium complexes at both ^{99m}Tc and ^{99}Tc levels.[95,97]

In principle, the ternary ligand system (HYNIC–BM, tricine and TPPTS) can be used for ^{99m}Tc-labeling of any small biomolecules. However, problem may arise when it is used for the ^{99m}Tc-labeling of small biomolecules containing one or more disulfide linkages, which are often vital to keep the rigid cyclic conformation of the biomolecule and to maintain the high receptor binding affinity. The use of a large amount of TPPTS in combination with high temperature heating may destroy the S–S disulfide bonds and cause adverse effects on the biological properties of the biomolecule. Replacing TPPTS with a pyridine analog will definitely avoid the use of the phosphine coligand. However, a large amount (>10 mg mL^{-1}) of pyridine coligand has to be used in order to achieve high radiochemical purity for the corresponding ternary ligand ^{99m}Tc complex. Therefore, there is a continuing need for a better chelating system, which does not require the use of large amount of phosphine or pyridine coligand.

Recently, Liu and coworkers reported a series of phosphine- and nicotinyl-containing HYNIC chelators (Fig. 11).[98,99] These HYNIC chelators are designed in such a way that when HYNIC binds to the Tc center, the "effective concentration" of phosphine-P or pyridine-N donor in the vicinity of technetium will be increased dramatically. This makes it much easier for phosphine-P or pyridine-N to bond to Tc and form a macrocyclic ^{99m}Tc chelate. Macrocyclic complexes [^{99m}Tc(L)(tricine)] (L = HYNIC-Ko-TPPB, HYNIC-Kp-DPPB, and HYNIC-Kp-Nic) were prepared by reacting the HYNIC chelator with $^{99m}TcO_4^-$ in the presence of tricine and stannous chloride.[98] It was found that these complexes are highly stable when tricine is used as coligand. The phosphine- and nicotinyl-containing HYNIC derivatives have the potential as BFCs for ^{99m}Tc-labeling of small biomolecules. However, the exact bonding mode of HYNIC in [^{99m}Tc(HYNIC-L)(tricine)] (L = phosphine or pyridine analog) remains unclear. Structural studies of the corresponding macrocyclic ^{99}Tc complexes will definitely help understand the coordination chemistry associated with HYNIC chelators in their macrocyclic ^{99m}Tc complexes.

Coordination chemistry of yttrium and lanthanide radiopharmaceuticals

While diagnostic radiopharmaceuticals rely on high target-to-background ratio, the success of tumor radiotherapy depends largely on the high concentration of radioactivity in the tumor for a long duration. Thus, the therapeutic radiopharmaceutical must have the following characteristics: high tumor uptake, high tumor-to-background ratio, long tumor residence time, and fast renal clearance. High tumor uptake and fast renal clearance are important to improve the tumor-to-background ratio and to reduce radiation burden to organs such as kidneys and bone marrow. The radiopharmaceutical must have high RCP $\geqslant$ 90% and high solution stability. Since the radiopharmaceutical is manufactured in a centralized facility, it must retain its chemical and biological integrity during storage and transportation. This requires that the BFC form a metal chelate with high thermodynamic stability and kinetic inertness. Once again, coordination chemistry plays a significant role in the development of therapeutic radiopharmaceuticals.

Fundamentals of trivalent yttrium and lanthanide metal ions

Yttrium and lanthanide metals favor the +3 oxidation state. Due to its similar charge, ionic radii (Fig. 12) and coordination

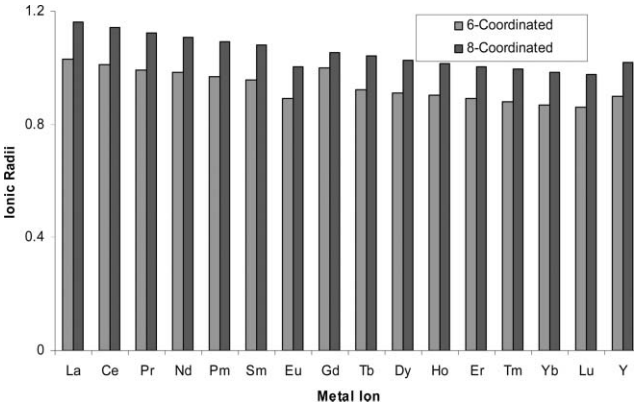


Fig. 12 Ionic radii (Å) for trivalent yttrium and lanthanide ions (data from ref. 147).

chemistry, yttrium is often treated as a "pseudo-lanthanide" metal. The 4f electrons are inner electrons, shielded from external influences by overlying $5s^2$-, $5p^6$ and $6s^2$-electron shells, and are not involved in the bonding; interactions between donor atoms and lanthanide metal ions are predominately ionic. Yttrium and lanthanide metal ions are coordinated by a number of water molecules in aqueous solution. The metal chelate formation involves replacement of water molecules by a chelator. Due to their large size, coordination numbers of yttrium and lanthanide ions are typically between 7 and 10. Very few six coordinate species are known while coordination numbers of 8 and 9 are common.[5]

Thermodynamic stability and kinetic inertness

In the blood stream, the concentration of the radiopharmaceutical may become so low that dissociation of the radiometal from metal chelate will eventually become favored. The loss of radiometal may result in accumulation of radioactivity in non-target organs. It has been reported that ^{90}Y and lanthanide isotopes are readily deposited on the bone.[100] As a matter of fact, if free ^{90}Y is injected in a human subject, about 50% of the injected dose will localize in the bone, 25% of the injected dose will go to the liver, 10% of the injected dose is evenly distributed in many other organs and tissues while only 15% of the injected dose will be excreted *via* the renal system. Therefore, the BFC must form a metal chelate with high thermodynamic stability to retain its chemical integrity in competition with natural chelators, such as transferrin.

Selection of BFCs

There are several requirements for an ideal BFC. The BFC must form a metal chelate with high thermodynamic stability

and kinetic inertness in order to keep the metal chelate intact under physiological conditions. Decomposition of the metal chelate produces free metal ion, which may deposit on the bone and cause bone marrow toxicity. The BFC must form a metal chelate with a minimum number of isomers. The tumor uptake of a radiopharmaceutical depends not only on the receptor binding affinity of the biomolecule but also on pharmacokinetics, which are determined by the physical and chemical properties of both the biomolecule and metal chelate. Formation of isomers may have a significant impact on the biological properties of the radiopharmaceutical. The BFC should have high hydrophilicity to improve blood clearance and renal excretion of the labeled and unlabeled BFC–BM conjugate. Fast renal clearance of unlabeled BFC–BM will minimize its competition with the radiolabeled BFC–BM for receptors. In addition, the BFC has to be able to withstand radiolysis because a large dose of β-radiation can produce free radicals and result in a significant amount of decomposition of the metal chelate during the manufacturing process and transportation.

The most common way to increase the thermodynamic stability and kinetic inertness of a metal complex is to use a polydentate chelator. The denticity requirement of a BFC is largely dependent on the size and coordination geometry preference of the metal ion. Yttrium and lanthanide metal ions are large and need 8–9 donor atoms to complete the coordination sphere. It is not surprising that most BFCs (Fig. 13)

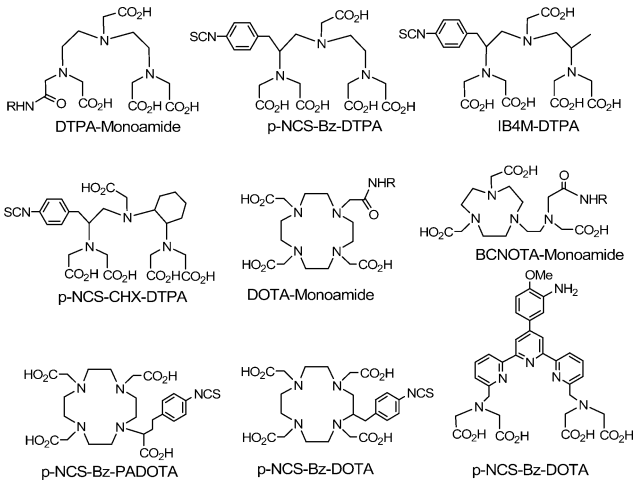


Fig. 13 Structures of selected acyclic and macrocyclic BFCs useful for the radiolabeling of biomolecules.

contain at least eight donor atoms. It should be noted that the denticity requirement for lanthanide radiopharmaceuticals is different from that for MRI contrast agents. For MRI contrast agents, the chelator is most likely hepta- or octadentate, leaving at least one site open for water coordination to enhance the proton relaxation rates. For radiopharmaceuticals, higher denticity may provide enhanced thermodynamic stability and the improved kinetic inertness, particularly when extra donors are incorporated into a chelating arm attached to the macrocyclic framework.

DOTA derivatives (Fig. 13) are of particular interest for ^{90}Y and lanthanide radiopharmaceuticals. The macrocyclic framework is well organized so that they form metal complexes with high thermodynamic stability and kinetic inertness. The pK_a values for the carboxylic groups are in the range 2–5. Lower pK_a values result in less competition from proton, high stability of the metal complex and minimum acid-assisted demetallation. The acetate groups attached to the nitrogen donor atoms have low molecular weight. Therefore, contribution of the BFC to overall molecular weight of the BFC–BM conjugate is minimized. The high hydrophilicity of acetate chelating arms will favor faster blood clearance and result in reduced competition between the labeled and unlabeled BFC–BM. Recently, Brechbiel and coworkers[101] reported synthesis of a new BFC (Fig. 13: BCNOTA), which has a combination of both macrocyclic and acyclic character. It was found that BCNOTA forms the ^{86}Y complex with high solution stability and high radiolabeling efficiency (fast and high yield radiolabeling).[101]

Isomerism

In the last decade, many acyclic and macrocyclic BFCs, selected examples of which are shown in Fig. 13, have been used for the radiolabeling of antibodies and peptides.[102–115] Although formation of isomers in yttrium and lanthanide complexes of DTPA and DOTA analogs has been studied by various NMR methods,[116–127] very little attention is paid to the isomerism of the metal chelate in radiolabeled DTPA– and DOTA–biomolecule conjugates at the tracer level. In many cases, ITLC is the only analytical tool for characterization of the radiolabeled biomolecule. It is not surprising that there has been no detailed discussion about isomerism and the impact of isomerism on biological properties of radiolabeled biomolecules. Solid state structures provide a wealth of information about the coordination chemistry of a specific chelating system. However, the solution structure may be different from the solid state structure because of possible dissociation of certain donor atoms or due to coordination of water molecules. The isomerism observed in the solid state may not be seen in solution due to interconversion of different isomers or fluxionality of the ligand framework. On other occasions, only one isomeric form is found in the solid state, and more isomers are observed in solution. Thus, it is imperative to study the solution structure in order to understand the biological properties of a radiopharmaceutical. Isomerism of yttrium and lanthanide metal complexes of DTPA and DOTA analogs has been discussed and reviewed recently.[13]

Radiolabeling efficiency

Radiolabeling efficiency is a term used to describe the ability of a chelator to achieve a high radiolabeling yield and high radiochemical purity (>90%) of its radiometal chelate. A major advantage of using DTPA analogs as BFCs is their extremely high radiolabeling efficiency (fast and high yield radiolabeling) under mild conditions,[128–131] but the kinetic lability of their metal chelates often results in dissociation of radiometal from the metal chelate, and leads to radiation toxicity to non-target organs such as bone marrow.[128,129] The advantage of using DOTA analogs as BFCs is the extremely high kinetic inertness of their metal chelates. However, the radiolabeling kinetics of DOTA-based BFCs is usually slow, and much more dependent on the radiolabeling conditions,[128–131] including DOTA–conjugate concentration, pH, reaction temperature and heating time, buffer agent and buffer concentration, and presence of other metal ions, such as Fe^{3+} and Zn^{2+}. Heating at elevated temperatures is often needed for successful radiolabeling of DOTA-conjugated biomolecules. At room temperature, radiolabeling of the DOTA–conjugate is slow with low radiolabeling yield, which requires post-labeling chromatographic purification. For small peptides, radiolabeling at elevated temperatures may not cause any significant degradation of radiolabeled DOTA-bioconjugates. For monoclonal antibodies, however, radiolabeling at elevated temperatures often causes a significant loss of immunoreactivity of the radiolabeled bioconjugates.[132] Although DOTA analogs form metal chelates with high solution stability, slow radiolabeling

kinetics remains a major obstacle that limits the wide use of DOTA analogs as BFCs in therapeutic radiopharmaceuticals.

Bioequivalence of ^{90}Y– and ^{111}In-labeled BFC–BM conjugates

Many acyclic and macrocyclic chelators (Fig. 13) have been used as BFCs for the radiolabeling of various targeting biomolecules, such as antibodies and peptides.[133–142] While ^{90}Y-labeled BFC–BM conjugates are used for radiotherapy, the corresponding ^{111}In-labeled BFC–BM conjugates are often used as surrogates for imaging and dosimetry determination.[133–142] This is largely due to the fact that ^{90}Y is a pure β-emitter without any γ-emission for imaging. ^{111}In is commercially available, and has a half-life ($t_{1/2}$ = 2.8 days) almost identical to that of ^{90}Yi ($t_{1/2}$ = 2.7 days). Although the coordination chemistry of indium and yttrium is similar, results from recent literature have shown different biodistribution properties between ^{90}Y- and ^{111}In-labeled BFC–BM conjugates.[143–145] This causes some concerns about the validity of the ^{111}In-labeled BFC–BM conjugates as imaging surrogates for their ^{90}Y analogs.

Many ^{90}Y-labeled biomolecules have been tested for their therapeutic efficacy in tumor radiotherapy. However, very few studies have been directed towards understanding differences between the ^{90}Y- and ^{111}In-labeled BFC–BM conjugates with respect to lipophilicity, structures and biodistribution characteristics. Before using ^{111}In-labeled BFC–BM conjugates as imaging surrogates for their ^{90}Y analogs, several critical questions need to be properly addressed. Are ^{90}Y- and ^{111}In-labeled BFC–BM conjugates biologically equivalent? What are the factors contributing to the differences, if any, in their physical and biological properties? How does the metal chelate affect biological properties of radiolabeled BFC–BM conjugates?

Lipophilicity differences

Recently Liu and coworkers reported a DOTA-conjugated nonpeptide integrin $\alpha_v\beta_3$ receptor antagonist and its complexes: ^{90}Y-TA138 and ^{111}In-TA138.[146] By a reversed phase HPLC method, it was found that the retention time of ^{111}In-TA138 is ~4.5 min shorter than that of ^{90}Y-TA138 (Fig. 14). Under isocratic conditions (7% B over 30 min), the HPLC retention time difference between ^{90}Y-TA138 and ^{111}In-TA138 was ~10 min. Since the only difference in ^{111}In-TA138 and ^{90}Y-TA138 is the metal, different HPLC retention times strongly suggest that In^{3+} and Y^{3+} do not share the same coordination sphere in solution even though they are coordinated by the same DOTA-conjugate.

Structure differences

In^{3+} and Y^{3+} are trivalent metal cations. The main difference is their size. As a result, In^{3+} and Y^{3+} often have different coordination chemistry with DTPA and DOTA derivatives. For example, Y^{3+} has an ionic radius of 1.02 Å,[147] which fits perfectly to the cavity of DOTA–monoamide. Y^{3+} complexes with DOTA derivatives are eight-coordinated and are able to maintain their rigid eight-coordinated structure in solution.[133] In^{3+} has an ionic radius of 0.92 Å,[147] which is smaller than that of Y^{3+}. The coordination number of In^{3+} is typically 6 or 7.[148–153] Only a few eight coordinated In^{3+} complexes are known.[154–158] Due to its smaller size, In^{3+} does not fit to the coordination cavity of DOTA-monoamide. Although In^{3+} is shown to be eight-coordinated in the solid state of In(DOTA–monoamide),[148] the carbonyl-oxygen may become dissociated in solution to give a seven-coordinated In(DOTA-monamide) complex. As a result, In(DOTA–BA) and Y(DOTA–BA) (BA = benzylamine) show significant differences in their solution properties as demonstrated by their ^{1}H NMR spectra. Y(DOTA–BA) is rigid and only becomes fluxional at temperatures higher than 60 °C while In(DOTA–BA) is fluxional at room temperature.[147]

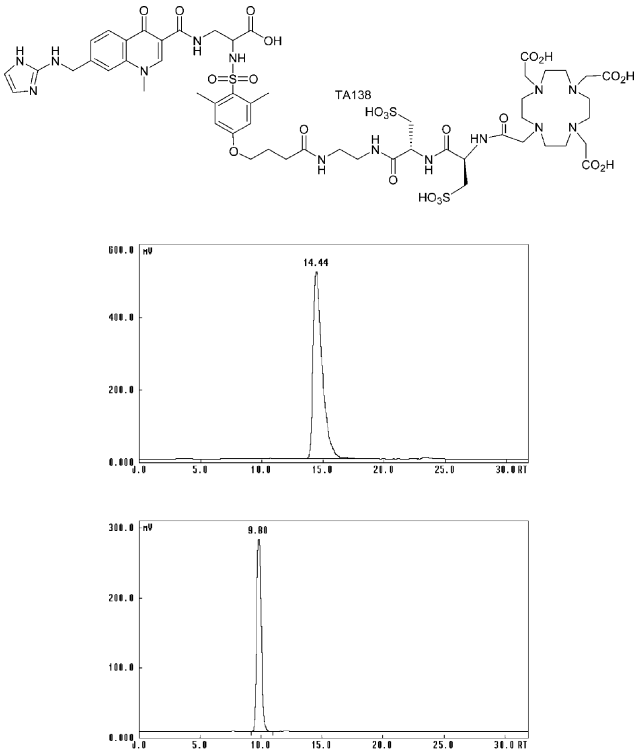


Fig. 14 Typical radio-HPLC chromatograms of ^{90}Y-TA138 (top) and ^{111}In-TA138 (bottom).

Biological equivalence

Onthank and coworkers recently reported the biodistribution data of ^{111}In-TA138 and ^{90}Y-TA138 in the c-neu Oncomouse® model (Fig. 15).[146] Despite their differences in lipophilicity, the biodistribution data clearly showed that ^{111}In-TA138 and ^{90}Y-TA138 are biologically equivalent with respect to their uptake in tumors and other major organs, such as blood, liver, spleen, bone marrow, and kidneys. Therefore, ^{111}In-TA138 is useful as an imaging surrogate for ^{90}Y-TA138, and should be able to accurately predict the radiation dosimetry of ^{90}Y-TA138, therapeutic radiopharmaceutical for systemic tumor radiotherapy. It should be noted that the metal chelate is only a small part of the ^{111}In- and ^{90}Y-labeled DOTA–BM conjugate. ^{111}In and ^{90}Y chelates may have different solution structures, which causes a slight difference in the lipophilicity between the ^{111}In- and ^{90}Y-labeled DOTA–BM conjugate. Ultimately, it will be the biological equivalence that determines if the ^{111}In-labeled DOTA–BM conjugate can be used to accurately predict the radiation dosimetry of its ^{90}Y analog.

Mäcke and coworkers[133] recently reported the radiolabeling, receptor binding and biodistribution studies on ^{67}Ga, ^{90}Y and ^{111}In-labeled DOTA–D-Phe^1-Tyr^3-Octreotide (Fig. 16: DOTATOC). It was found that the uptake of ^{90}Y-labeled DOTATOC in somatostatin receptor positive tissues is significantly higher than that of ^{111}In-labeled DOTATOC. In normal organs, both ^{90}Y- and ^{111}In-labeled DOTATOC conjugates are biologically equivalent. The solution stability of ^{67}Ga-DOTATOC, ^{111}In-DOTATOC and ^{90}Y-DOTATOC in the blood serum is very high with half-lives for radiometal exchange being 1250 h, 1850 h and 2100 h, respectively.[133] Considering their short biological half-life, these values suggest that the release of

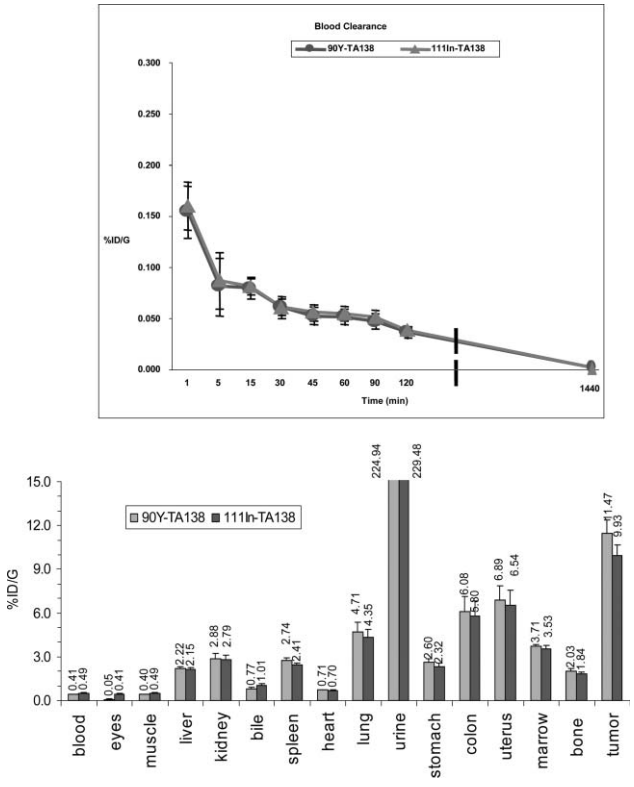


Fig. 15 Blood clearance curve (0–24 h post-injection) and biodistribution data (2 h postinjection) for ^{90}Y-TA138 and ^{111}In-TA138 in the c-neu Oncomouse® model. Each time point is the average ± the standard error of the mean (SEM) ($n = 6$).

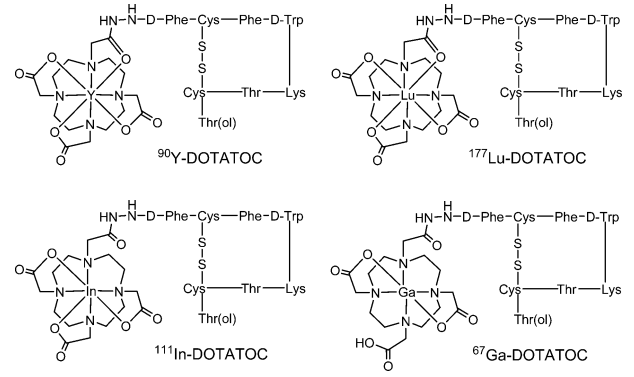


Fig. 16 Structures of ^{67}Ga, ^{90}Y, ^{111}In and ^{177}Lu-labeled DOTA-D-Phe^1-Tyr^3-Octreotide (DOTATOC): a somatostatin analog useful for tumor imaging and radiotherapy.

radiometal from radiolabeled bioconjugates may not be a significant problem. The IC_{50} values for ^{67}Ga-DOTATOC (0.46 ± 0.1 nM), ^{111}In-DOTATOC (2.57 ± 0.2 nM) and ^{90}Y-DOTATOC (2.2 ± 0.3 nM) were also determined in a receptor binding assay.[133] Apparently, there was no significant difference in the receptor binding affinity between ^{111}In-DOTATOC and ^{90}Y-DOTATOC. Biodistribution data were obtained for ^{67}Ga-DOTATOC, ^{111}In-DOTATOC and ^{90}Y-DOTATOC in nude mice bearing the AR4-2J tumor. It was found that there was no significant difference in kidney and tumor uptake for ^{111}In-DOTATOC and ^{90}Y-DOTATOC at 4 h and 24 h post-injection. However, the tumor uptake of ^{67}Ga-DOTATOC was significantly higher than that of both ^{111}In-DOTATOC and ^{90}Y-DOTATOC, and the kidney uptake of ^{67}Ga-DOTATOC was much lower than that of ^{111}In-DOTATOC and ^{90}Y-DOTATOC. The much improved kidney clearance for ^{67}Ga-DOTATOC has been attributed to the presence of free carboxylic group (Fig. 16), as observed in the complex Ga(DOTA–D-Phe-NH_2).[133]

Coordination chemistry of gallium, indium and copper radiopharmaceuticals

Gallium and indium chemistry

The interest in the coordination chemistry of gallium stems, at least in large part, from the potential application of ^{68}Ga-labeled small biomolecules as PET imaging agents. ^{111}In is a gamma emitter with the gamma photon energy of 173 and 247 keV (89% and 95% abundance, respectively) and is widely used (second only to ^{99m}Tc) in gamma scintigraphy. The coordination and radiopharmaceutical chemistry related to gallium and indium has been reviewed recently by Anderson and coworkers.[3,15]

Both gallium and indium are group IIIB metals in the periodic table. The most prevalent oxidation sate of gallium and indium in aqueous solution is +3. Due to their high charge density, Ga^{3+} and In^{3+} prefer chelators with hard donors, such as amine-N, carboxylate-O and phenolate-O atoms. Because of its small size, Ga^{3+} is often six-coordinated in order to maintain its high *in vivo* stability.[3,15] Both Ga^{3+} and In^{3+} are similar to Fe^{3+} with respect to their coordination chemistry and biological properties. Since they are highly charged cations, the hydrolysis of Ga^{3+} and In^{3+}, particularly at pH >4, remains a significant challenge during radiolabeling in aqueous solution. Another challenge is ligand exchange with the transferrin, which has extremely high affinity for Ga^{3+} and In^{3+}, when ^{68}Ga and ^{111}In radiopharmaceuticals are injected into the biological system. It is no surprising that BFCs for target-specific ^{68}Ga and ^{111}In radiopharmaceuticals are dominated by polydentate ones with hard donors, such as amine-N and carboxylate-O. DTPA and DOTA analogs (Fig. 13) are often the choice of BFCs for ^{68}Ga- and ^{111}In-labeling of small biomolecules in order to prevent hydrolysis during the radiolabeling process and to maintain the *in vivo* stability of the ^{68}Ga- and ^{111}In-labeled small biomolecule radiopharmaceuticals.

It should be noted that the free ^{68}Ga and ^{111}In tend to localize in liver and lungs due to their strong binding capability to transferrin while ^{90}Y and lanthanide isotopes are readily deposited on the bone.[100] For ^{90}Y- and ^{111}In-labeled small biomolecules, the release of a small amount of ^{90}Y and ^{111}In from their DTPA chelates may not cause a significant difference in their biodistribution characteristics mainly due their short biological half-life. However, the release of ^{90}Y and ^{111}In from the DTPA chelates will cause a significant difference in biological properties of ^{90}Y- and ^{111}In-labeled monoclonal antibodies, which have much longer biological half-lives. From this point of view, the difference in biodistribution patterns observed for ^{90}Y- and ^{111}In-labeled monoclonal antibodies is probably caused by the difference in solution instability of the radiometal–DTPA chelates.

Despite their similarities, Ga^{3+} and In^{3+} are different with respect to their size and charge density. This difference is often reflected by their different coordination chemistry with DTPA and DOTA analogs. For example, Ga^{3+} has an ionic radius of 0.65 Å,[147] and the coordination number of Ga^{3+} is 6 in Ga(DOTA-D-Phe-NH2).[133] In^{3+} has an ionic radius of 0.92 Å,[147] and In^{3+} is 8-coordinated in In(DOTA-BA).[148] This structural difference has also been attributed to the significantly higher tumor uptake of ^{67}Ga-DOTATOC than that of ^{111}In-DOTATOC, and the much lower kidney uptake of ^{67}Ga-DOTATOC than that of ^{111}In-DOTATOC.[133]

Copper chemistry

Copper is a first-row transition metal and has several radionuclides, such as ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu and ^{67}Cu. All aspects of copper radionuclide production, coordination chemistry, and radiochemistry have been reviewed exhaustively by Blower and coworkers.[158] Nuclear medicine applications and metabolism of ^{62}Cu and ^{64}Cu-labeled biomolecules (proteins and peptides) have recently been reviewed by Anderson and coworkers.[3,159] The rich coordination chemistry of copper in combination with the diverse nuclear properties of its radionuclides offers a lot of opportunities for the development of diagnostic (^{60}Cu, ^{61}Cu, ^{62}Cu and ^{64}Cu) and therapeutic (^{64}Cu and ^{67}Cu) radiopharmaceuticals. However, successful development of target-specific radiopharmaceuticals based on radiolabeled small biomolecules with copper radionuclides will depend not only on their clinical performance in but also on the commercial availability of the specific radioisotope for the radiolabeling and clinical accessibility of PET cameras if it is used for PET imaging.

Analytical tools for radiolabeled bioconjugates

ITLC

Instant liquid chromatography is the most frequently used procedure for quality control of radiolabeled biomolecules. It is simple and quick, usually taking only 5–15 min to complete the whole procedure. Ideally, one TLC paper strip or plate is needed for the separation of free radiometal, radiometal colloid, and the radiolabeled BFC–BM conjugate. The mobile phase often comprises an organic solvent (acetone, ethanol, acetonitrile, methyl ethyl ketone or isopropyl alcohol) and water or saline. The radiometal colloid and unlabeled free radiometal remain at the origin and the radiolabeled BFC–BM conjugate migrates to the solvent front. ITLC methods typically give only the radiolabeling yield. Rarely can they provide the radiochemical purity (RCP) data for the radiolabeled BFC–BM conjugate. ITLC methods are not suitable for separation of different isomers.

HPLC

For the last decade, high pressure liquid chromatography (HPLC) has become a routine technique for quality control of radiolabeled bioconjugates. The advantage of radio-HPLC is its capability to determine the RCP for the radiolabeled BFC–BM conjugate, and to separate different radiometal-containing species. It is a very powerful tool for separation of different isomers, such as epimers and diastereomers. The separation of optical isomers requires the use of chiral chromatographic conditions (chiral column or chiral mobile phase). However, radio-HPLC also has its limitations. For example, it can not be used for the assessment of the amount of radiometal colloid. Therefore, an ITLC method is needed in combination with the radio-HPLC to assess both radiolabeling yield and the radiochemical purity of the radiolabeled BFC–BM conjugate. It is very important to emphasize that a single peak in the radio-HPLC chromatogram does not necessarily mean that there is only one radiometal-containing species. This is particularly true when the chromatographic conditions are not optimized. Different chromatographic conditions (such as an isocratic mobile phase or a long and slow gradient mobile phase) are strongly recommended to confirm that the single peak observed in the radio-HPLC chromatogram is really one peak and that there are no other radio-impurities or isomeric forms co-eluting with the radiolabeled BFC–BM conjugate.

LC-MS

One of most important aspects of radiochemistry is to know the composition of a radiopharmaceutical. A quick and accurate method would help radiochemists understand the fundamental coordination chemistry at the tracer level. Since the concentration of radiometal is normally very low (10^{-8} to 10^{-6} M) in a radiopharmaceutical composition, it is impossible to use IR, UV/vis, NMR and X-ray crystallography to characterize the radiopharmaceutical. Therefore, there is a constant need for a quick and accurate analytical tool to determine the composition of the radiopharmaceutical at the tracer level.

Mass spectrometry has been used for a number of years as a powerful tool for the study of drug metabolism. Liu and coworkers recently reported the use of LC-MS for analysis of ternary ligand ^{99m}Tc complexes [^{99m}Tc(HYNIC–peptide)-(tricine)(L)] (L = water-soluble phosphines or pyridine analog).[97] It was found that all ternary ligand ^{99m}Tc complexes show the expected monoprotonated molecular ions, $(M + 1)^+$, and diprotonated molecular ions, $(M + 2)^{2+}$. Two isomers in these ^{99m}Tc complexes show the same molecular ions with almost identical fragmentation patterns, demonstrating that the two peaks in their radio-HPLC chromatograms are indeed due to resolution of two diastereomers. LC-MS is a quick and accurate analytical tool for determining the composition of ^{99m}Tc radiopharmaceuticals, and is particularly useful for those, the ^{99}Tc analogs of which are difficult to prepare at the macroscopic (^{99}Tc) level.[97]

LC-MS also has its limitations. For example, LC-MS may not be particularly useful for ^{90}Y radiopharmaceuticals because the reaction mixture contains other "cold" metal (*e.g.* Fe^{3+} and Zn^{2+}) complexes, which often co-elute with the ^{90}Y complex of the same BFC–BM conjugate. LC-MS does not give much structural information other than the molecular weight; thus it is only a complementary analytical tool for the radiolabeled compounds. The biggest obstacle for the widespread use of LC-MS as an analytical tool for radiopharmaceuticals remains the high cost and service charge for the instrument. Except those from industry, most researchers in academic institutions do not have or can not afford access to such a useful analytical tool. One way to overcome the obstacle is cost-sharing among several researchers in the same institution; but the instrument has to be installed in the restricted area for radioactive material handling and requires special personnel with sufficient radiation training for instrument repair and maintenance.

Conclusions

There is a tremendous effort in the development of target-specific radiopharmaceuticals for both early detection of diseases and radiotherapy of cancers. This effort relies heavily on identification and the use of receptor ligands as "carriers" for a radionuclide to localize at the diseased tissues. Because of their high specificity and selectivity, radiolabeled receptor ligands offer advantages over simple radiometal complex radiopharmaceuticals for both imaging and therapy. Imaging using radiolabeled small biomolecules allows us to monitor biological changes of diseased tissues at the molecular level rather than morphological or functional characterization of diseases or disease states. It is not surprising that many academic institutions start to set up their own "Molecular Imaging Centers" with the hope of developing imaging agents using SPECT or PET and of practising "individual nuclear medicine".

It is true that target-specific radiopharmaceuticals will have high specificity and sensitivity for certain disease or disease states; but they also suffer disadvantages over traditional simple ^{99m}Tc complex radiopharmaceuticals. For example, if the agent is too specific, there will be not a large population of

patients. If an agent or drug can not serve the unmet medical need of a large population of patients, it will not be successful from both commercial and medical application point of view. This may explain the limited success of ^{111}In–DTPA-Octreotide and ^{99m}Tc-P829 (Fig. 2). As Professor Susan Lever elegantly pointed out in her recent review,[157] the complicated issue that will impact the evolution of new radiopharmaceuticals for diagnostic imaging and radiotherapy is that the financial costs to validate a radiotracer through Phase III clinical trials continue to rise. Regardless of the beauty of the science involved in the development of radiotracer, the ultimate goal is not the science, but the ability to improve the quality of life for patients.[157]

Identification of appropriate biological targets and receptor ligands is critical for the successful development of a receptor-based target-specific radiopharmaceutical. Phage display and combinatorial chemistry are important tools for selection of targeting biomolecules. Ultimately, the challenge remains the fundamentals of synthetic organic and inorganic chemistry. There is no easy task such that one can simply attach a radiometal chelate onto the selected targeting biomolecule without significantly changing its receptor binding affinity and biodistribution characteristics. Coordination chemistry plays a significant role in the design of bifunctional chelators, radiolabeling kinetics, solution stability of the radiopharmaceutical, modification of pharmacokinetics, and formulation development for commercial products.

While efforts in radiopharmaceutical research have been focused on target-specific radiopharmaceuticals for early diagnosis and radiotherapy of cancers in the last decade, the "market" of diagnostic nuclear medicine is still in nuclear cardiology. Despite the wide spread applications of ^{18}F-FDG in both cardiology and oncology, further development of PET imaging agents will be severely limited by the availability of PET radiotracers and the accessibility of PET cameras for a large population of patients. Thus, there remains an unmet need for the next generation of ^{99m}Tc perfusion imaging agents, which have better myocardial uptake and faster liver/lung clearance than that of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin. Recent results from Professor Duatti's group have clearly demonstrated that it is possible to design simple ^{99m}Tc complex radiopharmaceuticals with better heart uptake and faster liver/lung washout than that of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin simply by controlling their physical and chemical properties.[49,50] Of course, the potential of these cationic ^{99m}Tc–nitrido complexes still needs to be validated in patients by future clinical trials. Successful development of new ^{99m}Tc perfusion imaging agents will have a profound impact on evaluation, risk stratification, and therapeutic decision-making in a large population of patients with coronary artery disease.

Coordination chemistry continues to play a pivotal role in the development of new target-specific radiopharmaceuticals. While it is critical to understand fundamentals of the coordination chemistry of different BFCs with radionuclides, it is more important to study the impact of metal chelates on biological properties of radiopharmaceuticals so that one can use different BFCs and PKM linkers for modification of their biological characteristics. One of the goals of this review is to introduce coordination chemists to a wide number of applications of our field in nuclear medicine and radiopharmaceutical development. At the same time, it is also the author's intent to show our colleagues in nuclear medicine that inorganic chemists can contribute in many aspects of the radiopharmaceutical development process. The ultimate goal is to develop a new generation of radiopharmaceuticals (target-specific or simple radiometal complex), which will satisfy the unmet medical need and serve a large population of patients for either early detection of cancer and cardiovascular diseases or systemic radiotherapy of cancers.

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