Coordination Compounds in Nuclear Medicine

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I. Introduction

Radiopharmaceuticals, drugs containing a radionuclide, are used routinely in nuclear medicine departments for the diagnosis of disease and are under investigation for use in the treatment of disease. Nuclear medicine takes advantage of both the nuclear properties of the radionuclide and the pharmacological properties of the radiopharmaceutical. Herein lies the real strength of nuclear medicine, the ability to monitor biochemical and physiological functions in vivo. Other imaging modalities such as nuclear magnetic resonance imaging and ultrasound imaging are able to delineate anatomical features with better resolution, but they provide only limited information on biological function.

Radiopharmaceuticals can be divided into two primary classes: (1) those whose biological distribution is determined strictly by blood flow, or perfusion, and (2) those whose ultimate distribution is determined by specific biochemical or receptor binding interactions. Obviously, the latter class is initially distributed by blood flow, but their tissue uptake and retention rely on specific interactions of the radiopharmaceutical in a biochemical process, such as enzymatic reduction, as is observed with misonidazole,[1-3] or specific receptor binding, as is observed in antibody–antigen interactions.[4] In both cases, the biological distribution of the radiopharmaceutical is indicative of the normal physiological or pathological status of the patient.

The term "pharmaceutical" generally connotes organic, medicinal, or natural products chemistry. The majority of therapeutic drugs are organic or bioorganic molecules. This is not surprising considering the composition of biological systems and the involvement of organic compounds in these systems. The most efficacious radiopharmaceuticals, diagnostic and therapeutic, would most likely be organic molecules if it were not for the fact that the radionuclide is an essential element of the radiopharmaceutical. The substitution of a radioisotope of carbon for a nonradioactive carbon atom in an organic or bioorganic molecule would probably be ideal. However, the radionuclides with physical (or nuclear) properties suitable for use in either a diagnostic or therapeutic radiopharmaceutical are predominantly metals. Figure 1 shows the radiopharmaceutical chemist's periodic table and illustrates the importance of coordination chemistry to the area of radiopharmaceutical chemistry, and thereby nuclear medicine.

Metals offer many opportunities for designing radiopharmaceuticals by modifying the environment around the metal and allowing specific in vivo targeting to be incorporated into the molecule. The radiopharmaceutical may be designed to be (1) metal essential, whereby the biological distribution is determined by the properties of the coordination compound, or (2) metal tagged, in which case the properties of a carrier molecule, such as an antibody, determine the biological distribution, and the metal or metal complex is simply along for the ride. The coordination chemistry of the metal will determine the ultimate geometry and stability of the radiopharmaceutical. Important considerations in the design and use of the radiopharmaceuticals are their stability and properties in the biological system in which they will be used. In vivo, stability may have a very different connotation than chemical or thermodynamic stability. The biological system consists of circulating blood at a pH of ca. 7.4 and a temperature of ca. 37 °C and contains various proteins, enzymes, cells, and so on. In addition, compounds in the blood (e.g., transferrin) could potentially challenge the integrity of the complex of interest. The stability that is important for a radiopharmaceutical is kinetic stability. The radiopharmaceutical must be stable sufficiently long to reach its destination, and in some cases it must remain intact during its lifetime in the body.

Different nuclear properties are required of the radionuclide depending on the application. For diagnostic imaging procedures the radiation must be able to penetrate the body and be detected by instrumentation that is external to the patient. This requires that the radionuclide emit photons of energy greater than 35 KeV, but realistically greater than ca. 80 KeV.[5,6] Radionuclides decaying by gamma ray (γ) or positron (β^+) emission without accompanying alpha (α) or beta (β^-) particle emission, having a relatively short half-life (less than a day), and decaying to a relatively stable daughter are suitable for incorporation into diagnostic radiopharmaceuticals. The half-life must be sufficiently long to synthesize the radiopharmaceutical, inject the drug into the patient and image the patient

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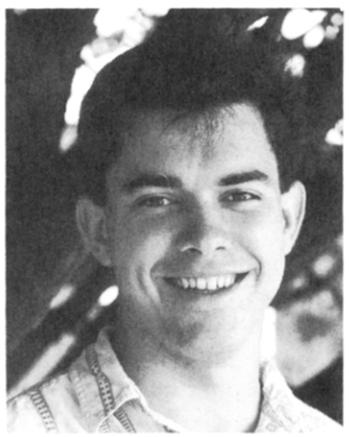
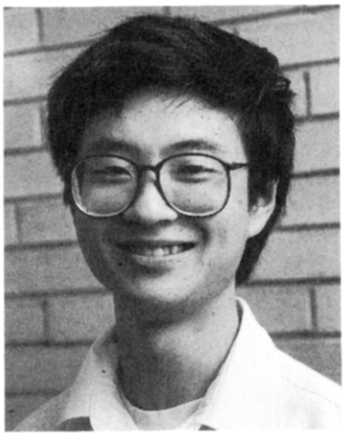
Silvia Jurisson was born and raised in Cumberland County, NJ. She received her B.S. degree in chemistry at the University of Delaware in 1978. She pursued her graduate degree with Prof. Edward Deutsch at the University of Cincinnati, studying the inorganic chemistry of technetium radiopharmaceuticals. On completion of her Ph.D. in 1982, she spent the next two years in Canberra, Australia, studying linkage isomerization reactions with Prof. W. G. Jackson at the University of New South Wales, Duntroon, and reactions of methionine coordinated to cobalt(III) with Prof. Alan Sargeson at the Australian National University. In 1984 she returned to the United States to work with Prof. David Troutner at the University of Missouri, investigating the inorganic and radiochemistry of technetium amine oxime brain imaging agents. She returned to New Jersey in 1986 to spend the next five years working as a Senior Research Scientist in the Radiopharmaceutical Research Department at Bristol-Myers Squibb developing potential radiopharmaceuticals based on technetium. In the Fall of 1991, she took her present faculty position in the Chemistry Department at the University of Missouri, Columbia. Her research interests include the inorganic and radiopharmaceutical chemistry of coordination compounds and their interactions with biochemical receptor systems.

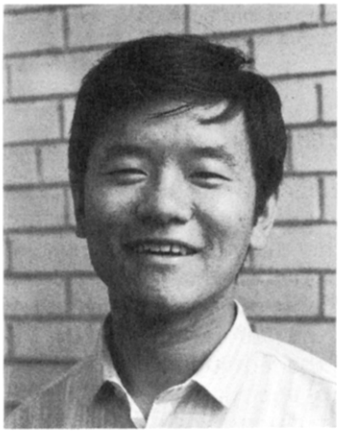


Doug Berning was born in Carrollton, MO, in 1969. He graduated Magna Cum Laude from Central Missouri State University with a double B.A. in chemistry and biology in 1991. He became interested in radiopharmaceutical chemistry while working under the supervision of Dr. Wynn Volkert at the Harry S. Truman Memorial Hospital and the University of Missouri-Columbia through a summer undergraduate research program sponsored by the University. He is currently a second year graduate student pursuing a Ph.D. under the supervision of Prof. Silvia Jurisson in the area of receptor chelates.

with the available instrumentation (planar and single photon emission computed tomography, or SPECT, for γ-emitters and positron emission tomography, or PET, for β^+-emitters). In practice, gamma ray energies between 80 and 300 KeV are necessary and between 100 and 200 KeV are optimum for instrumentation currently in use in Nuclear Medicine departments.



Wei Jia was born in Wuxi, China, in 1965. He received his B.S. degree in analytical chemistry from Jiangnan University in 1986. He then worked for Wuxi Titanium Dioxide Products. He came to the United States in 1989 to pursue a graduate degree, and in 1991 he received an M.S. degree working under the supervision of Dr. Gary Ehrhardt, specializing in radiopharmaceutical chemistry. He is currently working as Project Specialist at the University of Missouri Research Reactor and is also pursuing a Ph.D. under the supervision of Prof. Silvia Jurisson.



Dangshe Ma was born in China in 1963. He received his Bachelor's degree in applied chemistry from Tsinghua University in 1984 and then completed his Master's degree in energetic materials at the Beijing Institute of Technology in 1987. After graduation, he worked as a lecturer in the graduate school at Beijing Institute of Technology for four years. He is presently pursuing his Ph.D. in radiopharmaceutical chemistry with Prof. Silvia Jurisson at the University of Missouri.

Positron decay results in the emission of two 511-KeV gamma photons oriented 180° to each other. Special PET instrumentation is required for this type of imaging.

Radiotherapeutic applications involve cell destruction. This requires that radionuclides decay by particle emission (α, β^-, Auger e^-), and usually have a half-life in the range of 1–10 days. The particular energies of the particle emitted during radioactive decay are dependent on the radiotherapeutic application, as is the half-life of the radionuclide. The reader is directed to several reviews on this subject by Volkert,[7] Troutner,[8] Srivastava,[9] and others.[10-13]

The availability and cost of the radionuclide are almost as important as the nuclear properties of the radionuclide for potential use in radiopharmaceuticals. For example, although ^{11}C (20 m, β^+) has potential utility for incorporation into diagnostic radiopharmaceuticals, it requires a cyclotron to prepare, and, because of its

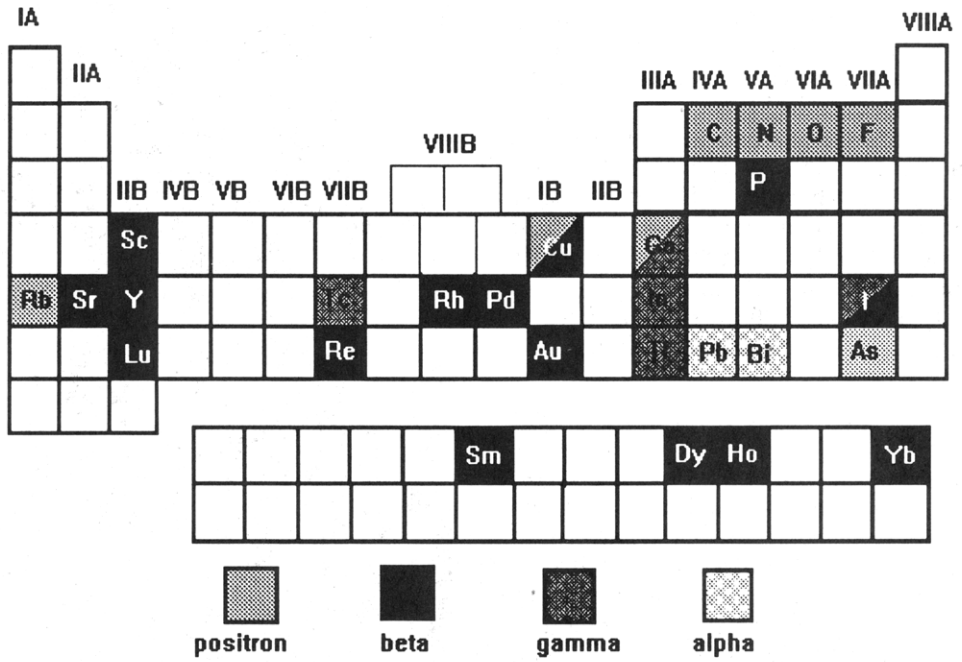


Figure 1. The radiopharmaceutical chemist's periodic table showing the most medically useful radionuclides. Split patterns indicate more than one type of radioisotope (e.g., iodine has both gamma- and beta-emitting radioisotopes).

short half-life, requires the cyclotron to be located at the hospital in which it will be used. In addition, the 20 min half-life requires very efficient and high yield incorporation of ^{11}C into the potential drug. Thus, the use of this radionuclide has been limited to research applications. In general, β^--emitting radionuclides are produced at nuclear reactors by neutron capture reactions and β^+-emitters are produced at cyclotrons or linear accelerators by charged particle reactions. The development of parent–daughter generator systems, in which a longer-lived parent decays to a shorter-lived daughter, has increased the availability of several radionuclides that would otherwise not receive such widespread use. A prime example of this is the 6-h γ-emitting ^{99m}Tc, a mainstay of diagnostic nuclear medicine. It is available from a generator containing 66-h ^{99}Mo, which is eluted every day for a constant supply of ^{99m}Tc. ^{99}Mo, as $^{99}MoO_4^{2-}$, is loaded onto an alumina column, which behaves in an anion exchange capacity. As the ^{99}Mo decays to ^{99m}Tc, $^{99m}TcO_4^-$ is eluted from the column with saline (0.15 M NaCl). The more highly charged $^{99}MoO_4^{2-}$ is retained on the alumina, providing a constant supply of essentially carrier-free ^{99m}Tc, which is then available for the preparation of technetium-based radiopharmaceuticals. Recently ^{82}Rb, a 76-s β^+-emitter available from a $^{82}Sr/^{82}Rb$ generator infusion system, became the first Food and Drug Administration (FDA) approved PET radiopharmaceutical. It is approved for use as a myoocardial perfusion agent,[14] and may in fact pave the way for the development and approval of PET radiopharmaceuticals that are based on generator available radionuclides. There are several potential generator systems in development which will allow for the routine use of positron-emitting diagnostic radionuclides and beta-emitting therapeutic radionuclides. Some of the generator systems with potential clinical utility are based on the following parent/daughter pairs: $^{188}W/^{188}Re$,[15,16] $^{62}Zn/^{62}Cu$,[17-20] $^{68}Ge/^{68}Ga$,[21,22] $^{90}Sr/^{90}Y$,[23,24] $^{115}Cd/^{115m}In$.[25]

Deutsch[26-29] and Davison[30-32] supplied the driving force that made coordination chemistry a vital component of radiopharmaceutical design with their contributions to the inorganic and radiopharmaceutical chemistry of technetium. The structural, chemical, and biochemical characterizations of many of the ^{99m}Tc radiopharmaceuticals approved for human use in the last five years or so is a clear demonstration of their influence. Their impact is witnessed in the continued development of the many potential diagnostic and therapeutic radiopharmaceuticals based on well-defined coordination compounds.

There continues to be much interest in the use of metal chelates in the field of nuclear medicine, and this area continues expanding to include new radionuclides and new applications. The last 10 years have produced excellent reviews discussing technetium chemistry,[28,30-44] technetium radiopharmaceuticals,[45-50] radiotherapeutic bone agents,[51-56] radiolabeled antibodies for diagnosis and therapy,[9,57-71] potential radionuclides for diagnosis and therapy,[7-14,61] and radiopharmaceuticals in general.[44,72,73] This review discusses the coordination chemistry that forms the basis for nuclear medicine applications of the FDA-approved radiopharmaceuticals that are in clinical use, and of the most promising diagnostic and therapeutic radiopharmaceuticals that are in various stages of development. Although we have attempted to be as complete as possible, we would like to apologize beforehand to those authors whose contributions we may have inadvertantly overlooked.

II. FDA-Approved Radiopharmaceuticals

A. Technetium-Based Radiopharmaceuticals

Diagnostic nuclear medicine relies heavily on the use of ^{99m}Tc because of its nuclear properties (6.02 h, $E\gamma$ 140 KeV), its availability from a $^{99}Mo/^{99m}Tc$ generator, and its relatively low cost. The main gamma emission, 140 KeV (89%), is of an energy such that the majority of it will be adsorbed by the thin NaI(Tl) crystals of the gamma cameras used for imaging.[6,42] ^{99m}Tc has no beta emissions, and emits only low-energy Auger electrons.

Its half-life is long enough to do the necessary chemistry to prepare the various radiopharmaceuticals, and yet it is short enough to minimize the radiation dose to the patient. In fact, some chemical form of ^{99m}Tc is used in more than 90% of the diagnostic scans performed in nuclear medicine departments in the United States.[74] Because ^{99m}Tc has such a short half-life and is used in nanomolar concentrations, its long-lived daughter ^{99}Tc (2.1×10^5 y, 0.292 MeV β^-) is used to investigate the chemistry of technetium. No stable isotopes of technetium exist, however, milligram quantities of ^{99}Tc can be handled safely if proper radiation safety procedures are followed.

The chemical properties of technetium are both a blessing and a curse. Its position in the middle of the second-row transition series imparts to it a very diverse chemistry. Many complexes of technetium are known, ranging in oxidation state from −1 to 7, having various coordination geometries (4–9), and a variety of ligands filling its coordination requirements (environment). This allows for specificity in targeting of radiopharmaceuticals containing ^{99m}Tc by designing the ligand system about the technetium. In some cases the ligand system (mostly organic) will determine the majority of chemical and physical properties of the complex which define its biological properties. For example, the technetium diphosphonate skeletal imaging agents are deposited on sites of actively growing bone because the diphosphonate ligand has a high affinity for actively growing bone. Since the diphosphonate ligand dictates the skeletal localization properties, any diphosphonate radiopharmaceutical (^{14}C, ^{32}P, ^{99m}Tc, ^{186}Re) will be taken up by bone.[53,75,76]

When the coordination characteristics of the Tc and the properties of the resultant complex dictate biological localization, the complexes are considered "technetium essential" radiopharmaceuticals. For example, lidocaine is an antiarhythmic drug known to accumulate in the heart. Lobert[77] serendipidously designed a class of ^{99m}Tc hepatobiliary imaging agents where the combination of the Tc and ligand in the complex formed accounts for specificity of uptake by the liver. Although the intent was to develop Tc compounds to be taken up by the heart, these complexes show only localization in the liver with no affinity for the heart.

A number of FDA-approved ^{99m}Tc radiopharmaceuticals are currently in use in nuclear medicine departments for assessing the status of organ function or morphology or for determining the pathological status of a patient. Figures 2 and 3 show typical diagnostic images obtained with ^{99m}Tc heart and brain radiopharmaceuticals. The small molecule ^{99m}Tc based radiopharmaceuticals that have been approved for human use in the last 5 years have been characterized both on the macroscopic ^{99}Tc level and on the nanomolar radiochemical or tracer level that is used for biological and clinical evaluation. Thus, the structures of the more recently approved radiopharmaceuticals are known. This is not true for the earlier radiopharmaceuticals, often because the chemistry on the macroscopic and tracer levels is different. Discussed below are the approved ^{99m}Tc radiopharmaceuticals, beginning with those of known chemical structure.

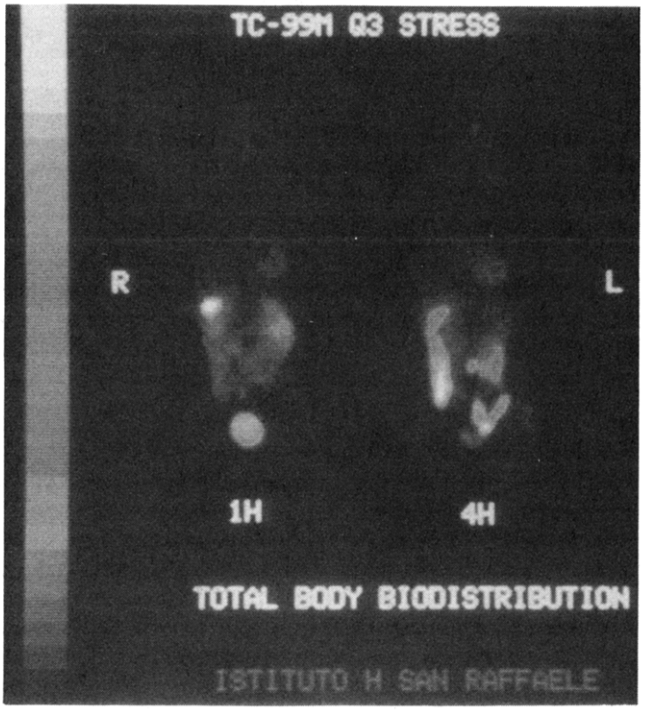


Figure 2. Whole body images taken 1 and 4 h after injection of a ^{99m}Tc myocardial perfusion radiopharmaceutical. The heart is clearly seen in the center of the chest. (These images were obtained from Dr. E. Deutsch, Mallinckrodt Medical.)

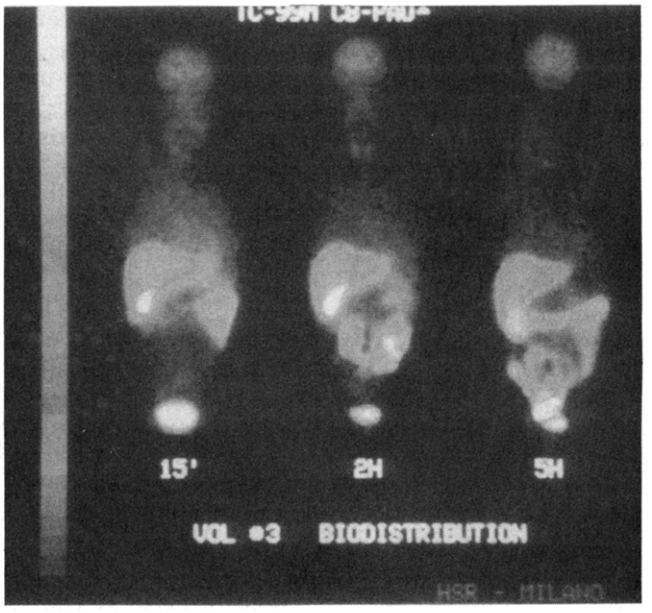


Figure 3. Whole body images of a ^{99m}Tc cerebral perfusion radiopharmaceutical taken 15 s and 2 and 4 h after injection; the brain is clearly visualized. (These images were obtained from Dr. E. Deutsch, Mallinckrodt Medical.)

1. ^{99m}Tc-*d,l*-HM-PAO

^{99m}Tc-*d,l*-HM-PAO (Ceretec, Amersham International; HM-PAO = hexamethyl propylene amine oxime; 3,6,6,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime) was the first technetium radiopharmaceutical completely characterized prior to FDA approval. This complex is approved as a cerebral perfusion imaging agent for evaluation of stroke. It is also claimed to be useful for evaluating various other cerebral diseases (hematomas, Alzheimer's disease, etc.), but it is not

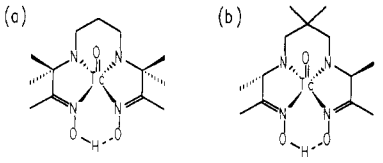


Figure 4. (a) TcO(PnAO) and (b) TcO(*d,l*-HM-PAO).

approved for these indications.[78-80] The development of this agent was based on work by Troutner,[81,82] who had synthesized and characterized TcOPnAO (PnAO = propylene amine oxime; 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime) and found that this neutral, lipophilic coordination complex (Figure 4a) is able to cross the intact blood–brain barrier (BBB) and be taken up by the brain in rat biodistribution studies.[83]

^{99m}TcOPnAO was found not only to diffuse across the intact BBB and be taken up by the brain, but also to diffuse back out of the brain with a half-life too short for imaging with conventional cameras.[84] Amersham synthesized a number of derivatives of PnAO in an attempt to develop a Tc(V) complex that would not only be taken up by the brain but would also be retained sufficiently long by the brain to allow for imaging. These efforts led to the development of TcO(*d,l*-HM-PAO) (Figure 4b).[85,86] The HM-PAO ligand loses two amine protons and an oxime proton on coordination to the Tc(V) monooxo core, resulting in a neutral complex.[87] Biodistribution studies show that ^{99m}TcO(*d,l*-HM-PAO) is retained in the brain significantly better than ^{99m}TcO(*meso*-HM-PAO).[88] ^{99m}TcO(*d,l*-HM-PAO) is taken up by the brain and then decomposes (or transforms) to a more hydrophilic species that is unable to diffuse back out of the brain.[89] Thus, brain retention is achieved with this complex. The *meso* analog undergoes this decomposition at a much slower rate and is, therefore, able to diffuse out of the brain, as does ^{99m}TcOPnAO. What role the *d,l* configuration of HM-PAO has in destabilizing the resultant Tc complex is not known. The Xray crystal structures of TcO(*d,l*-HM-PAO) and TcO(*meso*-HM-PAO) show them to be analogous to TcOPnAO.[87]

2. ^{99m}Tc-MAG$_3$

^{99m}Tc-MAG$_3$ (TechneScan MAG$_3$, Mallinckrodt) is marketed as a renal imaging agent. After intravenous (iv) injection, its passage into and through the kidneys is monitored to assess renal function. This tracer is rapidly excreted primarily by active tubular secretion. TcOMAG$_3^-$, mercaptoacetylglycylglycylglycinato-oxotechnetate(V), was developed by Fritzberg[90] as a renal agent. This particular complex shows good in vivo characteristics and, unlike earlier complexes studied, has no isomer problems associated with it since MAG$_3$ has no chiral centers. Previous work by Fritzberg[91-93] and Davison[93-95] with tetradentate diamide–dimercaptide ligands containing a carboxylic acid group on the carbon backbone yielded two isomers on complexation with Tc(V), one in which the carboxylate group is syn to the Tc=O bond and one in which it is in the anti configuration. The biological handling of the two isomers by the renal system was always found to be different, depending not only on the syn/anti configuration but also on the position of the carboxylate group on the ligand backbone.[96]

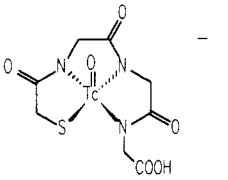


Figure 5. TcO(MAG$_3$)$^-$.

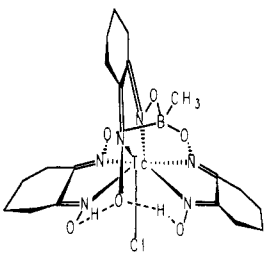


Figure 6. TcCl(CDO)(CDOH)$_2$BMe.

On coordination of MAG$_3$ to the Tc(V) center, the thiolate sulfur and the three amide nitrogens each lose their protons to yield an anionic complex.[97] The complex exhibits square-pyramidal geometry with the oxo group in the apical position, and the Tc(V) atom is situated above the plane containing the sulfur and the three amide nitrogens (Figure 5). The carboxylate group is not coordinated, even loosely, to the metal.[49] A free carboxylic acid group appears to be necessary for efficient renal excretion of an anion by the dianionic pathway, as was previously observed for iodohippuran and its analogs.[98]

3. ^{99m}Tc-teboroxime

^{99m}Tc-teboroxime (Cardiotec, Bristol-Myers Squibb) is a neutral, seven-coordinate technetium(III) complex marketed as a myocardial perfusion imaging agent that is useful in differentiating normal from ischemic and infarcted myocardium using rest and stress techniques for the evaluation of coronary artery disease.[99] Unlike other Tc myocardial perfusion agents that have been or are under development, this agent is neutral.

^{99m}Tc-teboroxime is a member of the BATO class (*b*oronic acid *a*dducts of *t*echnetium dioximes) of complexes and has the formula TcCl(CDO)(CDOH)$_2$-BMe (Figure 6), where CDOH$_2$ = cyclohexanedione dioxime.[100] The mechanism of myocardial uptake of this compound is unknown at this time. ^{99m}Tc-teboroxime is prepared by template synthesis whereby TcO$_4^-$, 3 equiv of 1,2-cyclohexanedione dioxime, and methyl boronic acid are reacted under acidic (HCl) reducing conditions.[99] The Tc(III) BATO complexes are interesting in that they are tris-dioxime metal complexes with the three dioxime ligands bound to the Tc(III) center in a trigonal configuration via the six nitrogens, but only one end of the molecule is capped by a boronic acid derivative.[100,101] The seventh ligand, chloride in the case of Tc-teboroxime, opens the angle between two of the dioximes to greater than the 120° expected with a trigonal arrangement of the three dioximes, making it impossible to cap the other end of the dioximes with a second boronic acid group.[102] The three uncapped oxime oxygens share two protons between them. The chloride ligand is labile under physiological conditions (pH 7.4, 37 °C, phosphate buffer) and undergoes chloro–hydroxy exchange with

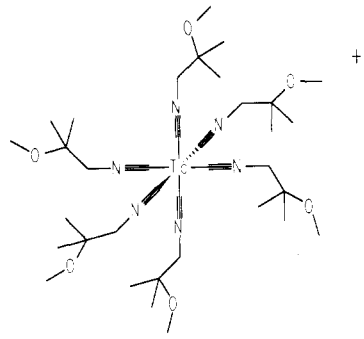


Figure 7. Tc[(2-methoxy-2-methylpropyl)isonitrile]$_6^+$.

a half-life of 13 min.[103] This chloro–hydroxy exchange does not affect the biological efficacy of ^{99m}Tc-teboroxime as a myocardial perfusion imaging agent since the first pass myocardial extraction is high (>90%)[99] and is achieved within a minute or two after injection. In addition, the blood clearance of this compound is rapid and the rate of myocardial washout is biphasic, with a fast component and a slow component.[104,105] Deutsch[27] has determined that the pK_a of the coordinated –OH group in Tc(OH)(CDO)(CDOH)$_2$-BMe is between 7 and 7.4, which suggests that there may be an equilibrium in vivo between Tc(OH)(CDO)-(CDOH$_2$)BMe and [Tc(OH$_2$)(CDO)(CDOH)$_2$BMe]$^+$. If this is the case, the retention of ^{99m}TcCl(CDO)-(CDOH)$_2$BMe may be affected by chloro–hydroxy exchange. The neutral BATO (Cl or OH) may be washed out of the heart, and the cationic OH$_2$-BATO may be the species that is retained in the heart. This behavior would be consistent with resuts Deutsch[27,106] reported for Tc(III)Cl$_2$(dmpe)$_2^+$/Tc(II)Cl$_2$(dmpe)$_2$ (dmpe = (dimethylphosphino)ethane) in which the cationic Tc(III) complex was reduced in vivo to the Tc(II) species and thus not retained in the heart.

4. ^{99m}Tc-sestamibi

^{99m}Tc-sestamibi (Cardiolite, duPont-NEN) is an octahedral, cationic technetium(I) complex that was developed as a myocardial perfusion imaging agent for evaluating the integrity of the myocardium (normal vs abnormal) in patients with suspected myocardial infarction. [Hexakis-2-methoxy-1,2-methylpropyl)isonitrile]technetium(I)]$^+$ is one member of the class of lipophilic hexakisisonitriletechnetium(I) cationic complexes developed as potential myocardial imaging agents (Figure 7).[108–110] Although this compound is a +1 cation, the hexakisisonitriletechnetium(I) complexes are not taken up by the myocardium by the Na-K-ATPase pump, as has been determined by challenge with K$^+$, oubain, etc.[111] Deutsch[112] hypothesized that lipophilic cationic complexes of technetium would be taken up by the myocardium, perhaps behaving as potassium ioin mimics. Several other lipophilic cationic complexes of technetium (e.g., TcCl$_2$(dmpe)$_2^+$)[113] have been studied as potential myocardial imaging agents, and some are currently under development.

The first complex of this class to show promising biological characteristics was Tc(*tert*-butylisonitrile)$_6^+$ (TBI), which was retained in the heart with a long half-life.[114] It suffered from high initial activity in the lungs and liver which precluded good myocardial images until at least 1 h after injection, by which time some redistribution of the activity in the heart had occurred.[114] Further development of this class of compounds, aimed to not only maintain high myocardial uptake and retention but rapid clearance from the nontarget tissues (blood, lungs, liver), led to derivatizing isonitriles with functional groups that would promote hepatobiliary clearance. Animal studies suggest that the methoxy group of the (2-methoxy-2-methylpropyl)-isonitrile of ^{99m}Tc-sestamibi is metabolized in the liver leading to more rapid clearance.[115] Reverse-phase HPLC analyses of guinea pig bile taken 15 min after injection of ^{99m}Tc-sestamibi showed seven new Tc-containing species of increasing hydrophilicity in addition to the parent ^{99m}Tc-sestamibi. The relative amounts of the seven species were consistent with the sequential metabolism of the methoxy group to a hydroxy group on the six identical isonitrile ligands of ^{99m}Tc-sestamibi.[115] The faster blood and lung clearance of this compound occurs because of greater hydrophilicity compared with Tc(*tert*-butylisonitrile)$_6^+$(TBI).[110,115] The development of this radiopharmaceutical is an example of utilizing in vivo biochemical processes to enhance the attributes of the first generation drug.

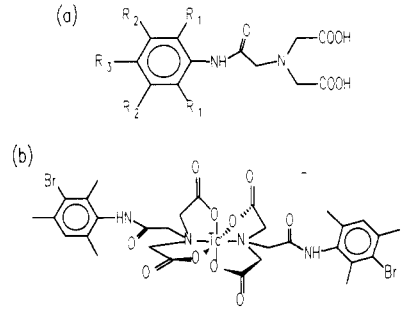


Figure 8. Part a shows the general structure for the HIDA ligand. Lidofenin: R_1 = CH_3, R_2 = R_3 = H. Disofenin: R_1 = isopropyl, R_2 = R_3 = H. Mebrofenin: R_1 = R_3 = CH_3, R_2 = H and Br. Part b shows the proposed structure of Tc^{III}(HIDA)$_2^-$, illustrated for Mebrofenin.

5. ^{99m}Tc-HIDA

^{99m}Tc-HIDA (HIDA = hepatobiliary iminodiacetic acid) compounds are a class of Tc(III) iminodiacetic acid derivatives that were shown by Loberg[116,117] to have biological characteristics that were suitable for imaging the hepatobiliary system (liver, gall bladder, bile duct, intestines). Currently, three ^{99m}Tc-HIDA analogs are on the market: ^{99m}Tc-Mebrofenin (Choletec, Bristol-Myers Squibb), ^{99m}Tc-Disofenin (Hepatolite, duPont-NEN), and ^{99m}Tc-Lidofenin (TechneScan HIDA, Mallinckrodt) (Figure 8a). All three of these agents are marketed as hepatobiliary imaging agents with similar behavior in normal individuals: ca. 13% of the injected dose (ID) is excreted in the urine within 2 h post injection (PI); peak liver uptake is observed between 10 and 15 min PI, with liver visualization occurring at ca. 5 min PI; hepatic duct and gall bladder visualization is observed between 10 and 40 min PI (depending on the agent), and intestinal activity is observed between 15 and 60 min PI.[118] In patients with hepatobiliary obstructions or dysfunction, greater urinary clearance, slow liver clearance, or no gall bladder visualization, etc., is observed depending on the disease.[118]

Loberg and Fields[119] demonstrated that the ligand to metal ratio in Tc-HIDA was 2:1, that the complex

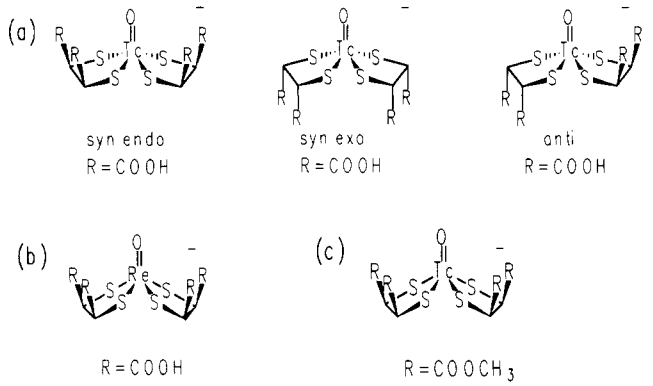


Figure 9. (a) The three possible isomers of $TcO(dmsa)_2^-$, syn-endo, syn-exo, and anti, (b) $ReO(dmsa)_2^-$, and (c) $TcO(1,2\text{-di(carboxymethyl)ethane-1,2-dithiolato})_2^-$.

did not contain Sn (which was present in the reaction as the reducing agent), and that the complex had an overall −1 charge. FAB mass spectral analyses reported by Davison[94] were consistent with Loberg's formulation of $[Tc(III)(HIDA)_2]^+$. Their results showed a molecular ion at $m/z = 685$ in the positive-ion FAB-MS consistent with the formulation $H_2[Tc(HIDA)_2]^+$ and at $m/z = 683$ in the negative ion FAB-MS consistent with $[Tc(HIDA)_2]^-$. A Tc(V) formulation of $TcO(HIDA)_2^-$ would also be consistent with the mass spectral data reported. A molecular ion at $m/z = 701/699$ for $TcO(HIDA)_2^-$ may be obscured by the intense $Sn(HIDA)_2^{2-}$ molecular ion cluster observed in this region. The absolute structure of the Tc-HIDA complexes remains unknown; if it is indeed a Tc(III) complex as suggested, it is undoubtedly an octahedral, bis-dianionic HIDA complex with the ligand coordinated to the Tc(III) center through the two imino nitrogens and the four deprotonated carboxylate oxygens (Figure 8b).

6. ^{99m}Tc-succimer

^{99m}Tc-succimer (MPI DMSA Kidney Reagent, MediPhysics) is marketed as an imaging agent for the evaluation of kidney morphology. This agent concentrates in the renal cortex after iv injection, with ca. 20% ID retained in each kidney at 6 h PI. Approximately 16% of the activity is excreted in the urine within 2 h PI.[120]

The formulation of ^{99m}Tc-succimer is $[TcO(dmsa)_2]^-$ where dmsa is dimercaptosuccinic acid (90:10 *meso*:*d,l* isomer in the marketed kit). Once coordinated to Tc(V), *meso*-dmsa can exhibit three possible isomer conformations, syn-endo, anti, or syn-exo orientation of the carboxylic acid groups with respect to the Tc=O bond (Figure 9a).[121] The presence of all three isomers has been observed for ^{186}Re-succimer and has been confirmed by chromatographic (HPLC) comparison to the macroscopically characterized $[Bu_4N][ReO(dmsa)_2]$.[122] Although no crystal structure analysis of the technetium complex has been done, *syn-endo*-$[Et_4N][ReO(dmsa)_2]\cdot 1.5H_2O$ (Figure 9b) has been structurally characterized and shows the complex in a square-pyramidal geometry, which is expected for five-coordinate monooxo complexes of both Tc(V) and Re(V).[121] Bandoli[123] reported the crystal structure of $(Bu_4N)[TcO(1,2\text{-di(carboxymethyl)ethane-1,2-dithiolato})_2]$, a $TcO(dmsa)_2^-$ analog, in which the methyl esters of the carboxylic acid groups were observed in the syn-endo conformation (Figure 9c). But as the authors clearly point out, this stereochemical orientation is the one that happens to crystallize on reaction with *meso*-1,2-dimercaptosuccinic acid dimethyl ester, in 21% yield.[123]

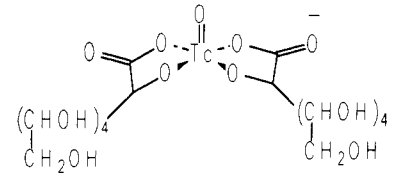


Figure 10. Proposed structure of $Tc^V(glucoheptonate)_2^-$.

7. ^{99m}Tc-gluceptate

^{99m}Tc-gluceptate (Glucoscan, duPont-NEN; TechneScan Gluceptate, Mallinckrodt) is approved for imaging the kidneys and brain lesions and to assess renal and brain perfusion. This agent is rapidly cleared from the blood after iv injection, with 40% of the activity excreted in the urine in the first hour and 70% excreted by 24 h. Up to 15% ID is retained in the kidneys, with greater retention in the cortex than in the medulla, giving information on kidney morphology.[120] ^{99m}Tc-gluceptate and ^{99m}Tc-succimer are used for the same types of diagnostic studies. Neither of these agents are used very often anymore because of the better resolution offered by other imaging modalities. In particular, ultrasound and magnetic resonance (MR) imaging have proven more useful for morphologic studies and do not require the use of radiolabeled drugs.

^{99m}Tc-gluceptate is believed to be a Tc(V) species with glucoheptonate as the ligand(s) (Figure 10). The structure of this compound is not known, although de Kievet[124] has shown that in the presence of excess glucoheptonate more than 1 equiv of Sn(II) per ^{99}Tc does not yield any more of the Tc-glucoheptonate complex, indicating that the Tc is being reduced from Tc(VII) (as TcO_4^-) to Tc(V). Infrared and Raman spectra of the Tc-glucoheptonate complex are consistent with the formulation of a Tc(V) monooxo core (970 and 975 cm^{-1}, respectively). Titrations with glucoheptonate and NMR studies suggest that two glucoheptonate molecules may be bound to each Tc through the carboxylate oxygen and one of the hydroxyl oxygens. The glucoheptonate titration studies, however, were not run at a controlled pH nor were appropriate control studies run with the glucoheptonate ligand (i.e., at different pH values) for the NMR experiments. Thus, the formulation of $TcO(glucoheptonate)_2^-$ remains to be confirmed. This complex is a relatively weak complex, as are, for example, $TcO(citrate)^-$ and $TcO(ethylene\ glycol)_2^-$, and requires the presence of excess ligand to remain complexed.[41] As with Tc-citrate, Tc-glucoheptonate is often used as a donor Tc(V) complex that can be utilized in ligand exchange experiments to synthesize other Tc(V) complexes that are more thermodynamically stable but may be kinetically slow to form. The use of this chelate and others slows down the disproportionation reaction of Tc(V) to form TcO_2 and TcO_4^- in aqueous media. ^{99m}Tc-glucoheptonate is potentially useful in this capacity, since it is available as an approved lyophilized sterile radiopharmaceutical kit formulation.

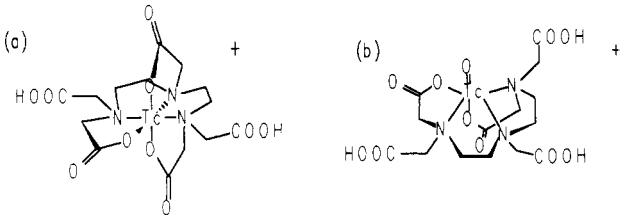


Figure 11. (a) Proposed structure of $Tc^{IV}DTPA^+$, the two free carboxylate groups are shown protonated (at pH 7.4 they are deprotonated), and (b) proposed structure of $Tc^{V}DTPA^+$, the three free carboxylate groups are shown protonated (at pH 7.4 they are deprotonated).

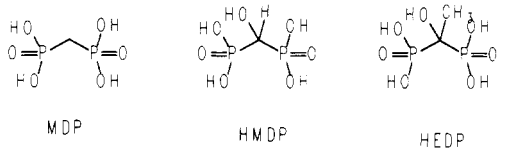


Figure 12. Diphosphonate ligands: MDP, HMDP, HEDP.

8. ^{99m}Tc-penetate

^{99m}Tc-penetate (AN-DTPA, Syncor International; MPI DTPA Kit, MediPhysics; Techniplex, Bristol-Myers Squibb; DTPA, duPont-NEN) is approved for kidney imaging, brain imaging, to assess renal perfusion, and to estimate the glomerular filtration rate. ^{99m}Tc-penetate is still used for renal imaging, although ^{99m}Tc-MAG_3 has claimed some of this market.

Technetium in ^{99m}Tc-penetate or ^{99m}Tc-DTPA is postulated to be in the +4 or +5 oxidation state (DTPA = diethylenetriaminepentaacetic acid).[125] The chemistry of Tc with polyaminecarboxylates is very complex. On the macroscopic level, primarily dimers containing Tc in the +3, +4 and/or +5 oxidation states have been observed in reactions with ^{99}Tc and aminecarboxylates.[42] Under the reaction conditions present in the ^{99m}Tc-penetate kit ($SnCl_2$ as the reductant, pH 1.5–2 with HCl, DTPA), Eckelman[126] reported the oxidatioin state of Tc in this radiopharmaceutical to be +4. To date, no structural characterization of this complex has been accomplished. The DTPA ligand is undoubtedly coordinated in a hexadentate fashion about the Tc(IV) through the three nitrogens and three carboxylate oxygens, leaving two uncoordinated carboxylate groups (Figure 11a). Deutsch and Packard,[127] however, observed three uncoordinated carboxylates on the complex by titration with base, suggesting the technetium may be in the +5 oxidation state. If Tc(V) is correct, then a 6-coordinate complex would be present with a carboxylate in the position trans to the Tc=O group (Figure 11b).

9. Bone Imaging Agents

Technetium phosphate and phosphonate complexes have been and are being used as bone imaging[53,56] and myocardial infarct imaging[128] agents. Three different diphosphonate ligands complexed with ^{99m}Tc are used as skeletal imaging agents (Figure 12). The three agents have different substituents on the α-carbon between the two phosphorus atoms. Two of the diphosphonates have a hydroxyl functionality on the α-carbon. All three of these complexes localize in bone due to the affinity of the coordinated diphosphonate ligand for calcium in actively growing bone.[129] The diphosphonate ligands

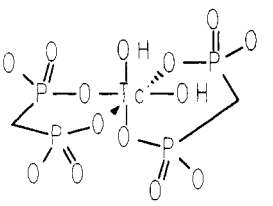


Figure 13. Coordination sphere of one Tc atom in the 1:1 polymer of Tc-MDP. The two OH groups shown bridge the Tc atom to two other Tc atoms. Each diphosphonate is coordinated to two Tc atoms.

can be considered as doubly bidentate or bidentate–tridentate ligand systems, depending on the ligand substituents, with the ability to complex two metals simultaneously. This feature was shown to indeed be reasonable from results of Ca^{2+} binding studies with metal-coordinated diphosphonate ligands.[130] Equilibrium binding values for Ca^{2+} with $[(en)_2Co(diphosphonate)]^+$ ranged from 0.2 to 250 × 10^4 M^{-1}, with the order of affinity for Ca^{2+} being consistent with the efficacy of the Tc-diphosphonate bone agents.

^{99m}Tc-MDP. ^{99m}Tc-MDP (AN-MDP, Syncor International; Osteolite, duPont-NEN; Technescan-MDP, Mallinckrodt; MPI MDP Kit, MediPhysics; MDP-Squibb, Bristol-Myers Squibb; Amerscan-MDP, Amersham International; MDP = methylenediphosphonate) is marketed as a skeletal imaging agent to delineate areas of altered osteogenesis. During the initial 24 hours after injection, the ^{99m}Tc-MDP that is not retained in the skeleton is renally excreted. Tc-MDP is believed to be a Tc(IV) complex that has a high affinity for sites of actively growing bone.[47,53] This radiopharmaceutical is believed to be a mixture of oligomers and polymers, especially at the macroscopic level.[53,131,132] The only Tc-MDP structure, reported by Deutsch,[133] shows it to be a 1 to 1 polymer in which each Tc atom is bound to two diphosphonate ligands and each diphosphonate is coordinated to two Tc centers (Figure 13). Although the oxidation state of the Tc cannot be definitively assigned because the degree of protonation of the Tc–O–Tc bridge cannot be determined from the crystal structure, it is most likely Tc(IV).

^{99m}Tc-HMDP. ^{99m}Tc-HMDP (Osteoscan-HDP, Mallinckrodt; HMDP = hydroxymethylenediphosphonate) is another diphosphonate skeletal imaging agent. Its chemistry is analogous to that of ^{99m}Tc-MDP, with the major difference being the hydroxyl substituent on the α-carbon of the diphosphonate. This would allow for tridentate binding to calcium in actively growing bone. This agent shows faster blood clearance and higher skeletal uptake than ^{99m}Tc-MDP.[129] Another diphosphonate bone agent that is approved for use in Europe is ^{99m}Tc-DPD (1,3-dicarboxypropane diphosphonate).

^{99m}Tc-pyrophosphate. Originally, technetium complexes with polyphosphates and pyrophosphate were used as skeletal imaging agents. The in vivo instability of the P–O–P bond to enzyme hydrolysis led to the development of the diphosphonates, which have an enzyme stable P–C–P linkage. Although still approved, the P–O–P type compounds are no longer used for skeletal imaging because of the improved efficacy of the diphosphonates. ^{99m}Tc-pyrophosphate (Techne-Scan PYP, Mallinckrodt; Pyrolite, duPont-NEN; Phosphatec, Bristol-Myers Squibb) is used for imaging myocardial infarcts. Pyrophosphate is known to ac-

cumulate in infarcted heart muscle. The mode of action is believed to be binding of the pyrophosphate ligand to calcium deposits in the infarct,[128] which is similar to the binding of diphosphonates to sites of actively growing bone. Even though diphosphonates also localize in infarcted tissue, the efficacy of ^{99m}Tc-pyrophosphate for this application is considered to be superior.

10. ^{99m}Tc-particulates

The ^{99m}Tc radiopharmaceuticals discussed up to this point are discrete molecules or complexes, even if their absolute identity is not known. There is a class of ^{99m}Tc radiopharmaceutical complexes of large molecules, colloids, or microspheres that are used to assess disease state or function in patients by taking the advantage of the biological distribution of these particles in vivo. The particle size, not the molecular composition, determines the biological fate of these molecules.

Particle sizes greater than 10–15 μm (but <100 μm) in size are trapped in the lung capillaries by a purely mechanical process, and thereby can be used to evaluate pulmonary lung perfusion.[134] ^{99m}Tc-MAA (macroaggregated albumin) is marketed for this purpose (AN-MAA, Syncor International; Pulmolite, duPont-NEN; Technescan MAA, Mallinckrodt; Macrotec, Bristol-Myers Squibb; MAA, MediPhysics).

Particle sizes below 1–10 μm in size are taken up by the reticuloendothelial system of the liver (primarily 0.3–1-μm particles), spleen (mainly >1-μm particles), and bone marrow (predominantly <0.1-μm particles).[135,136] In normal individuals, 80–90% of the reticuloendothelial (RE) cells are located in the liver, 5–10% in the spleen, and the remainder in the bone marrow. ^{99m}Tc-albumin colloid (Microlite, duPont-NEN) and ^{99m}Tc-sulfur colloid (AN-Sulfur Colloid, Syncor International; TechneColl, Mallinckrodt; Technetium Tc99m TSC, MediPhysics; Tesuloid, Bristol-Myers Squibb) are both used for this purpose.

The structures of ^{99m}Tc-MAA and ^{99m}Tc-albumin colloid are obviously not known, however, the coordination chemistry is believed to involve binding of reduced disulfide groups of the albumin to Tc in a reduced oxidation state (probably Tc(V) based on the chemistry of Tc-thiolates[137]). These radiopharmaceutical formulations are designed strictly to control the particle size of the product.

^{99m}Tc-sulfur colloid in the radiopharmaceutical preparations is most likely a colloid of the chemical form $Tc_2S_7 \cdot xS$, where sulfur colloid is tagged with Tc_2S_7. Steigman[138] has shown that the ratio of Tc to S is very dependent on the pH conditions, the source of sulfur, and the temperature of the reaction. They suggest that reduced Tc is the nucleation site for the formation of the colloid, although the nanomolar concentration of ^{99m}Tc makes elemental sulfur the more likely candidate to form colloid and coprecipitate Tc_2S_7.

11. ^{99m}Tc-Labeled Red Blood Cells (RBC)

Red blood cells can be labeled with ^{99m}Tc using either an in vitro method (Ultratag, Mallinckrodt) or an in vivo method (^{99m}Tc-pyrophosphate kit, reconstituted without ^{99m}Tc). ^{99m}Tc-RBCs are used for blood pool imaging, studying ventricular functioning of the heart, detecting gastrointestinal hemorrhages, and, when denatured, ^{99m}Tc-RBCs are used, for spleen imaging.[128,139]

Both labeling methods are based on the fact that stannous and pertechnetate ions are able to diffuse into RBCs. Once inside the RBCs, Sn remains reduced (Sn(II)), presumably by interaction with intracellular sulfhydryl groups. Subsequent addition of $^{99m}TcO_4^-$ results in intracellular stannous reduction of the pertechnetate and binding of the reduced Tc to the β-chain of the globin unit of hemoglobin.[140] Labeling yields of ca. 95% are observed.

The in vitro RBC labeling method is based on a modified Brookhaven Kit.[128,140–142] The method involves incubation of whole blood with stannous ion, followed by oxidation of any extracellular Sn^{2+} to Sn^{4+} with dilute hypochlorite. Since Sn^{2+} in the serum will reduce $^{99m}TcO_4^-$, the serum stannous ion must be oxidized to prevent reduction of the pertechnetate before it is able to diffuse into the RBCs. The RBCs are then labeled by the addition of $^{99m}TcO_4^-$, which diffuses into the RBC where it is reduced by intracellular Sn^{2+}. These labeled RBCs are reinjected into the patient for subsequent imaging studies.[128]

The in vivo RBC labeling procedure is based on the same mechanism as the in vitro method. A sterile solution of stannous pyrophosphate is intravenously injected. After allowing 30 min for the biological clearance of extracellular stannous pyrophosphate, $^{99m}TcO_4^-$ is injected. The RBC labeling yields are again about 95%.[128] Once the ^{99m}Tc-RBCs have equilibrated with the blood pool, imaging is performed.

12. $^{99m}TcO_4^-$

$^{99m}TcO_4^-$ (available directly from the ^{99}Mo/^{99m}Tc generator; duPont-NEN; Mallinckrodt; MediPhysics) is itself an FDA-approved radiopharmaceutical used for thyroid imaging, in addition to being the source of ^{99m}Tc in the radiopharmaceutical preparations described above. $^{99m}TcO_4^-$, like perchlorate, is an iodide mimic and is taken up by the thyroid.

B. Non-Technetium-Based Radiopharmaceuticals

Several approved radiopharmaceuticals are coordination compounds not based on technetium. Those approved are all diagnostic agents, but not all are imaging agents. The use of some of these radiopharmaceuticals has been superceded by ultrasound and magnetic resonance imaging methods, the anatomical resolution of which is much better than SPECT or planar imaging.

1. ^{201}Tl

^{201}Tl, as the thallous ion, (Thallous chloride Tl 201, duPont-NEN; Mallinckrodt; MediPhysics) is approved for use as a myocardial perfusion agent for assessing the integrity of the myocardium using stress and rest techniques. Although ^{201}Tl is technically not a coordination compound, it is probably the most important radiopharmaceutical in nuclear medicine, having been routinely used since ca. 1975. $^{201}Tl^+$ accumulates in viable myocardium via the Na-K-ATPase pump, behaving as a K^+ mimic. Clinical images show infarcted regions of the heart as "cold" or nonlabeled regions.

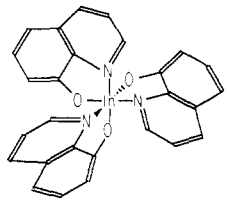


Figure 14. Proposed structure of $In(oxine)_3$.

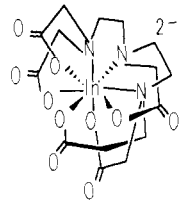


Figure 15. Eight-coordinate $In(DTPA)^{2-}$.

The less than optimal nuclear properties of ^{201}Tl (73 h, 65–83 KeV X-rays) for imaging will eventually result in the replacement of $^{201}Tl^{+}$ by a suitable ^{99m}Tc heart imaging agent.

2. ^{111}In-oxine

^{111}In-oxine (Indium In 111 Oxyquinoline Solution, Amersham International) is approved for the labeling of leukocytes (white blood cells) which are used for imaging sites of infection or inflammation.[143] The precise structure of the complex is unknown, although the empirical formula is accepted to be In(oxyquinoline)$_3$. It is a neutral and lipid soluble complex (Figure 14) that is able to penetrate the cell membrane.[143] Once inside the cell, the In is displaced from the oxyquinoline complex (K ca. 10)[144] and becomes firmly attached to cytoplasmic components, thus trapping the ^{111}In. The leukocytes are labeled in vitro with ^{111}In and then reinjected into the patients for imaging studies.

3. ^{111}In-DTPA

^{111}In-DTPA (MPI Indium DTPA In 111, MediPhysics) is used for radiographic cisternography studies (evaluation of cerebral spinal fluid pathways).[145] The DTPA is chelated to the In^{3+} center through three nitrogens and all five carboxylate oxygens, resulting in an eight-coordinate complex (Figure 15).[146] The molecule has an overall −2 charge. Martell has determined the stability of InDTPA to be very high (K_{LM} 29.0 at pH 7.4).[147]

3. ^{67}Ga-citrate

^{67}Ga-citrate (Neoscan, MediPhysics; Gallium Citrate Ga 67 Injection, Mallinckrodt; Gallium Citrate Ga 67 Injection, U.S.P., duPont-NEN) has been found to concentrate in certain viable primary and metastatic tumors as well as focal sites of infection.[143] The mechanism of concentration is unknown, although ^{67}Ga accumulates in lysosomes, being bound to intracellular protein.[143] The structure of this compound is not known, although the empirical formula is Ga(citrate-(3−)), presumably with three waters filling the remaining coordination sites (Figure 16).[143] This is a weak chelate, and as soon as it is injected into the blood stream the ^{67}Ga is transchelated to transferrin. Ga^{3+} mimics the ferric ion in its binding to molecules in serum, however,

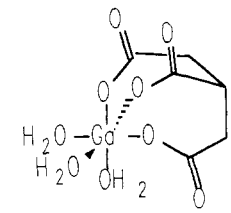


Figure 16. Proposed structure of Ga-citrate.

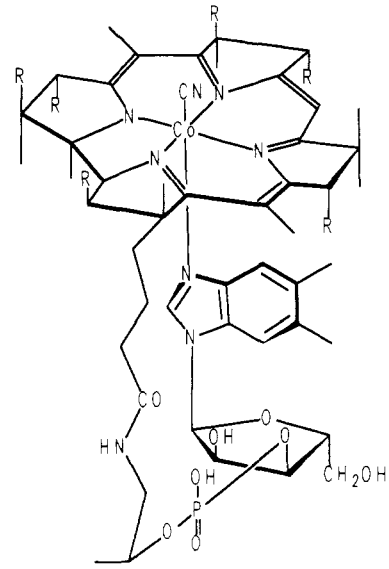


Figure 17. Cyanocobalamin, vitamin B_{12}; the groups R are not shown, for clarity.

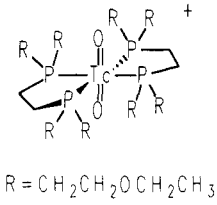
gallium is not reduced in vivo and does not become incorporated into hemaglobin.[143]

4. ^{51}Co-cyanocobalamin

^{57}Co-cyanocobalamin (Rubratope-57, Bristol-Myers Squibb; Cyanocobalamin Co57 Capsules, Mallinckrodt) is used for the diagnosis of pernicious anemia and as an adjunct in the evaluation of other defects of intestinal vitamin B_{12} absorption.[148] The drug is orally administered and allowed to be absorbed by the gastrointestinal system, and then the total ^{57}Co activity in the urine is monitored for 24 h. Since ^{57}Co has a 270.9 day half-life, the radiation dose to the patient is minimized by administration of less than 1 μCi of ^{57}Co. This is too low of a dose for imaging even though the gamma energies (122.1 KeV (85.5%), 136.5 KeV (10.6%)) are suitable for gamma camera imaging. Cyanocobalamin is an octahedral Co(III) complex with a macrocyclic corrin (porphyrin-like) ligand in the equatorial plane and a cyano group and an adenosyl imidazole nitrogen from a chelate arm of the corrin ligand bound in the two axial positions (Figure 17). This is one of the few metal containing radiopharmaceuticals in which an exact copy of the native molecule is used as the drug. In this agent, ^{57}Co is isotopically substituted for nonradioactive Co in the vitamin B_{12} molecule.

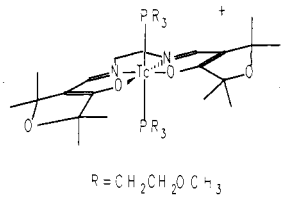
5. $Na^{51}CrO_4$

$Na^{51}CrO_4$ (Chromitope Sodium, Bristol-Myers Squibb; Sodium Chromate Cr 51 Injection, Mallinckrodt) is marketed for the determination of red blood cell (RBC) volume or mass, the study of RBC survival time, and the evaluation of blood loss in patients.[149] RBCs are



R = $CH_2CH_2OCH_2CH_3$

Figure 18. $TcO_2(P53)_2^+$.



R = $CH_2CH_2OCH_3$

Figure 19. Tc-Q12.

labeled in vitro by incubation with $^{51}CrO_4^-$, which is able to penetrate the RBC and become attached to hemoglobin. This step involves reduction of Cr(VI) to Cr(III). Once the RBCs are labeled, they are injected back into the patient, allowed to equilibrate with the patient's blood, and samples are then withdrawn for the appropriate study. The 27.7 day half-life of ^{51}Cr limits the injected dose to less than 200 μCi for a 70 kg man and thus, this radiopharmaceutical is not used for imaging.

6. ^{169}Yb-DTPA

^{169}Yb-DTPA, like ^{111}In-DTPA, is approved for use in radiographic cisternography studies. Its structure is not known, but the Yb is most likely complexed to the DTPA through the three amine nitrogens and at least three carboxylate oxygens. No structural determination has been performed, and whether the coordination number is 6 or more is not known.

III. Potential Radiopharmaceuticals

A. Diagnostic Perfusion Agents

Although ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime were recently approved by the FDA in 1991 as myocardial perfusion agents, neither of them is the ideal agent. Two new compounds are in phase II/III clinical trials as potential myocardial perfusion agents: ^{99m}Tc-tetrofosmin (Amersham International) and ^{99m}Tc-Q12 (TechneCard, Mallinckrodt). Both complexes are +1 cationic species with phosphines coordinated to the metal.

Tc-tetrofosmin is a *trans*-dioxotechnetium(V) complex with two bidentate phosphine ligands (1,2-bis(bis-(ethoxyethyl)phosphino)ethane); P53) bound to the metal. The structure of the complex is close to octahedral in geometry, with the formulation being $TcO_2(P53)_2^+$ (Figure 18).[150] This compound exhibits rapid lung and liver clearance on injection and good myocardial uptake.[151]

Tc-Q12 is an octahedral Tc(III) complex with a tetradentate Schiff base ligand occupying the equatorial plane and two monodentate tertiary phosphine ligands in the axial sites. The Schiff base ligand is 1,2-bis-[[(dihydro-2,2,5,5-tetramethyl-3(2*H*)-furanonato)methylene]amino]ethane and the phosphine ligands are tris(3-methoxy-1-propyl)phosphine (Figure 19).[152] The ether linkages on the backbone of the Schiff base ligand

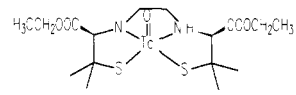


Figure 20. TcO(L,L-ECD).

and the phosphines serve to reduce in vivo protein binding by increasing hydrophilicity. In addition, the incorporation of the furanone moiety into the Schiff base backbone serves to stabilize the complex.[153] This results in rapid blood, lung and liver clearance allowing for good myocardial images.[154] This nonreducible, cationic Tc(III) complex resulted after studies by Deutsch[27,107] showed that the class of Tc(III) complexes, $TcX_2(L)_2^+$ (X = halogen; L = diphosphine), are taken up by the myocardium. The cationic Tc(III) complex is reduced to the neutral Tc(II) complex which washes out of the heart. The Re(III) analogs, whose reduction potentials are not accessible in vivo (ca. 200 mV more difficult to reduce), are taken up by the myocardium and retained.[27,107] Almost 1 V, positive or negative, is required to oxidize or reduce Tc(III)(Schiff base)-(phosphine)$_2^+$ complexes, making them inaccessible to in vivo redox processes.[155]

1. ^{99m}Tc-L,L-ECD

^{99m}Tc-L,L-ECD (Neurolite, duPont-NEN; ECD = ethylcysteine dimer) is a potential cerebral perfusion imaging agent that is in phase III clinical trials; FDA approval is anticipated sometime in 1993. ^{99m}Tc-L,L-ECD is a neutral, lipophilic Tc(V) complex with a monooxo core and L,L-ethylcysteine dimer bound to the metal via two amine nitrogens and two thiolate sulfur atoms (Figure 20). Two thiolate sulfurs and one of the amine nitrogens are deprotonated on coordination to the Tc(V) center, resulting in a neutral complex. Development of this $TcON_2S_2$ (where N_2S_2 is a diaminedithiol ligand) radiopharmaceutical is in part due to the efforts of Kung[156-158] and Lever[159-161] to synthesize, characterize, and understand the chemistry and biochemistry of a variety of $TcON_2S_2$ complexes and the properties necessary for brain retention. ^{99m}Tc-L,L-ECD is able to penetrate the blood–brain barrier (BBB) and is retained in the brain by ester hydrolysis.[162-164] One of the two ester substituents undergoes enzymatic hydrolysis in the brain to give the free acid group, which is sufficient to trap the complex in the brain, since this newly formed charged species is unable to diffuse back across the BBB. This hydrolysis is stereospecific; only the complex with the L,L enantiomer of ECD is trapped. The D,D enantiomer is not trapped.

2. ^{62}Cu-PTSM

The development of the ^{62}Zn/^{62}Cu generator[17-20] makes available the positron-emitting radionuclide ^{62}Cu and increases the potential utility of ^{62}Cu-PTSM [PTSM = pyruvaldehyde bis(4-methylthiosemicarbazone)] as a perfusion tracer for use with PET imaging devices (Figure 21a).[165-167] This neutral and lipophilic complex has been found to distribute as a "chemical microsphere" rather than a freely diffusible tracer on injection. A radiotracer that distributes as a true microsphere would allow the quantitation of regional blood flow as in myocardial or cerebral perfusion studies. Green[168] has reported an elegant study which elucidates the mechanism of the microsphere-like retention of Cu-

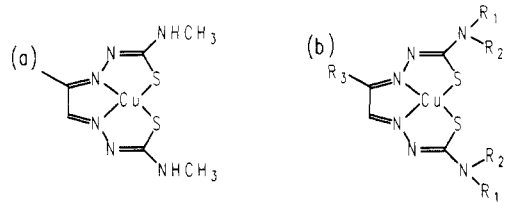


Figure 21. (a) Cu(PTSM) and (b) Cu[bis(thiosemicarbazone)], where R_1 = H or CH_3, R_2 = H or CH_3, and R_3 = CH_3.

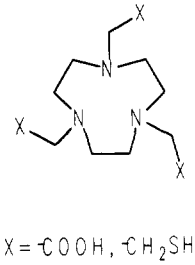


Figure 22. N_3X_3 ligand system, where X = S, O.

(II)-PTSM. A series of Cu(II)bis(thiosemicarbazone) complexes (Figure 21b), in which the substituents R_1, R_2, and R_3 were varied, clearly demonstrates that the retention mechanism of Cu(II)-PTSM in various tissues is intracellular glutathione reduction of the neutral Cu(II) complex to the Cu(I) anion, which is then bound intracellularly. The reduction potential of glutathione lies between those of the mono- and disubstituted bis(N^4-methylated thiosemicarbazone)Cu(II) complexes. The disubstituted derivatives are not retained intracellularly and do not show microsphere-like properties in vivo. Rather they behave as freely diffusible tracers. This is consistent with the resistance of Cu(II)bis(4,4-dimethylthiosemicarbazone) to intracellular reduction.[168] Glutathione is abundant in mammalian cells, being present in millimolar concentrations in the cells but only micromolar concentrations in plasma,[169-171] resulting in relatively rapid blood clearance and only intracellular retention of the Cu(I). Cu-PTSM is taken up and retained in practically all tissues. It has potential for myocardial and cerebral perfusion imaging, as well as determining regional blood flow to tissues.[165,168]

3. Gallium

The availability of the positron-emitting ^{68}Ga (68 min) from a ^{68}Ge/^{68}Ga generator increases the utility of this radionuclide for PET imaging because it removes the need for an on-site cyclotron.[22] In addition, ^{67}Ga (3.25 days, 93 KeV γ) is useful for immunoscintigraphy. The potential transchelation of Ga(III) complexes in vivo by transferrin (log K Ga-transferrin 20.3)[172,173] requires that kinetically inert complexes of Ga(III) be developed for radiopharmaceutical applications.

Martell,[174] Welch,[175] and Parker[173] have demonstrated that Ga(III) complexes with very high in vitro and in vivo stability are formed with hexadentate N_3X_3 ligands (X = S, O) (Figure 22) that essentially encapsulate the metal and insulate it from competing ligands. Transferrin is, in fact, unable to extract Ga(III) from Ga(TX-TACNH$_3$) (TX-TACNH$_3$ = 1,4,7-tris(3,5-dimethyl-2-hydroxybenzyl)-1,4,7-triazacyclononane).[175]

Martell[147,176] has shown that another class of hexadentate ligands having the N_2O_4 donor set (Figure 23) form very stable complexes with M(III) ions (M = Ga, In, Fe). log K_{ML} values of ca. 36 have been measured for all three metals with the ligand PLED (PLED = *N,N'*-bis(hydroxypyridyl)ethylenediamine-*N,N'*-diacetic acid).[147] Martell points out that stability constants by themselves do not provide a measure of the stability of these complexes to loss of the metal to other sequestering agents. He suggests that the conditional stability constant, or the pM value, determined at pH 7.4 is a much better measure of the in vivo stability of a potential radiopharmaceutical. The pM value accounts for ligand basicity, chelate protonation and hydrolysis, dilution effects, and metal–ligand stoichiometries. These conditional stability values may provide a more accurate measurement for comparing potential radiopharmaceuticals under physiologicial conditions.

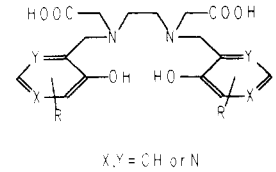


Figure 23. N_2O_4 ligand system, where either X or Y = N and R is any of a variety of substituents.

B. Phosphonate Complexes of ^{186}Re and ^{153}Sm for Radiotherapy

Phosphonates have a high affinity for sites of actively growing bone, as has been demonstrated by the diagnostic utility of ^{99m}Tc-diphosphonates for skeletal imaging (vide infra). This led to the investigation of ^{186}Re and ^{153}Sm phosphonate complexes as potential therapeutic radiopharmaceuticals for the palliation (or relief) of pain in patients with metastatic bone cancer. The β^--emitting radionuclides ^{186}Re and ^{153}Sm have nuclear properties suitable for therapeutic applications [^{186}Re, 90.64 h, 1.07 MeV β^- (77%), 0.934 MeV β^- (23%), 137 KeV γ (9.2%); ^{153}Sm, 46.27 h, 0.805 MeV β^- (20%), 0.710 MeV β^- (49%), 0.640 MeV β^- (30%), 103 KeV γ (29.8%)]. These properties are considered appropriate for palliative treatment of bone pain (1–5-day half-life, 0.5–1 MeV β^-, low % of γ emission to observe the in vivo distribution).[53]

Deutsch extended the chemistry of the Tc-diphosphonate bone agents to rhenium,[43] the third-row congener of Tc in group VIIB. Deutsch[43] showed, using various chromatographic methods, that like the ^{99m}Tc-diphosphonates, ^{186}Re-HEDP (HEDP = hydroxyethylidinediphosphonate) is a complicated mixture of species. The anion exchange HPLC analyses of ^{186}Re-HEDP are analogous to those of the carrier-added $^{99/99m}$Tc-HEDP.[177] The biolocalization of ^{186}Re-HEDP is also very similar to that of ^{99m}Tc-HEDP.[131,132] However, Re-HEDP is more readily oxidized to ReO_4^- in vivo than is Tc-HEDP, and this leads to an increase in the abnormal to normal bone uptake ratio with time because ReO_4^- is washed off of the bone and excreted.[56,177] This is beneficial from the radiotherapeutic standpoint because it reduces the radiation dose to normal tissue. The structure of Re-HEDP is not known, but it is undoubtedly a mixture of oligomeric and polymeric species with HEDP bound to Re through the phosphonate oxygens, as was found for the ^{99m}Tc-diphosphonate bone agents (vide infra).

A tetraphosphonate ligand, EDTMP [ethylenediamine-*N*,*N*,*N*′,*N*′-tetrakis(methylenephosphonic acid)], complexed with ^{153}Sm shows in vivo localization comparable to the ^{99m}Tc-diphosphonate bone agents.[51,52,178] Figure 24 shows the similarity of localization of the diagnostic ^{99m}Tc-MDP bone imaging agent and the radiotherapeutic ^{153}Sm-EDTMP agent in a patient with metastatic bone cancer. Although the structure of ^{153}-Sm-EDTMP has not been determined, the complex has been isolated on the macroscopic level as the analytically pure Rb^+ salt, $Rb_5[Sm(EDTMP)]\cdot 3H_2O$. Elemental, NMR, and FAB-MS analyses are consistent with this formulation. The coordination number of Sm in this complex is at least 6, although the coordination status of the three waters is not known (Figure 25).[179] Ion exchange chromatography and HPLC indicate the presence of a single species in solution at both macroscopic and radiochemical concentrations.[52] The predominant species in solution at physiological pH appears to be the completely deprotonated complex, $Sm(EDTMP)^{5-}$, with a smaller percentage of the monoprotonated complex, $Sm(HEDTMP)^{4-}$.[52] The Sm is presumably complexed to EDTMP through the two amine nitrogens and the oxygens from all four phosphonate groups, with possible involvement of the three water molecules.

Both ^{186}Re-HEDP and ^{153}Sm-EDTMP are currently in phase III FDA-approved clinical trials in the United States and overseas for use in the palliative treatment of metastatic bone cancer pain. The reader is directed to a number of excellent reviews on these two potential radiotherapeutic agents[51,52,178,180] and on bone agents in general.[53,55,56]

$^{89}Sr^{2+}$, although not a coordination compound, has completed clinical trials and is undergoing FDA review for radiotherapeutic use in the relief of pain from metastatic bone disease. The nuclear properties of ^{89}Sr (50.5 d, 1.43 MeV β^-) are suitable for this application. $^{89}Sr^{2+}$ localizes in bone being a Ca^{2+} mimic, and in particular, at sites of osteoblastic activity. Although its half-life is long, once the ^{89}Sr is incorporated in the osteoblast, it remains deposited at the metastatic site and thus delivers the majority of its dose to the tumor cells.[181-185]

C. Biochemical/Receptor Binding Radiopharmaceuticals

With the exception of the phosphonate bone agents, the radiopharmaceutical complexes discussed have biolocalization properties that are related to blood flow. In the last 10 years or so, the chemistry developed using radioimmunoassay methods to radioiodinate monoclonal antibodies and fragments in order to specifically target selective binding to tumors cells, has been extended to incorporate the medically more useful radiometals. This may allow the diagnostic and radiotherapeutic targeting of disease sites with high specificity. In addition, the strides that have been made in the PET field using ^{11}C- and ^{18}F-labeled compounds for imaging neuroreceptors have indicated the potential of specific targeting of radiopharmaceuticals with small molecules. Recently, the area of small-molecule receptor binding radiopharmaceuticals has been extended to the incorporation of ^{123}I and radiometals into these types of molecules. These two important areas of development are really one and the same. The primary difference is the size of the receptor binding molecule, with antibodies (MW > ca. 25 000, often >100 000) being significantly larger than the small molecule receptor binding radiopharmaceuticals (MW generally < ca. 2 500).

Monoclonal antibodies (MAbs) are being used as carriers for drugs, radionuclides, or toxins to target sites of cancer, cardiovascular and other diseases for both diagnosis and treatment. Advances in genetic engineering have made it possible to not only generate antibodies for specific antigens, but also to allow the incorporation of additional amino acids or amino acid sequences into these antibodies,[186,187] possibly for binding a particular radiometal. The potential use of radiolabeled antibodies for the diagnosis and radiotherapeutic treatment of cancer has been the aim of many investigations with mixed results. In fact, reviews in the last 10 years by Meares,[66,69,188] Troutner,[8] Volkert,[7] Srivastava,[9,13] Fritzberg,[60] Yuanfang,[57] Gansow,[58] O'Brien,[11] and others[59,61-65,67-71,189] have discussed various aspects of radioimmunoscintigraphy and radioimmunotherapy.

The important considerations for the use of MAbs in nuclear medicine include (1) selection of the radiometal, (2) attaching the radiometal to the MAb, (3) the stability of the radiolabeled MAb complex, (4) the retention of immunoreactivity by the radiolabeled MAb, and (5) the target to nontarget uptake of the radiolabeled MAb in vivo. The selection of the specific MAb or fragment (Fab, $F(ab')_2$, etc.) will be determined by the disease that is to be targeted, and the choice appears to be unlimited. The optimum radiometal for these applications is the subject of some discussion, but most agree that the clinical untility will be determined by the in vivo stability of the radiometal chelate. Metal chelate stability is critical for the delivery of the radiopharmaceutical to the target site, maximizing target to nontarget uptake (i.e., minimizing background), which is particularly important for visualizing small tumors, and minimizing the radiation dose to the patient, especially for radiotherapeutic applications.

MAbs are labeled with the radiometal primarily using the bifunctional chelate approach. The chelate is designed to form a stable complex with the particular radiometal and a functional group is incorporated for conjugation with the MAb. Functional groups that form amide, thiourea, urea, Schiff base, or thioether linkages with amine or thiol groups of the MAb have been utilized.[59,66-69] The antibody, and not the radiometal chelate, will determine the biolocalization of the radiolabeled MAb, and it is essential that the antibody is radiolabeled with the most kinetically stable (under physiological conditions) complex of the particular radiometal. Since it is not the intent of this review to reiterate what others have described in great detail, only those radiometal complexes showing the most promise for clinical utility in this area are discussed below.

Several radiolabeled MAbs are in clinical trials in the United States, with agents developed at Cytogen, NeoRx, and Centocor being closest to clinical use. Centocor's Myocint, ^{111}In-DTPA-antimyosin, has been approved for imaging myocardial necrosis, but only in Europe.[128] The DTPA molecule has been covalently linked to the Fab fragment of antimyosin antibody and

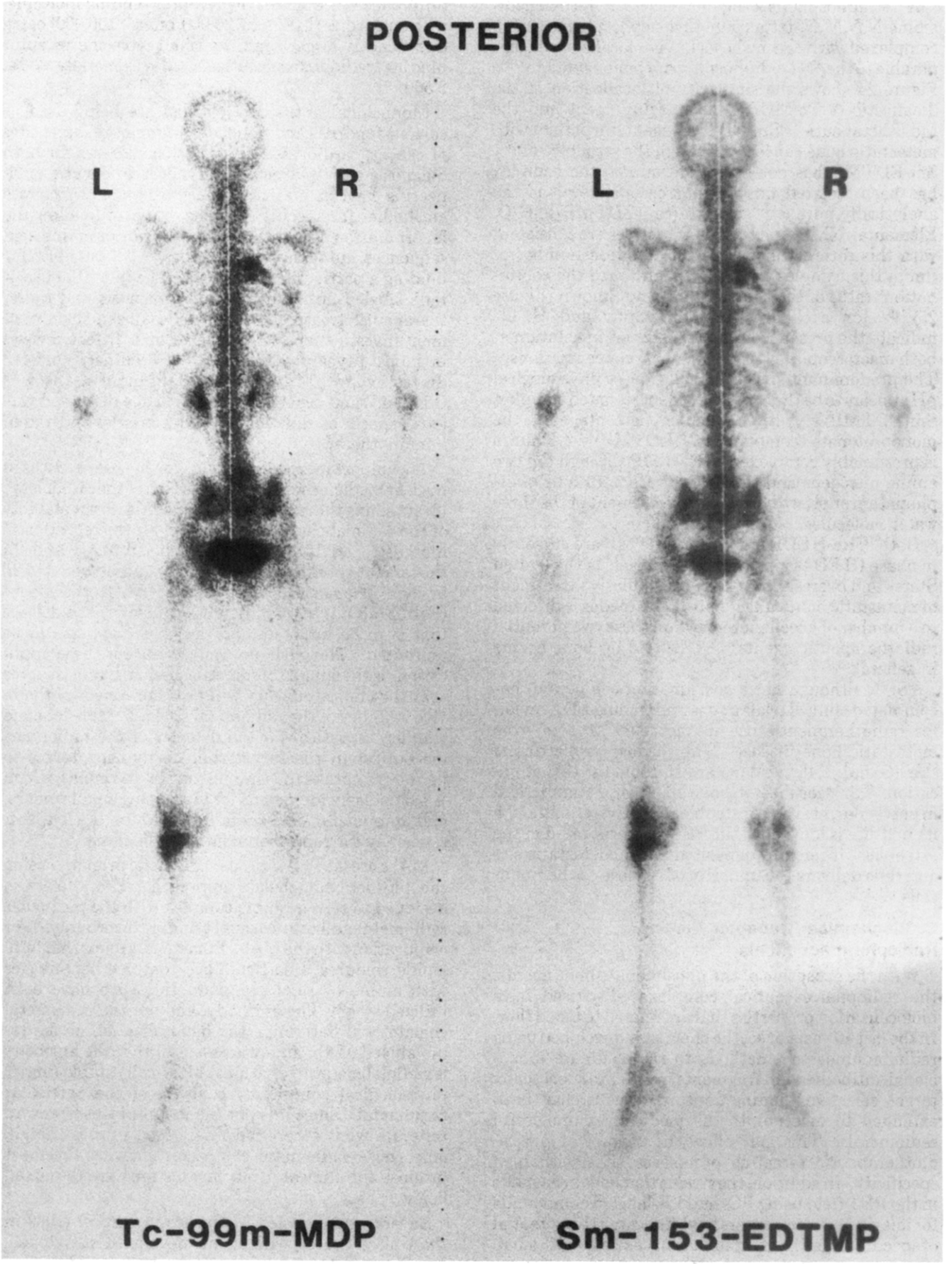


Figure 24. Whole body scan of a patient with bone metastases, on the left showing the distribution of the diagnostic agent ^{99m}Tc-MDP and on the right for the radiotherapeutic agent ^{153}Sm-EDTMP. The metastases are visualized as "hot spots". Both agents distribute similarly. (These images were obtained from Dr. W. Volkert, Harry S. Truman Veteran's Hospital and the Department of Radiology, University of Missouri.)

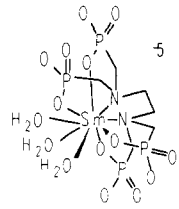


Figure 25. Proposed structure of $[Sm(EDTMP)\cdot 3H_2O]^{5-}$, showing a coordination number of nine for Sm with all three H_2O molecules bound to the Sm. It is not known how many, if any, of the three H_2O molecules are bound.

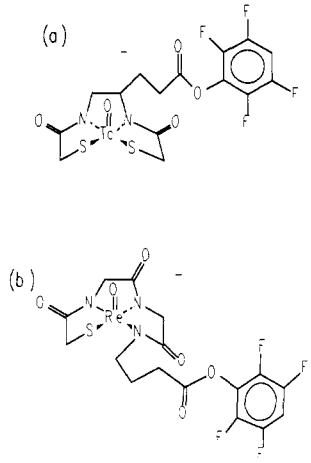


Figure 26. (a) $TcO(N_2S_2)$-TFP active ester and (b) ReO-(MAG_2-GABA-TFP).

requires only the addition of $^{111}InCl_3$ to the lyophilized kit.[190] The faster blood clearance of the Fab fragment compared to the whole antibody makes it more suitable for imaging. The ^{111}In presumably binds to the DTPA through three amines and three or four carboxylates, the fifth carboxylate being unavailable for coordination to In since it is covalently linked to the Fab fragment of antimyosin.

Cytogen has developed ^{111}In-DTPA-CYT-103 for the diagnosis of colorectal cancer. The DTPA is attached to the carbohydrate region of the antibody using site specific GYT-DTPA, for which Cytogen holds a patent.[191,192] The lyophilized kit, which contains DTPA-CYT-103, requires only the addition of $^{111}InCl_3$ for the preparation of ^{111}In-DTPA-CYT-103. This MAb targets the TAG-72 antigen found on >75% of colorectal tumors. This radiopharmaceutical has completed clinical trials and has been recommended for approval by an FDA review panel. If it receives FDA approval, this will be the first United States-approved radiolabeled MAb.

NeoRx has developed linker group technology that is being used in the development of ^{99m}Tc radioimmunoscintigraphic agents and ^{186}Re radioimmunotherapeutic agents. The linker group is an active ester with a tetrafluorophenyl (TFP) leaving group, which reacts to form an amide linkage with an antibody lysine amine group.[193] $^{99m}TcO(N_2S_2)$ (N_2S_2 = bis-amino bis-thio) derivatized with the TFP active ester (Figure 26a) has been used with Fab fragments of NR-ML-05 and NR-LU-10 for imaging melanoma and lung cancers, respectively. The $^{186}ReOMAG_2$-GABA-TFP (Figure 26b) has been conjugated with the whole NR-LU-10 MAb and the NR-CO-02 $F(ab')_2$ fragment for radioimmunotherapy.[195] The ^{99m}Tc-labeled NR-LU-10 Fab antibody fragment has completed phase III clinical trials as a diagnostic agent for small-cell lung and non-small-cell lung carcinomas. The FDA has requested an additional small number of studies to validate an alternative antibody manufacturer before approval.[194] The ^{186}Re-labeled antibodies, NR-LU-10 and NR-CO-02 $F(ab')_2$, used in over 100 patients with occasional responses seen in colon and ovarian cancer from systemic administration and more frequently when given intraperitoneally to ovarian cancer patients. The stability of both agents is reported to be excellent. $^{99m}TcO(N_2S_2)$-labeled NR-LU-10 $F(ab')_2$ shows negligible loss of ^{99m}Tc from the complex when challenged with human serum, DTPA, etc., at 37 °C.[193] Stability of ^{186}Re-MAG_2-GABA-labeled NR-CO-02 $F(ab')_2$ is inferred from in vivo clinical studies in which no thyroid uptake of ^{186}Re is observed.[195] Any ^{186}Re lost from the chelate would presumably be as perrhenate; free pertechnetate is known to localize to the thyroid and free perrhenate would be expected to behave analogously.[195]

Recent work reported by Abrams[196-198] and Katti[199,200] in which small monodentate hydrazines and phosphineimines can potentially be used to conjugate the MAb to the ^{99m}Tc or $^{186}Re/^{188}Re$ show promise. The work by Abrams allows the MAb to be conjugated to a molecule containing a hydrazine moiety which can subsequently be treated with ^{99m}Tc-glucoheptonate to form a very stable Tc=NNHR linkage.[196] The work reported by Katti allows direct reaction of $^{99m}TcO_4^-$ or $^{188/186}ReO_4^-$ with $R_3P{=}NSiMe_3$ to form $R_3P{=}N{=}MO_3$.[200] This chemistry shows great promise since the metal need not be reduced to a lower oxidation state for complexation. This is particularly useful for Re, because many Re complexes tend to undergo oxidation to perrhenate in vivo.[43,56]

Several other radiometals have been extensively studied for use in radioimmunotherapy. Various polyaminocarboxylate ligands have been shown to form kinetically stable complexes, in vivo, with ^{67}Cu (derivatized TETA; TETA = 1,4,8,11-tetraazacyclotetradecane-*N*,*N'*,*N''*,*N'''*-tetraacetic acid),[69,201,90]& (derivatized DOTA; DOTA = 1,4,6,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetic acid),[202,203] ^{153}Sm (derivatized DTPA),[204] and ^{212}Bi (derivatized DOTA).[58,70,205] In all of these cases, the metal is basically encapsulated by the ligand, thus stabilizing the metal to potential transchelation reactions in vivo. Various studies using these radiometal chelates conjugated to MAbs have been reported.

Preliminary in vitro studies on the use of ^{105}Rh,[206-209] ^{109}Pd,[210] and ^{199}Au[211,212] for radioimmunotherapy have been reported. Rh(III) and Pd(II) complexes should be kinetically inert regardless of the ligand. Unlike systems in which the most kinetically inert metal–ligand combination must be found, almost any Rh(III)–ligand complex will be kinetically inert. The stringent conditions required to synthesize Rh(III) and, also Pd(II) complexes, requires the Rh(III) and Pd(II) to be complexed to the bifunctional chelate before conjugation to the MAb. The aqueous chemistry of gold needs to be developed such that the gold radiolabel is not lost to in vivo reduction to the metal, Au(0). Studies by the Brookhaven group using gold clusters have been reported.[211] Future in vivo studies with these radiometals

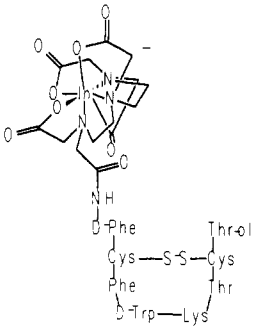


Figure 27. Proposed structure of InDTPA-D-Phe-octreotide, showing a seven-coordinate In.

will determine their utility to this field.

Vera[213-216] developed ^{99m}Tc-neogalactyl glycoalbumin (NGA) as a potential radiopharmaceutical for the hepatocyte binding protein (HBP), a plasma membrane bound hepatocyte-specific receptor that binds galactose-terminated glycoproteins. The ^{99m}Tc is electrolytically reduced in the presence of NGA and is probably bound to the molecule by sulfhydryl groups. Both in vitro and in vivo studies demonstrate that ^{99m}Tc-NGA binds to the HBP receptor and support the potential utility of this compound as a quantitative probe for the hepatic binding protein. HBP is implicated in several liver diseases, such as cirrhosis, hepatoma, and liver metastases, and ^{99m}Tc-NGA may show clinical utility staging liver diseases or monitoring therapeutic response.[217]

In general, radiolabeled MAbs suffer from the delivery of relatively low doses of radioactivity to the tumor(s) and relatively high doses of radioactivity to the liver, the primary filter of these molecules from the blood stream. The use of MAb fragments has somewhat alleviated the latter problem, unfortunately without addressing total tumor uptake. Recently, radiolabeled peptides have been used to show that perhaps only the amino acid sequence actually involved in binding to the receptor is necessary to achieve tumor uptake. This was shown to be true in probably the most exciting work in the receptor imaging area. ^{111}In-DTPA-octreotide (Figure 27) is a somatostatin receptor binding radiopharmaceutical.[218,219] Octreotide is an eight amino acid peptide containing the four amino acids (Phe-D-Trp-Lys-Thr) necessary for binding to the somatostatin receptor. The four essential amino acids are stabilized to proteases in the body by disulfide cyclization from the two cysteines that have been incorporated into the molecule, as well as by carefully placed substitution of D isomeric amino acids. To allow chelation to a metal, DTPA has been covalently linked to D-Phe at one end of the octapeptide. Both the ^{123}I- and the ^{111}In-labeled somatostatin analogs retain high affinity for the somatostatin receptor, in vitro and in vivo.[219] Natural somatostatin and unlabeled octreotide inhibit the binding of ^{111}In-DTPA-octreotide to rat brain cortex membrane receptor preparations. ^{111}In-DTPA-octreotide shows high binding to the somatostatin receptor with an IC_{50} value in the nanomolar range, and nonspecific binding is less than 10% of the total binding.[219] Imaging studies in rats with somatostatin receptor-positive tumors clearly show visualization of the tumors. Pretreatment of the rats with octreotide to block receptor binding reduces the uptake of ^{111}In-DTPA-octreotide and the tumors are not visualized during imaging.[220] Clinical studies in humans have demonstrated the utility of ^{111}In-DTPA-octreotide for imaging somatostatin receptor-positive tumors, expressed on carcinoid tumors[221] and malignant lymphomas.[222]

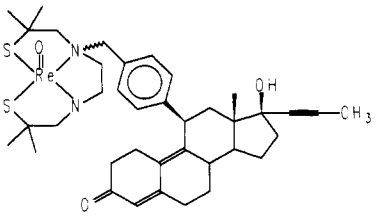


Figure 28. Proposed structure of 11β-ReO(N_2S_2)-progestin.

Neuroreceptors have been studied extensively with ^{11}C- and ^{18}F-labeled neurotransmitters and neuroreceptor agonists and antagonists. The isotopic substitution of ^{11}C for a carbon in the molecule, or ^{18}F for a hydrogen atom, results in very little, if any, change in the chemical and biological properties of the molecule. Thus, the uptake and retention of the radiolabeled molecule are virtually the same as that of the native, unlabeled molecule. This has allowed scientists to probe the involvement of various neuroreceptor populations in neurological disorders, such as Alzheimer's dementia,[223] and in substance abuse, such as cocaine use.[224]

In the last several years scientists have begun labeling receptor binding molecules with the medically more useful radiometals, such as ^{99m}Tc and ^{111}In. Since isotopic substitution is not an option, a metal chelate must replace either a hydrogen atom or a portion of the receptor binding molecule. Obviously, the chemical properties of the receptor binding molecule will be affected by this modification. Often, size and molecular weight will be increased, which, in turn, may affect lipophilicity. Drug delivery may be compromised, even if the specific receptor binding ability of this molecule remains high. Nonspecific binding (i.e., binding to other than the receptor site) has been observed in many cases.

Katzenellenbogen[225,226] has extended his work developing diagnostiic imaging agents for steroid-positive tumors with radiolabeled halogens to include progestin derivatized with a rhenium chelate at the 11β-, 16α-, 17α-, or 21-sites on the steroid skeleton. Introduction of an oxorhenium-N_2S_2 bis-amino bis-thio chelate system was found to lower the receptor binding affinity of the resultant molecule in all cases except the 11β-substitution. Three rhenium complexes are formed, one in which the progestin molecule is anti to the Re=O bond and a pair of diastereomers syn to the Re=O bond (Figure 28). Only the 11β-substituted technetium analogs were prepared and analyzed. The relative binding affinities (RBA) of these complexes are greater than that of progesterone. The RBAs were determined in vitro with competitive radiometric binding assays using uterine cytosol from estrogen-primed immature rats as the receptor source.[225,226] The direct radiometric binding assay using the ^{186}Re-labeled and ^{99m}Tc-labeled progestin complexes show they do bind to the progesterone receptor. Nonspecific binding is high, which is not surprising since the log P values of both the Tc and Re complexes are ca. 6.3 and 100 times higher than the simple steroidal progestins,[226] respectively. For diagnostic imaging, and especially for any radiotherapeutic

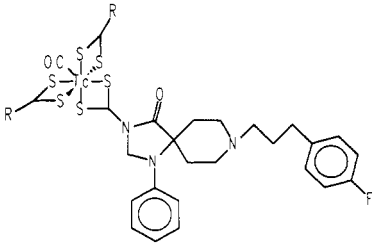


Figure 29. Proposed structure of Tc(CO)(spiperone dithiocarbamato)$_3$, only one spiperone moiety is shown.

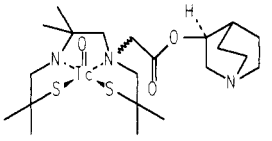


Figure 30. Proposed structure of TcO(N_2S_2)-quinuclidinol.

applications, the nontarget radioactivity must be low. This study shows that a steroid can be derivatized with a metal chelate of greater bulk than itself, and still show affinity for the receptor, but the problem of nonspecific binding must be addressed.

Three brief reports were published on neuroreceptor ligands labeled with ^{99m}Tc. Ballinger[227] has reported studies in which ^{99m}Tc was labeled with spiperone dithiocarbamate (Figure 29). No studies were carried out on the macroscopic level so it is unclear whether one, two, or three spiperone dithiocarbamate ligands are complexed to technetium. Studiies on the macroscopic ^{99}Tc level using analogous synthetic conditions (formamidine sulfinic acid as the reductant) with diethyl dithiocarbamate resulted in Tc(III)(CO)(diethyl dithiocarbamate)$_3$.[228] Only in vivo studies were reported in which ^{99}Tc-dithiocarbamatospiperone was injected intraperitoneally. The brain uptake was found to be very low, and negligible affinity for the dopamine D2 receptor was observed. If this complex is indeed a tris chelate, then the results are not surprising. The size of the ^{99}Tc(CO)(dithiocarbamatospiperone)$_3$ molecule would prohibit its crossing the blood–brain barrier.

Lever[229] has synthesized ^{99}TcON_2S_2-quinuclidinol (Figure 30) (N_2S_2 = bis-amino bis-thio ligand) and investigated its specific receptor binding for the muscarinic acetylcholine receptor (mAChR) in human brain. Two ^{99}Tc complexes were isolated, one having the syn configuration of the quinuclidinol group relative to the Tc=O bond and the other having anti configuration. In this complex, the Tc chelate, TcON_2S_2, replaces the diphenyl carbinol portion of R-QNB (3-(*R*)-quinuclidinyl benzilate), a high affinity ligand for mAChR. The measured affinities for the two Tc complexes, syn and anti, were in the micromolar range, about 3 orders of magnitude lower affinity than *R*,*S*-QNB.

Nanjappan et al.[230] used a different approach to prepare a QNB receptor binding radiopharmaceutical. The entire QNB molecule was incorporated as the R group on a Tc-BATO molecule (Figure 31). All four stereoisomers of QNB-boronic acid were synthesized (*RR*, *RS*, *SR*, *SS*) and the four $^{99/99m}$TcCl(DMG)-(DMGH)$_2$B-QNB complexes ($DMGH_2$ = dimethylglyoxime) prepared from them were assayed for specific binding for the muscarinic acetylcholine receptor (mAChR) from both rat caudate putamen and rat heart preparations. The four QNB-boronic acids were found

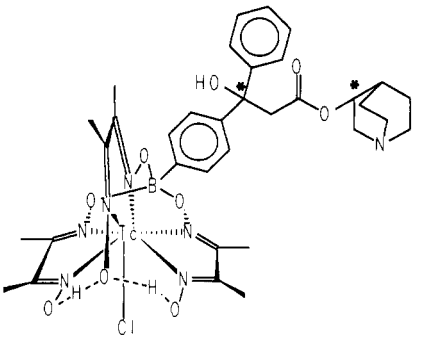


Figure 31. Proposed structure of TcCl(DMG)(DMGH)$_2$-BQNB.

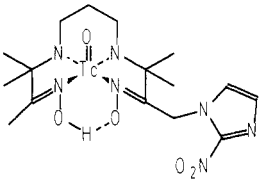


Figure 32. Proposed structure of TcO(PnAO)-1-(2-nitroimidazole).

to have 10–10 000 fold lower affinity (K_a) for mAChR than did *R*,*S*-QNB. The nonspecific binding of $^{99/99m}$TcCl(DMG)(DMGH)$_2$B-QNB was so high, however, that no specific receptor binding could be discerned from the in vitro studies. These results are not too surprising considering the size and high lipophilicity of these complexes.

Recently, DiRocco et al.[231] and Linder et al.[232] reported preliminary results on a potential new ^{99m}Tc radiopharmaceutical that appears to distribute initially by blood flow and then is retained by metabolism. ^{99m}TcO(PnAO)-1-(2-nitroimidazole) seems to localize in ischemic (hypoxic) regions of the heart in rabbit infarct models. The retention of this compound was shown to be similar to that of ^{14}*C*-2-deoxyglucose and ^{14}*C*-misonidazole, markers for glucose metabolism and hypoxia, using autoradiography. ^{99}TcO(PnAO)-1-(2-nitroimidazole) has been characterized on the macroscopic level (Figure 32). Results from electrochemical studies and enzyme studies at pH 7.4 with xanthine oxidase support reduction of the 2-nitroimidazole group under hypoxic, but not oxic, conditions, thus demonstrating a potential mechanism for preferential localization in ischemic tissue. TcO(PnAO) itself was found to be unaffected by xanthine oxidase under identical conditions. This is an example of a potential radiopharmaceutical in which the localization may be based on a biochemical process, namely reduction in hypoxic tissue.

IV. Conclusions

Small-molecule radiopharmaceuticals whose mode of localization involves biochemistry, either specific receptor interactions or metabolism, are the future of nuclear medicine. The receptor binding radiopharmaceutical ^{111}In-DTPA-octreotide and perhaps ^{99m}TcO-(PnAO)-1-(2-nitroimidazole) are the harbingers of this new generation of radiopharmaceuticals. Because so many radionuclides useful for diagnosis and radiotherapy are metals, we will undoubtedly witness some very complex organic chemistry utilized in designing these

new radiopharmaceuticals. Since size and lipophilicity are presumably critical to receptor binding and drug delivery, the organic molecule with the incorporated radiometal may be designed to have a three-dimensional structure very similar to the native receptor binding molecule. The study reported by Lever[229] with $^{99}TcON_2S_2$-quinuclidinol is a start in this direction. Molecular modeling will certainly become an important aspect of the design process. The challenge will ultimately be for the organic chemist to synthesize a chelate molecule that (1) has the properties of the receptor binding molecule when coordinated to the metal and (2) forms a very stable complex with the radiometal. Radiopharmaceutical chemistry is very much a multidisciplinary effort and requires the collaboration of scientists from various fields, including organic, inorganic, biochemistry, radiochemistry, and nuclear medicine. Without their joint efforts nuclear medicine would not be where it is today, nor will it progress. The design of receptor binding and metabolism marking radiopharmaceuticals which contain a radiometal will require integration of organic, inorganic, and biochemists to develop molecules that show the desired biochemical activity.

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