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Underscoring the Influence of Inorganic Chemistry on Nuclear Imaging with Radiometals

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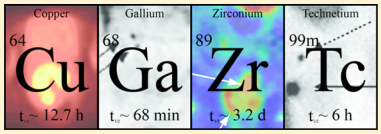
ABSTRACT: Over the past several decades, radionuclides have matured from largely esoteric and experimental technologies to indispensible components of medical diagnostics. Driving this transition, in part, have been mutually necessary advances in biomedical engineering, nuclear medicine, and cancer biology. Somewhat unsung has been the seminal role of inorganic chemistry in fostering the development of new radiotracers. In this regard, the purpose of this Forum Article is to more visibly highlight the significant contributions of inorganic chemistry to nuclear imaging by detailing the development of five metal-based imaging agents: ^{64}Cu-ATSM, ^{68}Ga-DOTATOC, ^{89}Zr-transferrin, ^{99m}Tc-sestamibi, and ^{99m}Tc-colloids. In a concluding section, several unmet needs both in and out of the laboratory will be discussed to stimulate conversation between inorganic chemists and the imaging community.



INTRODUCTION

Over the past 3 decades, nuclear imaging modalities have revolutionized clinical medicine, particularly cardiology, neurology, and oncology.[1,2] Indeed, the ability of positron emission tomography (PET) and single photon emission computed tomography (SPECT) to provide functional and biochemical information about tissues to complement the anatomical maps provided by other imaging modalities has proven vital in the diagnosis and management of disease. The advent of molecular imaging has in large part been due to remarkable advances in biomedical engineering, medical physics, halogen radiochemistry, and cancer biology. Yet the critical role of inorganic chemistry in the rise of nuclear imaging has often become lost in the margins. In the following pages, we will seek to remedy this oversight. We will first discuss the intersection of inorganic chemistry, radiochemistry, and nuclear imaging in general terms. Then, at greater length, we will use five particularly effective or promising metal-based imaging agents as case studies both to illustrate the fundamental role of inorganic chemistry in the development of radiopharmaceuticals and to more visibly celebrate the contributions of inorganic chemistry to nuclear imaging.

Why Use a Metallic Radioisotope? Before we delve any deeper into our discussion, we must first answer one simple question: "Why use a metallic radioisotope?" This question becomes especially important when considering that PET imaging is largely dominated by a radiohalogen, fluorine-18 (^{18}F, $t_{1/2}$ ~ 109.8 min). The answer is straightforward: radiometals provide flexibility, modularity, and facility unmatched by other imaging isotopes.

First, the wide variety of metallic radionuclides allows for the precise tailoring of the physical half-life of the radioisotope to the biological half-life of the targeting vector (Figure 1). For example, agents with short in vivo residence times can be labeled with gallium-68 (^{68}Ga; $t_{1/2}$ ~ 68 min) or technetium-99m (^{99m}Tc; $t_{1/2}$ ~ 6 h), while vectors that require longer amounts of time to reach their target can be labeled with copper-64 (^{64}Cu; $t_{1/2}$ ~ 12.7 h), yttrium-86 (^{86}Y; $t_{1/2}$ ~ 14.7 h), indium-111 (^{111}In; $t_{1/2}$ ~ 2.8 days), or zirconium-89 (^{89}Zr; $t_{1/2}$ ~ 3.2 days) (Figure 1 and Tables 1 and 2).[3−7]

Second, the simplicity and modularity of using different bifunctional chelators and radiometals facilitate the creation of a wide variety of imaging agents. For example, with relative ease, the same antibody can be conjugated to the chelators desferrioxamine (DFO), diethylenetriaminepentaacetic acid (DTPA), and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) for labeling with ^{89}Zr for PET imaging, ^{111}In for SPECT imaging, or lutetium-177 (^{177}Lu) for radioimmunotherapy. In some cases, particularly with the versatile chelators DOTA, DTPA, and 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), the radiometal may be exchanged without changing the chelator at all. Either way, this modularity becomes especially clinically useful when an imaging agent labeled with one isotope can be used as a companion diagnostic tool for a therapeutic agent bearing another.[8]

Third, generally speaking, radiometalation reactions are rapid and can be achieved under mild conditions. Purification procedures are also quite simple, typically involving cation-exchange chromatography or reverse-phase C_{18} cartridges. It is in this area that radiometals likely offer the greatest advantage over radiohalogens because probes bearing the latter often require multistep syntheses, harsh reaction conditions, and complicated purifications.

Fourth, many radiometals—for example, ^{86}Y, ^{89}Zr, and ^{111}In—are known to residualize inside cells following the uptake of their vector, resulting in increased retention of the radioactivity inside the target tissue and higher tumor-to-background activity ratios than nonresidualizing radiohalogens such as ^{18}F, iodine-124 (^{124}I), and bromine-76 (^{76}Br).[9]

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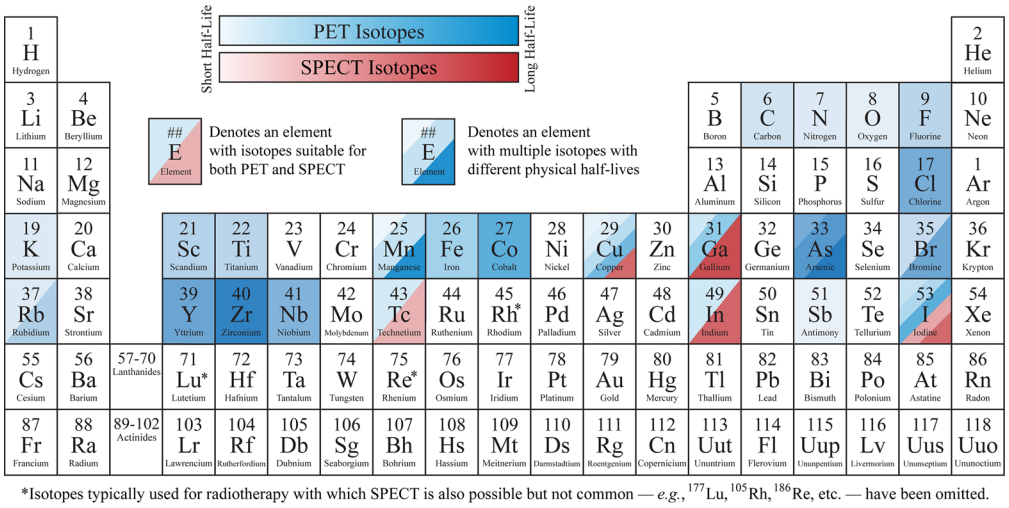

Figure 1. Illustration of the variety of metals with isotopes suitable for nuclear imaging. Elements with isotopes suitable for PET are color-coded blue, and elements with isotopes suitable for SPECT are color-coded red. The shading corresponds to half-life, with longer half-lives darker and shorter half-lives lighter. Elements with multiple shadings have multiple isotopes suitable for imaging.

Table 1. Physical Properties of Some Common PET Radiometals[a]

isotope	half-life/h	source	production reaction	decay mode (% branching ratio)	E_{β^+}/keV	abundance, $I_{\beta+}$/%	E_γ/keV (intensity, I_γ/%)	relevant oxidation states	common coordination numbers
^{64}Cu	12.7	cyclotron	^{64}Ni(p,n)^{64}Cu	$\varepsilon + \beta^+$ (61.5) β^+ (17.6) β^- (38.5)	278.2(9)	17.60(22)	511.0 (35.2)	1+, 2+	4, 5, 6
^{68}Ga	1.1	generator	^{68}Ge/^{68}Ga	$\varepsilon + \beta^+$ (100) β^+ (89.1)	836.02(56)	87.94(12)	511.0 (178.3)	3+	4, 5, 6
^{86}Y	14.7	cyclotron	^{86}Sr(p,n)^{86}Y	$\varepsilon + \beta^+$ (100) β^+ (31.9)	535(7)	11.9(5)	443.1 (16.9) 511.0 (64) 627.7 (36.2) 703.3 (15) 777.4 (22.4) 1076.6 (82.5) 1153.0 (30.5) 1854.4 (17.2) 1920.7 (20.8)	3+	8, 9
^{89}Zr	78.4	cyclotron	^{89}Y(p,n)^{89}Zr	$\varepsilon + \beta^+$ (100) β^+ (22.7)	395.5(11)	22.74(24)	511.0 (45.5) 909.2 (99.0)	4+	8

[a]Unless otherwise stated, standard deviations are given in parentheses (IT = isomeric transition; ε = electron capture).[208]

Table 2. Physical Properties of Some Common SPECT Radiometals[a]

isotope	half-life/h	source	production reaction	decay mode (% branching ratio)	E_γ/keV	abundance, I_γ/%	relevant oxidation states	common coordination numbers
^{67}Ga	78.2	cyclotron	^{nat}Zn(p,x)^{67}Ga ^{68}Zn(p,2n)^{67}Ga	ε (100)	91.265(5) 93.310(5) 184.576(10) 208.950(10) 300.217(10) 393.527(10)	3.11(4) 38.81(3) 21.410(10) 2.460(10) 16.64(12) 4.56(24)	3+	4, 5, 6
^{99m}Tc	6.0	generator	^{99}Mo/^{99m}Tc	β^- (0.0037) IT (99.9963)	140.511(1)	89.06	1− to 7+	4, 5, 6
^{111}In	67.3	cyclotron	^{111}Cd(p,n)^{111}In	ε (100)	171.28(3) 245.35(4)	90.7(9) 94.1(10)	3+	5, 6, 7, 8

[a]Unless otherwise stated, standard deviations are given in parentheses (IT = isomeric transition; ε = electron capture).[208]

Finally, yet no less critically, metallic radioisotopes present a tremendous opportunity to expand the availability of imaging agents beyond hospitals with nearby cyclotron facilities because many radiometals can be produced via portable generator systems (e.g., ^{68}Ga and ^{99m}Tc) or possess physical half-lives long enough such that they can be shipped to research

laboratories and hospitals without excessive decay (e.g., ^{64}Cu, ^{111}In, and ^{89}Zr).

Production and Purification of Radiometals. The first step in the synthesis of a radiometal-based imaging agent is production of the radiometal itself. Radiometals can be produced via three distinct routes: decay of longer-lived radionuclides in a *generator*, nuclear bombardment reactions in a *cyclotron*, or nuclear bombardment reactions in a *nuclear reactor* (see Tables 1 and 2). ^{68}Ga, for example, is formed via electron capture decay of its parent radionuclide, germanium-68 (^{68}Ge), and thus can be produced using a compact, cost-effective, and convenient ^{68}Ge/^{68}Ga generator system. ^{64}Cu, in contrast, can be produced either on a nuclear reactor [via the ^{63}Cu(n,γ)^{64}Cu or ^{64}Zn(n,p)^{64}Cu reaction] or, far more commonly, by use of a biomedical cyclotron via the ^{64}Ni(p,n)^{64}Cu reaction.[10] As an aside, it is important to note that each of these isotopes emits radiation other than the positrons and photons useful for imaging. Some of these emissions, such as the variety of high-energy photons from ^{86}Y and the 909 keV photon from ^{89}Zr, require special consideration with regard to handling, shielding, and dosimetry.[11]

Yet the process does not end with the creation of the desired radiometal. The radiometal must be purified from its parent isotope and other byproducts of the nuclear reaction and isolated in a useful form prior to its incorporation into an imaging agent. Here lies the first point of intersection between inorganic chemistry and radiochemistry.

^{86}Y, for example, is most often produced via the ^{86}Sr(p,n)^{86}Y reaction by the proton bombardment of [^{86}Sr]-enriched $SrCO_3$ or SrO targets on a cyclotron. A variety of different techniques have been employed to separate the $^{86}Y^{3+}$ cation from the target and byproducts, including cation-exchange chromatography, cation-exchange chromatography followed by coprecipitation with La^{III} or Fe^{III}, and chromatography using Sr-selective resins.[12,13] Recently, a particularly effective and economical method for isolating ^{86}Y using electrolysis has been developed.[14] After irradiation of a [^{86}Sr]-enriched SrO target coated onto a platinum disk, the entire target is dissolved in nitric acid with NH_4NO_3 as an electrolyte. This solution is then placed in an electrochemical cell in which two successive rounds of electrolysis are employed to separate ^{86}Y from residual Sr via electrodeposition on a platinum-wire electrode. This ^{86}Y-coated platinum wire electrode can then be removed from the cell and washed with EtOH and HNO_3. This solution can then be evaporated and reconstituted in 0.1 M HCl to yield $^{86}Y^{3+}$ in very high specific activity and radionuclidic purity. Importantly, this method also allows for the efficient recycling of the expensive, isotopically enriched ^{86}Sr target material.

In another example, ^{89}Zr is produced via the ^{89}Y(p,n)^{89}Zr reaction by proton bombardment of a solid ^{89}Y target on a cyclotron.[15,16] In order to produce an aqueous $^{89}Zr^{4+}$ species suitable for radiolabeling reactions, the solid target is first dissolved with 6 M HCl. Yet this process produces aqueous $^{89}Zr^{4+}$ and $^{89}Y^{3+}$ species that must be separated. To this end, the HCl solution is run through a hydroxamate resin that has high affinity for $^{89}Zr^{4+}$ and very low affinity for $^{89}Y^{3+}$, thus completely sequestering the $^{89}Zr^{4+}$ cations while allowing the $^{89}Y^{3+}$ cations to pass through. Finally, $^{89}Zr^{4+}$ is removed from the hydroxamate resin using an eluent of oxalic acid, producing a purified solution of $^{89}Zr^{4+}$ that can be employed in radiolabeling reactions.

Aqueous Coordination Chemistry of Some Common Radiometals. Prior to our discussion of metal-based imaging agents, a brief discussion of the underlying aqueous coordination chemistry of the radiometals is in order. For more detail, the reader can consult other excellent and more exhaustive reviews, chief among them a 2010 *Chemical Reviews* article from Wadas et al.[3−5,11,17−21]

To begin, four isotopes of copper have been used for PET imaging: ^{60}Cu ($t_{1/2}$ = 0.4 h; β^+ yield = 93%; $E_{\beta+}$ = 3.9 and 3.0 MeV), ^{61}Cu ($t_{1/2}$ = 3.32 h; β^+ yield = 62%; $E_{\beta+}$ = 1.2 and 1.15 MeV), ^{62}Cu ($t_{1/2}$ = 0.16 h; β^+ yield = 98%; $E_{\beta+}$ = 2.19 MeV), and, most notably, ^{64}Cu ($t_{1/2}$ = 12.7 h; β^+ yield = 19%; $E_{\beta+}$ = 0.656 MeV).[22] Of course, the chemistry of each is identical. Cu^{II} is the most biologically relevant oxidation state of the metal. Because of its electronic structure, the $3d^9$ cation typically forms square-planar four-coordinate, square-pyramidal or trigonal-bipyramidal five-coordinate, or octahedral six-coordinate complexes.[21,23] However, coordinatively saturating six-coordinate ligands have generally proven the chelators with the best in vivo performance.[3,24] Cu^{2+} is neither a particularly hard nor soft cation, so an effective chelator will almost always feature a mixture of uncharged nitrogen donors along with anionic oxygen or sulfur donors in order to neutralize the 2+ charge of the cation. While DOTA has been used as a chelator for Cu^{2+}, the Cu-DOTA complex has been shown to be unstable in vivo, often producing elevated levels of radiocopper uptake in the liver as a result of demetalation. Alternatively, other macrocyclic ligands with smaller or cross-bridged cavities, such as NOTA (N_3O_3) or 4,11-bis-(carboxymethyl)-1,4,8,11-tetrazabicyclo[6.6.2]hexadecane-4,11-diacetic acid (CB-TE2A; N_4O_2), have been shown to be excellent chelators of the radiometal.[25−27] More recently, neutral N_6 macrocyclic chelators based on sarcophagine scaffolds have been shown to be extremely adept at chelating the cation.[28,29] The in vivo reduction of copper from Cu^{II} to Cu^{I} is possible under some circumstances. In most cases, this reduction is undesirable, and macrocyclic complexes of Cu^{II} generally have reduction potentials far below the threshold for in vivo reduction. However, in some situations, as we shall see in the Cu-ATSM case study, the reduction of Cu^{II} to Cu^{I} is a critical step in the biological mechanism of the tracer.

Moving on, the only stable oxidation state of gallium in an aqueous environment is 3+. The amphoteric nature of Ga^{3+} allows for reactions in acidic and alkaline solutions. At pH > 3, insoluble $Ga(OH)_3$ precipitates out of aqueous solutions, but this species redissolves to soluble [$Ga(OH)_4^-$] at pH > 7.4.[30] However, on the radiochemical scale, the formation of insoluble $Ga(OH)_3$ has been shown to be inconsequential if the overall radiometal concentration is kept below $\sim 2.5 \times 10^{-6}$ M.[30−32] The Ga^{3+} cation is smaller and harder than the Cu^{2+} cation and thus typically binds ligands containing multiple anionic oxygen donors.[33,34] While some tetrahedral four-coordinate and square-pyramidal five-coordinate complexes are known, octahedral six-coordinate complexes are far more common. A variety of acyclic and macrocyclic chelators have been used with Ga^{3+}, with *N*,*N*′-ethylenedi-L-cysteine (EC; $N_2S_2O_2$), *N*,*N*′-bis(2-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic acid (HBED; N_2O_4), NOTA (N_3O_3), 1,4,7-trismercaptoethyl-1,4,7-triazacyclononane (TACN-TM; N_3S_3), and DFO (O_6) forming particularly stable complexes.[35−38] As we will discuss later, while DOTA has been employed quite often with $^{68}Ga^{3+}$, the chelator does not form a particularly stable complex with the cation.[39] Indeed, in this regard, Ga^{3+} provides an excellent example of the importance of the cavity size of macrocyclic chelators. While

NOTA binds the cation exceptionally tightly (log K = 30.1; pM = 26.4), the larger cavities of its cousins DOTA (log K = 21.3; pM = 15.2) and triethylenetetramine (TETA) (log K = 19.7; pM = 14.1) make for far less stable complexes.[40,41]

Not surprisingly, the chelation chemistry of indium is similar to that of gallium. Like its congener, indium's only stable aqueous oxidation state is 3+.[34,42] However, the In^{3+} cation is larger, has a higher pK_a, and exhibits faster water exchange rates than its Ga^{3+} counterpart.[34] As a result, In^{3+} is more tolerant of ligands bearing softer thiolate donors and can adopt higher coordination numbers than its group 13 neighbor. In part because of this flexibility, In^{3+} has been shown to form complexes with a variety of different coordination numbers and geometries. These include a five-coordinate trigonal-bipyramidal complex with tris(2-mercaptobenzyl)amine (NS_3 + an exogenous ligand), a six-coordinate distorted octahedral complex with EC ($N_2S_2O_2$), a six-coordinate distorted octahedral complex with NOTA (N_3O_3), a seven-coordinate pentagonal-bipyramidal complex with ethylenediaminetetraacetic acid (EDTA; N_2O_4 + an exogenous ligand), and an eight-coordinate square-antiprismatic complex with DTPA (N_4O_4).[36,43−48] In practice, however, the vast majority of ^{111}In-labeled bioconjugates have employed bifunctional derivatives of DTPA or DOTA.[34,42,49−52]

The biologically relevant oxidation state of yttrium is also 3+. However, the Y^{3+} cation is much larger than either Ga^{3+} or In^{3+}, allowing it to form complexes with coordination numbers up to 8 or 9. Despite its large size, the Y^{3+} cation is considered to be a hard Lewis acid, and thus ligands with multiple anionic oxygen donors are usually employed for its chelation. When a ligand offers fewer than eight donors, exogenous ligands fill the cation's coordination sphere, as in its eight-coordinate distorted dodecahedral complex with EDTA (N_2O_4 + two H_2O ligands) and nine-coordinate monocapped square-antiprismatic complex with 1,4,7-tris(carbamoylmethyl)-1,4,7-triazacyclononane (N_3O_3 + two H_2O ligands).[43,53−55] Not surprisingly, however, it has been shown that ligands capable of coordinatively saturating the metal form more stable complexes. As a result, the two chelators most often used in ^{86}Y-labeled radiopharmaceuticals both offer eight donors: DOTA forms an eight-coordinate square-antiprismatic complex with a K_d of ∼22, while DTPA forms an eight-coordinate monocapped square-antiprismatic complex with a K_d of ∼24.[49,50,52,56−60]

As a group IV metal, zirconium exists predominantly in the 4+ oxidation state in aqueous solution. The aqueous chemistry of the $Zr(H_2O)_x$ species can be quite complex, with both speciation between various mononuclear and polynuclear states and solubility highly dependent on the pH.[61−63] With regard to chelation chemistry, however, things simplify somewhat. The cation is relatively large, and its high charge makes it a very hard Lewis acid. As a result, Zr^{4+} displays a very strong preference for ligands offering anionic oxygen donors in high coordination numbers. For example, Zr^{4+} has been shown to make octadentate, dodecahedral complexes with the well-known chelators DTPA (N_3O_5), EDTA (N_2O_4 + two H_2O ligands), and DOTA (N_4O_4).[64,65] Interestingly, however, while the thermodynamic stability constants for both Zr-EDTA (∼29) and Zr-DTPA (∼36) have been shown to be quite high, the poor kinetic stability of these complexes has rendered them unsuitable for use in vivo.[53,58,66] Instead, the vast majority of, if not all, published ^{89}Zr-labeled radiotracers have employed DFO as the chelator.[67−70] DFO is an acyclic siderophore-derived molecule that binds $^{89}Zr^{4+}$ using three hydroxamate groups, thus providing three neutral and three anionic oxygen ligands. To date, neither a solid state nor an NMR structure has been determined for Zr-DFO, although density functional theory (DFT) calculations suggest that a seven- or eight-coordinate complex is formed involving exogenous water molecules in addition to the ligand's six oxygen donors.[71]

Finally, the chemistry of technetium represents a fairly significant departure from the radiometals we have discussed so far. As a group VIIB metal with a neutral electronic configuration of $[Kr]4d^6 5s^1$, the coordination chemistry of ^{99m}Tc is very complex: a large number of oxidation states (1− to 7+) and a wide variety of coordination geometries (square-pyramidal, octahedral, and heptahedral) are possible.[7,18,31,72−74] This diversity is a double-edged sword: it allows for construction of a range of different ^{99m}Tc species, but it also gives rise to ample redox chemistry and chemically labile species that complicate the design of imaging agents.[75]

Upon elution from the generator as tetrahedral $^{99m}TcO_4^-$, ^{99m}Tc exists in a 7+ state that is not immediately useful for chelation or binding directly to small molecules because of its negligible chemical reactivity.[18] Indeed, there are very few examples of the incorporation of Tc^{VII} into imaging agents, with ^{99m}Tc-sulfur-colloid (Tc_2S_7) standing as the only major example.[31,76] Rather, the vast majority of ^{99m}Tc-based imaging agents are prepared using ^{99m}Tc in a lower oxidation state. As a result, a reducing agent or the direct reduction of the metal through complexation with hard ligands is necessary in the synthesis of these probes.[7,31,75]

Not surprisingly, the different oxidation states of technetium have different coordination chemistries. Tc^V is a d^2 metal center that, in aqueous environments, typically forms either five-coordinate square-pyramidal or six-coordinate octahedral complexes around a Tc^VO core or six-coordinate octahedral complexes around a Tc^VO_2 core. Ligands featuring donors ranging from neutral phosphorus and sulfur atoms to anionic oxygen atoms have been employed, although tetradentate chelators based on mercaptoacetylglycylglycylglycine, diaminedithiol, or aminoaminedithiol scaffolds have proven most common.[77,78] Complexes based on technetium(V) nitrido cores and the condensation reaction between the Tc^VO center and hydrazinonicotinamide have also been explored as alternative Tc^V coordination strategies.[79,80] Unfortunately, however, much of the work with Tc^V cores has ultimately led to complexes that are unstable or preparations that are too cumbersome for clinical translation. For example, the $^{99m}Tc^VO$ core is relatively common in radiopharmaceuticals, but these complexes are often labile at the trans position or are hydrolytically unstable when exposed to physiological environments.[31]

Low-spin Tc^{III} d^4 complexes have also been studied as alternatives to Tc^V-based constructs. The Tc^{III} center has been shown to make both six- and seven-coordinate complexes with ligands featuring a variety of different donor types.[81,82] However, the relatively harsh reducing conditions currently employed to form Tc^{III} from pertechnetate represent a significant obstacle to its routine use.

Recently, many of the most successful developments have centered on $^{99m}Tc^I$, particularly complexes based on the kinetically inert, low-spin $[^{99m}Tc(CO)_3]^+$ d^6 core.[83,84] Water-soluble $[^{99m}Tc(CO)_3(H_2O)_3]^+$ can be prepared easily from ^{99m}Tc-pertechnetate under reducing conditions, and the H_2O ligands are easily exchanged with various types of ligands, including tris(pyrazoyl)methane derivatives and click-chemistry-derived scaffolds.[85−90] The lipophilicity of $[Tc(CO)_3]^+$ remains

somewhat of a concern, however. Tc^{I} is a relatively soft cation, and ligands bearing softer donors tend to increase the lipophilicity of the complex further. Thus, chelation systems must be chosen carefully in order to strike a suitable balance between stability and lipophilicity.

Regardless of the identity of the metal, synthesis on the radiochemical scale has a few critical features that set it apart from the macroscale synthesis of "cold" complexes. The limited amount of time allowed for synthesis and purification is the most obvious difference, because reaction and purification conditions must often be designed with the half-life of the radionuclide in mind. A less apparent difference is the strikingly low absolute concentration of radiometals in most radiolabeling reactions. Generally, the concentration of radiometal is at least 3 (and often more) orders of magnitude lower than that of any other reactants in a radiochemical reaction. This contrasts dramatically with the excess of metal typically employed in macroscale reactions that aim to achieve the best possible chemical yield. For this reason, during radiosynthesis reactions, any potential contaminants, particularly metals that may compete with the radiometal of interest, become a major concern.

Design and Structure of Radiometal-Based Imaging Agents. From a design perspective, radiometalated imaging agents can be grouped into three classes: small metal complexes, chelator-based conjugates, and colloids. Small-metal-complex radiotracers are the most structurally straightforward class, comprised of two essential parts: a central radiometal and a set of coordinating ligands. These agents represent the purest points of intersection between inorganic chemistry and nuclear imaging, for the metal complexes themselves are solely responsible for in vivo targeting, uptake, and retention. A number of small-metal-complex PET and SPECT imaging agents have had a significant impact in the clinic, including ^{99m}Tc-bisphosphonates for bone imaging, ^{99m}Tc-sestamibi for myocardial perfusion imaging, and ^{64}Cu-PTSM for blood perfusion imaging.[6]

Chelator-based conjugates, on the other hand, have four parts: a targeting vector, a radiometal, a chelator, and a linker connecting the chelator and targeting vector.[4,5,7] The targeting vector is typically a biomolecule such as a peptide, protein, or antibody. However, synthetic vectors such as nanoparticles and liposomes have come into vogue in recent years. The selection of a radiometal is governed by both the imaging modality and the biological half-life of the targeting vector. The most popular radiometals for SPECT imaging are ^{111}In and ^{99m}Tc, and the most popular radiometals for PET imaging are ^{68}Ga, ^{64}Cu, ^{86}Y, and ^{89}Zr. However, a variety of other metallic radioisotopes including gallium-67 (^{67}Ga), copper-60 (^{60}Cu), titanium-45 (^{45}Ti), and technetium-94m (^{94m}Tc) have also been produced and used. Once an imaging modality has been chosen, matching the radioactive half-life of the isotope to the biological half-life of the biomolecule is critical. For example, ^{68}Ga and ^{99m}Tc would not be ideal choices for labeling antibodies because the radionuclides would decay significantly before the antibody reaches its optimal concentration at the target. Conversely, neither ^{89}Zr nor ^{111}In would be the best choice for labeling a short peptide because their multiday half-lives would far exceed the residence time of the peptidic agent.

The job of the chelator—interestingly, from the Greek χηλή (chēlē) meaning "claw"—is simple: form a kinetically inert and thermodynamically stable complex with the radiometal in order to prevent its inadvertent release in vivo. Radiometal chelators fall into two structural classes: macrocylic and acyclic chelators. While macrocyclic chelators typically offer greater thermodynamic stability, acyclic chelators usually have faster rates of metal binding.[18] Generally, transition-metal chelators offer at least four (and usually six or more) coordinating atoms arrayed in a configuration that suits the preferred geometry of the metal in question. As we have discussed above, different metals prefer different chelators, and therefore the choice of chelator is dictated by the identity of the radiometal.

For the linkage between the chelator and targeting vector, the only requirements are that the link must be stable under physiological conditions and must not significantly compromise the binding strength or specificity of the vector. The specific chemical nature of the conjugation method is dependent on both the type of vector and the availability of bifunctional variants of the desired chelator. For vectors with free thiol groups, the reaction between a thiol and a maleimide has proven a popular route; for vectors with free amine groups, the formation of thiourea bonds using isothiocyanates or peptide bonds using activated carboxylic acids has been widely employed. It is important to remember, however, that the conjugation of a chelator to a vector may alter its ability to coordinate a given radiometal. For example, conjugating DOTA to a peptide using one of its carboxylate arms leaves only a three-armed DOTA, more properly termed DO3A, for chelation of the radiometal. In light of this, the use of bifunctional chelators with pendant conjugation handles, e.g., [*S*-2-(aminobenzyl)1,4,7-triazacyclononane-1,4,7-triacetic acid (*p*-NH_2Bn-NOTA) or *N*-(2-aminoethyl)-*trans*-1,2-diaminocyclohexane-*N*,*N*′,*N*″-pentaacetic acid (CHX-A″-DTPA), is often preferable.

The third class of radiometal-based imaging agents, colloids, is the oldest of the three, yet it boasts only one prominent example: the family of ^{99m}Tc-radiocolloids.[91−93] Nevertheless, ^{99m}Tc-radiocolloids have had a profound impact on the clinical imaging of the reticuloendothelial system (RES). Broadly speaking, colloids are particles that range in size from 1 nm to 4 μm. In the body, they are typically removed from circulation via phagocytosis, a process especially active in macrophages. Consequently, when radiolabeled, they can be used to image tissues with high concentrations of macrophages, such as the liver, spleen, bone marrow, and lymph nodes. As a result, ^{99m}Tc-radiocolloids have proven especially important in the imaging of the lymphatic system in oncology. ^{99m}Tc-colloids of a wide range of diameters have been created using a variety of materials, including denatured human albumin, sulfur, antimony, and stannous phytate. Somewhat surprisingly, the literature contains very few allusions to the use of other radiometals in colloidal imaging agents.[94] A more detailed discussion of the synthesis and application of ^{99m}Tc-colloids can be found in the last of the five case studies.

CASE STUDIES

In the following pages, our hope is to use five metal-based radiopharmaceuticals—^{64}Cu-ATSM, ^{68}Ga-DOTATOC, ^{89}Zr-transferrin, ^{99m}Tc-sestamibi, and ^{99m}Tc-colloid—as lenses to illustrate the fundamental role of inorganic chemistry in the development of both well-established and next-generation nuclear imaging agents. Taken together, we believe that these vignettes will provide both a sound overview of the different ways inorganic chemistry influences radiopharmaceuticals and an arena for the celebration of the integral contributions of inorganic chemistry to nuclear imaging, while

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