Review

Radiopharmaceuticals Labeled with Short-Lived
Positron-Emitting Radionuclides[†]

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Over the past decade there has been great interest in the application of positron emission tomography in medical research and diagnosis¹⁾. Over this time period many radiopharmaceuticals have been labeled with cyclotron-produced positron-emitting radionuclides oxygen-15 ($t_{1/2}=2.04$ min), nitrogen-13 ($t_{1/2}=9.98$ min), carbon-11 ($t_{1/2}=20.4$ min), and fluorine-18 ($t_{1/2}=110$ min)²⁻⁷⁾. There has also been increasing interest in generator-produced positron-emitting radionuclides. In this article we will review the method for labeling compounds with positron-emitting radionuclides with particular emphasis on radiopharmaceuticals being used in clinical studies.

1. Oxygen-15

The very short half-life (2.04 min) of oxygen-15 has severely limited the number of radiopharmaceuticals which can be prepared on a routine basis with this isotope. In practice, the use of oxygen-15 has been limited to simple radioactive gases which can be prepared by on-line procedures, i.e., $O^{15}O$, $C^{15}O$, and $CO^{15}O$, and radiopharmaceuticals quickly prepared from

these gases: water, carboxyhemoglobin, and oxy-hemoglobin. Deuteron bombardment of nitrogen gas containing a trace of oxygen produces ^{15}O by the $^{14}N(d,n)^{15}O$ nuclear reaction and forms $O^{15}O$, which can be converted to $C^{15}O$ (charcoal at 900°C) or $CO^{15}O$ (charcoal at 400°C)⁸⁾. Labeled water is simply prepared by bubbling $CO^{15}O$ through water, which leads to $H_2^{15}O$ by exchange⁹⁾, or by combustion of ^{15}O -oxygen and hydrogen over a catalyst. Labeled hemoglobins are prepared by the bubbling of $C^{15}O$ or $O^{15}O$ through blood¹⁰⁾.

Although relatively simple compounds, these oxygen-15-labeled radiopharmaceuticals are used extensively in conjunction with positron emission tomography to study hemodynamics (blood flow and volume)¹¹⁾ and oxygen metabolism¹²⁾. At Washington University these compounds are prepared several times a day for clinical studies and systems have been developed to deliver $O^{15}O$, $C^{15}O$, and $H_2^{15}O$ to a positron emission tomography (PET) facility in a reliable fashion with no radiation dose to the chemistry staff¹³⁾.

2. Nitrogen-13

Nitrogen-13 also has a very short half-life (9.98 min), and its usage in syntheses has also been restricted. Nitrogen-13-labeled nitrogen gas (^{13}NN) can be prepared by deuteron bombardment of carbon dioxide¹⁴⁾ or a graphite matrix target¹⁵⁾, or by proton irradiation of a ^{13}C enriched target¹⁶⁾ or a high pressure oxygen target¹⁷⁾. Nitrogen-13-labeled ammonia can be

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made by deuteron bombardment of inorganic carbides¹⁸⁾ or methane¹⁹⁾, or proton bombardment of an oxygen or water target²⁰⁾ (intermediate oxides of nitrogen need to be reduced).

Two chemical syntheses, the preparation of ¹³N-labeled 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea and *bis*(2-chloroethyl)-nitrosourea, have been reported using HO¹⁵NO²¹⁾. By far, the widest use of nitrogen-13 has been in the preparation of amino acids using enzymatic methods. These preparations are done using isolated, in some cases immobilized, enzymes. L-¹³N-glutamate, valine, alanine, leucine, and methionine have been prepared using ¹³N-ammonia, the appropriate α -keto acid^{22), 23)}, and glutamate dehydrogenase. Preparation first of ¹³N-glutamate, and then employing glutamate α -keto acid transaminases, was used in the preparation of ¹³N-labeled alanine, aspartic acid, tyrosine, and phenylalanine^{24), 25)}. Glutamine was prepared using glutamate and ¹³N-ammonia using glutamine synthetase²²⁾, and similarly amide-labeled asparagine using asparagine synthetase²⁶⁾.

3. Carbon-11

Carbon-11 has a sufficiently long half-life (20.4 min) to allow chemical syntheses, and to date, more than 220 compounds have been labeled with this radionuclide. A radioactive carbon, obviously, makes theoretically possible the labeling of nearly any important metabolic substrate, receptor ligand or drug which may be of physiological interest.

Preparation of complicated organic compounds labeled with carbon-11 begins with the production of a fairly simple labeled precursor. Fortunately, a number of these are readily available. Proton bombardment of a nitrogen gas target (¹⁴N(*p*, α)¹¹C) or deuteron bombardment of a solid boric oxide target (¹⁰B(*d*,*n*)¹¹C) yields ¹¹CO₂, which can be easily collected in a low temperature trap or on molecular sieves. This ¹¹CO₂ can be reduced to ¹¹CO by passage through a nickel furnace (400°C). The carbon monoxide can be further converted to phosgene (¹¹COCl₂) by treatment with PtCl₄ or by photolysis of a ¹¹CO with Cl₂ mixture. The ¹¹CO₂ can be chemically reduced (lithium aluminum hydride, LAH) to methanol, which can either be oxidized to labeled formaldehyde (silver or

Table 1 Methods for chemical syntheses with ¹¹C

Addition of ¹¹CO₂ to organometallics

M=Li, Mg

Alkylation reactions

Nucleophilic displacements with ¹¹CN⁻

Addition of ¹¹CN⁻ to carbonyl compounds

Miscellaneous

Carbonylations

Addition of organolithium reagents

ferric molybdenum catalyst) or reacted with hydriodic acid to yield labeled methyl iodide.

Proton bombardment of a nitrogen/hydrogen gas target yields ¹¹CH₄, which when mixed with ammonia and passed through a platinum furnace (1 000°C) produced H¹¹CN. Thus, a variety of one carbon "building blocks" are available for carbon-11 labeling of larger, more complex

molecules. Compounds which have been labeled with carbon-11 include carboxylic acids (esters, amides), alcohols, aldehydes, ethers, nitriles, amines, amino acids (peptides, proteins), ketones, ureas, and carbamates. In Table 1 are shown the major methods available for carbon-11 labeling. Products range from the very simple ($1\text{-}^{11}\text{C}$ -acetic acid)²⁷⁾ to the very complex (^{11}C -erythromycin)²⁸⁾. In the following sections are discussed several of the more important, and more often used, methods for carbon-11 labeling. Examples of labeled compounds will be given, but this is in no way meant to be all-inclusive. For a more extensive listing of the compounds which have been labeled with carbon-11, the readers are referred to several excellent reviews^{9), 29), 30)}.

3.1 Carboxylation of organometallic reagents

The very simple reaction of $^{11}\text{CO}_2$ with an organometallic reagent (Grignard and organolithium reagents) yields the ^{11}C -labeled carboxylic acid. A very large number of carboxylic acids have been so prepared, with the preparation of some achieved using remote³⁰⁾ or totally automated apparatus³¹⁾. Two of the simple acids, acetic acid³²⁾ and palmitic acid³⁰⁾ (hexadecanoic acid) are in routine preparation worldwide for PET studies of myocardial metabolism.

The synthesis of keto acids has been described. Reaction of the lithium enolate of acetone with $^{11}\text{CO}_2$ yields the β -keto acid acetoacetic acid³²⁾. Reaction of $^{11}\text{CO}_2$ with lithium aldimines (prepared by addition of an alkyl lithium to 1,1,3,3-tetramethylbutylisocyanide), followed by the hydrolysis of the intermediate α -imino acid, can be used to prepare α -keto acids³³⁾.

3.2 N-Alkylation reactions

A very widely used reaction is the methylation of a nitrogen atom in amines and amides:

Two reagents are available for the methylation of nitrogens: formaldehyde and methyl iodide.

Formaldehyde ($^{11}\text{CH}_2\text{O}$) is used in an adaptation of the Eschweiler-Clarke reaction:

Yields are good, and a large number of amines

have been labeled in this fashion, including morphine³⁴⁾, imipramine³⁵⁾, chlorpromazine³⁵⁾, and etorphine³⁶⁾. A related reaction which can be applied to the labeling of proteins (albumin, fibrinogen)³⁷⁾, is the use of labeled formaldehyde and a borohydride reducing agent (NaBH_4 or NaCNBH_3):

The reaction proceeds *via* the borohydride reduction of an intermediate imine, and thus can be extended to alkylation with other carbonyl compounds, such as in the synthesis of ^{11}C -practolol using ^{11}C -acetone³⁸⁾.

Methyl iodide is a good alkylating agent and has seen extensive application in *N*-, *C*-, *O*-, and *S*-alkylations. The alkylation of a secondary amine or amide proceeds in good yields, and can be applied to a wide variety of amines: the most important application has been in the synthesis of neuroactive compounds, such as *N*-methylpiperone³⁹⁾.

4. Fluorine-18

Fluorine-18, with a relatively long half-life of 110 minutes, should allow for fairly complicated organic syntheses (given the rule of thumb that syntheses should be complete within 3 half-lives, or in this case, 6 hours). However, the difficulties in fluorine chemistry (production of isotope through organic synthesis) have limited the number of compounds prepared.

Fluorine-18 can be produced by a variety of nuclear reactions, but those in most use are the $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$ and $^{18}\text{O}(p,n)^{18}\text{F}$ reactions. Fluorine-18 is available in quite a variety of forms for application in syntheses. Bombardment of a 1% F_2 /neon target yields the ^{18}F -labeled fluorine gas (^{18}FF)⁴⁰⁾. This can be converted to other fluorinating species, such as acetyl hypofluorite⁴¹⁾, perchloryl fluoride⁴²⁾, xenon difluoride⁴³⁾, and diethylaminosulfur trifluoride⁴⁴⁾. Bombardment of a water target enriched with ^{18}O results in the production of aqueous fluoride ion⁴⁵⁾⁻⁴⁷⁾, which can be rapidly and simply converted to useful nucleophilic fluoride salts of alkali metals (Cs, Rb) or tetraalkylammonium salts (e.g., tetrabutylammonium fluoride).

Although synthetic chemistry with ^{18}F has

Table 2 Methods of fluorination with ^{18}F

Aliphatic nucleophilic substitution	
$\text{R-X} + ^{18}\text{F}^- \longrightarrow \text{R-}^{18}\text{F}$	
$\text{X} = \text{I, Br, mesylate, tosylate, triflate}$	
$\text{CH}_2 - \text{CH}_2 \xrightarrow{^{18}\text{F}^-} ^{18}\text{FCH}_2\text{CH}_2\text{OSO}_2$

$\text{R-CH-CH}_2 \xrightarrow{^{18}\text{F}^-} \text{R-C-CH}_2\text{OH}$	^{18}F
Aromatic nucleophilic substitution	
$\text{XC}_6\text{H}_4\text{Y} \xrightarrow{^{18}\text{F}^-} ^{18}\text{F-C}_6\text{H}_4\text{Y}$	
$\text{Y} = \text{CN, RCO, NO}_2$	
$\text{X} = \text{I, Br, Cl, F, NO}_2$	
Aliphatic electrophilic addition	
$\text{R-CH=CH-R} \xrightarrow{^{18}\text{F-F}} \text{R-CH-CH}_2\text{R}$	^{18}F
	F
$\text{R-CH=CHR} \xrightarrow{\text{CH}_3\text{COOF}} \text{R-CH-CH}_2\text{R}$	^{18}F
	OAc
Aromatic electrophilic addition	
$\text{C}_6\text{H}_5\text{X} \xrightarrow{^{18}\text{F-F}_2} ^{18}\text{F-C}_6\text{H}_4\text{X}$	
$\text{C}_6\text{H}_5\text{-M} \xrightarrow[\text{AcOF}]{\text{F}_2 \text{ or}} \text{C}_6\text{H}_5\text{-}^{18}\text{F}$	$\text{M} = \text{Sn, Si}$
$\text{YC}_6\text{H}_4\text{-Li} \xrightarrow{\text{Cl}_3\text{OF}} \text{YC}_6\text{H}_4\text{-}^{18}\text{F}$	

proven in many cases intractable, numerous compounds have been labeled. The various methods of fluorination are summarized in Table 2. Most fluorinations can be divided into two main categories, nucleophilic and electrophilic fluorination, and then further subdivided into aliphatic and aromatic fluorinations. Examples of each of these reactions are described below. Again, this discussion is not exhaustive, and further examples can be found in other reviews^{(20), (48)}.

4.1 Aliphatic nucleophilic substitution

Under appropriate conditions (usually described as a lack of hydration by water molecules), fluoride ion is a very powerful nucleophile and base. The nucleophilic displacement of aliphatic halides and sulfonic acid esters (mesylates, tosylates, triflates) using ^{18}F fluoride ion has been used in increasing num-

bers of applications, as exemplified in the synthesis of fluorofatty acids⁽⁴⁹⁾ (F-for-Br) and fluorine-18-labeled steroids such as 16α -fluoro-estradiol- 17β (displacement of 16β -triflate)⁽⁵⁰⁾. Fluoride ion will also act as the nucleophile in the opening of the rings of cyclic sulfites and epoxides, in both cases yielding the fluorohydrin: this has been used in the synthesis of ^{18}F -2-fluoro-2-deoxyglucose (2-FDG) by opening of the appropriate cyclic sulfite⁽⁵¹⁾. In the synthesis of fluoroethanol by ^{18}F -fluoride opening of glycol sulfite⁽⁵²⁾, a specific activity of 3.7 PBq/mmol (10^5 Ci/mmol) was obtained, the highest yet reported for a fluorine-18 or carbon-11-labeled product.

4.2 Electrophilic aliphatic fluorination

The addition of ^{18}F -labeled F_2 to an alkene yields the difluoro adduct, and was the reaction initially used in the synthesis of 2-FDG, with the addition product being hydrolyzed to the desired sugar⁽⁵³⁾.

Other reagents can be prepared from F_2 , including XeF_2 , acetylhypofluorite (CH_3COOF), and trifluoromethylhypofluorite (CF_3OF). All of these reagents act similarly, and can be used to fluorinate an alkene: choice of fluorinating agent is made on the sensitivity of the substrate to side reactions with the harsher reagent F_2 . Besides FDG, this method of fluorination has been applied to the synthesis of fluorinated pyrimidines (5-fluorouracil⁽⁵⁴⁾ and 5-fluorouridine⁽⁵⁵⁾).

4.3 Nucleophilic aromatic substitution

The displacement of substituents on aromatic rings, suitably activated by electron-withdrawing groups, was reported in 1956 by Finger et al.⁽⁵⁶⁾ Recently, this method of fluorination has been extended to reactions using ^{18}F -fluoride ion, with displacement of halogens (I, Br, Cl, F), nitro-groups, and trimethylammonium substituents⁽⁵⁷⁾⁻⁽⁶⁰⁾. Yields in some cases are very high, and the reaction proceeds on a no-carrier-added level to give very high specific activity products. The major application of this reaction has been in the synthesis of numerous butyrophenone neuroleptics: spiroperidol^{(60), (61)}, *N*-methylspiro-

peridol, haloperidol, and benperidol⁶¹). Undoubtedly, this reaction will see increased application in the future for the synthesis of high specific activity fluoroaromatic compounds.

4.4 Electrophilic aromatic substitution

Fluorine-18-labeled F_2 can be used to fluorinate aromatic rings, as in the synthesis of ^{18}F -labeled 6-fluoro-3,4-dehydroxy-phenylalanin (6-fluoro-DOPA)⁶², but F_2 is a non-selective, highly reactive, and oxidative reagent. For these reasons, efforts have been made to "tame" the F_2 in the form of a less reactive reagent, such as XeF_2 and CH_3COOF . To obtain positional selectivity in ring fluorinations, however, it has been necessary to employ metalated aromatic rings:

using tin⁶³), silicon⁶⁴), and mercury⁶⁵) substituted aromatic rings. The fluorination of aromatic rings in this manner has also been employed in the synthesis of 6-fluoro-DOPA. It should be noted that the use of F_2 or its derivatives necessarily results in a carrier added product, and thus specific activities achieved using these reagents are several orders of magnitude less than that achieved using nucleophilic aromatic substitution.

5. Positron-Emitting Radiopharmaceuticals Available from Parent-daughter Generator Systems

One major obstacle to more widespread use of positron emission tomography in diagnostic nuclear medicine is that a cyclotron is required in the hospital where ^{18}O , ^{13}N , and ^{11}C are to be used. Of the cyclotron-produced positron-emitting isotopes discussed above, only ^{18}F is

sufficiently long lived that production at a site remote from the hospital could be considered feasible; however, no such service is currently offered by radiopharmaceutical manufacturers in the United States. The development of radiopharmaceuticals labeled with generator-produced positron-emitting isotopes would allow PET studies to be conducted at sites where the location of an in-house cyclotron is not practical.

The parent/daughter generator systems which produce positron-emitting isotopes are listed in Table 3. Of these, only the $^{68}Ge/^{68}Ga$ and $^{82}Sr/^{82}Rb$ generators have received much attention in the radiopharmaceutical literature. The development of radiopharmaceuticals which utilize the $^{62}Zn/^{62}Cu$, $^{52}Fe/^{52m}Mn$, and $^{122}Xe/^{122}I$ generators is seriously hindered by the rather short half-lives⁶⁶) of the parent nuclides. Commercial availability of the ^{62}Cu , ^{52m}Mn , and ^{122}I generators would greatly facilitate the investigation of their radiopharmaceutical potential, but ironically, is unlikely before their usefulness for radiopharmaceutical production has been demonstrated.

The ^{62}Cu ⁶⁷⁾⁻⁶⁹⁾ and ^{52m}Mn ⁷⁰⁾⁻⁷⁴⁾ generators employ ion exchange resins for separation of the daughter from the parent isotope. The ^{62}Zn parent of ^{62}Cu is produced by the $^{63}Cu(p,2n)^{62}Zn$ reaction⁶⁷⁾⁻⁶⁹⁾, while ^{52}Fe is available from either $^{55}Mn(p,4n)^{52}Fe$ or $^{58}Ni(p,3p4n)^{52}Fe$ reactions^{70), 71), 74)}. The 9.8 minute half-life of ^{62}Cu and the 21.1 minute half-life of ^{52m}Mn would be long enough to allow synthesis of a variety of radiopharmaceuticals containing these isotopes using suitable generator eluents. In animal studies, ^{62}Cu has been used to label colloidal copper sulfide for liver imaging and to label albumin microspheres for lung and myocardial

Table 3 Parent→daughter generator systems for position-emitting nuclides⁶⁶⁾

Parent isotope	Parent half-life	Daughter isotope	Daughter half-life	Daughter positron yield (%)	Daughter positron energy(MeV)	Daughter decay product (Stable)
^{68}Ge	288 days	^{68}Ga	68.1 min	90	1.899	^{68}Zn
^{82}Sr	25.0 days	^{82}Rb	75 s	96	3.15	^{82}Kr
^{62}Zn	9.2 h	^{62}Cu	9.73 min	98	2.93	^{62}Ni
^{52}Fe	8.27 h	^{52m}Mn	21.1 min	98	2.63	^{52}Cr
^{122}Xe	20.1 h	^{122}I	3.6 min	77	3.12	^{122}Te
^{118}Te	6.0 days	^{118}Sb	3.5 min	...	2.70	^{118}Sn
^{128}Ba	2.43 days	^{128}Cs	3.6 min	61	2.88	^{128}Xe

perfusion studies^{(67), (69)}. The ^{62}Cu chelate of *trans*-1,1-diaminocyclohexanetetracetic acid was prepared for renal imaging^{(67), (69)}. Manganese-52m chloride and acetate have been used to assess myocardial perfusion in dogs^{(71), (73)}, but detailed study of the myocardial kinetics of this tracer remains to be reported.

The very short half-life of ^{122}I is desirable for repeat imaging with low patient radiation dose, but is too short to allow elaborate chemical synthesis with this isotope. A generator consisting of a gaseous xenon reservoir eluted with sodium bicarbonate solution has been reported^{(71), (75), (76)}. It was suggested^{(75), (76)} that ^{122}I iodide might be useful for cardiac and large vessel angiography and the study of heart dynamics. Rapid iodination techniques have been developed allowing albumin to be labeled with ^{122}I for use as a plasma tracer⁽⁷¹⁾. The $^{119}\text{Te}/^{118}\text{Sb}$ and $^{128}\text{Ba}/^{128}\text{Cs}$ generators have received preliminary consideration^{(71), (72)}. It was suggested⁽⁷¹⁾ that ^{118}Sb , with a 3.5 minute half-life, might be suitable for angiography.

The $^{82}\text{Sr}/^{82}\text{Rb}$ generator^{(77)–(82)} conveniently provides the ^{82}Rb cation in aqueous saline solution. The ^{82}Sr parent is produced at Los Alamos⁽⁸²⁾ by spallation of molybdenum target and is contaminated with ^{86}Sr in at least a 1:1 ratio. Strontium-85 can account for a major portion of the patient radiation dose unless the Sr breakthrough in the generator eluent is kept very low, due to its 65 day half-life. The half-life of ^{82}Rb is desirably short, allowing rapid repeat studies; however, this short half-life and the limited chemistry of the alkali metal ions limits its potential radiopharmaceutical applications. The ^{82}Rb cation is taken up by myocardium and has been used for myocardial imaging by PET^{(83)–(86)}. The interpretation of ^{82}Rb myocardial images is complicated, since a number of studies have shown that ^{82}Rb uptake has a non-linear dependence upon myocardial blood flow^{(83)–(85)} and is significantly influenced by the presence of ischemia⁽⁸³⁾. A method of quantifying myocardial blood flow with ^{82}Rb using beta probes to measure both tracer uptake and extraction fraction in open-chested dogs has been reported^{(85), (86)}; however, the suitability of this technique for human studies with

fast time-of-flight positron cameras remains to be demonstrated. Aside from myocardial imaging, ^{82}Rb has also been reported to have potential for study of defects in the blood-brain barrier^{(79), (87), (88)}, as can occur with brain tumors. Extravasation of ^{82}Rb in the brain is indicative of blood-brain barrier disruption and can provide information on the size and vascularity of a tumor⁽⁷⁹⁾.

The generator-produced positron-emitting isotope with the greatest promise for allowing the synthesis of a diverse array of radiopharmaceuticals is gallium-68. Germanium-68 is cyclotron-produced by either the $^{68}\text{Ga}(p,2n)^{68}\text{Ge}$ or $^{68}\text{Zn}(\alpha,2n)^{68}\text{Ge}$ reactions⁽⁷⁷⁾ and decays with a half-life sufficiently long (288 days) that a generator can be delivered anywhere. A number of generator systems have been reported for separation of ^{68}Ga from its parent^{(89)–(100)}. The generator system offering the most versatility for chemical synthesis following elution^{(100)–(103)} contains ^{68}Ge adsorbed to a tin dioxide column, from which the daughter ^{68}Ga can be eluted in 1 N hydrochloric acid as the hydrated Ga^{3+} ion. The 68 minute half-life of ^{68}Ga allows the preparation of radiopharmaceuticals for a variety of purposes from this ionic generator eluent.

Gallium exists in aqueous solution exclusively in the 3+ oxidation state and exhibits chemistry similar to that of high-spin $\text{Fe}(\text{III})$ ^{(104)–(106)}. In the absence of stabilizing ligands, at physiological pH aqueous $\text{Ga}(\text{III})$ is hydrolyzed to insoluble $\text{Ga}(\text{OH})_3$. Any gallium compound to be used *in vivo* must resist hydrolysis of the metal ion and be sufficiently stable to prevent binding of the Ga by the plasma protein transferrin ($\log K=20.3$)⁽¹⁰⁷⁾ during the time frame of the nuclear medicine procedure. Some reported ^{68}Ga radiopharmaceuticals and their uses are listed in Table 4.

Gallium-68 complexes of alizarin red S and the polyaminocarboxylic acids ethylenediamine tetraacetic acid (EDTA) and diethylenetriamine pentaacetic acid (DTPA) are charged in aqueous solution at physiological pH and thus are excreted in the urine following intravenous injection. They can be used to assess renal function^{(89), (108)–(110)} as well as to detect defects in

Table 4 Gallium-68 radiopharmaceuticals

Radiopharmaceutical	Application
⁶⁸ Ga-EDTA	Renal and brain scanning ^{89), 108)–114)}
⁶⁸ Ga-DTPA	
⁶⁸ Ga-alizarin red S	
⁶⁸ Ga-transferrin	
⁶⁸ Ga-DTPA-serum albumin	Blood pool/plasma volume ^{115)–117)}
⁶⁸ Ga-albumin microspheres	Pulmonary and myocardial perfusion ^{117)–121)}
⁶⁸ Ga-iron hydroxide colloid	Liver and spleen scanning ^{109), 122)–124)}
⁶⁸ Ga-alizarin	
⁶⁸ Ga-EDTMP	Bone scanning ^{125)–128)}
⁶⁸ Ga-tripolyphosphate	
⁶⁸ Ga-citrate	
⁶⁸ Ga-(5-MeOsal) ₃ TAME	Myocardial perfusion ^{129)–131)}
⁶⁸ Ga-BP-IDA	Hepatobiliary function ^{132), 133)}
⁶⁸ Ga-(3,4-DiP-LICAM)	
⁶⁸ Ga-red blood cells	Blood pool/red cell volume ¹³⁴⁾
⁶⁸ Ga-platelets	Thrombosis localization ^{115), 134)}

the blood-brain barrier^{110)–114)}. Blood plasma volume can be measured using ⁶⁸Ga-transferrin¹¹⁶⁾, in which ⁶⁸Ga is bound at the iron binding site of the protein, or using ⁶⁸Ga-labeled albumin¹¹⁷⁾. The latter is labeled with ⁶⁸Ga after covalent attachment to the protein of a polyaminocarboxylic acid¹¹⁷⁾, which serves as the metal binding site. Monoclonal antibodies can be labeled with gallium radioisotopes following similar attachment of a polydentate chelating ligand to the antibody^{129), 130)}.

Particulate materials which are trapped in capillary beds following injection are useful agents for assessment of regional perfusion following injection^{109), 117)–124)}. Gallium-68-labeled human serum albumin microspheres are useful for lung imaging following intravenous injection^{117)–120)}. Arterial injection of labeled microspheres allows their use for assessment of perfusion in other organs. Noteworthy is a recent study¹²¹⁾ which employed ⁶⁸Ga-labeled microspheres in the validation of a model for quantitation of regional myocardial blood flow with ¹⁵O-labeled water. Colloidal iron hydroxide labeled with ⁶⁸Ga has been prepared and shown

to be useful for liver and spleen imaging^{122)–124)}. An uncharged lipophilic ⁶⁸Ga complex, ⁶⁸Ga-(5-MeOsal)₃TAME, can be used for evaluation of regional myocardial blood flow^{129)–131)}, but is less suitable than freely-diffusible ¹⁵O-water and ¹¹C-butanol for such measurements¹³¹⁾.

Bone scanning is possible with the ⁶⁸Ga complexes of ethylenediaminetetramethylene phosphate (EDTMP)¹²⁵⁾, tripolyphosphate¹²⁶⁾, and citrate^{127), 128)}. Hepatobiliary function can be assessed using the lipophilic anionic complexes ⁶⁸Ga-BP-IDA¹³²⁾ and ⁶⁸Ga-(3,4-DiP-LICAM)¹³³⁾. Red blood cells and platelets have been labeled *in vitro*^{115), 134)} by means of bidentate chelating ligands that weakly complex the ⁶⁸Ga to form lipophilic neutral complexes capable of crossing the cell membrane. These ⁶⁸Ga-labeled blood components have yet to find widespread application, however, due to difficulties in achieving efficient and reproducible labeling¹¹⁵⁾. These problems should be overcome as better techniques become available for separation of ⁶⁸Ga from the trace metal contaminants present in generator eluents^{109), 115)}.

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