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The next generation of positron emission tomography radiopharmaceuticals labeled with non-conventional radionuclides

Raisa N. Krasikova,[a,b] Ramiz A. Aliev[c,d] and Stepan N. Kalmykov*[c,d]

[a] *N. P. Bechtereva Institute of the Human Brain, Russian Academy of Sciences, 197376 St. Petersburg, Russian Federation*
[b] *Institute of Chemistry, St. Petersburg State University, 197376 St. Petersburg, Russian Federation. Fax: +7 812 328 2000*
[c] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: stepan@radio.chem.msu.ru*
[d] *National Research Centre 'Kurchatov Institute', 123098 Moscow, Russian Federation*

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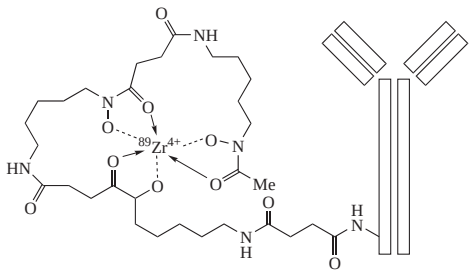
The nuclear and chemical properties of 'non-traditional' positron emission tomography (PET) radionuclides, *i.e.* ^{44}Sc, ^{61,64}Cu, ^{68}Ga, ^{86}Y, ^{89}Zr, as well as their production routes are discussed. The bio-conjugation of these radionuclides with various vectors for target delivery to tumor cells using bi-functional chelating agents is reviewed. The applications of various radiopharmaceuticals with 'non-traditional' PET radionuclides for molecular visualization of various tumors are summarized.



Introduction

Nowadays nuclear medicine imaging is well established clinical diagnostics tool for the detection, staging, and monitoring of various diseases. Among them the positron emission tomography (PET) allows real time visualization of physiological and pathological processes on the molecular level using *in vivo* tracing of radiopharmaceuticals labelled with β^+-emitting radionuclides, by detecting their 0.511 MeV annihilation gamma quanta with a coincidence technique. According to the statistics, about 70% of PET studies are currently performed in oncology, about 20% in cardiology and 10% in neurology. However, there is a trend toward an increase in the number of PET cardiac perfusion studies due to the availability of the short-lived ^{82}Rb from ^{82}Sr/^{82}Rb isotope generator.

As a key component of PET technique, an appropriate imaging probe [radiotracer or radiopharmaceutical (RP)] is able to be involved into specific biological or physiological processes or specifically reach the target of interest in the living body. Imple-

Dr. **Raisa N. Krasikova** is the head of the Radiochemistry Laboratory at the N. P. Bechtereva Institute of the Human Brain of the Russian Academy of Sciences and the associated professor at the Department of Radiochemistry, Institute of Chemistry, St. Petersburg State University. Her current research is focused on the development of new synthetic methods for radiopharmaceuticals for positron emission tomography including asymmetric synthesis of ^{18}F-fluorinated amino acids and direct nucleophilic synthesis methods for ^{18}F-fluorinated receptors radioligands; she is well recognized specialist in development of rapid, reliable and fully automated synthesis approaches for different clinically useful and new ^{11}C- and ^{18}F-labelled radiotracers.

Dr. **Ramiz A. Aliev** is the vice-head of the Branch of Nuclear and Radiation Medicine of National Research Centre 'Kurchatov Institute' and a head scientist of the Radiochemistry Division at the Department of Chemistry of M. V. Lomonosov Moscow State University. His research is focused on the radionuclide production, separation and pre-concentration methods, radioactivity detection and environmental radiochemistry. He was involved in the development of techniques for production of cyclotron radionuclides ^{95g}Tc, ^{237}Pu, ^{111}In, ^{211}At, ^{67}Ga and ^{225}Ac from protons irradiated thorium targets, and in research of photonuclear production of various medical isotopes.

Professor **Stepan N. Kalmykov** is the head of the Radiochemistry Division at the Department of Chemistry of M. V. Lomonosov Moscow State University and the head of the Branch of Nuclear and Radiation Medicine of National Research Centre 'Kurchatov Institute'. His scientific interests include radiopharmaceutical chemistry, separation and detection methods, radionuclide speciation and environmental radiochemistry. He is the author of more than 100 papers in per-reviewed journals and 3 books.

mentation of PET into clinical practice in the 1990s has revolutionised cancer imaging. PET is currently used for differentiation of cancer cells from benign tissues, determination of the extent of a tumor and staging, the identification of recurrent tumor and metastasis, assessment of a treatment response, radiotherapy planning *etc*. Traditionally, PET employs four short-lived cyclotron-produced radionuclides, three of which (^{15}O, $T_{1/2}$ = 2.04 min; ^{13}N, $T_{1/2}$ = 9.96 min; and ^{11}C, $T_{1/2}$ = 20.4 min) are isotopes of vitally important biological elements. Incorporation of these isotopes into the structures of various molecules does not affect the biochemical behaviour or metabolism, thus ensuring the exceptionally high biospecificity of the PET method. The fourth radionuclide, ^{18}F, does not belong to organogenic elements but is regarded as an 'ideal' PET radionuclide with optimum nuclear-physical characteristics (97% β^+, 3% E.C., β^+, 0.635 MeV). Owing to the low energy of emitted positrons and hence their minimum pathlength in a cell (2.4 mm), the use of fluorine-18 provides the best spatial resolution of PET images. The relatively long half-life (110 min) allows RP to be delivered to medical centres and hospitals that have no on site cyclotrons.

In comparison with the 'reference' fluorine-18, metal isotopes used in PET generally have a more complex decay scheme, lower yield and higher energy of positrons, associated gamma (as well as beta in case of copper-64) radiation, which results in poorer quality of PET images (PET image degradation) and spatial resolution (the degree of this effect depends on the isotope).[1]

Incorporation of a radioactive isotope in a radiotracer molecule considerably affects the *in vivo* metabolism. Fluorine-18 can replace a hydrogen atom or hydroxy group having similar van der Waals radii with minimum structural changes, which makes it possible to obtain so-called 'metabolism radiotracers'. The most important one is 2-[^{18}F]-fluoro-2-deoxy-D-glucose ([^{18}F]FDG), a unique radiotracer of glycolysis that is used in over 90% of all PET studies. Its metabolism has been well studied.[2] During the years of PET development, a number of RP classes based on fluorine-18 have been created: labeled analogues of amino acids, nucleosides, choline derivatives and various receptor radioligands. However, not all of them are used in clinical practice due to complexity of synthesis and automation of processes involving short-lived fluorine-18. In fact, incorporation of a fluorine-18 label into a peptide molecule requires a multistage synthesis using intermediate agents labeled with fluorine-18 (prostetic groups) that includes a stage of purification by semi-preparative HPLC and is accompanied by high radioactivity losses (and hence a low radiochemical yield).[3]

Unlike flourine-18, incorporation of metal isotopes is based on binding a radionuclide with a bifunctional chelating agent (BCA) that, in turn, can form covalent bonds with various biomolecules (vectors), with high specificity and selectivity toward certain targets. This simple and convenient method of synthesis ensures access to a broad range of radiotracers, such as labeled peptides, proteins, intact monoclonal antibodies (mAB) and their fragments (fAB), and others. Unlike ^{18}F-derivatives, RPs based on metal isotopes are not involved in cellular metabolism but bind to the target, for example, by interactions of the vector molecule with receptors expressed on the tumor surface.

Extremely important is the fact that many of the biomolecules listed above are used in peptide receptor radionuclide therapy (PRRT) and radioimmunotherapy where ^{90}Y, ^{177}Lu, ^{213}Bi and other isotopes are used as therapeutic radionuclides.[4]

Conducting a PET examination with an appropriate diagnostic RP allows one to clearly visualize its area of accumulation (target) and, accordingly, plan the treatment strategy, select the radiotherapy and subsequently evaluate its efficiency. Furthermore, based on PET data, one can calculate the optimal therapeutic dosage of a therapeutic RP to be administered, thereby minimizing the radiation dose received by the patient's organs and tissues. The use of radionuclide pairs, *i.e.*, a diagnostic and a therapeutic one, within the theranostics concept is the most efficient method for the treatment of tumor diseases (personalized medicine). In ideal case, an RP with isotopes of the same element is used, *e.g.*, the ^{86}Y/^{90}Y pair.[5] In certain cases, the isotope can have the properties of both a diagnostic and therapeutic radionuclide (^{64}Cu). RPs based on ^{68}Ga are widely used to calculate the radiation dose in PRRT created by compounds of ^{177}Lu, the most promising radionuclide[6] with the smallest range of β^- particles in a tissue (2 mm *versus* 11 mm for ^{90}Y), and two other trivalent metals (^{90}Y, ^{213}Bi). To estimate the efficiency of radioimmunotherapy (RIT) using labeled antibodies and their fragments whose biological action is from a few hours to a few days, isotopes with appropriate half-lifes are required, such as ^{86}Y (14.7 h), ^{89}Zr (78.4 h) and ^{64}Cu (12.7 h). These radionuclides are most often used to obtain radiodiagnostic agents based on intact monoclonal antibodies, their fragments, as well as RPs based on so-called engineered proteins (affibody, diabody, nanobody, *etc*.) considered in detail in another review.[7] Metal isotopes are advantageous over other long-lived PET radionuclides, such as ^{124}I ($T_{1/2}$ = 4.2 days), because they are retained in target cells after internalization (residualizing radionuclides).

Nuclear-physical characteristics of radionuclides for PET

The feasibility of using a certain radionuclide in medical diagnostics depends on its nuclear-physical characteristics and chemical properties. Radionuclides used in PET should meet the following main requirements:

– the half-life should match the residence time of the RP in the organism;

– the yield of positrons should be as large as possible, and *vice versa*, their energy should be as low as possible;

– the presence of high-energy gamma lines in the radionuclide spectrum is undesirable;

– the radionuclide should form compounds that are kinetically and thermodynamically stable *in vivo*.

Improvement of agents for delivery of radionuclides to tumor cells also changes the requirements for radionuclides. Development of agents based on antibodies rises the interest in positron emitters having relatively long half-lives comparable with the time of antibody accumulation in a tumor (immuno-PET). Yet another important trend is the use of isotope pairs, *i.e.*, a positron emitter and a therapeutic radionuclide. Agents based on the former are used for tumor visualization and selection of the strategy for application of the therapeutic agent. Pairs of this kind such as ^{44}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{68}Ga/^{67}Ga, ^{124}I/^{123}I, and ^{86}Y/^{90}Y may be pinpointed.

Methods of radionuclide production

Of the positron emitters listed in Table 1, ^{44}Sc (from ^{44}Ti, $T_{1/2}$ = = 59.1 years) and ^{68}Ga (from ^{68}Ge, $T_{1/2}$ = 270.8 days) can be obtained in generators. The other positron emitters are obtained in various types of charged-particle accelerators, mainly in cyclotrons (see Table 2).

Scandium-44. ^{44}Sc has a longer half-life in comparison with ^{68}Ga. Furthermore, it can be used as the isotope pair for the very promising therapeutic nuclide ^{47}Sc or as an analogue of widely used medical radionuclides ^{90}Y and ^{177}Lu. ^{44}Sc also attracts keen interest due to the fact that, like ^{68}Ga, it can be obtained in a generator from a long-lived precursor, ^{44}Ti ($T_{1/2}$ = 60.6 years). However, production of the latter involves considerable difficulties. The main method involves the reaction: ^{45}Sc(p,2n)^{44}Ti (σ_{max} ~ 40 mbarn at E = 24 MeV). According to optimistic estimates, about 560 MBq (15 mCi) can be produced by irradiation for one week of a thick scandium target with a beam of

Table 1 Some promising positron emitters and their nuclear properties.

Nuclide	$T_{1/2}$/h	$E_{max}\beta^+$ (%)	$E_{av}\beta^+$/keV	$E\gamma$ (%)
^{44}Sc	3.93	1473.5 (94.3)	632	1157.0 (99.9)
^{61}Cu	3.34	559.5 (2.6)	238	283.0 (12.2)
		932.5 (5.5)	399	656.0 (10.8)
		1148.1 (2.3)	494	
		1215.5 (51)	524	
^{64}Cu	12.70	653.0 (17.6)	278	1345.8 (0.47)
^{68}Ga	1.13	821.7 (1.2)	353	1077.3 (3.2)
		1899.1 (87.7)	836	
^{86}Y	14.74	1221 (11.9)	535	443.1 (16.9)
		1545 (5.6)	681	627.7 (32.6)
		1988 (3.6)	883	645.9 (9.2)
		3141 (2.0)	1437	703.3 (15.4)
^{89}Zr	78.4	902 (22.7)	396	908.9 (100)

30 MeV protons having 1 mA intensity.[8] The existing generator prototype makes it possible to obtain about 180 MBq ^{44}Sc. It proved to be operational for at least a year.[28] Therefore, the majority of studies were carried out with ^{44}Sc obtained in a cyclotron. The (p,n) reaction that can be performed in a standard medical cyclotron is the common solution. Irradiation of a target from $^{44}CaCO_3$ with 11 MeV protons (90 min, 50 μA) allows about 1.9 GBq ^{44}Sc to be obtained.[29] In addition to $CaCO_3$ targets, irradiation of a $Ca(NO_3)_2$ solution was suggested.[30]

Copper isotopes. Four copper isotopes (60, 61, 62, 64) are considered as potential medical positron emitters. ^{64}Cu is the most interesting one because it manifests the smallest average energy of positrons, almost does not emit high-energy γ-quanta, and its half-life allows the radionuclide to be delivered to clinics within a region. ^{61}Cu is also a promising nuclide. It is unlikely that isotopes 60 and 62 would find wide application due to relatively short half-lives, high energy of positrons, and high energy gamma rays accomplished ^{60}Cu decay.

A number of methods have been suggested for the preparation of ^{64}Cu and ^{61}Cu. They are listed in Table 2. The majority of the reactions have been studied quite thoroughly. A critical analysis of experimental data and the recommended cross-sections of ^{64}Cu formation can be found in ref. 22 and on IAEA, website www-nds.iaea.org. The available data on cross-sections and reaction yields are analyzed in refs. 10 and 31.

Copper-64. Currently, the mostly used production method of ^{64}Cu involves ^{64}Ni irradiation with protons. The method can be implemented in dedicated medical cyclotrons and allows up to 5.9 GBq μA^{-1} ^{64}Cu (11.4 MeV) to be obtained at saturation[32] with a specific activity of *ca*. 0.7 TBq μmol^{-1}. Advantages of the method include the absence of side reactions and a high yield, whereas the necessity for regeneration of the expensive target material is a drawback. As the proton energy increases to 30 MeV, the yield increases to 1 GBq $\mu A^{-1} h^{-1}$. The amounts of ^{64}Cu sufficient for preclinical trials can be obtained by irradiation of nickel with natural isotopic composition.[33] Irradiation of ^{64}Ni with deuterons by the (d,2n) reaction gives comparable yields, but it is used more rarely in practice due to the scarce availability of the required beams.

Upon ^{68}Zn irradiation with protons, ^{64}Cu is formed in two routes: ^{68}Zn(p,αn)^{64}Cu (Q = –7.8 MeV) and ^{68}Zn(p,2p3n)^{64}Cu (Q = –36.1 MeV). Accordingly, the excitation function has two maxima (www-nds.iaea.org): σ_{max} ~ 63 mbarn (E = 26 MeV) and σ_{max} ~ 53 mbarn (E = 75 MeV). Generation of an ^{67}Cu admixture starts by the reaction ^{68}Zn(p,2p)^{67}Cu (Q = –9.98 MeV) at energies above 55 MeV. Bonardi *et al*.[34] discussed the simultaneous formation of ^{64}Cu and ^{67}Cu upon irradiation of Zn target. It appears promising to obtain ^{64}Cu as a side product in the production of ^{67}Ga by the reaction ^{68}Zn(p,2n)^{67}Ga. Under typical irradiation conditions (29 MeV, 11 h, 225 μA), about 90 GBq ^{64}Cu (and < 1% ^{67}Cu) is produced.[35] The ^{66}Zn(p,2pn)^{64}Cu reaction (σ_{max} ~ 65 mbarn at 42 MeV) can be implemented in medium energy proton accelerators. It has a high yield but is complicated by the formation of ^{61}Cu[12] in the same region as the main reaction. The optimum energies for the ^{66}Zn(p,2pn)^{64}Cu and ^{68}Zn(p,x)^{64}Cu processes are complementary, therefore, in order to optimize the output, it was suggested[17] to use a tandem target, first ^{66}Zn (70 → 35 MeV), then ^{68}Zn (35 → 20).

The ^{67}Zn(p,α)^{64}Cu reaction (σ_{max} ~ 33 mbarn at 13–14 MeV[36]) is of potential interest since it gives a pure product. In this case, radioisotopic impurities are only determined by the degree of target enrichment. This approach can be implemented in a

Table 2 The main reactions giving the radionuclides considered and their yields.

Radionuclide	Reaction	Energy/MeV	Yield/MBq $\mu A^{-1} h^{-1}$	Impurities (%)	Reference
^{44}Ti	^{45}Sc(p,2n)^{44}Ti	38 → 0	0.005	–	8
^{44}Sc	^{44}Ca(p,n)^{44}Sc	11 → 9	~70	^{44m}Sc	29
	^{44}Ca(d,2n)^{44}Sc	14.9 → 7.5	220	^{44m}Sc (2.2)	9
^{61}Cu	^{61}Ni(p,n)^{61}Cu	15 → 7	1418	–	10
	^{62}Ni(p,2n)^{61}Cu	26 → 18	2100	^{62}Cu (330)	10
	^{60}Ni(d,n)^{61}Cu	10 → 4	486	^{60}Cu (1)	10
	^{58}Ni(α,p)^{61}Cu	18 → 10	90	–	10
	^{59}Co(α,2n)^{61}Cu	39 → 18	318	^{60}Cu (1.2)	11
	^{64}Zn(p,α)^{61}Cu	19 → 10	366	^{60}Cu (0.5)	12
	^{64}Zn(d,αn)^{61}Cu	19.5	131	^{64}Cu (28)	13
^{64}Cu	^{64}Ni(p,n)^{64}Cu	12 → 9	236	^{61}Cu (0.4)	14
	^{nat}Ni(p,xn)^{64}Cu	20	7	^{61}Cu (100)	15
	^{64}Ni(d,2n)^{64}Cu	19 → 15	370	^{61}Cu (0.3)	16
	^{68}Zn(p,x)^{64}Cu	35 → 20	167	^{67}Cu (0.9)	www-nds.iaea.org
	^{66}Zn(p,2pn)^{64}Cu	70 → 35	777	^{61}Cu (156)	12, 17
	^{67}Zn(p,α)^{64}Cu	20 → 0	42	–	18
	^{nat}Zn(p,x)^{64}Cu	66 → 0	360	^{61}Cu (no data), ^{67}Cu (no data)	19
	^{66}Zn(d,α)^{64}Cu	13 → 7	6.6	–	20
	^{64}Zn(d,2p)^{64}Cu	19.5	31	^{61}Cu (500)	21
	^{nat}Zn(d,x)^{64}Cu	25 → 10	57	–	22
	^{69}Ga(p,x)^{64}Cu	60 → 30	195	^{67}Cu (1)	23, 24
^{68}Ge	^{nat}Ga(p,x)^{68}Ge	35 → 0	1.6	–	www-nds.iaea.org
^{86}Y	^{86}Sr(p,n)^{86}Y	14 → 10	400	^{86m}Y (280), ^{87}Y (0.4), ^{87m}Y (1–4)	25
	^{88}Sr(p,3n)^{86}Y	43 → 33	1005	^{85}Y (36), ^{85}mY (3), ^{87}Y (5), ^{87}mY (28)	26
^{89}Zr	^{89}Y(p,n)^{89}Zr	14 → 9	58		27

standard medical cyclotron with a proton energy of 18 MeV. The yield of the ^{66}Zn(d,α)^{64}Cu reaction is not high but it gives a pure product: the presence of impurities is determined by the degree of enrichment of the target material.[20] The maximum cross-section (σ_{max} ~ 29 mbarn) is about 9–10 MeV.[22] Various production methods are compared in Table 2.

Copper-61. The simplest method for ^{61}Cu production involves ^{61}Ni irradiation with protons using the (p,n) reaction, σ_{max} ~ ~ 500 mbarn (E = 10 MeV). A yield of 1 GBq μA^{-1} h^{-1} ^{61}Cu can be obtained in a common medical cyclotron with a beam energy of 11 MeV.[10] If an average energy accelerator is available, the (p,2n) reaction on ^{62}Ni [σ_{max} ~ 350 mbarn (E = 22 MeV)] can be used, which provides an even higher yield (up to 3 GBq μA^{-1} h^{-1} at 30 MeV). Isotopes 60 and 62 that are formed concurrently do not constitute a serious problem due to short half-life time periods. Irradiation of ^{64}Zn with protons may be an alternative. The ^{64}Zn(p,α)^{61}Cu reaction (σ_{max} ~ 80 mbarn at E = 14.5 MeV) has a considerably lower yield, however, the material of the target is much cheaper.[31]

^{61}Cu can also be obtained nearly without impurities by the ^{59}Co(α,2n)^{61}Cu reaction [σ_{max} ~ 470 mbarn (E = 28 MeV)] from cobalt with natural composition.[31] Irradiation for 3.4 h (one half-life period) yields 777 MBq μA^{-1} h^{-1} in the energy range 39 → 18 MeV.[11] If an accelerator of α-particles is available, it can be regarded as the optimum method since it does not require the enriched target to be regenerated. The other methods presented in Table 2 are more likely of theoretical interest.

Gallium-68. Germanium-68, a parent radionuclide for ^{68}Ga, can be obtained by irradiation of gallium by protons in cyclotrons or in linear accelerators. This reaction gives no side products, while the yield of the end product increases with the beam energy. ^{68}Ge is formed by the ^{69}Ga(p,2n)^{68}Ge reaction [σ_{max} ~ 560 mbarn (E = = 20 MeV)]. Nuclear data for this reaction were obtained by Levkovskij[37] and by Porile *et al*.[23]

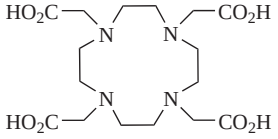
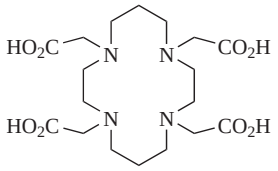
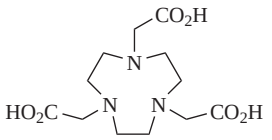
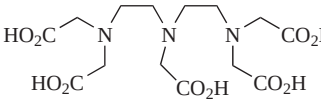
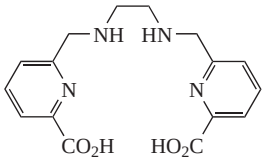
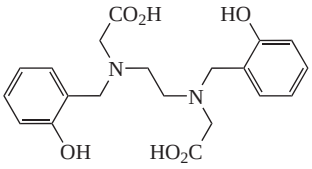
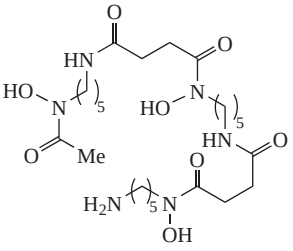
Yttrium-86. The ^{86}Sr(p,n)^{86}Y reaction (σ^{max} ~ 970 mbarn at E = 14 MeV) is the most common way for the production of ^{86}Y.[26] However, in this case the beam energy has to be limited to 14 MeV in order to avoid the formation of ^{85m,g}Y impurities by the (p,2n) channel.[25,37] Formation of an isomeric ^{86m}Y admixture cannot be avoided, but its activity quickly decreases during the treatment of the target ($T_{1/2}$ = 48 min). The ^{88}Sr(p,3n)^{86}Y reaction occurs with a considerably higher yield but gives side products, ^{87}Y (79.8 h) and ^{87m}Y (13.4 h).

Zirconium-89. Owing to the long half-life, ^{89}Zr is considered as a potential candidate for immuno-PET. It is mainly obtained by irradiation of yttrium (which consists of 100% ^{89}Y) with protons by the ^{89}Y(p,n)^{89}Zr reaction in a common medical cyclotron. The reaction has a maximum cross-section of 790 mbarn at 14 MeV,[38] but the beam energy should be limited to ~14 MeV in order to avoid the formation of long-lived ^{88}Zr by a (p,2n)-reaction (the threshold is 13.1 MeV). Small amounts of ^{89}Zr can be obtained by irradiation of strontium with natural isotopic composition by α-particles, but this method is unlikely to be of interest for industrial scale production.[39]

Bifunctional chelating agents for radionuclides

Metal radionuclides used in targeted delivery RPs are incorporated into their structure by binding with BCAs that can form covalent bonds with various biomolecules (vectors). The main requirements for BCAs include high stability of complex compounds with radiometals that should ensure *in vivo* stability of RPs. The coordination chemistry of radiometals was described previously in a number of reviews.[40,41] Table 3 presents information about some BCAs used and the stability of the corresponding complex compounds with medical radionuclides.

Table 3 Some most popular BCAs for radiometals.

Chelator	log K_{ML}[a]	Reference
 DOTA	^{61,64}Cu^{2+}: 22.2, 22.7	42–44
	^{68}Ga^{3+}: 21.3	45–52
	^{44}Sc^{3+}: 27.0	28, 53, 54
	^{86}Y^{3+}: 24.3–24.9	55–59
 TETA	^{61,64}Cu^{2+}: 21.9, 21.6	60, 61
	^{68}Ga^{3+}: 19.74	62
	^{86}Y^{3+}: 14.8	63
 NOTA	^{61,64}Cu^{2+}: 21.6	64
	^{68}Ga^{3+}: 31.0	45, 52, 65–67
	^{44}Sc^{3+}: 16.5	53
 DTPA	^{61,64}Cu^{2+}: 21.4	68, 69
	^{68}Ga^{3+}: 24.3, 25.5	68, 70
	^{86}Y^{3+}: 21.2, 22.0, 22.5	59, 71
	^{89}Zr^{4+}: 35.8–36.9	68, 71
 H2dedpa	^{61,64}Cu^{2+}: 19.2	73
	^{68}Ga^{3+}: 28.1	52, 74, 75
 HBED	^{68}Ga^{3+}: 38.5	76
 DFO	^{68}Ga^{3+}: 28.6	70

[a] K_{ML} = [ML]/[M][L].

The radiopharmaceutical chemistry of gallium-68

Of metal radionuclides used in PET, ^{68}Ga became the most popular isotope both in preclinical and clinical trials. A doubtless advantage of ^{68}Ga over other metal radionuclides used in PET and fluorine-18 is that it can be obtained in a ^{68}Ge/^{68}Ga isotope generator using long-lived ^{68}Ga as the parent radionuclide ($T_{1/2}$ = = 270.8 days). The life time of this generator is 1–2 years. Moreover, the optimum ratio of the half-lives of the mother and daughter radionuclides makes it possible to elute ^{68}Ga several times a day (each 4 h). Yet another positron emitter, ^{66}Ga ($T_{1/2}$ = = 9.49 h), is a promising isotope for the production of labeled

antibody fragments owing to its long half-life. However, it is used very seldom and mainly for research purposes. Though the first $^{68}Ge/^{68}Ga$ generators were suggested about 50 years ago, development of radiotracers and intense clinical use of the corresponding RPs began rather recently[77] after generators producing a ^{68}Ga eluate of an appropriate quality had appeared.[78] Application of RPs in syntheses requires an eluate with exceptionally high radionuclide and radiochemical purity with a minimum content of impurity metals (especially trivalent iron) that can compete with trivalent gallium at the step of incorporation into BCA-conjugates. Particular attention is paid to the preparation of the concentrated eluate with high specific molar activity in order to diminish the reaction mixture volume in labeling of substrates (*e.g.*, peptides) the amount of which is as small as 10–20 μg. $^{68}Ge/^{68}Ga$ generators are currently manufactured by a few companies on a commercial basis. The generator manufactured by Eckert and Zigler, Germany, has recently passed marketing authorization as a medical device in Europe, which in turn allows generator-produced gallium-68 to be used in RP syntheses for clinical diagnostics.

Unlike the classical generator for ^{99m}Tc production, elution and concentration of ^{68}Ga is a complex multistep process using solid-phase extraction on cation- and/or anion-exchange resins to eventually give $^{68}Ga^{3+}$ in dilute hydrochloric acid solution. A gallium-68 generator is normally used in combination with an automated synthetic module that controls both the ^{68}Ga elution/concentration process and the chemical synthesis of the radiotracer as such, including the stage of final purification by solid-state extraction in disposable cartridges. Automated modules of about ten different models have been developed by now.[79] The most convenient ones are so-called cassette synthetic modules widely used for automation of fluorine-18 handling.[80] Since all the required reagents, cartridges for solid-phase extraction and other components are installed in a sterile disposable cassette, the synthesis fully complies with the GMP (Good Manufacturing Practice) requirements and does not require highly skilled personnel (a radiochemist). Though these developments started rather recently in the case of gallium-68, sterile cassettes for syntheses of the most clinically important RPs are delivered by ABX company, Germany (for the SCINTOMICS GRP module), by the generator manufacturer, Eckert and Zigler, Germany (for the Modular Lab system), and by some others.

The necessity of using expensive synthetic modules and cassettes is among the factors that limit the clinical application of ^{68}Ga. The simplest and cheapest technology that largely determined the success of SPECT studies with generator-produced ^{99m}Tc involved RP synthesis using so-called reagent kits.[81] The coordination chemistry of gallium differs considerably from that of technetium,[82] and creation of reagent kits in the case of gallium-68 appears a non-trivial but solvable task. This was confirmed by recent studies on creation of reagent kits for syntheses of gallium-68 labeled DOTA-conjugated peptides used in clinical diagnostics of neuroendocrine tumors (NETs).[83] ANMI company, Belgium, that specializes in manufacture of BCAs for metal radioisotopes, and ABX/EckertZigler consortium, Germany, have started to produce reagent kits for the synthesis of RPs used in prostate cancer (PRC) diagnostics. Evidently, the availability of reagent kits for the most promising radiotracers will largely determine the popularity of gallium-68 in modern PET diagnostics.

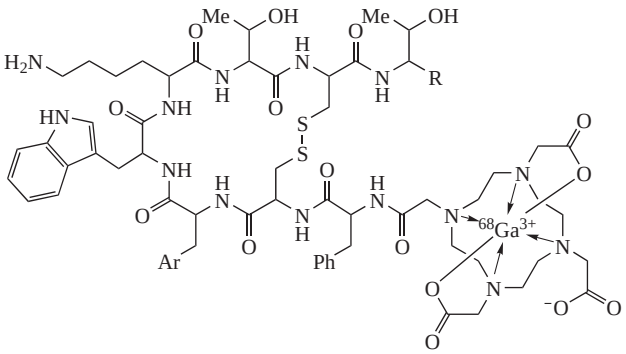
Dozens of radiotracers labeled with gallium-68 have been created and their viability confirmed in preclinical trials with PET chambers for small animals. Some of them are successfully used in clinical trials. Numerous reviews deal with this topic,[7,82–89] therefore we shall limit ourselves to the most popular and clinically important RPs for oncodiagnostics, while the readers are referred to literature sources.

The coordination chemistry of gallium, including gallium-68, has been studied quite thoroughly (see reviews[82,84]). Gallium belongs to the fourth period and third group (main subgroup) of the periodical system. The most stable oxidation state of gallium in aqueous solutions is +3. In aqueous solutions, the free hydrated Ga^{3+} cation is stable at pH < 3 only. At pH 3–7 in the absence of stabilizing ligands, Ga^{3+} is gradually hydrolyzed to give an insoluble hydroxide, $Ga(OH)_3$. At pH > 7 (including the physiological value of pH 7.4), $Ga(OH)_3$ is converted to a soluble complex anion, $[Ga(OH)_4]^-$. The main coordination number of Ga^{3+} is six, though tetra- and penta-coordinated gallium complexes are also known. However, gallium complexes with vacant coordination positions are more sensitive to hydrolysis under physiological conditions.

Chelators containing oxygen (carboxylate, phosphonate, phenoxide) as well as amino and thiol groups form stable complexes with Ga^{3+}. In an optimal variant, a chelator should form complexes with a high thermodynamic and/or kinetic stability, therefore, when choosing a BCA, its geometry, lipophilicity, total charge and other parameters should be considered; the requirements for BCAs are detailed in a review.[90]

Radiotracers for diagnostics of neuroendocrine tumors

The half-life of ^{68}Ga is perfectly suitable for RP syntheses based on short peptides that are quickly removed from blood and healthy tissues. The exceptional success of PET diagnostics using ^{68}Ga is due to the development of labeled peptides, analogues of octreotide (OC), conjugated with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) – a bifunctional cyclic chelator with high *in vitro* and *in vivo* stability. Three radiotracers of this group, ^{68}Ga-DOTA-TOC (Tyr^3-OC), ^{68}Ga-DOTA-NOC ($1\text{-}Nal^3$-OC) and ^{68}Ga-DOTA-TATE (Tyr^3-Thr^8-OC) (Figure 1), agonists of somatostatin receptors (ssrt) of subtypes 2, 3 and 5, are intensely used in clinical PET diagnostics of highly differentiated NETs, such as phaeochromocytomas, neuroblastomas, carcinoid tumors, insulinomas and others that have elevated density of somatostatin receptors [somatostatin receptor imaging (SRI)]. Despite the differences in affinity to different ssrt subtypes, high PET sensitivity (95–100%) in determination of neuroendocrinal neoplasias with various localizations was noted for any of the DOTA-conjugated peptides, while the quality of the tomograms obtained is higher than the 'gold standard' of SPECT with ^{111}In-DTPA-octreotide (Octreoscan). For some non-carcinoid NET types, PET with ^{68}Ga-DOTA-conjugated peptides is a more efficient method for visualization of the primary tumor and metastases than the traditional PET scan with 6-^{18}F-L-FDOPA.[91] A comprehensive overview of DOTA-conjugated and some other peptides labeled with ^{68}Ga and containing various BCAs is presented in refs. 87 and 92.



^{68}Ga-DOTA-TOC R = CH_2OH, Ar = 4-HOC_6H_4
^{68}Ga-DOTA-TATE R = CO_2H, Ar = 4-HOC_6H_4
^{68}Ga-DOTA-NOC R = CH_2OH, Ar = 2-naphthyl

Figure 1 Structures of three peptide RPs with ^{68}Ga.

Of particular interest is ^{68}Ga-DOTA-TATE, since this radiotracer is used for efficiency estimation of PRRT with radiotherapeutic analogues of ^{177}Lu-DOTA-TATE that are, in particular, used for the treatment of child neuroblastomas.[93] Application of ^{177}Lu as a radiotherapeutic radionuclide with 'mild' nuclear-physical characteristics is one of the most important achievements in the technology of cancer treatment by the PRRT method,[94] where a preceding PET study with ^{68}Ga-DOTA-TATE makes it possible to choose optimal doses of the therapeutic agent to be administered. Furthermore, ^{68}Ga-DOTA-TATE is used for molecular visualization in clinical trials of a new agent based on alpha-emitting ^{213}Bi-DOTA-TATE for the treatment of neuroendocrinal hepatic metastases and bone marrow carcinomatosis.[95]

Methodical guidelines for PET-CT diagnostics with ^{68}Ga-DOTA-conjugated peptides were developed in 2010 by the European Association of Nuclear Medicine (EANM).[96] To manufacture the corresponding RPs for clinical usage, it is recommended to use modern automated technologies that meet the GMP requirements,[97] as well as reagent kits.[83] Despite the rather fast development of PET in Russia where a ^{68}Ga generator was developed back in the 1970s,[98] ^{68}Ga-DOTA-TATE is the first and thus far the only radiotracer that is used in PET examinations of patients with NET at the Russian Research Centre of Radiology and Surgical Technologies, St. Petersburg (clinical trials stage).

In addition to successful clinical application of ^{68}Ga-DOTA-conjugated peptides in PET diagnostics of NET with overexpression of somatostatin receptors, quite a few receptor-specific RPs labeled with gallium-68 have been developed for other targets, in which both DOTA and other chelators are used as the BCAs.[90] Intense studies are in progress to create radiotracers for functional PET diagnostics with the use of ^{68}Ga: myocardial perfusion, cerebral perfusion, renal function, functions of hepatobiliary and other systems, in order to create a gallium-68 based set of radiotracers for the same types of diagnostics as those traditionally performed by SPECT with ^{99m}Tc. Such developments seem particularly important due to the much-debated 'molybdenum crisis' and its possible effect on the availability of ^{99m}Tc generators for clinical examinations. In general, replacement of SPECT and gamma-scintigraphy with ^{99m}Tc by PET examinations with ^{68}Ga is apparently advantageous owing to the high resolution of the PET method and a long service life of ^{68}Ga generators, though the cost efficiency of SPECT and PET examinations, including the cost of a single clinical dose of alternative RPs, is a matter of discussion.

Below we consider the most clinically significant receptor-specific RPs based on gallium-68.

Radiotracers for estimation of the tumor angiogenesis processes

Pathological angiogenesis, *i.e.*, uncontrollable formation of new blood vessels, is among the main hallmarks of the presence of a malignant tumor and metastasis, as well as ischemia and inflammation sites.[99] Modern cancer treatment methods include anti-angiogenic therapy by agents preventing the uncontrollable growth of blood vessels. Several RP classes have been suggested for PET estimation of the efficiency of these methods. Radiotracers that specifically bind to adhesive receptors of $\alpha_V\beta_3$ integrin group are the most promising. Overexpression of these receptors is noted on endothelial cells involved in angiogenesis and vascular remodeling, as well as on tumor cells. At the same time, expression of these receptors does not occur in mature vessels and in non-tumor epithelium. All the known RPs for estimation of integrin expression are based on the arginine–glycine–aspartic acid tripeptide (RGD) that binds with integrins containing the α_V subtype. It was suggested to obtain RPs specific to $\alpha_V\beta_3$ subtype using cyclic ligands, such as c(RGDfK). Based on the latter, ^{18}F-Galacto-RGD,[100] one of the first radiotracers for estimation of $\alpha_V\beta_3$ integrin expression in clinical examinations, was obtained. Despite the excellent tumorotropic characteristics and pharmacokinetics, as well as high resistance to metabolism, the use of this RP in clinical examinations is problematic due to the complexity and duration of radiochemical synthesis based on label incorporation *via* a prosthetic group, *i.e.*, ^{18}F-propionic acid. A DOTA-conjugated analogue, ^{68}Ga-DOTA-RGD, was obtained, which manifested a high affinity to $\alpha_V\beta_3$ integrins, but strongly bound to blood proteins as well. The first clinical examinations in patients were performed using radiotracers such as ^{68}Ga-NOTA-RGD[101] and ^{68}Ga-NODAGA-RGD[102] with a nine-membered BCA that strongly retained ^{68}Ga. Recently, another BCA was suggested for complexation with gallium-68 (TRAP chelator – 1,4,7-triazacyclononane-1,4,7-tris[(2-carboxyethyl)methylene phosphinic acid])[103] with more beneficial characteristics for angiogenesis visualization, however, clinical PET examinations with ^{68}Ga-TRAP(RGD)^3 were not performed. A key role in angiogenesis is played by the vascular endothelial growth factor (VEGF). It has been shown that many tumors express VEGF that is extremely important for the development and sustention of the tumor bloodstream. In was suggested to estimate the expression of VEGF receptors in experimental studies in animals with tumors using ^{68}Ga-NODAGA-VEGF$_{121}$.[104] RPs for angiogenesis visualization used in clinical examinations or in clinical trials are considered in detail in another review.[105]

Radiotracers for diagnostics of prostate cancer

PET diagnostics of PRC is traditionally performed using derivatives of choline, a precursor in biosynthesis of phosphatidylcholine – the main component of cell membranes whose level in proliferating PRC cells is considerably elevated. The synthesis of fluorine-18 labeled methyl derivatives of choline appears rather complex for automation since it includes a stage of preparation of a volatile alkylating agent (^{18}F-fluoromethyl bromide), where uncontrollable loss of radioactivity can occur. Furthermore, to obtain a high-contrast PET image with ^{18}F-derivatives of choline, rather a prolonged 'two-phase' procedure is required.[106] Development of highly specific RPs on the basis of metal isotopes bound to various receptors that are expressed on the surface of neoplasmatic prostate tumors is rather a new but already quite successful approach in PET diagnostics.

Recent developments in this field aim at creation of agents specific to prostate specific membrane antigen (PSMA), an integrated membrane protein consisting of 750 amino acids (100–120 kDa) with intracellular, intramembrane and extracellular domains.[107] In spite of its name, PSMA is not an antigen specific to prostate. It is also detected in healthy cells of other endocrine glands and expressed not only by prostate tumors but also by other carcinomas (rectal cancer, kidney carcinoma, *etc.*). However, the majority of studies deal with PSMA-specific radiotracers for PRC diagnostics, where it has been shown that high expression of this antigen is observed in case of castration-resistant and metastasizing cancer types.[108]

SPECT diagnostics traditionally used a PSMA-radiotracer based on monoclonal mice antibodies (7E11), ^{111}In-capromab pendetide (ProstaScint™), produced by EUSA Pharma. These antibodies (labeled, *inter alia*, by ^{89}Zr) are bound with PSMA inner domain (epitope), therefore a scan with ProstaScint™ only reflects the presence of 'dead' cells within the tumor tissue. ProstaScint™ has only a limited application in diagnostics of PRC with high prostate specific antigen (PSA) level not metastasizing into bone tissue; its application faces technical difficulties, while scintigraphy should be performed on day 4–6 after the RP has been administered.[109] An alternative is provided by the recently suggested radiotracers based on small molecules

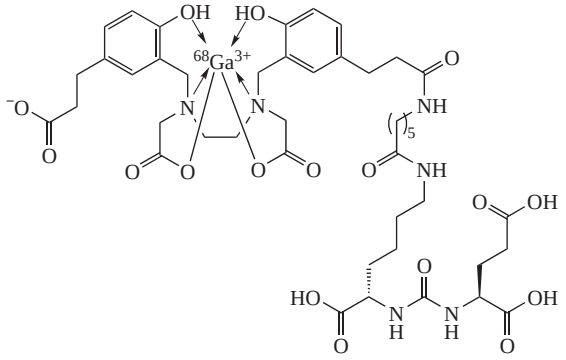


Figure 2 ^{68}Ga-PSMA-HBED-CC.

that are PSMA inhibitors allowing the visualization of living cells on the tumor surface.[108] ^{68}Ga-Glu-urea-Lys(Ahx)-HBED-CC (^{68}Ga-PSMA-11 or ^{68}Ga-DKFZ-11) (Figure 2), a PET radiotracer developed in 2012 by a scientific team from Heidelberg, Germany[110] (HBED-CC chelator: *N*,*N'*-bis[2–hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N*,*N'*-diacetic acid), proved to be the most successful. The preparation methods and radiopharmaceutic aspects of the synthesis of this RP were described in detail.[111] In a record-breaking time, ^{68}Ga-PSMA-11 worked its way up from development and first examinations in patients[112] to clinical application. A multicentre study carried out in European PET centres confirmed the exclusively high diagnostic properties of ^{68}Ga-PSMA-11 that allows a PRC backset to be identified at very low PSA levels (0.2 ng ml^{-1}), which is impossible in a traditional examination with ^{18}F-fluoromethylcholine. In 2015, the ^{177}Lu-DKFZ-11 radiotherapeutic agent was obtained within the framework of the theranostics concept. Application of this agent in the treatment of a patient with a metastasizing form of PRC resulted in a considerable response to radiotherapy accompanied by a significant decrease in PSA level from 38 to 4.6 ng ml^{-1}.[113]

Prostate tumors are characterized by overexpression of gastrin-releasing peptide receptors (GRPr). Radiotracers based on various bombesin (BBN) derivatives were suggested for estimation of the expression of these receptors.[114] BBN is a peptide that consists of 14 amino acids and has high affinity to GRPrs. Various BBN derivatives, both GRPr agonists and antagonists, were considered as PET radiotracers. Bayer Schering Pharma, Germany, developed a synthetic antagonist of GRPr and its DOTA-conjugated peptide, ^{68}Ga-DOTA-4-amino-1-carboxymethylpiperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2 peptide (BAY86-7548). The first multicenter PET studies in Europe[115] confirmed the prospects of this agent in diagnostics of primary PRC and identification of metastases in lymph glands. It has been shown that uptake of BAY86-7548 in a tumor is considerably higher in comparison with ^{11}C- and ^{18}F-cholin and ^{11}C-acetate, whose production requires a medical cyclotron and expensive synthetic modules. BAY86-7548 (another name: ^{68}Ga-PM2) currently undergoes clinical trials (phases II and III) by PET/MRI methods in order to estimate its safety, toxicity and suitability in diagnostics of prostate adenocarcinoma (https://clinicaltrials.gov/ct2/show/NCT02624518).

The approach by scientists from Heidelberg[116] who suggested a biospecific ^{68}Ga-radiotracer with high affinity both to PSMA and GRPrs seems very interesting; the new radiotracer is being studied in experimental PRC models.

In conclusion of this chapter, let us emphasize that the capabilities of PET diagnostics with RPs based on gallium-68 are not limited to the above discussion; dozens of other radiotracers exist. The prospects of further development of this approach are much discussed in reviews, such as refs. 117, 118 and many others.

Copper-64

Hypoxic agents that are selectively accumulated in tissues with insufficient oxygen supply due to redox processes were among the first RPs based on copper-64. In this case, accumulation of radiotracers is inversely proportional to the partial oxygen pressure p_{O_2} that can be measured by invasive methods using electrodes. The PET method makes it possible to identify regions of hypoxia in brain or in myocardium, as well as hypoxic tumors. The latter are known to be resistant to radiotherapy, so determination of the level (degree) of hypoxia by non-invasive methods provides very important information in selecting the treatment approach. It is interesting that nearly all positron-emitting copper isotopes (^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu), including the short-lived generator-produced radionuclide ^{62}Cu ($T_{1/2}$ = 9.74 min), were used to obtain RPs of this class. Bis(thiosemicarbazones) were mainly used as the ligands. Of these, diacetyl-bis(*N*-methylthiosemicarbazone) (Cu-ATSM) (Figure 3) and pyruvaldehyde-bis-(*N*4-methylthiosemicarbazone) (Cu-PTSM) derivatives suggested in the beginning of the 1990s[119] became most popular in clinical PET diagnostics. The main problem in PET visualization of hypoxic processes is that the images obtained with radiotracers of nitroimidazole class [^{18}F-fluoromisonidazole (F-MISO) and others] traditionally used in PET have low contrast. Therefore, to obtain a sufficiently high RP accumulation ratio in zones with reduced oxygen delivery (hypoxyc/healthy tissue ratio), a PET examination is performed for no less than 2 h. The use of bis(thiosemicarbazone) derivatives labeled with copper isotopes makes it possible to obtain images with higher contrast, though the kinetics of these RPs also requires improvement. The results obtained using these agents in visualization of solid hypoxic tumors or their parts (^{60,62,64}Cu-ATSM) in order to choose the therapy and estimate its efficiency, as well as in cardiologic (myocardial perfusion – ^{62}Cu-PTSM, ^{62}Cu) and more rarely in neurological examinations, were summarized in a recent overview.[120]

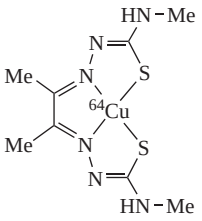


Figure 3 ^{64}Cu-ATSM.

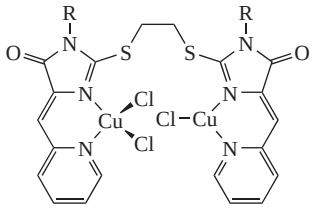
It has been shown[121–124] that Cu-ATSM specificity toward hypoxic cells is three orders higher with respect to normoxic cells. The reason for this specificity of Cu-ATSM has not been understood in full, but it is most likely to result from intracellular reduction of Cu^{2+} to Cu^{+} within the complex on exposure to NADH and peptides. Reduction in hypoxic cells is irreversible and results in formation and protonation of the unstable CuI-ATSM complex.

The specificity of Cu-ATSM toward hypoxic cells stimulated clinical trials with various copper β^+ emitting radionuclides, *i.e.*, ^{60}Cu, ^{62}Cu and ^{64}Cu, for visualization of lung, neck and uterine cervix cancer, as well as rectal carcinoma.[125–127]

The majority of PET studies with copper isotopes use ^{64}Cu. Copper-64 is a radionuclide with unique properties that has the qualities of both a diagnostic (β^+) and therapeutic (β^-) agent. The presence of a positron component allows one to visualize the RP accumulation in a pathological zone (tumor) of interest by PET and, based on these data, estimate the efficiency of radiotherapy, calculate the radiation exposure and the optimum radiotherapeutic dose. Similarly to ^{68}Ga, copper-64 is used to obtain receptor-specific RPs, but great care should be taken in

selection of BCAs for complexation with copper. In aqueous solutions, copper can exist in three oxidation states, namely, I, II and III. Monovalent copper does not form stable complexes under these conditions. In turn, trivalent copper only forms complexes under certain conditions that are difficult to implement. Therefore, radiopharmaceutic chemistry of copper-64 is the coordination chemistry of bivalent copper. As concerns $^{64}Cu^{2+}$, many of its complexes are stable in aqueous solutions but unstable *in vivo*. In fact, DOTA that forms stable complexes with ^{68}Ga is a suboptimal BCA for the preparation of ^{64}Cu-DOTA-conjugated peptides due to fast label loss as a result of trans-chelation reactions.[128] PET examinations of patients with NET were performed using ^{64}Cu-DOTA-TATE[129] and ^{64}Cu-TETA-OC (TETA is the 1,4,8,11-tetraazacyclotetradecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid).[130] TETA is considered as one of the most adequate BCAs for complexation with copper-64, though a wide range of diverse macrocyclic ligands with complex structures were suggested for chelation of copper isotopes, *e.g.* ^{64}Cu-AmBaSar-RGD[131] for estimation of angiogenesis processes. However, the majority of RPs obtained on their basis are only used in preclinical trials.

Previously,[132] binuclear complex compounds with derivatives of 2-alkylthio-5-arylmethylene-4*H*-imidazolin-4-ones were obtained where copper was present in two oxidation states, Cu^{I} and Cu^{II} (Figure 4). The compounds were shown to have high cytotoxicity in *in vitro* trials with a number of cancer cell lines. This property results from penetration of complexes into cell nucleus and inhibition of the activity of certain enzymes. High antitumor activity was shown for complexes containing non-radioactive copper.



R = Pr, allyl, Ph, cyclopropyl, $(CH_2)_3N_3$

Figure 4 Copper complex with 2-alkylthio-5-arylmethylene-4*H*-imidazolin-4-ones.

Radiotracers for radioimmunodiagnostics

In recent years, strong interest was noted in monoclonal antibodies (mAb) labeled with metal isotopes as RPs for radioimmunotherapy and diagnostics, where the required isotopes should possess a sufficiently long half-life for studies on relatively long-term processes of mAb accumulation in the target.[133] Efficient radiochemical approaches based on conjugation of metals with various BCA for the preparation of labeled antibodies and fragments thereof have been developed. The synthetic method should ensure a high radiochemical yield at low antibody concentrations (in order to obtain high specific activity). Furthermore, the reaction should be performed at room temperature in order to protect the antibody from decomposition. The choice of the BCA considerably affects the *in vivo* stability of the corresponding complex, since the loss of the label is accompanied by radioactivity accumulation in the liver and by an undesirable radiation dose. In turn, the resulting radioimmunoconjugate should ensure a high tumor/nontumor tissue accumulation ratio. These and other specific aspects of preparation and application of RPs based on mAb or fragments thereof are beyond the scope of this review.

The capabilities of PET in radioimmunodiagnostics with the copper-64, yttrium-86 and zirconium-89 isotopes, methods of RP preparation, BCA selection and other aspects were considered in detail in another review.[134]

Of these, ^{89}Zr ($T_{1/2}$ = 78.4 h) is only used for labeling monoclonal antibodies. Owing to its long half-life, it can be used to study processes 3–5 days long. Studies with this isotope started rather recently, hence most of them are preclinical trials. Desferal (DFO or Ff) that forms stable complexes with zirconium(VI) at room temperature was chosen as the optimum BCA. It was initially used for labeling monoclonal antibodies 7E11 with zirconium-89, however, ^{89}Zr-DFO-7E11 only bound to dead cells on the intracellular epitope of the tumor. Yet another alternative agent based on highly specific anti-PSMA antibody, ^{89}Zr-DFO-J591 (Figure 5), demonstrated excellent results in PRC diagnostics.[135] Detailed information about other RPs for PET radioimmunodiagnostics can be found in reviews (refs. 136, 137 and others).

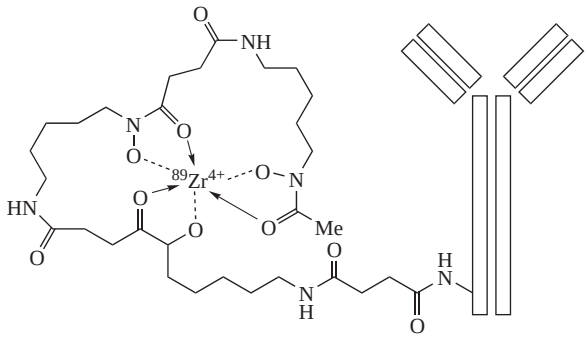


Figure 5 Schematic representation of DFO-conjugation of ^{89}Zr with mAb.

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