Review

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Prospects for the production of radioisotopes and radiobioconjugates for theranostics

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Abstract: The development of diagnostic methods in medicine as well as the progress in the synthesis of biologically active compounds allows the use of selected radioisotopes for the simultaneous diagnosis and treatment of diseases, especially cancerous ones, in patients. This approach is called theranostic. This review article includes chemical and physical characterization of chosen theranostic radioisotopes and their compounds that are or could be useful in nuclear medicine.

Keywords: biomolecules; cyclotron; radiation therapy; radioisotopes; radiopharmaceuticals; reactor; theranostic application.

Introduction

In nuclear medicine the word "theranostic" means an application of the same molecule radiolabeled with different radioisotopes of the same element (or its analogs), with the same (or similar) chemical properties for a specific molecular targeting. That is why pairs of radionuclides of the same element are preferable. This approach gives a possibility of application the theranostic radiopharmaceuticals in both – diagnostics and therapy according to the type of radionuclide [1]. It allows the personalization of treatment to each patient.

Radionuclides emitting positrons or gamma-radiation can be used for diagnosis, respectively, in positron emission tomography (PET) and single-photon emission computed tomography (SPECT) technique. Radionuclides that emit corpuscular radiation β^-, α, and Auger electrons emitters are applied for therapy.

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There are many examples of theranostic isotope pairs: $^{123,124}I/^{131}I$, $^{99m}Tc/^{186}Re$, $^{43,44}Sc/^{46,47}Sc$, $^{60,61,64}Cu/^{67}Cu$, $^{68}Ga/^{67}Ga$, $^{68}Ga/^{177}Lu$, $^{72}As/^{77}As$, $^{86}Y/^{90}Y$, $^{111}In/^{90}Y$, or less common $^{203}Pb/^{212}Pb$ and $^{197}Au/^{198}Au$.

Theranostic approach is suitable, mainly because of the same chemical properties of radionuclides and the possibility to use the same chelating compounds and guiding molecules for therapeutic and diagnostic agents. Additionally in case of so called *in vivo* generators, for example $^{44m}Sc/^{44}Sc$, there is no change in oxidation state after decay. The ideal theranostic pair should include the isotopes with proper nuclear properties and long enough half-life. The production for both of isotopes should be possibly easy at many production centers and stable compounds should be facile to synthesis. Basic characteristics of chosen theranostic pairs are presented at Table 1.

Gallium

^{68}Ga was considered for imaging at the beginning of PET history [2] and it is the β^+ emitter routinely used for labeling of PET receptor radiopharmaceuticals. ^{68}Ga ($T_{1/2}$=68.1 min, 89% β^+ and 11% EC, $E_{\beta+max}$=1.90 MeV) could be obtained through the electron capture decay of ^{68}Ge ($T_{1/2}$=270.95 days), which is absorbed on an appropriate solid phase, therefore it is easily achieved from commercially available $^{68}Ge/^{68}Ga$ generators.

The $^{69}Ga(p,2n)^{68}Ge$ nuclear reaction in which a target of ^{nat}Ga is irradiated with a 23 MeV proton beam is used to produce commercial $^{68}Ge/^{68}Ga$ generators. The separation of the ^{68}Ge isotope from the Ga target material is described in Refs. [3, 4]. The final product is placed on an inorganic substrate (SnO_2 or TiO_2) which is covered with a Pb layer.

There are alternative ways to make ^{68}Ge. One way is the $^{71}Ga(p,4n)^{68}Ge$ nuclear reaction using high energy protons, and the other one is the $^{66}Zn(\alpha,2n)^{68}Ge$ nuclear reaction using an alfa beam [5].

The cyclotron production of ^{68}Ga can be carried out on the basis of two target systems: solid targets and liquid targets.

Table 1: Decay properties of theranostic radioisotopes.

Diagnostic isotope	$T_{1/2}$	Decay/diagnostic technique	Therapeutic isotope	$T_{1/2}$	Decay
^{68}Ga	68.1 min	β^+/PET	^{67}Ga	3.26 days	EC, Auger
^{43}Sc	3.9 h	β^+/PET			
^{44}Sc	4.0 h	β^+/PET	^{47}Sc	3.35 days	β^-
^{60}Cu	23.7 min	β^+/PET	^{67}Cu	61.8 h	β^-, Eγ=185 keV (47%)/SPECT
^{61}Cu	3.3 h	β^+/PET			
^{64}Cu	12.7 h	β^+ 61% β^- 39%, EC			
^{86}Y	14.7 h	β^+/PET	^{90}Y	64.1 h	β^-
^{203}Pb	51.9 h	EC, Eγ=279 keV (81%)/SPECT	^{212}Pb	10.6 h	β^- (to ^{212}Bi, α)
^{197}Au	–	Optical properties	^{198}Au	2.7 days	β^-

Solid targets: ^{68}Ga production is possible using targets in which the target material is enriched ^{68}Zn or ^{nat}Zn. Then the ^{68}Zn(p,n)^{68}Ga nuclear reaction is used and the proton beam comes from medical cyclotrons with an energy at ~12 MeV. This proton energy is important to avoid the production of ^{67}Ga via the (p,2n) nuclear reaction at energies >12 MeV. Even using enriched ^{68}Zn targets, the coproduction of ^{66}Ga ($T_{1/2}$=9.49 h) and ^{67}Ga ($T_{1/2}$=3.26 days) cannot be avoided. By using natural copper and silver as a backing material, the production of contaminants in the form of long-lived ^{65}Zn ($T_{1/2}$=244 days) and ^{109}Cd ($T_{1/2}$=453 days) via the ^{65}Cu(p,n)^{65}Zn and ^{109}Ag(p,n)^{109}Cd nuclear reactions, respectively, are unavoidable. Platinum backing is also used. It has a lower thermal conductivity than copper and silver, however, it is considerably more expensive.

Due to the limited commercial availability of Zn-enriched foil, the possible direct production of ^{68}Ga [6] from such targets is not widely used.

For the large-scale production (up to 140 GBq) of ^{68}Ga [7], compressed ^{68}Zn enriched targets were used and effective molar activity was 77.4 ± 5.0 GBq/μmol with 89% recovery yield. Another group of scientists reports that they obtained ^{68}Ga (A_{sat}=141 MBq/μA and yield = 64 MBq/μA) from 1 h long irradiations on a 13 MeV cyclotron at TRIUMF [8].

Liquid targets: alternative production of ^{68}Ga by irradiating a liquid targets of zinc chloride and zinc nitrate with a ~13–14 MeV proton beam form medical cyclotrons have been described in several publications [9–11].

Comparing the cyclotron production of ^{68}Ga with the generator, it should be emphasized that cyclotron production of ^{68}Ga has the advantage of extremely high activities of ^{68}Ga over eluting product from a generator.

The half-lives of mother and daughter nuclides are advantageous for clinical application even if the hospital is not equipped with a cyclotron. The ^{68}Ge/^{68}Ga generator can be used for 1–2 years and allows to eluate the radiotracer daily. The half-live of ^{68}Ga is long enough to carry out the syntheses and data acquisition [12].

Radiolabeling with gallium is dominated by application of bifunctional chelating system. Bifunctional chelating agent, usually DOTA (1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid) or similar ligands and its analogs (Figure 1) [13] complexes the metal cation and simultaneously enables the connection with a proper biomolecule, for instance small peptide or monoclonal antibody.

Also other bifunctional chelators such as triazacyclononane triphosphinic acid have many valuable properties required for a chelating agent radiolabeled with ^{68}Ga. Fast and selective complex formation in high temperatures, easy synthesis and high complex stability looks promising for application of these chelators [14–16]. But for fast complexation in room temperature *N*,*N*′-Bis(2-hydroxybenzyl)ethylenediamine-*N*,*N*′-diacetic acid (HBED) is better selection [17].

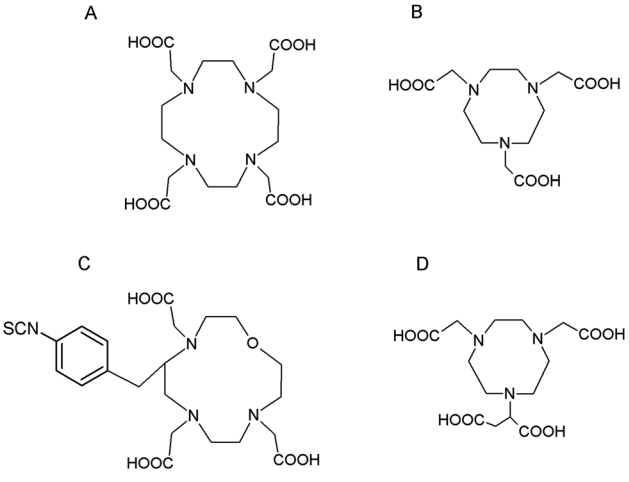

Figure 1: Ligands suitable for complexation of gallium, scandium, and similar metals: (A) DOTA, (B) NOTA, (C) OXO-DO3A, and (D) NODAGA.

The huge advantage of gallium isotopes is the possibility of labeling DOTA-derivatized peptides; the most important are somatostatin analogs DOTATOC ((DOTA-Phe^1-Tyr^3)octreotide) and DOTATATE (DOTA-Tyr^3-octreotate) (Figure 2). Both analogs have an affinity to somatostatin receptors (SSTRs) overexpressed on neuroendocrine tumors (NETs).

In 2016 the U.S. Food and Drug Administration (FDA) approved Netspot™, the first kit for the preparation of ^{68}Ga-DOTATATE injection for PET imaging, as a diagnostic tool to localization of NETs [18]. From this time the number of application of this radiotracer increased rapidly.

In 2019 ^{68}Ga-DOTATOC was approved by the FDA for PET imaging of somatostatin receptor SSTR-positive gastroenteropancreatic NETs [19].

^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE possess a comparable diagnostic value to disclosure of NETs. Both radiolabeled somatostatin analogs exhibit high capability to detect lesions from NETs, however, ^{68}Ga-DOTATOC could be superior to ^{68}Ga-DOTATATE, because of higher tumor affinity, as was indicated by higher values of SUVmax (maximal standardized uptake values) [20].

^{68}Ga-DOTATOC was also studied in patients with meningiomas, which express SSTRs in nearly 100% of cases, and SSTR2 is the most frequently detected subtype in benign meningiomas [21].

As the theranostic pair for ^{68}Ga could be applied an Auger emitter – ^{67}Ga ($T_{1/2}$=78.3 h, EC) [22], which has been also applied in SPECT technique. The simple compound – ^{67}Ga citrate is approved by U.S. FDA as a diagnostic agent. This isotope was applied for diagnosis a wide range of malignant diseases like lymphomas (Hodgkin's disease and non Hodgkin's lymphoma [NHL]) and additionally different tumors, e.g.,: lung carcinoma, melanoma, hepatocellular carcinoma, sarcomas, testicular tumors, multiple myeloma, head and neck tumors, and also for diagnosis neuroblastoma [23].

Gallium citrate is transported and extracted like iron, localizing in tumors and inflammatory conditions. It has multiple peaks and the most abundant photon has the lowest energy. In current practice, for diagnostic application, the lower three peaks (93 keV, 185 keV, 300 keV) are acquired [24]. ^{67}Ga could be used as a SPECT agent, but it does not have favorable properties for scintigraphy. However, besides of gamma emission, ^{67}Ga emits Auger electrons. Radioisotopes that emit Auger electrons with a shorter range in tissue (<1 μm) are interesting for targeted radionuclide therapy (TRT) and could be applied in treatment of micro metastases [25].

In tumors that expressed SSTRs like NETs or neuroblastomas, which are the most common solid pediatric malignancy, also ^{67}Ga-DOTATOC and ^{67}Ga-DOTATATE might be considered for its diagnosis or treatment [26]. Labeling with gallium isotopes is relatively easy in all well-equipped radiochemical laboratories, what is an additional advantage.

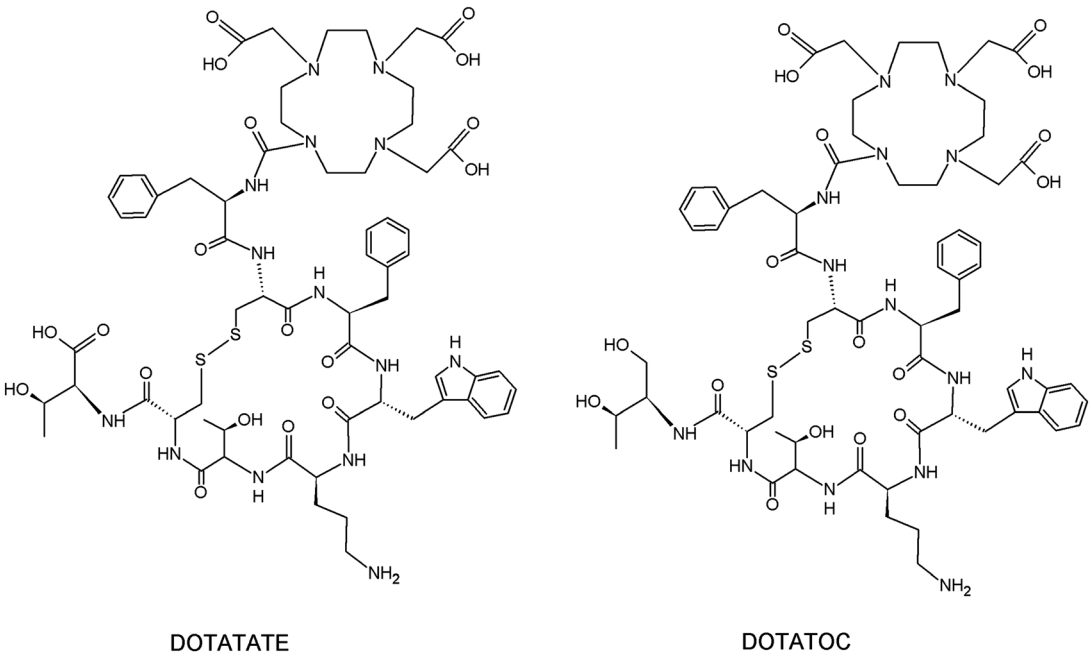

Figure 2: DOTA-derivatized peptides – somatostatin analogs DOTATATE (DOTA-Tyr^3-octreotate) and DOTATOC ((DOTA-Phe1-Tyr3)octreotide).

Scandium

Scandium is a very attractive element for theranostic application in nuclear medicine. The most important isotopes for diagnosis are ^{43}Sc (β^+, $T_{1/2}$=3.89 h, E_β=476 keV) and ^{44}Sc (β^+, $T_{1/2}$=3.97 h, E_β=632 keV). In turn ^{47}Sc (β^- (100%), $T_{1/2}$=3.35 days, E_β=162 keV) is suitable for therapy. ^{47}Sc also emits γ-ray with energy of 159 keV with branching ratio of 68%, which can be used for imaging in SPECT.

The requirement to use an enriched ^{43}Ca target [27] for the production of ^{43}Sc limits the use of accelerators on a large scale.

In order to obtain activity for medical applications [28–31], in the case of ^{43}Sc production with the use of a cyclotron, it was proposed to irradiate with alpha particles with energy in the range of 23.9–28.1 MeV of natural Ca targets for a period of 1–2 h.

The nuclear reaction ^{40}Ca(α,p)^{43}Sc and ^{40}Ca(α,n)^{43}Ti → ^{43}Sc is used to produce ^{43}Sc. When irradiating enriched ^{40}Ca targets, products are obtained with high radionuclide purity (>99%) and with impurities below 1.5*10^{-5}% of the ^{43}Sc activity produced. Another possibility to produce ^{43}Sc is to use the ^{42}Ca(d,n)^{43}Sc nuclear reaction in which a deuteron beam irradiates an enriched ^{42}Ca target.

Two different ^{43}Sc production methods using proton irradiation of enriched ^{46}Ti and ^{43}Ca targets were also compared [32].

Irradiation for 7 h of an enriched 97% ^{46}Ti target yielded ~200 MBq ^{43}Sc with high radionuclide purity (>98%) using the ^{46}Ti(p,α)^{43}Sc nuclear reaction [32].

In the case of the ^{43}Ca(p,n)^{43}Sc nuclear reaction, higher amounts of ^{43}Sc were obtained, except that the final product contained a mixture of ^{43}Sc and ^{44}Sc with an activity ratio of 2:1. An enriched target of 57.9% $^{43}CaCO_3$ was irradiated [33].

^{44}Sc in ground state or ^{44g}Sc with a half-life of 3.93 h, is also a β^+ emitter with branching ratio of 94%. This radioisotope can be produced in two ways. From the ^{44}Ti/^{44g}Sc generator [34], or directly by irradiation of an enriched ^{44}Ca target [35].

When comparing ^{44g}Sc with ^{43}Sc, it should be noted that ^{44g}Sc is more attractive to produce than ^{43}Sc because the starting material, ^{44}Ca, is more (2.1%) than ^{43}Ca (0.14%), which is reflected in the price of the target material. ^{44g}Sc is complementary to other PET isotopes. The attractiveness of ^{44g}Sc is due to the fact that the half-life of ^{44g}Sc is between ^{68}Ga ($T_{1/2}$=67.71 min) and ^{64}Cu ($T_{1/2}$=12.701 h) [36].

Associated with ^{44g}Sc decay, a high-energy gamma ray at 1.157 MeV, with a high probability of occurrence (99.9%), is emitted.

A new three-gamma imaging technique developed at the SUBATECH laboratory (Nantes, France) uses this γ ray in a coincidence with two 511 keV quanta from positron annihilation also emitted from the ^{44g}Sc isotope. Currently, this new three-gamma imaging technique is also developing at Marian Smoluchowski Institute of Physics, Jagiellonian University, Poland [37]. It is also interesting to note that ^{44}Sc is proposed as an isotope appropriate for the newly invented positronium imaging [38–40].

At Medical Physics Department, University of Wisconsin, Madison, developed a procedure for the preparation of a target by joining several 100–150 mg of dendritic pieces by pressing them into the target holder with the aid of a mechanical lever. A total of 400–600 mg of natural 99.99% metallic calcium (Sigma Aldrich, St. Louis, MO) was used as target material. Severin et al. wrote the holder was a short 4.2 mm cylinder (3.8 cm diameter) with a 1.26 cm^2 by 2.5 mm flat-bottom cavity in the center for holding the calcium. 1.7 mm of aluminum separated the calcium target from water-jet cooling applied to the back side of the holder. To protect the cyclotron from contamination with possible evaporated calcium, a piece of aluminum foil with a thickness of 12.5 μm was placed on the irradiated surface of the target. Irradiations were performed on the UW-Madison PETtrace at 16 MeV. Irradiations of a number of targets were performed at different currents, varying them in the range from 5 to 27 μA and the irradiation time 1 h [41].

^{44g}Sc and ^{44m}Sc can be effectively produced using $^{nat}CaCO_3$ or ^{nat}CaO and of course enriched $^{44}CaCO_3$ as target. In order to reduce the production of contaminants and maximize the production of scandium, enriched target material should be used. With the use of protons, production takes place in the ^{44}Ca(p,n) nuclear reaction. This reaction has an energy threshold of 4.536 MeV. Gained knowledge indicate that the most interesting production route is via ^{44}Ca(p,n) nuclear reaction with the $CaCO_3$ or CaO [42]. Irradiated material can be later easily dissolved for the chemical separation [43–45].

For the 15.2 MeV proton energy, the TTY value obtained for ^{44g}Sc was 17.2(6) MBq/μAh, with 3% of the largest impurity of ^{43}Sc. This value would be increased to about 48 MBq/μAh if metallic targets were used.

A standard 16 MeV proton beam of 1 μA can produce up to 20 MBq ($CaCO_3$) or 35 MBq (CaO) after 1 h of irradiation of natural targets and 40–50 times more if the commercially available >90% enrichment is used. In case of natural target, ^{43}Sc ($T_{1/2}$=3.89 h) is present at the level of 3% while the use of the enriched target eliminates the radioactive impurities almost completely [42].

By utilizing a cyclotron, reactor or electron linear accelerator, ^{47}Sc can be produced through a series of nuclear reactions. The list of possible nuclear reactions for production of ^{47}Sc is presented at Table 2.

Where the Q-value of a nuclear reaction is defined as the difference between the sum of the masses of the initial reactants and the sum of the masses of the final products, in energy units. For reactions in which there is a decrease in the kinetic energy of the products Q-value is negative.

By irradiating highly enriched $^{48}CaCO_3$ target material, reducible to ^{48}CaO, with an 17.75 MeV proton beam and a 500 μm thick target, a saturation yield of 12 GBq/μA of ^{47}Sc with a 85% of purity at EOB can be achieved. Carzaniga et al. indicated that the main impurity will be ^{48}Sc at 14%, while the amount of ^{43}Sc, ^{44}Sc, and ^{44m}Sc is predicted to be below 1% altogether. Since the purity will improve with time when the target is not irradiated, a fractionated bombardment can be envisaged. A saturation yield of 1.3 GBq/μA of ^{47}Ca can be achieved. This isotope could be separated from Sc after EOB and used as a high purity ^{47}Sc generator [46].

With a cyclotron with alpha particle beam, the possibility of producing ^{47}Sc by the ^{44}Ca(α,p)^{47}Sc nuclear reaction was tested. As a result, relatively lower yield and radionuclide purity were obtained [31].

^{47}Sc can be produced efficiently in a nuclear reactor [47]. The ^{47}Sc isotope can be produced by irradiating ^{46}Ca targets in a high neutron flux reactor using the ^{46}Ca(n,γ)^{47}Ca → ^{47}Sc nuclear reaction. This method was studied by Domnanich et al. [48].

Another proposed method of producing ^{47}Sc is the use of linear electron accelerators (linacs) [49].

Comparing the production of ^{47}Sc with ^{177}Lu, it should be noted that in the case of ^{47}Sc it is relatively easy to isolate this radionuclide from the target material, but a smaller cross-section for this nuclear reaction is obtained than for ^{177}Lu.

The chemical properties of scandium as a trivalent metal allow obtaining the stable complexes with a chelating agent – macrocyclic ligands like DOTA [27] – the "gold standard" for complexing scandium – or its analogs [50].

Generally that kind of ligands is usually used for complexation of metallic radionuclides due to their high stability. For instance, the thermodynamic stability constant (logK) of Sc(III) with DOTA equals 27.0. Majkowska-Pilip et al. [27] proved that ^{44}Sc radionuclide can be used instead of ^{68}Ga in PET technique. ^{44}Sc has a longer half-life and forms stable radiobioconjugates, which possess more similar than ^{68}Ga structure to radiobioconjugates with therapeutic radionuclides – ^{90}Y and ^{177}Lu. But the greatest advantage of ^{44}Sc usage in PET is possibility of application of different scandium radioisotope – ^{47}Sc, a low energy and carrier-free β^- emitter, as a therapeutic radionuclide in the same radiobioconjugate.

Thermodynamic stability of Sc(III) complexes with the macrocyclic ligands allows to label with radioactive scandium isotopes somatostatin analogs DOTATOC and DOTATATE with higher stability than gallium.

^{44}Sc is naturally compared with ^{68}Ga as a PET radionuclide. Singh et al. [51] applied the cyclotron produced ^{44}Sc conjugated with DOTATOC for restaging of neuroendocrine neoplasms in two male patients. The results showed that in comparison with images obtained with ^{68}Ga-DOTATOC, there was no visually significant uptake of ^{44}Sc-DOTATOC in the pituitary and salivary glands, or in the intestines, what means that ^{44}Sc is also proper for these applications.

The ^{44}Sc radionuclide with a β^+ branching of 94.3% is very suitable for clinical PET. Besides, ^{44}Sc can be produced via cyclotron [43, 52] or eluted for several decades from the long lasting ^{44}Ti/^{44}Sc generators [44, 53, 54] what is an additional benefit of this isotope usage.

Apart from the standard ligands and vectors, a very promising approach is osteosarcoma treatment using exopolysaccharide (EPS) derivatives also labeled with radioisotopes, instead of hazardous heparin.

EPS that mimic heparin molecule are produced by *Alteromonas infernus bacterium*, show antimetastatic

Table 2: The list of possible nuclear reactions for production of ^{47}Sc.

Installation	Nuclear reaction	Natural abundance, %	Q-value, MeV
Accelerator directly	^{48}Ca(p,2n)^{47}Sc	0.187	−8.741
	^{48}Ca(d,3n)^{47}Sc	0.187	−10.966
	^{46}Ca(d,n)^{47}Sc	0.004	6.261
	^{44}Ca(α,p)^{47}Sc	2.09	−1.996
	^{50}Ti(p,α)^{47}Sc	5.18	−2.231
	^{50}Ti(d,αn)^{47}Sc	5.18	−4.455
	^{49}Ti(p,^{3}He)^{47}Sc	5.41	−11.869
	^{49}Ti(d,α)^{47}Sc	5.41	6.483
	^{48}Ti(p,2p)^{47}Sc	73.72	−11.445
	^{48}Ti(d,^{3}He)^{47}Sc	73.72	−5.951
	^{48}Ti(γ,p)^{47}Sc	73.72	−11.445
	^{47}Ti(d,2p)^{47}Sc	7.44	−2.043
	^{51}V(p,αp)^{47}Sc	99.75	−10.292
Accelerator indirectly	^{48}Ca(p,d)^{47}Ca → ^{47}Sc	0.187	−7.727
	^{48}Ca(d,t)^{47}Ca → ^{47}Sc	0.187	−3.694
	^{46}Ca(d,p)^{47}Ca → ^{47}Sc	0.004	5.051
	^{50}Ti(p,p^{3}He)^{47}Ca → ^{47}Sc	5.18	−24.018
	^{50}Ti(d,αp)^{47}Ca → ^{47}Sc	5.18	−5.665
	^{49}Ti(p,3p)^{47}Ca → ^{47}Sc	5.41	−20.797
Reactor	^{47}Ti(n,p)^{47}Sc	7.44	0.181
	^{46}Ca(n,γ)^{47}Ca → ^{47}Sc	0.004	11.626

properties and could represent a new class of vectors to be combined with theranostic radionuclides, e.g., $^{47}Sc/^{44}Sc$ [55].

Copper

There are four copper radioisotopes that possess nuclear properties appropriate for nuclear medicine applications – ^{67}Cu, ^{64}Cu, ^{61}Cu, and ^{60}Cu.

^{60}Cu ($T_{1/2}$=23.7 min, 93% β^+, 7% EC) and ^{61}Cu ($T_{1/2}$=3.339 h, 61% β^+, 39% EC), the short lived β^+ emitters are suitable for PET technique.

^{60}Cu production route $^{60}Ni(p,n)^{60}Cu$. McCarthy et al. published that the nickel target (>99% enriched or natural nickel) was plated onto a gold disk (54–225 μm thickness) and irradiated with 14.7 MeV proton beam and yields of up to 865 mCi of ^{60}Cu have been achieved using enriched ^{60}Ni [56]. Specific activities (using enriched material) ranged from 80 to 300 mCi/μgCu for ^{60}Cu. ^{60}Cu emits prompt gamma rays in cascade with each positron in the 1–2 MeV range that are virtually unaffected by the typical lead and lead/tungsten shielding in the PET gantry.

For ^{61}Cu available direct production routes $^{61}Ni(p,n)^{61}Cu$, $^{60}Ni(d,n)^{61}Cu$ and $^{64}Zn(p,\alpha)^{61}Cu$. In the context of ^{61}Cu production, one additional advantage when compared with ^{64}Cu is that it is possible to obtain relatively high radioisotopic purity by irradiation of natural abundance targets, including proton irradiation of natural zinc or deuteron irradiation of natural nickel. By changing to enriched target materials, yields can be scaled accordingly.

Nevertheless, for nuclear medicine, especially for theranostic treatment most interesting are two other copper isotopes: ^{64}Cu (which emits β^+, β^-, and Auger electrons) and ^{67}Cu (β^- emitter 100%, also emits γ rays, E_γ=185 keV [48.7%]).

^{64}Cu has a half-life of 12.701 h. It decays through electron capture in 44% of the case, by β^- in 38.5% with a maximum energy of 579.4 keV and finally by β^+ emission in 17.5% of the case with a maximum energy of 653 keV. These emissions are accompanied by high-energy gamma radiation with an energy of 1,345.75 keV but with a low probability of occurrence. Considering the emitted radiations, it can be used for both therapy and PET imaging. The most commonly used is irradiation of ^{64}Ni enriched with protons, but in the available literature a number of methods for producing ^{64}Cu can be found [57–59]. For most (p,n) reactions, production cross-sections are high. The $^{64}Ni(p,n)^{64}Cu$ nuclear reaction is the preferred route because it results not only in a higher production yield but it can be used with so called medical cyclotrons, typically delivering up to 20 MeV protons. Irradiations are typically carried out with 8–14 MeV protons.

^{67}Cu (which emits β^-, γ) has a half-life of 2.6 days. As in the case of ^{64}Cu, a number of available nuclear reactions have been described for the production of ^{67}Cu. The known direct routes are: $^{67}Zn(n,p)^{67}Cu$, $^{70}Zn(d,\alpha n)^{67}Cu$, $^{64}Ni(\alpha,p)^{67}Cu$, $^{68}Zn(p,x)^{67}Cu$, $^{70}Zn(p,\alpha)^{67}Cu$, $^{68}Zn(\gamma,p)^{67}Cu$. ^{67}Cu decays to the ground state of stable ^{67}Zn in 20% of decay events and to the 93.3 and 184.6 keV excited states in 23% and 56% of decay events, respectively. Production of ^{67}Cu via deuteron irradiation of ^{70}Zn was also reported [60]. Also the production via $^{64}Ni(\alpha,p)^{67}Cu$ nuclear reaction with a 36 MeV alpha beam at 15 eμA (electrical microampere) conducted for 7 h was demonstrated. Under these irradiation conditions, a yield of 55 ± 10 MBq of ^{67}Cu at the end of bombardment (EOB) was obtained, with a production rate of 527 ± 96 kBq/μAh at EOB [61].

Copper is an important microelement for the proper functioning of the organism. It is located mainly in the skeletal system and muscles, but in smaller amounts also in the liver, brain, and blood. Copper is built into the active centers of many enzymes and is a cofactor of many enzymatic reactions. It has an influence on the formation and proper functioning of red blood cells, the circulatory system and the metabolism of fats and carbohydrates. The studies have shown that copper ions are also involved in cancer increase and progression. Experimental data revealed a higher level of copper accumulation in malignant then in normal tissues [62] and generally the important role of copper in tumor growth and metastasis [63].

The altered copper metabolism in tumor cells could be related to the role of the copper transport protein hCTR1, a 190-amino-acid protein comprising three transmembrane domains, which is overexpressed in many tumors – prostate, lung, breast, and liver cancers; glioblastomas; and melanoma. Therefore targeting this protein with radioactive copper ions could be relevant for molecular imaging of metabolic disorders in different cancers with use of simple salt $^{64}CuCl_2$ [64, 65].

Generally, copper on the +2 oxidation state is the most prevalent for radiopharmaceuticals [66]. ^{64}Cu in the simplest chloride form can be used in imaging of altered copper metabolism but ^{64}Cu complexes also can be applied as the theranostic agents in human malignancies.

There are many ligands that are complexing copper well and the complexes could be applied in nuclear medicine. Very important are for instance macrocyclic polyaminocarboxylates like DOTA and TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid). Derivatization of such type of ligands allows conjugating it to antibodies, proteins, and peptides [67].

Two most known are two copper complexes: ^{64}Cu-diacetyl-bis(*N*(4)-methylthiosemicarbazone) (^{64}Cu(ATSM)) and perfusion agent ^{64}Cu-pyruvaldehyde-bis(*N*4-methyl-thiosemicarbazon) (^{64}Cu(PTSM)) (Figure 3). ^{64}Cu(ATSM) as demonstrated in both preclinical and clinical studies, is one of the most effective radiopharmaceuticals to detect tumor hypoxia, which is associated with malignant progression, radiotherapy resistance, and poor prognosis. Due to the release of therapeutic Auger electrons from ^{64}Cu, making ^{64}Cu(ATSM) could be considered also as the theranostic agent [68].

There are undergoing studies for new stable chelators for copper, because the classical DOTA based ligands seem to be not very optimal. For instance very interesting chelators seems to be sarcophagine (Sar) (3,6,10,13,16,19-hexaazabicyclo [6.6.6] icosane) (Sar) derivatives such as MeCOSar (Figure 4), which complex the copper ions efficiently, with high stability and could be connected to PSMA, octreotide gastrin-releasing peptide receptor antagonists [69–71] or other biomolecules.

Sarcophagine ligand containing two glutamate-urea-lysine functional groups connected with PSMA (SarbisPSMA) and radiolabeled with $^{64/67}$Cu – $^{64/67}$Cu(SarbisPSMA) has very good tumor uptake and retention, which was revealed in the antitumor activity comparable to a ^{177}Lu based compound. This study deserves further investigation for the product as a theranostic agent for prostate cancer [72]. Clinical trials on ^{64}Cu-SARTATE and ^{67}Cu-SARTATE for imaging and treating pediatric patients with high-risk neuroblastoma were started in 2020 [73].

The really theranostic copper isotopes offer great opportunities to develop ^{64}Cu/^{67}Cu based radiopharmaceuticals as the radioimmunotheranostics due to the high specific activity, high radionuclidic purity, and production at sufficient quantity.

Radiobioconjugation of copper with monoclonal antibodies such as ^{67}Cu-NOTA-Pertuzumab demonstrates the potential of using ^{67}Cu for the treatment of HER2 positive cancers and application of ^{64}Cu/^{67}Cu as a complete theranostic radiopharmaceutical [74].

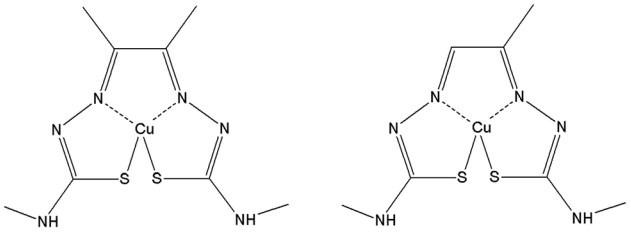

Figure 3: The structure of Cu complexes with thiosemicarbazon type ligands (ATSM) (left) and (PTSM) (right).

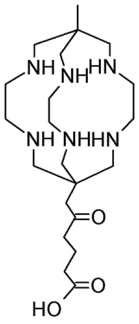

Figure 4: The structure of sarcophagine derivative 5-(8-methyl-3,6,10,13,16,19-hexaaza-bicyclo[6.6.6]icosan-1-ylamino)-5-oxopentanoic acid (MeCOSar).

Yttrium

The well-known radiopharmaceutical ^{90}Y ibritumomab tiuxetan (Zevalin®) (Figure 5) [75] is very effective in radioimmunotherapy for relapsed or refractory B-cell NHL with overall response from 74% to 82% and produces durable long-term responses [76] and is very important pharmaceutical for treatment of NHL. But the optimal nuclear and chemical properties of ^{90}Y put it at the forefront of the most important isotopes from the theranostic medicine point of view, what prompted scientists to search for other radiopharmaceuticals labeled with yttrium.

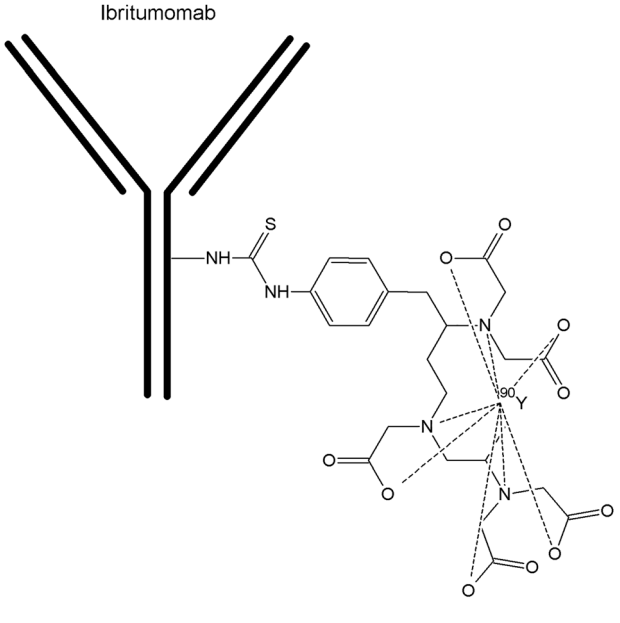

Figure 5: The schematic structure of Zevalin®.

^{90}Y is a high-energy pure beta-particle emitting radionuclide widely used for radiotherapy (E_{max}=2.28 MeV, $T_{1/2}$=64.1 h), which allows for high dose deposition with the maximum soft tissue penetration of 11 mm, mean 2.5 mm ^{90}Y decays to stable ^{90}Zr. Nevertheless, one should remember that ^{90}Y is not an ideal radionuclide for PET imaging. For this isotope, the branching ratio of pair-production is low. The high β^- ^{90}Y maximum energy, amounting to 2.28 MeV, generates the production of bremsstrahlung photons that meet the requirements for energy acceptance of the PET detector [77]. This causes the count of the frequency of single-event to increase.

The short-lived β^- emitter ^{90}Y can be received in two ways: 1) Irradiation by reactor thermal neutrons of natural compounds of yttrium on (n,γ) reaction; 2) from an equilibrium mixture of ^{90}Sr + ^{90}Y in the form of carrier-free radionuclide, where the parent ^{90}Sr radionuclide is obtained in large amounts from fission products of uranium. Usually the second way is used in practice. However, this way is favorable if ^{90}Y is required in large amounts. Extraction of parent ^{90}Sr radionuclide from the mixture of highly active uranium fission products demands special equipment and special operating conditions, and is bound to the problem of utilization of highly active waste.

The long enough half-life creates the possibility of connection to different biomolecules like peptides, monoclonal antibodies and also to microspheres and colloids, what gives a wide potential for applications in nuclear medicine. The emission of high-energy β^- particle produces a bremsstrahlung radiation which can be imaged using gamma cameras (SPECT) [78]. Additionally, ^{86}Y – a positron emitter (β^+, $T_{1/2}$=14.7 h) offers an attractive possibility for pretreatment dosimetry and PET imaging and is an ideal pair isotope for ^{90}Y, which means that ^{86}Y/^{90}Y isotope pair has a very good theranostic potential.

The most relevant nuclear reactions towards ^{86}Y at small to medium sized cyclotrons include ^{86}Sr(p,n)^{86}Y; ^{86}Sr(d,2n)^{86}Y; ^{88}Sr(p,3n)^{86}Y; ^{nat}Rb(3He,xn)^{86}Y [79]; ^{85}Rb(α,3n)^{86}Y; ^{90}Zr(p,αn)^{86}Y; and ^{nat}Zr(p,x)^{86}Y nuclear reactions [80–83], though 36 other possible reactions exist with very low cross sections.

It should be noted that if the incident proton energy is larger than 25 MeV, when using the ^{nat}Zr(p,x)^{86}Y route, the ^{87}Y impurity (via the ^{90}Zr(p,α)^{87}Y) is minimized, since the ^{90}Zr(p,αn)^{86}Y reaction is favored.

In order to produce ^{86}Y, most of the initial attempts focused on the ^{86}Sr(p,n)^{86}Y reaction at low energy cyclotrons (Ep ≤ 18 MeV) using highly enriched $^{86}SrCO_3$ [84] but also ^{86}SrO was used [85].

At the University of Wisconsin, ^{86}Y is produced via the nuclear reaction ^{86}Sr(p,n)^{86}Y using enriched $^{86}SrCO_3$ targets in a 16 MeV GE PETtrace cyclotron within the energy range Ep=14.1–7.1 MeV. Before irradiation, approximately 150 mg of $^{86}SrCO_3$ is pressed into a niobium crucible and covered with a 12.7 μm thick niobium foil to encase the target material and degrade the beam energy to 14.1 MeV. Typical irradiations are carried out at 5 μA for up to 2 h with direct water jet cooling on the back of the crucible. Under these conditions, ^{86}Y is produced with an EOB physical yield of 0.11 ± 0.02 GBq/μAh [86].

Scientists from TRIUMF reported that they obtained ^{86}Y (A_{sat}=31 MBq/μA and yield = 1.44 MBq/μA) from 1 h long irradiations on a 13 MeV cyclotron [8].

There are many chelating agents used for yttrium labeling. Yttrium exists in a tricationic state, Y(III), that can reach coordination numbers of 8 and 9 in its complexes, and it prefers octadentate coordinating ligands. As chelating agents for yttrium are used acyclic polyaminocarboxylates such as ethylenediaminetetraacetic acid (EDTA) or diethylenetriamine pentaacetic acid (DTPA) and also macrocyclic polyaminocarboxylates such as classic DOTA and its bifunctional derivatives [87] so the connection to a preferred biomolecule like octreotide or monoclonal antibody is quite simple [88].

Lead

The ^{203}Pb/^{212}Pb pair of theranostic radioisotopes shows great potential for use in TRT [89] and SPECT. Lead ^{203}Pb $T_{1/2}$=51.9 h and lead ^{212}Pb $T_{1/2}$=10.6 h.

^{212}Pb is suitable for therapy as it emits two β^- and one α particles during its decay chain. ^{203}Pb decays by electron capture to the ground state of ^{203}Tl. This nuclear reaction emits a gamma photon (279 keV; 81%), which can be easily recorded by SPECT imaging. At the same time, the lack of radioactive daughter products facilitates dosimetry calculations [90].

^{203}Pb is an isotope produced in a cyclotron. It is obtained by irradiating a thallium target with charged particles – protons, deuterons, and alpha particles. Natural thallium contains 29.5% ^{203}Tl, 70.5% ^{205}Tl [90]. At TRUMF ^{203}Pb has been produced via the ^{203}Tl(p,n)^{203}Pb nuclear reaction using TR13 cyclotron [91]. The target was irradiated with protons with an energy of about 12.8 MeV. The degrader in the form of an aluminum foil with a thickness of 25 μm was used here. This foil simultaneously separated the target from the cyclotron vacuum system. The proton beam was completely trapped in the backing plate. Irradiation was performed at 8–9 μA for 2–4 h. To reduce exposure of personnel to radiation, the target was left for 18–24 h. This time allowed for the decay of short-lived

radionuclides such as ^{202m}Pb ($T_{1/2}$=3.62 h). In the case of the described nuclear reaction, the cross section has a threshold energy of 8 MeV and a maximum at 26.5 MeV [92], which makes medical cyclotrons very useful tools for the production of the ^{203}Pb isotope.

The measured yields are in agreement with the calculated saturation efficiency of 134 ± 25 MBq/μA. Produced and isolated from the irradiated aluminum-backed thallium targets ^{203}Pb was radiochemically-pure. Irradiation of natural Tl targets with the current of 8 or 9 μA for 2 h allowed to obtain 27.3 ± 4.7 MBq and 32.9 ± 2.7 MBq ^{203}Pb, respectively. On the other hand, irradiation for 3.5–4 h of targets from the ^{203}Tl enriched with 8 μA current allowed for the production of 175.3 MBq and 201.9 MBq of ^{203}Pb, respectively. The results were consistent with the calculated saturation efficiency of 483 ± 3 MBq/μA [93].

^{212}Pb is a member of the ^{232}U and ^{232}Th decay chain, and is commonly produced by the decay of ^{228}Th ($T_{1/2}$=1.9 years) and ^{224}Ra ($T_{1/2}$=3.64 days). Produced in generator ^{212}Pb ($T_{1/2}$=10.6 h, β^- -emitter), which decays to alpha emitters: ^{212}Bi ($T_{1/2}$=50.6 min) and ^{212}Po ($T_{1/2}$=299 ns) is an interesting radionuclide for targeted alpha therapy (TAT).

α-emitters possess a superior efficacy in cancer cells damage if compared with to β^--emitters and their radiotoxicity mechanism is not dependent of tissue oxygenation, dose rate, and cellular resistance to γ or β^- irradiation and chemotherapy. This is caused by the higher LET, and also because the biological effect of alpha radiation differs from the other radiation types such as beta-particle emitters [94].

It is extremely important to employ the proper guiding molecule to avoid the toxicity of α-emitters and health tissue damages during TAT treatment.

Generally isotopes $^{203/212}$Pb could be complexed to a suitable chelate, usually DOTA analog, and then connected to an appropriate guiding biomolecule. For ^{212}Pb it must be taken into account its decay product – complexed the same way ^{212}Bi. In case of DOTA chelate both complexes (with ^{212}Bi and ^{212}Pb) are kinetically stable at pH from 4.5 to 7 [95]. However, the studies have found a better complexation of ^{212}Pb by the macrocyclic TCMC (1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamoyl methyl)-cyclododecane ligand). The Pb[TCMC]$^{2+}$ complex was less labile to metal ion release than Pb[DOTA]$^{2-}$ [96].

Recently, in preclinical models, the theranostic radionuclide pair has been evaluated ^{203}Pb/^{212}Pb to label bifunctional derivatives of PSMA. PSMA is the prostate-specific membrane antigen a transmembrane protein expressed in all types of prostatic tissue including carcinoma, and is one of diagnostic and therapeutic markers for prostate cancer [97]. It was demonstrated the delay of the tumor growth in large and micrometastatic tumor models. In this case the kidney was the dose-limiting organ. Therefore a further optimalization of these types of compounds is still needed [98].

A valuable application of $^{203/212}$Pb matching pair showed studies of peptide TAT for melanoma treatment using ^{212}Pb-DOTA-Re(Arg^{11})CCMSH – ^{212}Pb – radiolabeled, DOTA-conjugated melanotropin analog (Figure 6).

The therapy was effective in increasing the mean survival times of mice initially bearing melanoma tumors and even 20–45% of animals (dose dependent percentage) were completely cured [98]. Biodistribution and SPECT imaging studies demonstrated the potential of analogous ^{203}Pb-DOTA-Re(Arg^{11})CCMSH to image the melanoma lesions were also performed with a satisfactory results [99–101].

Gold

^{198}Au is a reactor-produced radionuclide from the natural ^{197}Au isotope by the nuclear reaction ^{197}Au(n,γ)^{198}Au with a half-life of 2.7 days. ^{198}Au decays to stable ^{198}Hg by emission of β^- particle with a maximum energy of 960 keV (99%) and a 412 keV (95.6%) γ-ray. ^{198}Au as well as ^{199}Au can be produced using charged particle reactions at cyclotrons. The following nuclear reactions are appropriate: ^{198}Pt(p,n)^{198g}Au, ^{198}Pt(d,2n)^{198m,g}Au, and ^{198}Pt(d,x)^{199}Au. For the investigation protons up to 40 MeV and deuterons up to 20 MeV were used. ^{198}Au has two long-lived isomeric states: the $T_{1/2}$=2.7 days ground state, and $T_{1/2}$=2.3 days metastable state. The metastable state completely decays to the ground state by internal transition. The ground state decays with medium energy β^- decay ($E_{\beta max}$=1.37 MeV) favorable for therapeutic applications. The presence of 411 keV gamma radiation (95.6%) creates an undesirable radiation hazard for patients and staff [102], which is a disadvantage of this isotope. Nevertheless, it can be used for SPECT imaging and localization in biodistribution studies as well as for therapeutic applications.

An attempt to complex gold were performed with use of the water-soluble phosphine ligands (THP, HMPE, and HMPB) (Figure 7) and bisthiosemicarbazone ligands (ATSM,

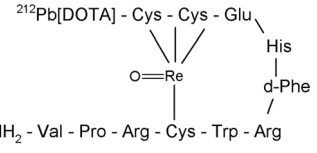

Figure 6: Schematic structure of ^{212}Pb-DOTA-Re(Arg11)CCMSH.

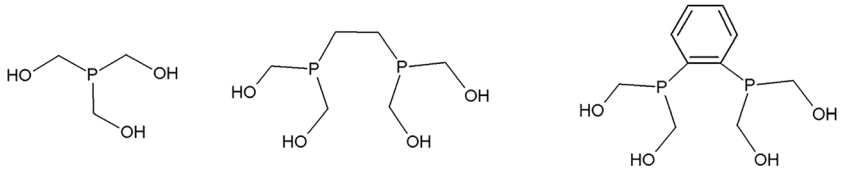

Figure 7: Structures of phosphine ligands used for chelating of gold.

PTSM). On the radiotracer level the ^{198}Au complexes with both types of ligands were stable *in vitro*, but turned out not stable *in vivo* [66].

Also reactor produced ^{199}Au ($T_{1/2}$=75.4 h) with the radiation characteristics such as the emission of low energy β^- particle ($E_{\beta mean}$=82.0 keV, $I_{\beta tot}$=100%) offers favorable nuclear and chemical properties for targeted radioimmunotherapy applications [103, 104] and its emission of low energy γ-rays (E_γ=158.38 keV, I_γ=40%, E_γ=208.20 keV, I_γ=8.72%) facilitate simultaneous scintigraphy and dosimetry studies without posing any extra radiation dose to the patients [105].

^{199}Au ($E_{\beta max}$=244 keV [21.5%], 294 keV [72%], and 452 keV [6.5%]) is an interesting therapeutic/SPECT radionuclide that has attracted attention due to its favorable chemical and nuclear properties. The 294 keV β^- particle emitted by ^{199}Au has a maximum tissue penetration range of 0.8 mm [106].

^{199}Au can be produced in two methods in the direct and indirect routes of the reactor production via ^{197}Au $(n,\gamma)^{198}$Au$(n,\gamma)^{199}$Au as the direct or ^{198}Pt$(n,\gamma)^{199}$Pt → ^{199}Au as the indirect method but also exists accelerator route via deuteron irradiations on natural or enriched platinum targets. The cross sections for the ^{nat}Pt$(d,x)^{199}$Au nuclear reactions were measured at the RIKEN RI Beam Factory. Deuteron beams in the energy range of 2–24 MeV from the AVF cyclotron were used. The irradiation was carried out with a water-cooled target holder that simultaneously served as a Faraday cup. A 24 MeV deuteron beam from the AVF cyclotron irradiated the stacked-foils for 127 min with an average current of 215 nA. The obtained results allowed to conclude that by irradiating the enriched ^{198}Pt target (100%) with a deuterons beam of energy <15 MeV can be obtained a no-carrier-added ^{198}Au with an efficiency of 12 MBq/μA*h [107].

Gold Au(0) as the noble metal is very inert and stable, on the other hand, Au(III) undergoes hydrolysis and for that reason is difficult to work. Gold nanoparticles (AuNPs) might be a solution for this problem. Colloidal gold has been known for centuries, but last 20 years showed the new perspectives of its application in medicine. The physical properties of different types of gold nanoparticles as well as their optical properties caused by surface plasmon resonance, and also nuclear properties of $^{198/199}$Au are an attractive combination for nuclear medicine. Additionally AuNPs could be used in photothermal therapy – the heating effect is related to the electron dynamics in metallic lattice [108].

Gold nanoparticles themselves possess the unique properties – low toxicity, high biocompatibility, and versatility due to the ease of surface functionalization and they are very promising candidates for potential clinical ways of drug delivery. For instance doxorubicin (DOX) conjugated with gold nanoparticles (DOX-AuNPs) has been already studied and it was established as a water-soluble and pH-responsive anticancer drug nanocarrier. These multifunctional DOX conjugated AuNPs were also considered to improve imaging contrast or for photothermal cancer therapy [109].

Żelechowska-Matysiak et al. [110] studied a novel multimodal radiobioconjugate containing simultaneously in a one structure β^- emitter – ^{198}Au (in the form of nanoparticles ^{198}AuNPs), a chemotherapeutic – DOX and a guiding vector – Trastuzumab. The preliminary results showed the high stability of this radiobioconjugate and its toxicity towards HER-positive SKOV-3 cells.

Arsenic

Arsenic is highly toxic for humans, but it also was employed in medicine to treat many diseases. Nowadays arsenic in the form of As_2O_3 is mainly used as a medicament for treating acute promyelocytic leukemia (APL) [111, 112], but research on the treatment of other cancers are in progress, because arsenic has antiproliferative and antiangiogenic effect against tumor cells [113, 114].

Arsenic is very interesting as a theranostic agent. It has four positron emitting isotopes (^{70,71,72,74}As) and three β^- emitters (^{73,76,77}As). The half-lives of these radioisotopes are in range from 53 min ^{70}As to 18 days ^{74}As, see Table 3.

^{71}As can be produced by the ^{70}Ge$(d,n)^{71}$As reaction [116] and by Ge$(p,x\text{-}n)^{71}$As processes [117].

Due to the relatively slow localization kinetics of the labeled species, ^{72}As is suitable for radiopharmacological studies. The parameters of ^{72}As are comparable to those of

Table 3: Decay data of the most relevant arsenic isotopes [115].

Property	^{70}As	^{71}As	^{72}As	^{73}As	^{74}As	^{76}As	^{77}As
$T_{1/2}$, days	0.04	2.7	1.1	80.3	17.8	1.1	1.6
Mode of decay, %	EC (9) β^+ (91)	EC (71.7) β^+ (28.3)	EC (12.2) β^+ (87.8)	EC (100)	EC (66) β^+ (29) β^- (34)	β^- (100)	β^- (100)
Most abundant γ-lines, keV	1,039 (82.0%) 668.2 (22.1%) 743.6 (22.1%)	175.0 (82.0%)	834.0 (79.5%) 629.9 (8.07%)	53.4 (10.6%)	595.8 (59.0%)	559.1 (45.0%) 657.1 (6.2%)	239.0 (1.6%) 520.6 (0.6%)
Mean positron energy, keV	980	350	1,170		440		

^{124}I ($T_{1/2}$=4.18 days). The disadvantage of this isotope is the β^+ branching of only 22%. ^{72}As is produced from the generator in the nuclear reaction ^{70}Ge(a,2n)^{72}Se → ^{72}As [112]. It can also be directly produced using small cyclotrons in high yields nuclear reaction ^{72}Ge(p,n)^{72}As [118, 119].

A 5 h irradiation of the $^{72}Ge_{(m)}$ target at 20 μA of 16 MeV proton current would result in the production of up to 10 GBq of ^{72}As activity. The produced ^{72}As had a radionuclidic purity of 99.4% 24 h after the EOD [120].

^{73}As is produced by the Ge(p,xn)^{73}As nuclear reaction. The isotope is separated by distillation and purification on a cation exchange column [121].

^{74}As can be produced best by the ^{74}Ge(p,n)^{74}As or ^{73}Ge(d,n)^{74}As reaction at a small-sized cyclotron. Excitation functions and target yields were described in detail [117].

^{76}As can be produced by irradiating of natural germanium dioxide powder with protons. Targets of 160–170 mg of GeO_2 were pressed at 150 MPa into a water-cooled stainless steel beam stop and covered with a 0.025 mm titanium containment foil. One hour, 2 μA proton irradiations of 160–170 mg GeO_2 targets yielded the activity, see Table 4 [122].

^{77}As can be produced at nuclear reactors via the ^{nat}Ge(n,γ)^{77}Ge reaction, ^{77}Ge decaying to ^{77}As with a half-life of 11.3 h. Direct or indirect production of ^{77}As is also possible via deuterons beam-induced nuclear reactions on enriched ^{76}Ge targets [123].

Table 4: Activity ranges of radionuclides produced in 1 h, 2 μA proton-irradiation of 160–170 mg GeO_2 targets.

Isotope	Activity, μCi
^{70}As	6,000–10,000
^{71}As	20–30
^{72}As	1,200–1,500
^{74}As	60–95
^{76}As	85–120
^{67}Ge	15–20
^{69}Ge	15–25

Especially ^{72}As (2.49 MeV β^+, $T_{1/2}$=26 h) and ^{77}As (0.683 MeV β^-, $T_{1/2}$=38.8 h) isotopes look promising as a theranostic pair for application in PET and therapy due to their high specific activity and suitable nuclear properties and also the possibility to connection with a biomolecules via for example bifunctional trithiol ligands [124].

^{72}As as a β^+ emitter is a PET radioisotope but also could be applied as so called three gamma radionuclide due to the $\beta^+ + \gamma$ coincidence and additional γ line. Besides, arsenic has a proper matching pair – a radionuclide emitting β^- ^{77}As – very favorable for therapeutic application [125].

The affinity of arsenic to sulfur atoms is very useful for the development of new arsenic compounds, which could be applied in cancer therapy and nuclear medicine.

For ^{72}As there is a possibility to usage of the ^{72}Se/^{72}As generator, but there are also some difficulties of its application that result from the chemical properties of both elements – a complex separation scheme is required. However, the separation of the ^{72}As from the parent ^{72}Se is feasible, especially if based on the solid phase extraction chromatography [126, 127] or distillation [128].

There are a lot of arsenic(III) complexes with organic compounds, with one, two, or more S donor atoms in their structure, such as dithiocarbamates, where arsenic is bound bidently or monodently [129–133] or dithiols [134, 135] and trithiols [136] that might be useful for theranostic application. For instance, the studies on arsenic(III) compounds with toluene-3,4-dithiolato and 1,2-benzenedithiolato ligands showed the stability of these compounds and also its *in vitro* cytotoxicity toward human APL cancer cells (NB4) [137].

For nuclear medicine application there is a need of application of the bifunctional ligands to bind arsenic isotopes to a proper biomolecule to treat tumors, like monoclonal antibody [138]. Ellison et al. showed the arsenic labeling strategies, using the dithiol-containing

chelator – dihydrolipoic acid, and thiol-modified mesoporous silica nanoparticles (MSN-SH) [120].

Therefore, the searching for novel radioarsenic compounds that could be applied in theranostic nuclear medicine is reasonable.

Labeling perspectives – summary

Due to the volume of this article, we have not reviewed literature of all the isotopes that are considered theranostic isotopes or constitute theranostic pair. We limited ourselves to selected isotopes, taking into account the possibilities of their production and synthesis of appropriate potential radiopharmaceuticals. Currently in Poland there is one heavy ion cyclotron, one high energy proton cyclotron, one reactor, and about 10 of medical cyclotrons located in PET centers. Taking into account the fact that most of the described isotopes have a comparatively short half-life, theranostic pairs that can be relatively easily produced and synthesized in centers equipped with medical cyclotrons will potentially be widely used. Several of the described isotopes have been or are currently being produced for the purposes of ongoing research in our collaborating institutes.

At present, several biomolecules are of interest due to their affinity to proper receptors overexpressed on cancer cells. Octreotide is a very promising vehicle to guide the theranostic radionuclides to the required receptors overexpressed in NET cells and other tumors expressed SSTRs. In our group we have been studied the methods for labeling of octreotide derivatives with scandium [44, 139]. Also PSMA seems to be very effective vector for theranostics. ^{68}Ga-PSMA-11 was approved for diagnostic application for patients with suspected prostate cancer metastasis and for patients with suspected prostate cancer who are potentially curable by surgery or radiation therapy [140, 141] what opens a way also for application of radiopharmaceuticals based on PSMA and labeled with therapeutic and/or theranostic radionuclides.

Both these biomolecules could be labeled via classical macrocyclic chelating ligands commonly used for complexing of the metal ions including radionuclides in radiochemical laboratories in Poland. Application of gold nanoparticles is one of the main research directions in INCT. AuNPs are widely studied in bio-imaging and phototherapy due to their highly sensitive optical and electronic properties. AuNPs possess the relevant properties to diagnostic and phototherapeutic applications such as structure, shape, optics, and surface chemistry [142]. They are considered as useful for cancer treatment, especially due to the facility of surface modification and convenience connection with any guiding biomolecule via peptide bond by simple linkers like e.g., polyethylene glycol [143].

Nowadays, an application of nanoparticles as the multimodal carriers for radionuclides and additionally chemotherapeutical which will guide the theranostic and synergistic pharmaceuticals directly to the desired cells seems to be promising.

For instance, an interesting approach is the application of the multifunctional lipidic nanoparticles – cubosomes – containing DOX and the radionuclide complex (DOX DOTAGA-OA-^{177}Lu or DOTAGA-OA-^{177}Lu), which increase the cytotoxicity if compared the both of agents used separately [144].

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