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Radiochemical Investigations for Radiopharmaceutical Nuclear Medicine at JINR Laboratory of Nuclear Problems

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Abstract—In recent years, radiopharmaceuticals have been increasingly used for diagnostics and treatment of cancer. In addition to a biological vector, a modern radiopharmaceutical includes a chelator that binds the radionuclide, as well as a linker for connecting the vector and the chelator. The development of such an approach requires the improvement of methods for obtaining and purifying radionuclides, and the development of methods for the synthesis of radiopharmaceuticals, i.e., preparative direction. It is also necessary to search for new vectors and chelators. This implies the development of methods for analyzing the properties of radiopharmaceuticals in general, as well as their precursors, i.e., analytical direction. In this review, we describe the prerequisites for successfully solving a wide range of challenges in these two areas of nuclear medicine at the Scientific and Experimental Department of Nuclear Spectroscopy and Radiochemistry of the Laboratory of Nuclear Problems of the Joint Institute for Nuclear Research (LNP JINR). These prerequisites are due to rich experience in obtaining the widest range of radionuclides and their application for various spectrometric studies. Both the past and present works on radiopharmaceutical topics carried out in the department are described, and ways of future development are outlined.

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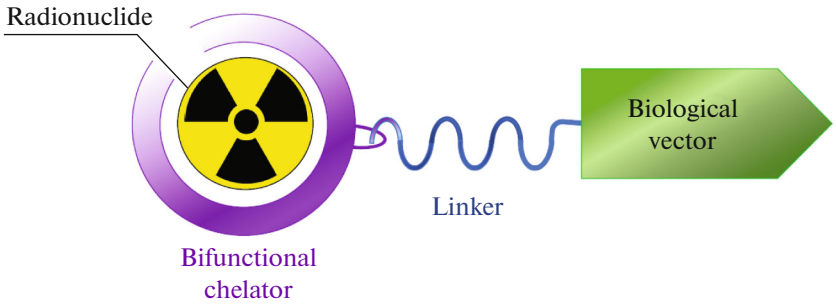


Fig. 1. The structure of a modern radiopharmaceutical.

INTRODUCTION

Cancer is one of the leading causes of global mortality, killing almost 10 million people every year [1]. The predicted increase in the number of diseases almost doubled by 2040 [2] necessitates the development of new, more advanced ways of diagnosis and therapy. Targeted radionuclide diagnostics and therapy are advanced technologies that make it possible to detect cancers at an early stage and selectively carry out subsequent therapy [3, 4].

The main principle of target diagnostics, as well as therapy, is the use of selective radioisotope delivery systems based on biomolecules (for example, antibodies or peptides) that can find and deliver a radioisotope to a cancer cell without affecting surrounding tissues. A modern radiopharmaceutical preparation (RPP) consists of several components (Fig. 1):

— Radionuclide (α-, β^--, β^+-, γ-, Auger-emitter).
— Linker.
— Bifunctional chelator.
— Biological vector.

Each component has its own specific function. The chelator provides reliable retention of the radionuclide, the linker connects the radionuclide and the biomolecule, the biological vector provides targeted delivery. The development of this type of radiopharmaceutical is a very difficult task. It is important to consider the thermodynamic stability and kinetic characteristics of metal complexes, the characteristics of radionuclides for the corresponding biological vectors that provide targeted delivery. On the other hand, the synthesis of radiopharmaceuticals itself, direct labeling with a radionuclide, should be carried out simply in routine use, and is usually automated. With this delivery system, the radionuclide is delivered directly to the site of the tumor or to its microenvironment, while the dose load on the surrounding healthy cells is reduced.

Depending on the choice of radionuclide, diagnostics can be carried out, that is, an assessment of the number and location of cancer cells. To this end, photon emission (single photon emission computed tomography (SPECT)) and positron emission (positron emission tomography (PET)) are used. The main examples of clinical application of target diagnostics are radiopharmaceuticals based on ^{99m}Tc ($T_{1/2} = 6.01$ h) for SPECT and ^{18}F ($T_{1/2} = 109.77$ min) for PET [5]. At the same time, research is being actively carried out to expand the available palette of radionuclides for diagnostics in parallel with the development of more selective delivery systems. The radiopharmaceuticals based on ^{68}Ga ($T_{1/2} = 67.71$ min) and ^{89}Zr ($T_{1/2} = 78.41$ h) [6, 7], which are widely used in modern diagnostics, are worthy of special attention. Molecular imaging has a set of available radionuclides, both gamma-emitting (^{99m}Tc) and positron-emitting (^{18}F, ^{68}Ga). Basically, the production of these radionuclides has been worked out, and the synthesis of radiopharmaceuticals based on them is automated.

In addition, in the future, based on the data obtained, therapeutic radiations (β, α-particles or Auger electrons) with identical delivery systems can be used to remove cancerous tumors. The main advantage of targeted therapy over other cancer treatments such as surgery and radiation therapy is its selectivity. This makes it possible to use this method for the treatment of metastatic tumors in the late stages and cause minimal damage to the healthy tissues of the patient. In addition to the choice of biomolecules, the selectivity of targeted therapy is also caused by the choice of radiation of radionuclides. Thus, β particles, having relatively high energies, as well as low linear energy transfer (0.2 keV/μm), are effective for sufficiently large tumors. At the same time, α particles (50–230 keV/μm) and Auger electrons (4–26 keV/μm) are effective for small tumors due to their high linear energy transfer, and the therapeutic effect can be assessed at the cellular level. The short range (2–500 nm) of Auger electrons limits their effect within individual cells, even DNA. This requires that the radionuclide be brought into the cell and placed near the DNA. They can also kill cancer cells by damaging the cell membrane. Alpha particles have a relatively short range (40–100 μm). They lose 1000 times more energy per unit path length than β particles. A few α particles crossing the cell nucleus are enough to kill

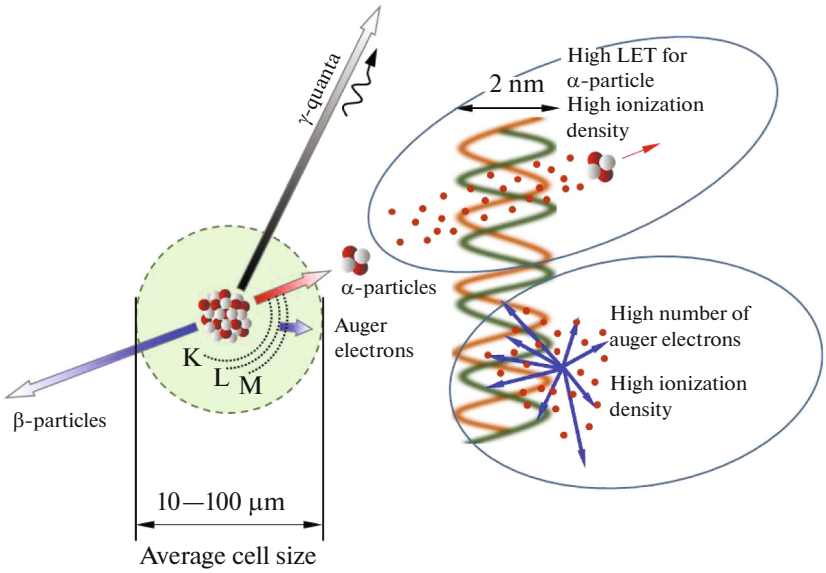


Fig. 2. Ranges and specific ionization of different types of radiation on the conventional scale of cells and DNA.

the cell, while more than 10000 β particles are needed to achieve the same biological effect [8].

Charged particles produce different radiobiological effects in the body depending on the free path and the magnitude of the linear energy transfer. Low linear-energy transfer (LET) of radiation results in more diffuse and uniform dosing. On the contrary, high LET radiation causes sufficiently dense ionization along the particle track, which contributes to localized DNA damage (Fig. 2). From a radiobiological point of view, α particles are more effective due to the high probability of breaking the DNA double strand, which blocks the ability of cells to divide and proliferate. Importantly, lethality from high LET radiation is independent of cell cycle or oxygenation.

Significant advances have been made in the field of targeted therapy in the last decade. Particularly, it is worth noting ^{177}Lu ($T_{1/2}$ = 6.64 d) (for β^-) and ^{225}Ac ($T_{1/2}$ = 9.92 d) (for α), which were shown to be effective in the treatment of several types of cancers, including tumors of the prostate and pancreas [9–13].

By choosing the nuclear-physical characteristics of a radionuclide, it is possible to carry out therapy and monitor its effectiveness. This concept of therapy and diagnostics is called *theranostics*. Theranostics is possible using radionuclides of the same element (^{131}I/^{124,122}I, ^{67}Cu/^{62}Cu, ^{90}Y/^{86}Y, ^{47}Sc/^{44}Sc) or with analogous elements (^{225}Ac, ^{177}Lu, ^{90}Y/^{68}Ga, ^{44}Sc). A successful theranostic pair is ^{177}Lu/^{68}Ga with *DOTA–5G* molecules for pancreatic cancer, PSMA for prostate cancer, and *DOTA–FAPI* for various types of cancer [14–16]. There are clinical studies with PSMA and *DOTATOC* molecules: in prostate cancer with lymphatic and bone metastases and in a functional pancreatic neuroendocrine tumor with liver metastases, in which the ^{225}Ac/^{68}Ga pair was effectively used [17].

The development and manufacturing of radiopharmaceuticals requires close cooperation between specialists from several fields of science and technology, including nuclear physics (for the production of radioisotopes); radiochemistry (for isolation of radionuclides from the target material); physics, radiobiology and again radiochemistry (assessment of primary, secondary, etc. processes of radiation destruction of molecules and tissues under the action of ionizing radiation from radionuclides, dosimetry and microdosimetry); biochemistry, organic chemistry and, again, radiochemistry (to design radiopharmaceuticals); and above all, of course, medicine (for clinical use). In practice, the role of cooperation between different disciplines for the development of nuclear medicine cannot be overestimated, since it is necessary to wander into related fields. For example, a radiochemist, in addition to isolation a radionuclide, must participate in the production of radionuclides, choosing the type and quality of the target and the radionuclide itself for successful isolation, as well as in the synthesis of radiopharmaceuticals. These actions determine the physicochemical form of the radionuclide and, at least, the process of labeling the radiopharmaceutical. Corresponding examples can be given for other specialties required for nuclear medicine.

For several decades, the radiochemistry department at the DLNP JINR (scientific and experimental association for nuclear systems and radiochemistry)

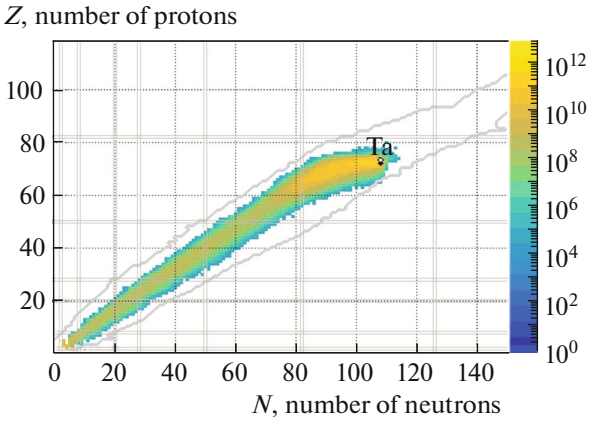


Fig. 3. Theoretical calculation of radionuclide yields upon irradiation of a tantalum target (target thickness 0.184 mol/cm^2) with 660-MeV protons, current 5 μA (Geant4).

has been one of the few global clusters for the development of radiochemistry for nuclear medicine. As already noted above, the expansion of the number of available radionuclides, their production methods, and methods of radiochemical separation is a necessary link in the development of nuclear medicine in the field of targeted diagnostics and therapy. The staff of the department took part in the development of such advanced research as the method of "fast" labeling of a diagnostic radiopharmaceutical ^{68}Ga from a generator system (^{68}Ge → ^{68}Ga) [18], reactor production and isolation of ^{177}Lu from ytterbium-enriched targets [19], as well as ^{225}Ac isolation from proton-irradiated high-energy thorium targets [20, 21]. The staff of the department is also actively involved in research activities aimed at studying new candidates for targeted diagnostics (for example, ^{44}Sc ($T_{1/2}$ = 3.97 h) and ^{90}Nb ($T_{1/2}$ = 14.60 h)) [22–26] or targeted therapy (^{119}Sb ($T_{1/2}$ = 38.19 h)) [27] and many other tasks [28, 29]. Along with many years of experience in the development of methods for the radiochemical isolation of medical isotopes, the radiochemistry department is actively engaged in research in the field of processes accompanying the decay of radioisotopes in the composition of radiopharmaceuticals using the method of perturbed angular correlation (PAC) [30–33].

All this became possible, among other things, due to access to the production of almost any radionuclide used in nuclear medicine at JINR nuclear facilities, namely the Phasotron (DLNP), IBR reactor (FLNP), U-200 (FLNR) and others. Such a wide range of different types of nuclear machines, probably, is not available in any nuclear center in the world. Although the production is possible in quantities slightly smaller than necessary for use in clinical practice (in some cases it is possible to obtain the necessary quantities, but not very practical in terms of cost), however, these quantities are quite sufficient to develop a technique for obtaining a radionuclide of the required quality. It should be noted that the development of the methodology for the "new" radionuclide introduced into the practice of nuclear medicine on high productivity nuclear machines is nearly impossible (or very difficult), it is better to carry it out in research centers. This is due to the problems of radiation impact on the target and personnel, as well as the flexibility of research machines, and, most importantly, the presence at JINR of many highly qualified specialists in various fields of physics and chemistry. Hence, the second important factor of success in proposing new techniques in nuclear medicine was the international status of JINR, and the team of in terms of internationality was and is now at the forefront. This, in turn, is due to the interest in many countries in research with radionuclides in general, and especially in nuclear medicine.

1. HISTORICAL TRENDS IN NUCLEAR SPECTROSCOPY AND THEIR PROJECTION ON THE PRODUCTION OF RADIOPHARMACEUTICALS FOR NUCLEAR MEDICINE

First, we would like to reveal prerequisites for the achievement by the staff of the department (or with their participation) of several valuable results and the development of productive techniques for nuclear medicine.

The main goal of the team was initially to study the properties of the atomic nucleus using the methods of (nuclear) spectroscopy and radiochemistry. Owing to the unique possibility of irradiating targets at the DLNP Phasotron (Synchrocyclotron) and producing virtually any radionuclides (Fig. 3) with a nuclear charge in the uranium–plutonium region and below, this led to a huge number of works (more than 500) on the study of the corresponding radionuclides, with the highest possible purity in relation to other radioisotopes. *This is the first parallel with nuclear medicine, where the maximum radionuclide purity of the radiopreparation is required to design a radiopharmaceutical.*

At the first stage (the end of the 1950s to the end of the 1960s), radiochemistry was the main method for isolating certain radionuclides for spectrometry. This determined the minimum period of the studied isotopes—about one hour (fraction of an hour), and affected the "park" of the spectrometric techniques used. "Calorimetric" studies were carried out mainly with the use of scintillation detectors (semiconductor detectors began to be used a little later). Methods of β–α spectrometry with the use of magnetic fields for

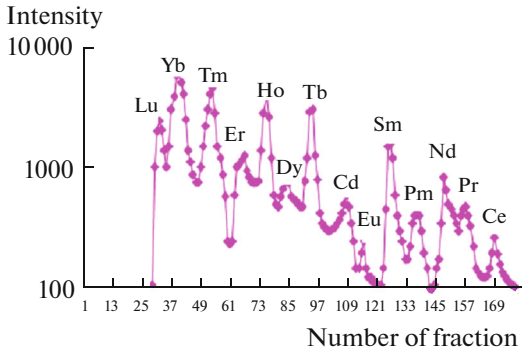


Fig. 4. Chromatogram of separation of radiolanthanides with ammonium α–hydroxyisobutyrarate.

the analysis of emitting (subsequently, electric fields) were also actively used. The latter methods required the preparation of unique sources with significant radioactivity, but at the same time monomolecular (ideally), or at least having a thickness of less than 1 μg/cm^2. We succeeded to fabricate such sources using radiochemistry and electromagnetic separation methods. The key factor in achieving these goals became the development of methods for obtaining radioactive preparations with the highest specific activity: ideally containing only atoms of the radioactive isotope, or (in practice) with a minimum fraction of impurity atoms to radioactive atoms. *This is already the second important parallel with nuclear medicine, where the highest specific activity of the original preparation is also needed to design a radiopharmaceutical.*

At the very end of the sixties, the resulting preparations of radiolanthanides began to be separated by mass using off-line mass separation with the help of an electromagnetic method. Here, the maximum possible purity of spectrometric sources of a wide range of studied isotopes in relation to other radioisotopes was implemented in full measure.

At that time, from the point of view of radiochemistry, the key technique for spectrometry became isolation and separation of radiolanthanides from a tantalum target irradiated in the internal beam of the Synchrocyclotron (Phasotron) with 660-MeV protons.

This can be considered as an example of using the best technical and scientific achievements of that time, extremely simple, effective and productive. The main merits of this method are the following:

(1) The irradiation density in the internal beam is 500 times higher than in the extracted one: the mass of the target is only 5 g of tantalum and more than 10 Ci of all radiolanthanides produced in 1 h of irradiation.

(2) An automated system placed in the hot cell for rapid isolation allowed and an automated system allowed chromatographic separations of 15 lanthanides in less than 2 h (Fig. 4).

(3) The work of only one chemist allow obtaining 14 (15) fractions of elements with an activity of 0.5 Ci of radiolanthanides with the highest specific activity suitable for electromagnetic mass separation. What is remarkable is that the lanthanides are ionized with a high yield in a rather simple and efficient source with surface ionization (Fig. 5).

The separation of radiolanthanides was carried out by a wide range of specialists, a great contribution in this area belongs to N.A. Lebedev [34, 35]. Chromatographic separation of lanthanides on a cation exchange resin using a solution of ammonium α-hydroxyisobutyrate as an eluent is still considered the reference "gold standard" [36]. On the one hand, due to the *f* shell filling, the lanthanides have almost identical chemical properties, so it is very difficult to separate these elements. In solution, these are 3+ charged cations, the ionic radii of which differ by only one percent from the radii of the nearest neighbor. On the other hand (for the same reasons), these are easily replaceable elements to be mixing. This has enormous potential for use in various fields of science and technology. One can fine-tune the properties of a substance by

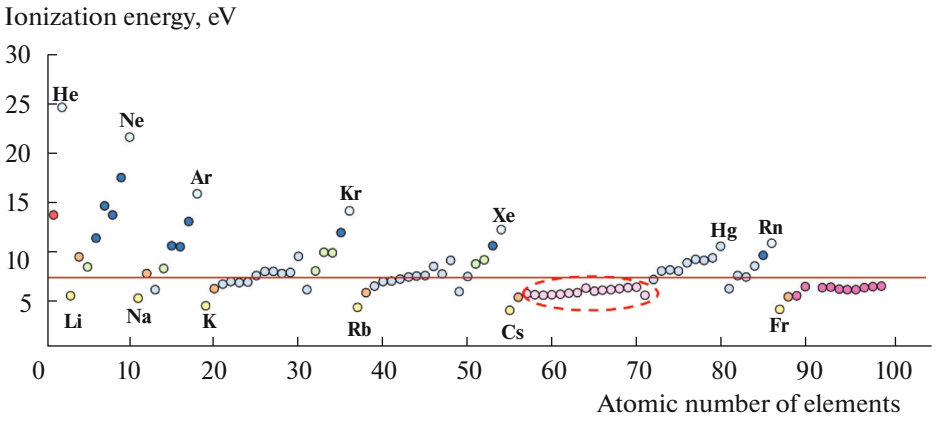


Fig. 5. Ionization energy of elements.

selecting one or another related element or using their mixture. This is clearly evident in nuclear medicine as well. On the one hand, there is a wide range of nuclear properties of many radiolanthanides. On the other hand, when creating a modern radiopharmaceutical, the same designing, for example, *DOTA*, is suitable for all these elements with almost the same efficiency. This opens the richest possibilities of theranostics, and, in particular, for PET and SPECT diagnostics, as well as α, β and Auger therapy. The advantages of lanthanides for nuclear medicine are emphasized by a number of other significant factors: (1) on the one hand, weak hydrolysis up to pH 7, on the other hand, already very stable complexes with macrocycles, which is generally very convenient for labeling radiopharmaceuticals, and in practice these issues have already been resolved; (2) Sc, Y, Ac and heavy actinides starting from Am are extremely close analogs of 15 lanthanides, which expand the versatility of using the same type of radiopharmaceuticals; (3) taking into account other trivalent elements (In, Ga, Fe, etc.), the available number of elements with +3 valence (with its own set of isotopes) reaches about 40. Thus, lanthanides become a kind of "core" of modern radiopharmaceuticals with chelators (macrocycles). Trivalent elements are complemented by about 15 divalent and 15 tetravalent. It is interesting to note that the labeling of radiopharmaceuticals with other types of elements, for example, nonmetals (F, I, etc.), is often also called "chelation," although from a chemical point of view for nonmetals, not complex compounds, but a covalent bond are most often responsible for complexation.

Almost immediately with the beginning of the off-line mass separation of chemically isolated samples, the YASNAPP-1 facility (nuclear spectroscopy in proton beams) with the so-called "semi-on-line" operation system began to operate in the early seventies. The irradiated target was delivered to the separator by pneumatic mail, and the separation was carried out when heated ("without chemistry"). In this case, it became possible to study radionuclides with a half-life of the order of a minute.

Over time, interest in the study of even shorter-lived nuclei began to increase in nuclear physics. From the late 1970s to the mid-1980s, the DLNP accelerator was modernized to increase the intensity of the extracted proton beam. Strictly speaking, during this modernization, the synchrocyclotron was upgraded into a phasotron. The spectrometric complex was also upgraded. A full-fledged installation for "on-line" research was designed. As known, they have a common name ISOL (isotope separation on-line). In DLNP, this facility was named YASNAPP-2 [37–39]. It was planned to study short-lived nuclei, at least with a half-life of the order of seconds. In this case, the target for electromagnetic separations was the tungsten ampoule (tantalum) of the ion source itself, irradiated by the extracted proton beam with an energy of 660 MeV. YASNAPP-2 setup was put into operation by the end of the eighties. Many results were obtained on it for radionuclides with a half-life of the order of several seconds [40, 41].

In fairness, it should be noted that obtaining a therapeutic relatively short-lived α radionuclide ^{149}Tb ($T_{1/2}$ = 4.1 h) can be effective in ISOL installations [42]. In the case of long-lived nuclei required for nuclear medicine, the use of ISOL facilities is generally not justified for the following reasons: (1) the yield of "daytime" radionuclides with ISOL facilities probably never exceeded 1%, but in practice it was much less. This is quite enough for research tasks, but with the existing technologies of particle beams and targets to produce therapeutic amounts of isotopes (with a factor of not less than a thousand from the research goals), a yield of tens of percent is an urgent requirement; (2) it is counterproductive to simultaneously operate an accelerator and a mass separator for isotopes with a half-life of several days, since unnecessary contamination of the preparation occurs.

As a result, experiments were started with off-line separation to produce long-lived radionuclides at the ISOLDE facility [43–45]. The published results of these studies so far inspire little enthusiasm for the fast application of this technique for the purification of reasonable quantities of medical grade radionuclides. Separation itself occurs, but the yield and separation degree are insufficient, and no work has even been carried out on real therapeutic amounts.

The method of obtaining radionuclides using off-line mass separation in our department paved the way to the study of radiation spectra, which was reflected in the atlas of the emission spectra of radioactive nuclides measured with semiconductor detectors [46], the atlas of emission spectra of medical radionuclides [47], and the electronic atlas [48]. *This is the third parallel with nuclear medicine, where it is also necessary to use modern spectrometry methods, both in diagnostics of diseases (PET, SPECT), and in assessing the quality of radiopharmaceuticals for radioactive impurities. In addition, spectrometric data are extremely important for assessing the irradiation dose to diseased and healthy tissues, as well as for understanding how the internal irradiation affects the structure of a substance at the microlevel.*

One can hope that off-line mass separation will find its application in the purification of large quantities of therapeutic isotopes in the future. But it must, apparently, go its own way of development in this direction, solving several fundamental problems. So, for example, when producing radionuclides, a degree of purification from the target material of 10^6–10^8 is almost always required. Usually, the degree of separation during mass separation does not separation factor 10^3. It is necessary to carry out a double mass separation. And as far as can be seen from the publications, researchers are not yet very ready for such a turn of technoligies.

So far, in the production of radionuclides for diagnostic and therapeutic purposes, it is possible to rely only on radiochemical separation, while most methods refer to "wet" chemistry. It is also necessary to select methods for producing radionuclides without significant impurities of isotopic stable and radioactive impurities.

2. METHODS AND TECHNIQUES DEVELOPED AT DLNP

The development of radiopharmaceuticals involves the solution of many different research problems. The pie chart (Fig. 6) symbolizes the continuity and interdependence of these processes. On the other hand, almost any of the tasks requires an independent scientific approach. Some of them are solved directly at DLNP: radiochemical (blue sectors), and nuclear-physical (red sector). Several tasks are being solved jointly with colleagues from other research centers. The main methods and techniques to produce radionuclides and the synthesis of radiopharmaceuticals are described in the relevant sections below.

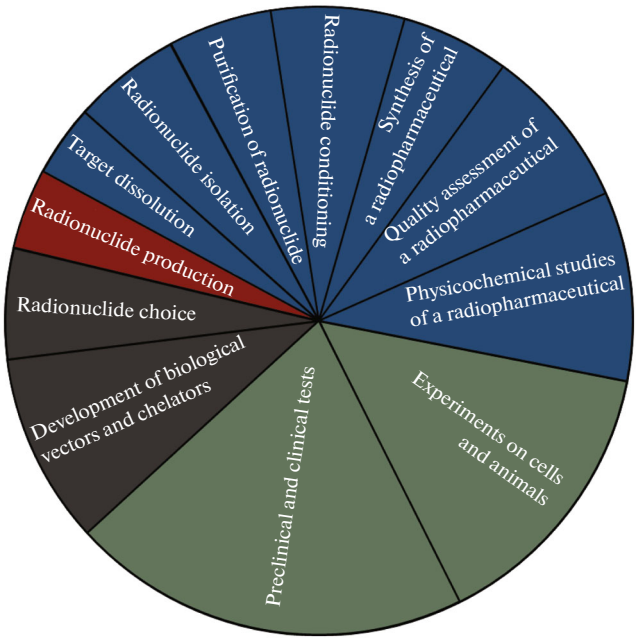


Fig. 6. Stages of development of a radiopharmaceutical.

2.1. Techniques for Obtaining Radionuclides from Irradiated Targets and Generators

As already noted above, our department historically deals with nuclear spectroscopy and radiochemistry. In recent years, the methods of these areas have been actively used to study rare double β-decay processes, search for dark matter particles, and other experiments [49–52].

The methods for obtaining a sufficiently large number of nuclear medical radionuclides are being also developed in our department. This is due to several factors.

(1) A pressing need to develop methods for obtaining "new" promising radionuclides for nuclear medicine, as well as effective methods for obtaining all nuclear medical radionuclides.

(2) The possibility to irradiate targets with protons of different energies (0–60 MeV–660 MeV) in the internal beam at the DLNP Phasotron, which, due to the high specific density for such an irradiation mode, perfectly correlates with the high density of target irradiation at high-flux accelerators.

(3) The possibility to carry out target irradiation at other JINR nuclear installations: reactor, microtron, etc.

(4) Good experience in developing methods for isolation and separation of almost all elements for the relevant radionuclides.

(5) Good experience in developing new *complex* methods for obtaining radiopharmaceuticals: radionuclide selection → radionuclide production method selection → radionuclide production → *target dissolution* → radionuclide preparation isolation → radionuclide preparation purification → *radionuclide preparation conditioning* → radiopharmaceutical synthesis → radiopharmaceutical quality assessment (including spectrometric). In this case, it is necessary to develop not just a specific stage, but a connected chain of methods, when the drug from the previous stage is well suited to start the next stage. Our list indicates *in italics* the stages at which (before or after) there is a fundamental change in technology and often the transfer of the processed material. On the other hand, modern approaches are just trying to ensure the continuity of processes. At present, the *conditioning of radionuclide preparation* is becoming less and less a stage in the transfer of a radionuclide from researcher to researcher. Moreover, recently the dissolution stage also changes its location.

(6) Good experience in the development of radionuclide generators, as well as complex methods for designing radiopharmaceuticals based on the obtained isotopes.

(7) A wide range of scientific cooperation primarily with the University of Mainz (Germany) and TRIUMF (Canada), as well as colleagues from the JINR Member States (Kazakhstan, Uzbekistan, Poland, Czech Republic, Bulgaria, etc.). The scientific cooperation in the development and use of radiopharmaceuticals cannot be overestimated. So, for example, to the chain of methods indicated in Section 5 when developing a radiopharmaceutical, it is necessary to add the stages of developing chelators and biological vectors, as well as various analytics up to clinical trials. All this requires both close cooperation and a certain specialization of a significant number of scientific groups.

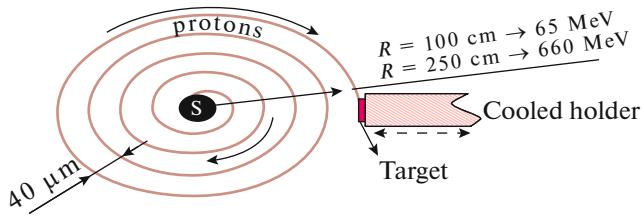


Fig. 7. Irradiation scheme at the Phasotron at DLNP JINR.

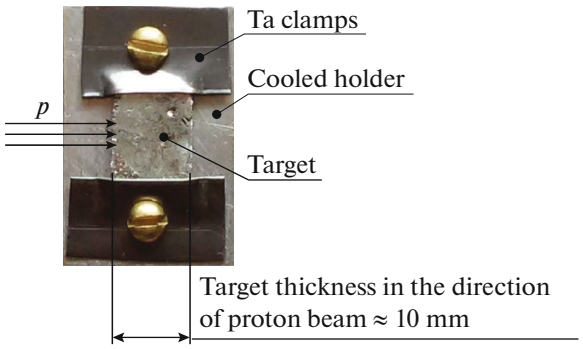


Fig. 8. A typical view of a metal target.

2.1.1. Target irradiation. The radionuclides used at DLNP JINR are mainly produced by irradiating the target at the proton accelerator, the DLNP Phasotron.

The energy of protons during target irradiation can vary in the range of 60–660 MeV. It is possible in principle to irradiate complex targets at lower energies. At high energies, the so-called spallation reactions mainly occur, when, after a proton enters the target nucleus, many protons and neutrons leave it. As a result, the formation of a large set of mostly neutron-deficient nuclei is possible. If the target has a large Z (as U, Th), then the formation of neutron-rich nuclei, also occurs, which are characteristic of the nuclear fission spectrum, but without a characteristic dip for the nuclear fission cross section on thermal neutrons in the intermediate region [21]. At energies of 60–100 MeV, the portion of the (p, xn) reaction increases, which is also used to obtain radionuclides, but in this case, difficulties arise due to increased heat release in the target.

A characteristic feature of interaction of 60–660 MeV protons with matter is their long range. Therefore, nuclear reactions can proceed almost along the entire range, thus compensating for the relatively low cross sections for the formation of some isotopes [35].

An important feature of the Phasotron, and earlier the DLNP JINR synchrocyclotron, is the possibility of irradiating targets inside the vacuum chamber using an internal beam (Fig. 7).

The energy of protons is varied by changing the radius on which the target is located relative to the source of protons. In addition, this allows the use of relatively thin foils (plates) as targets, but "thick" ones (10–40 g/cm^2) along the proton range direction, since the protons pass through the target by the tangent (Figs. 7, 8). The internal proton beam can be concentrated without losses on an area of 5–10 mm^2, which, at the maximum current of the DLNP Phasotron (≈2–5 μA), provides the target irradiation density orders of magnitude higher than in the extracted beam. This means that the same amount of radionuclides is obtained in the internal beam in a target with a mass approximately 500 times smaller than the target irradiated in the extracted beam at the same energy and proton flux. However, the high irradiation density leads to strong heat release in the target. This can lead to undesirable effects: target melting and evaporation (volatilization) of the produced isotope in the case of elements with a lower boiling point. A significant reduction in heat release in the target can be achieved by selecting (matching) the parameters of irradiation and the target material: it is possible to reduce the proportion of ionization losses by increasing the proton energy; to choose a smaller target thickness or a material with a lower density; to reduce the beam current and increase the exposure time. Also, to reduce the target heating, water cooling of the holder is provided.

The target heating is one of the main factors determining the possible set of materials for irradiation. In this regard, refractory metals are very suitable. There is good experience in using Ta and Th targets to produce lanthanides and some actinides [21, 35].

It is possible to prepare targets from a wide range of materials, including more fusible metals or their alloys, as well as from chemical compounds, primarily oxides.

For metals with a melting temperature above 1000°C, the target is made in the form of a plate (Fig. 8). The thickness in the direction of proton beam is usually ≈10 mm and is determined from the condition of minimizing ionization losses. In the direction of the proton beam radius, the size of the plate is 1–1.5 mm. Penetration of protons in this direction (to a depth greater than 40 μm) is associated with their scattering in the target material, multiple passage of the part of protons through the target, and radial fluctuations in the beam. The target height is 10–15 mm. It is determined both by the vertical size of the beam and by the need to ensure the fastening of the target (on cooled holder), which guarantees efficient heat removal in the absence of proton beam scattering on the fixation elements. Considering the above dimensions, the mass of a metal target, on average, is 0.5–2 g (0.005–0.01 mol). In some cases, by optimizing the irradiation parameters and taking several measures to improve heat removal from the target, it is possible to irradiate metals with a melting point well below 1000°C. A good example is the developed technique to

produce ^{111}In by proton irradiation of an antimony target [27].

The main advantage of oxides as a target material is their high thermal stability, but the fraction of the initial element (considering the density of the oxide) available for a nuclear reaction is usually an order of magnitude lower than in a single-element target. Even well-compressed oxide pellets can disintegrate under intense irradiation, so this type is irradiated in a shell (metal foil or a container). This greatly reduces the efficiency of irradiation. Therefore, irradiation of oxides in the form of a glassy layer (enamel) deposited on a metal substrate is promising. Such a layer has a much higher thermal conductivity and stability than compressed pellets, which allows more intense irradiation directly in the beam without using protective coating.

In addition to the targets irradiated at the Phasotron, the target irradiation in our department was also performed at other JINR nuclear facilities (IBR reactor, U-200, microtron, etc.). Often, we had to participate in the development of the corresponding targets. Here we also had to solve several scientific and technical problems. One can, for example, note a silver target for producing ^{111}In at U-200 when irradiated with α particles. In this case, the entire target assembly (target + holder in contact with cooling water) was made of silver (about 400 g). And the thin irradiated part of the target assembly with the accumulated ^{111}In was washed off with nitric acid solution. This unit was repeatedly used to produce radionuclide.

The first stage of target chemical prossesing (after irradiation) is its dissolution. Typically, the process is carried out in a mixture of acids. The specific composition of the solution depends on several factors, but the main condition is the complete dissolution of the target material in a relatively short time: usually no more than an hour, and preferably faster. Therefore, along with the melting temperature, an important factor determining the possible set of materials for irradiation is the reactivity (chemical) ability of the target material. In some cases, a compromise must be found. For example, platinum-group metals have a fairly high melting point and good heat resistance but are very difficult to dissolve. In some cases, the mode of dissolution of the target can be affected by radiation modification of the material due to irradiation.

The purity of the target material is also of great importance. Particularly undesirable are impurities of the element whose isotope needs to be produced. It is also necessary to beware of contaminants that have high cross sections for the formation of various types of undesirable radionuclides.

An important issue is the method of "mechanical" separation of the target from the holder. In most cases, if there was no "melting" of the target, this problem is successfully solved in our target designs. However, it is important to emphasize here that the "fastener" of the target must be fabricated from an inert material that does not contain undesirable impurities, and does not form fusible alloys with the target substance.

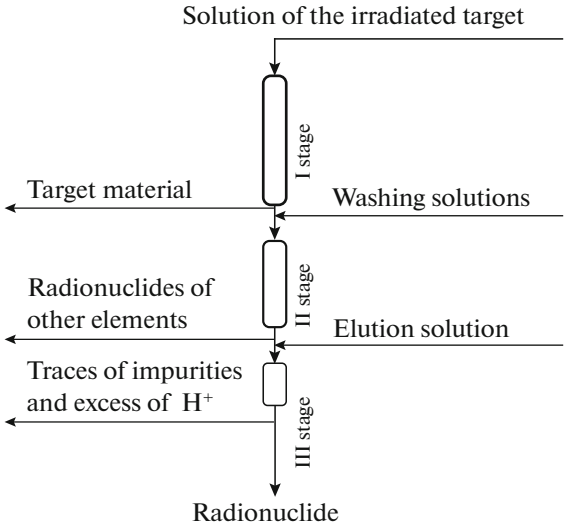


Fig. 9. General scheme for isolation a radionuclide preparation from an irradiated target.

In some cases, with the appropriate selection of the "chemistry" of dissolution and separation [53], and the correct selection of the target holder, it is possible to dissolve it without their mechanical separation.

An alternative to target dissolution is its thermal "opening." This issue will be discussed in Section 2.1.3.

2.1.2. Dissolution (opening) of targets, separation, isolation, conditioning of radionuclide preparation. When separating elements, one can often find various terms that characterize this process: purification, isolation, separation, disconnection, conditioning, etc. This is mainly due to the need to solve various problems during these processes. As already noted at the beginning of the section, when obtaining a radionuclide, it is necessary to carry out several related operations. In this section, we will focus on radiochemical ones: target dissolution, isolation of radionuclide preparation, purification of radionuclide preparation, and conditioning of radionuclide preparation. If a solid target is used for irradiation, then it must be dissolved to be separated. From a chemical point of view, separations can then be carried out in real time (we are talking about times from a fraction of an hour to several hours). Safe, complete, rapid dissolution of the target with the transfer to the desired form is half the success of all subsequent separation.

The next three stages after dissolution are conveniently highlighted (Fig. 9) as processes carried out on three chromatographic columns with usually reducing volume. The main challenges at these stages are the following:

(1) To separate the *microquantity* of radionuclide from the *macroquantity* of the target material with a purification factor of at least 10^6, and even more often 10^8.

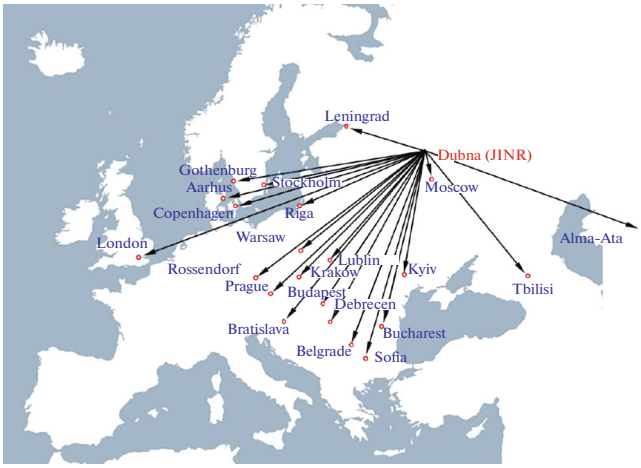


Fig. 10. Map of deliveries of spectrometric sources and radioactive preparations [35].

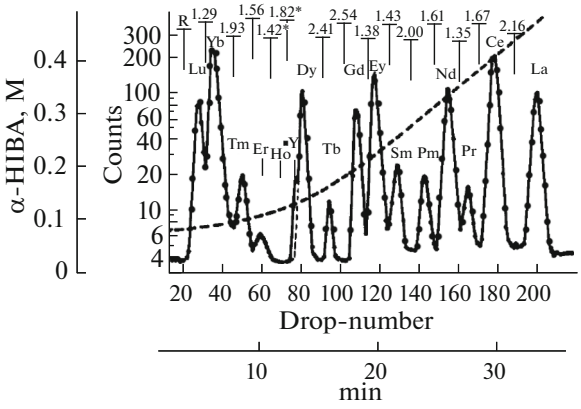


Fig. 11. Separation of lanthanides on Aminex A-5 with ammonium α-hydroxyisobutyrate pH 4.5 [34].

(2) To separate the microquantity of the target radionuclide from the microquantities of impurity radionuclides of other elements.

(3) To provide the necessary chemical form of a radiopharmaceutical to label the appropriate radiopharmaceutical (usually a minimum content of hydrogen ions, other interfering ions and undesirable impurities).

(4) To carry out these operations in the minimum time with a high yield of the target radionuclide.

It is important to note that it is the sequential performance of the above operations on two or three chromatographic columns that has recently become our choice [54] and, rather, is a global trend. This is due, on the one hand, to the ability to quickly obtain a radiopharmaceutical in the desired form with good repeatability, and on the other hand, commercial equipment already available now with the possibility of appropriate automation. Sometimes several stages are combined on one column, but this is not fundamental and so optimal. The "cocurrent" method for the target radionuclide using several columns reducing in volume at each stage enables the process to be carried out very quickly, almost inevitably provides a degree of purification factor of at least 10^9 from the target material and is already a kind of "logical" chemical filter for assessing the quality of the resulting preparation. Here it is interesting to note that historically, including at our department, the first stage of separation was preferred to be carried out by coprecipitation of the target radionuclide with the carrier added at this stage. Then one or two chromatographic separation stages were usually carried out. In many respects, this combination of methods, including coprecipitation, is very efficient chemically, but it still requires the stages of interfacial separation (filtration or centrifugation) and subsequent dissolution. This usually takes relatively longer time, and besides, these stages are more difficult to automate.

Another classical approach is liquid extraction separation. Liquid extraction often makes it possible to obtain large separation factors of elements (from 10^6 and higher) in one stage. This formed the basis for several methods of obtaining radiopharmaceuticals in one stage (although usually these are two stages: extraction and back extraction). However, in the case of radiopharmaceuticals for labeling, it is almost always necessary to obtain them in a small volume. If the target is massive, then the classical extraction–back extraction processes usually lead to a relatively large volume of radiopreparation, which is inconvenient. Currently, along with ion-exchange resins, a large set of extraction resins is also produced, and columns based on these resins are usually included in the scheme for obtaining radiopharmaceuticals using a series of steps described above.

Examples of Obtaining Radionuclides

Obtaining Lanthanides

Lanthanides and their analogs were obtained not only at the DLNP Phasotron, but also at other nuclear facilities of the Institute and external institutions. Spectrometric sources and radioactive preparations were supplied to many countries of the world (Fig. 10).

As mentioned earlier, an effective way to obtain neutron-deficient radiolanthanides is to irradiate a tantalum target with high-energy protons [34]. Irradiated tantalum targets were dissolved in an HF/HNO_3 mixture. Lanthanides were coprecipitated with LaF_3 and adsorbed onto Aminex A-5. Separation of all lanthanides was carried out using ammonium α-hydroxyisobutyrate with pH 4.5 (Fig. 11). The chemical yield of elements of ~90% with an admixture of neighboring lanthanides was no more than 1%.

Neutron-deficient radiolanthanides of the cerium group can be obtained by irradiating erbium targets with high energy protons [55].

The lanthanides were separated from the macroamount of Er using di-(2-ethylhexyl)phosphoric acid (D2EHPA) on silica gel. Extraction chromatography using D2EHPA is also effective in the extraction of lanthanides from Gd and Nd targets irradiated with 120-MeV protons [56]. This extraction procedure can potentially be used to obtain ^{161}Tb by the reaction ^{160}Gd(n,γ)^{161}Gd(β$^-$)^{161}Tb.

Obtaining At Isotopes

A significant contribution to the development of astatine chemistry was made by our colleagues and, first of all, by V.A. Khalkin and Yu.V. Norseev [57]. The main achievements at DLNP include the following. First, it was shown for the first time that the production of astatine by spallation reactions on a thorium target is at least as effective as irradiation of bismuth with α particles [58]; second, it was found that, unlike other halogens, astatine in aqueous solution has a more stable form of an aquated positive cation. Third, pioneering works were carried out to obtain organic derivatives of astatine, in particular, astatbenzene. The results obtained when studying the forms and compounds of At were included in the reference book on chemistry [59].

The first developed procedures for the separation of astatine isotopes from metallic thorium were rather laborious and lengthy (4–8 h) with many stages [60]. Later, when using tellurium columns, the isolation process was reduced to 2 h [61]. The target was dissolved in a mixture of concentrated HCl and HNO_3 with the addition of HF. The main part of thorium was separated on a tellurium column, while the separation of At from Te and I was carried out using a smaller tellurium column in a HCl–$SnCl_2$ medium. As a result, an At preparation was obtained in 2 M NaOH with a yield of 80 ± 5%. Another method of isolation from thorium targets, gas thermal chromatography, provided radionuclide-pure At with a yield of 80% [62]. In the combustion of thorium in the zones of the temperature gradient, radionuclides were absorbed: Po, on platinum foil at 750–650°C; I, Br and Tl on a silver filter at 480–400°C; and At on silver foil at 150–100°C.

Obtaining ^{177}Lu

^{177}Lu was produced on the TRIGA II (Mainz) and BER II (Berlin) reactors by the reaction ^{176}Yb(n,γ)^{177}Yb(β$^-$)^{177}Lu [19]. The irradiated target was dissolved in HCl with the addition of CH_3COONa. The radiochemical separation of ^{177}Lu and the macroquantity of ytterbium occurred by ytterbium extraction with Na(Hg) amalgam. Further purification was carried out on a cation exchange column. The Lu/Yb separation factor after the first stage was 10^4, and the ion-exchange separation makes it possible to improve it by another two orders of magnitude.

Obtaining Radionuclides from a Thorium Target

When natural thorium is irradiated with high-energy protons, hundreds of reaction and fission products are obtained. Thus, it is possible to obtain many unique radionuclides for radiochemical and spectrometric studies, as well as for nuclear medicine. We developed and tested a technique for the qualitative separation and isolation of a large number of radionuclides from thorium irradiated with 300-MeV protons [21].

At the first stage of the separation, the irradiated thorium plate was dissolved in hydrochloric acid, then evaporated to wet salts and transferred to the nitrate form. At the stage of anion exchange chromatography, the resulting solution was loaded onto a column with AG1× 8 resin and washed with a solution of nitric acid from 10–12 to 1 M. In the second stage, for reliable deposition to the AG 50× 8 resin and reducing the volume of the solution, the first fraction with radionuclides (~100 mL) was evaporated and dissolved in 0.3M HNO_3. After loading, the column was washed with various concentrations of nitric acid. The chromatogram is shown in Fig. 12.

Depending on the tasks set, the group of radionuclides obtained by elution can be further divided element by element. For example, several schemes for separating groups of radionuclides were proposed: separation of Ba, Bi, and Sn; separation and conditioning of ^{225}Ac, ^{144}Ce, and ^{88}Y (^{140}La); obtaining ^{230}U from ^{230}Pa.

Figure 13 shows the scheme of separation.

Using this radiochemical scheme, we obtain several radionuclides with high radionuclide purity, but it is laborious and time consuming.

A new radiochemical scheme was also developed for working with irradiated natural thorium targets focusing on the isolation of such promising radionuclides for targeted α-therapy as radium and actinium [20]. Irradiation was carried out by protons with an energy of 600 MeV at the DLNP Phasotron. The new scheme assumes a reduction in the quantity of resins used (1 g of resin per 1 g of target) and solutions to avoid large quantities of liquid radioactive waste. In addition, one of the advantages will be the elimination of evaporation stage of the target solution by its direct complexation with a suitable chelating agent in a medium with significant acidity. The technique is based on cation exchange chromatography in CCl_3COOH medium with further separation of Ac and its analogs on DN extraction resin with HNO_3, and Ra and its analogs on SR with HNO_3. The isolation scheme is shown in Fig. 14. We consider the new

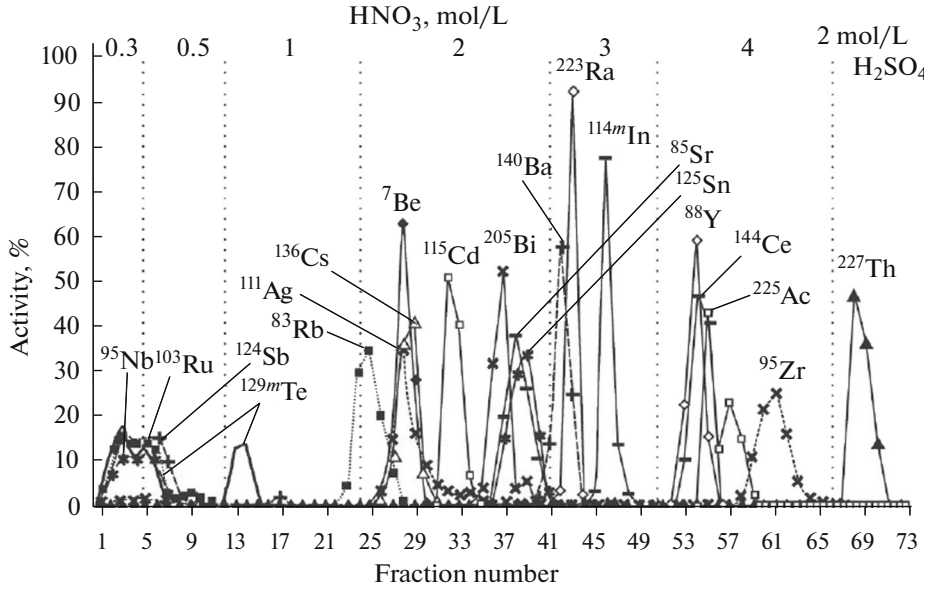


Fig. 12. Chromatographic separation of radionuclides on AG 50×8. Fraction volume is 4 mL.

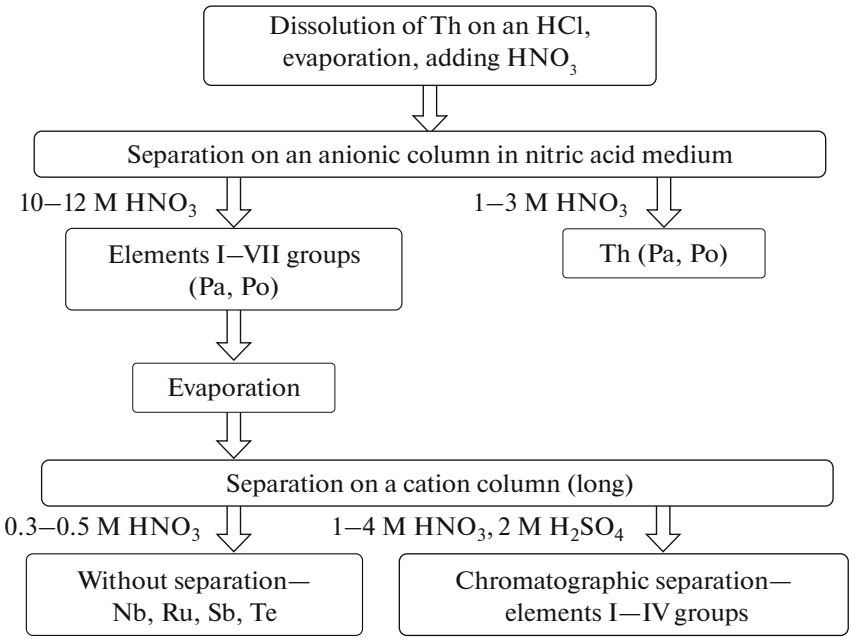


Fig. 13. Schematic diagram for separation of radionuclides from a thorium target irradiated with 300-MeV protons.

technique to be promising in the light of its application to massive thorium targets (up to 300 g).

Obtaining ^{86}Zr from an Y Target

^{86}Zr ($T_{1/2}$ = 16.5 h) is the parent radionuclide for the ^{86}Zr → ^{86}Y radionuclide generator. Sufficiently large reaction cross section (p, 4n) upon irradiation of natural ^{nat}Y targets with 70-MeV protons, together with a significant range of particles, makes it possible to obtain ^{86}Zr with a high yield of 970 MBq/μA h. The irradiated targets were dissolved in nitric acid. Separation of ^{86}Zr from an irradiated yttrium plate was carried out on anion exchange (Dowex 1×8) and extraction (UTEVA) resins (Fig. 15). The technique makes it possible to obtain ^{86}Zr preparations with a high yield (≥98%) and a separation factor of 0.7 × 10^7. It is also important to note the high chemical and

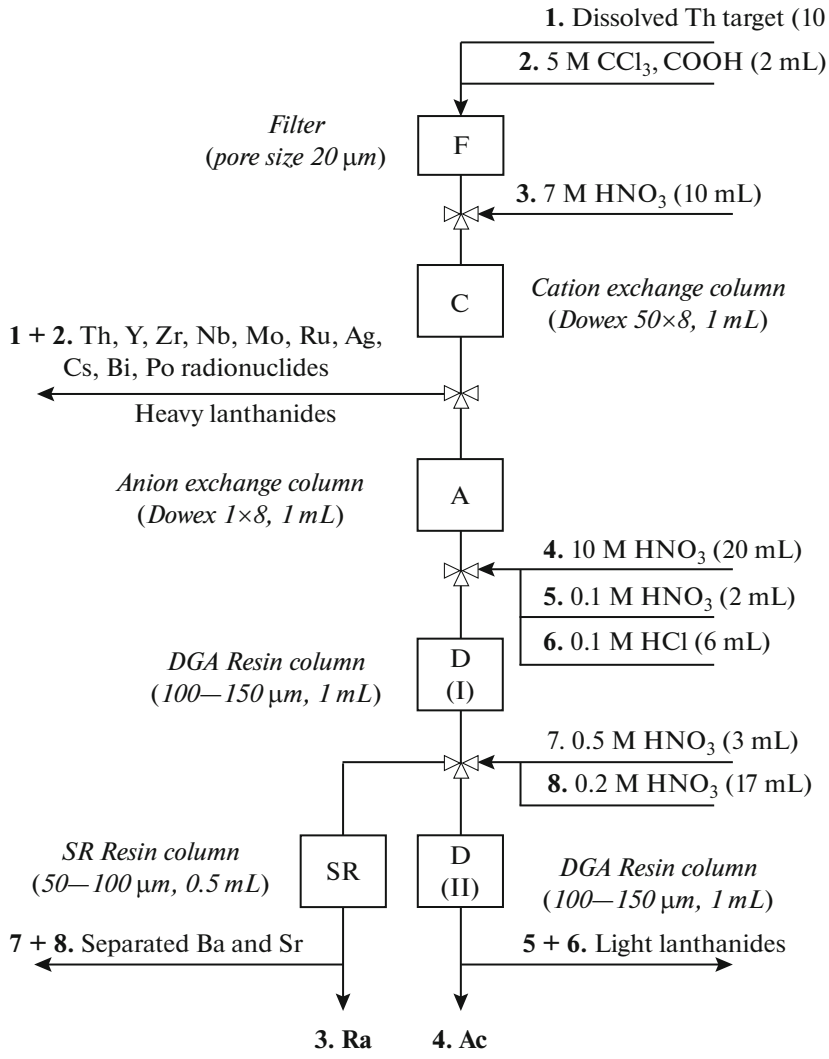


Fig. 14. Schematic diagram for isolating Ac and Ra isotopes from thorium targets irradiated with 600-MeV protons [20].

radionuclide purity of the obtained preparation, which is further used in the $^{86}Zr \rightarrow {}^{86}Y$ radionuclide generator [63].

Obtaining ^{90}Nb from Mo and Zr Targets

^{90}Nb ($T_{1/2}$ = 14.6 h) is a positron-emitting radionuclide with a high positron yield of 53% and their average energy E = 0.662 MeV, being a promising candidate for PET diagnostics. We developed a procedure for obtaining ^{90}Nb from proton-irradiated molybdenum and zirconium targets [23]. Cation exchange, anion exchange and UTEVA columns were connected in series. In the first stage, the target material is dissolved in concentrated hydrofluoric acid. Bulk target material is separated. at the stage of ion exchange chromatography (Dowex 50 × 8, AG 1 × 8). Additional purification from traces of the target material and the concentration of Nb preparations in 0.1 M $C_2H_2O_4$ (400 μL) is carried out at the conditioning stage. The separation scheme is shown in Fig. 16. The Nb separation takes less than 1 h with a yield of 93–95% and a purification factor ≥10^8 from Zr or Mo after all stages.

Obtaining ^{111}In from an Ag Target

^{111}In ($T_{1/2}$ = 2.80 d) was produced at the U-200 cyclotron with particle energy E_α = 30 MeV via the reaction $^{109}Ag(\alpha, 2n)^{111}In$. The active layer of the target was dissolved in concentrated HNO_3. Next, 3 mg of $La(NO_3)_3$ and NH_4OH were added to the target solution for enhancing pH ≥ 8. In this case, indium coprecipitates with lanthanum, while the Ag target material together with ^{109}Cd ($T_{1/2}$ = 461.9 d) remain in the solution. The precipitate was redissolved in concentrated HNO_3 followed by the addition of NH_4OH, and this procedure was repeated five times. Finally,

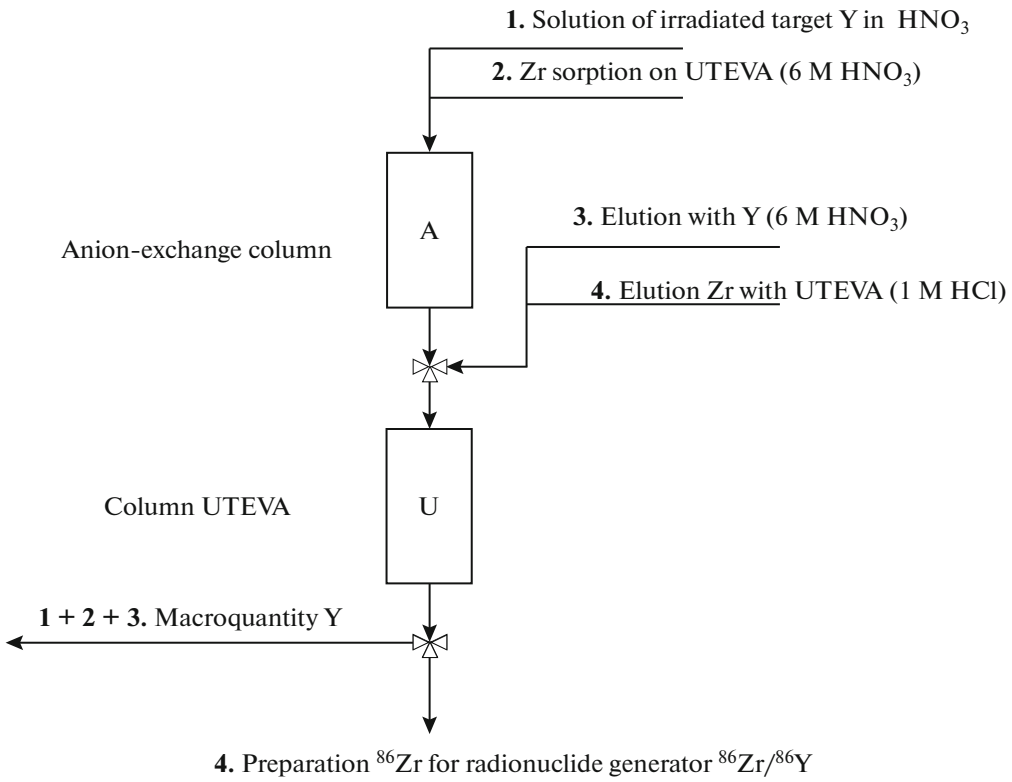


Fig. 15. Schematic diagram for ^{86}Zr isolation from irradiated yttrium targets [63].

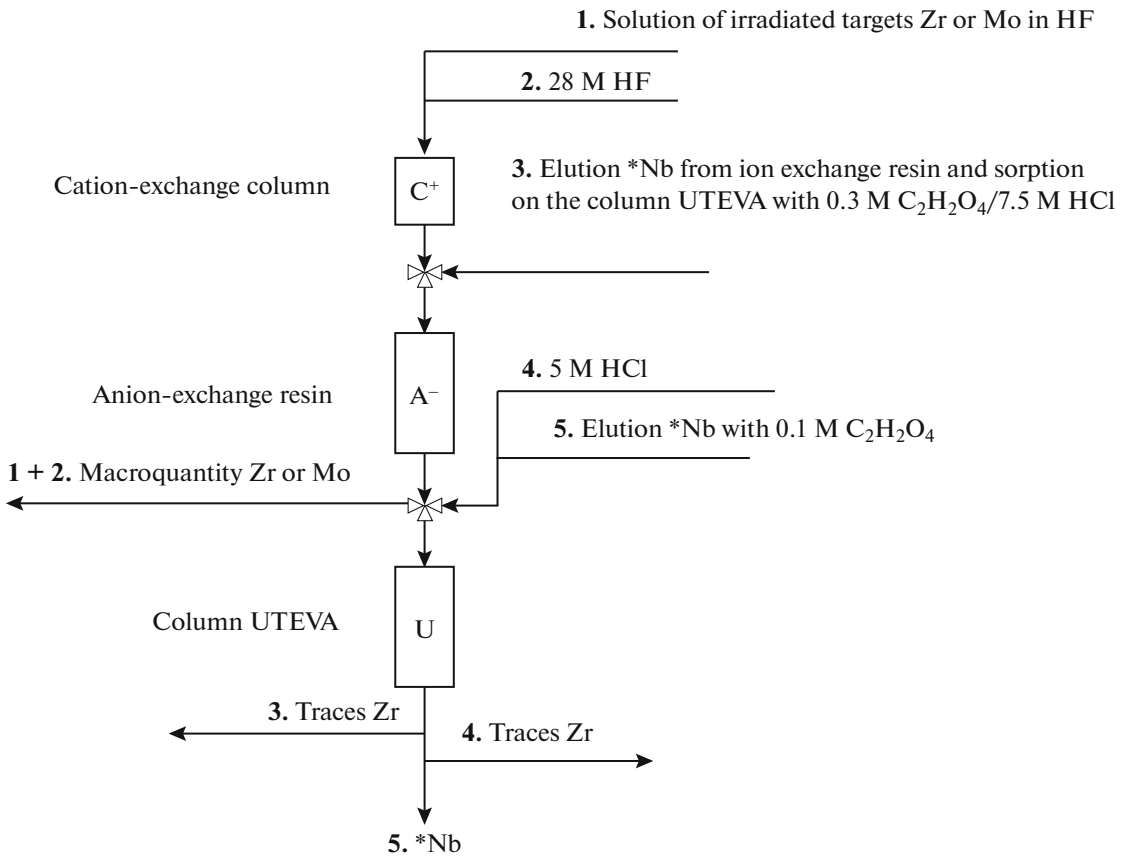


Fig. 16. Schematic diagram for ^{90}Nb isolation from irradiated molybdenum and zirconium targets [23].

the precipitate was dissolved in HCl to purify the desired product. The resulting solution (0.1 M HCl) was loaded onto a Dowex 50W×8 cation exchange column (200–400 mesh, H^+ form, $d = 3$ mm, $h = 100$ mm). The column was sequentially washed with solutions of 0.1, 0.25, and 0.5 M HCl. ^{111}In was eluted with a 0.5 M HCl solution, while La and other stable impurities remained on the column. The ^{111}In eluate was dried to dryness, and the resulting precipitate was dissolved in 0.1 M HCl. At the last conditioning step, a solution of ^{111}In in 0.1 M HCl was loaded onto an Aminex A–6 column (H^+ form, $d = 1.25$ mm, $h = 30$ mm). The elution was carried out similarly to the previous separation on a cation column: the target radionuclide ^{111}In was obtained in 0.5M HCl with a volume of 50 μL [64].

Obtaining ^{111}In from a Sb Target

^{111}In was produced by irradiating a natural Sb target (1 g) at the DLNP JINR Phasotron with a proton energy of 600 MeV. The target was dissolved in 10 mL of aqua regia under heating, followed by the addition of 6 M HCl to a volume of 50 mL. Further purification was carried out according to a three-stage scheme. First, the target solution was loaded onto a Dowex 1 × 8 anion exchange column (Cl^- form, 100–200 mesh, $d = 100$ mm, $h = 15$ mm) and washed with solutions of hydrochloric and hydrofluoric acids. Purification from macroquantities of the ^{nat}Sb/^{120m}Sb ($T_{1/2} = 5.76$ d) target material occurred at this stage. An ^{111}In was eluted from the column in 8 M HCl and 5 M HF solutions. After that, this mixture was dried to dryness, and the resulting precipitate was dissolved in 0.5 M HNO_3. At the second stage, a solution containing the ^{111}In target and trace amounts of ^{nat}Sb/^{120m}Sb was loaded onto a Dowex 50×8 cation exchange column (H^+ form, 200–400 mesh, $d = 100$ mm, $h = 3$ mm). The column was washed with nitric acid solutions, which made it possible to purify the target radionuclide from trace amounts of ^{nat}Sb/^{120m}Sb. The ^{111}In eluate in 2 M HNO_3 was evaporated to dryness, and the resulting residue was dissolved in 0.1 M HCl. At the final stage of purification (conditioning), this solution was loaded onto an Aminex A–6 column (H^+ form, $d = 2.5$ mm, $h =$ 45 mm). The column was washed with hydrochloric acid solutions, and the ^{111}In target was obtained in 0.6 M HCl with a volume of 300 μL [27].

Te/Sn Separation

According to the above reaction, ^{119m}Te ($T_{1/2} = 4.70$ d) and ^{117m}Sn ($T_{1/2} = 13.76$ d) are also produced along with ^{111}In and ^{120m}Sb. This system may be of interest in developing a method for separating tellurium from tin with subsequent use of tellurium as a ^{119m}Te → ^{119}Sb generator. The brightest candidate for Auger therapy is ^{119}Sb ($T_{1/2} = 38.19$ h) [65, 66].

As mentioned above, in the first stage, ^{120m}Sb, ^{119m}Te, and ^{117m}Sn were washed off by washing the anion-exchange column with solutions of hydrofluoric acid in high concentrations (15–26 M HF). These fractions were evaporated to dryness followed by dilution with 8 M HCl. The resulting solution was loaded onto a standard UTEVA column (100–150 μm, 2 mL). These two radionuclides were separated due to different distribution coefficients of tellurium and tin on UTEVA resin in hydrochloric acid solutions. ^{119m}Te was eluted from the column by 1 M HCl solution.

Irradiation of antimony targets using medium-energy cyclotrons (40–80 MeV), as well as further application of the described technique [27], makes it possible to obtain a ^{119m}Te preparation with a high specific activity and a minimum presence of radionuclide impurities.

Obtaining ^{44}Sc from a Ca Target

^{44}Sc ($T_{1/2} = 3.97$ h) was produced by irradiating ^{nat}Ca (70 mg) with low-energy protons (12.8 MeV) according to the reaction ^{44}Ca(p, n)^{44}Sc. The target was dissolved in deionized water, followed by the addition of concentrated HCl to obtain a solution in 6 M HCl. The separation was performed in two stages. First, the target solution was loaded onto a DGA extraction column (50–100 μm, 300 mg), where the ^{44}Sc target was eluted with a 0.05 M HCl solution and loaded in a cocurrent way onto the next Dowex 50W × 8 column (H^+ form, 200–400 mesh, 140 mg). Then, ^{44}Sc was washed off with a solution of 0.1 M ammonium α-hydroxyisobutyrate pH 4.8, after converting the resin into the form NH_4^+. The last stage is additional purification from the target material (Ca) and stable impurities (Al, Fe), as well as conditioning the final fraction: the target product is washed out in a volume of less than 300 μL in a form convenient for radiolabeling [53]. It should be noted that the analysis of the final product on an inductively coupled plasma mass spectrometer showed a low content of impurities of stable metal isotopes, which indicates the applicability of the preparation in radiopharmaceuticals.

2.1.3. Thermochemistry with radionuclides. Under the term "thermochemistry" with radionuclides in this section, we mean thermodynamic, kinetic and analytical studies of the course of chemical reactions, as well as the separation of radionuclides, when the course of reactions or technological processes is strongly influenced by the changes in temperature. At first glance, these are just studies at high temperatures. But here it is not just the temperature value that is important, but the ratio of any characteristic energy of the process and the energy of thermal motion: $\Delta G/RT$, $\Delta E/RT$, $\Delta Q/RT$, etc. (where ΔG is the Gibbs energy, ΔE is the activation energy of diffusion, ΔQ is the energy barrier of the reaction).

It is in this understanding of thermochemistry with radionuclides that very significant research was carried out in our department both in search depth and in coverage [67]. These include:

— Development of thermochromatography methods for a wide range of elements and compounds (astatine, radon and other noble gases, all spallogenic products from thorium and tantalum targets, lanthanides and actinides), participation in research on the chemistry of superheavy elements, etc.

— Development of thermochromatography methods for obtaining medical radioisotopes from solid targets (^{111}In [68, 69], ^{67}Ga [70, 71], ^{201}Tl [72], ^{211}At [73], ^{94m}Tc [74]), as well as for the ^{188}W/^{188}Re [75] generator.

— Development of distillation methods for obtaining medical radioisotopes, including those for generators (^{72}Se and ^{72}Se/^{72}As [76, 77]), as well as a number of other elements [78, 79]).

— Study of diffusion of radionuclides at high temperatures from irradiated targets for their subsequent thermochromatographic separation, or for their feeding directly into the ion source and subsequent mass separation. It is clear that these studies are closely related to studies on the ionization of the resulting products and mass separation (+ ISOL) [80].

— Development of methods for fabricating thin radioactive sources for α-, β-spectrometry by vacuum evaporation [81, 82].

A very large number of researchers from DLNP and colleagues from different JINR member countries participated in the development of these areas. Several papers were published in the series "Fast gas-thermochromatographic methods for separation of radioactive elements." Here it is necessary to highlight the contribution of A.F. Novgorodov, who was one of the leaders and apologists of radiochemical thermochemistry, developing all the above areas of research in this field. Examples include the title of his dissertation: "High-temperature separation and thermochromatographic purification of spallogenic products" [83], as well as a chapter in a reference book on nuclear chemistry: "Radiochemical separations by thermochromatography" [84]. Despite obvious efficiency and relative elaboration, the application of thermochemistry in nuclear medicine is still limited. This is due to several reasons. First, with objective problems of the efficiency of radionuclide isolation from massive targets. In addition, this is due to the much lower popularity of gas, solid state and other sections of thermochemistry among chemists and biologists compared to conventional wet chemistry. In this area (chemical reactions in a gaseous and solid-state environment at the laboratory level of work organization), there are often far fewer specialists, and the level of elaboration in conventional wet chemistry is much higher. Ultimately, most radiopharmaceuticals are liquid substances. In the future, however, in our opinion, thermochemistry has great potential for use in nuclear medicine.

Up to temperatures of 1200°C, most of the technical problems of thermochemistry were solved using quartz glass equipment. As a high temperature material, fused silica has three important advantages: gas impermeability (allows operation in various gases and vacuum), good weldability with a wide range of materials, and good hot ductility.

The use of temperatures above 1500°C opens access to the areas of oxide and even nitride (in air) chemistry. A particularly important practical application comes from the thermal "opening" of the target: the release of the produced isotope by heating the target. The opening mechanism is associated with several processes: volatilization of the produced isotope (in elemental form or in the form of oxide), formation of a depleted layer on the target surface, diffusion of the produced isotope to the target surface. The rate of these processes increases drastically with increasing temperature, and, therefore, for the effective application of thermochemistry methods, it is necessary to strive for higher temperatures.

To work in a higher temperature range, two issues must be resolved: obtaining such temperatures and new materials. At the present level, obtaining a high temperature is not so difficult. Laboratory furnaces are commercially available for operation in an air atmosphere up to 1800°C. Other heating methods are also available: induction—2000°C and above, gas burner—3000°C, and plasma—6000°C.

The issue of materials is much more acute. These are typically ceramic sinters, and except for heat resistance (and to some extent gas impermeability) they do not have any of the above properties of quartz glass. Therefore, it is necessary to look for other principles for constructing the facility and organizing the experiment.

A good example of the application of high temperature thermochemistry is the method developed at DLNP for separating ^{90}Mo ($T_{1/2}$ = 5.56 h) from a niobium target irradiated with protons. ^{90}Mo is the parent isotope to produce ^{90}Nb, which is considered as a promising radionuclide for PET diagnostics. ^{90}Mo was produced via the reaction ^{93}Nb(p, $4n$)^{90}Mo by irradiating a target of natural niobium (0.16 g) with 65-MeV protons in the internal beam of the DLNP Phasotron. First experiments using quartz glass devices showed that the chemical yield of molybdenum increased drastically with increasing temperature. Therefore, a high-temperature furnace and a thermochromatographic system of corundum tubes were used later on. The combustion ("opening") temperature of the target was 1590°C, and the time was 60 min. In this case, niobium oxide (V) $2Nb + 5O_2 \rightarrow Nb_2O_5$ and molybdenum oxide (VI) $2Mo + 3O_2 = 2MoO_3$ are formed. Niobium oxide melts at a temperature of 1521°C. Molybdenum (VI) oxide has a boiling point of 1155°C and is adsorbed on the surface of quartz or porcelain at temperatures of 950–1050°C. In our case, the yield of

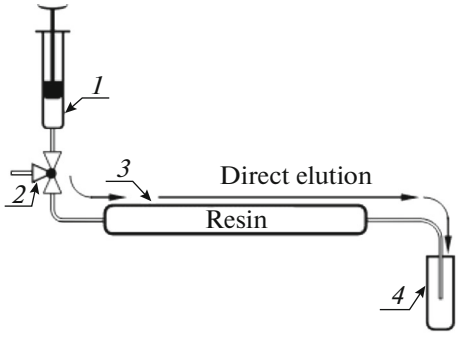


Fig. 17. Generator with direct elution scheme (Scheme I): (*1*) elution solution, (*2*) valve, (*3*) column with resin, (*4*) tank with the target radionuclide.

^{90}Mo was 51% in 1 h. There are grounds to assume that by increasing the opening temperature of the target, one can significantly increase the yield of Mo. In our case, the temperature was limited by the capabilities of the furnace.

The key feature of the experiment was the suction of air from the furnace cavity directly at the hot end of the tube, where the target is located. A section of the tube with a temperature gradient then follows (where volatilized products are absorbed), a suction pump hose is connected to the cold end of the tube. This approach has several advantages over the traditional scheme. It made it possible to overcome the abovementioned difficulties in the application of high temperatures. There are no data in the literature on the use of such a scheme of thermochromatographic separation.

2.1.4. Radionuclide generators. A radionuclide generator is a system where the decay of a parent radionuclide accumulates a daughter radionuclide that can be chemically extracted. The maximum accumulation of the daughter radionuclide occurs when equilibrium is reached after t hours/minutes. Provided that the parent radionuclide is much longer lived than the daughter one ($\lambda_1 \ll \lambda_2$), this time can be calculated using the formula:

$$t = \frac{1}{\lambda_2 - \lambda_1} \ln \frac{\lambda_2}{\lambda_1}, \quad (1)$$

where λ_1,λ_2 are decay constants of the parent and daughter radionuclides.

Requirements for radionuclide generator are as follows:

(1) Maximum yield of the target radionuclide.

(2) Minimal loss of the parent radionuclide.

(3) High specific activity.

(4) High chemical purity.

(5) High radionuclide purity.

(6) Reproducibility, process rapidity.

(7) Radiation resistance of adsorbents.

The radionuclide generator makes it possible to obtain a radionuclide with high radiochemical and radionuclide purity, as well as with high specific activity. The radionuclide generator is a source of medical radionuclides that can be obtained periodically away from the accelerator or reactor.

In the classical scheme (Scheme I) (Fig. 17) of a radionuclide generator, a column filled with a suitable adsorbent is used, and when the column is washed with a solution, the target radionuclide is eluted. Most existing generators operate in this way. To improve the final product quality, new generator schemes were proposed in our department: reverse (Scheme II) (Fig. 18) and reverse tandem. In the reverse scheme, the generator is regenerated by passing the solution in the opposite direction, which reduces penetrating the

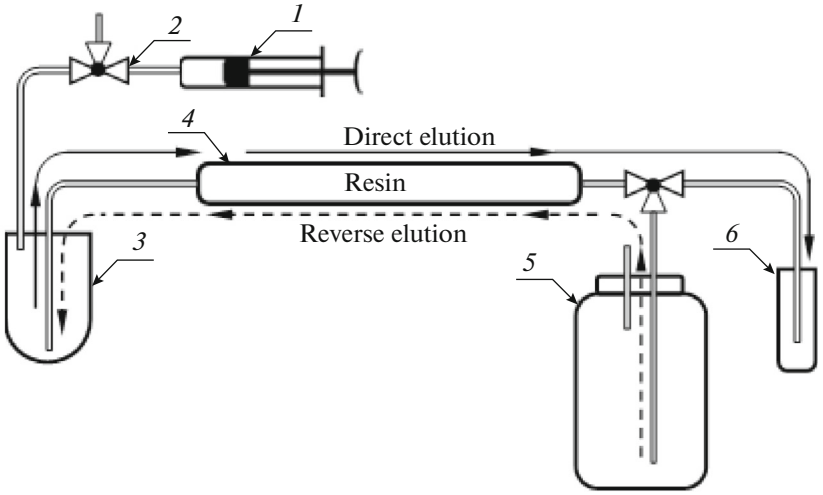


Fig. 18. Generator with reverse elution scheme (scheme II): (*1*) syringe for creating pressure and vacuum, (*2*) valve, (*3*) reverse storage tank, (*4*) resin column, (*5*) elution solution, (*6*) tank with target radionuclide.

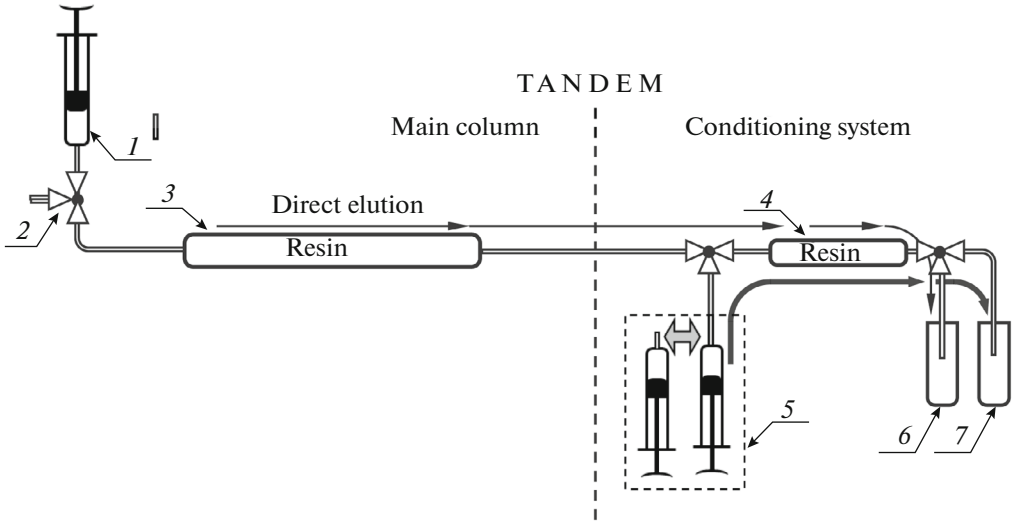


Fig. 19. Generator with tandem column (Scheme III): (*1*) elution solution, (*2*) valve, (*3*) main column, (*4*) tandem column, (*5*) solution for conditioning and elution of radionuclide, (*6*) container for the solution without radionuclide, (*7*) container with target radionuclide.

parent radionuclide outside by holding it at the beginning of the column. The tandem column (Scheme III) (Fig. 19) is intended for conditioning, additional purification of the daughter radionuclide and/or obtaining the final product in a form suitable for further labeling of a radiopharmaceutical. For some tasks it is possible to combine Scheme II and Scheme III and create a new reverse-tandem scheme. In addition, in order to save adsorbent from unwanted radiation exposure, it is possible to supplement the scheme of the developed generators with the option of washing the parent radionuclide from the column and storing it in an additional reservoir. This makes it possible to extend the operation time of the radionuclide generator, if necessary, for example, when the parent radionuclide has a long half-life: ^{229}Th ($T_{1/2}$= 7880 years), ^{44}Ti ($T_{1/2}$= 59.1 years), etc.

Over the years, our group developed and tested several radionuclide generators for the production of medical radionuclides, as well as for PAC research.

Examples of Radionuclide Generators

Radionuclide Generator $^{90}Sr \rightarrow {}^{90}Y$

The generator involved three columns filled with Aminex A-6 [85]. The first column was loaded with 2600 MBq of ^{90}Sr, the second column was to retain ^{90}Sr in case of a possible breakthrough. The ^{90}Y was eluted with a solution of 0.7 M and 0.15 M of ammonium α-hydroxyisobutyrarate. The resulting solution after two columns was adjusted to pH 1 with 4 M HCl and loaded onto column 3, whence the traces of ammonium α-hydroxyisobutyrarate were removed with 0.5 M HCl. Next, already purified ^{90}Y was eluted with 2 M HCl.

Radionuclide Generator $^{229}Th \rightarrow {}^{225}Ra \rightarrow {}^{225}Ac$

^{225}Ac ($T_{1/2}$ = 9.9 d) is one of the promising radionuclides for the targeted α-therapy. In 1996, a generator scheme was developed to separate ^{225}Ac from ^{229}Th [86, 87]. The parent radionuclide ^{229}Th is available from the decay products of ^{233}U produced from neutron irradiation of natural thorium. ^{229}Th and the decay products were adsorbed onto a column filled with Aminex A-5 resin. After deposition, Th is eluted from the column with a solution of 0.25 M ammonium citrate with pH 2.0–2.5, acidified to pH ≤ 1, and stored for further separations. Then, ^{225}Ac is sequentially washed out with a citrate solution at pH 4, after which ^{225}Ra is washed out with a solution of 4 M HNO_3.

Radionuclide Generator $^{111}In \rightarrow {}^{111m}Cd$

^{111}In ($T_{1/2}$ = 2.80 d) and ^{111m}Cd ($T_{1/2}$ = 48.50 min) radionuclides are widely used in studies using the method of perturbed angular correlation. The parent radionuclide ^{111}In was obtained in the (α, 2*n*) reaction by irradiating natural silver or from ^{109}Ag enriched with α particles using U-200 facility. Purified and isolated ^{111}In was deposited onto a generator column filled with KSK-2.5 silica gel. Separation of the mother and daughter radionuclide occurred using extraction chromatography with D2EHPA. The daughter ^{111m}Cd

radionuclide was obtained with a high yield (>95%) and a breakthrough of ^{111}In (<0.6%) [88].

Radionuclide Generator $^{72}Se \rightarrow {}^{72}As$

^{72}As radionuclide ($T_{1/2}$ = 26.00 h) is a candidate for PET. The parent ^{72}Se radionuclide ($T_{1/2}$ = 8.40 d) was produced at the CV28 cyclotron (Julich, Germany) by the (^{3}He, 3n) reaction on natural germanium targets. The concept of a radionuclide generator is based on the difference in the behavior of As and Se chloride complexes in the presence of HCl in the gaseous form. Above 80°C, arsenic chloride $AsCl_3$ is volatile, while selenium chloride $SeCl_4$ is not. At the optimum temperature of 110°C, more than 99% of ^{72}As is released with a breakthrough of the parent radionuclide ^{72}Se (<0.05%) [76].

Radionuclide Generator $^{44}Ti \rightarrow {}^{44}Sc$

^{44}Sc radionuclide ($T_{1/2}$ = 3.97 h) has a high positron yield (97%) and can be used as a diagnostic component in the ^{44}Sc/^{47}Sc theranostic pair. The parent ^{44}Ti radionuclide ($T_{1/2}$ = 59.1 years) was produced via the Sc(p, 2n) reaction. One has extracted 185 MBq of ^{44}Ti from an irradiated scandium target using cation exchange chromatography (AG 50W×8) [89]. A reverse scheme was chosen for the radionuclide generator, based on an anion exchange resin AG 1 × 8 with an elution solution of 0.07M HCl/0.005M $C_2H_2O_4$ (20 mL). This system provides a factor of 2 × 10^6 to separate ^{44}Sc from ^{44}Ti.

To reduce the volume of the final product and to facilitate subsequent radiolabeling, a tandem column was added to the main column, filled with AG 50W × 8. Subsequently, ^{44}Sc is washed out with 3 mL of 0.25 M ammonium acetate (pH 4). This scheme provides the labeling-ready ^{44}Sc with a high yield (150 MBq—90%) and a low content of ^{44}Ti (<10 Bq) [90].

Radionuclide Generator $^{86}Zr \rightarrow {}^{86}Y$

^{86}Y radionuclide ($T_{1/2}$ = 14.74 h) is a diagnostic component in the ^{90}Y/^{86}Y theranostic pair. Obtaining the parent ^{86}Zr radionuclide ($T_{1/2}$ = 16.5 h) is described above (Sec. 2.1.2). Two schemes of the radionuclide generator were proposed. The first is based on a Dowex 1×8 anion exchange chromatography in $C_2H_2O_4$/HCl mixture. Before deposition of ^{86}Zr onto the generator column, fine purification is performed on a cation exchange column. Target radionuclide ^{86}Y is eluted with Dowex 1×8 solution of 0.005 M $C_2H_2O_4$/0.07 M HCl.

The second generator is based on Zr resin. ^{86}Zr is reliably retained on this resin. And it is possible to elute yttrium in 0.1 M HCl.

Both generator systems showed a high yield of ^{86}Y (70–95%) and a low content of ^{86}Zr (≤10^{-3}%) [63].

Radionuclide Generator $^{68}Ge \rightarrow {}^{68}Ga$

^{68}Ga radionuclide ($T_{1/2}$ = 67.71 min) is widely used in PET diagnostics or in theranostics in combination with ^{177}Lu and ^{225}Ac. A chemical scheme of a radionuclide generator with two possible elution modes was developed: direct and reverse. Both schemes are based on anion exchange chromatography (Dowex 1×8) with 0.005 M $C_2H_2O_4$/0.33 M HCl elution solution. An assessment of the generator parameters yielded the following results: a ^{68}Ga yield of 75–80% and the ^{68}Ge breakthrough of 10^{-4}–10^{-3} [91].

Radionuclide Generator $^{172}Hf \rightarrow {}^{172}Lu$

^{172}Lu radionuclide ($T_{1/2}$ = 6.7 d) is used in the PAC research. The parent ^{172}Hf radionuclide ($T_{1/2}$ = 1.87 years) was obtained by irradiating natural tantalum with high energy protons. Separation and conditioning were carried out using anion-exchange and cation-exchange columns. Several schemes of a radionuclide generator based on an anion-exchange resin–oxalic and citric acids were proposed. The best results were obtained by a scheme of a reverse-tandem generator with the transfer of the parent radionuclide into the aqueous phase. The yield of ^{172}Lu was 90% and the breakthrough of ^{172}Hf was 3 × 10^{-6} [28].

2.2. Synthesis of Radiopharmaceuticals

One of the key aspects of using radionuclides in therapy, diagnostics, and theranostics is the labeling of organic molecules/bioconjugates with radionuclides to create a stable complex for subsequent use in clinical and preclinical studies.

Bifunctional chelators are called organic molecules capable of forming stable complexes with a radionuclide, and at the same time have a functional group for binding with a biological molecule. Depending on the particular radionuclide, the choice of a chelator is closely related to the coordination chemistry and donor ability (number of donor centers, organization of donor atoms, etc.) of the chelator, as well as to the size of the ionic radius and the charge of the radionuclide ion.

For the successful synthesis of complexes, it is important that they have the following properties:

(1) Thermodynamic stability.

(2) Kinetic inertia.

(3) Convenient complexation kinetics.

(4) Radiation resistance.

With a "convenient" kinetics of complex formation, the following labeling conditions must be provided: (1) *pH of the solution* should not reach extreme

values (for example, strongly acidic environment pH > 2); (2) *complexation time* should be minimal, which is especially important in synthesis of radiopharmaceuticals with a short-lived radionuclide (for example, ^{44}Sc); (3) *temperature*—the advantage of complex formation at room and mild temperatures greatly facilitates the synthesis of radiopharmaceuticals. An important role for some radionuclides (for example, ^{177}Lu and ^{161}Tb) is played by the radiation resistance of complexes and biomolecules. If this requirement is violated, the complex may be destroyed due to the processes of radiolysis, which will lead to difficulty in the use of such radiopharmaceuticals [92, 93].

Chelator labeling with radionuclide is routinely assessed by thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) methods in percent of radiochemical yield (RCY). In our department, the evaluation of RCY complexes is possible using the PAC method, which provides important information about complexes at the time level of 10^{-9}–10^{-6} s, as well as more than a minute. However, this method is limited to the use of specific radionuclides and will be described in what follows in more detail.

Many commercial chelators are now available that form stable complexes with most radiometals. The "gold standards" include acyclic diethylenetriaminepentaacetic acid (*DTPA*), deferoxamine (*DFO*), neunpa and cyclic 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (*DOTA*), TCMC and macropa (Fig. 20). These chelators have high stability constants with most metals. In studies, *DOTA* is most used. However, it should be noted that at elevated temperatures (≈85°C) the kinetics of complex formation with this chelator is rather slow (≈40 min), which is not always suitable when working with short-lived isotopes or with biomolecules sensitive to such temperatures.

Examples of the Synthesis of Radiopharmaceuticals

^{221}At-Based RPs

In the cationic form, astatine forms a stable complex with *DTPA* [94]. Therefore, it can be quite easily bound to monoclonal antibodies [95, 96]. In the case of labeling antibodies to the Anty-G4 antigen, the reaction yield was 30 ± 2% in pH 6 phosphate buffer.

In a *DTPA* solution (5×10^{-4} M), astatine was heated to 60°C for 5 minutes. After cooling to room temperature, a solution of monoclonal antibodies was added to it and left for 10 min (at a temperature of 37°C). The resulting solution was passed through a Sephadex G-25 column. Next, the column was washed with a 0.5% NaCl solution. Labeled monoclonal antibodies were eluted sequentially, then *DTPA* complexes with astatine were eluted. Free astatine remained on the column. This technique was registered as an invention [97].

^{68}Ga-Based RPs

To obtain the positron-emitting ^{68}Ga radionuclide ($T_{1/2}$ = 67.71 min), a commercial (TiO_2) ^{68}Ge → ^{68}Ga generator was used, followed by additional purification on a cation-exchange (AG 50W × 8, <400 mesh) column with a mixture of acetone solution and hydrochloric acid [18]. This technique solves a number of problems that are fundamental for radionuclide labeling, namely: 1) the target radionuclide has a high specific activity and a small volume of the final fraction (400 μL); 2) a two-stage separation scheme makes it possible to increase the radionuclide and chemical purity of the final product and demonstrates an excellent degree of purification from the main impurities (Zn(II)—10^5, Ti(IV)—10^2 and Fe(III)—10^3). In addition, the environment of the final product is favorable for subsequent labeling, since acetone evaporates easily in a short time. Labeling was performed with *DOTATOC* (7–14 nmol) for 10 min, 99°C, pH 3.9. The RCY of radiolabeling was 88% (specific activity 450 MBq/nmol). This method of radiopharmaceutical synthesis can be successfully used in preclinical/clinical studies using ^{68}Ga.

^{90}Nb-Based RPs

The positron-emitting ^{90}Nb radionuclide ($T_{1/2}$ = 14.6 h) was obtained by the method described above (Sec. 2.1.2). The second stage of this technique enables conditioning and obtaining of a small volume of the final fraction in a form convenient for labeling, and also allows eliminating the HF traces, the presence of which is unacceptable in the studies in vivo. Such a separation scheme makes it possible to increase the purification factor from the target material to 3×10^8, which corresponds to a high chemical purity. The end product ^{90}Nb was labeled with the monoclonal antibodies *rituximab* and *bevacizumab*, forming a ^{90}Nb–*N–suc–Df–mab* complex (Fig. 21). Complexation conditions were as follows: 37 MBq for ^{90}Nb, 250 μg *N-suc-Df-mab*, pH7 (HEPES buffer), 1 h at room temperature. The RCY was 93–95%, which is suitable for further use of the preparation in vivo [24].

^{44}Sc-Based RPs

The procedure for production of ^{44}Sc, described above (Sec. 2.1.2), allows one to increase the specific activity of the preparation by lowering the content of Ca(II), Al(III) and Fe(III) impurities in it. In addition, at the stage of conditioning, it is possible to obtain a small volume of a final product (≈300 μL) in the form convenient for radiolabeling, 0.1 M α-ammonium hydroxyisobutyrate with pH 4.8. Subsequent radiola-

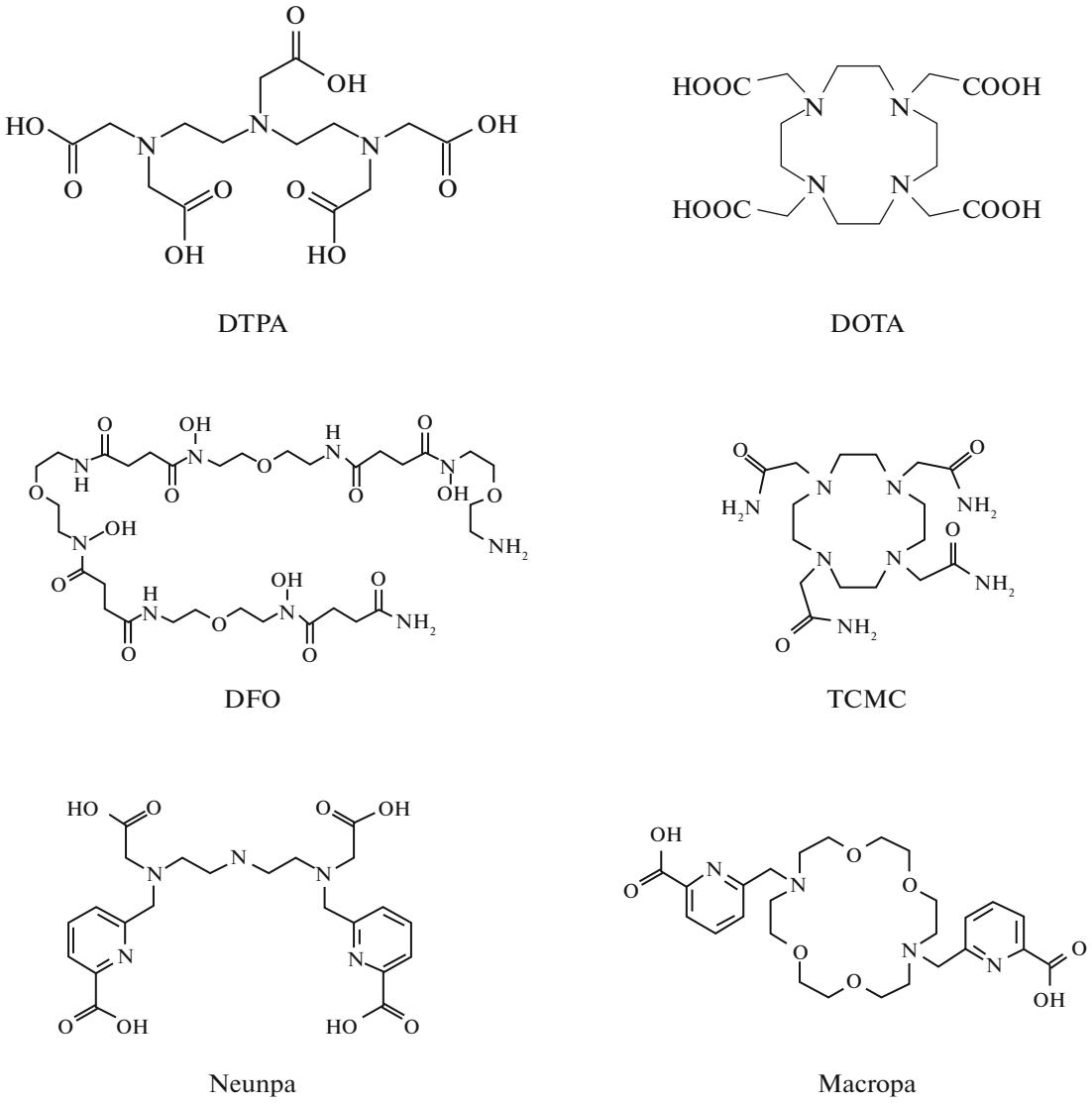


Fig. 20. Acyclic (*DTPA*, *DFO*, *neunpa*) and cyclic (*DOTA*, *TCMC*, *macropa*) chelators.

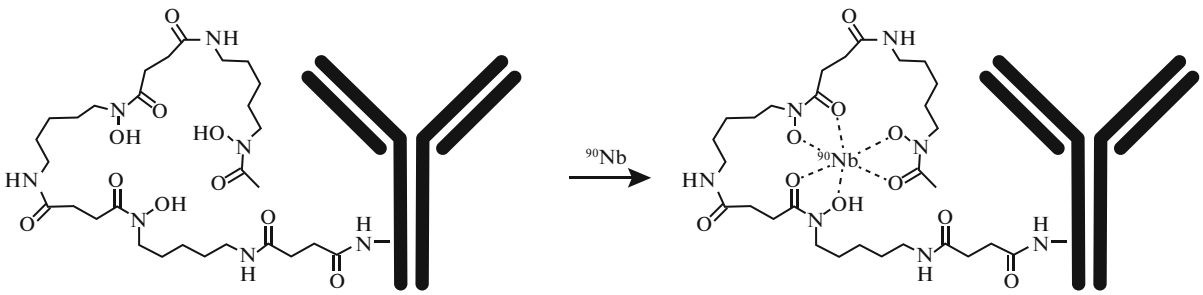


Fig. 21. Radiolabeling *N–suc–Df– rituximab* with ^{90}Nb (*Df*≡DFO).

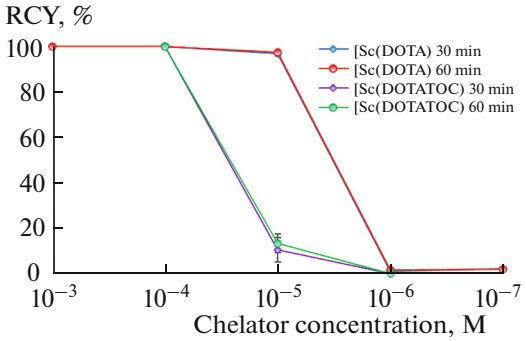


Fig. 22. Radiochemical yield for labeling by *DOTA* and *DOTATOC* with ^{44}Sc radionuclide for various chelator concentrations in 30 and 60 min.

beling with *DOTA/DOTATOC* (10^{-3}–10^{-7} M) occurred under the following conditions: 90°C, 30 and 60 min, pH 4.5, 1 MBq ^{44}Sc per reaction (Fig. 22) [53].

Figure 22 shows that radiolabeling with 10^{-4} M *DOTATOC* with the final ^{44}Sc preparation is characterized by a high chemical yield of about 100%, which indicates the applicability of the preparation in vivo.

2.3. Methods or the Analysis of Radiopharmaceuticals, Including the Properties of Radionuclides and Other Components

In the field of nuclear medicine, from a chemical point of view, one of the most important and interesting areas is the study of the interaction of a radionuclide, on the one hand, and precursors of radiopharmaceuticals, primarily a chelator, on the other hand. In other words, the thermodynamic and kinetic parameters of complexes of radionuclides with chelators are of interest both under conditions of synthesis and under conditions of use (in the body).

Usually, the value of the thermodynamic stability of the complex in the synthesis of radiopharmaceuticals is somewhat exaggerated. Actually, the stability of a radionuclide–chelator system is required throughout the entire cycle of radiopharmaceuticals (from complexation to screening/therapy). However, it should be appreciated that under real (and, what is important, under different) conditions of radiopharmaceutical action, processes of dissociation of the complex are probable, which can lead to increased cytotoxicity during therapy and to incorrect interpretation of tumor localization upon their diagnostics.

To test RPs in real conditions, more complete information about their stability is provided by the study of the temporal characteristics of radiopharmaceutical biodistribution in vivo. Thermodynamic stability is characterized by a stability constant (for example, $\log K = 28.4$ for an indium complex with *DTPA*) [98]. For microquantities of a substance, it can be determined by the methods of spectrophotometry and potentiometry, etc., and for microquantities, by the PAC and electromigration methods. The significance that is usually attributed to the thermodynamic stability of the metal complex in the radiopharmaceutical is determined by two factors: (1) consonance of this value with the concept of the RP stability in vivo; (2) the fact that data on the kinetic constants of formation k_1 and destruction k_2 of complexes are usually much poorer than on the thermodynamic constant $K = k_1/k_2$. It is often possible to predict quite well the order of magnitude of the kinetic constants from the value of the thermodynamic constant, but only if some similar systems are known.

An extremely small amount of radionuclide substance used in the composition of radiopharmaceutical is caused by fundamental restrictions on the capacity of receptors in the body, and often simply the toxicological properties of the element and related substances. The typical amount lies somewhere in the range of nmol, although in a broader sense, it is characterized by a range of one to two orders of magnitude above and below the declared value. If we consider the characteristic volume of the RP solution of the order of 1 mL, then we get typical concentrations of the order of 10^{-6} M. This is the region of extremely dilute solutions. Working with such concentrations implies the quality of all stages, first, obtaining a radiopreparation that is extremely pure from impurities, as well as using the appropriate level of reagents and methods for synthesizing the radiopharmaceutical. But the main problem (at least for research tasks) lies in the field of parametrization of the physicochemical state of the radionuclide at all stages of the synthesis of the radiopharmaceutical.

The fact is that for concentrations of elements at a level of 10^{-6} M and below, there are very few physicochemical methods that enable determining the physicochemical state of an element in solution. In essence, these are only unique methods, which we will consider below. Actually, for homogeneous systems, the thermodynamics and kinetics of complex formation in liquid solutions are usually studied at macroconcentrations of the element under study, using electrochemical and spectrometric methods for analyzing the state forms of the element. Even in the case of nuclear magnetic resonance, sufficiently high concentrations are required (at least 10^{-2}–10^{-3} M).

Thus, to parameterize the state of radionuclides in solutions, one has to use methods based on the study of the redistribution of various forms of a radionuclide between different phases, i.e., the systems must be heterogeneous. The most widespread of these methods is currently thin layer chromatography (TLC), which we will discuss below.

When studying heterogeneous equilibria, it becomes necessary to rigorously consider the redistribution between the phases of all components of the system, not only a radionuclide. Actually, this is a

rather difficult task. Often it is solved, but reference books provide few data on the stability constants of complexes determined by heterogeneous methods using microquantities of the element under study.

However, other problems arise when studying "slow" processes and reaction rates with slow kinetics of formation and destruction of complexes, which is often interesting for nuclear medicine. Generally speaking, TLC solves quite well the problems of studying the rates of radiopharmaceutical labeling (with a certain arrangement and the complex destruction) for the case with the known chelator and a beforehand known slow kinetics of yield from the complex. This is due to the fact that when obtaining results (i.e., during chromatography) it is possible to fix the distribution between forms, or at least to take into account the process of redistribution during chromatography [99, 100].

Principal problems arise if a *new chelator* with slow kinetics is being searched for. In this case, it is very difficult to compare all the results of the studies with each other. It is better to examine this process first for macroquantities of the element. Often this becomes inconvenient because in the development of chelators or radiopharmaceuticals in general, they are usually produced in extremely small quantities—mg. Another important and critical limiting factor appears when the radionuclide under investigation is a radioactive element. It should be noted that these include the most promising therapeutic radionuclides (actinium, radium, astatine). And the task is most difficult if no analogs of slow chelators for a certain element are found for a certain element for fundamental reasons, as is the case of Ra. Here it is very difficult to search for a slow chelator, since it is highly desirable to find regularities in the change in reaction rates when the structure of chelators changes, since TLC will most likely only answer the question "bound–unbound." At the present time, any slow suitable chelators for radium have not been found. But there are candidates [101].

Thus, for the development of modern radiopharmaceuticals, it is extremely important to search for and apply methods that make it possible to directly determine the physicochemical state in a liquid without using heterogeneous schemes. Particularly interesting are the methods that make it possible to study the physicochemical state of both the parent and daughter nuclides with the corresponding radioactive decay of the isotope under study.

2.3.1. Method of perturbed angular correlation. The interaction of various (magnetic and electric) moments of the nucleus with extranuclear fields, which can be created by the nearest environment as well, has to do with the physics of hyperfine interactions (HFI). The HFI methods include Mössbauer spectrometry (nuclear gamma resonance, NGR), nuclear magnetic resonance (NMR), nuclear quadrupole resonance (NQR), the method of perturbed angular correlation (PAC) of nuclear radiation, and the method of oriented nuclei (ON).

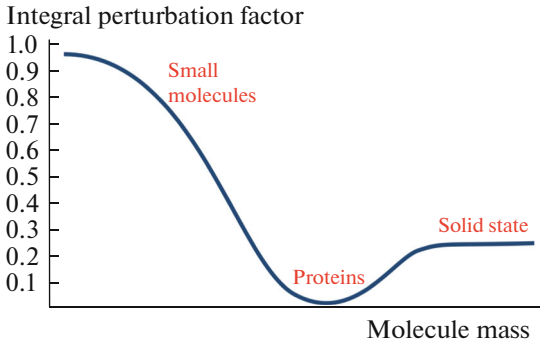


Fig. 23. Perturbation factor of the angular correlation as a function of the molecule size.

Among the HFI methods of radiolabeling, the $\gamma\gamma$-PAC method correlates best with the study of radiopharmaceuticals. The perturbation of the angular correlation provides information about the structure and field dynamics in the nearest environment of the mark-nucleus, both in a solid and in a liquid. In the liquid, the key feature of the method is the dependence of the perturbation factor on the size of the molecule, which includes the probe nucleus (Fig. 23). This is best suitable for the direct study of the properties of radiopharmaceuticals [102–105].

When studying the structure and dynamics of metal complexes in liquid, the PAC method is superior in "informativeness" (in several aspects) even to electromigration. In this respect, it has one drawback—the limited number of radionuclides (elements) that can be used. Nevertheless, it is in our department that studies are carried out with radionuclides that are either medical themselves or are close analogs of medical ones. Thus, the study of radiopharmaceuticals in liquid media, their interaction with cell substrates, as well as in vivo, using the PAC method, is an important area of current interest for the development of nuclear medicine.

The PAC method is based on the one hand, on the phenomenon of angular correlation in the direction of emission of cascade gamma quanta (nuclear phenomenon), and on the other hand, on the perturbation of this correlation due to the interaction of electromagnetic moments of the nucleus with electromagnetic fields created by the electron environment. In the PAC method, the angular correlation of two sequentially emitted gamma quanta is perturbed by the hyperfine interaction of the nuclear quadrupole moment and the electric field gradient, or the nuclear magnetic moment with extranuclear fields [106]. A prominent

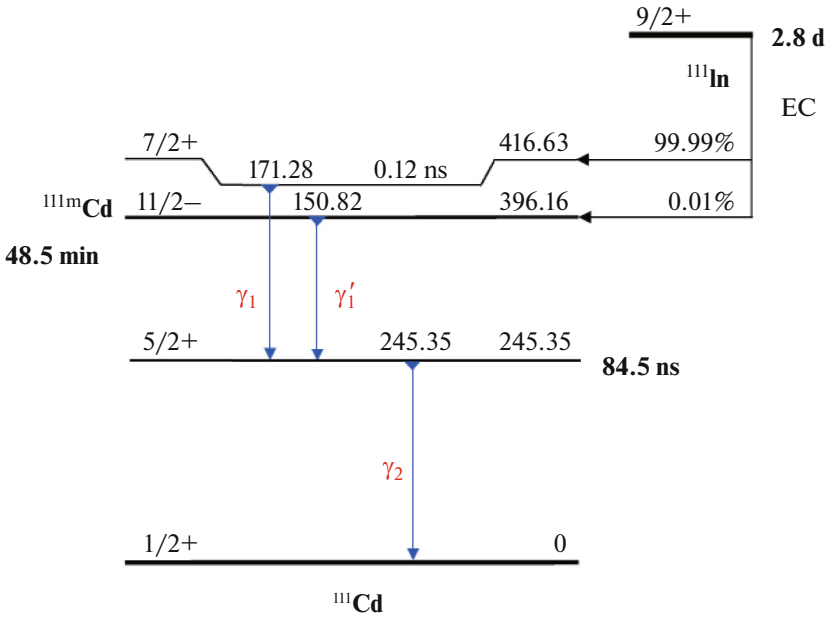


Fig. 24. Decay scheme for ^{111}In and ^{111}mCd PAC isotopes.

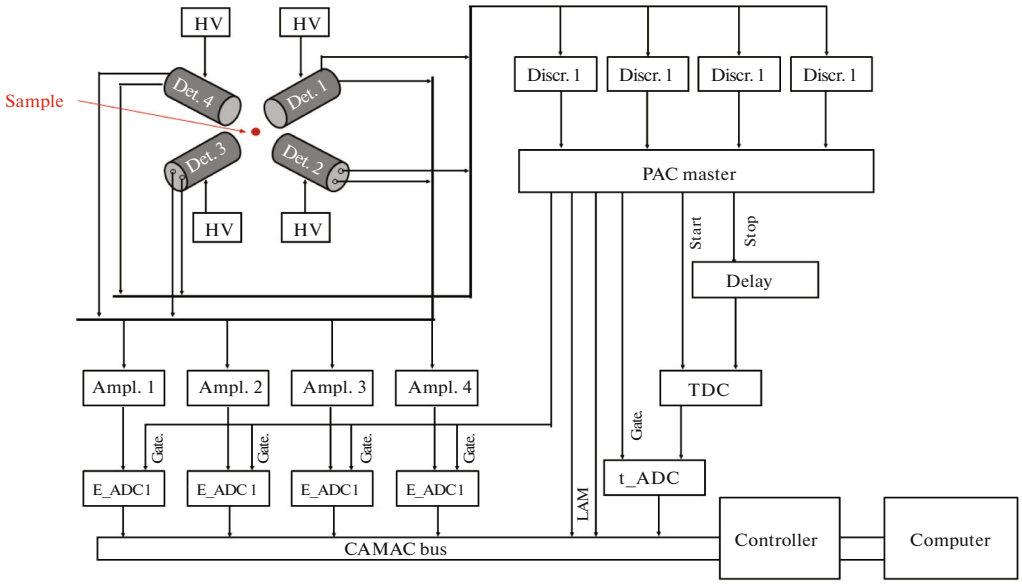


Fig. 25. Block diagram of a four-detector spectrometer.

example of the radionuclide used in this method is ^{111}In, which, due to its nuclear-physical characteristics, is suitable for studying the 171–245 keV γ–γ cascade. The intermediate state of this nucleus is characterized by the anisotropy $A_{22} = -0.178$, lifetime $\tau =$ 84.5 ns, spin +5/2 and quadrupole moment $Q = +0.77$ (Fig. 24).

In our department, PAC spectra are studied using a four-detector spectrometer based on BaF_2 (50 × 50 mm) or $LaBr_3$ (40 × 40 mm) crystals located at an angle of $\theta = 90°$ and 180° to each other (Fig. 25).

The anisotropy of angular correlation is determined from the spectra of delayed coincidences according to the equation:

$$R(t) = 2\frac{N(180°,t) - N(90°,t)}{N(180°,t) + 2N(90°,t)} = -A_{22}G_{22}(t)Q_{22}, \quad (2)$$

Table 1. Some radionuclides and their properties used in the PAC method

Parent radionuclide	Daughter radionuclide	Decay type	$T_{1/2}$	γ_1–γ_2 (keV–keV)	τ, ns	I	Q (b)	μ (μ_N)	A_{22}
^{68m}Cu	^{68}Cu	IT	3.75 min	526–84	7.84	2+	–0.11	+2.857	–0.154
^{111}In	^{111}Cd	EC	2.8 d	171–245	84.5	5/2+	+0.77	–0.7656	–0.178
^{111m}Cd	^{111}Cd	IT	48.6 min	151–245	84.5	5/2+	+0.77	–0.7656	+0.160
^{172}Lu	^{172}Yb	EC	6.7 d	91–1094	8.14	3+	–2.90	+0.65	+0.330
^{181}Hf	^{181}Ta	β–	42.39 d	133–482	10.8	5/2+	+2.28	+3.29	–0.289
^{199m}Hg	^{199}Hg	IT	42.67 min	374–158	2.46	5/2–	+0.95	+0.88	+0.184
^{204m}Pb	^{204}Pb	IT	66.93 min	912–375	265	4+	+0.44	+0.225	–0.220

where A_{22} is the anisotropy of the measured cascade, G_{22} is the perturbation factor, Q_{22} is the geometrical factor, $N(x, t)$ is the number of coincidences of cascade γ quanta registering at fixed angles (t is the time of hyperfine interaction).

The perturbation factor provides information on the interaction of the probe nucleus with its local environment, which is valuable in studies of the RP precursors. For the dynamic and static nature of the perturbation, two types of the perturbation factor can be distinguished: differential and integral, which can be described by the following equations.

Differential perturbation factor:

$$G_k(t) = e^{-\lambda_k t}, \quad (3)$$

where $\lambda_k = K\omega_Q^2\tau_C$ is the relaxation constant, ω_Q is the quadrupole frequency of hyperfine interaction, K is the constant depending on nuclear characteristics.

The correlation time can be expressed as:

$$\tau_C = \frac{4}{3}\pi r^3 \frac{\eta}{kT}, \quad (4)$$

where η is the viscosity at temperature T, and r is the molecule radius.The integral perturbation factor is:

$$G_k(\infty) = \frac{1}{\tau}\int_0^\infty e^{-\lambda_k t} e^{\frac{1}{\tau}} d\tau = \frac{1}{1+\lambda_k\tau}, \quad (5)$$

where τ is the intermediate state lifetime.

The perturbation factor $G_k(\infty)$provides less information about the HFI nature compared to the differential factor $G_k(t)$. However, the integral factor makes it possible to expand the list of radionuclides used in the PAC method.

The main requirements for radionuclides used in PAC [105, 106] are as follows.

(1) The decay scheme must pass through a sequential γ–γ cascade.

(2) The lifetime of the intermediate level of this cascade varies from 1 ns to 1 μs.

(3) The "suitable" quadrupole electric moment of the intermediate level is ~1 barn.

(4) The γ–γ cascade should have a significant angular anisotropy.

A list of isotopes that meet these criteria is shown in Table 1 below.

Examples of the Study of Complex Formation by the PAC Method

Complexes of ^{111}In, ^{111m}Cd, ^{152,154}Eu with DTPA

This set of radionuclides, which have suitable properties for measuring PACs, is of interest from the point of view of nuclear medicine. Thus, ^{111}In ($T_{1/2}$ = 2.80 d) is a diagnostic agent for SPECT, ^{111m}Cd ($T_{1/2}$ = 48.50 min) is its daughter isotope (nuclear isomer), ^{152,154}Eu ($T_{1/2}$ = 13.52 and 8.60 years) are representatives of lanthanides, which are actively used in preclinical and clinical studies as diagnostic, therapeutic or theranostic agents (^{177}Lu, ^{161}Tb etc.).

The samples for four radionuclides were prepared identically: the volume of the solution was 0.5 mL, the activity of the samples 30–100 kBq, the ionic strength 0.5 ($HClO_4$, $NaClO_4$), the pH range 0.3–5 ($HClO_4$, $NaClO_4$, NaOH), the concentration of *DTPA* at room temperature 10^{-4} M. Thus, a series of samples with different pH values (about 20 samples) was prepared for each radionuclide [104]. The measurement was carried out using BaF_2 detectors with the best time resolution, which is critical in the case of ^{152,154}Eu.

Figure 26 shows the PAC spectra of samples for complexes with *DTPA* for four isotopes. In the case where the probe nucleus is in two states, the perturbation factor can be described by a superposition of partial perturbation factors having the corresponding weight fraction (a_i is the molar fraction of the corresponding form of the radionuclide, $\lambda^{(i)}$ is the relaxation constant for the given form):

$$G_2(t) = a_1 e^{-\lambda_2^{(1)} t} + (1-a_1) e^{-\lambda_2^{(2)} t}. \quad (6)$$

However, this equation has three free parameters. Therefore, in many cases it is inconvenient to use them to plot composition–property diagrams. Therefore, to process the spectra, we proposed to use the parameter

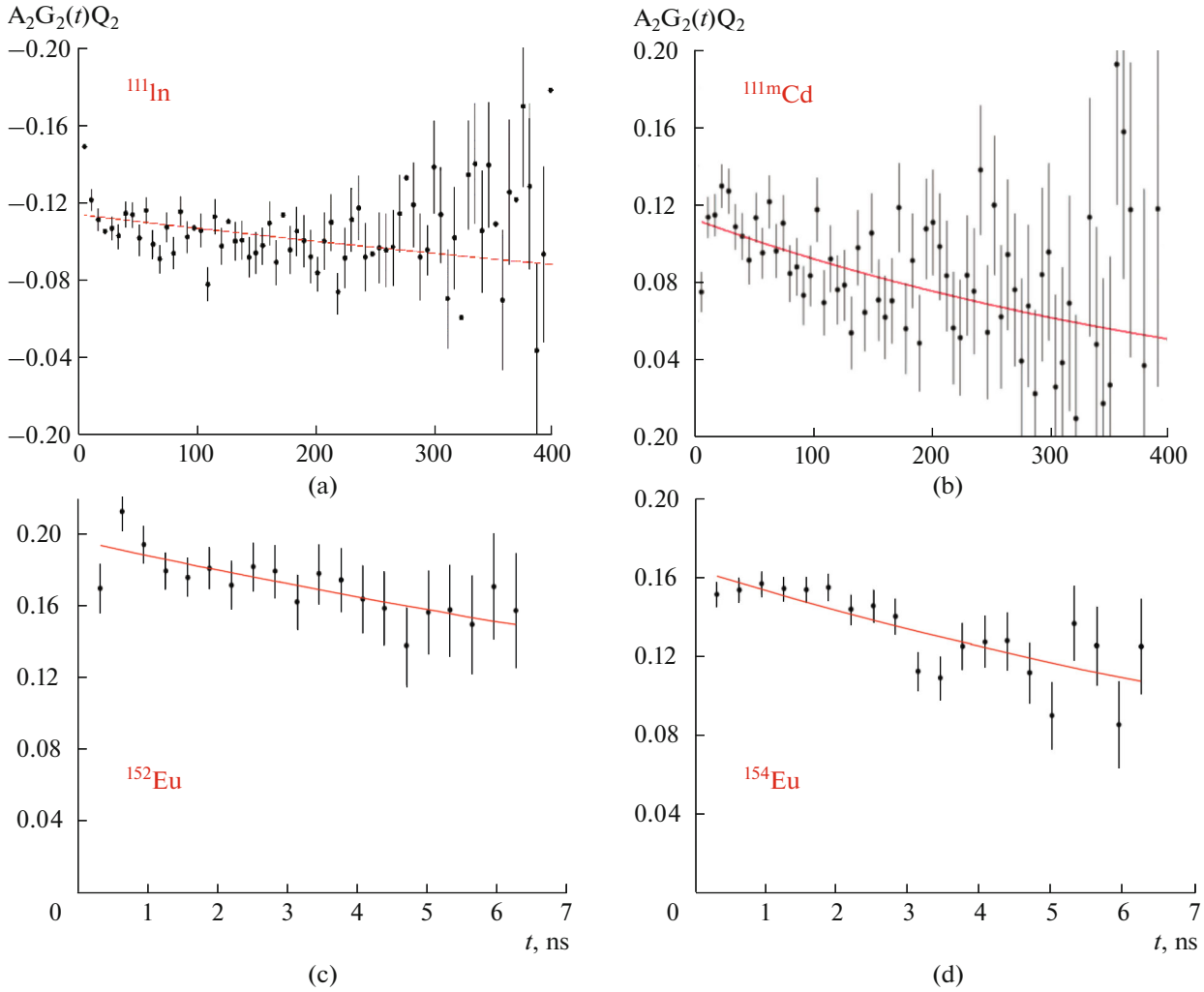


Fig. 26. PAC spectra for complexes with 10^{-4} M *DTPA*: (a) ^{111}In–*DTPA* for pH 1.67; (b) ^{111m}Cd–*DTPA* for pH 2; (c) ^{152}Eu–*DTPA* for pH 1.92; (d) ^{154}Eu–*DTPA* for pH 1.72. Processing is shown by the red curve [104]. Only statistical measurement errors are shown on the spectra.

L_2—a generalized integro-differential relaxation parameter:

$$G_2(t) \approx e^{-L_2 t}. \quad (7)$$

Dependences of L_2 on pH (Fig. 27) make it possible to visually reveal the transition from the metal aqua complex to the complex with *DTPA*.

However, in the case of the electron capture ^{152}Eu (Fig. 27c), the transition is not detected, since the complex formed after radioactive decay is not stable due to after-effects. Table 2 compares stability constants determined by the PAC method and literature data. Table 2 shows that the data obtained are in good agreement with the literature ones. Thus, the PAC method is suitable not only for studying complex formation, but also capable of detecting the after-effects of radioactive decay, which is especially important in the development of generators (for example, ^{44m}Sc → ^{44}Sc, ^{140}Nd → ^{140}Pr, etc.) [29, 107, 108].

Complexes of ^{111}In with DOTA

As already mentioned, *DOTA* is one of the "gold standards" for labeling radionuclides, which is due to slow kinetics and the formation of stable complexes with most elements.

Complexes with *DOTA* were measured using a PAC spectrometer to obtain kinetic constants. The activity of the samples was about 100 kBq, the volume of each sample was 0.5 mL. The experiments were carried out at room temperature in aqueous solutions with ionic strength of 1 (HCl, NaCl) and 10^{-5} M *DOTA*. For each sample, the PAC spectra were recorded, and after processing by the integral perturbation factor, a time dependence was obtained (Fig. 28). At time $t = 0$, $A_2G_2(\infty)Q_2$ is equal to –0.13, while its value becomes

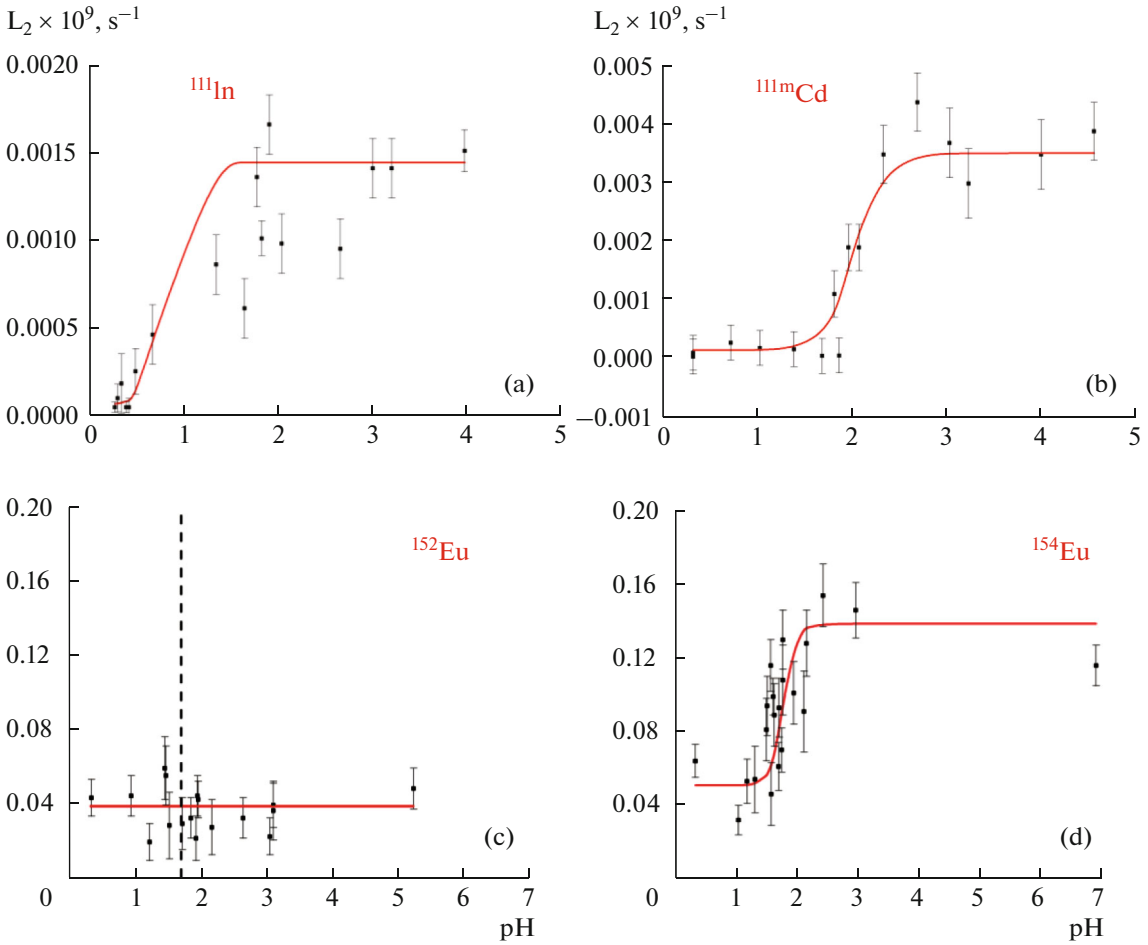


Fig. 27. Dependence of L_2 on pH for complexes with 10^{-4} M *DTPA*: (a) ^{111}In; (b) ^{111m}Cd; (c) ^{152}Eu; (d) ^{154}Eu. Red line shows the results of fitting.

equal to –0.10 with time. This reflects the transition of In from an aqua complex to the complex with *DOTA*. The change in A_2G_2 (∞)Q_2 is related to the dependence of the perturbation factor G2(∞) on the size of the molecule containing ^{111}In.

For trivalent cations in an aqueous solution, the MY^- complexes are thermodynamically stable. *DOTA* contains four carboxyl groups that can donate protons in solution. These complexes are formed through various intermediate states (M—metal (In), Y—*DOTA*):

$$M^{3+} + [H_nY]^{n-4} \leftrightarrow [MH_{n-m}Y]^{n-m-1} + mH^+. \quad (8)$$

with subsequent deprotonation:

$$[MH_{n-m}Y]^{n-m-1} \leftrightarrow [MY]^- + (n-m)H^+. \quad (9)$$

Table 2. Stability constants of radionuclides under study with *DTPA*

Radionuclide	Reaction*	log*K*	
		PAC method	Literature data [98]
^{111}In	M + Y ↔ MY	28.20	28.42 29.00
^{111m}Cd**	M + Y ↔ MY M + HY ↔ MHY	22.09 13.70	19.30 12.63
^{154}Eu	M + Y ↔ MY	23.26	23.17 22.50

* M—metal, Y—ligand, quintuple-deprotonated form of DTPA.
** For ^{111m}Cd, constants for two reactions were determined. We believe that in this region (pH ≈ 2) the complexation proceeds via the reaction M + HY ↔ MHY.

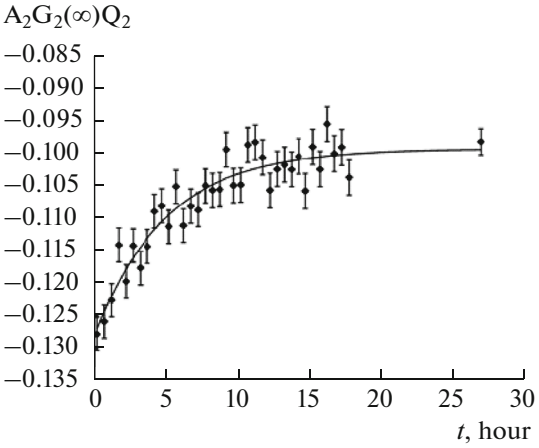


Fig. 28. Integral perturbation factor for ^{111}In (without carrier, n.c.a.) in a 10^{-5} M *DOTA* solution, ionic strength is 1 (NaCl), pH 3.02, as a function of time at room temperature.

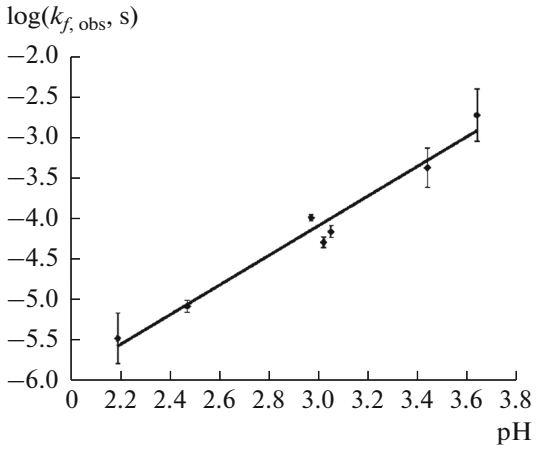


Fig. 29. Dependence of $\log k_{f,\,obs}$ on pH for ^{111}In (without carrier, n.c.a.) in a 10^{-5} M *DOTA* solution with an ionic strength of 1 (NaCl) at room temperature.

Thus, the data can be conveniently described by the following equation:

$$k_{f,\mathrm{obs}}[\mathrm{M}^{3+}] = \frac{d\sum_{n,m}[\mathrm{MH}_{n-m}\mathrm{Y}]^{n-m-1}}{dt}, \qquad (10)$$

where $k_{f,\mathrm{obs}}$ is the observed pseudo-first-order constant of formation for all forms of In–*DOTA* complexes.

The dependence of $\log k_{f,\mathrm{obs}}$ on pH in a range of 2–4 was plotted in Fig. 29. This dependence turned out to be linear with a proportionality factor of 1.86. This may indicate that In^{3+} in such solutions interacts primarily with the H_2DOTA^{2-} form, whose concentration is inversely proportional to $[H^+]^2$. This means that the obtained constants characterize the rate of the reaction with this very form [106].

2.3.2. Electromigration. The study of the behavior of radionuclides in terms of the rate of electromigration in liquid media was proposed quite a long time ago, in the 1950s, and possibly even earlier [109]. However, the study of the zone of radionuclide motion in a horizontal tube in a free electrolyte is closely related to works performed at JINR (Fig. 30). In this case, it is possible to separate the forms of an element in solutions, and often to study the kinetics of their transition into each other. Which, in turn, creates a powerful tool for studying both the physical chemistry of electrolytes in general, and the study of the properties of elements and their compounds, specifically, at extremely low concentrations. The development of this technique from the late 1970s to the late 1980s was closely associated with radiochemistry department and its leader V.A. Halkin, with German colleagues I. Dreyer and R. Dreyer, F. Roesch, Bulgarian colleague M. Milanov, Vietnamese colleague Chan Kim Hung and other collaborators. Several works devoted to electromigration are combined into a cycle called "Electromigration of carried–free radionuclides." A large set of elements was studied radionuclides in a state of high specific activity (low concentration of the

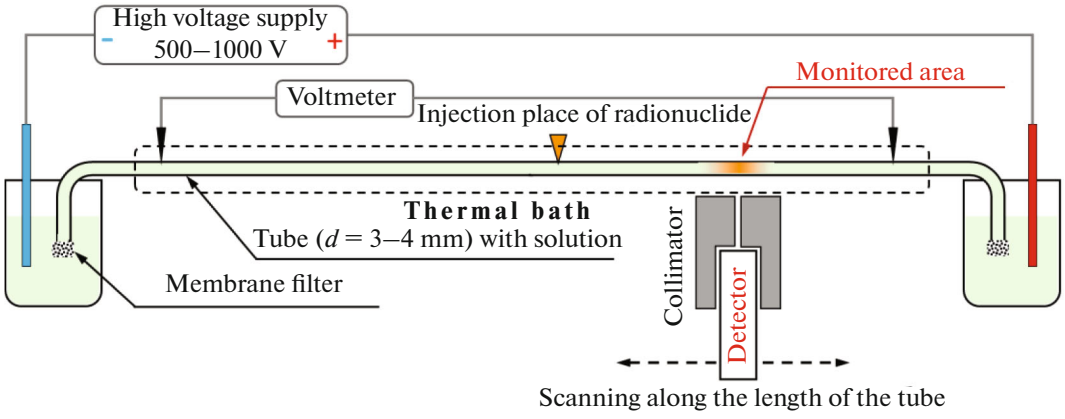


Fig. 30. Electromigration setup layout.

element). For example, the properties of At [110], medical radionuclides ^{201}Tl ($T_{1/2}$ = 3.04 d) [111, 112], ^{131}I ($T_{1/2}$ = 8.03 d) [113] and others [114] were studied, as well as the behavior of lanthanides [115] and actinides [116–122].

From the end of 1990 to 2010, at the FLNR and DLNP JINR, initiated by Milanov, several studies were carried out using the electromigration method with the equipment designed at JINR. The electromobility and complex formation of a number of radionuclides, including medical ones, were studied, a number of unique results were obtained, and the possibility of studying the kinetics of complex formation processes for a very wide range of radionuclides was also shown [64, 123, 124]. It can also be noted that approximately at the same time, similar studies were carried out in Mainz (Germany) under the guidance of Professor F. Roesch [125].

The study of the mobility and shape of the radionuclide zone in a horizontal tube filled with an electrolyte under the action of a potential difference determines the experimental foundations of the electromigration method.

Investigating the electrophoretic mobility of a radionuclide zone (U) as a function of the concentration of the chelator ($[L]$), it is possible to determine the thermodynamic constant of complex formation for a given element (β) with a given chelator [123, 124]:

$$\bar{U} = \frac{U_M + U_{ML}[L]\beta}{1 + [L]\beta}, \tag{11}$$

where U_M is the electrophoretic mobility of the cationic form of radionuclide, and U_M is the electrophoretic mobility of the complex form of radionuclide.

In addition, it is possible to study the kinetic constants of formation (k_1) and disintegration (k_2) of the complex of metal (M) and chelator (L):

$$M + L \underset{k_2}{\overset{k_1}{\rightleftarrows}} ML. \tag{12}$$

Sometimes this equality is written in a simplified form (I):

$$M \underset{k_2^*}{\overset{k_1^*}{\rightleftarrows}} ML. \tag{13}$$

To this end, it is necessary to study the diffusion of a radionuclide in various forms by changes in the shape of the radionuclide zone, with and without an applied field. Kinetic constants can be determined using the following dependences:

$$\beta = \frac{k_1}{k_2}, \tag{14}$$

and

$$D_e = D_{exp} - D, \tag{15}$$

where D_e is the electrodiffusion coefficient, D_{exp} and D are the diffusion coefficients measured with and without field applied,

$$D_e = \frac{E^2 k_1 k_2 [L](U_M - U_{ML})^2}{(k_1[L] - k_2)^3}, \tag{16}$$

with E being the electric field gradient in the tube.

For the simplified form of equilibrium (I), the equation for D_e has a different form:

$$D_e = \frac{E^2 k_1^* k_2^* (U_M - U_{ML})^2}{(k_1^* - k_2^*)^3}. \tag{17}$$

From a scientific point of view, it is very important that both the thermodynamic and kinetic constants of the complex formation of *DTPA* with indium, hafnium and other elements were determined [124]. It is the broadening of the zone of the negatively charged complex that made it possible to determine rather rare processes of metal release from the complex.

Unfortunately, at present, studies of the complex formation of radionuclides in a free electrolyte using the electromigration method are barely conducted. One of the main factors is that for slow chelators, such as *DOTA*, the behavior of zones during electromigration should become fundamentally different. If the kinetics of metal release from the complex is determined by days, then the electromigration broadening of the zone becomes very large.

On the other hand, experimental difficulties with measuring the slow output (input) kinetics have a solution within the framework of the electromigration method. Similar measurements were carried out in the 1960s and 1970s mainly in Leningrad [126] at installations with quartz fillers. The method is based on the study of electrodiffusion in nonequilibrium solutions. The change in the shape of the zone of radionuclide is being studied when it either forms a complex or abandons it.

There are several possible experimental techniques that can provide data on the kinetics of the interaction of "slow" chelators with metals using electromigration. The development of this method for the study of radiopharmaceuticals of radium, actinium, astatine and other radionuclides is quite possible, and it seems to us extremely relevant.

2.3.3. Chromatographic and other physicochemical methods of analysis based on heterogeneous equilibria. We use a simple and convenient method of radioactive tracers to assess the complex formation of many elements in solution in sorption systems, in particular, by the nature of the dependences of sorption coefficients on solution concentration [127–132]. However, as already mentioned, in heterogeneous equilibria, a hard-to-describe redistribution of all phase components among themselves occurs. Accordingly, such studies yield rather a qualitative assessment of com-

plex formation, especially since the interaction with a relatively simple ligand (F^-, Cl^-, etc.) is usually analyzed. In the case of complex chelator, and even more so of an entire radiopharmaceutical, the abovementioned fundamental difficulties arise.

Currently, in the case of chelation with a deliberately slow complexing agent of a radiopharmaceutical, chromatographic methods (thin-layer and high-performance liquid chromatography) are almost the only way to assess the labeling of the corresponding substance. This method was used and is being used in the relevant developments in preparation of radiopharmaceuticals. The method is used by our team as well. However, as already mentioned, this method reveals complex formation with a deliberately slow chelator. In addition, in the development of new ligands, as, indeed, in determining the kinetic constants of the interaction of a chelator with an element, this method has limited possibilities.

Based on the foregoing, we can conclude that we certainly use these methods, but rather for utilitarian purposes. There is, however, one very important direction that we are trying to develop precisely for research purposes. These studies are closely related to the stability of radiopharmaceuticals and apply to other aspects of nuclear medicine. We are talking about the use of slow chelators to study the after-effects of radioactive decay, as well as the use of the Szilard–Chalmers method in order to obtain radiopharmaceuticals with high specific activity.

Study of After-Effects of Radioactive Decay for Genetically Related Radionuclide Pairs

If the daughter nucleus (recoil atom) acquires an energy of more than 30 eV in radioactive decay, then it leaves the environment of the parent nucleus [106]. Such a process necessarily occurs in α decay. In β decay, as well as in the emission of high-energy gamma quanta and conversion electrons, such a process is also possible (Fig. 31), but it already has a probabilistic character, being usually characteristic only for light nuclei.

In addition, a change in the environment with a high probability occurs as a result of cascade Auger processes occurring after electron capture, or internal conversion upon removal of nuclear excitation (Fig. 32) [66, 133].

Such processes are generally known and have previously been observed, for example, in α decay in a vacuum for thin sources, collecting radioactive recoil nuclei. To observe such processes in the substance, it is necessary to fix a physicochemical state of both the parent and daughter atoms. At the same time, their mutual transformations due to the usual "thermal" chemical exchange should be minimized. Usually this is sufficient to provide covalent bonds, but they are not typical for metals, which include most elements of the periodic system. Therefore, such experiments were limited to a small variety of isotope pairs used. The situation changed drastically with the advent of a wide range of slow chelators. As a result of the after-effects of radioactive decay, even in an aqueous solution, after the release, the daughter radionuclide may not have time to return to the complex with the chelator at room temperature due to the slow kinetics of the latter (Fig. 33). Initial experiments were carried out with a relatively slow *DTPA* chelator to separate genetically related isobars and lanthanide isomers [134]. Similar experiments were carried out with *DOTA* macrocyclic ligand, which are described below.

Radionuclide Generator $^{140}Nd \rightarrow {}^{140}Pr$

The ^{140}Pr radionuclide ($T_{1/2}$ = 3.39 min) can potentially be used in PET diagnostics. The parent radionuclide ^{140}Nd (EC, $T_{1/2}$ = 3.37 d) was produced by irradiation of CeO_2 and Pr_2O_3 in reactions (^3He, xn) and (p, $2n$) with a yield of 3.5 and 15.5 MBq/μAh, respectively. ^{140}Nd was isolated from the target material using cation exchange chromatography with a separation factor of $\geq 10^8$ for the cerium target and $\geq 7 \times 10^5$ for Pr. The purified ^{140}Nd bound to the *DOTATOC* molecule was loaded onto a C–18 cartridge (octadecyl, reverse phase adsorbent). In the ^{140}Nd decay, due to after-effects, ^{140}Pr accumulates in the form of a cation, then it was periodically washed off with a *DTPA* solution [29].

Application of the Szilard–Chalmers Method to Obtain Radiopharmaceuticals with High Specific Activity

Most nuclear reactions are characterized by the phenomenon of resulting radionuclide yield from the environment typical of the target atoms. In nuclear reactions, the nucleus usually acquires significant energy. It is well known, for example, the application of this phenomenon in obtaining and studying the properties of superheavy elements [135].

In the case of thermal neutron capture ($^aZ(n,\gamma)^{a+1}Z$, where Z characterizes the element), the recoil energy of the nucleus for most elements lies in the "boundary" region of energies required for the nucleus to be released from the parent environment. In practice, it is usually possible to choose the chemical states of the target to ensure the yield of the daughter nucleus. This process is called the Szilard–Chalmers effect and is quite well known because of the possibility of obtaining radionuclides with high specific activity. Since there is no change in the nuclear charge in thermal capture of a neutron, it is impossible to chemically separate the target atoms and the product of the neutron thermal capture—this is the same element. On the other hand, the production of radionuclides in a reactor is quite economical, and it is possible to obtain necessary or promising radionuclides for

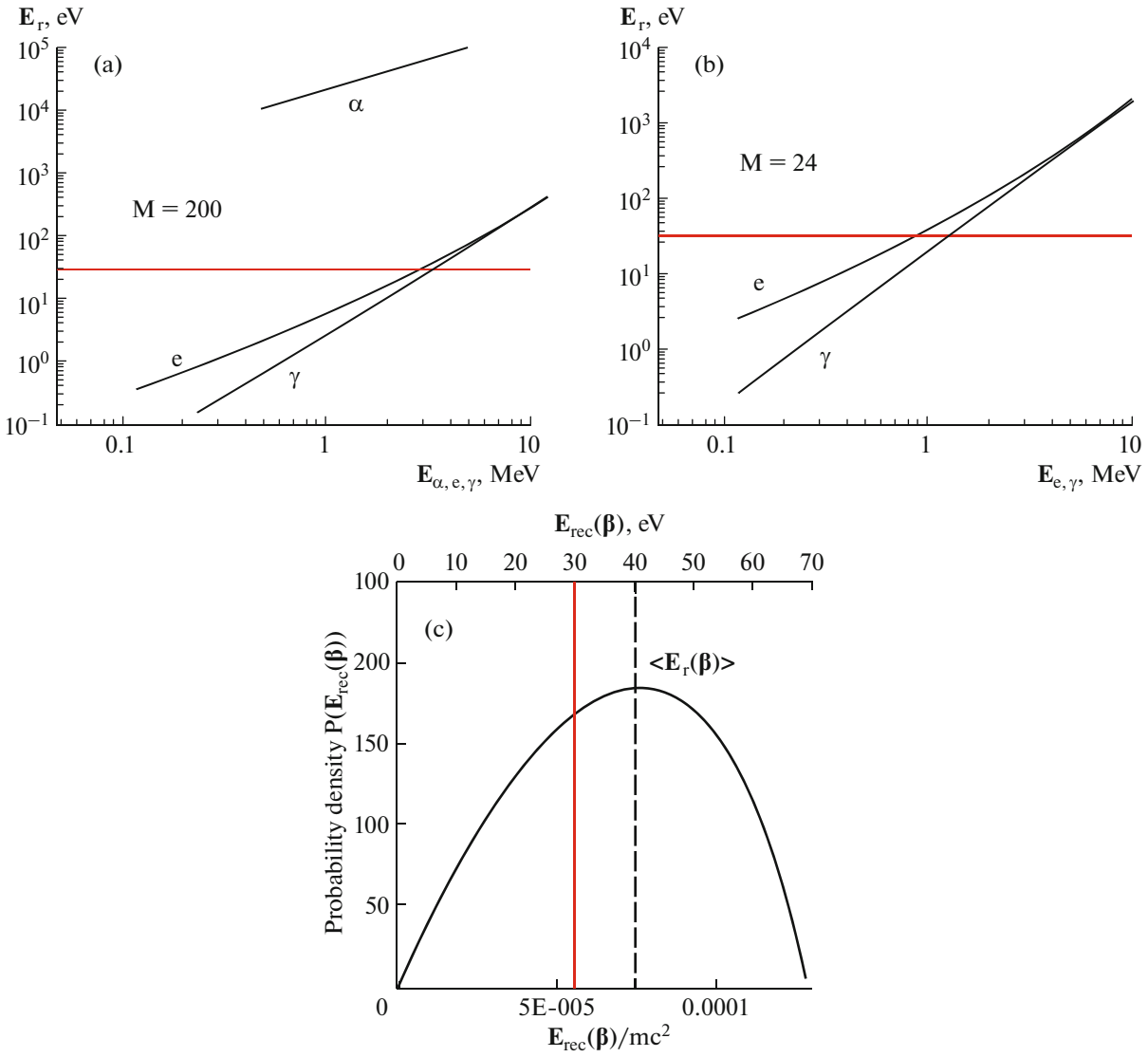


Fig. 31. Nuclear recoil energy: (a) in α, β decays, as well as in the emission of γ quanta and conversion electrons for elements with an atomic mass M = 200; (b) when emitting γ quanta and conversion electrons for elements with an atomic mass M = 24; (c) in β decay of ^{24}Na.

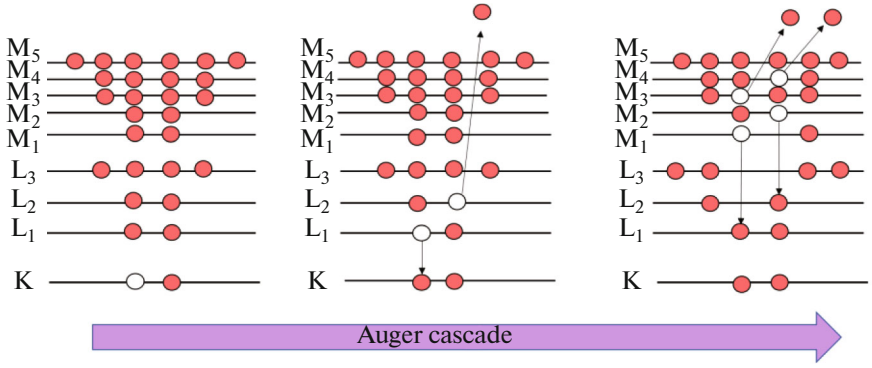


Fig. 32. Auger cascade.

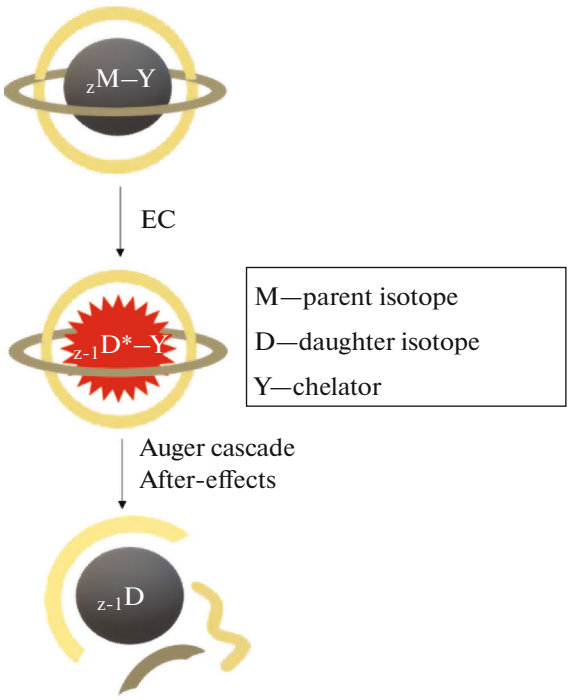


Fig. 33. Scheme of the after-effects of radioactive decay.

nuclear medicine. At the same time, the use of physical methods for the separation of isotopes is very expensive. As we have already mentioned (Chapter 1), such experiments are currently being carried out, but apparently, they are still quite far from practical application.

The use of the Szilard–Chalmers effect, from its very discovery, was always considered as a method for obtaining radionuclides with high specific activity, including for nuclear medicine. Previously, studies were carried out with elements that can form strong covalent bonds (I, Br), but in practice, such methods did not find wide applications. The renewal of interest in the method appeared against the background of the emergence of a wide range of slow ligands, primarily macrocyclic ones, such as, for example, *DOTA*. In this case, the application of the Szilard–Chalmers effect became possible for all metals, i.e., for most elements of the periodic system.

We also took part in such experiments together with colleagues from Mainz (Prof. F. Roesch's group) [136]. In that work, the possibility of increasing the specific activity of ^{166}Ho ($T_{1/2}$ = 26.82 h) produced in the (n, γ) nuclear reaction was studied. The target material was a holmium complex with the ^{165}Ho–*DOTA* macrocyclic ligand. Irradiation was carried out at the TRIGA II reactor in Mainz (Germany) using a neutron flux of the order $\Phi_0 = 4 \times 10^{12}$ cm^{-2} s^{-1}. After irradiation, the produced ^{166}Ho and the ^{165}Ho–*DOTA* target substance were separated after dissolving the latter in water on a cationite column.

When irradiated for 6 hours, a ^{166}Ho preparation was obtained with a specific activity of 2 GBq/mg ^{166}Ho. If ^{165}Ho is simply irradiated in the same reactor, then in 6 hours of irradiation one can obtain a ^{166}Ho preparation with only a specific activity of 0.13 GBq/mg ^{166}Ho. At the same time, the maximum achievable specific activity of the ^{166}Ho preparation (saturation specific activity) upon ^{165}Ho irradiation in the presented reactor can be 0.9 GBq/mg.

However, this technique is not suitable for obtaining radionuclides of "therapeutic quality." Of key importance is the fact that the rate of radionuclide production is proportional to the neutron flux and the neutron capture cross section ($\sigma \times \Phi_0$), but radiative decay of the ^{165}Ho–*DOTA* molecule is also proportional to the neutron flux ($k_p \times \Phi_0$), with k_p being the proportionality coefficient. The measured coefficient k_p for the experimental conditions was $(7.5 \pm 1.5) \times 10^{-19}$ cm^2. This value corresponds to 750000 barn. At the same time, for *DOTA*, the sum of the neutron capture cross sections for all atoms of the $C_{16}H_{24}N_4O_8$ molecule is 15.6 barn, while the capture cross section for ^{165}Ho is 65 barn.

For the case of isotope irradiation in the radionuclide production in a particular reactor, the maximum achievable specific activity S_∞ is:

$$S_\infty = \frac{\sigma \times \Phi_0}{\lambda}, \qquad (18)$$

where Φ_0 is the neutron flux, σ is the neutron capture cross section for an isotope, λ is the decay constant of the resulting radionuclide.

As a result of comparison of three characteristic values of rates ($\sigma \times \Phi_0$, $k_p \times \Phi_0$ and λ), it can be concluded that the Szilard–Chalmers effect gives the gain in obtaining relatively short-lived nuclei at relatively low neutron fluxes, that is, for low-flux reactors. When obtaining therapeutic radionuclides with a half-life of several days in high-flux reactors, the profits of using the Szilard–Chalmers effect with the considered molecules are not visible indeed.

On the other hand, a certain potential for using the Szilard–Chalmers effect to produce therapeutic radionuclides in a reactor was not fully exhausted. Of key interest is the multiple excess of the measured value of k_p for a *DOTA* molecule over the sum of the cross sections of its atoms in the TRIGA reactor. It is quite obvious that this is caused by the destruction of this molecule under the action of secondary radiation in the reactor, and not directly from the interaction with neutrons. Thus, the potential remains to search for suitable irradiation conditions (reactors with low secondary radiation), as well as possibly more suitable chelator molecules. This statement receives additional support, in view of the possible use of the Szilard–Chalmers effect as one of the stages of increasing the specific activity of the preparation, followed by iso-

tope separation or radiochemical separation of lanthanides [137].

Evaluation of Sorption of Elements Using Radioactive Labels

To develop new radionuclide generators, as well as to develop new methods for separating and isolating elements, it is necessary to study their behavior in various chemical media. The selection of chemical systems and the subsequent study of the behavior of elements in these systems is a fundamental and integral part of the vast process of obtaining radionuclides not only for the purposes of nuclear medicine, but also for many other industries. To assess the sorption of elements, distribution coefficients are used, which are defined as the ratio of the concentrations of elements in two phases in an equilibrium state. For classical separation schemes consisting of columns connected in series, it is very important to have a set of K_d for various resin–solution systems.

When determining K_d for some very important elements in nuclear medicine, such as radium, actinium, astatine and several others, only radioactive labels can be used. The use of radioactive labels makes it possible to determine a microquantity of a substance with a high accuracy. Also, the technique allows one to simultaneously determine the microconcentrations of a set of radioactive elements (up to ten) in one sample. The K_d value is determined by the following formula:

$$K_d = \frac{C_{eq1}}{C_{eq2}} = \frac{A_0 - A_{eq}}{A_{eq}} \frac{V}{m}, \quad (19)$$

where C_{eq1} is phase 1, C_{eq2} is phase 2, A_0 is the isotope radioactivity in the initial solution, A_{eq} is the radioactivity of an isotope in an equilibrium solution, V is the volume of the solution, m is the adsorbent mass.

The purposes of determining the distribution coefficients can be conditionally divided into the following:

(1) A systematic study of the sorption of several elements in unstudied systems.

(2) Developing generator schemes.

(3) Isolation of microquantities of radionuclide from macroquantities of the target material.

(4) Purification of substances for low background experiments.

(5) Predicting the behavior of superheavy elements.

For the purpose of a systematic study of sorption, the values of K_d were determined for Sr, Cd, Ba, Ra, Sc, Y, Pm, Lu, Ac, Ti, Zr, Hf, Th, As, Sb, Se on ion exchange resins (Dowex 1, Dowex 50) in an acetic acid medium and an acetic acid–ammonium acetate mixture [130].

For REE and Ac (as well as for Sr, Ba, Ra in the case of SR resin), the K_d were determined on extraction resins (TriskemInt) in media:

DN resin—HCl, $HClO_4$, CH_3COOH, CCl_3COOH [127].

UTEVA resin—HCl, HNO_3, $HClO_4$, HPF_6, CCl_3COOH [128].

SR resin—HNO_3, HCl, HBr, $HClO_4$, and HPF_6 [138].

In addition, the K_d values were obtained on UTEVA resin: in HCl, H_2SO_4, HNO_3 for In, Sn, Sb, Te, Bi, Co, Fe, Nb, Sr, Ba, Ag, Cd, Zr, Hf, Ti [129]; Zr and Y in $C_2H_2O_4$ medium [63]. In addition, the K_d values were obtained on UTEVA resin in HCl, H_2SO_4, HNO_3 for In, Sn, Sb, Te, Bi, Co, Fe, Nb, Sr, Ba, Ag, Cd, Zr, Hf, Ti [129]; Zr and Y in $C_2H_2O_4$ media [63].

In order to obtain medical radionuclides, K_d were determined for the elements Ti and Sc [89], Hf and Lu [28], Ge [91], Zr and Y [63], Nb and Zr [23] on ion exchange resins in $C_2H_2O_4$/HCl medium; Hf and Lu in $C_6H_8O_7$ [28]; Th and Ac in ammonium citrate medium [86]. The resulting K_d are successfully used for the corresponding radionuclide generators.

Ra and Ac isotopes were extracted from irradiated Th using the K_d values determined on Dowex 50 in CCl_3COOH in the presence of a macroamount of Th [20]. Using K_d of Nb and Zr in $HCl/C_2H_2O_4$, HCl/H_2O_2 media on AG 1 and UTEVA resins, a procedure was developed for isolating ^{90}Nb from irradiated Mo and Zr [23], as well as from irradiated Zr using a technique based on HCl/H_2O_2—AG1 and HCl—UTEVA [25].

For low-background measurements (Nemo-3/SuperNemo experiments), large amounts of enriched ^{82}Se with ultralow contents of radioactive impurities were obtained. To develop this technique, K_d were determined on Dowex 50 in H_2SeO_3 medium for Co, Y, Cs, Ce, Pm, Tm, Yb, and Lu [139], as well as H_2SeO_3/HNO_3 for Th, U, Ra, and Ac [140].

Studies were carried out to explore the ion-exchange behavior of superheavy elements based on the behavior of analog-elements. Ti, Zr, Hf, Nb and Ta elements [141] were used as Rf and Db analogs. Based on the K_d in AG 1–HF/acetone system, the optimal separation conditions were chosen: 6 M HF/10 M acetone for IV valence elements; 15–25 M HF/1–4M acetone for V valence elements. Tungsten W was adopted as an analog of Sg in another study [142]. Based on the results, a suitable system of 0.1–1.0 M HCl and 0.5–2.0% H_2O_2–Dowex 50 resin was determined to separate W from Hf, Th, and lanthanides. As an analog of Sg, U was considered [143], and the sorption of U, W, and Mo on Dowex 1 and Dowex 50 in HCl/HF mixture was studied. Based on Dowex 50–HCl/HF [144], a system was proposed also for sepa-

rating VI-valence elements (Mo, W analogs of Sg) and V-valence elements (Nb, Ta, Pa analogs of Db) from IV-valence elements (Zr, Hf analogs of Rf) and III-valence elements (heavy actinides).

Evaluating the Sorption of Stable Elements Using the Method of Inductively Coupled Plasma (ICP)

As noted earlier, in our department, there is a wide range of radioactive labels, both for various analytical studies and for the development of radiochemical systems for obtaining radionuclides. It is also possible to obtain labels of interest during irradiation at accelerator facilities and the JINR reactor. When a radioisotope is not available for studying the sorption behavior of elements for any reason, it is not possible to use the method of radioactive tracers. For such cases, a technique was developed for determining K_d using methods for determining the concentrations of substances, using inductively coupled plasma (ICP). This work was carried out jointly with the Laboratory of Nuclear Physics and Mass Spectral Methods of Analysis of the Institute for Problems of Microelectronics Technology and High-Purity Materials of the Russian Academy of Sciences, as well as CTU—Czech Technical University (Prague, Czech Republic). There are known methods for the determination of substances using ICP, such as MS-ICP mass spectrometry and AES/OES-ICP atomic emission spectrometry (or optical emission spectrometry).

Regardless of the ion separation and detection method (ICP-MS or AES/OES-ICP), the method makes it possible to determine microconcentrations of elements with high sensitivity. Using this method, one can simultaneously determine a larger number of elements (a few tens) than in the method of radioactive tracers. In principle, this allows one to get a very large array of data in real time.

Using this method, the K_d values were determined for 60 elements in the systems of ion-exchange resins–ammonium acetate [131] and ammonium chloride [132] (Fig. 34). We are planning further systematic study of the behavior of ions in cooperation with the Department of Neutron Activation Analysis and Applied Research at the FLNP.

3. RESEARCH PROSPECTS

To consider the further development of our work within the framework of radiopharmaceutical nuclear medicine, the following points should be emphasized once again:

(1) Nuclear medicine has two main areas—diagnostic and therapeutic.

(2) Currently, the most promising for nuclear medicine is the development and use of "modern radiopharmaceuticals" involving a biological vector and a chelator for labeling the corresponding radionuclide.

(3) The use of modern radiopharmaceuticals, differing only in suitable radionuclides, is naturally interwoven into a new direction—theranostics (diagnosis + therapy).

(4) To date, diagnostics using radiopharmaceuticals is already largely a commonly used area of nuclear medicine, acquiring the features of a developed industry.

(5) At present, therapy with the use of radiopharmaceuticals, despite a long history (primarily based on β emitters) and certain achievements, is only in its infancy, or at least undergoing a strong transformation.

(6) Recently, the very high efficiency of α emitters with a high LET value for therapy has been proven. At the same time, for the treatment of oncology in the bones (and potentially for all types of tumors), the effectiveness of not only the ^{223}Ra radiopharmaceutical, but precisely modern radiopharmaceuticals, α emitters based on biological vectors, has been proven.

(7) The widespread use of α emitters for therapy is currently constrained, first, by a relatively small set of suitable radionuclides; second, by fundamental difficulties in the production of therapeutic quantities of radionuclides of the required quality; third, by a limited set of tools for labeling the corresponding radionuclides, requiring the development of the chemical and radiochemical components of production of radiopharmaceuticals (At, Ra, Ac are radioactive elements).

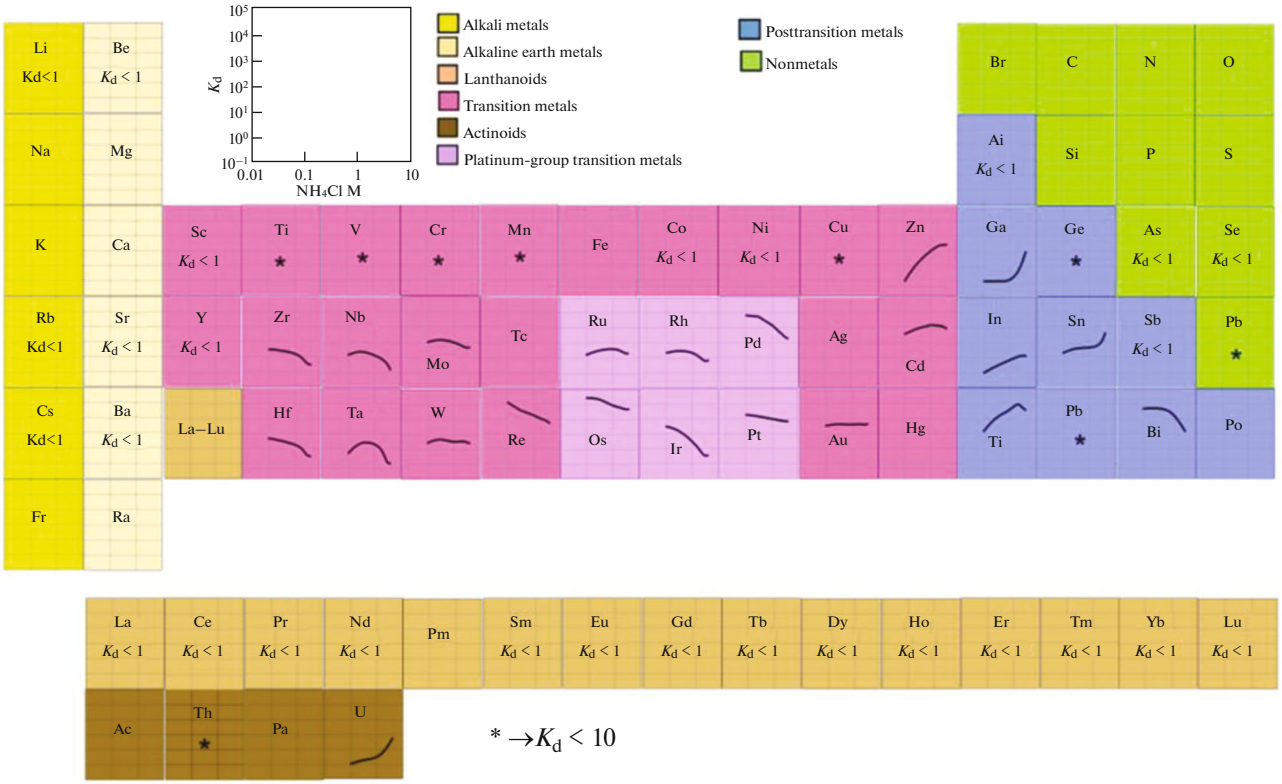
(8) Most researchers involved in studies of radiopharmaceuticals agree on the good prospect of using Auger emitters, also having a relatively high LET value, for therapy. However, almost no pharmaceutical preparations on this basis have yet reached clinical testing. Searches are being intensively carried out, including due to the fundamental efficiency and at the same time in connection with the "tactical" problems of α emitters.

(9) The emergence of new biological vectors, as well as the development of theranostics, stimulate research work on the entire spectrum of precursors (radionuclides, chelators, etc.) of radiopharmaceuticals, in addition, on methods and techniques for their synthesis and analysis.

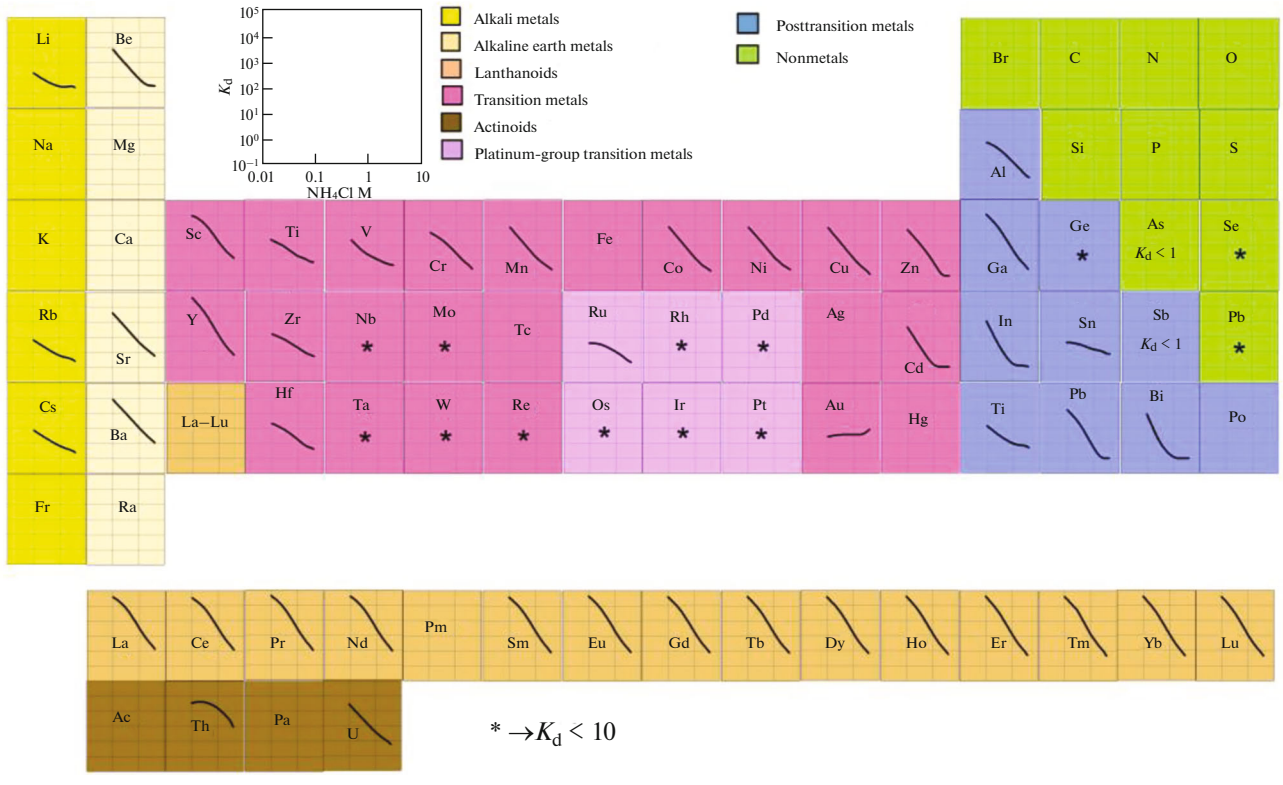
Based on the foregoing, it becomes quite obvious that there is a need for intensive development of a number of radiochemical techniques and methods for obtaining and evaluating therapeutic radiopharmaceuticals based on α emitters, as well as Auger-emitters, and other medical radionuclides. The range of tasks can be divided into two principal directions—analytical and preparation-fabricating.

3.1. Analytical Direction of Radiochemical Research in the Field of Radiopharmaceutical Nuclear Medicine

1. Development and implementation of methods for determining thermodynamic and kinetic constants of radiopharmaceuticals and their precursors using the



(a)



(b)

Fig. 34. Distribution coefficients of elements in ammonium chloride solutions on resins: (a) Dowex 1×8 (Cl^- form, 200–400 mesh); (b) Dowex 50×8 (NH_4^+ form, 200–400 mesh).

method of perturbed angular correlation (PAC). Of fundamental importance is the almost unique possibility of this method to study the behavior of these RPs, which have extremely slow kinetics, while being at very low concentrations (up to nmol/L and below). It is important that a sample of up to 100 μL is sufficient for the study (at pharmaceutical concentrations of 10^{-4}–10^{-6}–10^{-8} M and below), which is extremely important when studying new radiopharmaceuticals, for which prices of the order of \$100000 per mg are quite normal. Therefore, most analytical methods that require above a 1-g mass of preparations become, if not inapplicable, then "applicable with a low probability." In addition, PAC studies are possible both in conventional solutions and in systems with in vitro cell cultures, up to in vivo studies. Using this method, it is also possible to study the after-effects of radioactive decay in the environment of the probe nucleus in real time in the time range of 1 ns–1 μs. When studying the kinetics of processes at the macro level, the characteristic times for this method are minutes–weeks (years).

The main radionuclides include ^{111}In (purchased, Phasotron), ^{181}Hf (reactor, purchased), ^{152,154}Eu (long-lived and available, reactor, purchased).

Thus, unique information about the thermodynamics and, above all, the kinetics of radionuclide complexes used as radiopharmaceuticals will be obtained, which in turn will make it possible to evaluate and improve the synthesis of radiopharmaceuticals. This may be the key to overcome several bottlenecks in this area, for example, to develop chelator for ^{201}Tl, etc.

The study of the after-effects of the nuclear decay of radionuclides in the composition of radiopharmaceuticals using PAC remains an urgent problem. Generally speaking, this is likely the only available on-line channel of information about the processes occurring in the environment of the radionuclide immediately after decay (10^{-9}–10^{-6} s) in liquid media (cell). Knowledge of these processes is of fundamental importance for radiation chemistry, and hence for radiobiology and nuclear medicine. In addition, it seems to us that the possibilities of creating chelators, or rather "retaining systems" for paired radionuclides smaller than nanoparticles, have not been fully exhausted. The importance of developing such a system for the ^{212}Pb/^{212}Bi pair for α therapy can hardly be overestimated. Currently, such a system seems unlikely due to after-effects from the radioactive decay of ^{212}Pb. However, it should be noted that the details of these processes have barely been studied experimentally. On the other hand, knowledge of these processes can help the search for a stable molecule, for example, when it is "significantly" increased relative to the *DOTA* chelator.

In all respects, it is very promising to study new chelator systems separately and as part of a radiopharmaceutical using the PAC method. Such studies will be of significant value when they are carried out jointly with the developers of such chelators (TRIUMF, University of Mainz).

2. Development and implementation of methods for determining the thermodynamic and kinetic constants of radiopharmaceuticals and their precursors using methods for studying the diffusion and electromigration of probes in thin tubes (capillaries). This method requires for studies one or two orders of magnitude larger quantity of pharmaceuticals relative to PAC. On the other hand, it is suitable for almost any radionuclide. This fact is extremely important for studying the properties of radiopharmaceuticals based on radioactive elements, including At, Ra, and Ac α emitters. Currently, the use of ^{223}Ra, ^{225}Ac and ^{211}At is a trend in alpha-therapy of oncological diseases. At the same time, there is a lack of knowledge for these elements not only in the field of radiopharmaceuticals, but also simply in chemistry. This particularly hinders the use of Ra and At. Radionuclides ^{223}Ra and ^{225}Ac are available both from thorium targets when they are irradiated with protons at the Phasotron, and from radionuclide generators. ^{211}At is available from bismuth targets irradiated with alpha particles, as well as from thorium targets when irradiated with protons.

It is possible to use almost all available radionuclides in the electromigration method. But, probably, the main "super task" in this area is the search for a suitable slow chelator for radium. As we already mentioned, ^{223}Ra is an available α emitter for therapy, but no chelator has yet been found for its use as part of a "modern" radiopharmaceutical. At the same time, there were almost no systematic studies of the kinetics of complex formation with chelators, including due to the limitations of available analytical methods.

Here, one can also state the promise of studying new chelation systems separately and as part of a radiopharmaceutical using the electromigration method. Such studies will be of significant value if they were carried out jointly with the developers of chelators (TRIUMF, University of Mainz).

3. Study of frozen solutions of radiopharmaceuticals based on ^{119}Sb and ^{161}Tb in the emission mode of Mössbauer spectrometry using resonant counters. In this mode, it is sufficient to have 1 to 10 MBq of preparation activity in the source. The construction of these spectrometers together with colleagues from Rostov-on-Don (spectrometer manufacturers) is in the process of implementation.

^{119}Sb ($T_{1/2}$ = 38.19 d) and ^{161}Tb ($T_{1/2}$ = 6.89 d) are two promising radionuclides for Auger cancer therapy. Using the data of Mössbauer spectrometry, it is possible to obtain information about the distribution of isotopes by physical and chemical forms, as well as unique information about the local environment of probe nuclei. And what is important, it is possible to obtain information about the after-effects of radioac-

tive decay, which are caused by the emission of Auger-electrons.

^{161}Tb is available from reactor irradiation; ^{119}Sb is readily available from Phasotron irradiations. It is also possible to produce parent ^{119}Te ($T_{1/2}$ = 16.05 h) and ^{119m}Te ($T_{1/2}$ = 4.7 d) for ^{119}Sb ($T_{1/2}$ = 38.19 h) on external accelerators or on a microtron. For ^{119}Sb, it is possible to test the spectrometer on commercial ^{119m}Sn ($T_{1/2}$ = 293.10 d).

4. The study of new radiopharmaceuticals must be correlated with the traditional method of their study using thin layer chromatography. To intensify these works, an analyzer for TLC was purchased. It is necessary to organize work on the study of the kinetics of labeling of radiopharmaceuticals, as well as the optimization of labeling, using the TLC method.

5. Study of the after-effects of radioactive decay using column chromatography and chelators with "slow kinetics." As a result of the after-effects of radioactive decay, after the collapse of the complex (molecule), the daughter nucleus does not return to the chelator due to the slow kinetics of the process. In this case, it can be separated from the phase of the parent radionuclide. Using this method, it is possible both to study the results of the after-effects of radioactive decay, including for characteristic generators in vivo, and to create generators.

The study of processes is possible on several radionuclides, many of them are available from irradiation at the Phasotron. A very important (for alpha therapy) pair ^{212}Pb/^{212}Bi is available without irradiation from the generator. In addition, the equipment of this method is simple, and it is possible to conduct field experiments.

6. Evaluation of the behavior of elements on existing adsorbents but using "new solutions" (water–organic mixtures, several acids not yet used for these purposes). Carrying out such works is possible both with the involvement of a large range of radionuclides, indicators, and with the use of ICP methods. In addition, it is interesting to study sorption on newly created adsorbents. Here we have good experience in the joint development of composite adsorbents with CTU (Czech Republic) and Triskem, one of the leaders in the production of extraction resins.

3.2. Preparative Direction of Radiochemical Research in the Field of Radiopharmaceutical Nuclear Medicine

1. The development of a large range of radionuclide generators will be continued on the basis of reverse-tandem methods (^{44}Ti → ^{44}Sc, ^{68}Ge → ^{68}Ga, ^{90}Sr → ^{90}Y, ^{238}U → ^{234}Th, ^{237}Np → ^{233}Pa, ^{229}Th → ^{225}Ra → ^{225}Ac, ^{227}Ac → ^{227}Th → ^{223}Ra, ^{202}Pb → ^{202}Tl, ^{194}Hg → ^{194}Au, ^{32}Si → ^{32}P etc. up to 40–50 pairs) to expand the possibilities of conducting physical and chemical research, as well as to obtain nuclear medical radionuclides (^{225}Ac, ^{223}Ra, ^{44}Sc, etc.). One should emphasize that the development of a generator takes a lot of time. We have a significant basis for many pairs, several papers were published for ^{44}Ti → ^{44}Sc, ^{68}Ge → ^{68}Ga, ^{172}Hf → ^{172}Lu. Our results are in high demand for nuclear medicine even at "test" amounts of radionuclides. With certain funding for purchasing parent isotopes with $T_{1/2}$ > 10 years, it is quite realistic to create two or three generators at DLNP, preparations of daughter isotopes of which can be produced in significant quantities and used for "external" research, including diagnostics, or therapy.

In addition to the good experience in creating reverse-tandem generator schemes, a significant contribution to the success of creating generators should be made by searching for new sorption schemes (item 6, Sec. 3.1).

2. Development of methods for the production and separation of radionuclides from targets irradiated with protons, neutrons and gamma rays (bremsstrahlung). One should note our experience: to solve a wide range of physical problems, a large number (>300) of radionuclides of most elements were obtained from targets irradiated at the DLNP Phasotron. We also participated in the development of methods to produce several medical radionuclides at other facilities, including collaboration with foreign colleagues. Even if the Phasotron is shut down, we will have a significant number of radionuclides for testing methods for production of medical radionuclides.

We should also note that we used and partially developed methods based on chromatography (the tandem method, the ability to effectively separate lanthanides). We also use and develop high-temperature methods for separating elements. But, of course, we see the three- (two)-column method of separation as the main solution for separating medical radionuclides from targets.

This knowledge and methods are in demand and will be used by us when obtaining medical radionuclides, namely ^{225}Ac, ^{223}Ra, ^{44}Sc, ^{119}Sb, etc. from irradiated targets.

In this case, the results of the studies mentioned in item 6 (Sec. 3.1) will also be in demand.

3. Development of methods for labeling radiopharmaceuticals with radionuclides. Here we have a very valuable experience: together with German colleagues, we developed a method for fast and efficient ^{68}Ga labeling. This method is now widely used throughout the world in PET studies with this isotope.

The data from items 1 and 2 (Sec. 3.1) are necessary for the development of methods for the rapid and efficient labeling of radiopharmaceuticals with ^{225}Ac, ^{44}Sc, ^{119}Sb, ^{68}Ga, etc.

4. Using the experience of low-background research in nuclear medicine. The method we developed for obtaining a low-background flux based on ammonium

chloride allows us to expand it to obtain a large amount of "ultrapure" ammonium salts. Such salts can be in great demand in the development of procedures for the separation and labeling of radionuclides, since they do not introduce undesirable contaminants of di-, tri-, and tetravalent metals. This is very valuable due to the low concentrations of pharmaceuticals used.

The development of solutions for labeling radiopharmaceuticals with a very low content of contaminants and in the form of colloids will also be carried out. This is interesting for both nuclear medicine and low-background research. It is important to note that renovated clean rooms are suitable for these purposes.

CONCLUSIONS

Based on the presented description of the studies carried out, as well as prospects for the development of these areas, the following important points can be emphasized.

— Over the years, the radiochemistry department at DLNP JINR continues to play an important role as one of the world's few centers for the development of radiochemistry.

Therefore, it is important to maintain the existing long-term base and experience obtained and the achievements of the outstanding scientists of the department and the Institute, as well as create the necessary conditions for attracting and training young personnel for the further development of this promising area. An important aspect to achieve this aim is the creation of a modern platform for research, based on the renewal of available laboratories and the acquisition of the necessary equipment.

— Development of a wider range of studies and methods for the creation and testing of modern radiopharmaceuticals.

As mentioned above, the international status and reputation of JINR, as well as the existing platforms for interdisciplinary cooperation, provide unique opportunities for the development of a wider range of methods for testing new radiopharmaceuticals based on existing knowledge in such methods as PAC, emission Mössbauer spectroscopy, electromigration and a number of other ways of materials research. This will significantly expand the range and completeness of research needed to analyze the most effective compounds and complexes for use in nuclear medicine. Along with the development of methods to produce medical radioisotopes, this will allow us to study their chelation and subsequent formation of radiopharmaceuticals based on the proposed isotopes and to study the processes of complex formation in real time. In a number of ways for the production of radionuclides, the competence of the department for the development of generator methods, as well as for the radiochemistry of rare earth metals, should be especially emphasized. The combination of such technologies is not available almost anywhere in the world and will allow JINR to take a leading position in this field.

— Formation of an independent area in the development of nuclear medicine at JINR.

The formation of an independent branch of nuclear medicine at JINR based on a group at the radiochemistry department seems to be very promising. Many world centers such as CERN, TRIUMF, ILL, Los Alamos, Brookhaven and many other national laboratories declare nuclear medicine as an active applied area of research. In many aspects, this makes it possible to more effectively attract additional funding and public attention to ongoing research. The formation of an independent direction in the development of nuclear medicine at JINR will strengthen existing areas of cooperation and create a basis for new promising collaborations and joint projects with national and international organizations working in this field.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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