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INSTRUMENTS AND METHODS OF INVESTIGATION

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Radioisotope research and development at the Linear Accelerator of the Institute for Nuclear Research of RAS

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Contents

Abstract. Radioisotope research at the linear accelerator of INR RAS has been developing since 1989. In 1992, a facility for the irradiation of isotope targets and radioisotope production was built, operating on a diverted proton beam with an energy of 160 MeV and a current of more than 120 μA, which was the most productive facility in the world at that time. The facility is used for both fundamental and applied research. The main focus is the study of the processes of the generation and recovery of medical radioisotopes, as well as the development of technology for their production. The main radionuclides produced now are strontium-82 and actinium-225. A Russian ^{82}Sr/^{82}Rb generator for PET-diagnostics has been developed by INR RAS and is being introduced for medicine. New types of ^{225}Ac/^{213}Bi generators are also being developed for the treatment of oncological diseases. In addition, the study of the process for the production and chemical recovery of medical radionuclides ^{117m}Sn, ^{68}Ge, ^{72}Se, ^{64,67}Cu, ^{223}Ra, ^{230}Pa, and ^{230}U is being carried out, as is the study of some generators with some of these isotopes. The technology developed at INR is used in Russia and abroad. Physical processes of proton interaction with different nuclei are also investigated in the laboratory of the radioisotope complex of INR RAS. The produced ^{22}Na, ^{83}Rb, ^{109}Cd, and radioactive sources with these radionuclides are used in physical research and technology.

Keywords: radioisotopes, linear accelerator of protons, fundamental and applied research, nuclear medicine, strontium-82, rubidium-82 generator, actinium-225, bismuth-213 generator

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1. Introduction. History of radioisotope research at the Institute

The Laboratory of Radioisotope Complex (LRC) was established at the Institute for Nuclear Research of the Russian Academy of Sciences (INR RAS) in 1989. It fell under the Experimental Physics Department headed at that time by V M Lobashev, a corresponding member of the Academy of Sciences of the USSR. A S Il'inov, Doctor of Sciences in Physics and Mathematics, a noted theorist and specialist in nuclear physics, headed the laboratory. Associates from the Joint Institute for Nuclear Research (JINR) (Dubna), Lomonosov Moscow State University (MSU), and other leading Russian organizations made up the base of the laboratory staff. The Linear Accelerator (LA) at the Institute — a meson factory — was then under construction. From the very beginning, it was planned to carry out both fundamental and applied research at LRC. The main stages of the development of radioisotope research at INR RAS are presented in Table 1.

The Linear Accelerator at INR RAS is distinguished by the fact that it is capable of producing proton beams having a relatively high energy of particles (100–600 MeV) and at the same time a high intensity (up to 500 μA). Such characteristics were initially aimed at studying the physics of mesons. However, at present, neutron and radioisotope studies are of great importance and are under development [1]. The accelerator parameters determine its potential for isotope research and production. First, at such proton energies, it is possible to obtain a variety of isotopes in a carrier-free state, including those that cannot be produced in significant amount at reactors and cyclotrons with a low energy of particles. Second, at such a high intensity of the proton beam, it becomes reasonable to conduct not only research, but also the large-scale production of radionuclides that can find application in various fields. It is exactly the combination of these characteristics that allows a full realization of the accelerator's capabilities.

Table 1. Most important stages in the development of radioisotope research and production of radionuclides at INR RAS.

Year	Stage
1989	Organization of the Radioisotope Complex Laboratory
1989	Development of the design for a facility to accelerate radioactive heavy ions
1989	Beginning of technology development to produce strontium-82 from metallic rubidium in various accelerators, as well as a rubidium-82 generator
1989	First linear accelerator experiment, activation of internal combustion engine parts
1991	Development and design of Isotope Target Irradiation Facility
1992	Construction of Isotope Target Irradiation Facility
1993	First processing of irradiated INR-targets containing strontium-82 at Cyclotron Co. (Obninsk) and GIPH* (St. Petersburg)
1994	Processing of irradiated INR-targets containing sodium-22 and cadmium-109 at Cyclotron Co. and GIPH enterprises, delivery of products to customers
1997	Beginning of regular deliveries of targets to Los Alamos National Laboratory (LANL) (USA) for processing and obtaining pure strontium-82, delivery of the product to customers
2002	Beginning development of methods to produce germanium-68 and palladium-103 at the INR RAS accelerator
2003	Starting research and development to produce tin-117m
2006	Starting research and development to produce actinium-225 from irradiated metallic thorium
2007	Development and approval of a project for a new radiochemical laboratory with 'hot' cells at INR RAS
2014	Completing clinical trials at the Russian Scientific Center of Radiology and Surgical Technologies named after Academician A M Granov (RSCRST) and obtaining a registration certificate for a medical generator of rubidium-82 developed at INR RAS
2015	Beginning research aimed at the development of a medical generator of bismuth-213
* State Institute of Applied Chemistry, now Russian Scientific Center Applied Chemistry (GIPH).	

One of the promising fields in radioisotope research, which initially was considered to be of primary importance, was the production of beams of accelerated heavy ions of radioactive isotopes [2]; it was planned to obtain short-lived isotopes using an LA proton beam, immediately extract them, and inject them into the ion source of another accelerator of heavy ions. Part of the equipment was manufactured, while calculations and preliminary design work were performed, which had shown that the intensity of the beam of various heavy ions could reach 10^{11} s^{-1}, which could be a record-breaking high characteristic. Using such beams, it could be possible to study the nucleus structure and to obtain new isotopes, including those of new superheavy elements. Such beams of radioactive isotopes could be used for applied purposes. However, work along these lines had to be terminated due to a lack of financing.

Another field of activity, which later became dominant, was research and development aimed at using a beam of accelerated protons to produce isotopes for medical, scientific, and technical purposes. Possessing an accelerator is the most important, but by no means the only, condition for the efficient production of isotopes. There are accelerators in the world that have no less potential, but no large isotope production is organized using them. One more critical condition is the development of target preparation and irradiation technologies.

Figure 1 illustrates the advantages and drawbacks of producing radioisotopes with a beam of protons at various energies. Protons with energies from 70 to 200 MeV have important advantages over those with higher or lower energies, namely, large cross sections of formation, a high isotope yield in sufficiently thick targets, and, in most cases, a limited content of impurities. However, at the same time, this approach requires efficient cooling of thick and massive targets during the irradiation and then an efficient technology for their chemical postprocessing to extract the products.

In order to implement the radioisotope program at INR RAS, it was decided to create a facility with the 160-MeV proton beam extracted from the LA under construction at that time. Such a facility (the Isotope Target Irradiation Facility) [3, 4] was developed, constructed, and launched as soon as possible in 1992 (see Table 1). The design of the facility was original, and although there were great doubts about its future performance, it turned out to be the largest in the world in terms of energy accumulated for the production of isotopes at that time, and it operates reliably to this day. Almost every year, work is carried out at the facility to modernize it, improve its characteristics, and increase its productivity and safety.

At present, already several facilities of this type operate around the world (Table 2) and new ones are under construction.

One more factor of major importance in isotope production is the capacity to extract the desired radionuclides from targets irradiated in the accelerator, from the point of view of both the radiochemical technique and the technical conditions for its implementation.

The extraction technique must provide both high chemical yields, since radionuclide production at such accelerators is very expensive, and the achievement of high factors of product purification from impurity radionuclides and material of the target, since there are high product purity requirements for isotopes for medical purposes. These requirements for the purity of products for medical purposes are getting more and more rigorous. A feature of targets irradiated with 70–200-MeV protons is that they have relatively large masses of several tens of grams, while the isotopes are extracted from them in ultramicroscopic amounts. Therefore, some standard approaches to chemical separation are not applicable here. It is also important that the technique be suitable for remote execution in 'hot' cells, since the activity of the irradiated targets is rather high.

The technical implementation of radiochemical postprocessing required 'hot' cells with master-slave manipulators, a high degree of shielding, high-power gas purification, and a system of utilization and transportation of radioactive waste. Moreover, at present, to produce a medical-purpose final product, it is necessary to execute the extraction under the conditions of Good Manufacturing Practice (GMP), which imposes additional requirements. INR RAS completed the design of such a radiochemical laboratory long ago, but no funds were allocated for its construction.

As part of the realization of radioisotope projects at INR RAS, methods of radiochemical postprocessing were usually

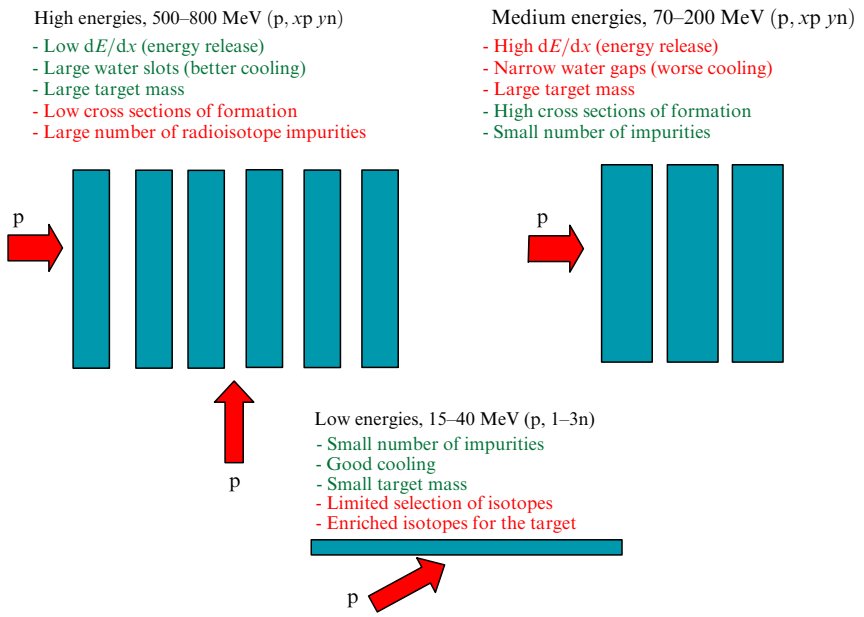

Figure 1. (Color online.) Advantages and disadvantages of obtaining isotopes by irradiating targets with protons of different energies (arrows indicate the possible directions of the proton beam, which irradiates targets of different thicknesses).

developed by INR RAS, and their large-scale implementation was carried out at partner enterprises around the world. Table 3 presents the targets irradiated at the Linear Accelerator, which were processed using the methods developed mostly with the leading participation of INR RAS. The target preparation and radiochemical methods and technologies of INR RAS have also been used in the accelerators of foreign organizations.

The next stage in realizing medical isotopes is producing a medicinal radiopharmaceutical preparation (MRPP), the final medicinal product to be input into the human body for diagnostics or the treatment of diseases. Research and development at INR RAS are restricted to the realm of isotope generators based on those radionuclides which are most advantageous for production at the Linear Accelerator, in particular, ^{82}Sr and ^{225}Ac. In medicinal generators, the daughter short-lived radionuclide is multiply obtained as a result of the decay of longer-lived parent radionuclide and consequent separation from the parent radionuclide. Then, the MRPP based on the short-lived radionuclide is introduced into the body. The synthesis of complex MRPPs and research on nuclear medicine itself are carried out at other institutes and partner enterprises of INR RAS, and our Institute also takes part in these studies.

2. Research, development, and production of medical isotopes

2.1 Strontium-82

Strontium-82 is the most promising isotope for production at INR RAS, because it is in demand and cannot be produced in a reactor, nor can it be produced in sufficient amounts in cyclotrons with a low energy of particles. It is used to produce generators of rubidium-82, which is used in positron emission tomography (PET) diagnostics of the heart [5] and a number

Table 2. Main operating facilities for the production of radionuclides in a beam of medium-energy protons.

Organization	Location	Energy of protons used for the production of radionuclides, MeV	Beam current used for the production of radionuclides, μA
Institute for Nuclear Research, RAS	Troitsk–Moscow, Russia	160	120
Los Alamos National Laboratory (LANL)	Los Alamos, New Mexico, USA	100	200
Brookhaven National Laboratory (BNL)	Upton, New York, USA	200	120
Canada's Particle Accelerator Centre TRIUMF	Vancouver, Canada	110 500	80
iThemba Laboratory for Accelerator Based Sciences (LABS)	Faure, South Africa	66	250
ARRONAX (Accelerator for Research in Radiochemistry and Oncology at Nantes Atlantique)	Nantes, France	70	2 × 150
Curium	Indianapolis, USA	70	2 × 200

Table 3. Targets irradiated in the INR RAS linear accelerator and shipped to consumers for postprocessing to isolate target radionuclides.

Main target material	Target radionuclide	Number of targets sent	Year of delivery	Consumer (target processing)
Rubidium	Strontium-82	2	1993	GIPH (St. Petersburg)
		9	1993 – 1994	Cyclotron Co. (Obninsk)
		150	1997 – 2017	LANL
		1	2004	BNL
		11	2002 – 2013	IPPE JSC* (Obninsk)
Indium	Cadmium-109	5	1994 – 1995	GIPH
Aluminum	Sodium-22	3	1994 – 1995	Cyclotron Co.
		13	2002 – 2020	IPPE JSC
Gallium	Germanium-68	4	1999 – 2003	LANL
Silver	Palladium-103	3	1999 – 2003	LANL
		9	2000 – 2005	NIFKhI** (Obninsk)
		2	2003	Mayak Production Association (Ozersk)
Rhodium		2	2003	BNL
Antimony	Tin-117m	11	2004 – 2007	IPPE JSC
		1	2005	MSU
Thorium	Actinium-225	10	2011 – 2017	MSU
		5	2012 – 2013	NIFKhI

* State Scientific Centre of the Russian Federation — Leypunsky Institute for Physics and Power Engineering.
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of diseases (see below). The first experiments on developing a new technology of ^{82}Sr production from targets of metallic rubidium via the nuclear reactions ^{85}Rb(p, 4n) and ^{87}Rb(p, 6n) were carried out by us in the TRIUMF (Vancouver, Canada) and I-100 (Institute for High Energy Physics (IHEP), Protvino) accelerators. The radiochemical technology of extraction was developed using the 'hot' cells of the Nuclear Power Engineering Institute of the National Academy of Sciences of Belarus [6].

The method of producing ^{82}Sr from metallic rubidium targets ensures a much higher yield of the target product than does the method used earlier of obtaining ^{82}Sr from molybdenum irradiated by 500–800-MeV protons. In metallic rubidium fewer radionuclide impurities are formed, mainly ^{83}Rb, ^{84}Rb, and ^{86}Rb, as well as minor amounts of ^{75}Se and ^{74}As, which are removed during chemical postprocessing. The content of a chemically nonremovable admixture of ^{85}Sr in the product is also much lower: the ^{85}Sr and ^{82}Sr activity ratio in the product is less than 1, while the acceptable value is 5 [6–8]. A target of metallic rubidium is also more productive than the target of rubidium chloride used earlier. The metallic target provides better heat removal upon the irradiation and is safer, since there is no the formation of atomic chlorine, which destroys the target shell.

The development of the technology of rubidium target irradiation was continued at a new facility constructed in 1992 in a 160-MeV proton beam extracted from the INR RAS Linear Accelerator. The radiochemical processing of the irradiated targets was first carried out using traditional ion-exchange methods at the Cyclotron Co. (Obninsk) [7], then at the Los Alamos National Laboratory [8] and Brookhaven National Laboratory. This collaborative work with the USA started within the Global Initiative for Proliferation Prevention (GIPP) and also included many Russian enterprises of the Rosatom State Corporation [9]. As a result of the successful fulfilment of this program, a joint production of strontium-82 was organized at INR RAS and LANL and, till 2017, a large number of irradiated rubidium targets (150) were sent to LANL (see Table 3). Later, INR RAS developed a new, original, and more efficient method of radiochemical recovery of strontium-82 by direct sorption from a liquid metal [10, 11], and technology based on this was successfully introduced at the French Center ARRONAX (Nantes), as well as at the State Scientific Centre of the Russian Federation — Leypunsky Institute for Physics and Power Engineering (IPPE JSC, Obninsk).

The target of metallic rubidium, which is used at present to produce strontium-82 at INR RAS, is designed to be irradiated with an oblique proton beam at an angle of 26°. The target has a complicated structure. The thickness of rubidium along the beam is 68 mm and the range of proton energies is from approximately 95 to 35 MeV. The efficient cooling of such a target is achieved due to the circulation of metallic rubidium during the irradiation (Fig. 2), rigorous optimization of flows of cooling water, the energy of protons, and the position, intensity, and shape of the beam by means of original monitoring systems. The proton beam continuously rotates around a circle with the frequency of 50 Hz.

The maximal yield of strontium-82 production with a proton current of 120 μA reached 20 MBq μA^{-1} h^{-1} (0.54 mCi μA^{-1} h^{-1}), which is a world record for a high-intensity beam. These yields cannot be compared with those calculated from the cross sections in experiments with a low-intensity beam, because, under irradiation with a high-intensity beam, the yield is much lower. The production of strontium-82 in one target at the end of irradiation reached

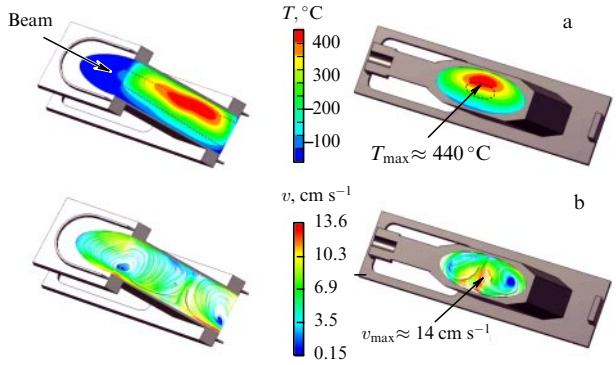

Figure 2. (Color online.) Distribution of temperature (T) and convection circulation velocity (v) of metallic rubidium in an irradiated target (calculations performed using the ANSYS software for finite element analysis [12]); proton beam current of 100 μA. (a) Cross section by a vertical plane passing through the proton beam axis. (b) Cross section by a vertical plane at an angle of 26° to the proton beam passing through the point of maximum temperature.

230 GBq (6.2 Ci) of strontium-82 during a few days of irradiation. However, productivity also depends on beam intensity and the stability of the accelerator operation, and it is no longer record high at INR RAS. The best production characteristics are now being achieved at the new facility of the Curium company (USA) (see Table 2), which was developed with the participation of INR RAS.

For the long time the facility at the INR RAS accelerator has been in operation, all deliveries to LANL and other customers (see Table 3) have been carried out on time, although problems of a different nature often arise: fires in Los Alamos, freezing of the accelerator due to extremely low temperatures in Troitsk, difficulties with customs and transportation (a container was even lost by an airline). In collaboration with American colleagues, as well as those from TENEX JSC, and then the Regional Alliance Isotope JSC of the ROSATOM State Corporation, all problems have been promptly resolved. Problems with product quality were also quickly resolved, when new increased requirements arose or unexpected impurities appeared in the product. At some point, supplies from Troitsk turned out to be decisive in preserving the use of rubidium-82 generator in nuclear medicine at all [13]. With the help of INR RAS, LANL has developed and launched its own facility for target irradiation with a 100-MeV proton beam at the Los Alamos accelerator (see Table 2). At the same time, LANL supplied the extracted strontium-82 produced at accelerators in both Troitsk and Los Alamos for the needs of American and Russian nuclear medicine.

Recently, large-scale production of strontium-82 from metallic rubidium has also been successfully organized by ARRONAX in France and Zevacor Molecular (now Curium) in the USA. INR RAS entered into agreements with both companies, which contributed to their success. While the consumption of strontium-82 is increasing, national laboratories in the United States — LANL and BNL — are phasing out strontium-82 production, because they do not have to compete with private enterprises. INR RAS also licensed its technology for producing strontium-82 to the American company Meta Isotope Technologies (MIT). New facilities for producing strontium-82 are being designed and created in different countries.

Chemical separation in 'hot' cells is equally important — it accounts for about half of the effort and cost of the product. Previously, it was allowed to carry out the separation of strontium-82 in conventional hot cells without special requirements for cleanliness. Currently, the production of the final product is allowed only under GMP conditions, which is not yet achievable with heavy shielding cells available in Russia. It is possible, however, to obtain an intermediate product in Russia with its further additional treatment abroad at partner enterprises. But the most promising development is the construction of a new radiochemical laboratory at INR RAS, which would meet all current requirements (see below).

There are other projects to set up production of strontium-82 in Russia, but, unfortunately, they are still very far from completion. INR RAS is interested in creating a parallel back-up production of strontium-82 and other radionuclides at partner enterprises, since the Linear Accelerator cannot operate in the summer months, and medicine needs regular supplies. However, our experience and the experience of manufacturers in other countries have shown that at least five years should pass from obtaining the first results of development and samples of low activity to well-established large-scale production, provided that the direction is correctly chosen and intensive work with the involvement of specialists from INR RAS is carried out.

According to rough estimates, about 350 thousand patients have been diagnosed using strontium-82 produced directly at INR RAS. And there are already several million patients diagnosed with the help of technologies developed with the active participation of INR RAS in LANL, ARRONAX, and Zevacor Molecular (Curium).

2.2 Medical generator of rubidium-82

Strontium-82 is used exclusively for the manufacture of the $^{82}Sr/^{82}Rb$ medical generator, which is already widely used in the United States, while in other countries it is employed only in select clinics. The rubidium-82 generator is an ion-exchange column with a sorbent (usually hydrated tin dioxide) on which $^{82}Sr^{+2}$ ions are applied in a certain way. The column is enclosed in a protective container. Strontium-82 (half-life $T_{1/2} = 25.5$ days) decays into short-lived rubidium-82 ($T_{1/2} = 1.3$ min). During the operation of the generator, $^{82}Rb^{+}$ ions are washed out with saline (0.9% NaCl) and injected into the patient's body using a special injection system. Rubidium-82 ions are distributed in the circulatory system while the patient is placed in a positron emission tomograph. ^{82}Rb decays with the emission of a positron, which annihilates with the formation of two oppositely directed gamma quanta with an energy of 511 keV, recorded by the tomograph detectors in the coincidence mode. Thus, blood flow in the heart and other organs is accurately visualized, and, in some cases, metabolic processes can also be studied [5]. Such diagnostics determine the effective treatment of the patient.

The Russian GR-01 generator (Fig. 3) [14], which includes an ion-exchange column in a protective tungsten container, has a complex design that ensures its operation in accordance with all medical requirements. GR-01's performance is superior to the Cardiogen® generator distributed in North America. GR-01 (and its modification GR-02) can be operated for a long time (up to 60 days), can contain a high activity of ^{82}Sr (up to 5.9 GBq), provides a larger volume of solution passed through the generator (up to 30 l), and,

Figure 3. View of the Russian GR-01 generator developed at INR RAS.

therefore, allows diagnosing a larger number of patients with one generator — up to 700 people.

Initially, the development of the generator at INR RAS was carried out with the participation of TRIUMF (Vancouver, Canada) and the Medradiopreparat plant (Moscow), but decisive success was achieved in cooperation with the Russian Scientific Center of Radiology and Surgical Technologies named after Academician A M Granov (RSCRST) (St. Petersburg). Laboratory, preclinical, and clinical trials have been successfully carried out here. RSCRST received a registration certificate for the medical device ''Generator GR-01 (GR-02) of rubidium-82'' (no. RZN 2014/1669 dated July 01, 2014), as well as a license for the production and maintenance of medical equipment (no. FS-99-04-005321 dated December 25, 2017; FS 0031099 series), which is necessary for the regular production of generators. The entire large work run to create the generator was carried out by INR RAS and RSCRST with minimal funding and with the involvement of funds from contractual work, as well as foreign grants.

Clinical trials with the rubidium-82 generator were carried out at RSCRST not only in cardiology [15] but, for the first time in the world, also in neuro-oncology [16]. Such a generator is also promising for diagnosing prostate cancer [17] and a number of other diseases [18]. The use of rubidium-82 allows monitoring important processes in the body, which are difficult to observe by other methods.

However, so far only about 700 patients have been diagnosed using this Russian generator at RSCRST. For the wide distribution of the generator in Russia with the organization of regular production, a distribution system, and personnel training at existing PET centers, substantial funding is required, which can be provided by the state or a large pharmaceutical company. INR RAS is working in this direction. The French company Naogen Pharma, under license from INR RAS, is also launching production for Europe of the Rubigen® generator, which is developed based on the Russian generator.

For this type of generator to function, a special injection system is required, with the help of which MRPP is administered to a patient; universal systems are not applicable here. GR-01 has successfully passed all clinical trials with a semi-automatic system. The French company Lemer Pax developed the modern automatic Rubijet® system for this generator; such a system is also being developed at RSCRST.

For efficient use of the rubidium-82 generator, it is desirable to have two or more PET scanners, of which at least one is constantly operating with the rubidium-82 generator. If the center had a cyclotron, then the second scanner could work with MRPP based on fluorine-18 — the most popular radionuclide in PET, obtained in a cyclotron. The combination of MRPPs with rubidium-82 and fluorine-18 opens up new possibilities for diagnostics [16, 19]. However, a great advantage when using generators is that, in this case, the cyclotron does not have to be located in or near a clinic. This allows PET diagnostics to be carried out in remote regions of Russia. With the correct organization of the procedure, its cost can be even lower than using conventional PET methods. But for better efficiency, it is advisable to have, along with an $^{82}Sr/^{82}Rb$ generator, which is mainly used in cardiology, a $^{68}Ge/^{68}Ga$ generator, which has already been produced in Russia by Cyclotron Co. (Obninsk) [20] and is an effective tool for the diagnosis of many oncological diseases [21].

Other projects in Russia aimed at developing a similar rubidium-82 generator are still very far from completion, although large public funds have been allocated for their implementation. The creation of such new generators seems to be inexpedient, since, on the basis of GR-01, several other modifications have already been developed at INR RAS: GR-02 — a cheaper but heavier generator in a lead container; GR-03 — lightweight, with less activity of strontium-82; GR-04 — increased productivity, with a larger column in the same container. This entire range of modifications is able to satisfy fully the needs of domestic consumers.

2.3 Actinium-225

Actinium-225 is the second very promising isotope to be produced in the INR RAS Linear Accelerator. This radionuclide has a half-life of 9.9 days, and short-lived products of its decay emit alpha particles with a range of up to 0.1 mm in living tissues, providing a high density of local energy release. Vector delivery to cancer cells minimizes the radiation dose to healthy organs and tissues [22, 23]. ^{225}Ac is obtained around the world by different methods (Table 4), but the production volume is only 70–110 GBq (2–3 Ci) per year, while the need for it is already several dozen times greater.

Most actinium-225 is produced from uranium-233, previously produced in reactors, and the product of its decay thorium-229 (see Table 4). The availability of ura-

Table 4. Existing and most promising methods for producing actinium-225.

Initial material	Setup for production	Nuclear reaction
Metallic ^{232}Th	Slow neutron reactor	$^{232}Th(n,\gamma) \rightarrow {}^{233}U(1.6\times10^5\ \text{years}) \rightarrow {}^{229}Th(7340\ \text{years}) \rightarrow {}^{225}Ra(14.8\ \text{days}) \rightarrow {}^{225}Ac$
Metallic ^{232}Th	100–500-MeV proton accelerator	$^{232}Th(p, xp, yn) \rightarrow {}^{225}Ac$
Compounds of ^{226}Ra	30–40-MeV proton accelerator	$^{226}Ra(p, 2n) \rightarrow {}^{225}Ac$
Compounds of ^{226}Ra	Accelerator of electrons	$^{226}Ra(\gamma, n) \rightarrow {}^{225}Ra \rightarrow {}^{225}Ac$
Compounds of ^{226}Ra	High flux reactor	$^{226}Ra(3n, 2\beta^-) \rightarrow {}^{229}Th \rightarrow {}^{225}Ra \rightarrow {}^{225}Ac$

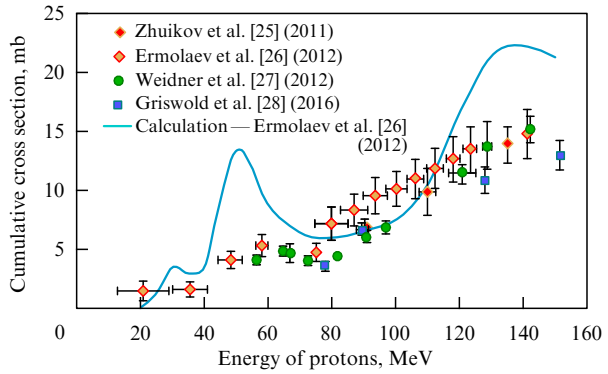

Figure 4. (Color online.) Experimental [25–28] and calculated (using the ALICE-IPPE computer code) [29] cumulative cross sections for ^{225}Ac production in thorium under irradiation with protons.

nium-233, a weapons-grade material, is extremely limited and is no longer being produced. There are several methods for obtaining ^{225}Ac from targets containing ^{226}Ra (see Table 4), which is available in the required quantities. However, the irradiation, processing of such targets, and regeneration of the irradiated material are difficult and very dangerous. Therefore, sufficiently productive technologies based on these methods are still far from complete.

In 2008, INR RAS proposed a method for producing actinium-225 from a target of metallic thorium irradiated with medium-energy protons [24]. To date, a lot of research and development has been carried out in this area. The cumulative cross sections for ^{225}Ac production at proton energies below 160 MeV, measured at INR RAS [25, 26] and then in the USA [27, 28], turn out to be very large (Fig. 4). This will make it possible to produce ^{225}Ac at the INR RAS facility over 10 days of irradiation with a current of 100 μA in an amount of up to 96 GBq (2.6 Ci) with an exposure time of 10 days. The competitive advantage of INR RAS in the production of actinium-225 using a 160-MeV proton beam is that, at a number of other existing accelerators (see Table 2) with a proton energy of 70–100 MeV, the yield of this radionuclide is much lower.

Efficient thorium targets were developed in a shell of metallic niobium, fabricated by diffusion welding, which makes it possible to irradiate them with a high-intensity beam. The foundations of the radiochemical procedure for the extraction of actinium-225 from a complex mixture of radionuclides were laid in cooperation with the Department of Radiochemistry of MSU (Moscow) and tested in hot cells at the Karpov Research Institute of Physical Chemistry (Obninsk) [30]. Subsequently, the technique was significantly improved [31]. The radiochemical procedure allowed efficient separation of ^{225}Ac from the target material, thorium, as well as from more than 80 isotopes of about 30 elements (including actinides and lanthanides — chemical analogs of actinium), arising as products of nuclear fusion, spallation, and fission reactions. This ensured the production of a high-purity preparation that meets the requirements of nuclear medicine (radionuclide purity is more than 99.9%, with the exception of ^{227}Ac impurities). These developments make it possible to start regular production of actinium-225 at INR RAS LA in commercial quantities of up to 900 GBq (24 Ci) per year (assuming maximum optimization). However, the start of production is delayed due to the lack of a suitable radiochemical laboratory with hot cells.

2.4 Generator of bismuth-213

A significant part of actinium-225 is used in medicine through the short-lived daughter product of its decay bismuth-213 ($T_{1/2}$ = 46 min), which, in turn, decays to form ^{213}Po ($T_{1/2}$ = 4.2 μs), emitting alpha particles with an energy of 8.4 MeV. The use of the ^{225}Ac/^{213}Bi generator is especially promising for a product obtained by irradiating thorium-232 with medium-energy protons, since such actinium-225 contains a noticeable amount of activity of long-lived actinium-227 ($T_{1/2}$ = 21.8 years) — about 0.1% at the end of exposure — the injection of which into the human body together with actinium-225 is undesirable. Currently existing generator setups (Table 5) are designed to use ^{225}Ac without ^{227}Ac impurity. At INR RAS, we are developing ^{225}Ac/^{213}Bi generators that provide efficient production of ^{213}Bi with a low content of both actinium isotopes in the eluate and ^{227}Ac decay products.

The principle of operation of the two most promising generators at INR RAS, presented in the last two lines of Table 5, is shown in Fig. 5.

The first generator, AFRABIS (Fig. 5a), is a direct-type generator, in which the parent ^{225}Ac radionuclide is strongly fixed and the daughter one is separated. The original feature of this generator is that, in the closed-loop mode, the intermediate daughter ^{221}Fr, which is continuously separated from the parent ^{225}Ac, decays into ^{213}Bi, which in turn is concentrated in the second column [33, 34]. As a result of circulation, the system comes to a state in which ^{213}Bi is in radioactive equilibrium with ^{225}Ac, but spatially separated from it. Then, ^{213}Bi is removed from the generator and used.

The second generator, TIG (Fig. 5b), is a reverse type and operates with an inorganic sorbent produced in Russia by the TERMOXIDE company (Zarechnyi, Sverdlovsk region) [35, 36]. When a solution with ^{225}Ac and ^{213}Bi in equilibrium with it pass through the column filled with this sorbent, ^{213}Bi is retained and ^{225}Ac passes freely. The circulation of the solution used in TIG allows achieving a high degree of concentrated ^{213}Bi in a small-size column; the resulting ^{213}Bi is extracted from the generator using a rather small volume of solution, which is attractive for medical use.

Testing has showed that the ^{213}Bi generators developed at INR RAS are not inferior to the well-known generators presented in Table 5 as regards stability and efficiency of

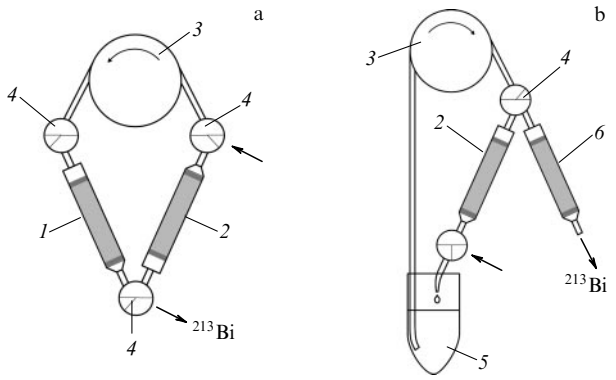

Figure 5. ^{225}Ac/^{213}Bi generators developed at INR RAS: (a) direct (Afrabis), (b) inverse (Termoxide Inverse Generator — TIG). *1* — column with sorbent absorbing ^{225}Ac, *2* — column for concentrating ^{213}Bi, *3* — peristaltic pump, *4* — three-way tap, *5* — solution with ^{225}Ac, *6* — column for afterpurification of ^{213}Bi.

Table 5. Characteristics of existing generator schemes for producing ^{213}Bi in comparison with those developed at INR RAS [32].

Institute	Generator type	^{213}Bi yield, %	^{225}Ac admixture, %	Extraction time, min
Institute for Transuranium Elements (ITU), Karlsruhe, Germany	Direct	76	$< 2 \times 10^{-5}$	2–3
INR RAS, Russia	Direct	85	$< 10^{-4}$	2–3
National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, USA	Direct	85	No data	7–8
Pacific Northwest National Laboratory (PNNL), Washington, USA	Inverse	85	≈ 0.07	No data
PG Research Foundation, Inc., Lisle, USA	Inverse	87	$< 10^{-7}$	19
INR RAS, Russia	Inverse	80	$< 10^{-6}$	4–5
INR RAS, Russia	Direct	80	$< 10^{-6}$	2–3

production. The reverse generator developed at PG Research Foundation, Inc. (Lisle, USA) [37] demonstrates a somewhat better performance in terms of ^{213}Bi yield and ^{225}Ac impurity content (see Table 5); however, the loss of ^{213}Bi during the long time of the extraction procedure negates these benefits. The INR RAS generators provide ^{213}Bi a with lower admixture of long-lived isotopes than the presently most widespread generator at ITU (Institute for Transuranium Elements) (Karlsruhe, Germany) [38], used in most clinical studies, and the ^{213}Bi radionuclide purity can be made even higher.

2.5 Other prospective medical radionuclides obtained in the linear accelerator at INR RAS

The production of strontium-82 and actinium-225 in the accelerator at INR RAS has practically no competitors in Russia in terms of productivity and is quite competitive abroad. However, there are a number of other radionuclides whose production prospects at INR RAS are problematic, since there is strong competition with products obtained by other methods, or the practical application of these radionuclides is not yet sufficiently developed.

Tin-117m. This radionuclide is extremely promising for both the diagnosis and therapy (theranostics) of a number of oncological diseases, as well as atherosclerosis [39]. When decaying, it emits gamma quanta with an energy of 159 keV, which is convenient for registration with common medical SPECT tomographs.[1] At the same time, this radionuclide, which has an optimal half-life of 14.0 days and emits monoenergetic Auger electrons with energies of 127, 129, and 152 keV with a range in living tissues of 0.2–0.3 mm, is also promising for immunotherapy. Tin-117m of relatively low specific activity (i.e., with a stable tin carrier) can be produced in a high-flux neutron reactor (SM-3), but such a product has only limited applications. INR RAS with the participation of BNL, Lomonosov Moscow State University, and IPPE JSC conducted a series of studies [40–42] and developed target and radiochemical technologies for obtaining ^{117m}Sn by irradiating targets of metallic antimony [43] or intermetallic TiSb [44, 45] with protons. A number of samples obtained (see Table 3) were sent to the USA for testing. However, clinical trials in humans have not been completed there, and tin-117m is used only for the treatment of animals. This is holding back the start of mass production. The studies have shown that, due to the possible presence of an ^{113}Sn isotope impurity, the target product ^{117m}Sn is better obtained using available cyclotrons with proton energies of about 70 MeV (see Table 2), and not at the INR RAS accelerator. In addition, ^{117m}Sn with high specific activity can also be obtained with alpha-particle accelerators from targets enriched in ^{116}Cd by the nuclear reaction $^{116}\mathrm{Cd}(\alpha, 3\mathrm{n})$, and the chemical separation of tin in this case is much easier. However, such accelerators are not enough for mass ^{117m}Sn production. Therefore, INR RAS technology may be in demand in the future.

Germanium-68. This radionuclide ($T_{1/2} = 271$ days) has long been in demand on the world market. It is used to calibrate PET tomographs and manufacture medical generators of short-lived ^{68}Ga ($T_{1/2} = 68$ min), which are increasingly used for PET diagnostics of oncological and a number of other diseases. It is especially promising to use ^{68}Ga together with the therapeutic isotope ^{213}Bi, which is obtained from an $^{225}\mathrm{Ac}/^{213}\mathrm{Bi}$ generator, because in many chemical systems the behavior of trivalent gallium and bismuth is similar [46]. INR RAS obtained ^{68}Ge as a by-product when irradiating targets of metallic gallium (in a niobium shell) or intermetallic compound GaNi with degraded low-energy (about 30 MeV) protons simultaneously with the production of strontium-82, which is produced by irradiating rubidium targets at higher proton energies. In view of the significant scattering of degraded protons in energy, as well as in the angle of incidence on the target, the yield at the INR RAS facility was low. Thus, the level of competition with production in the 23-MeV low-energy proton accelerator at Cyclotron Co., as well as in foreign accelerators, turns out to be fairly high.

Palladium-103. ^{103}Pd ($T_{1/2} = 17$ days) can also be obtained at INR RAS as a by-product of strontium-82 production [47], since in the proton energy range of 100–160 MeV the cross sections of the reactions $^{107,109}\mathrm{Ag}(\mathrm{p}, x\mathrm{n}, y\mathrm{p})^{103}\mathrm{Pd}$ are rather high, and this range is not used for the production of strontium-82. ^{103}Pd possesses X-ray radiation with an energy of 20.6 keV. It is used to manufacture cylindrical metal seed sources for prostate therapy and is mainly produced in cyclotrons with low-energy protons or deuterons according to the reactions $^{103}\mathrm{Rh}(\mathrm{p}, \mathrm{n})$ and $^{103}\mathrm{Rh}(\mathrm{d}, 2\mathrm{n})$ using metal rhodium targets. Irradiation of silver targets using the INR RAS accelerator produces a large amount of ^{103}Pd, but it is heavily contaminated with another, relatively short-lived, isotope, ^{100}Pd (3.7 days). The latter has intense gamma lines of 74, 84, and 126 keV, which is considered harmful for medical use. It is possible to keep the product until a sufficiently complete decay of ^{100}Pd, but then the residual activity

[1] Single-Photon Emission Computed Tomography (SPECT) — a type of emission tomography; diagnostic method for creating tomographic images of the distribution of radionuclides.

of ^{103}Pd is not high. Nevertheless, in some cases, the presence of ^{100}Pd may even be useful. The treatment can be carried out not with the help of seeds themselves but with the introduction of albumin microspheres [48] containing ^{100}Pd, which, after the decay of the radionuclide, dissolve in the human body. Then, with palladium-100, it is possible to determine the localization of these microspheres. However, such promising medical technologies have not yet been developed. In addition, recently, seeds with iodine-125 have become widespread, which are cheaper and in some cases preferable. Within the framework of a research program with LANL and BNL, INR RAS developed methods of production and shipped irradiated silver targets for isolation of ^{103}Pd to the Karpov Research Institute of Physical Chemistry and Mayak Production Association (see Table 2). However, this work has not yet met further development.

Selenium-72. Selenium-72 ($T_{1/2} = 8.4$ days) is the initial radionuclide for the generator of daughter arsenic-72 ($T_{1/2} = 26$ h), which has great potential for use in PET diagnostics of a number of oncological diseases [49]. Physical characteristics of the decay of ^{72}As emitting positrons with energies of 2.5 and 3.3 MeV and a variety of chemical properties make ^{72}As attractive for the synthesis of various radiopharmaceuticals. ^{72}Se can be produced using protons, deuterons, and α-particles with different energies using different targets. We obtained selenium-72 by the most productive method via the reaction ^{75}As(p, 4n)^{72}Se using thermally stable gallium arsenide targets in a niobium shell, followed by the gas-chemical separation of selenium [50]. Later, BNL also began to develop this area [51]. There, as well as at other centers, an efficient ^{72}Se/^{72}As generator and ^{72}As-based radiopharmaceuticals are being actively developed. However, these developments are still far from regular mass use in medicine.

Copper-64 and 67. ^{64}Cu ($T_{1/2} = 12.7$ h) is a promising isotope for theranostics. When decaying, this radionuclide emits both β^-- and β^+-particles, and, therefore, it can be used simultaneously for therapy and PET diagnostics. In collaboration with the University of Milan and Lasa Laboratorios LLC, we investigated the formation of ^{64}Cu in targets of metallic zinc irradiated by 31–141-MeV protons at the INR RAS accelerator [52]. In this case, another β^--active isotope of copper, ^{67}Cu ($T_{1/2} = 62$ h), is also produced, which is used in the therapy of oncological diseases. Both of these radionuclides, ^{64}Cu and ^{67}Cu, are already in demand by medicine, but they are not yet used in Russia, and due to their high cost and short half-life, it is irrational to transport them abroad. In addition, in some centers abroad, ^{64}Cu is obtained by a simpler, albeit less productive, method, namely, by irradiating enriched nickel-64 (only 0.9% in the natural mixture) with deuterons, the nuclear reaction being ^{64}Ni(d, 2n).

Radium-223. This radionuclide ($T_{1/2} = 11.4$ days) has already found wide application in different countries, including Russia, in the form of Xofigo® [53] for α-therapy of prostate cancer with bone metastases and other diseases. ^{223}Ra is obtained by irradiation of metallic thorium even in larger quantities than ^{225}Ac [26]. According to calculations, in the proton energy range of 60–140 MeV for 10 days of irradiation with a current of 100 μA and after decay within 16 days, 165 GBq (4.5 Ci) of radium-223 can be produced. We have developed a chemical technique for the separation of radium from metallic thorium [54]. However, it turns out that extracting this radionuclide from the decay products of ^{227}Ac ($T_{1/2} = 22$ years), which is formed by irradiation of ^{226}Ra by thermal neutrons in a reactor, is many times cheaper and more efficient than in the INR RAS accelerator.

Protactinium-230 and Uranium-230. ^{230}Pa ($T_{1/2} = 17.4$ days), like ^{223}Ra, appears as a by-product during the production of ^{225}Ac in a metallic thorium target. ^{230}Pa decays with a partial probability of 7.8% into ^{230}U ($T_{1/2} = 20.8$ days), which seems to be a promising new radionuclide for α-therapy. It can also be used for the generation of daughter thorium-226 ($T_{1/2} = 31$ min) [55]. The advantage of ^{230}Pa and ^{230}U is that they can be obtained in accelerators with a lower accelerated proton energy of 70 MeV or below (see Table 2). However, when thorium is irradiated at the INR RAS facility (taking into account decay at the time of consumption), uranium-230 is formed in quantities that are an order of magnitude less than actinium-225. Thorium-226 has a significantly shorter half-life than bismuth-213, which is obtained from actinium-225. Radiopharmaceuticals based on ^{230}U and ^{226}Th have not yet been developed. In addition, ^{230}Pa, ^{230}U, and ^{226}Th decay into long-lived ^{210}Pb ($T_{1/2} = 22$ years), which decays into ^{210}Po, the uptake of the radionuclides of which into the human body is undesirable. For these reasons, the regular production of protactinium-230 and uranium-230 at INR RAS is still problematic, although it is possible at other accelerators.

In principle, the accelerator at INR RAS can also produce many other promising and already in-demand medical isotopes, for example, thallium-201, iodine-123, 124, 125, and 131, titanium-44 (as a generator for scandium-44), and even molybdenum-99 (for a technetium-99m generator). However, their production in the linear accelerator of the Institute of Nuclear Research, RAS, even as by-products, seems to be uncompetitive in comparison with production by other methods.

3. Most important fields of research for fundamental science and technology

The first experiment at a linear accelerator in Troitsk for applied purposes was carried out back in 1989 (see Table 1), when protons from the first resonator were accelerated only to an energy of 20 MeV. In cooperation with the AvtoVAZ and ZiL factories, we carried out experiments on the surface activation of industrial materials to study the process of wear in parts of combustion engines [56]. It was assumed that this use would develop when it became possible to implant radioactive heavy ions at a given depth. These plans were not destined to come true. However, research was carried out on the production and use of various isotopes for technical and scientific purposes.

The first isotope for technical use, produced commercially in 1994 at a facility with a 160-MeV proton beam, was **cadmium-109**. This radionuclide is used, in particular, as a source of 22.5-keV X-ray radiation in X-ray fluorescence analysis. The measured cross sections for the formation of cadmium-109 and theoretical calculations have shown that, in the nuclear reaction ^{115}In(p, 7n) and in other reactions with 80–140-MeV protons, this product can be obtained with a yield of about 10 MBq μA^{-1} h^{-1} (0.3 mCi μA^{-1} h^{-1}), which is many times higher than that of cadmium-109 in reactions with 800-MeV protons in LANL, and then isolated chemically using different methods [57, 58]. Samples of ^{109}Cd with an activity of up to 30 GBq (800 mCi) were obtained by irradiating metallic indium targets in a linear accelerator with subsequent isolation of the desirable radionuclide at the State

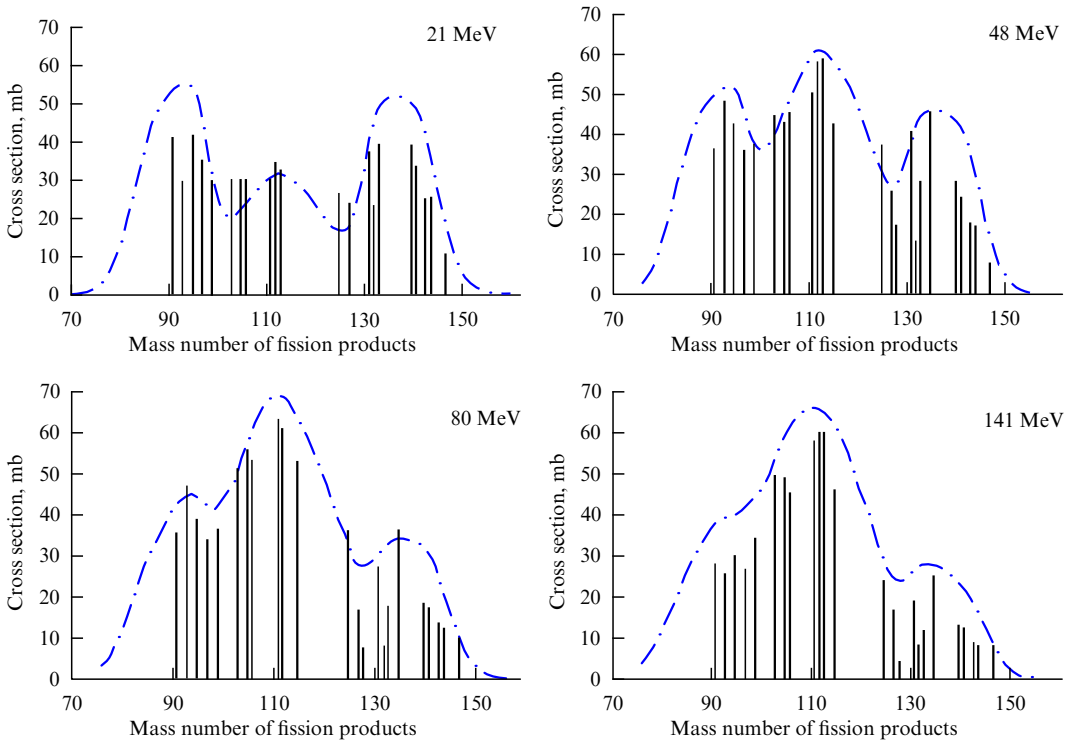

Figure 6. Mass distribution of products of ^{232}Th fission by accelerated protons with different energies. Results of experiment and calculation (dashed line) using the cascade–evaporation–fission (CEF) model [69].

Institute of Applied Chemistry (GIPH) (St. Petersburg), and then supplied abroad (see Table 3). There are competing methods for obtaining this radionuclide. ^{109}Cd (with a carrier) is produced in large quantities by irradiating enriched ^{108}Cd (0.89% in the natural mixture) in nuclear reactors. In the carrier-free state, ^{109}Cd is obtained by irradiating metallic silver (^{109}Ag) targets in accelerators with low proton or deuteron energies. Such production is organized in Russia at the Cyclotron Co. (Obninsk) [59, 60]. Therefore, in the future, it is advisable to produce cadmium-109 at the INR RAS LA only as a by-product in the production of other radioisotopes.

At about the same time, we began to produce sodium-22 (see Table 3) as a by-product in the production of the main medical radionuclide strontium-82. To reduce the proton energy when strontium-82 is produced in a beam with an initial proton energy of 160 or 143 MeV to the optimal one (about 100 MeV at the INR RAS facility), aluminum degraders are usually used. In the aluminum target, the nuclear reaction ^{27}Al(p, α2n) occurs with the formation of ^{22}Mg ($T_{1/2} = 3.9$ s), which decays into ^{22}Na ($T_{1/2} =$ 2.6 years). This neutron-deficient isotope is a long-term source of 0.5-MeV positrons and a source of monochromatic gamma radiation with an energy of 1274.5 keV. Sodium-22 is used in technology to determine the thickness of metal parts and to calibrate radiation measurements, as well as in various scientific research, including the study of positronium and the study of decoherence of annihilation photons [61]. The maximum activity of sodium-22 in the aluminum target supplied from INR RAS was 23 GBq (620 mCi). Sodium-22 is also produced using low-energy protons via the reaction ^{24}Mg(p, 3n). At INR RAS, sodium-22 remains a by-product.

Rubidium-83 ($T_{1/2} = 86$ days) is a radionuclide that is of great interest for various physical studies. It is used as a generator of a short-lived isomer of ^{83m}Kr ($T_{1/2} = 1.8$ h), emitting monoenergetic electrons, and which is released from thin sources of rubidium-83 when heated. ^{83}Rb was produced in a linear accelerator, irradiating strontium fluoride targets, and this radionuclide was obtained in the form of thin sources using high-temperature gas-chemical methods. INR RAS has successfully used such sources in the setup to determine the neutrino mass [62]. They were also used in experiments at the Alikhanov Institute of Theoretical and Experimental Physics (ITEP) in an attempt to detect dark matter by the method described in Ref. [63].

But, most of all in nuclear physics research, the Isotope Target Irradiation Facility at INR RAS is used to measure cross sections for the formation of various radionuclides under irradiation with protons of different energies. These studies are important for both fundamental and applied purposes.

Notably, based on the systematics for isomeric ratios obtained by measuring cross sections for the formation of radionuclides on a tantalum target [65, 66], it was possible to estimate the cross sections for the yield of the medical radionuclide ^{117m}Sn (see above) and impurity targets containing antimony [40–42]. In some cases, this system gives better agreement with experimental data than the well-known modern statistical model TALYS [67].

The measured cross sections for producing ^{74}As, ^{68}Ge, and ^{60}Co under irradiation with protons in germanium were used to calculate the background from radioactive isotopes produced by nuclear muon cascades of cosmic rays in experiments on the search for a neutrinoless twin of ^{76}Ge beta decay [68].

When a thorium target is irradiated with protons of various energies, the radionuclides ^{225}Ac, ^{223}Ra, ^{230}Pa, and ^{230}U for medical purposes are formed. However, the study of the cross sections for the formation of many other radio-

Table 6. Annual production of some radionuclides for medical purposes (at the time of consumption) in the existing linear accelerator and a future cyclotron with a proton energy of 120 MeV.

Radionuclide	Application	Half-life	Annual production, GBq (Ci)		Number of patients per year (new cyclotron)
			Linear accelerator	New cyclotron	
^{82}Sr	PET diagnostics (cardiology)	25.5 days	1100 (30)	20,000 (540)	1,000,000
^{225}Ac	Therapy (oncology)	9.9 days	900 (24)	6000 (160)	10,000
^{117m}Sn	Therapy, γ-diagnostics (bone oncological, cardiovascular diseases)	14 days	300 (8)	1100 (30)	6000
^{68}Ge	PET diagnostics (oncology)	287 days	100 (3)	20,000 (500)	1,000,000
^{103}Pd	Therapy (prostate, breast, liver cancer, rheumatoid arthritis)	17 days	7000 (200)	30,000 (800)	10,000
^{72}Se	PET diagnostics (oncology)	8.5 days	1000 (27)	4000 (100)	100,000
^{67}Cu	Therapy (oncology)	62 h	700 (20)	100 (3)	1000
^{64}Cu	Therapy, PET diagnostics (oncology)	12.7 h	5000 (130)	700 (20)	1000

nuclides in thorium under irradiation with protons is also of interest for the study of the physics of fission [69]. At different energies of protons, competition between symmetric and asymmetric fission is observed (Fig. 6).

4. Prospects of creating a new facility to produce medical isotopes

For more than 25 years, INR RAS has been producing a significant number of isotopes for medical, scientific, and technical purposes. These isotopes are isolated from irradiated targets in various organizations in Russia and abroad, as a rule, using methods developed by INR RAS. The lack of capacity for radiochemical processing on site dramatically reduces the efficiency of production. First, the mastering of techniques by partners always encounters difficulties. At INR RAS — an academic institute — there are opportunities for the detailed scientific study of physical and chemical processes, while in organizations belonging to other departments — the ROSATOM State Corporation and the National Research Center Kurchatov Institute — and in private organizations, these opportunities are limited, and their staff is not focused on this. Bureaucratic procedures also greatly complicate developments with nonstandard technological solutions. As a result, this kind of work is done slowly and not very efficiently. Second, most of the radionuclides produced in the accelerator are short-lived, and transporting highly active irradiated targets over long distances in large containers is expensive, logistically complex, and often irrational. Third, the 'hot' cells available in other organizations, as a rule, are occupied with other processes, do not comply with GMP requirements, are heavily contaminated, or are not adapted for postprocessing INR RAS targets, some of which have specific characteristics.

Therefore, the construction of a new radiochemical laboratory at INR RAS seems to be absolutely necessary for the efficient production of radionuclides. The design for such a laboratory was approved back in 2007, but it has not been possible to start construction yet.

But besides providing radiochemical release, it is important to increase the potential for the production of radionuclides at the accelerator. The INR RAS linear accelerator was originally aimed mainly at meson studies. Isotope research, development, and production should be further developed based on a specially built new-generation accelerator, preferably a cyclotron, which provides a continuous rather than pulsed beam. This improves the stability of the targets during irradiation. Plans for the construction of a new accelerator at INR RAS to supply the world market with strontium-82 and other isotopes were announced back in 2005. Since then, several accelerators with a proton energy of 70 MeV have already been put into operation or are being built abroad. Therefore, at present, it seems more rational to build a new cyclotron with a proton energy of at least 120 MeV and a total current in one or two extracted beams of about 700 μA. There is no such accelerator in the world yet. The new cyclotron could be used to organize the large-scale production of actinium-225, strontium-82, and other radionuclides. Moreover, strontium-82 could be produced using a new technology with a circulating liquid rubidium target and 'online' extraction of ^{82}Sr [11], which can greatly increase productivity.

In the future, on the territory of INR RAS in Troitsk, it is possible to set up a laboratory for charging medical generators, equipped in accordance with GMP requirements.

Table 6 shows the potential to produce the most important medical radionuclides at the existing linear accelerator and a future accelerator at INR RAS, as well as the number of patients whose diagnosis and treatment will be ensured using isotopes produced at the new cyclotron with a proton energy of 120 MeV.

5. Conclusion

During the development of isotope research for more than 30 years, INR RAS has made great progress both in fundamental research and in the mass production of medical radionuclides based on this research.

The Institute has developed effective cooperation with many institutions in Russia and abroad. Together with its partners, INR RAS went through all the stages, from the original idea and scientific substantiation of the development to the widespread application of the final product.

Significant progress in the future is possible with the construction of new modern facilities for the radiochemical separation of various radionuclides and a cyclotron for their efficient production at INR RAS. However, the realization of this potential requires a significant revision of the development strategy for the production of medical radioisotopes in the country [9].

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