

*Form of opening (renewal) for Project***APPROVED****JINR DIRECTOR**

/

" _____ " _____ **202** г.**PROJECT PROPOSAL FORM**

Opening/renewal of a research project within the Topical plan of JINR

1. General information on the research project of the theme**1.1 Theme code / LRIP (for extended projects): 04-2-1132-2017****1.2 Project (for extended projects)****1.3 Laboratory: DLNP****1.4 Scientific field: 6 – Life Science****1.5 Title of the project: Further development of methods, technologies, schedule modes and provision of radiotherapy****1.6 Project leader: G.V. Mytsin****1.7 Project deputy leader: S.V. Shvidkiy****2. Scientific case and project organization****2.1 Annotation**

The project assumes continuation of the research started at the DLNP JINR back in 1967, when, under the leadership of V.P. Dzhelepov, the first proton beam for biomedical research in the USSR and Eastern European countries was formed. By the end of the 90s of the last century, a Medical-technical complex was created here on the basis of a 660 MeV proton accelerator, Phasotron, where about 1300 patients underwent a course of fractionated proton therapy from 2000 to 2019. The irradiation was carried out using the developed technique of three-dimensional conformal proton radiation therapy, in which the maximum of the formed dose distribution most accurately corresponds to the shape of the irradiated target. At the same time, the dose drops sharply beyond the boundaries of the neoplasm, which makes it possible to irradiate tumours that were not previously available for radiotherapy, closely adjacent to the vital radiosensitive organs of the patient.

With the Phasotron shutting down in March 2023, it is planned to reorient biomedical research to a linear electron accelerator (LINAC-200), on which it is supposed to form an electron beam with an energy of 20-25 MeV for irradiation of cell cultures and small laboratory animals (mice, rats).

Currently, JINR has already begun work together with the D.V. Efremov "NIIEFA" (St. Petersburg) on the creation of the MSC-230 superconducting proton cyclotron, which will become the basic installation for conducting radiobiological, as well as experimental and clinical studies in the

field of proton therapy in the future. It is assumed that the accelerator will be able to provide the output of a beam with an ultra-high dose rate (up to 10 μA per pulse), which will allow irradiating biological objects, and subsequently patients, in the so-called flash mode, when the dose required for tumor sterilization is supplied in just a few tens of milliseconds. As the results of a large number of experiments conducted around the world show, such a regime turns out to be the most sparing for healthy tissues entering the irradiation field.

The project assumes the following works necessary for the creation of the center and its successful functioning: participation in the preparation of the project of the center building with all relevant premises, calculation of the beam transportation channel to irradiation facilities, development and manufacture of detectors for the dosimetric support of flash therapy, development and approbation of all technological stages of planning and proton therapy delivery.

It is also planned to continue a broad program of research in the field of radiobiology that meets the most popular needs of both clinical radiology and such as determining the degree and mechanisms of influence of the effects of various types of ionizing radiation on the central nervous system of animals.

2.2 Scientific case (aim, relevance and scientific novelty, methods and approaches, techniques, expected results, risks)

Aim of the Project

- Participation in the creation of the JINR innovation center for experimental and clinical research in the field of proton therapy, the main installation of which will be the new proton accelerator MSC-230;
- Formation of an electron beam with an energy of 25 MeV at the DLNP LINAC-200 installation and conducting radiobiological studies on it to study various fractionation schemes of radiotherapy, as well as the effectiveness of the use of various types of radiomodifiers;
- Obtaining new scientific results in the field of studying the effect of ionizing radiation of different quality on the structures and functions of the central nervous system (CNS).

Relevance and scientific novelty

In recent years, intensive research of the flash radiotherapy method has been conducted in the world. In particular, the flash proton therapy method is of great interest to radiologists, since it not only reduces the impact on healthy tissues, but also reduces the number of treatment procedures. Currently, not only preclinical studies are being actively conducted, but clinical trials have already begun: the first patients with bone metastases have been treated. However, before proton flash therapy can be fully implemented in practice, it is necessary to solve a number of engineering and technical problems, in particular, an accelerator is needed that provides an average beam current of about 10 μA per pulse, lasting up to 100 ms. Such parameters are not achievable for serial machines, which are currently equipped with proton therapy centers manufactured by big firms, such as IBA, Varian, etc.

Therefore, the project of creating an innovation center based on the MSC-230 superconducting cyclotron is high-tech and highly demanded by both radiobiologists and clinicians. One of the tasks of this project is just the work on the design and creation of various equipment of this center.

However, the creation of such a center is quite difficult and may take several years. At the same time, due to the shutdown of the DLNP Phasotron accelerator in March 2023, there is practically no stable operating facility at JINR today on which experiments on radiobiology and testing of new detectors being developed for dosimetry of high-intensity beams used for flash therapy could be carried out.

In the project, in order to be able to continue the above-mentioned experiments, it is supposed to form an electron beam with an energy of 20-25 MeV at the installation of the DLNP LINAC-200, which is already close to commissioning. This linear electron accelerator has in its initial section a branch from the beam transport channel, equipped with a vacuum channel, a banding magnet and a

focusing lens. The beam energy in this place is quite sufficient both for irradiating cell cultures and for irradiating small laboratory animals (mice, rats), since its range is about 5 cm of water. The maximum current of this beam is planned to be obtained in fractions of mcA, which, in principle, can allow the formation of a high-intensity electron beam with a diameter of 1-2 cm to conduct research on the radiobiological basis of the flash effect.

One of the main tasks of radiation therapy is to deliver a therapeutic dose of radiation to the tumor while preserving the healthy tissues surrounding it. The main efforts are focused in two directions: bringing the delivered dose in accordance with the volume of the tumor and increasing the sensitivity of the tumor to therapeutic radiation. Proton therapy successfully copes with the task of matching the delivered dose with the tumor form due to the high degree of consistency of the dose distribution of proton beams. This leads to a reduction in side effects and a lower integral dose compared to conventional photon therapy.

One of the options for radiosensitivity is an artificial increase in energy release in the tumor. In particular, the effect of radiotherapy can be further enhanced through the use of nanoscale radiosensitizers. An increase in the absorbed dose is achieved by introducing or delivering substances into tumor cells with a significantly larger radiation absorption cross-section than in normal cells. These are chemical elements with a high atomic number (Z), more than 52 (I, Gd, Au, Pt, etc.). Due to the greater probability of interaction of such elements with radiation, it is possible to achieve a local increase in the absorbed dose in the area of accumulation of a substance with a high atomic number. The resulting secondary short-range radiation localizes energy release near these elements and affects only nearby biological structures.

In our earlier studies of the use of gold nanoparticles as a radiosensitizer when irradiating tumor cells of human lung carcinoma A 549 with gammas from the ^{60}Co source and the therapeutic proton beam of the Phasotron of the DLNP, the expected positive effect was clearly observed. Unfortunately, both of these sources of ionizing radiation have become unavailable today. Therefore, we are faced with the task of transferring all previously developed techniques to experiments with the electron beam being created. The same applies to studies to identify the laws of the flash effect, conducted in recent years on a high-current Phasotron beam.

Experimental data indicate a high radio sensitivity of certain parts of the brain to the effects of heavy charged high-energy particles. However, to date, many aspects of the manifestation of neurophysiological effects of exposure to ionizing radiation with different physical characteristics remain unclear.

In recent years, within the framework of the project, new scientific results have been obtained in the field of studying the effect of ionizing radiation of different quality on the structures and functions of the central nervous system (CNS). Thus, a comparison of various molecular mechanisms associated with radiation damage to the central nervous system, in conjunction with functional changes at the level of behavior, as well as with molecular mechanisms potentially relevant for the development of promising drug countermeasures against the negative effects of ionizing radiation. Radiation-induced neurochemical changes are considered in the appendix to the problem of assessing ergonomic risk for astronauts in conditions of long-term flights associated with exposure to cosmic radiation. In the same aspect, a number of issues related to the mechanisms of radiation damage to the central nervous system functioning at the level of hierarchical networks of the brain have been investigated. The concepts that have prospects of being laid down as the basis for measures that reduce the effect of cosmic types of radiation in conditions of a long manned flight outside the Earth's magnetosphere are formulated.

Computational work has been performed to simulate DNA damage and repair in mammalian cells after exposure to ionizing radiation of different quality using the Geant4-DNA software package. All these promising studies from the point of view of both the accumulation of fundamental knowledge in the field of studying the mechanisms of radiation damage to the central nervous system and the purely practical application of this knowledge are supposed to be continued in the project.

Methods and approaches, techniques

As already noted, today there is not a single proton or photon therapy center in the world that is suitable for conducting full-scale flash therapy in a clinical setting. The creation of such a center in Dubna will be a truly pioneering work, requiring the project executors to carefully study such things as: the choice of circuit solutions for the design of the new building of the center, the calculation and creation of a channel for transporting the proton beam to the treatment rooms, equipping the rooms with all the necessary related equipment (patient positioner, devices for dosimetry, equipment for verification of the patient position) and many others. However, accumulated in the Medical-Technical Complex (MTC) of JINR extensive experience in the formation of therapeutic proton beams and in conducting three-dimensional conformal radiation therapy allows us to hope for the successful implementation of the set work program.

So, together with the Design Bureau of the DLNP, work has already begun to determine the main structure of the future building of the center. It is assumed that in addition to the MSC-230 accelerator itself, it will have two treatment rooms, the first of which will contain both a high-intensity beam for conducting research in the field of flash therapy and a beam with a standard dose rate. In the second room, irradiations are supposed to be carried out by scanning with a narrow pencil proton beam over the volume of the target.

It should be noted that for flash therapy, the most suitable (and perhaps the only possible) is a static technique of irradiation with a wide beam homogeneous in cross-section using beam modifiers: ridge filters, individual shaped collimators and boluses (range shifters). This is explained by the fact that in order to have a flash effect that spares healthy tissues, all irradiation from one direction must be carried out in a time not exceeding 100 ms. It is unlikely that this will ever be possible with the help of dynamic irradiation technique.

Just such a static method of irradiation has been used to irradiate patients in the MTC for almost 20 years, in connection with which a huge experience has been accumulated here: the formation of beams with the necessary characteristics, the development and manufacture of a system for monitoring its parameters, calculations and manufacture of all necessary modifiers, therapy planning, verification of the patient positioning and many other aspects of work.

To date, the channels for transporting the beam to the treatment rooms have already been designed in the first approximation. Transportation losses according to the calculations carried out should not exceed 10-20 %, which is extremely important when forming a high-intensity beam. Also, everything points to the fact that it is quite possible to form in the treatment room a beam of 10-15 cm diameter in cross section (90% of the dose level) with an energy in the range of 100-230 MeV. However, these calculations should be rechecked using various corresponding software packages.

Also, the development of methods for calculating and manufacturing proton beam Bragg peak modifiers using a 3D printer has already begun - ridge filters that allow forming a beam with a flat top at the end of the beam range with a length corresponding to the size of the irradiated tumor, as well as individual boluses (shaped decelerators) that form the posterior drop of the dose field in according to the shape of the target.

For conducting flash therapy, the task of ultrafast control of beam parameters and adequate dose release is extremely important. The fact is that practically all currently manufactured industrial detectors for measuring the dosimetric characteristics of the beam are already nonlinear at a dose rate of 50 Gy/min and higher. The development of appropriate detectors in the MTC is already underway and will be continued in this project.

It seems to us that it is somewhat easier to implement the second direction of work - the formation of an electron beam with an energy of 20-25 MeV and the creation of a stand for conducting radiobiological experiments. But even here there are certain difficulties associated with the creation of a beam parameter control system. This is primarily due to the pulsed structure of the beam generation by the accelerator. According to our data, the maximum pulse repetition frequency can reach 100 Hz, and the maximum duration of the pulse itself does not exceed 3 microseconds, so the intensity of the beam in the pulse will be almost 3 orders of magnitude higher than its average value. In the case of conducting studies on this flash effect beam, the use of detectors capable of operating in a linear mode at high dose rates will also be required.

The beam is supposed to be formed by the double scattering technique in such a way that it is homogeneous in its cross-section in diameter 10-15 cm (90% of the dose level) for irradiation in the mode of standard dose rate (2-3 Gy/min) and 1-2 cm when irradiated in flash therapy mode (dose rate not less than 40 Gy/min).

The list of works planned in the project can be represented by the following list.

The works related to the creation of the center for applied research based on the MSC-230 superconducting cyclotron include:

- Participation in the preparation of project documentation for the creation of a new building for the placement of the MSC-230 accelerator, transportation channels, treatment rooms, technical rooms and related equipment.
- Design and calculation of proton beam transportation channels from the accelerator to the treatment rooms. The work includes the calculation of magnetic optics, the selection of appropriate electromagnetic elements, the preparation of technical requirements for equipment, cooling system, automated control system, etc.
- Development of beam formation techniques in treatment rooms. Design of radiation stands for passive, dynamic and active irradiation methods. Development of methods and technologies for calculating and manufacturing devices for the formation of a therapeutic proton beam, such as ridge filters, aperture collimators, boluses, a multi-leaf collimator and a moderator of variable thickness.
- Supplying treatment rooms with diagnostic and dosimetric equipment. Development and creation of ionization chambers for diagnostics of a high dose rate beam, as well as devices for dosimetric phantom measurements in a water phantom.
- Design of patient positioning and immobilization systems during radiotherapy. Preparation of technical specifications for production.
- Creation of specialized software for monitoring the parameters of the proton beam, control of its formation devices and the patient positioning system. Development of software for radiation planning by various techniques and verification of the patient's position during radiotherapy.

Works related to the implementation of the radiobiological research program on the electron beam of the LINAC-200 linear accelerator include:

- Participation in the work on the formation of the beam after the initial acceleration sections (with an electron energy of 20-25 MeV) for radiobiological studies.
- Creation of a radiation stand with the possibility of placing diagnostic and dosimetric equipment, as well as biological samples and objects at the irradiation site.
- Adaptation of the existing dosimetric equipment of MTC to the technical conditions at the LINAC-200 accelerator. Development and testing of a dose release system.
- Technical support of radiobiological experiments at the LINAC -200 accelerator, monitoring of the parameters of the output beam and its dosimetry.

Research in the field of radiobiology:

- Study of the relative biological efficiency of electrons on the beam of the LINAC-200 linear accelerator by the following methods: study of cell survival (clonogenic analysis); study of cytogenetic damage in cells (micronuclear test); study of the formation of reactive oxygen species.
- Conducting a study of the cytotoxic and cytogenetic effects of electrons on the LINAC-200 linear electron accelerator under irradiation of normal and tumor cultures of human cells in the presence of gold nanoparticles by various methods.
- Conducting studies involving the irradiation of human cell culture with an extremely high dose rate (flash mode) on the linear electron accelerator LINAC-200.
- Comparative study of the kinetics of individual stages of repair of double-stranded DNA breaks using markers of repair protein complexes after exposure protons and accelerated heavy ions. Modeling of DNA damage and repair processes in mammalian and human cells using the Geant4-DNA software package.

- Study of the fundamental properties of DNA repair in certain areas of the brain and their relationship with the metabolism of neurotransmitters after exposure to ionizing radiation of different quality.
- Identification of integrative connections between brain regions after exposure to radiation of different quality based on the analysis of the dynamics of neurotransmitter exchange. To study the role of hierarchical brain networks in functional changes of the central nervous system after irradiation. Application of computational approaches to assessing the dose load on brain neurons under the action of beams of heavy charged particles of high energies.
- Development of models of electrophysiological activity of brain neurons. Development of a neural model of the pathophysiology of radiation damage to brain structures based on the nature of the dynamics of metabolism of neurotransmitters of DA-, NA-, ST-ergic systems in the prefrontal cortex, hippocampus, striatum, nucleus accumbens and hypothalamus.

Expected results

The implementation of the work program outlined in the project will solve the following tasks:

- To create a new innovation center based on the MSC-230 accelerator, designed both for conducting various radiobiological studies and, in the future, for conducting clinical trials of the proton flash therapy technique using the Bragg peak of the beam. There are no installations with such capabilities in the world today.
- To form an electron beam and create a stand for conducting radiobiological experiments at the LINAC-200 installation.
- To continue conducting radiobiological research in a wide range of areas: the use of heavy metal nanoparticles as radiomodifiers during radiotherapy, the study of the radiobiological foundations of the flash effect, studies of the effect of ionizing radiation of various qualities on the structures and functions of the central nervous system, and others.

2.3 Estimated completion date: 2024-2028

2.4 Participating JINR laboratories: DLNP

2.4.1 MICC resource requirements

Computing resources	Distribution by year				
	1 st year	2 nd year	3 rd year	4 th year	5 th year
Data storage (TB) - EOS - Tapes					
Tier 1 (CPU core hours)					
Tier 2 (CPU core hours)					
SC Governorun (CPU core hours) - CPU - GPU					
Clouds (CPU cores)					

2.5. Participating countries, scientific and educational organizations

Organization	Country	City	Participants	Type of agreement
MSU	Moldova	Kishinev	Chumak D.	Agreement
IMBP	Russia	Moscow	Abrosimova A.N. Shurshakov V.A.	Joint work
Burnazyan FMBC	Russia	Moscow	Osipov A.N.	Joint work
ITEB RAS	Russia	Pushchino	Shemyakov A.E. Dyukina A.R.	Joint work
Chernyshevsky SSU	Russia	Saratov	Bucharskaya A.B.	Agreement
iLABS	SA	Faure	Vandevoorde C.	Agreement

2.6. Key partners (those collaborators whose financial, infrastructural participation is substantial for the implementation of the research program. An example is JINR's participation in the LHC experiments at CERN).

3. Manpower

3.1. Manpower needs in the first year of implementation

No.№ n/a	Category of personnel	JINR staff, amount of FTE	JINR Associated Personnel,
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			amount of FTE
1.	research scientists	7	
2.	engineers	7.5	
3.	specialists	2	
4.	office workers		
5.	technicians		
	Total:	16.5	

3.2. Available manpower

3.2.1. JINR staff

No.	Category of personnel	Full name	Division	Position	Amount of FTE
1.	research scientists	Agapov A.V.	PhD DLNP	senior res.	1
		Belokopytova K.V.	PhD DLNP	researcher	1
		Belov O.V.	ОНМИ ЛФБЭ	dep. head of dep.	0.2
		Mytsin G.V.	PhD DLNP	head of dep.	1
		Molokanov A.G.	PhD DLNP	senior res.	1
		Rzyanina A.V.	PhD DLNP	senior res.	0.8
		Shvidkiy S.V.	PhD DLNP	dep. head of dep.	1
		Shipulin K.N.	PhD DLNP	researcher	1
2.	engineers	Alexandrova I.V.	PhD DLNP	engineer	1
		Breev V.M.	PhD DLNP	leading engineer	0.5
		Gaevsky V.N.	PhD DLNP	leading engineer	1
		Griytskova Ye.A.	PhD DLNP	engineer	1
		Gustov S.A.	PhD DLNP	head of group	1
		Klochkov I.I.	PhD DLNP	senior engineer	1
		Pisareva S.A.	PhD DLNP	engineer	1
		Uglova S.S.	PhD DLNP	engineer	1

3.	specialists	Donskaya G.V.	PhD DLNP	senior specialist	1
		Miller I.Ye.	PhD DLNP	specialist	1
4.	technicians				
	Total:			18	16.5

3.2.2. JINR associated personnel

No.	Category of personnel	Partner organization	Amount of FTE
1.	research scientists		
2.	engineers		
3.	specialists		
4.	technicians		
	Total:		

4. Financing

4.1 Total estimated cost of the project: 160 000 USD

The total cost estimate of the project (for the whole period, excluding salary).

The details are given in a separate table below.

4.2 Extra funding sources

Expected funding from partners/customers – a total estimate.

Project Leader _____/ G.V. Mytsin /

Date of submission of the project to the Chief Scientific Secretary: _____

Date of decision of the laboratory's STC: _____ document number: _____

Year of the project start: _____

(for extended projects) – Project start year: _____

Proposed schedule and resource request for the Project / LRIP subproject

Expenditures, resources, funding sources		Cost (thousands of US dollars)/ Resource requirements	Cost/Resources, distribution by years					
			1 st year	2 nd year	3 rd year	4 th year	5 th year	
	International cooperation	50	10	10	10	10	10	
	Materials	60	12	12	12	12	12	
	Equipment, Third-party company services	50	10	10	10	10	10	
	Commissioning							
	R&D contracts with other research organizations							
	Software purchasing							
	Design/construction							
	Service costs (<i>planned in case of direct project affiliation</i>)							
Resources required	Standard hours	Resources						
		– the amount of FTE,	92,5	16,5	16,5	16,5	16,5	16,5
		– accelerator/installation,	DLNP LINAC 150	30	30	30	30	30
		– reactor,...						
Sources of funding	JINR Budget	JINR budget (<i>budget items</i>)	160	32	32	32	32	32
	Extra funding (supplementary estimates)	Contributions by partners Funds under contracts with customers Other sources of funding						

Project (LRIP subproject) Leader _____/_____/

Laboratory Economist _____/_____/

APPROVAL SHEET FOR PROJECT

TITLE OF THE PROJECT

Further development of methods, technologies, schedule modes and provision of radiotherapy

SHORT DESIGNATION OF THE PROJECT / SUBPROJECT OF THE LRIP

PROJECT/LRIP SUBPROJECT CODE

THEME 04-2-1132-2017

NAME OF THE PROJECT: G.V. Mytsin

AGREED

JINR VICE-DIRECTOR

SIGNATURE NAME DATE

CHIEF SCIENTIFIC SECRETARY

SIGNATURE NAME DATE

CHIEF ENGINEER

SIGNATURE NAME DATE

LABORATORY DIRECTOR

SIGNATURE NAME DATE

CHIEF LABORATORY ENGINEER

SIGNATURE NAME DATE

LABORATORY SCIENTIFIC
SECRETARY

SIGNATURE NAME DATE

THEME LEADER

SIGNATURE NAME DATE

PROJECT LEADER

SIGNATURE NAME DATE

APPROVED BY THE PAC

SIGNATURE NAME DATE

