Form № 21

APPROVED BY
JINR Vice Director

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SCIENTIFIC AND TECHNICAL JUSTIFICATION FOR EXTENDING THEME
to be included in the
TOPICAL PLAN FOR JINR RESEARCH FOR 2020–2022

Theme code: 04-2-1132

Laboratory of Nuclear Problems
Phasotron Division

Research area: 04 – Condensed Matter Physics, Radiation and Radiobiological Researches

Theme title: «The Biomedical and Radiation-Genetic Studies using Different Types of Ionizing Radiation»

Theme leader – G.V. Mytsin

Abstract:

The main aim of the Theme is the conducting of medical-biological and clinical research on the basis of the Medico-Technical Complex (MTC) of DLNP JINR Phasotron, to study the effectiveness of hadron radiotherapy for treatment of various neoplasms, modernization of the equipment and devices and development of new methods of radiotherapy for cancer patients at the medical hadron beams from the JINR Phasotron. Also, research is planned in the field of radiobiology and molecular genetics, aimed at both obtaining new knowledge in the relevant fields of science, and the practical use of the results of these studies to improve the effectiveness of radiotherapy, as well as to reduce the side effects that arise during its conducting.

By now, the Medico-Technical Complex has been established and operates at the Laboratory of Nuclear Problems JINR, on the basis of the 660 MeV proton accelerator (Phasotron) where therapeutic exposure can be conducted of patients with various neoplasms using the method of 3D conformal proton beam radiotherapy when the maximum of the formed dose distribution conforms most accurately to the shape of the irradiated target. The dose decreases sharply beyond the borders of the neoplasm that allows conducting the irradiation of inaccessible for earlier radiotherapy localizations that are very close to vital radiosensitive organs of the patient.

In 1999 a specialized Radiological Department of Health Care Facility № 9 of FMBA (Dubna, Russia) was opened in the city that provided an extension of clinical research in hadron therapy for cancer patients at medical beams of JINR. For example, in the period from 2000 to April 2019, 1287 patients with various neoplasms (including foreign citizens from JINR Member States) underwent courses of proton radiotherapy at the Phasotron beams.

Irradiation was usually carried out fractionated (on average about 10-20 sessions per patient) and from several directions. Thus, the total number of fields (single therapeutic exposures) annually was about 5000. The DLNP accelerator was used for these studies for about 900 hours a year.

The activities proposed in the project for the coming 3 years are logical continuation of medical biological and radiation-genetic research conducted lately, maintaining the basic aims of the studies and the number of participating institutions.

So far, over 200000 patients in more than 80 centres all over the world have received treatment at proton beams. The results of these clinical studies have clearly shown that proton therapy is a very effective method of treatment of cancer and some other diseases, and in some cases it is almost no alternative. Thanks to this accumulated positive experience, by the end of the last century, specialized proton therapy centers were being built at large radiological clinics. Today in the world there are several dozens of projects to create such centers at different stages of implementation.

At the same time, methodic issues of delivering the dose to the abnormal focus, fixing and centering adjustment of the patient and some other aspects have not been solved to the full as for today and are open for further research. The main purpose of the project for the 2020-2022 will be the development of methods of patients' irradiation with a proton beam that will provide the highest degree of conformability of the dose field for the irradiated target. Clinically it will show in a decrease of the dose that arrives at healthy tissues and organs surrounding the target and in general growth of efficiency of the conducted therapy.

In the field of radiobiology, research will continue to determine the forms of fibroblast cell death depending on the dose of ionizing radiation. In order to clarify the mechanism of radioprotective action of laser radiation on biological objects, it is supposed to determine the ratio of forms of cell death after exposure to ionizing radiation, as well as after combined exposure to ionizing radiation and laser radiation. It is planned to identify new mechanisms of combined methods of tumor cell damage using metal nanoparticles and to identify their role in enhancing the effect of γ-rays and protons on tumor cells. Studies will be conducted on the patterns and mechanisms of functional and neurochemical disorders in the Central nervous system of laboratory animals under the action of radiation with different values of linear energy transfer.

It is also planned to continue molecular genetic studies that track changes in the structure of animal and human genes caused by exposure to ionizing radiation with different values of linear energy transfer. The main objectives are: 1) study of the molecular nature of structural changes of the gene without and in association with the aberration rupture during inversions and translocations in the genome of sperm cells of male Drosophila melanogaster induced by γ-radiation and neutrons using a set of methods, including In situ hybridization and filtering Southern, polymerase chain reaction (PCR) and sequencing and carrying out general genomic analysis of radiation-induced DNA changes in the offspring of the first generation from irradiated males after the action of γ-radiation in different doses, using the shotgun sequencing method with a comparison of the results obtained with similar literature data in mice; 2) To study the transcript (a set of all RNA) in the control Drosophila lines contrasting in radiosensitivity using the device Afimetrix equipment.

List of activities:

Clinical research:

- To continue clinical studies on proton therapy of various neoplasms at the JINR Phasotron beams in treatment room Num. 1 (after receiving all permits from the Ministry of Health of the Russian Federation).
- To carry out a statistical analysis of the results of proton therapy clinical studies on the irradiation of patients with different diagnoses.

Development and upgrade of proton therapy methods:

- Further development and construction of equipment for dynamic conformal proton beam irradiation of deep seated targets will be continued, including the creation of a computer-controlled moderator of variable thickness and a full-scale version of a multileaf collimator.
- It is supposed to design and construct a computerized dose control system for proton therapy.
- Work will continue to expand the functionality of the three-dimensional conformal proton radiotherapy planning software being developed at the MTC and its clinical testing in irradiation sessions.

Dosimetry and microdosimetry of therapeutic hadron beams:

- Activities will be continued on LET spectra measurements of clinical proton beam of DLNP Phasotron with Si detectors Liulin and Medipix.
- During radiotherapy, in devices of proton beam forming secondary particles appear, in particular neutrons and photons that irradiate surrounding healthy tissues. Doses from such fields should be minimized as they can lead to negative effects, up to formation of secondary radiation-induced tumours. Work is planned at the medical proton beam of the Phasotron to measure background conditions in the proton therapy room. Such measurements will also be conducted at the scanning clinical proton beam in the Proton Therapy Center in Prague (PTC). The obtained data will be compared with the results of measurements at the proton beam DLNP JINR.

Radiobiology:

- Continuation of studies to determine the forms of fibroblast cell death depending on the dose of ionizing radiation. To study the lethal effect of laser radiation with a wavelength of 532 nm on the survival of fibroblast cells. In order to clarify the mechanism of radioprotective action of laser radiation (633nm and 532 nm) on biological objects to determine the ratio of forms of death after exposure to ionizing radiation, as well as after the combined effect of ionizing radiation and laser radiation.
- Study of the effects of increased cytotoxic effects of radiation therapy in the presence of metallic nanoparticles in animal cells. Determination of characteristics of radiation produced during radiotherapy (with and without nanoparticles) inside cells. These parameters can be calculated with a high degree of accuracy based on measurements with the Timepix-3 detector. Identification of new mechanisms of combined methods of treatment of tumor cells using metal nanoparticles and identification of their role in enhancing the effect of γ-rays and protons on tumor cells.
- Study of regularities and mechanisms of functional and neurochemical disorders in the central nervous system under the action of radiation with different values of linear energy transfer. Obtaining comparative data on the laws of induction of functional disorders in the brain structures under the action of rare and dense ionizing radiation used in the treatment of cancer diseases. Search and study of drugs with neuroprotective effect to the influence of ionizing radiation of different quality.

Molecular genetics:

- Molecular genetic analysis of gene structural changes: analysis of gene mutations associated with aberration rupture, genomic analysis of inherited DNA changes, transcriptome (RNA) analysis of *D. melanogaster*.

Results expected upon completion of the theme.

The implementation of the planned programme will give evaluations of the hadron therapy efficiency for a number of neoplasms, practical recommendations will be issued on the choice of optimal variants of radiation treatment of oncological patients and further development of radiotherapy methods with the use of hadron beams, new means and methods will be elaborated and tested of irradiation of oncological patients at these beams.

New experimental and fundamental results will be obtained in the field of radiobiology and Molecular genetics as well.

Participants from DLNP JINR.

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Participating countries, institutes and organizations.

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RMANPO HM RF (Moscow, RF) – Ye.V. Kizhaev

IMBP FMBA RF (Moscow, RF) – A.N. Abrosimova

FMBC FMBA RF (Moscow, RF) – A.N. Osipov

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SFU (Rostov-on-Don, RF) – V.A. Chistyakov

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Firm “Advacam” (Prague, Czech Republic) – K. Granya, C. Oanchea

IFIN-HH (Magurele, Romania) – D.I. Savu, C. Oanchea

iThemba LABS (Faure, SAR) – K. Slabbert

Time frame of the theme: 01.01.2020 – 31.12.2022 гг.

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Proposed timetable and necessary resources on the Theme 04-2-1132
«The Biomedical and Radiation-Genetic Studies using Different Types of Ionizing Radiation»
for the period 2020-2022

Name of units and systems of equipment, resources, sources of financing	Costs of parts (th. dollars); resources needed (hours)	Proposals for the funding and resources		
		1 year	2 year	3 year
Main parts and equipment				
1. Materials and equipment for radiotherapy	21	7	7	7
2. Equipment for dosimetry of hadron beams	12	4	4	4
3. Materials and equipment for radiobiological researches	12	4	4	4
4. Materials and equipment for molecular-genetic researches	96	34	34	28
Resources needed (hours)				
DLNP Phasotron	2700	900	900	900
DLNP Workshop	500	500		
Source of financing				
JINR budget	141	49	49	43
Extrabudget	0	0	0	0

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Cost estimates by the Theme 04-2-1132
«The Biomedical and Radiation-Genetic Studies using Different Types of Ionizing Radiation»
for the period 2020-2022

NN	Costs item	Total expenses	1 year	2 year	3 year
1.	DLNP Phasotron	hours	900	900	900
2.	DLNP Workshop	hours	500		
3.	Materials	th. dollars	33	33	33
4.	Equipment	th. dollars	16	16	10
5.	Travel expenses	th. dollars	13	13	13
	Total cost:	180	62	62	56

AGREED:

JINR Chief Scientific Secretary

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"_____" _____ **2019**

Laboratory Director

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"_____" _____ **2019**

Head of Planning and Finance Department

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"_____" _____ **2019**

Laboratory Scientific Secretary

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Head of Science Organization Department

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"_____" _____ **2019**

Laboratory Economist

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Theme leader

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"_____" _____ **2019**