Biomedical Research Center for Proton Therapy of Oncological Diseases in Dubna

Annotation

JINR has accumulated half a century of experience in treating cancer patients with proton beams of the phasotron, as well as in the field of development and creation of specialized accelerators for these purposes. The latest results of the study in LRB of the action of proton beams on various biological objects in order to study the patterns and mechanisms of the formation of molecular disturbances in the genetic apparatus of human and animal cells promise a breakthrough in the effectiveness of using proton beams for the treatment of cancer. This creates the conditions for the establishment of a research biomedical center for proton therapy of cancer. It is proposed to use the IBA Proteus ONE compact complex with an additional proton beam channel for biological research as the technical basis of the new biomedical research center.

Remarks

In Russia, about 500 thousand people fall ill with cancer annually and up to 270 thousand people die from cancer. Currently, 3.2 million cancer patients are registered. According to doctors, the number of patients in Russia for whom radiation therapy using proton beams can give significant advantages leaves more than 50 thousand patients per year.

The use of proton beams and nuclei of light elements (hadrons) in a cancer radiation therapy clinic for a number of reasons is more preferable than photon irradiation (gamma and X-ray radiation, beams of accelerated electrons). The main reason for the exceptional interest of specialists in the use of such hadron beams in oncological practice is the difference in the distribution of absorbed radiation doses in the patient's body when using electromagnetic and corpuscular radiation. First of all, this is due to the distribution of the absorbed dose from the depth of penetration of charged particles into the irradiated region. The maximum energy during the passage of particles through tissue matter is transferred at the end of their path to the so-called Bragg peak (Figs. 1 and 2) and dose distribution are characterized by high conformity with respect to the irradiated target. In this case, when irradiating deeply lying tumors, a lower level of irradiation of normal tissues adjacent to the tumor, as well as critical organs, is achieved.

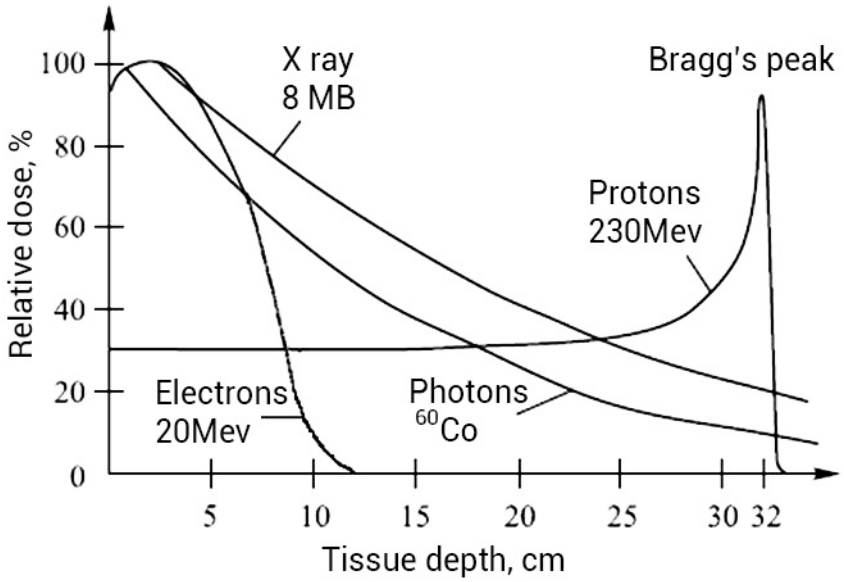

Fig. 1. *Bragg peak - a rapid increase in ionization losses at the end of the trajectory in matter for protons with an energy of 230 MeV in comparison with photons (X-rays) and electrons.*

Since the width of the Bragg peak of monoenergetic protons is not large, methods are used to increase the peak width by modifying the beam spectrum from monoenergetic to continuous. The resulting dose distribution is therefore a superposition of deep dose distributions for protons of different energies. The magnitude of the linear energy transfer (LET) in different parts of the Bragg curve is not the same. At the entrance of particles to the substance of the irradiated region, their LET has small values and increases sharply towards the end of the particle path in the region of the Bragg peak. The realized differences in the distribution of absorbed radiation doses during the passage of a proton beam are one of the important circumstances for the use of protons in radiation therapy.

Even greater differences in the level of absorbed doses in different parts of the Bragg curve are inherent in accelerated carbon ions (Fig. 2). The differences for particles with an energy of 250-300 MeV / nucleon in this case reach values of 3 or more. With this in mind, a number of countries (Japan, Germany, China, France) have created and are creating specialized centers for carbon therapy on the basis of accelerator sets of various types.

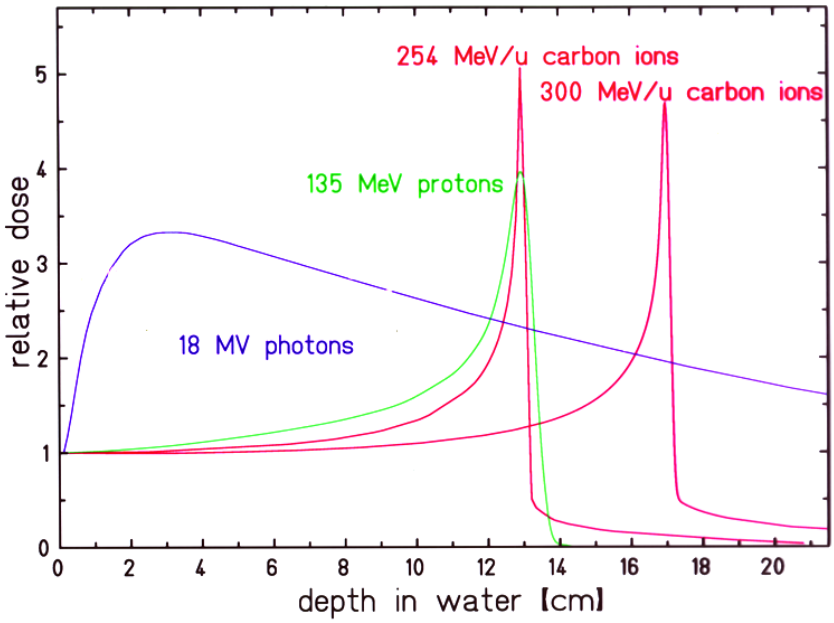

***Fig. 2**. Bragg peaks and relative dose depending on the target thickness for 18 MeV photons, 135 MeV protons, 254 MeV / nucleon and 300 MeV / nucleon of carbon ions.*

The use of carbon ions in cancer therapy is promising, especially in the treatment of radiation-resistant types of tumors. It should be noted that the cost of such accelerators is extremely high in comparison with proton machines, as a result of which carbon therapy centers are single until recently and the cost of treatment courses for patients is also extremely high.

In general terms, the radiation therapy strategy is based on creating the conditions under which the following basic principles should be implemented.

The first is based on the creation of a conformal nature of target (tumor) irradiation - the transfer of the maximum necessary amount of energy of the used radiation to the tumor tissues with minimal damage to adjacent healthy tissues. This condition, as indicated above, is satisfied by the use of accelerated charged particles, and, above all, proton beams and carbon ions. In contrast to

electromagnetic radiation, the use of charged particle beams creates a dose distribution in the irradiated target with a high degree of conformity.

The second principle associated with the first is based on the need for maximum damage to tumor tissue cells during irradiation. This is achieved, as indicated, by the physical features of the transfer of energy of charged particles to matter. An increase in the LET with a decrease in the energy of charged particles, and especially in the Bragg peak, leads to an increase in the yield of radiation damage in irradiated cells, causing their death. The high biological efficiency of accelerated carbon ions compared to protons is due to the high LET of heavy ions. During the passage of multiply charged ions through sensitive targets of cells, severe violations of genetic structures are formed, leading to the formation of chromosome breakdowns and cell death.

Among the wide spectrum of various DNA damage caused by ionizing radiation, the most serious violations leading to cell death are simultaneous violations of the integrity of two DNA strands - double-strand breaks (DR) [1, 2]. Double-strand breaks are formed either as a result of a direct break of two complementary sites — direct DRs (PDRs), due to the transfer of energy to a local DNA site and leading to a violation of its integrity, or are formed from other injuries as “repair costs” in the process of repair enzymes. This type of damage belongs to the category of enzymatic DR (EDR) [3, 4]. Under the action of radiation with increasing values of LET, changes in the spectrum of induced damage to the DNA of cells are observed. At low LET values, base damage and single-stranded DNA breaks (OR) are formed with the highest frequency.

When irradiated with heavy charged particles with high LET values, predominantly double-stranded breaks are formed, mainly of the PDR type, and the number of single-strand breaks decreases [5, 6].

The probability of death of mammalian and human cells upon irradiation depends on the amount of DNA of various nature formed in the DR genetic apparatus. For the average lethal radiation dose D0, when the number of surviving cells decreases by a factor of e with an increase in the radiation dose, the number of DNA DRs is ~ 38–40. The yield of double-stranded DNA breaks of an enzymatic nature upon irradiation depends on many factors of a biological nature and the frequency of their formation can be influenced using certain approaches based on modifications of DNA repair processes. Given these circumstances, we can conclude that the biological efficiency of radiation will be determined by factors of various nature: a physical factor associated with the nature of energy release in sensitive cell targets and a biological factor that affects the yield of damage that causes cell death. The latter makes it possible to increase the efficiency of proton beams in therapeutic use.

Proton Therapy at JINR

The first sessions of the clinical use of proton beams generated by the phasotron (before reconstruction of the synchrocyclotron) of JINR, the institute's first proton accelerator, were started in 1967 on the initiative and ongoing support of the director of the Laboratory of Nuclear Problems Prof. Dzhelepov. This accelerator was launched in 1949 and was created for fundamental research in the field of nuclear physics [7, 8].

At present, the phasotron is the oldest among the accelerators of this type operating in the world. This year, the installation will celebrate its 70th anniversary. The proton energy at the output of the accelerator is 660 MeV, the weight of the magnets reaches 8000 tons, the consumed electric power is about 3 MW and it is served by a relatively large staff of about 50 people. The total

operating costs from the JINR budget for maintaining the operation of the phasotron annually amount to about $ 1 million. It should be noted that when the proton beam is decelerated from 660 MeV to 100 - 200 MeV (typical energy of the therapeutic beam for irradiating tumors), the beam initially extracted from the accelerator is lost, which does not allow forming a dose field in the treatment room with the best parameters for radiation therapy. In addition, significant beam losses during its transportation and deceleration lead to significant radiation activation of accelerator structural elements.

Currently, more than 100 patients have irradiation courses on the proton beam of the phasotron annually. Since 1999, a radiological department has been operating in Dubna at MSCh-9 of the FMBA of Russia. For the first time in Russia, the technique of three-dimensional conformal proton radiation therapy was implemented. Between 2000 and 2018 about 1300 patients (including non-Russian citizens from JINR member states) with various neoplasms took proton radiation therapy using phasotron beams.

Given the design features of the phasotron, it is obvious that the use of such a device for the treatment of cancer patients is not only extremely inefficient economically, but also organizationally unreliable and therefore the accelerator requires an early replacement with a modern specialized proton machine. The creation of a new center for biomedical research, in which almost all the JINR member states are interested, on the basis of a new compact specialized proton accelerator, is very relevant today and will solve two problems at the same time: reduce operating costs for research and form a therapeutic and research proton beam with the best parameters.

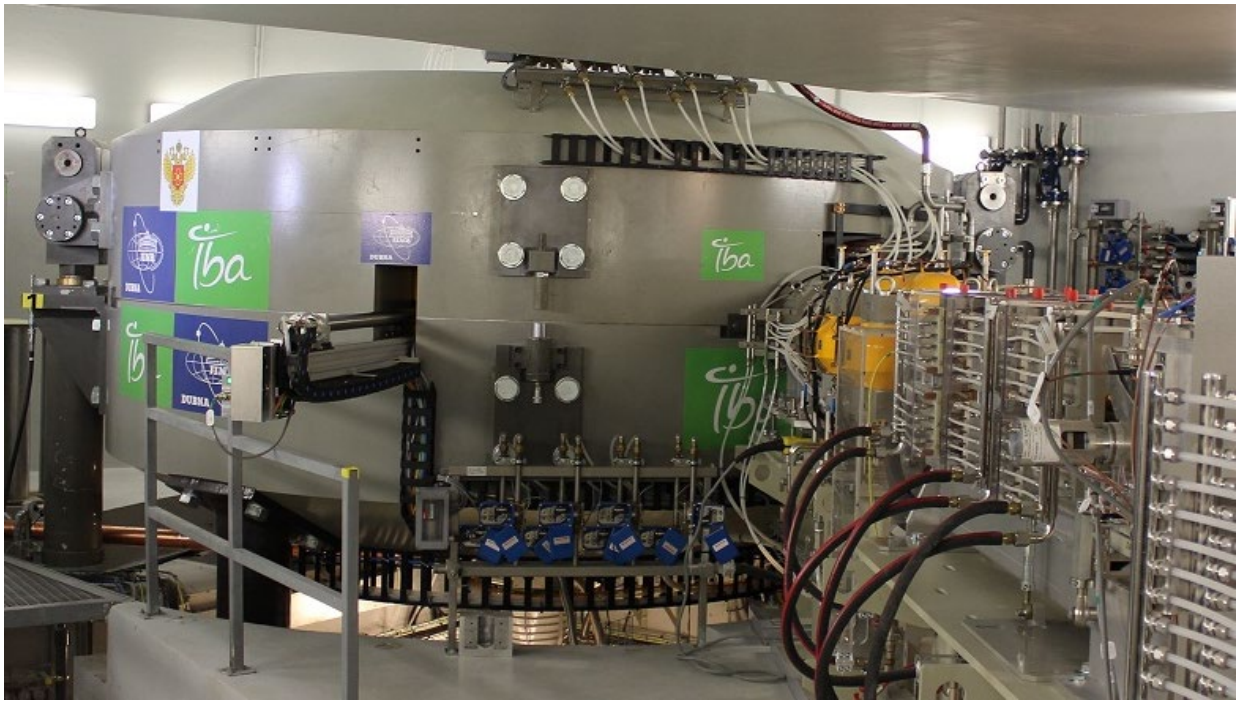

Fig. 3. *The IBA C235-V3 proton cyclotron, designed and launched jointly with JINR, at the Federal Center for Microbiology of FMBA of Russia in Dimitrovgrad.*

Currently, JINR, having many years of experience in creating accelerators and physical facilities for basic and applied research, is developing medical accelerator technology, collaborating with IBA, the world leader in the field of proton therapy facilities, and is developing, assembling, tuning and launching specialized medical cyclotrons for these goals. More than 10 years ago, JINR and IBA jointly developed the project of the world's first superconducting carbon cyclotron C400 [8,

9]. This accelerator is currently under construction in Caen, France. Along with this, calculations and modernization of the serial proton cyclotron C230 were carried out. The first copy of C235-V3 was assembled, configured, and launched at JINR in 2012 [10]. Currently, the C235-V3 has been installed, launched, and has become part of the first medical center with proton therapy in Russia - the Federal High-Tech Center for Medical Radiology (FCMC) of the FMBA of Russia in Dimitrovgrad (Fig. 3), which went into operation in 2019.

Since 2016, at JINR, in collaboration with the Institute of Plasma Physics of the Chinese Academy of Sciences (ASIPP) in Hefei, China, a small-sized superconducting proton cyclotron SC200 has been developed and is currently being commissioned [11]. The second version of this cyclotron [12] has been developed and will be manufactured specifically for JINR. Our version of SC230 (Fig. 4) can be placed in the wiring room of the phasotron beams and provide proton beam up to 230 MeV with the proton beam for treating cancer patients of the JINR Medical Radiological Complex. This will make it possible to turn off the unreliable and expensive phasotron in the next two to three years, while preserving the long-standing traditions of proton therapy and the staff of highly skilled specialists in this field in Dubna.

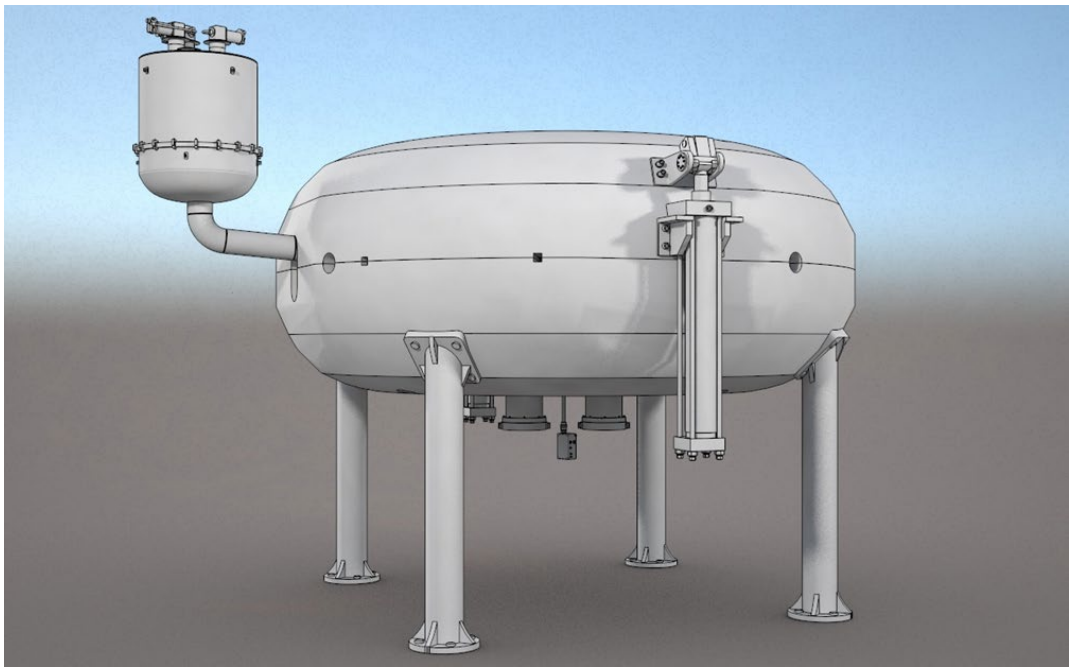

Fig. 4 *Overall view of the SC230 cyclotron*

Radiobiological studies on the phasotron

The first radiobiological experiments at JINR using proton beams of the synchrocyclotron were started in 1959. They concerned the solution of the radiation safety issues of astronauts during orbital space flights. The aim of these works was to establish the relative biological efficiency (RBE) of high-energy protons. Radiobiologists needed to establish: how much more (or less) are high-energy protons effective compared to x-rays or γ-rays when they act on living organisms. At the synchrocyclotron, experiments were conducted on the irradiation of various biological objects: from viruses to various mammals with protons with energies from 25 to 645 MeV. The reactions of various cellular and tissue systems under the influence of acute, fractionated, and chronic proton irradiation were studied [13]. The modifying effect of various types of physical and chemical agents on radiation effects was also investigated.

An analysis of the data obtained on the reaction of cells and tissue systems of organisms showed that, in their effect, high-energy protons are similar to the effects of electromagnetic types of radiation — γ- and X-rays. However, an increase in the relative biological efficiency of protons was noted with a decrease in their energy to 25 MeV and lower. Simultaneously with these works in 1968, the first preclinical radiobiological studies on proton beams were started.

In experiments conducted on cell cultures and animals with inoculated tumors, the main radiobiological parameters of protons with an energy of 180 MeV were determined, which made it possible to subsequently begin radiation treatment of patients. Radiobiologists studied the biological effectiveness of the proton medical beam in various parts of the Bragg curve, the magnitude of the "oxygen effect", the effect of some radioprotective drugs.

Later, specialists undertook studies of the biological effect of π-mesons on a beam formed on the same DLNP accelerator. Priority data were obtained on the relative biological effectiveness and the “oxygen coefficient” of this type of radiation, which was thought to be effective when used in radiation therapy of tumors. Subsequently, studies were carried out on the biological effect of ultrahigh-energy neutrons with a long-range goal of using this type of particles when irradiating radio resistant large tumor formations.

Currently, the Laboratory of Radiation Biology (LRB) is conducting studies of the action of proton beams on various biological objects in order to study the patterns and mechanisms of the formation of molecular disturbances in the genetic apparatus of human and animal cells, the formation of various kinds of mutations, and is studying the neuroradiobiological effects of radiation.

In recent years, radiobiologists, when studying the mechanisms of the formation of lethal double-strand DNA breaks for cells under the action of γ-quanta, protons, and accelerated heavy ions, have identified important patterns of practical interest for radiation therapy. It was found that when irradiating normal and tumor cells with radiation with different LET under the influence of some drugs, the yield of double-stranded DNA breaks, damage that leads to death in the post-radiation period, is modified to varying degrees. These include the official drugs 1-β-D-arabinofuranosylcytosine (AraC) and hydroxyurea (GM). It was shown that, under γ-irradiation under the influence of modifying agents, the yield of DR DNA increased significantly during the post-radiation incubation of human lymphocytes and cells in culture. At the same time, under the action of accelerated heavy ions, the modifying effect of these agents decreased with increasing LET of particles and disappeared at high LET of accelerated ions [6]. When studying the mechanism of the enhancing effect of these agents on the radio sensitivity of cells, it was found that Ara C is a kind of “Trojan horse” at the molecular level.

During DNA synthesis in reparative and replicative processes, Ara C blocks the work of DNA polymerase □. Hydroxyurea, being an inhibitor of rib nucleotide reductase, affects the intracellular pool of nucleotides, in particular, cytosine, and reduces it. As a result of this, long-term fixation of the occurring direct single-stranded DNA breaks (OR DNA), or OR DNA, formed during excision repair occurs. Such lesions can be sites of the formation of enzymatic DR of DNA as a result of an attack on a strand opposite the damaged site, endonuclease type S1. Given that Ara C (cytarabine) and hydroxyurea are official drugs and are used in the clinic for the treatment of acute and chronic leukemia, and as a part of the combined or complex treatment, GM is used in the treatment of head and neck tumors, skin melanoma, and thick and straight cancer intestine, with cervical cancer, kidney cancer and prostate cancer, it seemed extremely important to study the

effect of these drugs on the formation of molecular abnormalities in human cells under the action of protons in different parts of the Brae curve huh. The clinical use of these drugs is currently based only on the effect of inhibiting the passage of cells through the cycle in the S phase. Taking into account previously obtained materials in the LRB about the modifying effect of these agents on the output of DR DNA under the action of ionizing radiation of different quality, as well as the prospects for their practical application, a series of studies of the effect of these agents on the biological efficiency of various types of ionizing radiation was carried out, including proton beam in the modified Bragg peak [14].

To study the frequency of formation of DNA DR in cells under the action of protons under ordinary conditions and in the presence of modifying agents, as well as accelerated boron ions, immunocytochemical and immunohistochemical methods for determining γH2AX/53BP1 radiation-induced foci (RIF) were used. Along with this, the DNA-comet method was used. It was found that when cells are irradiated with protons in the absence of modifiers, an increase in the number of RIFs is observed with their subsequent decrease in the post-radiation period (Fig.5).

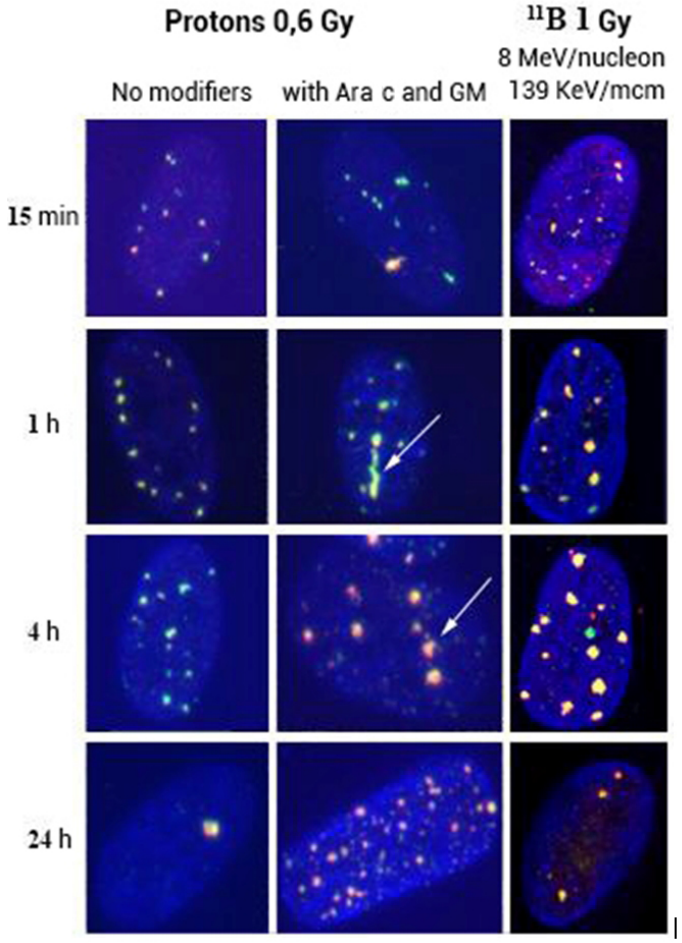

Fig. 5. *Images of individual γH2AX / 53BP1 foci in the nuclei of human cells under the action of protons in the modified Bragg peak and accelerated boron ions with an energy of 8 MeV / nucleon when irradiated under ordinary conditions and in the presence of AraC and GM.*

The greatest number of tricks is formed 1 hour after radiation exposure and their number after 24 hours is minimal. A completely different type of kinetics of the formation of γH2AX / 53BP1 foci is observed upon irradiation of cells with protons in the presence of modifiers. The effect of AraC

and GM is such that over time post-radiation incubation of the cells, not a decrease in the number of RIFs occurs, but their sharp increase, which persists until 24 hours of observation (Fig. 6).

The increase in the number of γH2AX / 53BP1 foci in the presence of AraC and GM is explained by an increase in the amount of DR of DNA of enzymatic origin. The data obtained indicate that the damaging effect of the genetic structures of cells by protons in the expanded Bragg peak sharply increases in the presence of arabinosidcytosine and hydroxyurea - agents that block reparative and replicative DNA synthesis. Single-strand DNA breaks resulting from irradiation remain unrepaired for a long time and are transformed into enzymatic double-strand breaks during the processing of opposite OP sites by endonucleases. In the post-radiation period, the number of such double-strand breaks increases.

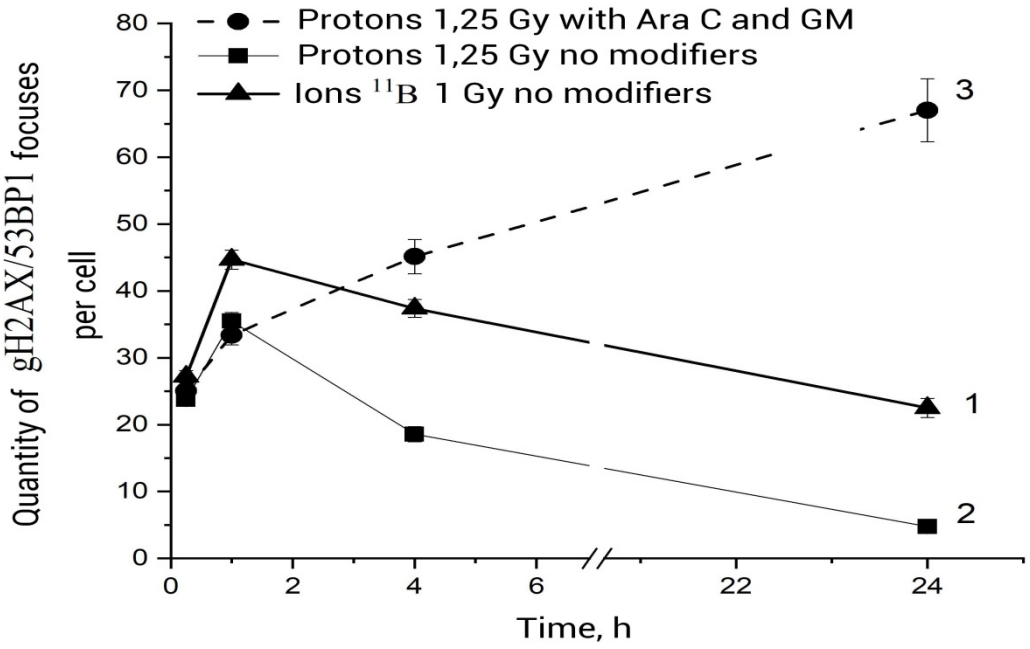

Fig. 6. *Kinetics of the formation and elimination of γH2AX / 53BP1 foci in the nuclei of human cells under the action of protons in the modified Bragg peak and accelerated boron ions with an energy of 8 MeV / nucleon when irradiated under ordinary conditions and in the presence of AraC and GM.*

Experiments were conducted on irradiation with protons in the presence of arabinosidcytosine at the Bragg peak of the radio resistant human glioblastoma cells (U87), the most aggressive brain tumor. The high biological efficiency of the proton beam during irradiation under these conditions was also revealed (Fig. 7).

In vitro experiments have established that under the action of ionizing radiation on human cells in the presence of this drug, the transformation of single-stranded DNA breaks into lethal double-stranded breaks occurs, which leads to a sharp increase in cell death. A patent has been obtained for the invention of a new method for enhancing the radiation effect on living cells.

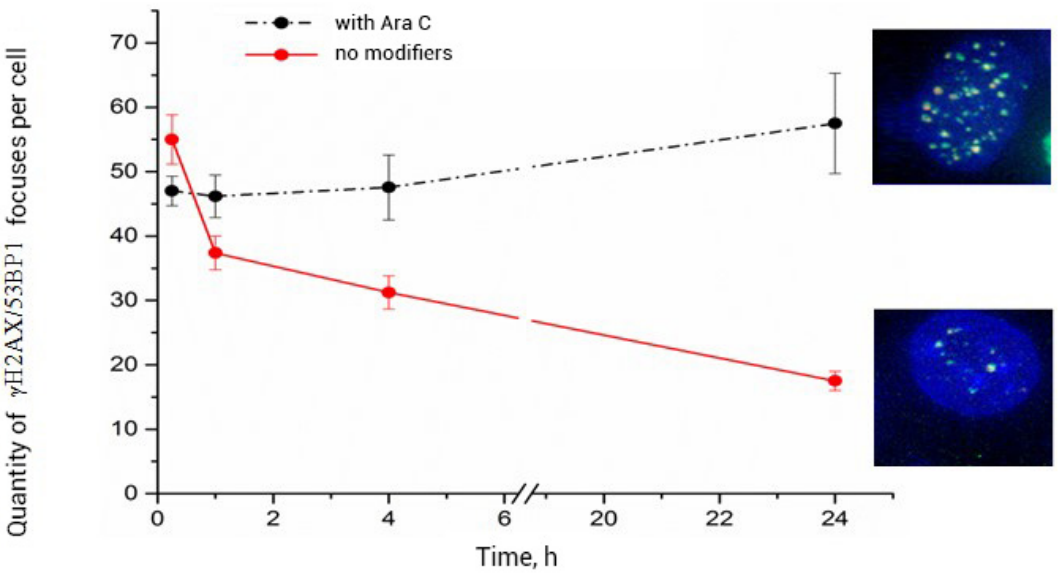

Fig. 7*. Kinetics of the formation and elimination of γH2AX / 53BP1 foci in the nuclei of human glioblastoma cells (U87) irradiated with a dose of 1.25 Gy protons in the extended Bragg peak.*

In the summer of 2019, a group of specialists from the LRB JINR and the Center for Medical Radiology (Obninsk) performed studies of the effectiveness of the proposed method in the treatment of melanoma. (Fig. 8) Based on the results obtained, a group of animals (mice) was inoculated with a melanoma tumor and the tumor was irradiated with protons at the Bragg peak in the group with and without drug administration. On day 30, control animals died without irradiation (green line with Ara C and black line without Ara C). On day 40, both groups of irradiated animals are alive and differences in the size of tumors in the groups: proton irradiation (red line) and proton irradiation + the drug Ara C (blue line) reaches ~ 2.5 ÷ 3.4 times.

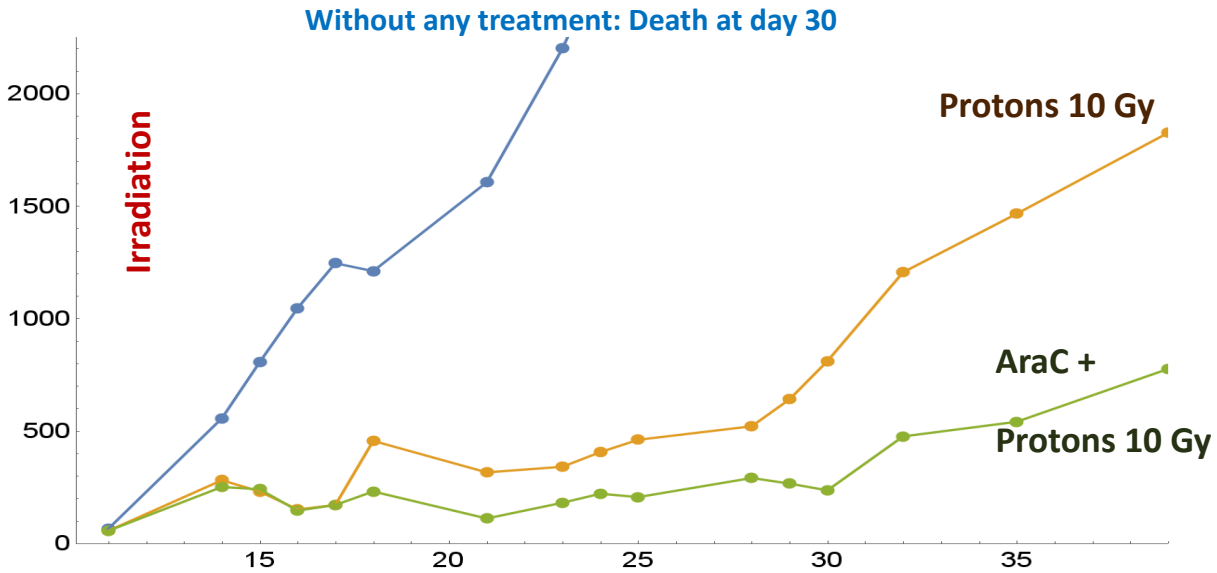

Fig. 8*. Kinetics of the development of a melanoma tumor in mice without proton irradiation (blue without AraC) and with proton irradiation (orange without AraC and green with AraC) in experiments in Obninsk in the summer of 2019.*

The application of the proposed approach, which provides a significant increase in the biological efficiency of proton beams and gamma therapeutic units, significantly brings together the field of use of proton and carbon accelerators for therapeutic purposes.
These circumstances give reason to believe that the combined use of the official drugs used should be promising for use in the clinic of radiation therapy and significantly brings together the field of application of proton and carbon accelerators for therapeutic purposes.

Further research plans.

Further research is planned in the following main areas:

- Study of the effect of arabinosidcytosine and hydroxyurea on the survival of human cells under the action of protons. The patterns of lethal action (by the criterion of colony formation, apoptosis formation) of protons and γ-quanta on various human cell lines will be investigated. The values of the radiosensitizing effect of modifiers on the sensitivity of cells upon irradiation with protons at the Bragg peak and the action of photon radiation are established.
- Study of the influence of DNA synthesis inhibitors on radioresistant lines of human tumor cells (glioblastoma, etc.) when irradiated with protons and γ-quanta. Using immunocytochemistry methods, it is proposed to study the formation of γH2AX / 53BP1 foci in the culture of U87 glioblastoma cells of other radioresistant lines upon irradiation with protons in the Bragg peak under normal conditions and in the presence of Ara C. It is planned to study the kinetics of the formation and elimination of radiation-induced DR DNA.
- Investigation of the effect of DNA synthesis inhibitors on the biological effectiveness of protons and gamma rays when irradiated in vivo. In experiments on rodents using immunohistochemistry and other molecular biological methods, it is planned to study the patterns of the formation of double-stranded DNA breaks in various parts of the central nervous system when irradiated with protons and γ-quanta without the use of a radio modifier and in the presence of Ara Ts. Information on the kinetics of formation and elimination of DR DNA - the most severe violations of genetic structures when irradiated under various conditions, will allow you to judge the severity of damage to brain structures.
- Development of approaches to the creation of vector molecules for targeted delivery of arabinosidcytosine to tumor tissue. Given the high radiosensitizing effect of the inhibitors used, in the presence of which there is a long fixation of the occurring direct or enzymatic single-stranded DNA breaks, causing the transformation of such lesions into enzymatic double-stranded DNA breaks, it seems very important to create transport molecules (vectors) with affinity for tumor cells. Their creation would make it possible to further increase the effectiveness of proton therapy using DNA synthesis inhibitors with the above mechanism of action.

For the effective implementation of the proposed experiments, a reliable specialized accelerator complex is required.

Project proposal for the establishment of the Proton Therapy Biomedical Research Center in Dubna

Many years of practical experience in treating cancer patients with proton beams, a team of trained specialists in the field of radiation medicine, the presence of a radiological department at MSC-9 of the FMBA of Russia creates the conditions for the continuation and development of hadron

therapy at the JINR in the coming years. The treatment of patients with the participation of JINR specialists should naturally be combined with biomedical research at the Institute.

Recent results of a study of the action of proton beams on various biological objects in order to study the patterns and mechanisms of the formation of molecular disturbances in the genetic apparatus of human and animal cells promise a breakthrough in the effectiveness of using proton beams for the treatment of cancer. For their continuation, a medical center with a modern and reliable proton accelerator is required, which must be certified for the irradiation of cancer patients. The world experience in creating such medical centers shows that treating patients and conducting research on proton beams can be successfully combined using the same accelerator, using additional beam conclusions and spreading the time of patient irradiation and scientific research. The fastest and cheapest option for creating a compact biomedical proton center is currently the IBA Proteus ONE compact turnkey module, which has passed all the necessary certification in Russia.

Proteus ONE is (Fig. 9 and 10):

• Superconducting synchrocyclotron with proton energy 230 MeV

• One treatment room, 220□ compact gantry (PBS spot scan)

• The ability to create a specialized proton beam output for biomedical research

• The maximum size of the irradiated field 20cm × 24cm

• Required area (Hopper) 32.6 m × 16.1 m (area 524.86 m2)

• Advantage - Compact size, smaller investment

• Number of patients up to 400 per year; (this figure will be less when the distribution of time "on the beam" between the medical and scientific programs of the Center)

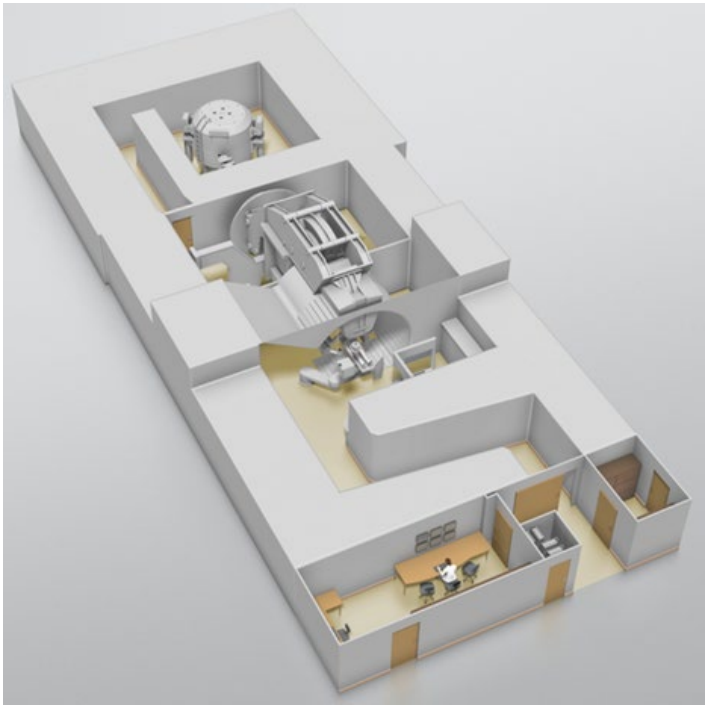

Fig. 9. *General view of the Proteus ONE module*

The commercial cost of creating the Proteus ONE complex, including all equipment, gantry, cabins, a specialized channel for scientific research, construction and installation works, etc., is about 25-30 million Euro. In the case of direct participation of JINR specialists in the assembly, commissioning and launch of the Proteus ONE complex in Dubna, IBA offers special conditions for JINR to significantly reduce costs. The General Agreement on Cooperation between the FMBA and JINR dated 06/27/2016 could become the basis for a joint project to create a research biomedical center for proton therapy in Dubna based on the IBA Proteus ONE small-sized complex.

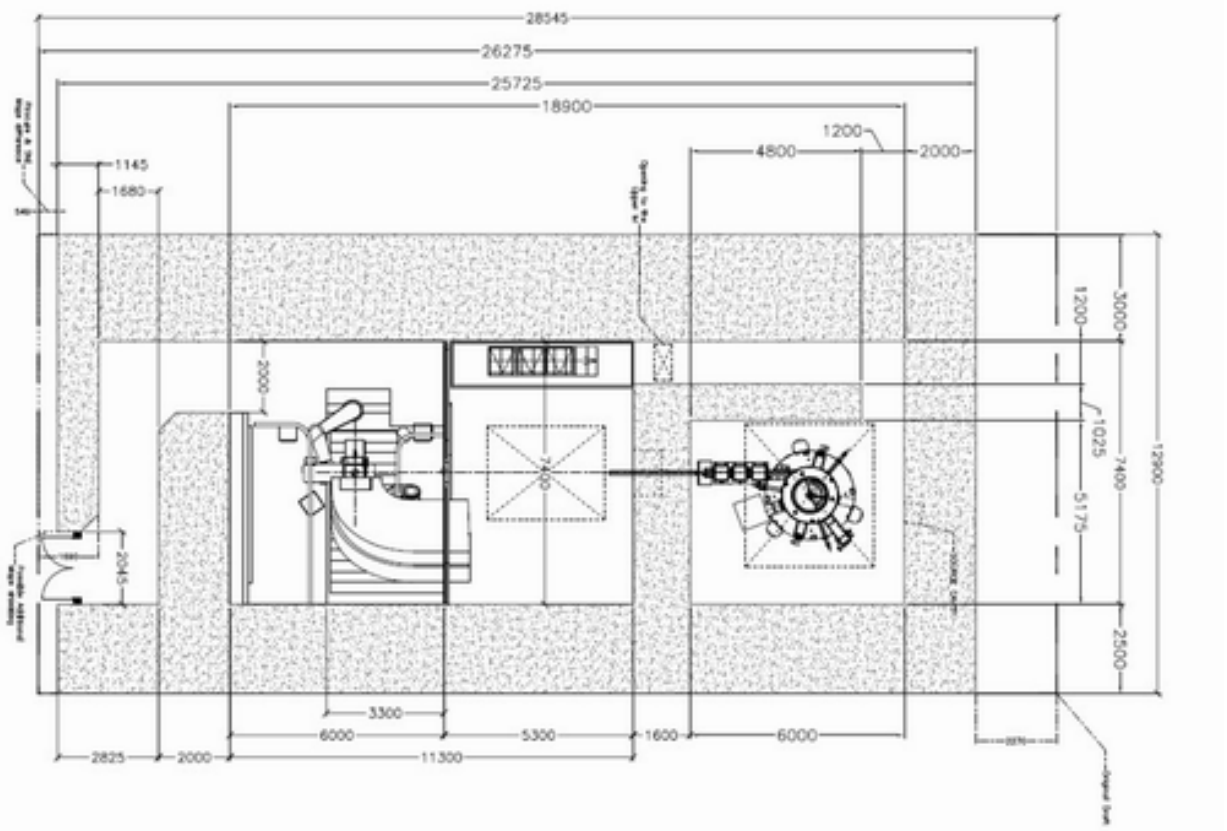

***Fig. 10**. Characteristic dimensions and dimensions of the IBA Proteus ONE complex*

Prerequisites for creating a radiological proton therapy complex in Dubna based on IBA accelerator equipment:

• 50 years of JINR experience in the field of proton therapy;

• the radiological department at MSC-9 of the FMBA of Russia and special relations with the FMBA of Russia;

• a team of trained JINR specialists in the field of nuclear medicine and radiation biology;

• many years of fruitful cooperation between JINR and IBA, the world leader in the field of proton therapy;

• localization of design (if necessary), assembly, commissioning, start-up and maintenance of accelerators for proton and, subsequently, carbon therapy in Dubna;

• a significant reduction in the cost of IBA equipment and the entire project as a whole with the participation of JINR specialists in it.

Currently, patients are irradiated at the phasotron, the oldest JINR accelerator, which is located on the technical site of the LNP JINR in the immediate vicinity and in the sanitary protection zone of the IBR-2 nuclear reactor. Special safety and security regimes of the site area create significant difficulties for working with patients and interfere with the work of the scientific center. For this reason, the new biomedical center should be moved out of the JINR protected area. The location of the center is possible, for example, on the territory of the Ministry of Emergencies-9 of the FMBA of Russia (Fig. 11).

***Fig. 11**. An example of the location of the center on the territory of the Ministry of Emergencies-9 FMBA of Russia.*

The creation of a joint JINR - FMBA of Russia biomedical research radiation medical center based on Proteus ONE in collaboration with IBA, JINR could become a pilot project to create a series of compact and relatively inexpensive proton therapy centers for leading oncological clinics in Russia.

Concluding remarks

Based on the foregoing, it can be concluded that Dubna currently has unique conditions for creating a scientific and medical center for proton therapy of cancer. For half a century, on the basis of the first JINR accelerator - the synchrocyclotron, the biological, biological and clinical developments initiated by the initiative of academicians V.P. Dzhelepov and N.N.Blokhin.

For the first time among European countries, proton beams with the necessary physical-dosimetric characteristics for clinical use were formed and their radiobiological characteristics were studied by radiobiologists. Using a wide range of methods, we studied the relative biological effectiveness of accelerated charged particles in different parts of the Bragg curve, the magnitude of the oxygen effect, and other characteristics that have to be studied before the clinical use of proton beams. Under the guidance of radiologists from the Oncological Scientific Center of the Russian Academy of Sciences, and later from other centers, the first successful clinical trials of a new method of irradiation of cancer patients were conducted on the basis of the radiological department MSCh- 9 of the FMBA of Russia. Up to this date, about 1,500 patients have took treatment courses at the beams of the JINR medical complex. During this period, vast experience has been gained in the clinical use of proton beams, and a school of highly qualified physicists and radiobiologists has been established that continues successful research in this area.

For more than twenty years, the University of Dubna has trained specialists in physics and radiobiologists who have successfully mastered the modern methods used in various fields of dosimetry physics and radiation biology of accelerated charged particles.

Recently, JINR radiobiologists have been developing fundamentally new approaches to increase the biological efficiency of proton beams to a level comparable to accelerated carbon ions, which significantly brings together the field of application of proton and carbon accelerators for therapeutic purposes.

It is planned to use the compact IBA Proteus ONE complex with an additional proton beam channel for biological research as the technical basis of the new medical research center. Proteus ONE equipment has all the necessary permits for working with patients in Russia.

In view of the foregoing, the creation in Dubna of a joint JINR - FMBA of Russia biomedical research radiation medical center would be an important step in providing the necessary medical care to cancer patients in the northwestern region of the Moscow region and other regions of Russia, as well as JINR member countries, based on high-tech equipment.

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