Referee's report on

«Research on the Biological Effect of Heavy Charged Particles with Different Energies»

Theme 04 - 9-1077

Further advances in research on biological effects of beams of charged particles heavier than electrons (such as protons or heavier ions) are of prime importance, both in developing further fundamental understanding of the radiobiological mechanisms involved at all systemic levels (molecular, cellular, tissue or organism), in providing basic input to various applications of ion beams – in medicine (cancer radiotherapy, radio-diagnostics, nuclear medicine), in technology applications (radiation physics, production of radiation sources and detectors, information technology) and also in aspects of social importance (radiation protection, radiation safety in space travel, energy production). Therefore the theme "Research on the Biological Effect of Heavy Charged Particles with Different Energies" is quite extensive and requires a broad range of expertise within such a wide range of topics. The team of the Laboratory of Radiation Biology at JINR has the capacity to cover this range and has demonstrated its competence in radiation biology of particle beams - in fundamental research (modelling radiation effects *in vitro*, *in vivo* and *in silica* – at molecular and higher systemic levels) and in applications, especially in ion radiotherapy – in enhancing the biological effectiveness of proton beams by concurrent application of radiation and chemotherapy agents (Ara-C – JINR patent) and in introducing and studying a novel aspect of radiation protection in space, namely radiation – induced central nervous system (CNS) disorders. The Laboratory of Radiobiology at JINR is well-staffed, well-equipped and has access to several ion beams at other JINR Laboratories, including a dedicated medical proton beam facility. Through its wide network of international collaborations with leading research laboratories in this area, both inside and outside Russia, the Laboratory of Radiation Biology is able to acquire external expertise and collaborative effort. Despite the main present thrust of JINR being the NICA and Super-Heavy Element Factory, the Laboratory of Radiation Biology is being sufficiently well funded to be able to carry out the planned objectives of the Theme 04 - 9-1077.

The proposed collaborative program will have two main directions: modelling the biological action of space radiation (in particular, its action on the CNS), and development of new approaches to ion beam radiotherapy of cancer (in particular, enhancing the biological effectiveness of proton beams). The program will likely cover a wider area, but these two directions offer well-specified particular goals within an ambitious, pertinent and current more general background.

Charged ions of high energy which form the Galactic Cosmic Radiation in deep space constitute a significant health risk to astronauts during manned space missions. Within the LRB a new concept has been proposed, revising the traditional approach to evaluating the radiation hazard to the space crew, by including the risk of central nervous system (CNS) disorder, thus affecting the mental capacity of space crew members. To address the likely mechanisms of this hazard, behavioural studies will be conducted using animal models, pathomorphology of the CNS - including DNA damage, neuronal and glial death, will be studied, as well as the response of the hematopoietic, immune, and other regulatory systems of the organism after exposure to energetic ions. The *in silica* contribution to mathematical modelling of this experimental work is a major strength of this project.

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The JINR group has initiated and patented the technique of enhancing, at the cellular *in vitro* stage, the biological effectiveness of proton radiotherapy by combining beam irradiation with Ara-C, a generally approved chemotherapy agent in treating cancer patients. The suggested mechanism of the action of this agent is by converting single-strand breaks into double-strand breaks in ion-irradiated cells. Application of such a combined technique in clinical proton therapy could significantly improve the treatment outcome and decrease the number of proton therapy sessions (fractions) required.

The planned timetable, planned costs, description of the work plan, benefits to the JINR arising from realisation of this programme, and its structure and planned procedures are well specified and clearly determined. The LRB team has access to several unique sources of ion beams available at JINR, especially to heavy ion beams of a broad range of charges and energies. Participation of researchers from JINR member countries in this programme is foreseen. The results expected over the next three years have been well formulated and are realistic, considering the past achievements of the LRB team. The research staff of the LRB is young but already experienced, as well as their leadership, which combines a solid record of past achievements with youth and demonstrated competence.

In conclusion, I strongly recommend that the theme 04 - 9-1077 "Research on the Biological Effect of Heavy Charged Particles with Different Energies" be continued over the years 2021-2023.

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