„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY
BUCHAREST, ROMANIA
1

RESEARCH ON THE BIOLOGICAL EFFECT OF HEAVY CHARGED PARTICLES OF DIFFERENT ENERGIES - THEME 04-9-1077
review

1. Scientific importance, novelty aspects and relevance of the project.

I.   A merit of the presented research is the **revision of the laws of radiobiology through LET** in the sense of parallelism and dependence of lysis efficiency and the generation of defects, mutations induced by hadron beams, beams with high LET. In this sense, the team proposes the introduction of the concept of **Radiation Induced Outbreaks (RIF)**, a network of biochemical pathways triggered by cells in response to the appearance of a DNA lesion to the restoration of DNA integrity. The **RIF** study is another chance to generate breakthrough findings in the diagnosis and treatment of chronic diseases of the central nervous system.

II.   Addresses the efficacy of proton radiotherapy of brain tumors, issues related to the radiosensitivity / radioresistance ratio and how to increase the radiosensitivity of brain tumors in proton therapy by adding inhibitors of DNA synthesis such as 1-β-D-arabinofuranosyl cytosine (Ara-C) and hydroxyurea (HU). This treatment with sensitizers is not one of the panoply of therapeutic guidelines, it is a novelty, a discovery and offers hopes that the *proton therapy associated with these inhibitors will be able to compete with hadron therapy with carbon ions,* a much more expensive, less accessible and *rarer* method of radiotherapy.

III.   It is possible that the study of modeling the radioresistance / radiosensitivity ratio by the inhibitors mentioned above will open a way or offer a solution, perhaps medicinal, to increase the *radioresistance of* _normal tissues_ *of cosmonauts* exposed to the spectrum of **Galactic Cosmic Rays** (GCR) and, why not to other situations of exposure (professional or accidental) to other types of ionizing radiation.

IV.   **Mathematical modeling** of radiation-induced effects together with experimental analysis of biological phenomena from genetic to macroscopic, functional level, not only follows the main line of research but, by affecting a functional link, can make an important contribution to the goal. proposed research as well as the discovery of the mechanisms of spatial, temporal and neurological functional support of the nervous structures affected by the irradiation with ionizing radiation; another application of this mathematical modeling may be in the discovery of new valences in artificial intelligence, through the same mechanism of translational research as above but posing the inverse problem. The team of the mathematical modeling department contributes to this chapter by *developing a hierarchy of models* using a *wide range of calculation methods from different fields of knowledge,* thus necessarily and multidisciplinary filling the lack of knowledge. It proposes interesting *models such as death models, detailed models of tumor growth, models of the functioning of the neural networks of the brain,* complex models and why not, essential in biological modeling, especially in radiobiological. The team proposes the use of GEANT4 software packages - DNA, FLUKA and PHITS therapy planning software packages, with formidable computing resources such as the JINR supercomputer, all in order to *choose the optimal parameters of combined therapy* and / or decipher the mechanisms of living matter in case *acute local exposure and total chronic exposure.* Mathematical research planning is integrated into the entire research process.

V.   **The research methodology** is another valuable feature and is not as much an international integration in procedures and equipment as in the one specific to the Laboratory of Radiation Biology (LRB), JINR Dubna. In this sense, we start from the level of **molecular radiobiology, going through** *immunocytogenetic and immunohistochemical* **techniques,** *looking for mechanisms that determine the choice of repair pathway,* integrating them spatially and making comparative analysis of patterns and mechanisms of induction and repair of DNA molecule damage in normal

On the other hand, this team uses equipment specific to each type of laboratory equipment, methods and procedures that allow them to perform the experiments mentioned above and hence the production of data with great relevance, accuracy and realism and that can allow the implementation of this project in specified terms in the project description, in each of its subchapters.

3. Adequacy of funding requested for project tasks.

Summarizing briefly from the chapter on the **resources needed to implement the project,** we will notice that only the use of the run time of the beams is estimated to cost 548.2 k $, for the direct expenses of the project another 548. 2 k $. The estimation and distribution by years and categories of expenses is done correctly but one of the advantages is that the project is integrated in the research system of JINR Dubna which can lead to lower costs, compared to experiments done in independent laboratories in different countries. However, it is possible that additional expenses may arise which delegations in each country may be able to bear in part from their own funds.

4. Availability of human resources to JINR and cooperating organizations.

The human resource is impressive: 74 employees of LRB JINR of which 39 young employees (under 35 years old) in addition to a RAS academician, a corresponding RAS member, 6 PhD and 12 PhD students . In addition, research teams from Armenia, Belarus, Bulgaria, Cuba, the Czech Republic, Germany, Italy, Mongolia, Poland, Romania, Russia, Serbia, Slovakia, South Africa and Vietnam participate .

Only one of the three research teams in Romania, and here I quote the one from the "Carol Davila" University of Medicine and Pharmacy in Bucharest, the Discipline of Oncological Radiotherapy and Medical Imaging has in its composition an associate professor with two doctoral specializations [1] and three doctoral students, all being at the same time radiotherapists with knowledge and daily practice of radiotherapy, radiobiology, radiation protection, radiopathology.

The work program covers step by step the planned and described needs of the project, for the period 2021-2023.

5. Critical notes and weaknesses of the project

The project is very complex, extremely difficult because it evaluates two seemingly opposite processes: radioresistance and radiosensitivity. It also aims to study the mechanisms of correction, influencing the genome subjected to irradiation.

What gives an excellent note to this project is the continuous multilevel integration of the proposed research, which is difficult but, as seen in the description of this project, possible and well done.

6. Concomitant evaluation of the overall performance of the project and recommendation on the category of the project you suggest to assign.

It is a category A project because it aims at research topics of the third millennium, necessary for both medicine, radiotherapy and astronautics by studying the problems of radiation protection and radiopathology; it is possible that the results of this research may be necessary in other areas such as accidental and / or professional post-irradiation repair problems. It also includes radiobiogenesis issues which can generate more than one new paradigm in the field, the project opens and expands the global area of knowledge.

It is an excellent project, which should be fully funded with adequate resources and encouraged to continue and expand its impact.

Referent,

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[1] *For completion and in case it will be necessary, we will be able to list the following qualifications: he is an expert in radiotherapy of the Romanian Ministry of Health, expert evaluator in Artificial Intelligence projects of the European Research Agency and qualified guide for doctoral students. from radiology and radiotherapy.*