

Referee reports on: RADIOGENE PROJECT: The molecular genetics of radiation-induced changes at the gene, genome and transcriptome level in *Drosophila megalonogaster*

Scientific merits and intellectual contribution:

Statement of problem, research and significance in the presented proposal of project is innovative in soundness of the challenge in the genetic risk estimation. Background of the prediction of the additional risk of genetic diseases in human populations exposed to ionizing radiation occurs naturally as a result of spontaneous mutations. The concept of radiation-inducible genetic diseases, which emerged at around environment, is based on two established facts and an inference:

- (1) hereditary diseases result from mutations that occur in germ cells
- (2) ionizing radiation is capable to induce similar changes in all experimental systems, which are adequately to investigated into account of the project.

The inference, therefore, has been that radiation exposure of human germ cells can result in an increase in the frequency of genetic diseases in the population. Worth noting the fact that although there is a vast amount of evidence for radiation-induced mutations in diverse biological systems, there is no exact evidence for radiation-induced germ cell mutations that cause genetic disease in humans. The objectives of the research project are well presented and clearly structured. The partners have complementary knowledges of the expertise process. The joint research programme of collaboration is of good quality. The project is original and the overview of state of the project is adequately presented. The essential goals are consistent with results from the previous scientific work (in years 2017-2019) ended by 4 publications and 4 reports at conferences.

Technical feasibility of the project within the proposed timescale:

Modern research of proposed problem requires a wide range of the main methods from molecular biology and the methods of condensed matter physics, and it does take to account of all participants in project in the JINR. Experience related to the planned years will be very good in conclusions, when expected results will be obtained in planned periods and when will be the JINR organisation is the best place for conducting and coordinating these studies among all other participate institutions in present project. The methodology for the project is convincing. The data collection strategy, potential sources of information and data accessibility are clear. The proposals of planned methods could to sufficiently demonstrate that the group has the necessary expertise and capabilities to obtain the necessary information needed for the project. Firstly, the transcriptome analysis will allow to identify the gene sets responsible for differences in *Drosophila* genome radiosensitivity. The results of structural changes in the gene, gene mutations and inhibited DNA changes in irradiated germline cell genome of the studied *Drosophila* present the main streams of planned research. The working group will plan to compare the results with similar literature data obtained in mice that significantly increase the validity of using this experimental data for extrapolation to humans. Owing to the paucity of human data on radiation-induced mutations, animal data on radiation-induced mutations, are used to predict the risk of genetic diseases in humans using this type of methods. Secondly, in the process of performing the above works and plans, in the project will be studied the genetic control of the radiosensitivity of the *D. melanogaster* genome at the transcriptome level (RNA) using lines that contrast in radiosensitivity. Checking of previously

established differences in radiosensitivity for high inbred lines maintaining in their "Drosophila collection" and confirmation the genotypic purity of these lines, to obtain transcriptome from the first instar larvae irradiated at this and later stages of ontogenesis will be useful for the solution of the next experiments of other problems and groups of researchers after accomplishment of all goals for this field of research.

Compliance of the requested financial resources with the project objectives

The experimental justification of radiation genetic risk is an original and rewarding, the form and content has the required character and the requested funding are realistic for the estimated budget. The management plan is adequate. It does include clear overall responsibility for the activities; it includes a problem-solving mechanism in the event of assignment experiments between partners including of JINR and other institutions expressed an interest of the joint studies within the proposed project.

Availability of adequate human resources of JINR and in the cooperating institutions:

Planned activities, balance between time frame and the costs, description of the work plan, benefits for JINR arising from this activity, structure and planned procedures are listed, the proposal includes a clear experimental strategy. Planned timetable of works, of resources in case of knowledges demonstrates, in the proposal an adequate level of experience of special preparation in this field and the correlation with the scientific groups.

Conclusion:

Project Proposal Application for Funding Form is specific enough to clearly show its innovative and original aspects. The contribution of concur sectors in propose project is adequate and is described clearly. The connection between the basic research topics and with the translational project is well presented. The resources in scientific merit, technical ability and funding are given the complex of the activity proposed. No factual errors were found in fact there (only what I did find is the correct write of equipment Affymetrix Gene Chip - in the text of proposal author of project - was sometimes as like Afimetrix equipment or Afimetrix and is not correct), no discriminatory comments were found. Partners are capable to fulfil tasks from stated periods as they show to us the previous results in the report on project titled as Experimental justification of radiation genetic risk estimation according to the frequency of heritable DNA changes in human and animal structural genes. Proposal is meeting the all relevant criterion of such project any shortcomings are in minor form. I propose the submitted application of project has been accepted as functional research project and has been funded within the scheduled period.

STRENGTHS of the project:

- Planned timetable, balance between the time frames and costs, description of the work plan, benefits for JINR arising from this activity, structure and planned procedures are clearly determined.
- The study of the radiation level risk using the technique of the neutron activation and the gamma radiation facilities, are also meaningful for the using and application of JINR's

experimental facilities, as it regards obtaining the worldwide level of the research results at JINR.

- If the working group will be theoretically able to predict the potential human data on radiation-induced mutations, and the risk of genetic diseases in humans it will be the successful strength of this project.

WEAKNESSES of the project:

- As was initiated in proposed project, the small number of young professionals (3 employees) is weakness of it and as well that not yet opened the collaborations with planned other institutions and organisations, besides institutions enumerated in project

Within the five usually used limits of projects (Excellent, Very good, Good, Fair, Poor and Proposal fails) the evaluation of the project is on Excellent level. Proposal successfully addresses all relevant aspects of the expected criterion. Report had not found any major shortcomings in this application of project management.

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