“Multiomic analysis of serum and exosomal biomolecules associated with total body irradiation.”

A human organism exposed to high doses of ionizing radiation irreversibly loses the capability of producing new circulating blood cells, which rapidly results in death. This effect is due to the complex, severe damage of bone marrow stem cells which die if exposed to sufficiently high doses of radiation. The toxicity of radiation is a result of free radical formation as well as direct and indirect DNA damage. Both of these mechanisms are used if radiation is applied therapeutically during the course of oncological treatment. However, in such instances, the doses are carefully calculated and delivered in a way that maximizes the local dose within the tumor while sparing the adjacent healthy tissues and organs. On the other hand, intentional, completely uncontrolled exposure of a large number of civilians is a terrifying, but likely scenario in the global terrorism era.

If such a calamity happens, either due to a dirty bomb being used, or a catastrophic nuclear reactor meltdown, the dose received by those exposed is unknown. This considerably limits the possibilities of the emergency and medical services in helping the afflicted and providing them with adequate care. Individuals who receive extremely high doses will die unless provided with a bone marrow transplant, while those exposed to lower doses will likely survive if provided with supportive care. Unfortunately, estimating of the received dose on the basis of symptoms manifested by the patient becomes possible the soonest after 3-7 days, which poses a major stress on the medical teams and delays the time to initiate the search for a bone marrow donor.

This project is aimed at resolving the problem by proposing a novel, innovative diagnostic test for high-dose, potentially lethal irradiation. The test utilizes microRNAs – short fragments of ribonucleic acid which are detectable in the blood and can be readily measured using standard molecular medicine methods. The goal will be achieved through identification of microRNAs significantly affected by high doses of ionizing radiation in patients undergoing high dose total body irradiation as a part of their oncologic treatment in preparation for a bone marrow transplant. This series of experiments will refine our concept of a microRNA-based diagnostic test and allow for its calibration for clinical application in triage of post-exposure individuals.

Afterwards, to discern the mechanisms regulating microRNAs in response to radiation exposure, the Applicant and the American partner will carry out the experiments aimed to characterize the presence of microRNAs associated with exposure to radiation in exosomes, which are vesicles secreted actively by the cells. Determination of the microRNA profile in exosomes, the application of this information to proteomics and the characterization of proteins present on the surface of extracellular vesicles are one of them aims of this project. All of this should enable discovering the tissue origin of exosomes secreted in response to radiation and will allow us to identify or predict the functional role of radiation-related microRNAs.