THE EFFECT OF HIGH LET RADIATION ON DIFFERENTIATION AND TUMORIGENESIS IN THE HUMAN HEMATOPOIETIC SYSTEM: MODELING *IN VITRO* AND *IN VIVO* FOR RISK ASSESSMENT

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The study was just selected for funding and there is no experimental data to be presented. Here we outline the background, the goals of the study and the methodology that we plan to use.

The main goal of the NASA radiation program is to reduce the uncertainties in space radiation cancer risk projections and risks to the CNS and other degenerative tissue diseases. Of major concern are the short- and long-term radiation-induced injuries to the hematopoietic system. The hematopoietic compartment is one of the most radiosensitive tissues in the human body, comprised of a large number of continuously and rapidly proliferating cells. The effect of exposure to the space environment is illustrated in studies that show changes in the immune response of T lymphocytes following space flight and decreased T and B cell counts of crewmembers of STS-41B and STS-41D [1]. Altered differentiation of human bone marrow hematopoietic progenitor cells were also observed during STS-63 and STS-69 [2]. Studies in mice that were aboard STS-108 and STS-118 show hematologic changes of $CD34^+$ cells, early blast cells and macrophage progenitors in the bone marrow and reveal alterations in leukocyte subpopulations of the bone marrow and spleen [3, 4] . Ground –based studies found changes in virtually all blood cell populations arising from bone marrow and spleen to mature populations in circulating blood in mice after irradiation with proton, carbon or iron radiation [5, 6]. There are, in addition, supporting 'real world' forensic dosimetry findings which report lesions in astronauts' peripheral blood lymphocytes after long-term missions [7, 8]. Together, these data support a consensus that space radiation may have important short- and long-term effects on the hematopoietic system including tumor formation.

Human data for high-LET induced carcinogenesis is non-existent. Animal studies for high-LET induced carcinogenesis are also are very limited. The available data (reviewed in [9]) indicates that HZE particles have higher RBE for tumor endpoints measured in mice or rats, for tumors of the skin [10], mammary gland [11] hepatocellular carcinoma [12] and in intestinal tumor models [13]. Ongoing studies are focused on lung cancer risk from high LET radiation [14]. The general conclusion is that more studies are needed for better understanding of the GCR cancer risks. The goal of this study is to contribute to the high-LET carcinogenesis risk estimation. This goal will be achieved using *in vivo* data acquired from an irradiated human hematopoietic system reconstituted in immunodeficient NSG mice. The study is based on a stepwise enrichment strategy, the first stage of which will be to irradiate mice engrafted with a human hematopoietic system followed 3 months later by analysis of human stem and progenitor cells from mouse bone marrow for chromosomal damage and developmental abnormalities. The goal in this initial stage will be to identify human pre-leukemic stem cells and progenitor cells which exhibit altered karyotypes and abnormal differentiation patterns. The second stage involves engraftment of human hematopoietic stem cells with known abnormalities in secondary mouse hosts for further tumor developmental studies. This secondary host transplantation strategy (commonly used in human tumor engraftment studies) will allow the enrichment of the engrafted mouse cohorts for potentially tumorigenic carriers and permit elimination of the mice with normal karyotypes which usually don't develop tumors. We expect the planned studies to show the effects of high LET radiation on a live human hematopoietic system providing information on 1) induction of in vivo chromosomal aberrations of human hematopoietic stem and progenitor cells 2) in vivo ablation of human haematopoiesis and 3) radiation induced carcinogenesis.

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