LET is a critical factor in accelerating development of lymphoma in irradiated Bax transgenic C57/B6 mice.

James Jacobus[1], Chester Duda[2], Sean Martin[3], Mitchell Coleman[1], Kranti Mapuskar[2], Mike Knudson[3], Douglas Spitz (PI)[1].
[1]Free Radical and Radiation Biology Program, Department of Radiation Oncology, Carver College of Medicine, University of Iowa, Iowa City, IA
[2]Human Toxicology Program, Graduate College, University of Iowa
[3]Department of Pathology, Carver College of Medicine, University of Iowa

A major risk during exposure to both low and high linear energy transfer (LET) radiation is the development of lymphoma. Both occupationally and therapeutically exposed individuals are at risk for lymphoma development induced by low LET radiation, while deeply penetrating high LET radiation is a significant concern for those planning and undertaking long duration missions in space where a high degree of uncertainty on actual risk exists due to the lack of epidemiologically-based datasets.

The C57/B6 transgenic mice used in this study have been genetically engineered to possess either one (Bax 1) or two (Bax 38/1) extra copies of the pro-apoptotic Bax gene under the T cell specific Lck promoter. Bax expression causes reduced cellularity of the thymus, increased relative cell proliferation, genomic instability, and development of T cell lymphoma, with an average age to death of 28 weeks in untreated Bax 38/1 animals and > 60 weeks for Bax 1 animals. Using these model systems we tested the hypothesis that overexpression of Bax would significantly affect lymphoma development in response to low (10 cGy) and high (100 cGy) dose radiation from either low LET or high LET sources. Mice were whole body irradiated using low LET radiation from a cesium-137 source or high LET irradiated with iron nuclei accelerated at Brookhaven National Laboratory, NASA Space Radiation Laboratory.

Our results indicate that 100 cGy of 1 GeV iron in whole body irradiated double transgenic Bax 38/1 mice is significantly more potent at accelerating lymphoma development in the thymus than 100 cGy of low LET γ rays. While this study is currently ongoing, at twenty-four weeks of age 80% (16/20) of 100 cGy high LET Bax 38/1 mice have died from lymphoma, versus 40% (5/12) of control Bax 38/1 mice. Low LET 10 and 100 cGy exposed Bax 38/1 and Bax 1 mice show a trend toward accelerated lymphoma development that is not dose-dependent nor statistically significant at this time. In contrast, there appears to be a dose response for accelerated lymphoma development using high LET radiation, with 10 cGy being less effective than 100 cGy in the Bax 38/1. These results suggest that the effects of high LET radiation on T cell lymphoma development may be greater than expected based on our low LET epidemiological data. (supported by a joint grant from DOE/NASA, DE-SC0000830)