CHARACTERIZATION OF THE TUMOR SPECTRUM ARISING IN HZE ION IRRADIATED OUTBRED MICE

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All of the studies of HZE ion carcinogenesis to date have utilized inbred mice or rats, or rat stocks with limited genetic heterogeneity. Experimental designs employing inbred strains are well suited to comparing the relative effectiveness of various HZE ions for inducing specific types of tumors. But, since the tumor types that arise in irradiated mice are largely determined by their strain background, the spectrum of tumors that might arise in an HZE ion exposed outbred population is unknown.

This ongoing project is designed to determine the spectrum of tumors that arise in an HZE ion irradiated population of genetically heterogeneous mice and compare it to tumor spectra determined in matched unirradiated or gamma-ray irradiated populations. The intent is to more closely model human genetic heterogeneity, and the study design has the potential to detect unanticipated tumor types resulting from HZE ion radiation exposure and to expand the variety of radiogenic tumor types that can be studied in the mouse. We have irradiated 1,800 outbred mice of the heterogeneous stock HS/Npt with gamma-rays or HZE ions, or sham irradiated them. The mice are currently being monitored for tumors as well as being followed for ocular deficits by slit lamp examination and Virtual Optometry Testing. All of the mice have been phenotyped for radiation-induced cognitive deficits by fear conditioning testing.

The tumor types that arise in the mice will be compared between radiation groups. Each mouse is being genotyped for ~77.8K SNP markers and the data will be used to localize the genetic factors that predispose individuals to specific spontaneous tumors, gamma-ray-induced tumors and HZE ion-induced tumors, and determine their overlap. The SNP genotypes will also be used to identify loci that control susceptibilities to cognitive and ocular effects.

To date about 500 mice, predominantly in the irradiated groups, have become moribund and been euthanized and necropsied. Histopathology has been completed on about 50 cases. Based on gross pathology, cancer is the leading cause of mortality. A number of tumor types have been observed, mostly lymphomas and leukemias. It is likely that solid tumors will predominate as the mice age.

Our initial genotypic analysis is limited to 600 mice, but will be expanded to all 1800 mice over the course of the project. Based on the fear conditioning data, we selected 600 mice for genotyping. DNA samples from all 600 were successfully SNP genotyped and the data is being used to identify loci that control susceptibilities for cognitive effects (contextual and cued fear conditioning) and other outcome measures. Overlaps in susceptibility loci between radiation qualities would suggest overlaps in pathways underlying the cognitive deficits. Our analysis indicates that the effects of different types of radiation on cued fear conditioning are associated with different genotype markers and suggests that we can genotype a mouse prior to radiation exposure and classify it as either likely to be affected or not likely to be affected by radiation.

For ocular effects, it is clear that the prevalence and severity of posterior subcapsular opacities in irradiated animals is increasing as compared to unexposed controls, which, in general have very mild to no posterior lens changes. In addition to frank opacities, a number of other ocular disorders have been noted and recorded, including corneal haze, inflammation and, in a few cases, orbital or intraocular tumors.

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