Chimeric mouse models for space radiation risk investigations

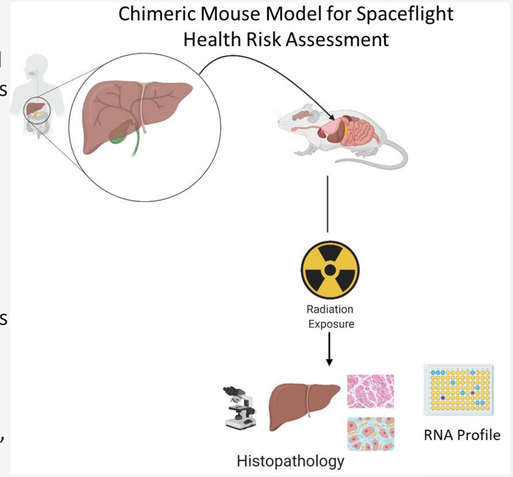
Kristyn Hoffman[1,2], Stephanie Krieger[1,3], Chris Ngo [4], Stephanie Bassett[1,2] and Honglu Wu[1]
[1]NASA Johnson Space Center; [2]University of Houston, [3]KBR, University of Central Florida[4]

Abstract

Assessment of human health risks associated with space radiation exposure is based largely on the knowledge learned from studies in which animals, mostly rodents, are exposed to high-LET radiation on the ground. It has been recognized that translation of animal results to meaningful implications for human disease can be challenging, particularly for certain risk categories such as the high-LET radiation effects in the central nervous system (CNS). Considering limitations in utilizing non-human primates and clinical studies in humans, chimeric animals can potentially bridge the knowledge gap between rodents and humans. In a chimeric animal, a specific organ or a cell type is replaced with respective human cells that are functional. A number of chimeric mouse models have been developed in the medical research community to study human diseases, and some of the models can potentially be used for NASA applications. Here we investigate use of mice engrafted with human hepatocytes, which have been used in studies of genotoxicity from carcinogen exposures, for assessment of space radiation damage. In a pilot study, we use PXB mice whose livers contain >90% human cells and have been found to function nearly identically to human liver tissues. These mice were exposed to gamma rays for investigations of DNA damage, transcriptomics, and histopathological changes in the humanized livers. Results obtained from PXB mice were compared non-engrafted control animals from the same background strain that are exposed to identical conditions. Preliminary data from histopathological analysis suggest chimeric mouse models are suitable for investigations of space radiation risks, as the humanized liver tissue exhibited changes induced by radiation and was markedly distinct from the liver tissue from the control animals (Fox Chase SCID mice).

Project Summary

- Chimeric animals can potentially bridge the knowledge gap between rodents and humans
- Expand translational research = preclinical animal models of astronaut health hazards
  - Risk assessment
  - Countermeasure development
  - Mitigation planning
- Mouse models = multiorgan mammalian test system
  - Mouse ≠ Human → Chimeric/humanized mice
  - PhoenixBio PXB Mouse = human livers in mouse model system
- PXB mice and controls exposed to radiation
  - Controls = genetic background of PXB, Fox Chase SCID
  - Liver tissue analyzed with histopathology and RNA analysis

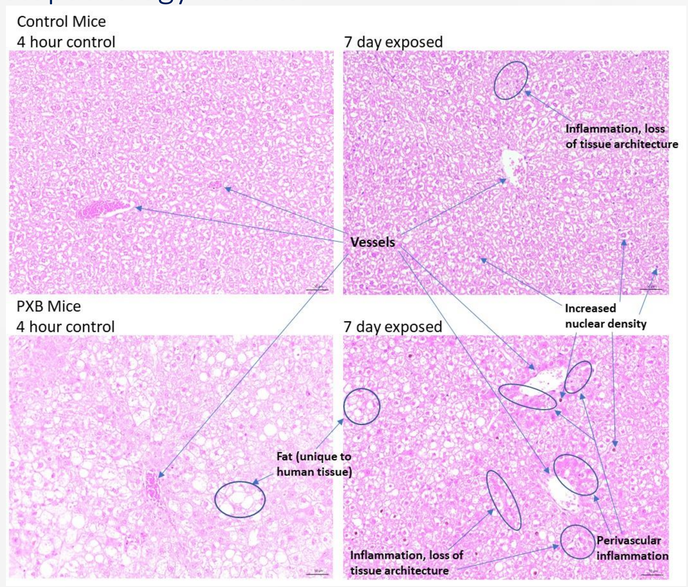


Study Plan

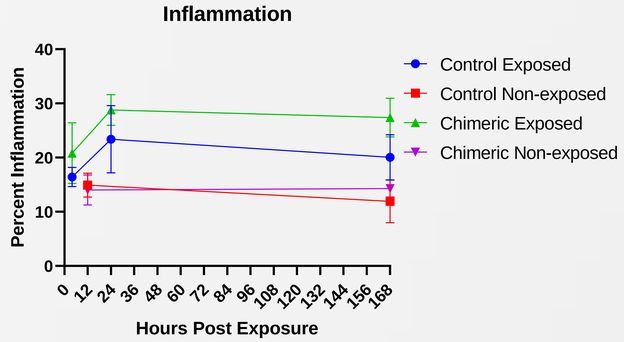
- Animals: PXB mice with chimeric livers and controls (Fox Chase SCID), 24 Male, 70 days old
- Timeline: 7 days environmental acclimation, 3 days restraint device acclimation, 1 day treatment (table below), tissue collection day 0-7 post-treatment
- Radiation: 2 Gray, with 1 Gray delivered from each side acutely, expose from side
- Analysis of liver tissue damage from radiation exposure: histopathology and transcriptomics.

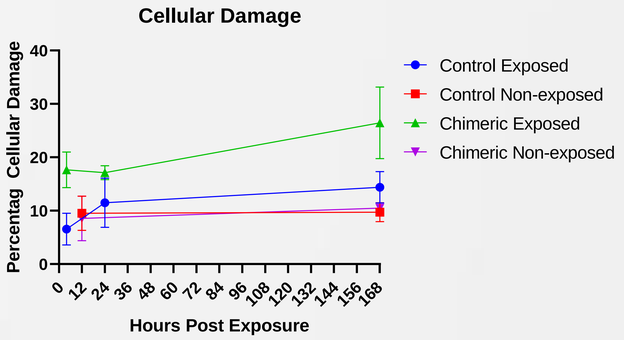
Group	Treatment
12 hr control 7 day control	Restraint only
4 hr exposed 24 hr exposed 7 day exposed	2 Gy Exposure

Histopathology Results

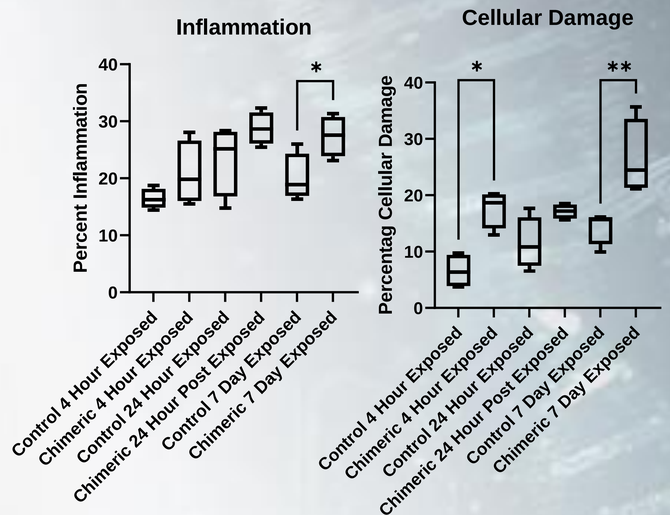


Increased nuclear density in irradiated animals 7 days after radiation, both groups. Increased inflammation, focused in perivascular areas in the PXB-mouse group 7 days after radiation.





Chimeric mice = PXB mice, human livers
Control Mice = FoxChase SCID mice, normal livers
Exposed = Exposed to 2 Gray gamma radiation
Non-exposed = Not exposed restraint controls

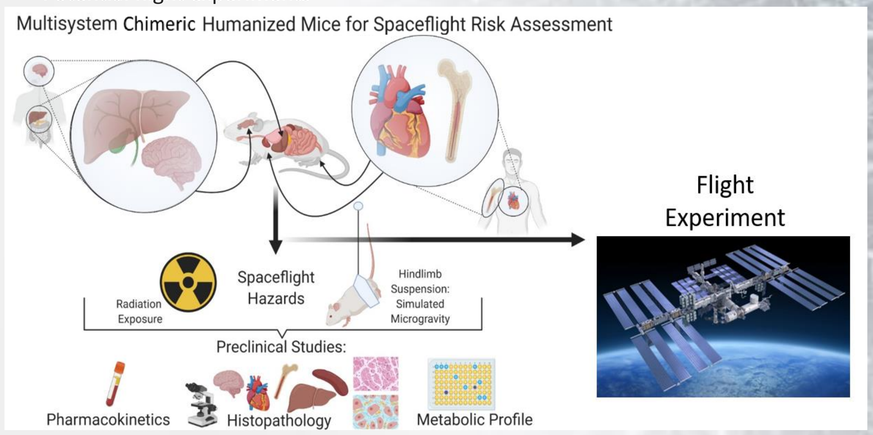


Preliminary Conclusions

- Chimeric mice are an opportunity to increase translatability from research animal data to implications in clinically-relevant human disease
- Human liver tissue in chimeric mice responds differently than mouse liver tissue to gamma radiation on the cellular level, as evidenced by differences in inflammation and cellular damage seen on histopathology
- Tissue samples from this study will be assessed for cellular damage markers with gene expression assay

Future Directions

- Use of this model for high-LET particle exposure, investigating other health risks associated with spaceflight
- Potential flight experiments



Acknowledgements

- Funding: Johnson Space Center Innovative Charge Account (ICA) and NASA Human Research Program Space Radiation Element support
- PhoenixBio, Co. support with supplying animals and collaborating on animal care