EXPRESSION OF ENZYMES THAT METABOLIZE MEDICATIONS
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INTRODUCTION
Increased exposure to radiation is one physiological stressor associated with spaceflight and it is feasible to conduct
ground experiments using known radiation exposures. The health of the liver, especially the activity rate of its
metabolic enzymes, determines the concentration of circulating drugs as well as the duration of their efficacy.
While radiation is known to alter normal physiological function, how radiation affects liver metabolism of
administered medications is unclear. Crew health could be affected if the actions of medications used in spaceflight
deviated from expectations formed during terrestrial medication use. This study is an effort to identify liver
metabolic enzymes whose expression is altered by spaceflight or by radiation exposures that mimic features of the
spaceflight environment.

METHODS
Using procedures approved by the Animal Care and Use Committee, mice were exposed to either 137Cs (controls,
50 mGy, 6Gy, or 50 mGy + 6Gy separated by 24 hours) or 13 days of spaceflight on STS 135. Animals were
anesthetized and sacrificed at several time points (4 hours, 24 hours or 7 days) after their last radiation exposure, or
within 6 hours of return to Earth for the STS 135 animals. Livers were removed immediately and flash-frozen in
liquid nitrogen. Tissue was homogenized, RNA extracted, purified and quality-tested. Complementary DNA was
prepared from high-quality RNA samples, and used in RT-qPCR experiments to determine relative expression of a
wide variety of genes involved in general metabolism and drug metabolism.

RESULTS
Results of the ground radiation exposure experiments indicated ~65 genes of the 190 tested were significantly
affected by at least one of the radiation doses. Many of the affected genes are involved in the metabolism of drugs
with hydrophobic or steroid-like structures, maintenance of redox homeostasis and repair of DNA damage. Most
affected genes returned to near control expression levels by 7 days post-treatment. Not all recovered completely by
the final time point tested: with 6 Gy exposure, metallothionein expression was 132-fold more than control at the 4
hr time point, and fell at each later time point (11-fold at 24 hrs, and 8-fold at 7 days). In contrast, there were other
genes whose expression was altered and remained relatively constant through the 7 day period we tested. One
examples is Cyp17a1, which showed a 4-fold elevation at 4 hrs after exposure and remained constant for 7 days
after the last treatment. Spaceflight samples evaluated with similar methods and comparisons will be made between
the radiation-treated groups and the spaceflight samples.

CONCLUSION
It seems likely that radiation exposure triggers homeostatic mechanisms, which could include alterations of gene
expression. Better understanding of these pathways could aid in optimizing medications doses given to
crewmembers who require treatment and eventually, to development of new countermeasures to ameliorate or
prevent radiation-induced damage to cells and tissues.