INTRODUCTION
Most administered pharmaceuticals are metabolized by the liver. The health of the liver, especially the rate of its metabolic enzymes, determines the concentration of circulating drugs as well as the duration of their efficacy. Most pharmaceuticals are metabolized by the liver, and clinically-used medication doses are given with normal liver function in mind. A drug overdose can result in the case of a liver that is damaged and removing pharmaceuticals from the circulation at a rate slower than normal. Alternatively, if liver function is elevated and removing drugs from the system more quickly than usual, it would be as if too little drug had been given for effective treatment. Because of the importance of the liver in drug metabolism, we want to understand the effects of spaceflight on the enzymes of the liver and exposure to cosmic radiation is one aspect of spaceflight that can be modeled in ground experiments. Additionally, it has been previously noted that pre-exposure to small radiation doses seems to confer protection against later and larger radiation doses (reviewed by Tapio, 2007). This protective power of pre-exposure has been called a priming effect or radioadaptation. This study is an effort to examine the drug metabolizing effects of radioadaptation mechanisms that may be triggered by early exposure to low radiation doses.

METHODS
Using procedures approved by the JSC Animal Care and Use Committee, male C57 mice were exposed to 137Cs in groups: controls (no radiation exposure, but handled similarly to the other groups), low dose (50 mGy), high dose (6 Gy) and a fourth group that received both radiation doses separated by 24 hours. Animals were anesthetized and sacrificed 4 hours after their last radiation exposure. Livers were removed immediately and flash-frozen in liquid nitrogen. Tissue was homogenized, RNA extracted (Totally RNA, Agilent), purified and quality-tested (Agilent 2100 Bioanalyzer). Complementary DNA was prepared from high-quality RNA samples (RIN > 8; RT2 First Strand, SABiosciences), and used to run RT-qPCR screening arrays for DNA Repair and Drug Metabolism (RT2 Profiler Arrays, SABiosciences). The data shown here are preliminary, in that they only show changes in gene expression. Additional experiments to corroborate these findings at the protein level are planned.

RESULTS
Of 91 drug metabolism genes examined, expression of 7 was altered by at least one treatment condition. Genes that had elevated expression include those that metabolize promethazine and steroids (4 to 8-fold), many that reduce oxidation products, and one that reduces heavy metal exposure (>200-fold). Of the 91 DNA repair and general metabolism genes examined, expression of 14 was altered by at least one treatment condition. Note that in some cases (Apex2, Ung, Rad51c, etc.) expression was not strictly dose-dependent.

CONCLUSION
The greatest expression changes were in MT2 (metallothionein) and Cyp17a1, one of the cytochrome p450 enzymes. In these two cases, large expression increases were seen in response to high and both low + high exposures. Metallothionein is usually thought to remove heavy metals from the body, but may also play a role in inflammation and oxygen free radical regulation (Sato et al., 2002). Gene expression is regulated by redox state (which can be affected by radiation exposure) in addition to metal concentrations and glucocorticoids. Increases in metallothionein expression (and glutathione reductase, GSR) have also been reported in livers of fish exposed to 75 mGy γ radiation (Olsvik et al., 2010). Cyp17a1 encodes an enzyme that adds an hydroxyl group to progesterone, which can then be converted to testosterone, estrogen or glucocorticoids. It can also contribute to the metabolism of administered medications that have complex ring structures, like hormones or promethazine. It is interesting to note that expression of the related Cyp19a was unchanged by all treatments, as were dozens of other genes. The results of the DNA Repair Array showed a similar number of alterations in expression, with up to 3-fold expression changes, consistent with other studies (Ding et al., 2015).

ACKNOWLEDGEMENTS
The authors would like to thank Ms. Ashley Purgason and Ms. Stephanie Bassett for technical assistance, and Dr. Robert Ploutz-Snyder for statistical expertise. The animal treatment portion of this study was funded by DOE to H. Wu. Additional funds for qPCR experiments on liver were provided to V. Wotring by NASA JSC Human Research Program.