

## ***In Vivo* Murine Dose-Response Calibration Curves for Early-Response Exposure Assessment Using Multiple Radiation-Responsive Blood Protein Biomarkers**

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The present need to rapidly identify severely irradiated individuals who require prompt medical treatment in mass-casualty incidents, as well as exposed vs. non-exposed individuals in population-monitoring radiation scenarios, prompted a murine *in vivo* dose- and time course-dependent study to evaluate the potential utility to use radiation-responsive blood protein biomarkers for exposure assessment purposes. Protein targets were measured by enzyme linked immunosorbent assay (ELISA) in male BALB/c mice (6–8 weeks old) blood plasma after whole-body  $^{60}\text{Co}$   $\gamma$ -exposure (10 cGy/min) to a broad dose range (0–7 Gy) and time-points (4–96 h).

Our research strategy involves the use of human, non-human primate, and murine models involving *ex vivo* and *in vivo* radiation exposure to identify and validate radiation-responsive protein biomarkers. Using an *ex vivo* model of human peripheral blood lymphocytes as well as an *in vivo* murine model, we earlier reported radiation-responsive changes in the expression of proteins *ras*-p21, *raf*-1, GADD45a, p53, and p21WAF1/CIP1, IL-6, each with a progressive time- and radiation dose-dependent increase. These results also revealed dose-dependent correlations among this subset of protein biomarkers, demonstrating their utility to identify potentially exposed individuals during the early assessment of radiation exposure. In addition, we recently presented similar data from non-human primates exposed to whole-body 6-Gy 250-kVp x-irradiation and 6.5-Gy  $^{60}\text{Co}$   $\gamma$ -irradiation. Data analyzed with use of multivariate discriminant analysis established very successful separation of animal groups before and after irradiation.

Here we present results from on-going murine *in vivo* studies demonstrating time- and dose-dependent increases in multiple blood protein biomarkers (i.e., GADD45a, IL-6, serum amyloid A or SAA). The use of multiple protein targets was evaluated using multiple regression analysis to provide dose-response calibration curves to enhance radiation sensitivity. Our efforts show for the first time the proof-of-concept that protein expression profile can be developed not only to predict radiation exposure in mice but also to distinguish the level of radiation exposure, ranging from 1 to 7 Gy.

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