

FINAL TECHNICAL REPORT
Supported by the Low Dose Radiation Research Program, Office of Science
U.S. Department of Energy
Grant No. DE-FG02-07ER64345
Project ID: 0012965
Award Register#: ER64345
Project Manager: Noelle F. Metting, Sc.D.
Phone: 301-903-8309 Division SC-23.2
noelle.metting@science.doe.gov

Submitted March 2012
To: <https://www.osti.gov/eliink/241.3.jsp>

Title: Th Cell Gene Expression and Function in Response to Low Dose and Acute Radiation
PI: Daila S. Gridley, Ph.D.

Human low dose radiation data have been derived primarily from studies of space and airline flight personnel, nuclear plant workers and others exposed occupationally, as well as victims in the vicinity of atomic bomb explosions. The findings remain inconclusive due to population inconsistencies and complex interactions among total dose, dose rate, radiation quality and age at exposure. Thus, safe limits for low dose occupational irradiation are currently based on data obtained with doses far exceeding the levels expected for the general population and health risks have been largely extrapolated using the linear-nonthreshold dose-response model. The overall working hypothesis of the present study is that priming with low dose, low-linear energy transfer (LET) radiation can ameliorate the response to acute high-dose radiation exposure. We also propose that the efficacy of low-dose induced protection will be dependent upon the form and regimen of the high-dose exposure: photons versus protons versus simulated solar particle event protons (sSPE). The emphasis has been on gene expression and function of CD4⁺ T helper (Th) lymphocytes harvested from spleens of whole-body irradiated C57BL/6 mice, a strain that provides the genetic background for many genetically engineered strains. Evaluations of the responses of other selected cells, tissues such as skin, and organs such as lung, liver and brain were also initiated (partially funded by other sources). The long-term goal is to provide information that will be useful in estimating human health risks due to radiation that may occur during exposures in the work environment, nuclear/radiological catastrophes, as well as radiotherapy. Several papers have been published, accepted for publication or are in preparation. A number of poster and oral presentations have been made at scientific conferences and workshops. Archived tissues of various types will continue to be evaluated via funding from other sources (the DoE Low Dose Radiation Research Program, Office of Science and this specific grant will be appropriately included in the Acknowledgements of all subsequent publications/presentations). A post-doc and several students have participated in this study. More detailed description of the accomplishments is described below.

PARTICIPATING POST-DOC AND STUDENTS

Asma Rizvi, Graduate student, later Post-doctoral Fellow
Adeola Y. Makinde, Graduate student
Sisi Tian, Medical student

PUBLISHED PAPERS

Rizvi A, Pecaut MJ and Gridley DS. Low-dose gamma-rays and simulated solar particle event protons modify splenocyte gene and cytokine expression patterns. *J. Radiat. Res. (Tokyo)*. 52(6):701-711, 2011.

Tian J, Zhao WL, Tian S, Slater JM, Deng Z and Gridley DS. Expression of genes involved in mouse lung cell differentiation/regulation after acute exposure to photons and protons with and without low dose pre-irradiation. *Radiat. Res.* 176(5):553-564, 2011.

Rizvi A, Pecaut MJ, Slater JM, Subramaniam S and Gridley DS. Low-dose γ -rays modify CD4⁺ T cell signalling response to simulated solar particle event protons in a mouse model. *Int. J. Radiat. Biol.* 87(1):24-35, 2011.

Gridley DS, Luo-Owen X, Rizvi A, Makinde AY, Pecaut MJ, Mao XW and Slater JM. Low-dose photon and simulated solar particle event proton effects on Foxp3⁺ T regulatory cells and other leukocytes. *Technol. Cancer Res. Treat.* 9(6):637-649, 2010.

MANUSCRIPTS IN REVIEW

Gridley DS, Rizvi A, Makinde AY, Luo-Owen X, Mao XW, Tian J, Slater JM and Pecaut MJ. Space-relevant radiation modifies cytokine profiles, signaling pathways and Foxp3⁺ T cells. *Int. J. Radiat. Biol.* In review, 2012.

Tian J, Tian S and Gridley DS. Gene expression profiles relevant to extracellular matrix, adhesion, and profibrotic molecules after acute exposure to photons or protons with or without low dose pre-irradiation. *J Radiat Res (Tokyo)*. In review, 2012.

MANUSCRIPTS IN PREPARATION

Gridley DS, Michael J. Pecaut MJ, Makinde AY, Rizvi A and Xiao Wen Mao. Apoptosis/oxidative stress-related gene expression in the CNS after protracted low-dose and acute gamma and proton radiation. In preparation, 2012.

At least 2 additional manuscripts are in progress.

PRESENTATIONS AT SCIENTIFIC MEETINGS

Mao XW, Mekonnen T, Kennedy AR, Gridley, D.S. Gene expression analysis of oxidative stress-initiated extracellular matrix remodeling in low-dose/low-dose-rate photon irradiated skin. Presentation at 56th Annual Meeting of the Radiation Research Society (RRS). Maui, HI. Sept. 25-29, 2010.

Tian J, Tian S, Slater JM, Gridley DS. Comparison of acute photon and proton effects on lung profibrosis and tissue remodeling-related genes and protein expressions with low-dose photon pre-irradiation. Presented at 56th Annual Meeting of the Radiation Research Society (RRS). Maui, HI. Sept. 25-29, 2010.

Rizvi A, Luo-Owen X, Gridley DS. Cytokine profiles induced by exposure to low-dose radiation and simulated solar particle event protons. Presented at 56th Annual Meeting of the Radiation Research Society (RRS). Maui, HI. Sept. 25-29, 2010.

Gridley DS, Luo-Owen, X., Rizvi, A., Makinde, A.Y., Tian, J., Mao, X.W., Slater, J.M., and Pecaut, M.J. Proton versus photon radiation effects on immune and other normal tissues. Invited oral presentation by D.S. Gridley during Symposium on "Radiation Treatment Factors: Effects on Immune and Normal Tissue Responses." Presented at 56th Annual Meeting of the Radiation Research Society (RRS). Maui, HI. Sept. 25-29, 2010.

Gridley DS, Luo-Owen X, Rizvi A, Makinde AY, Pecaut MJ, Mao XW, Slater JM. Low-dose photon and simulated solar particle event proton effects on Foxp3⁺ Treg cells and other leukocytes. Presented at U.S. Department of Energy (DOE) Low Dose Radiation Research Investigators' Workshop IX, Washington, DC. Abstract Book pp. 63-64. April 12-14, 2010.

Rizvi A, Pecaut MJ, Slater JM, Gridley DS. Low-dose photons modify CD4⁺ T cell signaling response to simulated solar particle event protons. Presented at U.S. Department of Energy (DOE) Low Dose Radiation Research Investigators' Workshop IX, Washington, DC. Abstract Book pp. 65-88. April 12-14, 2010.

Gridley DS, Luo-Owen X, Rizvi A, Makinde AY, Tian J, Pecaut MJ. Long-term effects of low-dose photons on Treg and other CD4⁺ lymphocyte responses to high-dose photons and protons. Presented at U.S. Department of Energy (DOE) Low Dose Radiation Research Investigators' Workshop IX, Washington, DC. Abstract Book pp. 69-70. April 12-14, 2010.

Mao XW, Mekonnen T, Gridley DS. Gene expression analysis of apoptosis and oxidative stress in mouse brain after low-dose and acute radiation exposure. Presented at U.S. Department of Energy (DOE) Low Dose Radiation Research Investigators' Workshop IX, Washington, DC Abstract Book pp. 67-68. April 12-14, 2010.

Tian J, Slater JM, Gridley DS. Stem cell marker expression in mouse lung after exposure to acute photons and protons with and without pre-exposure to low-dose photons. Presented at U.S. Department of Energy (DOE) Low Dose Radiation Research Investigators' Workshop IX, Washington, DC. Abstract Book pp. 71-72. April 12-14, 2010.

Tian J, Pecaut MJ, Slater JM, Gridley DS. Extracellular matrix regulators in lung tissue after exposure to low-dose photons and simulated solar particle event protons. Presented at 55th Annual Meeting of the Radiation Research Society (RRS). Savannah, GA. Abstract Book, PS1.26, p. 62. October 4-7, 2009.