FINAL REPORT – DOE AWARD NO. DE-FG07-99ER62876

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Project Title: Adaptive Response Against Spontaneous Neoplastic Transformation *In Vitro* Induced by Ionizing Radiation.

Research Objective

As indicated in previous reports the goal of this project was to establish a dose response curve for radiation-induced neoplastic transformation of HeLa x skin fibroblast human hybrid cells *in vitro* under experimental conditions where an adaptive response, if it were induced, would have an opportunity to be expressed. During the first two years of the grant an exhaustive series of experiments were performed and the resulting data were reported at the 2000 Annual Meeting of the Radiation Research Society and then subsequently published (*Redpath et al., 2001*). The data showed that an adaptive response against spontaneous neoplastic transformation was seen up to doses of 10cGy of Cs-137 gamma rays. At dose of 30, 50 and 100 cGy the transformation frequencies were above background. This indicated that for this system, under the specific experimental conditions used, there was a threshold of somewhere between 10 and 30 cGy. The results also indicated some unexpected, though very interesting, correlations with relative risk estimates made from human epidemiologic studies (for details see the *Redpath et al., 2001*).

Research Progress and Implications

As of midway through the third year, and into the fourth no-cost extension year, we performed similar experiments using a 60 kVp x-ray beam. This is the energy of x-rays routinely used in fluoroscopic examinations in diagnostic radiology. Apart for the important implications of this study to diagnostic radiology, the studies also had the potential to examine how the adaptive response may depend on radiation quality as 60 kVp x-rays have a higher mean LET than Cs-137 gamma rays. Prior to carrying out these experiments we expected that the 60 kVp x-rays would be more effective at higher doses and the low dose adaptive response would be less or perhaps absent compared to Cs-137 gamma rays. The data obtained are in press (*Redpath, Lu et al., 2003*). We correctly predicted the higher efficacy at inducing transformation at high doses. However, we were incorrect in our hypothesized reduced adaptive response. Indeed, just the opposite was the case, namely the low dose suppression of transformation was more powerful for the 60 kVp x-rays. The implications of this are that the risks associated with diagnostic energy x-rays may be much less than are currently estimated.

Also in the third and the fourth no-cost extension year, through collaboration with Susan Short and Peter Johnston at the Gray Cancer Institute, Northwood, UK, we explored the possible role of hyper-radiosensitivity of a

transformation prone sub-population as a mechanism underlying the observed suppression of transformation at low doses. The results indicated that G2 cells are uniquely hyper-radiosensitive at low doses. This finding, together with our earlier studies that showed G2 cells to be more prone to spontaneous transformation, was shown to be a feasible mechanism at least at a dose of 5 cGy. This study was recently published (*Redpath, Short et al., 2003*).

In view of our already demonstrated dependence of the suppressive effect of low doses of radiation on radiation quality within the low LET range, during the fourth no-cost extension year we began some experiments with mammography energy (28 kVp) x-rays. While these experiments are still underway, preliminary data does suggest that a similar suppression of transformation at doses of 2 cGy and lower.

Since the suppression of transformation by low doses of low LET radiation is seen over a wide dose range, in our opinion it is likely that multiple mechanisms are involved. These are being explored as part of another grant (DE-FG03-02ER63309).

Information Access

The publications cited above are listed below:

REDPATH, J. L., LIANG, D., TAYLOR, T. H., CHRISTIE, C., ELMORE, E., 2001, The shape of the dose-response curve for radiation-induced neoplastic transformation in vitro: Evidence for an adaptive response against neoplastic transformation at low doses of low-LET radiation. *Radiat. Res.*, 156: 700-707.

REDPATH, J.L., SHORT, S.C., WOODCOCK, M. AND JOHNSTON, P.J., 2003, Low dose reduction in transformation frequency compared to unirradiated controls: the role of hyper-radiosensitivity to cell kill. *Radiat. Res.*, 159: 433-436.

REDPATH, J.L., LU Q., LIAO, X., MOLLOI, S. and ELMORE, E., 2003, Low doses of diagnostic energy x-rays protect against neoplastic transformation *in vitro*, *Int. J. Radiat. Biol.*, 79: 235-240.