

# Mechanisms of Intrinsic Radiation Sensitivity: The Effects of DNA Damage Repair, Oxygen, and Radiation Quality

David J. Carlson, Ph.D.

*School of Health Sciences, Purdue University, West Lafayette, IN, USA.*

*Thesis Supervisor: Robert. D. Stewart, Ph.D.*

*Ph.D. awarded August 2006 in Medical Physics by Purdue University, USA.*

*[Current E-mail: dave.carlson@stanford.edu]*

A kinetic repair-misrepair-fixation (RMF) model is developed to link double-strand break (DSB) induction to reproductive cell death. The linear-quadratic (LQ) survival model is an approximate time-integrated solution to the RMF. Expressions relating LQ radiosensitivity parameters to DSB induction, repair, and fixation are used to investigate the effects of DNA damage repair, oxygen, and radiation quality on intrinsic radiosensitivity. Published survival data for prostate cancer cells is re-analyzed. Seemingly small corrections for dose rate effects, such as those expected in high-dose-rate experiments, can have a significant impact on estimates of  $\alpha$  and  $\alpha/\beta$ . By neglecting dose rate effects, estimates of the  $\alpha/\beta$  ratio may be too high by factors as large as 1.3 to 6.2. The prostate radiosensitivity parameters  $\alpha$  and  $\alpha/\beta$  are approximately the same *in vitro* and *in vivo* and the *in vitro* data are consistent with an  $\alpha/\beta$  ratio for prostate cancer less than 3 or 4 Gy. Mechanistic considerations suggest that LQ parameters for hypoxic ( $H$ ) and aerobic ( $A$ ) cells are related by  $\alpha_H = \alpha_A/OER$  and  $(\alpha/\beta)_H = OER(\alpha/\beta)_A$ , where  $OER$  is the ratio of the dose to the hypoxic cells to the dose to the aerobic cells required to produce the same number of DSB per cell. These expressions are tested against cell survival data. For low-LET radiation, estimates of the  $OER$  are between 2.3 and 3.3 for extreme levels of hypoxia. Analysis of patient survival data for cervix cancer suggests an average  $OER \leq 1.5$ . The dose to hypoxic tumor regions needs to be escalated by a factor of the  $OER$  to achieve the same level of tumor control as in well oxygenated tumor regions. Monte Carlo methods are used to estimate the yield of various classes of DSB for low- and high-LET radiations. The DSB yields are used to investigate the contributions of potential mechanisms to cell killing. Analysis of cell survival data suggests intra-track DSB interactions are negligible for low-LET radiations and all DSB are potentially rejoinable. The importance of intra-track pairwise DSB interactions increases with increasing LET but misrepaired and fixed DSB still contribute significantly to cell killing through one-track mechanisms.

**Dissertation can be downloaded from:**

<http://rh.healthsciences.purdue.edu/student/djcarlson/>