

There is growing evidence that low doses and low dose rates of low linear energy transfer (LET) ionizing radiation can induce a protective process that leads to a reduction in frequency of mutations, neoplastic transformation, and cancer below the spontaneous level. High doses and dose rates of low-LET radiation and low and high dose rates of high-LET alpha radiation however, appear to inhibit the protection, leading to elevated risks for the indicated biological effects. In this presentation, a dose-response model called NEOTRANS₃ (Fig. 1) is discussed which attributes the low-dose protection to stimulation of apoptosis among genomically compromised cells (Scott BR, Mutation Research 568:129-143, 2004). The indicated apoptosis selectively removes genomically compromised cells and has been named the **protective apoptosis mediated** (PAM) process. The PAM process (a protective bystander effect) is thought to be mediated via reactive oxygen and nitrogen species, and in the case of fibroblast, by extracellular transforming growth factor β 1 (TGF- β 1) (Scott BR et al. NonLinearity 2:185-211, 2004). Apoptosis is presumed to occur via the mitochondrial pathway.

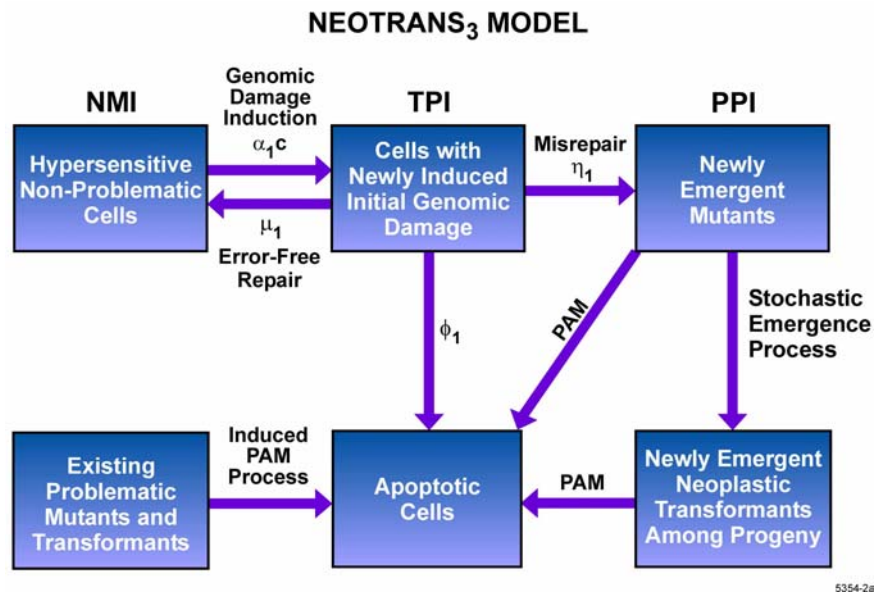


Figure 1.

Figure 1 shows NEOTRANS₃ model transitions. The abbreviations NMI, TPI, and PPI respectively stand for normal minor instability, transient problematic stability, and persistent problematic instability (a characteristic assigned to mutant cells) in the genome. The parameter α_i when multiplied by the instantaneous dose rate c accounts for genomic damage induction. Parameters μ_i , η_i , and ϕ_i relate to error-free repair, misrepair, and normal apoptosis respectively. Misrepair leads to newly emergent viable mutants (PPI cells). Progeny of mutant cells with PPI undergo neoplastic transformation as a stochastic emergence process. The PAM process when activated eliminates some mutant cells, neoplastically transformed cells as well as some other genomically compromised cells (e.g. micronucleated cells).

Activation of PAM appears to require a stochastic threshold, D_{PAM} , which varies for different individuals (*in vivo*), and also *in vitro* for different replicate samples. Also, above a stochastic threshold, D_{off} , PAM appears to be inhibited. Because of the indicated stochastic thresholds, dose-response relationships for mutagenesis, neoplastic transformation, and cancer induction by low-LET radiation are predicted to be of the nonlinear hormetic type, involving a dose zone over which risk is suppressed below the spontaneous level when PAM is

activated. The level of suppression as well as the dose range over which suppression occurs is expected to increase with decreasing dose rate of low-LET radiation.

The NEOTRANS₃ model has been applied to *in vitro* neoplastic transformation data of Dr. Leslie Redpath's group for Cs-137 gamma-ray (Redpath JL et al. Radiat. Res. 156, 700-707, 2001), 28 kVp mammographic-energy x-ray (Ko SJ et al. Radiat. Res. 162:646-654, 2004), and proton (L. Redpath, personal communications) irradiation of Hela x skin fibroblast hybrid cells. Key findings obtained using Bayesian inference methods to apply the NEOTRANS₃ model to these data are as follows: (1) The mammographic-energy x rays (28 kVp) on average appear about 2.7 times more effective than gamma rays for inducing genomic instability associated with the occurrence of neoplastic transformation, while gamma rays appear to be about 1.5 times more efficient than the low-energy x rays in suppressing neoplastic transformation via the PAM process. (2) Protons on average appear about 1.6 times more effective than gamma rays for inducing genomic instability associated with the occurrence of neoplastic transformation, while gamma rays appear to be about 2 times more efficient than protons in suppressing neoplastic transformation via the PAM process. (3) Stochastic thresholds D_{off} for inactivating PAM appear significantly lower for both mammographic-energy x rays (50 to 100 mGy) and protons (50 to 90 mGy) than for gamma rays (150 to 250 mGy).

The NEOTRANS₃ model has also been applied to *in vivo* mutation frequency data from Dr. Pamela Sykes' group for whole body x-irradiation of pKZ1 mice (Hooker AM et al. Radiat. Res. 162:447-452, 2004). The pKZ1 recombination mutagenesis mouse model is extremely sensitive for detecting chromosomal inversion in the spleen after exposure to low doses of DNA-damaging agents. The indicated mutagenesis data are currently the only available data suitable for estimating the stochastic threshold D_{PAM} for PAM activation. Results for two experiments are presented in Figure 2 and place D_{PAM} in the narrow dose window 0.01 to 0.02 mGy, supporting the view that PAM is a bystander effect. However, higher doses also activate PAM so long as the dose is not $\geq D_{off}$. For doses < 0.01 mGy, DNA repair activation was assumed not to occur. This was found necessary in order to explain the initial steep rise in the dose-response curve at doses below 0.01 mGy. The indicated mean is Bayesian posterior mean based on the NEOTRANS₃ model. The steep rise above about 10 mGy is currently explained based on D_{off} being uniformly distributed over the interval 20 to 100 mGy.

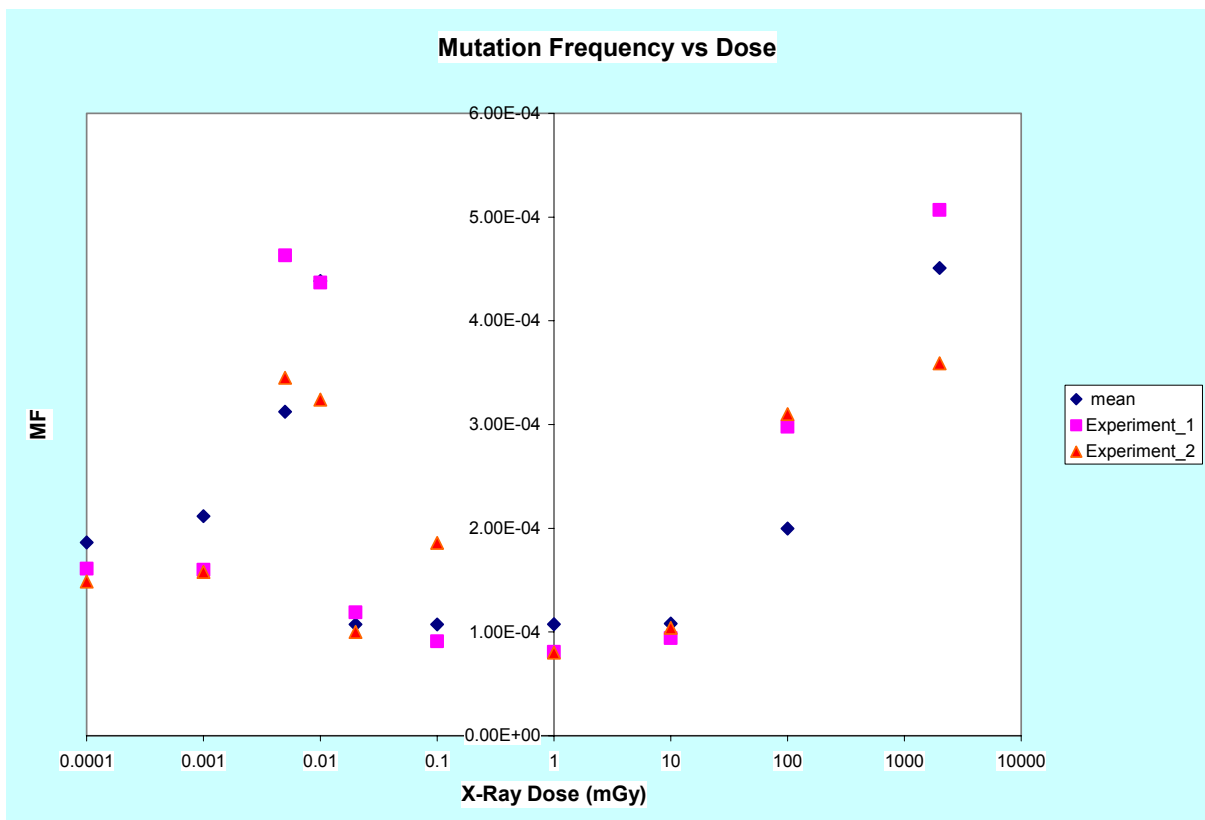


Figure 2.