Mitochondrial Targeted Antioxidants Protect Against Total Body Irradiation Induced Hematopoietic Syndrome, and Mitigate Against Irradiation Induced Life Shortening

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Intravenous administration of mitochondrial localized MnSOD-Plasmid Liposomes prior to 9.5 Gy total body irradiation (TBI) (LD 50/30) of adult C57BL/6NHsd male or female mice in cohort sizes of 50 animals per group was evaluated for protection against the hematopoietic syndrome, and for late irradiation-induced life shortening. Other cohorts received 1.0 Gy total body irradiation or no irradiation. A significant increase in survival at 30 days after 9.5 Gy TBI was detected in both male and female MnSOD-PL treated mice. Conditional survival of all survivors from day 30 was also measured. There was no significant increase in irradiation-induced life shortening between groups of female survivor mice observed for over two years. There was a decrease in irradiation-induced life shortening in MnSOD-PL treated male mice followed for over 1 ½ years. I.V. delivery of a mini circle-MnSOD-PL construct devoid of bacterial CPG sequences and appropriate for intravenous administration to primates or humans was similarly radioprotective. Small molecule mitochondrial targeted GS-nitroxides including JP4-036 and XJB-5-131 demonstrated radioprotection against 9.5 Gy TBI by a mechanism involving mitochondrial targeting of antioxidant action.

Mitochondrial targeted antioxidants may prove valuable for mitigating the total body irradiation effects leading to the hematopoietic syndrome and irradiation-induced life shortening.