The GS-nitroxide JP04-39 is a potent topical antioxidant that can mitigate skin damage from ionizing radiation. R Brand, M Epperly, J Stottlemyer, X Gao, S Li, S Huq, P Wipf, V Kagan, J Greenberger, L. D. Falo, Jr. Departments of Dermatology, Radiation Oncology, and Pharmacology, University of Pittsburgh School of Medicine.

There is considerable need to design mitigating agents to reduce ionizing irradiation-induced cutaneous injury. Cutaneous manifestations of radiation damage are generally divided into acute radiation-induced dermatitis (days to weeks later) and chronic radiation-induced dermatitis (months to years later). Mitochondrial damage plays a critical role in the initiation of ionizing irradiation-induced cellular apoptosis and tissue injury. In an effort to ameliorate ionizing irradiation induced skin damage, we designed a small molecule nitroxide, JP04-39, that combines several important anti-oxidant and electron-scavenging properties in a single mitochondrial-targeted functional moiety. To evaluate the effectiveness of this novel drug, the hind legs of C57/BL6 mice were irradiated with 30-35 GY with or without topical treatment with JP04-39 15 minutes after irradiation and then daily for 5 consecutive days. For clinical evaluation, photos were taken for visual evidence of skin damage and leg contracture was measured as a functional evaluation of tissue damage. Histological comparison, including characterization of skin thickening and cellular infiltrates, was also performed. Further, to evaluate the mechanism of radiation damage mitigation, skin samples were assayed for evidence of apoptosis and oxidative stress. Taken together, these studies revealed that topically applied JP04-39 mitigates clinically evident acute skin damage, and damage mitigation correlates with reductions in cellular infiltrates. The GS-nitroxide also demonstrated potent antioxidant function and prevented radiation-induced apoptosis in the skin. These results suggest that topically applied JP04-39 is a potent antioxidant that can prevent/reverse acute irradiation damage.