Development of radiation countermeasures for acute radiation syndrome: Current status of biomarker identification and validation

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Exposures to ionizing radiation, whether intended or unintended, are currently an undeniable reality and carry potentially catastrophic health consequences. Therefore, medical preparedness and countermeasures are critical security issues, not only for the individual, but for the nation as a whole. Acute radiation exposure induces apoptosis leading to acute radiation syndrome (ARS). Significant scientific advances have been made toward the development of safe, non-toxic and effective radiation medical countermeasures (MCMs) for ARS. However, to date only four radiomitigators including Neulasta, Leukine, and Nplate have received United States Food and Drug Administration (US FDA) approval for countering hematopoietic-ARS. A MCM capable of protecting the population at large from the effects of lethal radiation exposure which can be administered pre-exposure remains a significant unmet need and has been recognized as a high priority by the US government. A number of promising MCMs (radioprotectors and radiomitigators) are currently under development. Two radioprotectors, gamma-tocotrienol (GT3, a nutraceutical and a component of vitamin E) and BIO 300 (a novel formulation of genistein - 4',5,7-trihydroxyisoflavone) are noteworthy.

The above listed MCMs under development following the Animal Rule need to be evaluated and their dose for humans needs to be established based on appropriate biomarkers to improve relevance. Currently, we are investigating various biomarkers for radiation injury and MCM efficacy using cytokines and various omics platforms including metabolomics/lipidomics, proteomics, transcriptomics, microRNA (miRNA), and the microbiome. Using an NHP model, we have demonstrated that a signature of seven conserved miRNAs are altered by irradiation (also in mice), and a combination of three (miR-133b, miR-215, and miR-375) can identify irradiated NHPs compared to unirradiated animals. Several protein/metabolite biomarkers for GT3 and BIO 300 using irradiated murine and NHP models have been identified and are being further validated in follow-up studies. The effects of BIO 300 on the gut microbiota and metabolome of mice exposed to cobalt-60 γ-radiation were characterized by bacterial 16S rRNA amplicon sequencing and untargeted metabolomics, respectively.

Following FDA-approval, these promising agents would be useful at a local, national, or global level after a radiological or nuclear event.

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