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## The Delayed Effects of Acute Radiation Exposure (DEARE): characteristics, mechanisms, animal models, and promising medical countermeasures

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### Abstract

**Purpose:** Terrorist use of nuclear weapons and radiation accidents put the human population at risk for exposure to life-threatening levels of radiation. Victims of lethal radiation exposure face potentially lethal acute injury, while survivors of the acute phase are plagued with chronic debilitating multi-organ injuries for years after exposure. Developing effective medical countermeasures (MCM) for the treatment of radiation exposure is an urgent need that relies heavily on studies conducted in reliable and well-characterized animal models according to the FDA Animal Rule. Although relevant animal models have been developed in several species and four MCM for treatment of the acute radiation syndrome are now FDA-approved, animal models for the delayed effects of acute radiation exposure (DEARE) have only recently been developed, and there are no licensed MCM for DEARE. Herein, we provide a review of the DEARE including key characteristics of the DEARE gleaned from human data as well as animal, mechanisms common to multi-organ DEARE, small and large animal models used to study the DEARE, and promising new or repurposed MCM under development for alleviation of the DEARE.

**Conclusions:** Intensification of research efforts and support focused on better understanding of mechanisms and natural history of DEARE are urgently needed. Such knowledge provides the necessary first steps towards the design and development of MCM that effectively alleviate the life-debilitating consequences of the DEARE for the benefit of humankind worldwide.

### Keywords

Delayed effects of acute radiation exposure (DEARE); animal models; medical countermeasures (MCM); radioprotectant; radiomitigator

### Background

There is an urgent demand for effective medical countermeasures (MCM) in the event of high-dose radiation exposure (prompt exposures of  $>2\text{Gy}$  (Coleman et al. 2015; Winters et al. 2023)) ranging from nuclear plant disasters to nuclear warfare. Less than 24 hours

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after exposure to high-dose ionizing radiation, victims develop a continuum of multi-system symptoms referred to as acute radiation syndrome (ARS). Survivors of ARS are at risk for developing the delayed effects of acute radiation exposure (DEARE), a spectrum of chronic illnesses involving multiple organ systems and occurring months to years after radiation exposure. The DEARE are believed to result from some combination of oxidative stress, inflammation, senescence, fibrosis, and loss of stem cell self-renewal potential in the ARS survivors (Robbins and Zhao 2004; Zhao and Robbins 2009; Chua et al. 2012; Unthank et al. 2015; Wang et al. 2016; Al-Jumayli et al. 2022). DEARE remain an understudied area of radiation injury, with most knowledge gleaned from observing atomic bomb survivors and post-radiotherapy cancer survivors.

There are three types of DEARE: somatic, genetic (hereditary), and fetal (*in utero*). “Somatic” DEARE encompass injury to organs and tissues. “Genetic” DEARE indicate effects on the offspring of the exposed individual, while “Fetal” DEARE are effects on individuals exposed *in utero*. The focus of this review is somatic DEARE. Considering the radiation dose-response relationship (DRR) model, somatic DEARE can be a deterministic or stochastic effect. “Deterministic” means the dose of radiation determines the severity of the effect. It occurs when the radiation dose that the victim is exposed to exceeds a certain level (threshold), resulting in sufficient cellular damage to cause specific DEARE. There are two characteristics of the deterministic effect: 1) the severity of the effect is proportional to the absorbed dose, and 2) symptoms occur only when the dose is at or above the threshold. The shape of the curve is sigmoidal. Effects on testis and bone marrow (BM), two organs with the lowest thresholds for radiation damage in the body (0.15 Gy for testis and 0.5 Gy for BM), are examples of the deterministic effect (López and Martín 2011). In contrast, stochastic effects occur by chance. The probability of occurrence is proportional to the dose of radiation, but there is no obvious threshold, and the effect can occur even if only one cell is damaged. The shape of the curve is linear. Malignancy induced by irradiation is an example of a stochastic effect (Blakely 2000; Dainiak et al. 2003).

### Late effects in atomic bomb survivors and after radiotherapy

According to the Life Span Study (LSS) and Adult Health Study (AHS) of the Hiroshima and Nagasaki atomic bomb survivors, cataracts, thyroid disease, hyperparathyroidism, chronic liver disease and cirrhosis, uterine myoma, hypertension, myocardial infarction, stroke, chronic kidney diseases, and pneumonia/influenza are significantly associated with radiation exposure (Yamada et al. 2004; Ozasa et al. 2012). Cancer survivors who received radiotherapy of the abdomen or pelvis have been reported to develop delayed radiation enteropathy, presenting as malabsorption or dysmotility (Hauer-Jensen et al. 2014). Dr. Moulder’s group was one of the first to describe the increase in late-onset chronic kidney disease in patients receiving high-dose total body irradiation (TBI) as a conditioning treatment for hematopoietic stem cell (HSC) transplantation (Cohen et al. 2010; Cohen et al. 2012). In patients receiving thoracic radiotherapy, 5–15% develop symptomatic pneumonitis, and 43% experience radiation-induced pneumonitis or pulmonary fibrosis 6–24 months after treatment (Movsas et al. 1997; Williams et al. 2010). Neurocognitive deficits occur several months to years after treatment in 30–50% of patients who received radiotherapy for brain tumors (Durand et al. 2015; Yamada 2016). The lens is the most

sensitive ocular structure and cataracts are a radiotherapy side-effect for the treatment of retinoblastoma (as well as a risk for astronauts due to exposure to space radiation (Cucinotta et al. 2001)). Radiation-induced cataracts represent a deterministic effect where the minimum cataractogenic dose ranges from 2–8 Gy according to whether it is a low or high-LET exposure, fractionated, or single treatment (Cogan et al. 1952; Schipper et al. 1985; Chodick et al. 2008).

The DEARE observed in atomic bomb survivors and patients that have received radiotherapy are different. In general, late effects have been greatly reduced after radiotherapy through the years due to advanced technologies, such as proton therapy, which better target radiation to the tumor, sparing normal tissue. Fractionated delivery of relatively smaller doses of radiation over time in radiotherapy allows for better DNA repair and thus fewer late effects, compared to the vast tissue injury that results from a single blast exposure as is the case for atomic bomb survivors. The LD50/60 for humans is approximately 4 Gy for an acute TBI exposure, but not for a protracted low dose rate exposure such as that used to eradicate an epithelial tumor (i.e., 60–80 Gy, delivered in multiple fractions). Medical interventions and dose limits in radiotherapy also lead to improved outcomes, which aren't always practicable in the chaotic aftermath of a radiation accident or malicious exposure. Animal models of both types of radiation exposure have been developed to study late effects in each scenario. Due to the increased degree of normal tissue exposure in atomic bomb survivors versus the targeted irradiation of tumors in radiotherapy patients, atomic bomb survivors experience an increased risk for developing malignancies in later life compared to radiotherapy patients. Over the years following radiation exposure, the risk for solid tumor development gradually increases to a greater extent than the age-related risk of tumors in non-exposed humans. There is a significant linear dose-response relationship to tumor development in cancers of the oral cavity, esophagus, stomach, colon, liver, lung, etc. Other factors also impact tumor risks, such as gender, age at exposure, time after exposure, and lifestyle. The relative risk for total solid tumors is 50% higher in females than males, and two-fold higher in survivors exposed at a younger age than at an older age (Furukawa et al. 2009; Douple et al. 2011; Ozasa et al. 2012).

The latent period for hematopoietic malignancies is much shorter than for solid tumors. Leukemia is the predominant radiation-related cause of death in the early years post-atomic bomb exposure. The first instance of radiation-induced leukemia was reported 7 years after the atomic bombing of Japan (Finch et al. 1965). In atomic bomb survivors, the risk of developing leukemia peaked 8–10 years after exposure and then rapidly decreased (Preston et al. 2004). Risk for myelodysplastic syndromes is also associated with radiation exposure, but, unlike leukemias, these develop later in life (Iwanaga et al. 2011). There is little evidence to indicate that radiation exposure increases the risk of lymphomas or multiple myeloma in humans (Preston et al. 1994).

DEARE on the hematopoietic system are known as Residual Bone Marrow Damage (RBMD), a latent condition characterized by prolonged inhibition of hematopoiesis leading to immunosuppression and increased infection risk, which has been observed in mice, nonhuman primates (NHP), and atomic-bomb human survivors (Wang et al. 2010; Chua et al. 2012; Farese et al. 2015; Kamiya et al. 2015; Chua et al. 2019). Radiation-induced

apoptosis of HSC causes hematopoietic acute radiation syndrome (H-ARS). The injury on the hematopoietic system can persist long-term (Chua et al. 2012; Chua et al. 2019), though this phenomenon has been largely ignored due to the seemingly complete recovery of peripheral blood cell counts, BM cellularity, and number of colony-forming units early after exposure with the treatment of colony stimulating factors in murine and NHP models (Shinjo et al. 1997; Wang et al. 2006). Long-term hematopoietic injury likely results from a combination of persistent hematopoietic damage and the “second hit” that aging imparts on the hematopoietic system.

## Mechanisms of DEARE

Although different organs express their own unique DEARE and have different susceptibilities to radiation damage, several DEARE mechanisms are common to multiple organs, as follows:

### Cell apoptosis.

Highly specialized cells, such as cardiomyocytes (Woodcock and Matkovich 2005), neurons (Rakic 1974), red blood cells (Kuhn et al. 2017), and skeletal muscle cells (Rocheteau et al. 2015), etc, lose the ability to undergo cell divisions shortly after birth. Radiation exposure results in DNA double-strand breaks (DSBs) within the cell which leads to the activation of ataxia telangiectasia mutated (ATM) and subsequent downstream signaling events. ATM phosphorylates downstream p53 and PUMA, which inhibits Bcl-2 and activates pro-apoptotic Bax and Bak. Bax and Bak activate mitochondrial caspase-9, leading to the release of cytochrome C, which induces apoptosis in murine cells (Chong et al. 2000; Lozano and Zambetti 2005; Tichy et al. 2010; Yu et al. 2010). When radiation-induced apoptosis overwhelms cell replenishment systems and apoptotic cells cannot be replaced by new cells from differentiation of progenitors and stem cells, or when cell replenishment systems are inherently slow in a given organ, atrophy of the organ occurs and the DEARE ensue (Crossen et al. 1994; Furby et al. 2010; Mittal and Katirji 2017; Brook 2020; Obrador et al. 2020).

### Cell senescence.

The pathophysiological processes of aging and radiation injury are similar and both can induce cellular senescence (Al-Jumayli et al. 2022). Radiation-induced cell senescence results from ROS or p53-mediated activation of p38 and downstream p16. Activation of p16 results in irreversible cell cycle arrest and senescence (Beausejour et al. 2003; Herranz and Gil 2018). HSC senescence is believed to contribute to RBMD, which is characterized as a combination of loss of self-renewal ability and aberrant multilineage differentiation, as demonstrated in murine models (Mauch et al. 1988; Meng et al. 2003; Wang et al. 2006; Wang et al. 2010; Chua et al. 2012; Chua et al. 2019) and in atomic-bomb survivors (Kajimura et al. 2016). Radiation-induced endothelial cell senescence and subsequent progressive vasculopathy are mechanisms for cardiovascular DEARE in survivors of murine H-ARS (Unthank et al. 2019).

## Inflammation and fibrosis.

Senescent cells secrete proinflammatory factors which trigger chronic inflammation in multiple organs (Herranz and Gil 2018). Sustained inflammation is observed in the ventricle myocardium and arterial wall in murine models and human biopsies, possibly initiated by NF- $\kappa$ B activation (Halle et al. 2010; Unthank et al. 2019). The anti-inflammatory cytokine transforming growth factor beta (TGF- $\beta$ ) increases its expression post-radiation and persists for months. Radiation-induced apoptosis and senescence can induce fibrosis via canonical and non-canonical TGF- $\beta$  signaling pathways in murine models (Farhood et al. 2020). The accumulation of collagen and fibronectin in the fibrotic process impairs normal organ functions (Pohlert et al. 2009). MCMs targeting the TGF- $\beta$  signaling pathways are in development and show efficacy in attenuating cardiac and pulmonary fibrosis, which are discussed in the following sections.

## Animal models

### Species.

Efficacy studies for ARS and DEARE must adhere to the FDA Animal Rule (AR) (Crawford 2002) and the FDA guidance document (FDA-CDER 2015), drafted to guide drug development when human efficacy studies are unethical to perform, such as those with lethal radiation. Well-characterized animal models for ARS and DEARE are essential for MCM development under the AR, and the most heavily-utilized models have been developed in mice, rats, and nonhuman primates (NHP). Lesser-used models have been developed in guinea pigs, rabbits, ferrets, canines and minipigs, but their use in MCM development studies is hampered by their limited database necessary for regulatory review. The FDA generally recommends use of two animal models, a large and a small, for drug approval under the AR, but will accept data in a single model if a sufficient database exists that supports its efficacy and safety as a radiation MCM. Mice are the preferred small animal model for MCM screening studies due to the existence of a large database for murine radiation studies, economics, ease of performing aging studies, and existence of sophisticated research tools and genetic models for determining mechanisms, among others. C57BL/6 and C3H/HeN mice are the two strains recommended by the Centers for Medical Countermeasures against Radiation (CMCRs) for developing MCMs (Williams et al. 2010). Confirmatory studies are conducted in large animals, primarily the NHP.

### Radiation exposure.

Radiation exposures in these models include whole thorax lung irradiation (WTLI), partial body irradiation (PBI), and TBI. The WTLI model is used for developing organ-specific (heart, lung, and other intra-thoracic organs) ARS and DEARE, but it does not mimic an actual radiation accident/terrorist event because organ-specific exposures are unlikely to occur in a nuclear disaster (MacVittie and Farese 2020). Several well-characterized PBI and TBI rodent and NHP models have been developed by teams funded by the National Institute of Allergy and Infectious Diseases (NIAID) under their Product Development Support Services mechanism [originally awarded to the University of Maryland (2005–2015) (MacVittie 2012; MacVittie 2014; MacVittie et al. 2019; MacVittie and Farese 2020) and since to the Stanford Research Institute (SRI) International] to develop, standardize,

validate, and refine animal models of ARS and DEARE according to the FDA AR, discover biomarkers to predict disease progression and outcome, and develop effective MCMs that can prevent or mitigate ARS and DEARE for eventual FDA approval and addition to the Strategic National Stockpile.

### **PBI models.**

In the PBI model, the animal is uniformly exposed to radiation but a certain degree of BM is spared (left/right hemi-body irradiation, anterior/posterior hemi-body irradiation, single limb-irradiation, 2.5 to 7.5% leg-out BM sparing irradiation, etc.) (Meadows et al. 2010; Valente et al. 2015; Ostheim et al. 2020; Fish et al. 2021), thereby better mimicking the heterogeneous and nonuniform irradiation in a real nuclear accident or wartime scenario. Animals exposed in a PBI fashion can survive H-ARS or gastrointestinal-ARS (GI-ARS) under a relatively high dose of radiation, allowing development of organ-specific DEARE at a later time.

Drs. Medhora and Fish, building upon the TBI BM transplant model developed with John Moulder to investigate radiation-induced nephropathy (Medhora et al. 2014; Moulder et al. 2014), developed a PBI model as a more relevant model for the terrorist radiation scenario (Fish et al. 2016). This PBI model was developed in WAG/ RjCmcr rats and shields one hind limb, sparing ~7.5% of BM. The model has been defined with regards to the DRR, sex differences in DRR, latency of lung- and kidney-DEARE, and has been used extensively to evaluate the efficacy of the angiotensin-converting enzyme inhibitor lisinopril in mitigating DEARE (Fish et al. 2016; Fish et al. 2020; Fish et al. 2021).

MacVittie et al. (MacVittie et al. 2012; MacVittie et al. 2014; MacVittie et al. 2015) established the NHP 5% PBI/BM-sparing model in rhesus macaques (10 Gy exposure, sparing tibiae, ankles, and feet), and has described the development of multi-organ DEARE in this model, primarily RBMD, lung-DEARE, and GI-DEARE. He has documented a prolonged and differential lymphopenic period, lung fibrosis, loss and disorganized regeneration of crypts and villi, and increased numbers of goblet cells occurring up to 6 months post-PBI/BM5.

Booth et al. (Booth et al. 2012) established a C57BL/6 murine model with 40% BM shielding (head, forelimbs, and thorax) and 12 Gy exposure to investigate GI-DEARE. GI-DEARE, in this model, presented as blunted crypts and villi and increased fibrotic submucosa, along with microadenomas as late as 200 days post-PBI/BM40. Dr. Booth also evaluated crypt function by microcolony assay in a CBA/Ca PBI/BM5 murine model after an initial exposure of 13 Gy followed by a re-challenge exposure of 11–13 Gy 200 days later (Booth et al. 2015). Data indicated higher crypt survival and regeneration in previously irradiated mice than in age-matched controls, which is contrary to the common belief that irradiation damages GI regenerative response. The authors speculate that crypts in the previously-irradiated animals were either more radioresistant (possible due to increased quiescence), or that they were present in increased numbers.

## TBI models.

The TBI model delivers radiation as a uniform, unshielded exposure, in which H-ARS, GI-ARS, and neurovascular-ARS develop in a dose-escalating pattern. Survivors of these ARS will experience organ-specific DEARE later in life, albeit with increased latency compared to PBI or WTLI models due to the relatively lower radiation doses used in TBI models.

The hematopoietic system is one of the most radiosensitive systems in the body, with radiation doses as low as 1 Gy inducing sub-clinical damage and recovery as late as day 20–30 post-exposure. As such, H-ARS and RBMD manifest at lower radiation doses than those that cause GI-ARS and other organ damage. H-ARS models using PBI or TBI exposures have been developed in mice, rats, canines, mini pigs, and NHP (Maillie et al. 1966; Cole et al. 1967; Rauchwerger 1972; Monroy et al. 1988; Bertho et al. 2005; Hérodin et al. 2007; Moroni et al. 2011; Chua et al. 2012; Farese et al. 2012; MacVittie et al. 2012; Plett et al. 2012; Moroni et al. 2013; Medhora et al. 2014; Plett et al. 2015; Fish et al. 2016; Fish et al. 2020; Gasperetti et al. 2021). Dr. Orschell's laboratory has developed a well-characterized murine model of H-ARS in young adult C57BL/6 mice and has used this model to study mechanisms and efficacy of MCM against radiation for licensure and treatment strategies (Hoggatt et al. 2009; Plett et al. 2012; Shakhov et al. 2012; Chua et al. 2014; Garrett et al. 2014; Plett et al. 2014; Plett et al. 2015; Unthank et al. 2015; Fish et al. 2016; Dynlacht et al. 2017; Chua et al. 2019; Garrett et al. 2019; Jones et al. 2019; Unthank et al. 2019). Survivors of H-ARS were used to develop a DEARE model (Chua et al. 2012; Chua et al. 2019), which showed lifelong hematopoietic cell dysfunction in all classes of hematopoietic cells. The most primitive hematopoietic cell, the HSC, was reduced in total number but exhibited increased cell cycling rate, as determined phenotypically by flow cytometry. As shown in competitive transplantation models, HSC were severely functionally compromised for life, providing only minimal donor chimerism in transplant recipients and multi-lineage reconstitution skewed towards the myeloid lineage. These results illustrate loss of the two most important properties of HSC, 1) the ability to undergo self-renewal divisions to generate sister HSC, and 2) multi-lineage differentiation divisions into all the formed elements of the blood. Tong et al. (Wu et al. 2020) further defined the deficient lymphoid lineage recovery after lethal TBI in this model, and showed reduced numbers of naïve T cells in secondary lymphoid organs, altered thymocyte generation, and a ~90% reduction in the number of BM primitive lymphoid-primed multipotent progenitors and common lymphoid progenitors, compared to aged-matched non-irradiated controls. Sex difference in lymphoid recovery were also apparent, where irradiated males had improved reconstitution of thymocyte subgroups, peripheral lymphocytes, and other blood elements. These sex differences became more apparent as mice aged, reflecting the “double hits” of irradiation and aging stress in DEARE.

Kidney and heart DEARE are generally observed in PBI models exposed to higher “threshold” doses of radiation (>10 Gy) (Glatstein et al. 1977; Down et al. 1990; Yarom et al. 1993; Baker et al. 2009), but have been shown to develop with increased latency in subthreshold models where doses of radiation are lower. For example, Unthank et al. (Unthank et al. 2015; Unthank et al. 2019) reported increased blood urea nitrogen (BUN),

glomerular hypertrophy, renal tubular atrophy, loss of coronary arteriole endothelial cells, and increased cardiac and pulmonary fibrosis from 4 to 21 months post-TBI in mice exposed to <10 Gy TBI. Given the subthreshold exposure, these results may be more relevant to an actual radiation accident/terrorist scenario than those in threshold models. In addition, these data suggest interactions between the kidney and heart in generation of DEARE (Lenarczyk et al. 2013; Unthank et al. 2015), as well as organ differences in latency of and mechanisms of radiation-induced senescence, inflammation, and oxidative imbalance (Unthank et al. 2019).

### **Pediatric and geriatric models.**

Young adult animals are the most widely used age group for studying radiation effects, but cannot substitute as suitable models for pediatric and geriatric mice, which have different radiosensitivities, physiologies, maturation rates, muscle mass, drug metabolism rates, stem cell cycling kinetics, and repair functions (Grahn and Hamilton 1957; Grahn 1958; Casarett 1968; Yuhas et al. 1977; Milsap and Jusko 1994), all of which affect their radiation response and sensitivity to MCM. To address the need for H-ARS and DEARE models in young and old mice, Orschell's group has developed pediatric C57BL/6J murine models irradiated at 3, 4, 5, 6, 7, and 8 weeks old (w/o) (Patterson et al. 2021; Orschell et al. 2022), and geriatric C57BL/6J models irradiated at 12 and 24 months old (m/o) (Patterson et al. 2022). In agreement with pediatric mouse models developed in other strains (Abrams 1951; Kallman and Kohn 1956; Crosfill et al. 1959; Lindop and Rotblat 1962; Spalding et al. 1965; Langendorff and Langendorff 1966; Fred and Smith 1967; Morton and Siegel 1971; Rauchwerger 1972; Patterson et al. 2021), all pediatric age groups were more radiosensitive than 3m/o young adult mice, with 3w/o mice exhibiting the greatest H-ARS radiosensitivity, but better resiliency to DEARE, compared to other pediatric ages (Patterson et al. 2021). Prepubescent males were more radioresistant than females until puberty (5w/o), at which time females became more radioresistant, and renal DEARE (assessed by BUN at 12 mo post-TBI) was higher in females than males irradiated at a pediatric age. In contrast to pediatric H-ARS models, geriatric mice were found to be significantly more radioresistant than young adult mice, with geriatric males exhibiting significantly increased radioresistance compared to age-matched females (Patterson et al. 2022).

### **Jackson Diversity Outbred (JDO) models.**

Inbred mice have many advantages over outbred strains in medical research, primarily due to their genetic homogeneity and resultant homogenous biological responses. However, they are poor models for the genetically diverse human population. JDO mice are the most genetically diverse mouse strain available (Churchill et al. 2004; Roberts et al. 2007; Collaborative Cross 2012; Svenson et al. 2012), and are believed to be more representative of the human population. To develop a model that offers the economics, lifespan, and ease of use of rodent models, but with the genetic diversity and enhanced human-relevance of large animals, H-ARS and DEARE models were developed in JDO mice (Patterson et al. 2020). JDO mice were found to be more radioresistant in H-ARS, and to exhibit less severe DEARE than C57BL/6 mice (Patterson et al. 2020). Long-term JDO survivors exhibited enhanced recovery of blood cells and BM hematopoietic progenitors, and more quiescent HSC (albeit more decreased in number) compared to C57BL/6 (Patterson et al. 2020).

The increased quiescence of JDO HSC in DEARE may be responsible for the less severe DEARE, since quiescence is essential for maintaining HSC function.

Radiomitigation with granulopoietic growth factors (i.e., Neupogen, pegylated G-CSF, etc.) did not affect the latency or severity of DEARE in any of the age, sex, or strain murine models developed in the Orschell laboratory (Chua et al. 2014; Patterson et al. 2020; Patterson et al. 2021; Patterson et al. 2022).

## Potential new therapeutics of DEARE

The standard management of H-ARS includes supportive care such as blood and platelet transfusions and hematopoietic growth factor therapy including FDA-approved Neupogen (filgrastim, G-CSF), Neulasta (pegfilgrastim, pegylated G-CSF), Leukine (sargramostim, GM-CSF) and Nplate (romiplostim) (Singh and Seed 2020; MacVittie and Farese 2021; Satyamitra et al. 2021). Although essential in the clinical setting, HSC transplantation for H-ARS has been met with limited success and its utility in H-ARS is debatable (Qian and Cen 2020). Although these FDA-approved hematopoietic growth factor MCMs increase survival and life-saving recovery of disease-fighting blood cells and clotting elements, survivors of H-ARS are plagued with multi-organ insufficiency for life, and none of these FDA-approved show efficacy in DEARE (MacVittie and Farese 2021). To date, there are no MCM approved for the DEARE (MacVittie and Farese 2021). This review will cover MCMs with a significant database supporting their potential usefulness in DEARE. Due to limited space, it is not feasible to provide an exhaustive list of all MCM under evaluation for DEARE. Routinely used therapeutic drugs, glucocorticoids, antibiotics, nutritional support, surgical treatments, and therapies for inhaled/ingested radionuclides are not included in this review.

## Interleukin-11 (IL-11)

IL-11 belongs to the IL-6 family and has a heterodimer receptor composed of IL-11R $\alpha$  and gp130. IL-11 activates downstream Jak/Stat, RAS/MAPK and PI3K/AKT signaling pathways to promote thrombopoiesis and erythropoiesis. IL-11 is also known to prevent intestinal crypt cell apoptosis after radiotherapy and chemotherapy (Orazi et al. 1996; Hauer-Jensen 2014; Yang et al. 2014). Recombinant human IL-11 (Oprelvekin, Neumega<sup>®</sup>) is FDA-approved for treatment of chemotherapy-induced thrombocytopenia but has not been approved for radiation. Recombinant IL-11 has a longer half-life than natural IL-11, but still requires daily injections (Maier et al. 1993; Kaye 1996). Polyethylene glycol (PEGylated)-hematopoietic growth factors (PEG HGF) have reduced renal clearance and possess longer half-lives than their non-PEG counterparts, hence only one or two administrations are needed (Kumar et al. 2018; Cox et al. 2020). Plett et al. (Plett et al. 2014) showed that PEG IL-11 (BBT-059), used as a radiomitigator in a C57BL/6 TBI H-ARS mouse model, increases 30-day survival and accelerates red blood cell and platelet recovery in H-ARS. Sharma et al. (Sharma et al. 2020) reported that PEG IL-11 was not only an effective H-ARS radioprotector (administered 24 hrs prior to TBI in CD2F1 mice), but also increased numbers of peripheral blood cells, BM hematopoietic progenitor cells, and megakaryocytes up to 12 months post-TBI in DEARE. In a WAG/RijCmcr rat leg-out PBI model, Gasperetti

et al. (Gasperetti et al. 2021) showed that PEG IL-11, when given as a radiomitigator in a polypharmacy regimen with PEG G-CSF, PEG muGM-CSF, and lisinopril, did not inhibit the radiomitigative effects of lisinopril on radiation-induced pneumonitis or nephropathy. Recombinant human IL-11 or PEG IL-11 protects against renal ischemia reperfusion injury when given before or after ischemia reperfusion in a murine model (Lee et al. 2012).

## TGF- $\beta$ receptor 1 inhibitor

When the formation of extracellular matrix exceeds its degradation, radiation-induced fibrosis occurs. Radiation-induced fibrosis is a serious DEARE complication, presenting in many organs and tissues and resulting in tissue stiffness, thickness and organ dysfunction. The production of TGF- $\beta$  RNA and protein increases within hours post-irradiation and persists for several months, setting the framework for fibrosis. Boerma et al. (Boerma et al. 2013) showed enhanced GI and myocardial fibrosis after induction of TGF- $\beta$ 1 in PBI rat models, consistent with its role in radiation-induced fibrosis. TGF- $\beta$  exists as three isoforms (TGF- $\beta$ 1, - $\beta$ 2 and - $\beta$ 3). TGF- $\beta$ 1, together with its downstream mediators SMAD2 and 3, are the primary mediators of radiation-induced fibrosis, thus providing a target for mitigation using TGF- $\beta$  receptor 1 inhibitors (TGF- $\beta$ 1i). Rabender et al. (Rabender et al. 2016), by using a thoracic “top-up” C57L/J mouse model (5 Gy TBI plus 6.5 Gy thoracic irradiation), reported that IPW-5371, a small molecule TGF- $\beta$ 1i given PO daily for 20 weeks starting 24 hrs post-irradiation, prolonged survival, preserved cardiopulmonary function, and attenuated fibrosis in heart and lung, whereas a 6-week course failed to show benefit. Similarly, Anscher et al. (Anscher et al. 2008) showed improved pulmonary function and reduced fibrosis and inflammation in irradiated rats (28 Gy-hemithorax) given the TGF- $\beta$ 1i SM16 delivered in chow from 7 days prior to until 26 weeks after exposure, compared to a shorter 3-week course. Flechsig et al. (Flechsig et al. 2012) showed that a 4-week course of the TGF- $\beta$ 1i LY2109761 beginning 24h post-WTLI (20 Gy) in C57BL/6 mice increased survival and reduced pulmonary fibrosis up to 6 months post-irradiation. All the above studies observed reduced downstream SMAD2/3 activation, consistent with inhibition of the TGF- $\beta$ 1/SMAD2/3 pathway. Other reports showed attenuated fibrosis after TGF- $\beta$ 1i in rat liver (Du et al. 2010). Inhibition of the TGF- $\beta$ 1 signaling pathway is implicated in mechanisms of other DEARE MCM as well (KGF, genistein, somatostatin analogues, etc.).

## Keratinocyte growth factor (KGF)

KGF (Palifermin) is known to protect epithelial cells from radiation damage (Farrell et al. 1998; Dainiak et al. 2003). Chen et al. (Chen et al. 2004) reported that intravenous injection of a single dose of recombinant human KGF 10 mins after hemithorax irradiation of female Fischer 344 rats attenuated alveolar macrophage recruitment and lung fibrosis at 6 mo. Decreased activation of the TGF- $\beta$  fibrosis pathway implicates a TGF- $\beta$ -dependent mechanism for KGF mitigation. Choi et al. (Choi et al. 2017) showed that two KGF injections (1 hour before and immediately after head and neck irradiation) directly into the submaxillary gland protected female rats from irradiation-induced salivary gland hypofunction 16 weeks post-irradiation. Jaal et al. (Jaal and Dörr 2007) reported that a single subcutaneous injection of recombinant human KGF 2 days before irradiation (but not 2 days after) protected female inbred C3H/Neu mice from radiation-induced urinary bladder

dysfunction up to 1 year later (assessed by cystometry). Further studies including more species, strains, and both sexes are needed to further validate the efficacy of KGF as a MCM for DEARE.

## Genistein

Genistein is a commercially available isoflavone product which has multiple functions including scavenging free radicals and stimulating estrogen receptors. One dose of subcutaneous genistein, given 24 hrs prior to TBI in C57BL/6J mice, increased 30-day survival and prevented collagen deposition and the reduction in TGF- $\beta$  receptor 1 in lung at 90 days post-irradiation (Day et al. 2008). To overcome solubility issues and low oral bioavailability, Humanetics Corporation (Edina, MN, USA) has developed BIO 300, a nanosuspension of genistein with improved bioavailability (Singh and Seed 2020). BIO 300 provides significant survival efficacy in ARS after subcutaneous or intramuscular injection 24–12 hrs prior to TBI in CD2F1 mice (Ha et al. 2013; Landauer et al. 2019; Singh and Seed 2020) and, as a radiomitigator, BIO 300 orally administered daily for 4–6 weeks starting 24 hrs post-WTLI in C57L/J mice increased survival and attenuated fibrotic scarring and airway loss in lung at 6–7 months post-irradiation (Jackson et al. 2017).

## Amifostine

Amifostine/WR1065 is an FDA-approved cytoprotectant used for tissue protection in patients undergoing chemotherapy and/or radiotherapy. Its sulfhydryl (thiol) group acts as a free radical scavenger, providing radioprotection in H-ARS. However, toxicities at the dose required for H-ARS radioprotection have hindered its approval as an MCM for H-ARS and DEARE (Glover et al. 1988; Singh et al. 2015). Investigations focused on overcoming these side effects via alternate administration routes (inhalation (Chen et al. 2022), oral sprays (Pamujula et al. 2004), or implanted pellets (Srinivasan et al. 2002)), or combining amifostine at a lower dose with other MCM (G-CSF (Patchen et al. 1992; Patchen 1995), gamma-tocotrienol (Singh et al. 2016), or prostaglandins (Hanson 1987; Hanson et al. 1988)) are ongoing. Due to its accumulation in kidney and salivary glands, amifostine effectively ameliorates dry mouth (xerostomia) after head and neck radiotherapy and kidney malfunction associated with repeated cisplatin administration and is approved for these indications (Singh and Seed 2020; Singh and Seed 2021). “Off-label” usages of amifostine take advantage of its radioprotective effect on other organs, including: 1) intrarectal use during external radiation for prostate cancer, which improved quality of life and bowel function for up to 30 months post-irradiation (Simone et al. 2008), and 2) intravenous injection before thoracic irradiation for non-small-cell lung cancer, which reduced the incidence of pneumonitis, lung fibrosis, and esophagitis up to 6 months post-irradiation (Antonadou et al. 2001). Other free radical scavengers, such as PrC-210 aminothiols, glutathione, and other existing aminothiols (Hospers et al. 1999; Peebles et al. 2012) may also have efficacy to alleviate DEARE, but studies have not yet been conducted to our knowledge.

## Somatostatin and its analogues

Radiation induces intestinal mucosal barrier breakdown through crypt cell death, allowing pancreatic enzymes to gain access to stromal tissue and initiate autodigestion of the intestinal wall. The inflammatory products of autodigestion are cytotoxic and fibrotic, which in turn exacerbate mucosal injury and subsequent fibrosis. Somatostatin and its analogues inhibit exocrine pancreatic secretions and reduce proteolytic enzymes in the bowel lumen, thus inhibiting this damaging cycle. Based on this mechanism, the utility of somatostatin and its analogues as MCMs for GI-ARS and DEARE was explored. Octreotide, a synthetic somatostatin analogue, administered from 2 days prior to localized ileum irradiation and continuing for 10 days in a Sprague-Dawley rat model, reduced mucosal injury and intestinal wall thickening at 26 weeks post-irradiation (Wang et al. 1999). Octreotide attenuated radiation-induced TGF- $\beta$  overexpression and the increased collagen deposition and smooth muscle cell proliferation (Wang et al. 2001). Another synthetic somatostatin analogue, SOM230 (pasireotide), administered 24–72 hrs through day 14 after irradiation in a CD2F1 TBI murine model, not only enhanced 30-day survival, but also reduced intestinal output of the T cell chemoattractant CXCL9 and inhibited trypsin production by pancreatic acinar cells at day 30 post-TBI (Fu et al. 2009; Fu et al. 2011).

## AEOL 10150

AEOL 10150 is a broad-spectrum, low molecular weight catalytic metalloporphyrin antioxidant with superoxide dismutase mimetic properties. It provides radioprotection via scavenging reactive oxygen and nitrogen species. Rabbani et al. (Rabbani et al. 2007) demonstrated that a 10-week course of 10 or 30mg/kg/day AEOL-10150, initiated on 1-day post-hemithorax irradiation in Fisher-344 rats, decreased radiation-induced lung injury and fibrosis at 20 weeks. Garofalo et al. (Garofalo et al. 2014) reported that a 28-day course of AEOL 10150, initiated 24 hrs post-WTLI in rhesus macaques, increased 180-day survival and reduced radiation-induced lung injury at 60 days (CT scan) and 160 days (histology), as well as the need for dexamethasone during the 180-day in-life phase of the study. A similar WTLI study with AEOL 10150 treatment on days 1–28, but in CBA/J mice, demonstrated enhanced survival and improved pulmonary function as late as 180 days post-irradiation (Murigi et al. 2015). MacVittie et al. (MacVittie et al. 2017) extended the AEOL 10150 administration to 60 days post-WTLI in rhesus macaques and showed increased survival, mean survival time of decedents, and pulmonary function. A trend toward lower inflammatory cytokine levels in lungs of irradiated rhesus macaques treated with AEOL 10150 was associated with reduced innate immune cell infiltration, suggesting a possible role for AEOL 10150 to reduce inflammatory outcomes in DEARE (Cui et al. 2021).

## Angiotensin converting enzyme inhibitors (ACEi)

The renin-angiotensin system is known for its role in regulating blood pressure and electrolyte homeostasis (Schmieder et al. 2007). Angiotensin-converting enzyme (ACE) catalyzes angiotensin I into angiotensin II, which acts to increase blood pressure. ACE inhibitors (ACEi) block ACE and thus angiotensin II production, which in turn reduces blood pressure. ACEi have recently been shown to increase survival and reduce the DEARE

in H-ARS and DEARE animal models. One of the most widely used ACEi, lisinopril, combined with hydration and antibiotics, was found to attenuate lung, cardiac, and renal DEARE in a PBI WAG/RijCmcr rat model up to 100–150 days post-irradiation (Moulder and Cohen 2007; Davis et al. 2010; Fish et al. 2016; Jacobs et al. 2019; Medhora et al. 2019). Mechanisms of ACE inhibition are believed to be due to its anti-inflammatory and anti-oxidant activities (Gao et al. 2013; Sharma et al. 2022). An attractive feature of ACEi radiomitigation is the maintenance of efficacy when administration is delayed, which is important in the chaotic aftermath of a radiation event when delivering medical care would be logistically difficult. Enalapril, initiated on day 35 post-WTLI in WAG/RijCmcr rats, maintained survival efficacy and attenuated pneumonitis and lung fibrosis at day 210 (Gao et al. 2013). Captopril, and an angiotensin II type-1 receptor blocker, losartan, both effectively delayed radiation-induced nephropathy up to 47 weeks post-TBI in WAG/RijCmcr rats (Moulder et al. 2011). Results in radiation studies with ACEi are sometimes in contrast, making it difficult to draw conclusions regarding optimal administration times, routes, doses, formulations, etc. (Molteni et al. 2000; Ghosh et al. 2009; Moulder et al. 2011). Differences in laboratories, species, strains, study endpoints, radiation delivery methods, or MCM administration time points are likely responsible for discrepancies among studies, warranting the evaluation of such variables in side by side studies conducted with similar protocols for optimal interpretation.

## Prostaglandin E2 (PGE2)

Arachidonic acid is a component of the inner cell lipid membrane. It is released by phospholipase A2 and converted to prostaglandins (PG) by cyclooxygenases (COX) and tissue-specific synthases (Harizi et al. 2008). The rate of PG synthesis depends on the local expression and activity of COX, which has two isozymes, COX-1 and COX-2. The main products of COX-1 are prostaglandin I2, thromboxane A2, and PGE2, and the main product of COX-2 is PGE2 (Smyth et al. 2009; Ricciotti and FitzGerald 2011). PGE2 regulates physiological processes such as renal blood flow and natriuresis (Norregaard et al. 2015; Nasrallah et al. 2016), and it also mediates many pathological processes, including pain, fever, and inflammation (Claria 2003). PGE2 interacts with four specific G-protein coupled receptor isoforms (EP1, EP2, EP3, and EP4) (Kalinski 2012). EP1 and EP2 are low-affinity receptors requiring high PGE2 levels for activation, whereas EP3 and EP4 are high-affinity receptors. Different EP receptor pathways are both alternative and overlapping; therefore, PGE2 effects are diverse and depend on tissue-specific receptor expression and G protein coupling (Markovic et al. 2017).

The role of PGE2 in promoting HSC survival and self-renewal prompted investigations into its possible efficacy as a radiation MCM. Hanson et al. (Hanson and Thomas 1983; Hanson and Grdina 1987) demonstrated that 16,16-dimethyl prostaglandin E2 (dmPGE2), a long-acting formulation of PGE2, protected intestinal clonogenic cells from radiation damage in B6D2F1 mice when used as a radioprotectant one hour prior to irradiation. Walden et al. (Walden et al. 1987) found that dmPGE2 increased the LD50/30 survival rate of CD2F1 mice when administered 30 mins prior to irradiation. Hoggatt et al. (Hoggatt et al. 2013) demonstrated significantly increased 30-day survival when dmPGE2 was administered 6 or 24 hrs post-TBI in C57Bl/6 mice. Patterson and Tong et al. (Patterson et al. 2021) further

optimized the time of administration of dmPGE2 for radioprotection and radiomitigation in pediatric, young adult, and geriatric mice. Patterson et al. showed that inhibition of cell cycle in HSC by dmPGE2 is a likely mechanism for radioprotection (Patterson et al. 2020). Irradiated mice that received radioprotective dmPGE2 had higher CBC parameters, and higher numbers of HSC and mesenchymal stem cells in BM compared to vehicle-injected mice by day 30. Given its efficacy as a radioprotectant for H-ARS, and the fact that other efficacious H-ARS radioprotectants often show promise in DEARE, investigations of the use of dmPGE2, given as a radioprotectant for H-ARS, to alleviate multi-organ DEARE are underway with promising initial results (unpublished observations).

## Conclusions

Terrorist activities, nuclear warfare, and radiation accidents have the potential to expose humans to dangerous levels of radiation. Victims of lethal radiation exposure face acute and chronic multi-organ injuries, including ARS and DEARE. Cancer patients undergoing radiotherapy also have the potential to develop DEARE. Developing effective MCMs is a serious need that relies heavily on studies conducted in reliable and well-characterized animal models according to the FDA animal rule. Although relevant ARS animal models have been developed in several species and four MCM for H-ARS are now FDA-approved, DEARE models relevant to the radiation blast/accident scenario have only recently been developed, and there are no licensed MCM for DEARE. More research and support are needed to better understand the mechanisms and natural history of DEARE and to further develop promising MCM and identify new MCM that effectively alleviate the life-debilitating consequences of the DEARE. An overview of the concepts presented in this review is illustrated in Figure 1.

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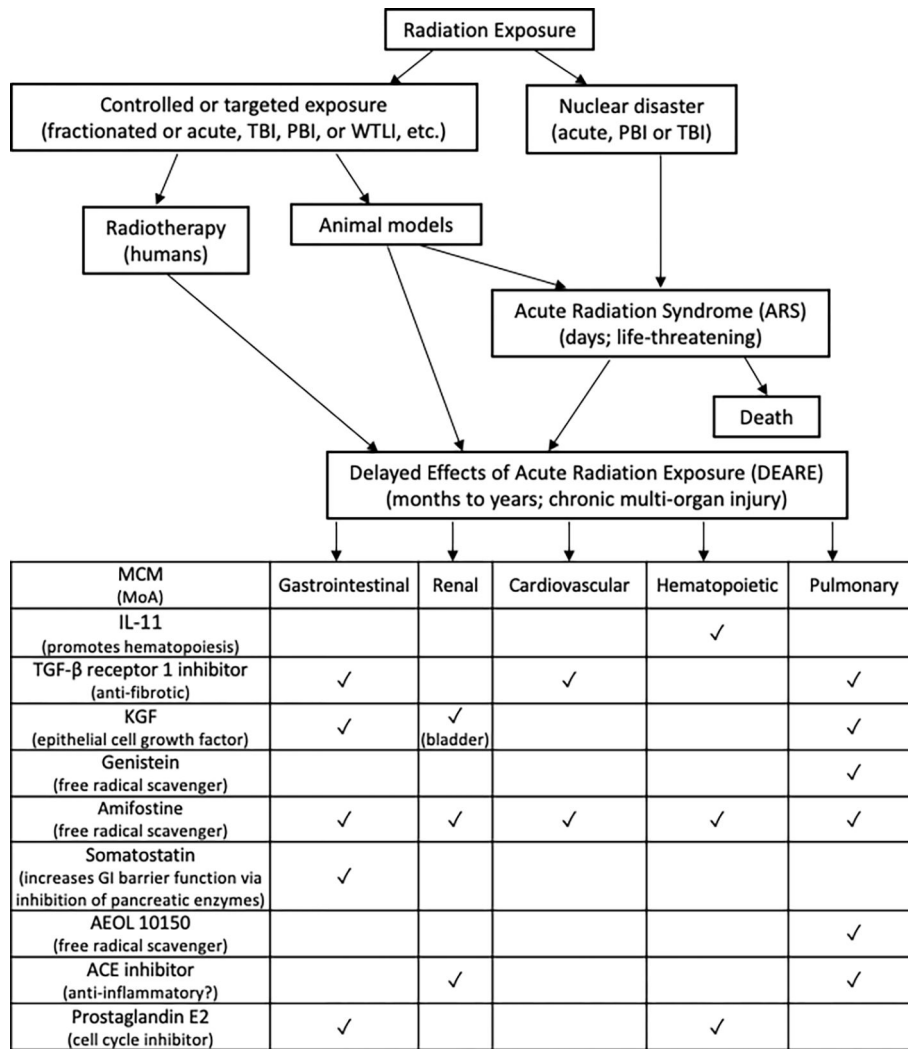
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**Fig. 1.** Overview of DEARE concepts and MCM presented herein.

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