HHS Public Access

Author manuscript

Int J Radiat Biol. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Int J Radiat Biol. 2019 July ; 95(7): 920–935. doi:10.1080/09553002.2019.1589654.

Saving Normal Tissues – A Goal for the Ages

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Abstract

Purpose: Almost since the earliest utilization of ionizing radiation, many within the radiation community have worked towards either preventing (i.e. protecting) normal tissues from unwanted radiation injury or rescuing them from the downstream consequences of exposure. However, despite over a century of such investigations, only incremental gains have been made towards this goal and, with certainty, no outright panacea having been found. In celebration of the 60th anniversary of the *International Journal of Radiation Biology* and to chronicle the efforts that have been made to date, we undertook a non-rigorous survey of the articles published by normal tissue researchers in this area, using those that have appeared in the aforementioned journal as a road map. Three ‘snapshots’ of publications on normal tissue countermeasures were taken: the earliest (1959–1963) and most recent (2013–2018) 5-years of issues, as well as a 5-year intermediate span (1987–1991).

Conclusions: Limiting the survey solely to articles appearing within *International Journal of Radiation Biology* likely reduced the number of translational studies interrogated given the basic science tenor of this particular publication. In addition, by taking ‘snapshots’ rather than considering the entire breadth of the journal’s history in this field, important papers that were published during the interim periods were omitted, for which we apologize. Nonetheless, since the journal’s inception, we observed that, during the chosen periods, the majority of studies undertaken in the field of normal tissue countermeasures, whether investigating radiation protectants, mitigators or treatments, have focused on agents that interfere with the physical, chemical and/or biological effects known to occur during the acute period following whole body/high single dose exposures. This relatively narrow approach to the reduction of normal tissue effects, especially those that can take months, if not years, to develop, seems to contradict our growing understanding of the progressive complexities of the microenvironmental disruption that follows the initial radiation injury. Given the analytical tools now at our disposal and the enormous benefits that may be reaped in terms of improving patient outcomes, as well as the potential for

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

offering countermeasures to those affected by accidental or mass casualty exposures, it appears time to broaden our approaches to developing normal tissue countermeasures. We have no doubt that the contributors and readership of the *International Journal of Radiation Biology* will continue to contribute to this effort for the foreseeable future.

Introduction

Since the late 1800s, when the scientific community first began to utilize the cytotoxic properties of ionizing radiation, in particular for the treatment of cancer-related diseases, efforts have been underway to prevent off-target normal tissue injuries (Williams & Newhauser 2018). The potential acute and delayed/late normal tissue outcomes that can confront patients and accident victims alike, and that have been the subject of countermeasure research to date, cover a broad spectrum: for example, acute effects of concern can range from the relatively localized and transient skin reddening (erythema) seen in many patients (Singh et al. 2016) to the potentially lethal acute radiation syndromes (Singh & Seed 2017), whereas the late effects include quality-of-life issues, such as fatigue, cognitive dysfunction and fibrosis (Williams et al. 2016), as well as morbid conditions, such as pneumonitis and kidney failure (Medhora et al. 2014). Although many of these observed outcomes can be considered relatively benign by treating oncologists, all can dramatically affect the well-being and quality of life of cancer survivors (Yang et al. 2012; McDowell et al. 2018; Sun & Cooper 2018).

To date, the vast majority of successful modifications that have led to a reduction in normal tissue exposure parameters have been associated with alterations in the physical delivery of radiation therapy and have been biological or physical in nature. On the biological side, there has been the adoption of fractionation (Williams & Newhauser 2018), aided by the qualitative and quantitative determination of normal tissue radiation tolerance levels that have provided clinicians with treatment dose limits (Emami et al. 1991; Rubin 1995). The physical aspects include the many technological modifications developed by medical physicists and engineers that have enabled radiation oncologists to more accurately conform radiation beams to tumors, thereby reducing normal tissue exposures (Macia 2017). Indeed, the advancements in radiation delivery systems over the past few decades, such as image-guidance, respiration gating and the use of altered fractionation protocols, have contributed greatly to the much improved survival rates seen in cancer patients (Wai et al. 2017). However, the absolute elimination of all normal tissue from radiation treatment fields is an unlikely goal due to the irregular geometry of tumors, the clinical need for treatment margins, as well as, with most radiation modalities, the physical necessity of beam entry and exit. As a result, a sizeable cohort of the cancer survivor population will continue to be plagued by post-treatment side effects, outcomes that are predominantly blamed on irradiation of the inherently involved normal tissues (Gawade et al. 2014; Taibi et al. 2014). Another population at risk of normal tissue injuries is those that have been subjected to accidental or deliberate whole-body exposures; in such situations, where therapeutically relevant constraints are not present and doses often are unknown, medical responders require access to low toxicity, broadly efficient and easily administered agents (Rios et al. 2014), none of which are currently available. Therefore, given that irradiation is a mainstay of cancer therapy, with approximately 50% of patients receiving radiation therapy as part of

their treatment (Baskar et al. 2012), and the ongoing global fears of nuclear or radiological terrorism (Brenner et al. 2015), it is incumbent on the radiation community to seek pharmacological interventions that can be used to counter the development of radiation-induced normal tissue toxicities.

As part of the celebration of the 60th anniversary of the *International Journal of Radiation Biology*, we undertook a non-rigorous survey of the articles published by researchers in the area of normal tissue countermeasures, using those that appeared in the aforementioned journal to provide us with an overview of the field. Three 'snapshot' blocks of articles were taken: the earliest (1959–1963) and most recent (2013–2018) 5-years of issues, as well as a 5-year intermediate span (1987–1991). Although using the 'snapshot' approach inevitably has led to our failing to include some important publications from the field, for which we beg the affected authors' forgiveness, nonetheless, given the inherently international reach of the journal, this survey has provided us with a global picture of the state of play during each period and, taken together, offers hints as to how best we can move forward towards the prize of preventing the off-target effects of radiation exposure.

Kick-off (1959–1963)

Over the years, multiple articles have described progress in the development of countermeasures (Weiss & Landauer 2003, 2009; Oliai & Yang 2014; Singh et al. 2017a; Singh et al. 2017b; Singh & Seed 2017). In order to refrain from simply recapitulating these excellent reviews, but nonetheless still gaining an insight into the major directions that have been taken in the field of radiation countermeasures, we took a non-rigorous survey of publications that have appeared in the *International Journal of Radiation Biology*, beginning with the first 5 years of the journal's publication (then titled the *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine*). 36 out of a total of 366 articles were identified as describing studies that assessed the use of pharmacologic (chemical) countermeasures in their ability to reduce or prevent normal tissue outcomes; selection was based solely on the article titles containing pertinent keywords, such as 'protection', 'modification' and 'normal tissue', in conjunction with a specifically named agent (Table 1). Of note, several foreign language articles that likely fitted the criteria were excluded from this survey, as were technical reports, reviews and articles that dealt only with a pharmacologic mechanism of action, as distinct from determining modification of a biological outcome.

Our survey produced some interesting insights into the research directions being taken at the time. For example, all but one of the studies used pre-radiation administration of the agents, with the single exception being an *in vitro* study in rat thymocytes that compared pre- versus post-radiation treatment schedules (Grant & Vos 1962). This seeming focus on a single dosing approach likely reflects a prevailing drive towards the development of radiation protectants, a not unsurprising goal given that this period represents the peak of the Cold War (Gaddis 2006). Indeed, fears of a potential nuclear war between the U.S.A. and U.S.S.R. together with our growing understanding of the long-term outcomes from the use of such weaponry (Folley et al. 1952; Harada & Ishida 1960), as well the potential risks from the increased use of nuclear technology, would have provided a strong incentive in

support of efforts to prevent unwanted radiation injury. Interest in the development of chemical radiation protectants was especially high in the U.S., where federally sponsored research was performed across the country, involving both animal and human subjects, the latter being the subject of much hand-wringing in subsequent years (McCally et al. 1994; Report of the Advisory Committee on Human Radiation Experiments 1996).

The availability of well-characterized *in vitro* cell lines for use in biological research was still in its infancy at this time; as a result, the majority of studies described in Table 1 make use of animal models, with roughly half of those being performed in mice and the majority of the remainder using rats. Total-body irradiation was used in all but a few of the *in vivo* models with a primary endpoint of survival. No time points were analyzed beyond 30 days post-radiation; indeed, although radiation-induced late effects had been recognized by this time, including carcinogenesis, developmental disturbances, and radiation cataracts, none of these endpoints were the subject of interest in the surveyed articles. A degree of mechanistic evaluation was attempted in a number of the studies, with investigators examining oxygen tension in various organs post-radiation and comparing aerobic versus hypoxic/anoxic conditions (van der Meer & van Bekkum 1959; Grant & Vos 1962; Vos & Kaalen 1962; Vergroesen et al. 1963); interestingly, some investigators used hypothermia as an induction mechanism for the hypoxia in *in vivo* models (Weiss 1961; Vergroesen et al. 1963; Zatz 1963), ignoring the potential for any radiation protective features of the hypothermia itself (Cheng et al. 2015).

Overall, 3 main groups of potential countermeasures were under investigation at this time (Pihl & Eldjarn 1958) (Table 1): thiols related to cysteine and cysteamine, as well as other sulphur-containing agents, e.g. thiourea (Stratton & Davis 1962); substances with significant pharmacological or toxicological properties which often resulted in tissue hypoxia and/or vascular constriction, e.g. cyanide, histamine, and tryptamine (van der Meer & van Bekkum 1959); and inert metabolites, e.g. glycerol (Vos & Kaalen 1962). By this time, cysteine (Patt et al. 1949) and cysteamine (Bacq & Herve 1952), compounds that contain thiol/sulfhydryl groups, had been identified as relatively efficient radioprotectors through their activity as free radical scavengers and, indeed, roughly half of the studies surveyed during this period assessed sulfhydryls and related agents (Table 1). Thus, broadly speaking, the majority of investigations during this time appear to reflect the community's understanding of the immediate physicochemical radiation reaction; thus, the overarching target was to reduce the presence and/or impact of free radicals and their role in the initial biological response. Although this led to a somewhat narrow spectrum of agents being assessed, nonetheless, this approach was supplemented by some of the investigators with respect to their growing appreciation that low oxygen levels, whether directly or indirectly induced, also offers a level of normal tissue protection (Davis et al. 1958; Larsson & Stenson 1965). However, these latter studies might also speak more to a search for mechanism, rather than a practical means of preventing radiation injury in the field. Finally, investigators demonstrated an awareness of differential radiation sensitivities among organs, although, as mentioned previously, only a few of the journal's articles focused on specific tissues versus whole body responses. Those that looked beyond survival had examined protection in the more radiation-sensitive tissues, such as bone marrow (Weiss 1961; Praslicka et al. 1962), gut/mucosa (Prasad et al. 1963; Prasad & Osborne 1963) and testes (Mandl 1959; Ashwood-

Smith 1961; Starkie 1961), suggesting a continued focus on the acute radiation response and its associated syndromes.

Half time (1987–1991)

As with the first survey period, the countermeasure articles identified in the *International Journal of Radiation Biology* between 1987–1991 offer insights into some of the leading radiation scientific directions of the day. Of note, some 'mechanistic' publications (denoted as (M)) were included in the survey's results where a normal tissue endpoint was part of the analysis; this inclusion was rationalized by our interpretation that these studies reflected efforts to broaden the potential classes of modifiers and/or attempts to modify promising agents through improved administration routes and/or a reduction in unacceptable toxicities. In addition to radiation protectors, 'treatment' strategies were being assessed during this time period, i.e. chelating agents. The investigation of such agents had only just begun during our first survey period (Galli 1959; Norwood 1962), providing an explanation for their lack of an earlier appearance. However, despite the time lapse, the number of studies still being performed with these agents likely reflects the ongoing and, indeed, continuing concerns over the development of diseases due to worker exposures to radioactive isotopes (Shore 1990; Schubauer-Berigan et al. 2007) and the limited availability of non-toxic, but efficient, treatment regimens. Indeed, the lack of such strategies had been exposed by the limited resources available following the Chernobyl incident (van den Hoek 1989; Ioannides et al. 1991).

A slightly reduced number of pertinent articles was identified during this period compared to the previous (29 vs. 36) (Table 2); furthermore, this was a much smaller percentage of the now significantly expanded issues and represented only 3.3% of the ~870 total number of articles compared to the earlier ~10%. Interestingly, articles describing investigations into radiation *sensitizers* had now appeared, and in larger numbers than normal tissue countermeasures (~40), suggesting that the decline in the number of countermeasure articles reflected a general shift in research emphasis away from the quasi-military need for radiation protectants towards agents with more therapeutic relevance. The conditions that might have led to this move are unclear from such a limited survey, although a personal 'history' published by Dr. Jack Fowler (Fowler 2006) provides an insightful overview of the dramatic changes that had been wrought in the field of normal tissue radiation biology during the late 1970s and early 1980s. These changes had included a deeper theoretical understanding and modelling of the fractionation effect, including a broad acceptance of the α/ß ratio (Barendsen 1982), the role played by oxygen/hypoxia in radiation damage induction (Hendry 1979) and a growing appreciation of the differential mechanisms underlying acute versus late normal tissue effects, the latter highlighted by the tremendous body of work from Withers (Withers et al. 1982; McBride et al. 2015) and others. From such revelatory findings, it is relatively easy to understand why researchers would see the utility of using this expanding database of knowledge to achieve a real improvement in patient outcome, a contrast to the more esoteric problem of developing protection measures against an existential threat from nuclear bombs and their like.

Even a cursory examination of Table 2 in comparison to Table 1 indicates a much greater use of *in vitro* analyses, with roughly half of the studies being conducted using cell lines alone. In addition to the improvements that had been made in this experimental approach and the advantages offered by its more rapid data turn-over, the trend towards increased use of this methodology in radiation biology supports the notion that researchers were making greater use of mathematical models, both as a justification for their work and a means of providing an explanation for their findings (Fowler 2006). The derivation and use of these models have been, and for the most part still are, based on the more simplistic 'yes-no' outcomes that result from *in vitro* studies (e.g. cells dead or alive, transformed or not). Perhaps, at a simplistic level, the use of such models eliminated the need to deal with the significantly more complex and nuanced (i.e. frustrating) data that can arise from *in vivo* animal experimentation. This conclusion is supported by the observation that, even among those radiation protection studies that made use of animal models (see Table 2), only 1 group assessed an endpoint not associated with survival, that of skin moist desquamation (van den Aardweg et al. 1991), and only 2/7 of the chelator/treatment studies included an assessment of late disease (Bruenger et al. 1991; Schoeters et al. 1991).

Of the studies that investigated radiation protectors during this period, the majority (14/25 studies) continued to be an assessment of thiol-related drugs; the list of agents was dominated by compounds arising from the work being performed at the Walter Reed Institute of Research, commonly known as the WR-series. Indeed, the trend away from cysteine and its more closely related compounds had essentially begun in the late 1960s with the identification of a dose modifying factor of >2 for S-2-(3-aminopropylamino) ethyl phosphorothioic acid (WR-2721/amifostine) for the 30-day mortality endpoint in mice (Yuhas & Storer 1969). Decades of subsequent investigations by multiple laboratories culminated in WR-2721 becoming the first, and to date only, FDA-approved cytoprotector, marketed under the trade name of Ethyol (Mishra & Alsbeih 2017). Unfortunately, variations in its differential normal tissue uptake rates relative to its uptake into tumors and the significant issues of dose-limiting toxicity (i.e. nausea, vomiting and hypotension) (Mabro et al. 1999) have continued to limit the use of amifostine, which is currently only approved for use in the prevention of xerostomia in head and neck cancer patients (Varghese et al. 2018).

Likely as a response to the list of toxicities associated with the free radical scavenger class, Table 2 indicates an expansion in the number of investigations assessing agents with alternative pharmacological activity (see Relevant Biologics/Miscellaneous); this is underscored by the studies that included *post*-radiation administrations (Brook et al. 1988; Norman et al. 1988; Kalinich et al. 1991). Inference of a broader search being underway might reflect a collective despair regarding our inability to sufficiently reduce off-target ionizing events or a growing realization that the prevention of radiation-induced normal tissue effects might require more than the prevention of the immediate physicochemical reactions. Either way, it is evident that investigators were beginning to more critically interrogate a wider number of early biological events associated with radiation injury progression, with some even suggesting the need to combine agents with different modes of action (Weiss et al. 1990).

Current state of play (2013–2018)

In our final ‘snapshot’, we once more excluded review articles, technical reports and, on occasion, entire issues that were dedicated to a single topic not relevant to this survey. We also did not include articles describing countermeasures against non-ionizing irradiation, of which there were a small number; we eventually arrived at a review of 42 articles out of a total of ~480 (~9%). Interestingly, although our primary assignment of agents into the various categories was determined by the article’s title, scrutiny of the analyses and/or endpoints (Table 3) suggests that many of the compounds were deemed relatively non-specific in their activity. For example, many of the agents assigned to the antioxidant category also exhibited strong anti-inflammatory effects and vice versa (Cheng et al. 2014; Fukuda et al. 2016; Aricigil et al. 2017; Miller et al. 2017; Talebpour Amiri et al. 2018). This likely represents a deliberate choice by the investigators as it reflects our current understanding of radiation-induced normal tissue effects being the culmination of progressive physiological changes in multiple aspects of the injured volume, all of which might need to be addressed as part of any comprehensive countermeasure approach (Williams et al. 2016). Interestingly, there is a significant move towards the testing of natural products during this period, particularly with respect to anti-oxidant compounds. This might be part of the global interest in dissecting the mechanisms and active ingredients found in herbal and traditional medicines (Li & Weng 2017; Wang et al. 2018), but also likely reflects a desire to develop agents that have minimal toxicities that would otherwise limit future development, as occurred in the amifostine story.

The most notable change seen in Table 3 is the addition of an entirely new class of agents, the radiation mitigators; these are agents that are delivered after radiation exposure, but prior to the expression of the target effect (Moulder 2003; Stone et al. 2004). Compounds being investigated in this class included antioxidants and anti-inflammatories, recognition of the roles that oxidative stress and inappropriate inflammation appear to play in the progression of normal tissue effects, and also growth factors (Watanabe et al. 2014; Pejchal et al. 2015; Sumikawa et al. 2017) and vascular modifiers (Moulder et al. 2014; Huang et al. 2018). Since these additions are accompanied by a return to the almost exclusive use of *in vivo* versus *in vitro* models (39/42), we believe that there is now a collective appreciation of the role played by microenvironmental disruption in normal tissue injury, whether acute or delayed, and an acceptance of the necessity to take a more holistic approach to countermeasure development. Supporting this conclusion is the reduction in use of survival as an endpoint (10/42), whether at the whole animal or cellular level, and the expansion of primary endpoints that address effects in specific organs and tissues; the organs of interest included not only acutely responding tissues, such as bone marrow, GI and the oral mucosa, but also late responding tissues, i.e. liver, brain, eye, thyroid, kidney, lung and heart. It is not clear if this expansion in the number of tissues of interest simply supports the need for a potential therapeutic use for such compounds, a subject referred to in the text of the majority of the articles, or the need to draw the pharmaceutical industry into the endeavor (Prasanna et al. 2015). However, such conclusions are contradicted by the observation that a majority of the studies (30/42) persisted in the use of total body irradiation versus localized fields (4), with only 3 of those studies using fractionation; nonetheless, this also may be explained by a lack of available small animal radiation resources in many of the investigators’ institutions.

What might be less obvious to the reader is the changing geographic bias that becomes apparent when comparing the distribution of authors' countries of origin across all three of the Tables. The bulk (66%) of the work featured in Table 1 was performed in Europe, a possible reflection of the trepidation felt by countries in that region that they might become the unwilling proxies of a nuclear dispute between the main participants of the Cold War, the U.S.A. and the U.S.S.R. In the period represented by Table 2, the distribution of authors' country of origin had shifted, with a roughly equal number of studies being published from the U.S. (13/29) versus Europe (11/29). Interestingly, this shift might be an illustration of the competition being held between the pharmaceutical industries of the two respective regions since this period was in the middle of a so-called biotechnology revolution (Malerba & Orsenigo 2015). However, what caught us by surprise was the distribution in authorship seen in the most recent snapshot (Table 3). Only 12% of the articles came from Europe and 14% from the U.S., whereas 33% come from the Middle East, most notably Egypt. Of course, this particular distribution may simply reflect recent publishing trends, with investigators in both Europe and the U.S. moving either towards greater use of on-line publishing venues or journals with higher impact factors. However, given that unrest and the increased use of nuclear energy in the Middle East may be prompting their surge in interest, we might also consider that geopolitical influences also may be affecting investigators' fields of study, particularly through their sources for funding. For example, in Europe, a 2009 report from the High Level Expert Group (HLEG, http://www.hleg.de/) had expressed concerns that many European Union members appeared to have lost key competencies in radiation research, such that it was felt that individual countries were no longer capable of maintaining research activities in the radiation sciences, most especially in the low dose field. The formation of a network of institutions with expertise or interest in radiation research was recommended and, in 2010, the Network of Excellence, DoReMi (http://www.doremi-noe.net/), was funded. This centralization of interest and funding in the area of low dose radiation, with a significant focus on training and education of radiation biologists, may provide an explanation for the decline in countermeasure articles from that particular region being submitted to the *International Journal of Radiation Biology*. However, the fall in the number of articles from the U.S. obviously requires a different explanation.

Since the events of 9/11, similar concerns to those heard from Europe have been expressed as to the continued loss of radiation expertise in the U.S. (Rosenstein et al. 2009; NCRP Statement 12 2015) and the overall lack of resources in the event of a mass radiological or nuclear event (Coleman & Parker 2009). In response to this perceived need, a Radiation Countermeasures Program was launched (Hafer et al. 2010) with the stated goal of operationalizing the development of medical countermeasures for use in a radiological or nuclear emergency (Homer et al. 2016). In the near 15 years since its initiation, this Program has funded several institutions as centers of excellence, although the number of centers has declined across the intervening years from an original 8 (in which this review's senior author was a funded participant) to the current 4. This focused effort has resulted in many advances in the field as a whole, for example in animal model characterization (Williams et al. 2010; Iversen et al. 2018), the development of biodosimetry technologies (Brenner et al. 2015; Flood et al. 2016; Repin et al. 2017; Jacobs et al. 2018) and identification of potential biomarkers of exposure (DeBo et al. 2015; Himburg et al. 2016; Laiakis et al. 2016; Lee et

al. 2018). Unfortunately, however, there does not yet appear to have been a significant breakthrough in countermeasure development *per se* by the Program, at least at the level of agents entering human trials. This impasse in progress may indicate a functional disconnect between government-run programs, regulatory bodies and profit-based industries, such as pharma (Price & DiCarlo 2018), but nonetheless is a disappointing outcome. Furthermore, the concentration of funds in such a limited number of institutions may well have acted as a disincentive to the broader community since it inherently reduces the depth and breadth of innovation that is needed to overcome this seeming perennial problem.

How to take home the prize

To try and understand why more progress has not been made, we need to take a time-out and step back from the field. In order to develop a pharmacologic strategy that prevents off-target normal tissue effects, one must understand not only the chemical nature of the radiation injury itself for protection purposes, but also, and more importantly for radiation mitigation and treatment, the mechanisms that underlie the physiologic initiation and progression to the ultimate disease end points. In general terms, current radiobiological understanding of tissue injury indicates that, following irradiation, in addition to acute cell death, there is an immediate inflammatory response that appears to follow the same canonical processes seen under the majority of wound conditions (McBride et al. 2004; Bentzen 2006). However, unlike the normally prescribed termination of a wound-healing process, which involves a well-orchestrated secretion of positive and negative regulators of proliferation, inflammation, angiogenesis, etc. (Kareva et al. 2016), a range of parameters in addition to the injury *per se*, i.e. dose, volume, genetic and physiological characteristics, result in the microenvironments of irradiated normal tissues failing to return to their baseline state, i.e. homeostasis. Instead, tissues become prone to recurrent or persistent DNA damage (Minakawa et al. 2016; Beach et al. 2017), aberrant inflammation (Schaue et al. 2015), exhibiting characteristics associated with premature aging and/or senescence (Zhang et al. 2016; Lafargue et al. 2017) and chronic oxidative stress (Iadecola et al. 2001; Zhao & Robbins 2009).

At this point, it is worth also noting a field of radiation research that, to date, generally has not been included as part of countermeasure development; that is consideration of the role(s) that may be played by non-targeted effects in normal tissue injuries. These include phenomena such as the bystander effect, low dose hyper-radiosensitivity, genomic instability, and the adaptive response (Bright & Kadhim 2018), all of which have the potential to act as a benefit or detriment in normal tissue outcomes. To date, the majority of these effects have been studied in the context of cancer risk (Truta-Popa et al. 2011; Burtt et al. 2016; Baulch 2018), although some investigators have assessed their role in therapy-related outcomes (Pinho et al. 2015; Najafi et al. 2018; Mukherjee & Chakraborty 2019). It is highly likely that non-targeted effects add further complexity to the signaling interplay that takes place among surviving, dead and dying cells post-irradiation and, potentially, provide feedback mechanisms that may exacerbate or mitigate the fate of both indirectly and directly irradiated cells and, therefore, the resultant normal tissue outcomes. At present, it is not clear whether the pharmaceutical efforts aimed at treating directly irradiated tissues will

have corresponding beneficial effects on the non-targeted cells, especially given the noted inherent biological variability seen with respect to these phenomena (Sowa et al. 2010).

Additional areas for consideration as countermeasures are the use of the low dose radioadaptive response (Blyth 2018; Cohen et al. 2018), hypoxia (Fallowfield 1962; Rahbeeni et al. 2000) and heat (Marigold & Hume 1982; Sabel et al. 2017), all of which have been shown to have the potential to reduce therapy-related normal tissue injury. However, given the skepticism that has revolved around such concepts as 'hormesis' (Szumiel 2012), the biological variability associated with their efficacy (Brooks 1999; Cohen et al. 2018), the overall lack of specificity for these approaches with respect to normal versus tumor tissues, and the mostly non-pharmaceutical aspect of these approaches, we have ignored their potential use in the overall review. Nonetheless, at some point, it is likely that all of these various research fields will need to be merged if complete treatment efficacy for normal tissue radiation injury is to be truly achieved.

Returning to the results from our survey, as can be seen from Tables 1 through 3, the majority of studies on developing countermeasures in this field have evolved and revolved around the conditions and symptoms seen during the immediate and early stages of progression towards normal tissue effects. As a result, efforts to date have tended to focus on the assessment of agents that target the acute pathophysiologic changes, such as free radical production and DNA/mitochondrial damage; intermittent attention has been paid to attenuating the more overt delayed symptoms, such as chronic inflammation (Schaue et al. 2015) and fibrosis (Medhora et al. 2014; Rabender et al. 2016). However, as suggested by some (Williams & McBride 2011), the observed acute symptoms may not be the most critical steps in the context of delayed or late effects, but, instead, simply be reflective of the dysregulated homeostatic mechanisms that are consequent to, or the initiators of, a disrupted microenvironment (Williams & McBride 2011; Williams et al. 2016). As such, focusing on mitigating the acute symptoms alone, particularly those seen in the immediate period post-exposure, is unlikely to lead to normalization of an irradiated tissue or organ, providing an explanation for the almost complete lack of success in the long-term hunt for a universal radiation protector. Indeed, the practice of addressing imbalance in only one of the affected homeostatic systems seen following total body irradiation would provide an explanation for the dismal late outcomes seen following radiation accidents (Hirama et al. 2003; Williams & McBride 2011) and, indeed, some bone marrow transplantation protocols (Gifford et al. 2014).

A more rational approach to long-term mitigation is to not only promote growth and recovery of critical cell populations, but also 'normalize' key aspects of the disrupted microenvironment within which those cells reside. Support for this more holistic strategy has been demonstrated in multiple preclinical models using combined therapies of, for example, antioxidants administered together with anti-inflammatories and/or angiotensin converting enzyme (ACE) inhibitors, an approach that has shown greater than additive effects compared to the efficacy of the single agents alone (Mahmood et al. 2013; Mahmood et al. 2014; Fish et al. 2016). Importantly, the probability of success when using such a multi-target approach would be enhanced by using temporally appropriate schedules, with each agent's administration being informed by a firm understanding of the patterns of dysregulation,

including their onset and periodicity (Williams et al. 2003; Bentzen et al. 2010). This is not a new concept, as such an approach was voiced in earlier issues of the *International Journal of Radiation Biology* (Weiss et al. 1990).

However, given the concentrated and/or declining resources available for performing the necessary studies, coordinated and collaborative efforts are needed between interested groups of scientists, together with the provision of robust financial support. Unfortunately, our observation of the ways in which countermeasures research has appeared to swing with the political winds, leveraging these funds may not be possible unless a catastrophic event prompts such support. We can only hope that such an extreme solution is not necessary to provide the needed impetus, but it certainly appears that there is little current interest in radiation countermeasure development by the pharmaceutical industry, despite the potential for therapeutic benefit.

Conclusions

To end with our sporting metaphor, the need for countermeasures against the plethora of acute and late normal tissue radiation-induced effects continues to be a worthwhile goal for researchers since it offers the possibility of providing benefits to the military and, more importantly, cancer survivor populations. Indeed, with the technological advances that have been made in radiation delivery systems and the ever-growing panoply of chemotherapeutic and biologic agents available to oncologists, developing agents that would abrogate the treatment-related after effects experienced by hundreds, if not thousands, of patients would have untold worth. However, despite decades (and decades and decades) of work, researchers in this field have made little progress. This disappointing outcome can be partly blamed on the complexity and non-specificity of ionizing radiation injury since, following this insult, there is no single cellular ‘target’ that is amenable to pharmacological manipulation, and certainly not one that is universal across all irradiated volumes, leaving researchers with moving goal posts.

However, from our limited survey of articles that have appeared during a few selected periods in the *International Journal of Radiation Biology* across its 60 years of existence, other, less scientific explanations might be pointed to as possible factors that have limited progress, such as changing political environments potentially affecting the interest in, and financial support for, this work. Given the limitations of a single journal as a data source and the use of a ‘snapshot’ survey, some of the shifts suggested also may be attributed to changes in authors’ choice of publication outlet or our missing significant publications that may have provided explanation, for which we apologize. Nonetheless, the global reach of the *International Journal of Radiation Biology* provides us with a 30,000-foot view that might be lost on those of us battling in the competitive arena of countermeasures development. With the continued threat of radiological or nuclear geopolitical terrorism and the ever-growing cancer survivor population, we can only hope that a future snapshot from the *International Journal of Radiation Biology*, taken in another 30 years’ time, will provide us not only with a view of a more rational and consensual approach to agent development in this field, but the actual prize of a normal tissue countermeasure for all.

Acknowledgements

The authors acknowledge financial support from U19 AI067773 and P30 ES 001247.

References

Aricigil M, Dundar MA, Yucel A, Eryilmaz MA, Aktan M, Alan MA, Findik S, Kilinc I. 2017 Melatonin prevents possible radiotherapy-induced thyroid injury. Int J Radiat Biol. 93(12):1350–1356. [PubMed: 29095094]

Ashwood-Smith MJ. 1961 Inability of dimethyl sulphoxide to protect mouse testis against the effect of X-radiation. Int J Rad Biol Rel Stud Phys Chem Med. 3(1):101–103.

Bacq ZM, Herve A. 1952 A new protection against x-rays. Schweizerische medizinische Wochenschrift. 82(40):1018–1020. [PubMed: 12994860]

Barendsen GW. 1982 Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys. 8(11):1981–1997. [PubMed: 6759484]

Baskar R, Lee KA, Yeo R, Yeoh KW. 2012 Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 9(3):193–199. [PubMed: 22408567]

Baulch JE. 2018 Radiation-induced genomic instability, epigenetic mechanisms and the mitochondria: a dysfunctional ménage a trois? Int J Radiat Biol. [Epub ahead of print].

Beach TA, Johnston CJ, Groves AM, Williams JP, Finkelstein JN. 2017 Radiation induced pulmonary fibrosis as a model of progressive fibrosis: Contributions of DNA damage, inflammatory response and cellular senescence genes. Exp Lung Res. 43(3):134–149. [PubMed: 28534660]

Bentzen SM. 2006 Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer. 6(9):702–713. [PubMed: 16929324]

Bentzen SM, Parliament M, Deasy JO, Dicker A, Curran WJ, Williams JP, Rosenstein BS. 2010 Biomarkers and surrogate endpoints for normal-tissue effects of radiation therapy: the importance of dose-volume effects. Int J Radiat Oncol Biol Phys. 76(3 Suppl):S145–150. [PubMed: 20171510]

Blyth BJ. 2018 The paradox of adaptive responses and iso-effect per fraction. Int J Radiat Biol. 94(8):737–742. [PubMed: 29236558]

Brenner DJ, Chao NJ, Greenberger JS, Guha C, McBride WH, Swartz HM, Williams JP. 2015 Are We Ready for a Radiological Terrorist Attack Yet? Report From the Centers for Medical Countermeasures Against Radiation Network. Int J Radiat Oncol Biol Phys. 92(3):504–505. [PubMed: 26068482]

Bright S, Kadhim M. 2018 The future impacts of non-targeted effects. Int J Radiat Biol. 94(8):727–736. [PubMed: 29569509]

Brook I, Walker RI, MacVittie TJ. 1988 Effect of antimicrobial therapy on bowel flora and bacterial infection in irradiated mice. Int J Rad Biol Rel Stud Phys Chem Med. 53(5):709–716.

Brooks AL. 1999 Biomarkers of exposure, sensitivity and disease. Int J Radiat Biol. 75(12):1481–1503. [PubMed: 10622256]

Bruenger FW, Taylor DM, Taylor GN, Lloyd RD. 1991 Effectiveness of DTPA treatments following the injection of particulate plutonium. Int J Radiat Biol. 60(5):803–818. [PubMed: 1680951]

Burtt JJ, Thompson PA, Lafrenie RM. 2016 Non-targeted effects and radiation-induced carcinogenesis: a review. J Radiol Prot. 36(1):R23–35. [PubMed: 26910391]

Cheng L, Lisowska H, Sollazzo A, Wegierek-Ciuk A, Stepien K, Kuszewski T, Lankoff A, Haghdoost S, Wojcik A. 2015 Modulation of radiation-induced cytogenetic damage in human peripheral blood lymphocytes by hypothermia. Mutat Res Genet Toxicol Environ Mutagen. 793:96–100. [PubMed: 26520378]

Cheng PC, Huang CC, Chiang PF, Lin CN, Li LL, Lee TW, Lin B, Chen IC, Chang KW, Fan CK et al. 2014 Radioprotective effects of Antrodia cinnamomea are enhanced on immune cells and inhibited on cancer cells. Int J Radiat Biol. 90(10):841–852. [PubMed: 24708166]

Cohen J, Vo NTK, Seymour CB, Mothersill CE. 2018 Parallel comparison of pre-conditioning and post-conditioning effects in human cancers and keratinocytes upon acute gamma irradiation. Int J Radiat Biol. [Epub ahead of print].

Coleman CN, Parker GW. 2009 Radiation terrorism: what society needs from the radiobiology-radiation protection and radiation oncology communities. J Radiol Prot. 29(2a):A159–169. [PubMed: 19454803]

Davis AK, Cranmore D, Alpen EL. 1958 Alteration of beta-radiation lesions of the skin by cysteine nitrite, hypoxia, spleen homogenate, and bone marrow homogenate. Radiat Res. 9(2):222–228. [PubMed: 13579190]

DeBo RJ, Register TC, Caudell DL, Sempowski GD, Dugan G, Gray S, Owzar K, Jiang C, Bourland JD, Chao NJ et al. 2015 Molecular and cellular profiling of acute responses to total body radiation exposure in ovariectomized female cynomolgus macaques. Int J Radiat Biol. 91(6):510–518. [PubMed: 25786585]

Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. 1991 Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 21:109–122. [PubMed: 2032882]

Fallowfield TL. 1962 The influence of hypothermia involving minimal hypoxia on the radiosensitivity of leucocytes in the rat. Int J Rad Biol Rel Stud Phys Chem Med. 4:457–464.

Fish BL, Gao F, Narayanan J, Bergom C, Jacobs ER, Cohen EP, Moulder JE, Orschell CM, Medhora M. 2016 Combined hydration and antibiotics with Lisinopril to mitigate acute and delayed high-dose radiation injuries to multiple organs. Health Phys. 111(5):410–419. [PubMed: 27682899]

Flood AB, Williams BB, Schreiber W, Du G, Wood VA, Kmiec MM, Petryakov SV, Demidenko E, Swartz HM. 2016 Advances in in vivo EPR Tooth BIOdosimetry: Meeting the targets for initial triage following a large-scale radiation event. Radiat Prot Dosimetry. 172(1–3):72–80. [PubMed: 27421468]

Folley JH, Borges W, Yamawaki T. 1952 Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. Am J Med. 13(3):311–321. [PubMed: 12985588]

Fowler JF. 2006 Development of radiobiology for oncology - a personal view. Phys Med Biol. 51(13):R263–286. [PubMed: 16790907]

Fukuda K, Uehara Y, Nakata E, Inoue M, Shimazu K, Yoshida T, Kanda H, Nanjo H, Hosoi Y, Yamakoshi H et al. 2016 A diarylpentanoid curcumin analog exhibits improved radioprotective potential in the intestinal mucosa. Int J Radiat Biol. 92(7):388–394. [PubMed: 27043482]

Gaddis JL. 2006 The Cold War: A new history. New York, NY USA: Penguin Books.

Galli G 1959 The therapeutic possibilities of various chelating substances in radiation sickness. Minerv Fisioter Radiobiol. 4:322–327.

Gawade PL, Hudson MM, Kaste SC, Neglia JP, Wasilewski-Masker K, Constine LS, Robison LL, Ness KK. 2014 A systematic review of selected musculoskeletal late effects in survivors of childhood cancer. Curr Pediatr Rev. 10(4):249–262. [PubMed: 25403639]

Gifford G, Sim J, Horne A, Ma D. 2014 Health status, late effects and long-term survivorship of allogeneic bone marrow transplantation: a retrospective study. Int Med J. 44(2):139–147.

Grant GA, Vos O. 1962 Chemical protection of rat thymocytes irradiated in vitro. Int J Rad Biol Rel Stud Phys Chem Med. 5:413–425.

Hafer N, Cassatt D, Dicarlo A, Ramakrishnan N, Kaminski J, Norman MK, Maidment B, Hatchett R. 2010 NIAID/NIH radiation/nuclear medical countermeasures product research and development program. Health Phys. 98(6):903–905. [PubMed: 20445403]

Harada T, Ishida MI. 1960 Neoplasms among A-bomb survivors in Hiroshima: first report of the Research Committee on Tumor Statistics, Hiroshima City Medical Association, Hiroshima, Japan. J Natl Cancer Inst. 25:1253–1264. [PubMed: 13711417]

Hendry JH. 1979 Quantitation of the radiotherapeutic importance of naturally-hypoxic normal tissues from collated experiments with rodents using single doses. Int J Radiat Oncol Biol Phys. 5(7):971–976. [PubMed: 389904]

Himburg HA, Sasine J, Yan X, Kan J, Dressman H, Chute JP. 2016 A molecular profile of the endothelial cell response to ionizing radiation. Radiat Res. 186(2):141–152. [PubMed: 27387861]

Hirama T, Tanosaki S, Kandatsu S, Kuroiwa N, Kamada T, Tsuji H, Yamada S, Katoh H, Yamamoto N, Tsujii H et al. 2003 Initial medical management of patients severely irradiated in the Tokai-mura criticality accident. Br J Radiol. 76(904):246–253. [PubMed: 12711644]

Homer MJ, Raulli R, DiCarlo-Cohen AL, Esker J, Hrdina C, Maidment BW, Moyer B, Rios C, Macchiarini F, Prasanna PG et al. 2016 United States Department of Health and Human Services Biodosimetry and Radiological/Nuclear Medical Countermeasures Programs. Radiat Prot Dosimetry. 171(1):85–98. [PubMed: 27590469]

Huang EY, Peng CT, Wang CC. 2018 Effects of radiation response modifiers given after lethal whole-abdominal irradiation. Int J Radiat Biol. 94(3):289–294. [PubMed: 29355463]

Iadecola C, Niwa K, Nogawa S, Zhao X, Nagayama M, Araki E, Morham S, Ross ME. 2001 Reduced susceptibility to ischemic brain injury and N-methyl-D-aspartate-mediated neurotoxicity in cyclooxygenase-2-deficient mice. Proc Natl Acad Sci USA. 98:1294–1299. [PubMed: 11158633]

Ioannides KG, Mantzios AS, Pappas CP. 1991 Influence of Prussian blue in reducing transfer of radiocesium into ovine milk. Health Phys. 60(2):261–264. [PubMed: 1989947]

Iversen ES, McCarthy JM, Bell Burdett K, Lipton G, Phillips G, Dressman H, Ross J, Chao N. 2018 Bridging the gaps: using an NHP model to predict single dose radiation absorption in humans. Int J Radiat Biol. [Epub ahead of print].

Jacobs AR, Guyon T, Headley V, Nair M, Ricketts W, Gray G, Wong JYC, Chao N, Terbrueggen R. 2018 Role of a high throughput biodosimetry test in treatment prioritization after a nuclear incident. Int J Radiat Biol. [Epub ahead of print].

Kalinich JF, Catravas GN, Snyder SL. 1991 Radioprotective properties of DNA methylation-disrupting agents. Int J Radiat Biol. 59(5):1217–1226. [PubMed: 1710643]

Kareva I, Abou-Slaybi A, Dodd O, Dashevsky O, Klement GL. 2016 Normal wound healing and tumor angiogenesis as a game of competitive inhibition. PLoS One. 11(12):e0166655. [PubMed: 27935954]

Lafargue A, Degorre C, Corre I, Alves-Guerra MC, Gaugler MH, Vallette F, Pecqueur C, Paris F. 2017 Ionizing radiation induces long-term senescence in endothelial cells through mitochondrial respiratory complex II dysfunction and superoxide generation. Free Radic Biol Med. 108:750–759. [PubMed: 28431961]

Laiakis EC, Strawn SJ, Brenner DJ, Fornace AJ Jr. 2016 Assessment of saliva as a potential biofluid for biodosimetry: A pilot metabolomics study in mice. Radiat Res. 186(1):92–97. [PubMed: 27332953]

Larsson B, Stenson S. 1965 Reduction of radiation damage to the intestinal mucous membrane by local hypoxia. Nature. 205:364–365. [PubMed: 14245955]

Lee Y, Pujol Canadell M, Shuryak I, Perrier JR, Taveras M, Patel P, Koller A, Smilenov LB, Brenner DJ, Chen EI et al. 2018 Candidate protein markers for radiation biodosimetry in the hematopoietically humanized mouse model. Sci Rep. 8(1):13557. [PubMed: 30202043]

Li FS, Weng JK. 2017 Demystifying traditional herbal medicine with modern approach. Nat Plants. 3:17109. [PubMed: 28758992]

Mabro M, Faivre S, Raymond E. 1999 A risk-benefit assessment of amifostine in cytoprotection. Drug Saf. 21(5):367–387. [PubMed: 10554052]

Macia IGM. 2017 Radiobiology of stereotactic body radiation therapy (SBRT). Rep Pract Oncol Radiother. 22(2):86–95. [PubMed: 28490978]

Mahmood J, Jelveh S, Zaidi A, Doctrow SR, Hill RP. 2013 Mitigation of radiation-induced lung injury with EUK-207 and genistein: effects in adolescent rats. Radiat Res. 179(2):125–134. [PubMed: 23237541]

Mahmood J, Jelveh S, Zaidi A, Doctrow SR, Medhora M, Hill RP. 2014 Targeting the Renin-angiotensin system combined with an antioxidant is highly effective in mitigating radiation-induced lung damage. Int J Radiat Oncol Biol Phys. 89(4):722–728. [PubMed: 24867538]

Malerba F, Orsenigo L. 2015 The evolution of the pharmaceutical industry. Business Hist. 57(5):664–687.

Mandl AM. 1959 The effect of cysteamine on the survival of spermatagonia after X-irradiation. Int J Rad Biol Rel Stud Phys Chem Med. 1(2):131–142.

Marigold JC, Hume SP. 1982 Effect of prior hyperthermia on subsequent thermal enhancement of radiation damage in mouse intestine. Int J Rad Biol Rel Stud Phys Chem Med. 42(5):509–516.

McBride WH, Chiang CS, Olson JL, Wang CC, Hong JH, Pajonk F, Dougherty GJ, Iwamoto KS, Pervan M, Liao YP. 2004 A sense of danger from radiation. Radiat Res. 162(1):1–19. [PubMed: 15222781]

McBride WH, Mason KA, Peters LJ, Thames HD. 2015 Dr. H. Rodney Withers (1932 - 2015). Int J Radiat Biol. 91(5):459–461. [PubMed: 25908167]

McCally M, Cassel C, Kimball DG. 1994 Government-sponsored radiation research on humans 1945–1975. Med Global Surv. 1(1):4–16.

McDowell LJ, Rock K, Xu W, Chan B, Waldron J, Lu L, Ezzat S, Pothier D, Bernstein LJ, So N et al. 2018 Long-Term Late Toxicity, Quality of Life, and Emotional Distress in Patients With Nasopharyngeal Carcinoma Treated With Intensity Modulated Radiation Therapy. Int J Radiat Oncol Biol Phys. 102(2):340–352. [PubMed: 30191868]

Medhora M, Gao F, Wu Q, Molthen RC, Jacobs ER, Moulder JE, Fish BL. 2014 Model development and use of ACE inhibitors for preclinical mitigation of radiation-induced injury to multiple organs. Radiat Res. 182(5):545–555. [PubMed: 25361399]

Miller AC, Rivas R, McMahon R, Miller K, Tesoro L, Villa V, Yanushkevich D, Lison P. 2017 Radiation protection and mitigation potential of phenylbutyrate: delivered via oral administration. Int J Radiat Biol. 93(9):907–919. [PubMed: 28749244]

Minakawa Y, Atsumi Y, Shinohara A, Murakami Y, Yoshioka K. 2016 Gamma-irradiated quiescent cells repair directly induced double-strand breaks but accumulate persistent double-strand breaks during subsequent DNA replication. Genes to cells : devoted to molecular & cellular mechanisms. 21(7):789–797. [PubMed: 27251002]

Mishra K, Alsbeih G. 2017 Appraisal of biochemical classes of radioprotectors: evidence, current status and guidelines for future development. 3 Biotech. 7(5):292.

Moulder JE. 2003 Pharmacological intervention to prevent or ameliorate chronic radiation injuries. Semin Radiat Oncol. 13(1):73–84. [PubMed: 12520466]

Moulder JE, Cohen EP, Fish BL. 2014 Mitigation of experimental radiation nephropathy by renin-equivalent doses of angiotensin converting enzyme inhibitors. Int J Radiat Biol. 90(9):762–768. [PubMed: 24991882]

Mukherjee S, Chakraborty A. 2019 Radiation-induced bystander phenomenon: insight and implications in radiotherapy. Int J Rad Biol. [Epub ahead of print].

Najafi M, Motevaseli E, Shirazi A, Geraily G, Rezaeyan A, Norouzi F, Rezapoor S, Abdollahi H. 2018 Mechanisms of inflammatory responses to radiation and normal tissues toxicity: clinical implications. Int J Radiat Biol. 94(4):335–356. [PubMed: 29504497]

National Council on Radiation Protection and Measurement: NCRP Statement No. 12. Where are the radiation professionals (WARP)? Bethesda, MD.

Norman A, McBride WH, Bennett LR, Santos Mello R, Iwamoto K, Hidmi H. 1988 Postirradiation protection of chromosomes by linoleate. Int J Radiat Biol. 54(4):521–524. [PubMed: 2902149]

Norwood WD. 1962 Therapeutic removal of plutonium in humans. Health Phys. 8:747–750. [PubMed: 13939004]

Oliai C, Yang LX. 2014 Radioprotectants to reduce the risk of radiation-induced carcinogenesis. Int J Radiat Biol. 90(3):203–213. [PubMed: 24164532]

Patt HM, Tyree EB, Straube RL, Smith DE. 1949 Cysteine protection against X irradiation. Science. 110(2852):213–214. [PubMed: 17811258]

Pejchal J, Sinkorova Z, Tichy A, Kmochova A, Durisova K, Kubelkova K, Pohanka M, Bures J, Tacheci I, Kuca K et al. 2015 Attenuation of radiation-induced gastrointestinal damage by epidermal growth factor and bone marrow transplantation in mice. Int J Radiat Biol. 91(9):703–714. [PubMed: 25994811]

Pihl A, Eldjarn L. 1958 Pharmacological aspects of ionizing radiation and of chemical protection in mammals. Pharmacol Rev. 10(4):437–474. [PubMed: 13613941]

Pinho C, Timotin E, Wong R, Sur RK, Hayward JE, Farrell TJ, Seymour C, Mothersill C. 2015 Assessing patient characteristics and radiation-induced non-targeted effects in vivo for high dose-rate (HDR) brachytherapy. Int J Radiat Biol. 91(10):786–794. [PubMed: 26136084]

Prasad KN, Kollmorgen GM, Kent TH, Osborne JW. 1963 Protective effect of ß-mercaptoethylamine and mesenteric clamping on intestine-radiated rats. Int J Rad Biol Rel Stud Phys Chem Med. 6(3):257–269.

Prasad KN, Osborne JW. 1963 Influence of ß-mercaptoethylamine on mucosal uptake of ^{59}Fe by intestine-irradiated rats. Int J Rad Biol Rel Stud Phys Chem Med. 7(3):245–253.

Prasanna PG, Narayanan D, Hallett K, Bernhard EJ, Ahmed MM, Evans G, Vikram B, Weingarten M, Coleman CN. 2015 Radioprotectors and radiomitigators for improving radiation therapy: The Small Business Innovation Research (SBIR) gateway for accelerating clinical translation. Radiat Res. 184(3):235–248. [PubMed: 26284423]

Praslicka M, Hill M, Novak L. 1962 Protective action of 2,4-dinitrophenol against X-radiation injury. Int J Rad Biol Rel Stud Phys Chem Med. 4(6):567–579.

Price PW, DiCarlo AL. 2018 Challenges and benefits of repurposing licensed/approved/cleared products for a radiation indication. Radiat Res. [Epub ahead of print].

Rabender C, Mezzaroma E, Mauro AG, Mullangi R, Abbate A, Anscher M, Hart B, Mikkelsen R. 2016 IPW-5371 proves effective as a radiation countermeasure by mitigating radiation-induced late effects. Radiat Res. 186(5):478–488. [PubMed: 27841740]

Rahbeeni F, Hendrikse AS, Smuts CM, Gelderblom WC, Abel S, Blekkenhorst GH. 2000 The effect of evening primrose oil on the radiation response and blood flow of mouse normal and tumour tissue. Int J Radiat Biol. 76(6):871–877. [PubMed: 10902742]

Repin M, Pampou S, Karan C, Brenner DJ, Garty G. 2017 RABiT-II: Implementation of a high-throughput micronucleus biodosimetry assay on commercial biotech robotic systems. Radiat Res. 187(4):492–498. [PubMed: 28231025]

Report of the Advisory Committee on Human Radiation Experiments. Research ethics and the medical profession. 1996 JAMA. 276(5):403–409. [PubMed: 8683820]

Rios CI, Cassatt DR, Dicarlo AL, Macchiarini F, Ramakrishnan N, Norman MK, Maidment BW. 2014 Building the strategic national stockpile through the NIAID Radiation Nuclear Countermeasures Program. Drug Dev Res. 75(1):23–28. [PubMed: 24648046]

Rosenstein BS, Held KD, Rockwell S, Williams JP, Zeman EM. 2009 American Society for Radiation Oncology (ASTRO) survey of radiation biology educators in U.S. and Canadian radiation oncology residency programs. Int J Radiat Oncol Biol Phys. 75(3):896–905. [PubMed: 19733012]

Rubin P 1995 Special issue: Late Effects of Normal Tissues (LENT) Consensus Conference, including RTOG/EORTC SOMA scales. San Francisco, California, August 26–28, 1992. Int J Radiat Oncol Biol Phys. 31:1035–1360. [PubMed: 7713773]

Sabel M, Kalm M, Bjork-Eriksson T, Lannering B, Blomgren K. 2017 Hypothermia after cranial irradiation protects neural progenitor cells in the subventricular zone but not in the hippocampus. Int J Radiat Biol. 93(8):771–783. [PubMed: 28452566]

Schaue D, Micewicz ED, Ratikan JA, Xie MW, Cheng G, McBride WH. 2015 Radiation and inflammation. Semin Radiat Oncol. 25(1):4–10. [PubMed: 25481260]

Schoeters GE, Maisin JR, Vanderborght OL. 1991 Protracted treatment of C57B1 mice with Zn-DTPA after ^{241}Am injection reduces the long-term radiation effects. Int J Radiat Biol. 59(4):1027–1038. [PubMed: 1674269]

Schubauer-Berigan MK, Daniels RD, Fleming DA, Markey AM, Couch JR, Ahrenholz SH, Burphy JS, Anderson JL, Tseng CY. 2007 Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature. Br J Haematol. 139(5):799–808. [PubMed: 17922878]

Shore RE. 1990 Occupational radiation studies: status, problems, and prospects. Health Phys. 59(1):63–68. [PubMed: 2358360]

Singh M, Alavi A, Wong R, Akita S. 2016 Radiodermatitis: A review of our current understanding. Am J Clin Dermatol. 17(3):277–292. [PubMed: 27021652]

Singh VK, Garcia M, Seed TM. 2017a A review of radiation countermeasures focusing on injury-specific medicinals and regulatory approval status: part II. Countermeasures for limited indications, internalized radionuclides, emesis, late effects, and agents demonstrating efficacy in large animals with or without FDA IND status. Int J Radiat Biol. 93(9):870–884. [PubMed: 28657406]

Singh VK, Hanlon BK, Santiago PT, Seed TM. 2017b A review of radiation countermeasures focusing on injury-specific medicinals and regulatory approval status: part III. Countermeasures under early stages of development along with 'standard of care' medicinal and procedures not requiring regulatory approval for use. Int J Radiat Biol. 93(9):885–906. [PubMed: 28657400]

Singh VK, Seed TM. 2017 A review of radiation countermeasures focusing on injury-specific medicinals and regulatory approval status: part I. Radiation sub-syndromes, animal models and FDA-approved countermeasures. Int J Radiat Biol. 93(9):851–869. [PubMed: 28650707]

Sowa MB, Goetz W, Baulch JE, Pyles DN, Dziegielewski J, Yovino S, Snyder AR, de Toledo SM, Azzam EI, Morgan WF. 2010 Lack of evidence for low-LET radiation induced bystander response in normal human fibroblasts and colon carcinoma cells. Int J Radiat Biol. 86(2):102–113. [PubMed: 20148696]

Starkie CM. 1961 The effect of cysteamine on the survival of foetal germ cells after irradiation. Int J Rad Biol Rel Stud Phys Chem Med.. 3(6):609–617.

Stone HB, Moulder JE, Coleman CN, Ang KK, Anscher MS, Barcellos-Hoff MH, Dynan WS, Fike JR, Grdina DJ, Greenberger JS et al. 2004 Meeting Report. Models for evaluating agents intended for prophylaxis, mitigation and treatment of radiation injuries. Report of an NCI workshop, December 3–4, 2003. Radiat Res. 162:711–728. [PubMed: 15548121]

Stratton K, Davis EM. 1962 The radioprotective action of guanylthiourea and related compounds. Int J Rad Biol Rel Stud Phys Chem Med. 5(2):105–121.

Sumikawa S, Watanabe S, Tanaka M, Tanaka A, Araki H. 2017 Effect of basic fibroblast growth factor on radiation-induced oral mucositis in male Syrian hamsters. Int J Radiat Biol. 93(12):1343–1349. [PubMed: 29034752]

Sun LR, Cooper S. 2018 Neurological Complications of the Treatment of Pediatric Neoplastic Disorders. Pediatr Neurol. [Epub ahead of print].

Szumiel I 2012 Radiation hormesis: Autophagy and other cellular mechanisms. Int J Radiat Biol. 88(9):619–628. [PubMed: 22702489]

Taibi R, Lleshi A, Barzan L, Fiorica F, Leghissa M, Vaccher E, De Paoli P, Franchin G, Berretta M, Tirelli U. 2014 Head and neck cancer survivors patients and late effects related to oncologic treatment: update of literature. Eur Rev Med Pharmacol Sci. 18(10):1473–1481. [PubMed: 24899605]

Talebpour Amiri F, Hamzeh M, Naeimi RA, Ghasemi A, Hosseinimehr SJ. 2018 Radioprotective effect of atorvastatin against ionizing radiation-induced nephrotoxicity in mice. Int J Radiat Biol. 94(2):106–113. [PubMed: 29268056]

Truta-Popa LA, Hofmann W, Fakir H, Cosma C. 2011 The effect of non-targeted cellular mechanisms on lung cancer risk for chronic, low level radon exposures. Int J Radiat Biol. 87(9):944–953. [PubMed: 21770704]

van den Aardweg GJ, Hopewell JW, Adams GE, Barnes DW, Sansom JM, Stratford IJ, Nethersell AB. 1991 Protection of pig epidermis against radiation-induced damage by the infusion of BW12C. Int J Radiat Biol. 59(4):1039–1051. [PubMed: 1674270]

van den Hoek J 1989 European research on the transfer of radionuclides to animals--a historical perspective. Sci Total Env. 85:17–27. [PubMed: 2683067]

van der Meer C, van Bekkum DW. 1959 The mechanism of radiation protection by histamine and other biological amines. Int J Rad Biol Rel Stud Phys Chem Med. 1(1):5–23.

Varghese JJ, Schmale IL, Mickelsen D, Hansen ME, Newlands SD, Benoit DSW, Korshunov VA, Ovitt CE. 2018 Localized delivery of amifostine enhances salivary gland radioprotection. J Dental Res. 97(11):1252–1259.

Vergroesen AJ, Budke L, Vos O. 1963 Protection of tissue-culture cells against ionizing radiation. III. The influence of anoxia on the radioprotection of tissue-culture cells by cysteamine. Int J Rad Biol Rel Stud Phys Chem Med. 6(2):117–126.

Vos O, Kaalen MCAC. 1962 Protection of tissue culture cells against radiation. II. The activity of hypoxia, dimethyl sulphoxide, dimethyl sulphone, glycerol and cysteamine at room temperature and at −196°C. Int J Rad Biol Rel Stud Phys Chem Med. 5(6):609–621.

Wai ES, Lesperance M, Lu L, Alexander CS, Truong PT. 2017 Effect of referral patterns and treatment type on oncologic outcomes for women with ductal carcinoma in situ. Cureus. 9(3):e1128. [PubMed: 28465875]

Wang R, Han L, Gao Q, Chen D, Wang Y, Zhang X, Yu X, Zhang Y, Li Z, Bai C. 2018 Progress on active analgesic components and mechanisms of commonly used traditional Chinese medicines: A comprehensive review. J Pharm Pharmac Sci. 21(1):437–480.

Watanabe S, Suemaru K, Nakanishi M, Nakajima N, Tanaka M, Tanaka A, Araki H. 2014 Assessment of the hamster cheek pouch as a model for radiation-induced oral mucositis, and evaluation of the protective effects of keratinocyte growth factor using this model. Int J Radiat Biol. 90(10):884–891. [PubMed: 24827853]

Weiss JF, Kumar KS, Walden TL, Neta R, Landauer MR, Clark EP. 1990 Advances in radioprotection through the use of combined agent regimens. Int J Radiat Biol. 57(4):709–722. [PubMed: 1969903]

Weiss JF, Landauer MR. 2003 Protection against ionizing radiation by antioxidant nutrients and phytochemicals. Toxicology. 189(1–2):1–20. [PubMed: 12821279]

Weiss JF, Landauer MR. 2009 History and development of radiation-protective agents. Int J Radiat Biol. 85(7):539–573. [PubMed: 19557599]

Weiss L 1961 The effect of cysteamine on the radiosensitivity of the haemopoietic system of severely hypoxic mice. Int J Rad Biol Rel Stud Phys Chem Med. 3(3):285–292.

Williams J, Chen Y, Rubin P, Finkelstein J, Okunieff P. 2003 The biological basis of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol. 13:182–188. [PubMed: 12903008]

Williams JP, Brown SL, Georges GE, Hauer-Jensen M, Hill RP, Huser AK, Kirsch DG, Macvittie TJ, Mason KA, Medhora MM et al. 2010 Animal models for medical countermeasures to radiation exposure. Radiat Res. 173(4):557–578. [PubMed: 20334528]

Williams JP, Calvi L, Chakkalakal JV, Finkelstein JN, O'Banion MK, Puzas E. 2016 Addressing the symptoms or fixing the problem? Developing countermeasures against normal tissue radiation injury. Radiat Res. 186(1):1–16. [PubMed: 27332954]

Williams JP, McBride WH. 2011 After the bomb drops: a new look at radiation-induced multiple organ dysfunction syndrome (MODS). Int J Radiat Biol. 87(8):851–868. [PubMed: 21417595]

Williams JP, Newhauser W. 2018 Normal tissue damage: its importance, history and challenges for the future. Br J Radiol. [Epub ahead of print].

Withers HR, Thames HD Jr, Peters LJ. 1982 Differences in the fractionation response of acutely and late-responding tissues. In: Karcher KHea, editor Progress in Radio-Oncology. New York: Raven Press; p. 287–296.

Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, Cassivi SD, Midthun DE, Marks RS, Aubry MC et al. 2012 Quality of life and symptom burden among long-term lung cancer survivors. J Thor Oncol. 7(1):64–70.

Yuhas JM, Storer JB. 1969 Chemoprotection against three modes of radiation death in the mouse. Int J Rad Biol Rel Stud Phys Chem Med. 15(3):233–237.

Zatz LM. 1963 The radioprotective effects of combined hypoxia and AET in mice. Int J Rad Biol Rel Stud Phys Chem Med. 6(2):105–115.

Zhang X, Ye C, Sun F, Wei W, Hu B, Wang J. 2016 Both complexity and location of DNA damage contribute to cellular senescence induced by ionizing radiation. PLoS One. 11(5):e0155725. [PubMed: 27187621]

Zhao W, Robbins ME. 2009 Inflammation and chronic oxidative stress in radiation-induced late normal tissue injury: therapeutic implications. Curr Med Chem. 16(2):130–143. [PubMed: 19149566]

Table 1:

Survey of articles on radiation countermeasures in the *International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine* from 1959–1963.

Class of drug	Volume/dose range (Gy)	Models used	Normal tissue endpoint	Investigator(s) reference and year
RADIATION PROTECTANTS				
Sulfhydryl compounds:				
AET:	TBI / 5	Mice	5-HIAA urinary excretion	Maisin et al., 1960
(+ hypoxia)	TBI / 9–20	Mice	GI protection	Zatz, 1963
Pyridoxine derivatives	TBI / ~5–30	Mice	Survival	Bridges & Koch, 1961
	TBI / 5–8	Mice	Survival	Dacquisto et al., 1961
Cystamine: (vs. *cysteamine)*	TBI / 5.5	Mice	Hair/hair follicle preservation	Smoliar & Betz, 1963
Cysteamine:	Scrotum / 2–5	Rats	Spermatogonia survival	Mandl, 1959
	TBI / 3–8	Rats	Liver glycogen levels	Chatterjee et al., 1959
(+ hypoxia/hypothermia)	TBI / 2.5–95	Mice	Bone marrow histology	Weiss, 1961
	TBI / 0.5–1.5	Pregnant rats	Testes survival in male offspring	Starkie, 1961
(cysteine derivatives)	5	*in vitro* thymocytes	Cell survival; O_2 content	Grant & Vos, 1962
	TBI / 1.2	Grasshoppers	Chromosome aberrations	Ray-Chaudhuri et al., 1962
(vs. cysteine, AET)	5–15	*in vitro* thymocytes	Colony-forming assay	Vos et al., 1962
	GI / 14–18	Rats (exteriorized gut)	Mucosal function (Fe uptake)	Vergroesen et al., 1963
(± anoxia)	5–35	*in vitro* kidney cells	Cell survival; O2 content	Vergroesen et al., 1963
	GI / 18–30	Rats (exteriorized gut)	Survival; histology	Prasad et al., 1963
(+ derivatives)	TBI / 7.5–13.3	Mice	Survival	van Bekkum & Nieuwerkerk, 1963
(vs. cystamine)	5–15	*in vitro* thymocytes	Colony-forming assay	Vos et al., 1962
DMSO:	TBI / 1–8	Mice	Testicular weight/ histology	Ashwood-Smith, 1961a
(+ other sulphoxides)	TBI / 10.07	Mice	Survival	Ashwood-Smith, 1961b
(vs. dimethyl sulphone)	5–40	*in vitro* kidney cells	Colony-forming assay	Vos & Kaalen, 1962
	TBI / LD98/30	Mice (2 strains)	Survival; O2 tension	van der Meer et al., 1963
(± AET/cysteamine)	TBI / 10–14	Mice	Survival	Ashwood-Smith, 1962
Guanylthiourea	TBI / 9	Mice	Survival	Stratton & Davis, 1962
MEG:	TBI / 9	Mice	Survival	Deanovic et al., 1963
(vs. cysteine, DMSO)	60–250	*Serratia marcescens*	Bacterial survival	Dewey, 1963
Thiuronium salts	TBI / 10.07	Mice	Survival; body temperature	Ashwood-Smith & Smith, 1959
Toxic compounds:				
5-hydroxytryptamine:	5–15	*in vitro* thymocytes	Colony-forming assay	Vos et al., 1962
	TBI / 5–19	Mice	Survival	van den Brenk & Haas, 1961

Class of drug	Volume/dose range (Gy)	Models used	Normal tissue endpoint	Investigator(s) reference and year
(vs. tryptamine)	TBI / 10–16	Rats & mice	Survival	van der Meer & van Bekkum, 1961
	TBI / 6.75–12.5	Mice	Survival	Langendorff et al., 1959
Cyanide	TBI / 8	Rats	^{39}Fe uptake	Bose, 1959
Histamine, epinephrine, etc.:	TBI / 6.75–12	Mice (2 strains)	Survival; O2 tension	van der Meer & van Bekkum, 1959
(indolealkylamines)	9	Rats	Survival	Supek et al., 1961
	5	*in vitro* thymocytes	Cell survival	Grant & Vos, 1962
Metabolites/Misc.:				
2,4 dinitrophenol	TBI / 5.6–7.2	Mice	Survival; bone marrow recovery	Praslicka et al., 1962
EDTA	TBI / 7.4 Gy	Rats	Survival	Rixon & Whitfield, 1961
Glycerol	5–40	*in vitro* kidney cells	Colony-forming assay	Vos & Kaalen, 1962
Olive oil	TBI / 6.25	Mice	Survival	Maqsood & Ashikawa, 1962
Parathyroid hormone	TBI / 7–10 Gy	Rats	Survival	Rixon & Whitaker, 1961

Abbreviations: 5-HIAA: 5-hydroxyindoleacetic acid; AET: 2-aminoethyl isothiuronium bromide hydrobromide; DMSO: dimethyl sulfoxide; EDTA: ethylenediaminetetraacetic acid; GI: gastrointestinal tract; MEG: 2-mercaptoethylguanidine;TBI: total body irradiation.

Table 2.

Survey of articles on radiation countermeasures in the *International Journal of Radiation Biology* from 1987–1991.

Class of drug	Volume/dose range (Gy)	Models used	Mechanism (M) / Normal tissue endpoint (N)	Investigator(s) reference and year
RADIATION PROTECTANTS				
Sulfhydryl compounds:				
2-mercaptoproprionol glycine	3.2 & 4.8	*in vitro* erythrocytes / microsomes	(M) Lipid peroxidation; enzyme activity	Ayene et al., 1988
Cysteamine (± hypoxia)	0–26	*in vitro* HeLa/CHO	(N) Cell survival	Vos & Roos-Verhey, 1988
	10	*in vitro* CHO	(N) Cell survival; DNA repair	Murray et al., 1990
Dithiothreitol (DTT) (± hypoxia)	29, 87	*in vitro* V79–379A	(N) DNA breaks	Solen et al., 1990
(± hypoxia)	29, 57, 86	*in vitro* CHO	(N) DNA breaks	Solen et al., 1991
(+ hypothermia)	0–750	*in vitro Escherichia coli*	(N) Colony-forming assay	Smith & Claycamp, 1988
	10	*in vitro* CHO	(N) Cell survival; DNA repair	Murray et al., 1990
DMSO	0–5	*in vitro* human lymphocytes	(N) Chromosome aberrations	Littlefield et al., 1988
Glutathione (± hypoxia)	0–26	*in vitro* HeLa/CHO	(N) Cell survival	Vos & Roos-Verhey, 1988
WR-2721:	TBI / 5, 15	Mice	(N) DSBs; GI survival	Hanson & Grdina, 1987
	TBI / 6–20	Mice	(N) Survival	Fatome et al., 1987
(± EDTA)	66–399	*in vitro* erythrocytes / microsomes	(M) Lipid peroxidation; enzyme activity	Ayene & Srivastava, 1989
WR-255591	5–30	*in vitro* CHO	(N) Cell survival; DNA repair	Murray et al., 1988
WR-151326	10	*in vitro* CHO	(N) Cell survival; DNA repair	Murray et al., 1990
Relevant Biologics:				
5-azacytidine vs. sodium butyrate (pre- and post-RT)	0–10	V79A03 (hamster lung fibroblasts)	(N) Cell survival; DNA Methylation	Kalinich et al., 1991
16–16 dimethyl prostaglandin E2 (pre-RT)	TBI / 5, 15	Mice	(N) DSBs; gut clonogen survival	Hanson & Grdina, 1987
Antimicrobial therapy (GEN ± MTZ post-RT)	TBI/10	Mice	(M/N) Bowel flora; bacterial infection	Brook et al., 1988
Calmodulin antagonists (CPZ, PMZ, TMZ)	0–1092	Rat liver microsomes	(M) Lipid peroxidation	Varshney & Kale, 1990
Human G-CSF	TBI / 2, 3.5	Dogs	(N) Survival; bone marrow recovery	MacVittie et al., 1990
Human interleukin 1-a	TBI / 8	Mice	(N) Survival; bone marrow recovery	Wu et al., 1989
OK432 (polysaccharide)	TBI / 8.5	Mice	(N) Survival	Kurishita et al., 1991
PARP inhibitor	5–15	*in vitro* human lymphocytes	(N) Cell survival; DNA repair	Marini et al., 1990
Polyacrylamide beads (re. inflammation)	TBI / 8.5–12	Mice	(M/N) Survival	Herodin et al., 1987
Miscellaneous:				

Class of drug	Volume/dose range (Gy)	Models used	Mechanism (M) / Normal tissue endpoint (N)	Investigator(s) reference and year
BW12C (anti-sickling agent)	15–50 90Sr	Pig skin	(N) Moist desquamation	van den Aardweg et al., 1991
Linoleate (post-RT)	2	*in vitro* bone marrow / lymphocytes	(N) Chromosome damage	Norman et al., 1988
Papaya juice	0–640	--	(M) Free radical scavenging	Webman et al., 1989
RADIATION TREATMENTS				
Chelating agents				
Ca-DTPA	17–69 kBq 241Am	Dogs	(M) Translocation from lungs	Guilmette & Muggenburg, 1988
(vs. LICAM(C))	5 kBq 238Pu / 5 kBq 241Am	Rats	(M) Efficacy	Stradling et al., 1989
(vs. Zn-DTPA)	31.4 kBq 239Pu	Dogs	(N) Survival; carcinogenesis (osteosarcoma)	Bruenger et al., 1991
DFO-HOPO vs. DTPA-PX vs. DTPA	200 Bq 238Pu, 450 Bq 241 Am	Rats	(M) Drug efficacy	Stradling et al., 1991
Tetra-THB-spermine	6.6 kBq 239Pu	Mice	(M/N) Efficacy; toxicity	Szot et al., 1989
Zn-DTPA	111 kBq 141Ce	Rat pups	(M) Gut/whole body retention	Kostial et al., 1987
	58, 373 kBq 241Am	Mice	(N) Survival; late disease	Schoeters et al., 1991

Abbreviations: CHO: Chinese hamster ovary; CMZ: calmidazolium; DFO-HOPO: desferrioxamine-2,3-dihydroxy-(4-carboxybenzoyl)-tetra-azatetradecane; DSB: double strand breaks; DTPA: diethylenetriaminepentaacetic acid; G-CSF: granulocyte colony stimulating factor; GEN: gentamycin; GI: gastrointestinal tract; MTZ: metronidazole; PARP: poly (ADP-ribose) polymerase; PMZ: promethazine; TBI: total body irradiation; THB: tetrahydrobiopterin; TMZ: temozolomide.

Table 3.

Survey of articles on radiation countermeasures in the *International Journal of Radiation Biology* from 2013–2018.

Class of drug	Volume/dose range (Gy)	Models used	Mechanism (M) / Normal tissue endpoint (N)	Investigator(s) reference and year
RADIATION PROTECTANTS				
Sulfhydryl and related compounds:				
WR 2721/amifostine (pre-RT)	TBI/7	Mice	(N) Bone marrow progenitor survival	Seed etal., 2014
Natural/Synthetic Antioxidants:				
a-tocopherol ± ascorbic acid (pre-RT)	TBI/2–100	Rats	(M) Chromosome aberrations; apoptosis	Vasilyeva et al., 2015
Antrodia cinnamomea extract (pre-RT)	10–40	*in vitro* mouse spleen vs. human tumor	(M) Cell survival; apoptosis; inflammatory mRNA expression	Cheng et al., 2014
Black grape juice (pre- and post-RT)	Whole brain /4x8 (fx)	Rats	(N) Body weight; mandibular osteoradionecrosis	Freitas etal., 2017
BP-2 (lignin-derived polyphenol, pre- and post-RT)	TBI / 4–8	2 strains of mouse	(N) Survival; bone marrow/GI endpoints	Bykov etal., 2018
Curcumin (synthetic analogue, pre- + post-RT)	TBI / 11	2 strains of mouse	(N) GI protection; apoptosis	Fukuda et al., 2016
(liposome preparation, pre-RT)	1–3	Human whole blood	(M/N) Drug uptake; micronuclei induction	Nguyen etal., 2017
Date pit extract (containing range of phenols, pre-RT)	TBI/5–10	Rats	(N) Survival; liver function and redox markers	Abdel-Magied et al., 2018
Emodin (anthraquinone derivative)(pre-RT)	3–12	in vitro splenocytes	(M) Cell survival; redox markers; DNA damage	Sharma & Tiku, 2014
Epigallocatechin-3-gallate (pre-RT)	TBI/4	Rats	(N) Hippocampal histology; DNA damage; apoptosis; cytokines	El-Missiry et al., 2018
Ferulic (hydroxycinnamic) acid (pre-RT)	TBI/10	Mice	(M) Splenic oxidative stress response,e.g. GSH content	Das et al., 2016
Fish oil omega-3 fatty acid (pre- and post-RT)	TBI/4x2	Rats	(M) Brain neurotransmitter and redox markers	Saada etal., 2014
Gingko biloba vs. Angelica archangelica extracts (pre-RT)	1 mCi 99mTc	Rats	(N) Lens protein changes; redox markers	Khedr etal., 2018
Melatonin (pre-RT)	Local / 9x2	Rats	(M/N) Thyroid histology; apoptosis; redox markers; cytokines	Aricigil et al., 2017
Morus alba (mulberry leaf) extract (pre-RT)	TBI/7	Rats	(N) Bone marrow and blood markers	Mohamed & Ashour, 2018
Phenylbutyrate (HDAC inhibitor, pre- and post-RT)	TBI/8.5	Mice / in vitro 32Dcl3	(N) Survival; bone marrow effects; DNA damage; inflammation	Miller et al., 2017
Podophyllum hexandrum extracts (pre-RT)	TBI/9	Mice	(N) Bone marrow suppression; chromosome aberrations	Verma & Gupta, 2015
Resveratrol (+3,3 '-diindolylmethane, pre-RT)	TBI/4–10	Mice	(N) Survival; bone marrow function; chromosome aberrations	Thekkekkara et al., 2018
(pre- and post-RT)	TBI/6	Mice	(N) Late immune function	Zhang etal., 2018
Selenium nanoparticles vs. selenium selenite (pre-RT)	TBI / 2, 8	Mice	(N) Renal function/ nephropathy; redox markers	Karamietal., 2018

Class of drug	Volume/dose range (Gy)	Models used	Mechanism (M) / Normal tissue endpoint (N)	Investigator(s) reference and year
Tetrahydroxyisoflavone (vs. DMSO, pre-RT)	TBI/4–12	Mice / AHH1 cells	(N) Survival; bone marrow function	Liu etal., 2017
Anti-inflammatories:				
Atorvastatin (pre-RT)	TBI/2	Mice	(N) Acute kidney damage; redox	Talebpour Amiri et al., 2018
Montelukast (CysLTIR antagonist, pre- and post-RAI)	111 MBq/kg 131I	Rats	(N) Lung inflammation/ fibrosis; cytokine expression	Tokatetal. 2018
STW-5/Iberogast (pre- and post RT)	TBI/6	Rats	(N) GI damage; inflammation & redox markers	El-Ghazaly et al. 2015
Biologies:				
Human hepatocyte growth factor (pre-RT)	TBI / 6.5	Mice	(N) Bone marrow histomorphometry; cell survival	Li et al., 2014
PARP inhibition: 3-aminobenzamide (pre-RT)	TBI/6	Rats	(N) Apoptosis; redox/ inflammation markers in brain, liver, kidney	El-Sheikh et al., 2018
Miscellaneous:				
Cimetidine (pre-RT)	TBI / 10	Mice	(N) Thyroid histomorphometry	Fazelipour et al., 2015
RADIATION MITIGATORS				
Natural/Synthetic Antioxidants:				
Black grape juice (pre- and post-RT)	Whole brain / 4x8 (fx)	Rats	(N) Body weight; mandibular osteoradionecrosis	Freitas et al., 2017
BP-2 (lignin-derived polyphenol, pre- and post-RT)	TBI / 4–8	2 strains of mice	(N) Survival; bone marrow/GI endpoints	Bykovetal., 2018
Curcumin (synthetic analogue, pre- + post-RT)	TBI/11	2 strains of mouse	(N) Gl protection; apoptosis	FukudaetaL, 2016
Diospyros kaki (persimmon leaf) extract (post-RT)	TBI/6	Rats	(N) Liver function assays; redox markers	Ashry etal., 2017
Filipendula ulmaria (Meadowsweet) extract (post-RT)	TBI/4	Rats	(N) Long-term survival; carcinogenesis	Bespalov et al., 2017
Fish oil omega-3 fatty acid (pre- and post-RT)	TBI / 4x2	Rats	(M) Brain neurotransmitter and redox markers	Saada et al., 2014
Green tea + grape seed extracts (post-RT)	TBI/5, 10	Rats	(N) Blood counts; immune markers	El-Desouky et al., 2017
Phenylbutyrate (HDAC inhibitor, pre- and post-RT)	TBI / 8.5	Mice / in vitro 32Dcl3	(N) Survival; bone marrow effects; DNA damage; inflammation	Miller etal., 2017
Portulaca oleracea (Purslane) extract ±fish oil (post-RT)	TBI/6	Rats	(N) Liver, kidney and heart function; redox markers	Abd El-Azime et al., 2014
Anti-inflammatories:				
Curcumin (nanoparticles) (post-RT)	0–6	in vivo THP monocytes	(N) Cell viability; foam cell formation; redox markers	Soltani et al., 2017
Montelukast (CysLTIR antagonist, pre- and post-RAI)	111 MBq/kg 131I	Rats	(N) Lung inflammation/ fibrosis; cytokine expression	Tokatetal., 2018
STDCM-MPL (± antimicrobial therapy, post-RT)	TBI / 9.75 (+ wound)	Mice	(N) Survival; bacterial translocation; sepsis	Elliott et al., 2015
STW-5/Iberogast (pre- and post RT)	TBI/6	Rats	(N) GI damage; inflammation & redox markers	El-Ghazaly et al., 2015
Thalidomide (post-RT)	Heart/16	Mice	(N) Heart histomorphometry; inflammation markers	Hovingetal., 2013
Biologies:				

Class of drug	Volume/dose range (Gy)	Models used	Mechanism (M) / Normal tissue endpoint (N)	Investigator(s) reference and year
Anginex (angiogenesis inhibitor) *vs. IL-6 vs. flagellin* (post-RT)	TBI/7.5; WAI/18	2 strains of mouse	(N) Survival; GI morphology; tumor growth	Huang et al., 2018
Basic fibroblast growth factor (post- RT)	Local / 30	Hamster cheek pouch	(N) Oral mucositis; wound healing	Sumikawa et al., 2017
Epidermal growth factor (± BMT, post-RT)	TBI/12–13	Mice	(N) Survival; GI apoptosis; inflammation markers	Pejchal et al., 2015
Keratinocyte growth factor (post-RT)	Local / 20–50	Hamster cheek pouch	(N) Oral mucositis; proliferation; inflammation	Watanabe et al., 2014
Miscellaneous:				
A CEi (captopril, enalopril, fosinopril, lisinopril, Ramipril, post-RTJ	TBI/10 + BMT	Rats	(N) Radiation nephropathy; kidney function	Moulder et al., 2014
Ginseng, eleutherococcus, leuzea (post-RT)	TBI/4	Rats	(N) Radiation carcinogenesis	Bespalov et al., 2014
RADIATION TREATMENTS				
Chelating agents				
3,4,3-LI(l,2-HOPO) vs. Ca-DTPA (post-RT)	0.75 kBq ^{238}Pu	Mice	(M) Efficacy	Anetal., 2014
DTP A di-ethyl ester (post-RT)	Inhaled /111 kBq^{241}Am	Dogs	(M) Safety and efficacy	Huckleetal., 2015
Novel polyethylene glycol compound (post-RT)	Inhaled/25.3 mSvU	Dogs	(N) Lung and kidney pathology	Ren etal., 2018

Abbreviations: ACEi: angiotensin converting enzyme inhibitor; BMT: bone marrow transplant; CysLT1R: type 1 cysteine-leukotriene receptor; DTPA: diethylenetriaminepentaacetic acid; GI: gastrointestinal tract; GSH: glutathione; HDAC: histone deacetylase; HOPO: 2,3-dihydroxy-(4-carboxybenzoyl)-tetra-azatetradecane; IL: interleukin; PARP: poly (ADP-ribose) polymerase; PBMC: peripheral blood mononuclear cells; RAI: radioactive iodine administration; RT: radiation treatment; STDCM-MPL: synthetic trehalose dicorynomycolate and monophosphoryl lipid A; TBI: total body irradiation; WAI: whole abdominal irradiation.