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Interagency approaches to animal models for acute radiation exposure

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Abstract

Ionizing radiation can cause devastating injuries including hemorrhage, immune suppression, increased susceptibility to infection, and death. Medical countermeasures (MCMs) that address and mitigate radiation-induced injuries are the most important tools for countering the consequences of radiation exposure. Likewise, in matters of public health security, the development and advancement of radiological MCMs are fundamental for establishing an effective response to radiological and nuclear threats. United States Government agencies such as the Biomedical Advanced Research and Development Authority (BARDA), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Aeronautics and Space Administration (NASA) have dedicated significant efforts to advance the development of MCMs to treat radiation injury and facilitate their introduction into the public sphere. Due to the severe nature of radiation

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injuries, clinical trials are unethical. Therefore, nonclinical models that accurately replicate clinical manifestations of ionizing radiation injury observed in humans are essential to MCM advancement. The most frequently used nonclinical models of radiation injury are rodents and non-human primates (NHPs). These species reproduce many aspects of human disease caused by ionizing radiation and have been pivotal for the development and licensure of radiological MCMs. Despite these successes, model drawbacks have prompted the exploration and development of additional nonclinical models. Minipigs and rabbits show promise as acceptable models of radiation injury and demonstrate the potential to contribute significantly to MCM advancement. This collection of research showcases the capabilities of minipigs and rabbits in mirroring clinically relevant aspects of radiation-induced disease and documents the potential value these models may hold for radiological and nuclear MCM research. Together, these government-funded studies represent advances in radiological MCM development that can facilitate the emergence of cutting-edge technologies.

Keywords

Radiation; MCM; Countermeasure; Nonclinical; ARS

In 2006, the Biomedical Advanced Research and Development Authority (BARDA) was established to support the research, development and procurement of medical countermeasures (MCMs) to address public health and medical consequences of chemical, biological, radiological, and nuclear (CBRN) incidents; pandemic influenza; and emerging infectious diseases. Within this mission, a priority is the development of MCMs to mitigate acute radiation syndrome (ARS). In support this effort, BARDA has funded studies to establish novel, nonclinical models of ARS. In addition to BARDA, other government agencies also play a role in supporting the research and development of radiation MCMs. For example, the Radiation and Nuclear Countermeasures Program (RNCP), within the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), was initiated in 2004 to support the accelerated development and deployment of new MCMsfor radiation exposure. This mandate includes basic research on mechanisms of radiation injuries, including establishing pivotal nonclinical models of radiation injury and supporting efficacy studies needed for regulatory approval. BARDA and NIAID have also worked closely to transition promising MCMs from the RNCP program to BARDA for advanced development. In addition, the National Aeronautics and Space Administration (NASA) has partnered with BARDA and NIAID to evaluate MCMs that may be suitable for space exploration missions. While galactic cosmic radiation is pervasive in space, solar particle events have the potential to cause acute, high-dose radiation exposures, much like ARS exposure concerns on Earth, albeit at lower doses than would be observed in a nuclear event. Although NASA has unique radiation exposure concerns for astronaut missions conducted in deep space over long periods of time, teaming with interagency partners to address potential ARS adverse health effects has accelerated NASA’s awareness of MCMs that may serve to protect astronauts on future exploration missions.

Preparedness for a devastating radiological or nuclear incident relies on the availability of effective MCMs that mitigate and treat injuries caused by these threats. In the aftermath

of a radiological or nuclear incident, it will be critical to quickly administer therapeutics that address the manifestations of ARS including radiation-induced immuno-suppression, hemorrhage, and infection. The radiosensitive nature of progenitor cells within the bone marrow results in pancytopenia that culminates in the previously listed complications. The availability of MCMs to broadly treat these aspects of ARS will be crucial for mounting swift, effective responses that minimize morbidity and mortality. The extent of damage caused by ARS-inducing doses of ionizing radiation makes the testing and evaluation of candidate therapeutics in human subjects unethical. Therefore, nonclinical animal models of injuries are required for MCM approval/licensure via the U.S. Food and Drug Administration (FDA) Animal Rule (21 CFR 314.600–650; 21 CFR 601.90–95). Advancement of these MCMs requires development and elucidation of nonclinical models to accurately recapitulate the human pathophysiology of ARS.

Currently, there are four FDA-approved MCMs indicated to treat ARS via mitigation of neutropenia or thrombocytopenia, all of which would not have achieved licensure without testing in nonclinical models. Neupogen®, a granulocyte-colony stimulating factor (G-CSF), was the first MCM to gain FDA licensure in March 2015 for the treatment of neutropenia due to myelosuppressive doses of radiation. Neulasta®, a pegylated form of G-CSF, was approved in November 2015. Leukine®, a granulocyte/macrophage-colony stimulating factor (GM-CSF; sargramostim), achieved licensure in March 2018. These MCMs address neutropenia by stimulating the production of progenitor cells in the bone marrow. Due to the risk of infection during the vulnerable, neutropenic period of ARS, early administration of leukocyte growth factors (LGFs) to reconstitute neutrophil populations is imperative. The fourth MCM for ARS is a thrombopoietin (TPO) receptor agonist (Nplate®) that gained FDA licensure in January 2021. This product addresses thrombocytopenia by stimulating the production of platelets in the bone marrow. Increasing platelet counts can be a life-saving intervention for individuals at risk of bleeding during the thrombocytopenic period of ARS. While these are remarkably safe and effective therapeutics, it is still necessary to develop additional MCMs to address other aspects of ARS and enhance our radiological/nuclear therapeutic toolset is still needed. This will require the establishment of new nonclinical models, not only to advance MCM development, but to also study the toxic and long-lasting effects of ionizing radiation, a critical component for elucidating ARS pathophysiology and MCM mechanisms of action.

To date, various species, including canines, lagomorphs, swine, rodents, and nonhuman primates (NHPs), have been used to study the natural history of ARS and to develop MCMs (Ricciuti 1969; Singh et al. 2015). These models have all contributed considerably to our understanding of ARS; however, none are perfect in reproducing every aspect of radiation-induced human injuries, and each has drawbacks. In the early days of development of animal models for radiation biology, canines were one of the most frequently used nonclinical models. Canines are advantageous for their medium size, long lifespan, and similarities to the human immune system and gastrointestinal-ARS manifestations (Singh et al. 2015; Spatola et al. 2021). Despite many positive aspects associated with the canine model, physiological differences between humans and canines exist, specifically regarding pulmonary anatomy and function (Singh et al. 2015). Furthermore, the canine’s status as a

companion animal has caused researchers to move away from the use of this model in recent years.

Currently, the most commonly used models of ARS are rodents (primarily mice) and NHPs. Mice share 95% genetic homology with humans, in addition to many anatomical and physiological similarities (Singh et al. 2015). Mice are valued due to their small size, short generation time, relatively low cost to maintain, and recapitulation of some hematological manifestations of ARS (Singh et al. 2015; Butterworth and Williams 2021). However, many of the features that give value to the model can simultaneously present impediments for research. The species' relatively short lifespan makes it difficult to longitudinally follow the effects of ionizing radiation and draw correlations to human disease. Likewise, their small body sizes confound the variable of radiation dose distribution, which tends to be heterogenous in humans because of larger body size and thickness. Additionally, concerns have been raised about data reproducibility in murine models of ARS. In this special issue, DiCarlo et al. conducted a comprehensive literature review that highlights inconsistencies in radiation responses across various murine strains, and underscores confounding factors to consider when conducting radiation studies in this species.

NHPs are valued for their high genetic (greater than 95%), physiological, and molecular similarities to humans. Their long lifespan, comparable body size/thickness, and similar requirements for supportive care allow for the correlation of dose-effect relationships between NHPs and humans (Singh et al. 2015). NHPs accurately recapitulate nearly every clinical and pathophysiological aspect of radiation injury observed in humans and, as a result, are often referred to as the gold standard for radiological research (Singh et al. 2015). Despite these advantages, obstacles have hindered the extensive use of NHPs. Ethical considerations, high costs for procuring animals and maintaining animal care facilities, and current shortages in animal availability all significantly impact the ability to continue to use NHPs as a predominant model of ARS.

The previously described limitations of canines, mice, and NHPs emphasize the need for additional nonclinical models that recapitulate aspects of human disease while also being readily available and reasonably cost-effective. Rabbits and minipigs have previously been used to support radiobiology research and radiation MCM development; however, these models have not nearly been developed to the extent of canines, NHPs, and mice. Minipigs, which have been used as a model for cutaneous radiation injuries, recently gained traction as a nonclinical model in other areas of medical research. In the context of radiation injury, despite exhibiting increased radiosensitivity compared to humans and other large animal species, minipigs have been found to be relevant models for studying the GI aspect of ARS, and their thick skin has been identified as valuable for its comparability to human skin (Singh et al. 2015). In addition, minipig's size and lifespan lend support to their use as a nonclinical model to supplement NHPs. While rabbits have been used as a model for radiation injury studies, data are limited. Furthermore, rabbits exhibit substantial physiological differences from humans, including heart size, heart rate, and body weight; these differences may confound the interpretation and extrapolation of data as they relate to the physiological effects of radiation on humans. Regardless, ease of handling due to small size, ability to longitudinally collect blood samples, availability of animals and rabbit-

specific research reagents, as well as high homology to humans make rabbits appealing for use as models of ARS.

The use of minipigs and rabbits in radiation research holds promise, and articles within this special issue further detail the characteristics that they possess, supporting their value as models of human radiation injuries. Specifically, these models have exhibited usefulness for studying the natural history of ARS and the clinical signs of the hematopoietic component of ARS as well as for potential MCM evaluation. As options for nonclinical models become limited with scarcity of other large animal species, further exploration of minipigs and rabbits as suitable models for studying the impact of ionizing radiation could be advantageous. Thus, to support radiological and nuclear MCM development, BARDA and, to a smaller degree, NIAID have invested in the development and characterization of radiation injury in rabbit and minipig models. This special issue serves as a collection of data to document the progress of this latest BARDA-led initiative.

Work by Thrall et al. in this issue, entitled ‘A Göttingen minipig model of radiation-induced coagulopathy’, demonstrates that, when compared to well-established models of radiation injury in NHPs, minipigs exhibit similar characteristic pancytopenia due to ARS. In a second publication that investigates the impact of supportive care in large animal models of total body irradiation (TBI), Thrall et al. further illustrate the suitability of studying hematological complications of ARS, such as coagulopathy, in minipigs. Likewise, Doyle-Eisele et al. establish a similar case for minipigs by characterizing hemorrhagic consequences post-TBI in two minipig strains, Göttingen and Sinclair.

Studies within this issue also support the use of a rabbit model of ARS, focusing on hematological and vascular injuries. Two studies presented by Jackson et al. demonstrate that the New Zealand White rabbit (NZWR) model of ARS exhibits similarities to human radiation injuries, most notably presenting with pancytopenia and hematological complications. These findings are corroborated by Paredes et al., who show that NZWRs exhibit radiation dose responses and hematological consequences that are similar to other established ARS models. Data presented by Poirier et al. demonstrate a method of validating irradiation of rabbits, ensuring consistency of radiation doses administered to them in animal ARS experiments. Together, these studies support the use of minipigs and NZWR as appropriate models of ARS.

In further support of the advancement of radiological/nuclear MCMs, Zhong et al. present evidence of an extended period of efficacy beyond 24 h for the readily available radiation therapeutic, sargramostim, using NHPs. Their data indicate a survival benefit of sargramostim administration on hematological parameters, even when administered as late as 120 h post-irradiation. Studies like these have the potential to impact the standard of care administered during a mass casualty incident and extend the feasible therapeutic window of response following a radiological/nuclear incident, when immediate care may be inaccessible.

The ARS nonclinical models described have the capacity to impact not only national preparedness for large-scale radiological and nuclear incidents but also the protection of

NASA astronauts. In two publications by Carnell et al., the current state of preparedness for deep space missions is examined, gaps in preparedness are reviewed, and MCMs to adequately protect astronauts from common and uncommon (but anticipated) radiological effects of space flight necessary to fill said gaps are identified.

This special issue provides an overview of ongoing work to bolster the nation's preparedness for radiological/nuclear incidents. The work presented herein largely involves the development of nonclinical models of ARS to support the advancement of radiological and nuclear MCMs, and their approval through the FDA Animal Rule pathway. Numerous articles within this issue explore the use of minipigs and rabbits as suitable models for various hemopathies due to ARS. Use of an NHP model of ARS to examine how changes in standard of care following a radiological/nuclear incident can improve survival is also described. In addition, rodent models are explored for their utility in modeling central nervous system damage due to radiation as well as thoroughly examined to highlight limitations that should be considered when used for radiation MCM development. Further, work aimed at supporting preparedness research initiatives in other capacities (i.e. space travel) are detailed herein. Collectively, these works highlight current advancements in ARS nonclinical models that will facilitate the development of cutting-edge radiological and nuclear MCMs, while also showcasing the close collaborations between US government agencies engaged in supporting research to develop approaches to address a significant public health threat.

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