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Authors: Satyamitra, Merriline M., Cassatt, David R., and Marzella, Libero

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WORKSHOP COMMENTARY

A Trans-Agency Workshop on the Pathophysiology of Radiation-Induced Lung Injury

Merriline M. Satyamitra,[a,1] David R. Cassatt[a] and Libero Marzella[b]

[a] *Radiation and Nuclear Countermeasures Program (RNCP), Division of Allergy, Immunology and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Rockville, Maryland; and* [b] *Division of Imaging and Radiation Medicine, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, Maryland*

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As of January 2021, the U.S. Food and Drug Administration has approved four radiation exposure medical countermeasures (MCMs) to treat hematological acute effects, but no MCM is yet approved for radiation-induced lung injury (RILI). MCM approval for RILI and other subsyndromes utilizes the FDA Animal Efficacy Rule (Animal Rule), that requires demonstration of MCM efficacy in animal models with well-characterized pathophysiology, therefore, allowing translation to human use. A good animal model replicates the clinical condition and natural history of the disease, while allowing for studying the mechanism of action of the applied MCM and exhibiting clear benefits in terms of primary and secondary endpoints. However, there is much conversation regarding the advantages and limitations of individual models, and how to properly apply these models to demonstrate MCM efficacy. On March 20, 2019, the Radiation and Nuclear Countermeasures Program (RNCP) within the National Institute of Allergy and Infectious Diseases (NIAID), Food and Drug Administration (FDA), and the Biomedical Advanced Research and Development Authority (BARDA) sponsored a workshop to identify critical research gaps, discuss current clinical practices for different types of pulmonary diseases, and consider available animal models for RILI.

INTRODUCTION

X rays were discovered in 1895 and reports of radiation-induced lung injury (RILI) emerged as early as 1898 (*1*). RILI results from both an immediate cytotoxic injury to lung tissue and prolonged processes like inflammation and cellular signal transduction. Lung injury after irradiation occurs in five phases; the immediate acute phase, the latent phase, the pneumonitis phase (4–12 weeks postirradiation), intermediate phase, and finally, fibrosis (*2*). Pneumonitis is characterized by lymphoid and myeloid cell infiltration, with cough, chest pain, dyspnea and fever, and can resolve over time, while lung fibrosis is chronic, occurring months after exposure; and is accompanied by the remodeling of the extracellular matrix, activation of fibroblasts and buildup of collagen, resulting in reduced pulmonary function (*3*).

Medical countermeasures (MCMs) development under the U.S. Food and Drug Administration (FDA) Animal Rule (*4*) is built on the foundation of animal models that can simulate expected clinical outcomes, including the understanding of the pathophysiology and progression of injury and recovery mechanisms. One limitation of the clinical experience or animal models, however, is that radiation exposure experienced in the clinic (thoracic or localized) or research facility does not recapitulate exposure to a large-scale, inhomogeneous body exposure after a radiological/nuclear incident. Research developing lung MCM has evolved from a whole-thorax lung injury (WTLI) model (*5*) to a ''top-up'' exposure protocol [total-body irradiation (TBI) coupled with an additional WTLI exposure] (*6*) and finally the partial-body irradiation (PBI) model in which 2.5–5% of the bone marrow is shielded (*7*), allowing for an even closer approximation to the expected human situation.

Given the danger of RILI after exposure during a radiological or nuclear public health emergency, the U.S. Government prioritized the development of treatments to counter the damaging effects of ionizing radiation. The National Institute of Allergy and Infectious Disease (NIAID), in collaboration with the U.S. Food and Drug Administration (FDA) and the Biomedical Advanced Research and Development Authority (BARDA) convened a two-day workshop entitled ''A Trans-Agency Workshop on the Pathophysiology of Radiation-Induced Lung Injury'' on March 20–21, 2019. In five sessions and one panel discussion, conference participants explored several aspects

[1] Address for correspondence: DAIT, NIAID, NIH, 5601 Fishers Lane, Room 7A67, Bethesda, MD 20892; e-mail: Merriline.satyamitra@nih.gov.

of RILI, including pathophysiology, mechanism of action, current treatments, animal models, biomarkers of lung injury, and the regulatory landscape for MCMs (full meeting report available online at https://doi.org/10.1667/RADE-21-00127.1).

SESSION I

Clinical Perspectives of Radiation-Induced Lung Injury

Based on the clinical approach to treating RILI, researchers can acquire insight into standard of care, discover novel therapeutic strategies, learn about diagnosis and medical management, as well as imaging techniques in the clinics that can be extended to refining the animal model for testing lung MCM efficacy. The current standard of care, for patients with radiation pneumonitis (RP) that typically manifests 4 to 12 weeks after therapy as dry cough, shortness of breath and fever, involves analgesia and prednisone-induced immunosuppression, supplemented by oxygen, pulmonary rehabilitation, or tyrosine kinase inhibitors. However, these interventions are not curative, and most patients with radiation pneumonitis develop chronic pulmonary fibrosis (*8*).

The development of animal models for RILI is hampered by inconsistencies in animal and lung responses to radiation according to strain, sex and age of the animal, and the site and mode of irradiation (*9*), but experimental approaches open new possibilities for therapeutic strategies. For instance, simvastatin protected WTLI-irradiated C5BL/6J mice against lung damage, increased levels of cytokines, proteins and inflammatory cells (*10*). Sphingosine 1-phosphate (S1P) receptor 1 activation reduced vascular leakage by reinforcing the vascular endothelial barrier (*11*), while genomic analysis in preclinical models of RILI yielded novel intervention targets such as the protein coded by *Gadd45α* that regulates Akt or *Nampt* that encodes a B-cell maturation factor, that are both associated with the pathogenesis of acute respiratory distress syndrome.

Much can be inferred from actual radiological/nuclear incidents involving radioactive actinide isotopes; radioisotopes that are ingested are mostly coughed up or swallowed, but about 5% of the <5 μm radionuclide particles measured in a nasal swab — the standard dose-estimation method — reach the alveoli, where they can persist for $\geq$100 days. High-activity insoluble radionuclides can be removed from the lung by broncho alveolar lavage (BAL), with surfactants improving elimination. Radionuclide-specific decorporation therapy using an ion exchange resin and extracorporeal dialysis or chelator (e.g., diethylenetriaminepentaacetic acid, DTPA) requires continued use lasting several years to be effective at removing radionuclides from bone. Further, radiation-induced pneumonitis leads to heavy, edematous, bleeding lungs with septal thickening, interalveolar fibroblast proliferation, and lymphocytic infiltration, resulting in systemic inflammatory response syndrome and ultimately multiple organ failure. Therefore, therapeutics to address these imbalances are urgently needed.

Quantitation of Lung Injury Using Imaging. The ideal imaging modality to evaluate MCM for RILI would yield quantitative data, and be predictive of human pathophysiology and therapeutic efficacy. The most widely available quantitative imaging modality is computed tomography (CT), which delivers high resolution and four-dimensional data (*12*). Data generated by CT and other imaging modalities are analyzed densitometrically [monitoring of the density of a region of interest (ROI)] or volumetrically (monitoring of the volume of a ROI) and may be used to assess the severity of pulmonary fibrosis — the greater the density on imaging, the more severe the fibrosis, and correlate to lung function (*13*). The reliability of any quantitative imaging modality is influenced by a host of factors related to the patient (e.g., variation in physiology and anatomy), means of acquisition (e.g., protocol, slice thickness, reconstruction), and measurement method (e.g., degree of automation, algorithm, software version).

SESSION II

Regulatory Considerations for Drug Development for RILI

Sponsors of MCMs under development for RILI are encouraged to pursue FDA approval under the Animal Rule, which allows product development to proceed using adequate and well-controlled efficacy studies in appropriate animal models to establish that the MCM is likely to benefit humans (*4*). A nuclear detonation can result in compound injuries, that could include blast injury, blunt force trauma, hemorrhage, thermal burns, in addition to radiation exposure. Due to the complexity of the issue, it is prudent to first focus drug development on the isolated effects of radiation, rather than attempting to model complex exposure scenarios. Given the monumental difficulty in simulating a nuclear detonation, use of linear accelerator (LINAC) devices to model high dose irradiation in animals is recommended, with institutes establishing lethality curves in keeping with their in-house dose rate and applied filter, and to ensure dose accuracy using well-established dosimetry approaches.

Clinical Pharmacology Considerations for Products Developed for Radiation-Induced Lung Injury under the Animal Rule. In the absence of human efficacy trials, the selection of a human dosage for a novel RILI MCM is formulated based on a combination of animal research and pre-existing knowledge (*4*) using two main approaches: pharmacokinetics (PK) and pharmacodynamics (PD). The PK approach is applicable when: 1. The dose-response relationship has been established in animals; 2. Dose-response has not yet been established in humans; and 3. Based on the drug's mechanism of action (MOA) that is comparable among species. Using the PK approach, a dose determination is made (drug absorption, metabolism, etc.) in

both healthy and irradiated animals. Ideally, the dose for humans should be higher than the effective dose used in animals, to minimize the risk of delivering a sub-therapeutic dosage.

The PD approach is based on identification of a biological marker that corresponds to a desired clinical outcome and the drug's MOA. The human dose is estimated based on the dose that results in comparable PD marker alterations as achieved in the animal model. For example, in selecting a dose for pegfilgrastim (Neulasta®) for hematopoietic acute radiation syndrome (H-ARS) indication, the dose that significantly shortened the duration of neutropenia was chosen because the drug's MOA is known to directly increase neutrophils, and animal studies showed that shortening the duration of neutropenia (the PD marker) raised the probability of survival (the desired clinical outcome).

Nonclinical Considerations for Product Development Under the Animal Rule. Animal studies should always be conducted in accordance with the U.S. Animal Welfare Act and the Public Health Service (PHS) policy on the humane care and use of laboratory animals.[1] It is also important to note that Animal Rule applications are eligible for various forms of expedited FDA review such as fast track and priority review. While Good Clinical Practice (GCP) standards are not required for applications under the Animal Rule, data collected from animal studies will be held to the same standard of quality. Therefore, experiments should be well designed (i.e., controlled, randomized, blinded), should model the human condition closely, and data quality controls and assurances must be in place. Animal models should reflect the supportive care that irradiated humans would receive. Furthermore, animal studies of RILI should encompass the entire natural course of the disease, and model RILI as a complex multi-organ disease, rather than a disease of the lungs alone. PBI models represent the real-world evolution of the various radiation sub-syndromes of H-ARS and GI-ARS, followed by delayed disease of the lung and other organs. Due to challenges in developing NHP models, initially establishing dose efficacy, MOA endpoints and pulmonary function in small rodent models could be considered by the FDA. It is strongly recommended that the sponsors discuss animal models, and primary and secondary endpoints with the FDA early and often.

Session III

Animal Models

There are several challenges in developing animal models of lung injury: 1. Radiation-induced lung injuries are well above levels that cause fatal bone marrow injury; 2. The length of time between radiation exposure and mortality (the accepted endpoint for studies under the FDA Animal Rule) may be many months; and 3. The animal injury and its medical management may not mimic the clinical experience.

Rodent models of lung-DEARE (Delayed Effects of Acute Radiation Exposure). Mouse studies demonstrated that different mouse strains have varied susceptibilities to pneumonitis and fibrosis (*14*): the C57BL/6J strain develop fibrotic lungs, with late pleural effusions; CBA/J mice develop pneumonitis and pleural effusions; while C57L/J mice develop early pneumonitis and late fibrosis, similar to the progression observed in humans. The radiation exposures that induce mortality in the latter strain are similar to doses resulting in mortality in humans and NHP WTLI models.

Secondary endpoints are crucial for understanding RILI progression and the potential efficacy of the MCM being tested. Some non-invasive lung parameters to monitor injury progression include lung density (CT scans), enhanced pause (Penh) to assess airway constriction, and assays for gene expression linked to tissue damage and repair pathways. While indicators of RILI such as increased lung mass, wet lung weights, and inflammation/collagen deposition are queried for model development, their use in injury progression is limited. For example, pleural effusions observed in CBA/J and C57BL/6J mice are not commonly seen in human RILI (*14*), however, in the C57L/J strain, progression and exposure thresholds of pneumonitis and fibrosis are similar to clinical observations.

Rats have also been extensively studied for RILI, using both WTLI and PBI models, with similar findings. Although WTLI does not represent the full spectrum multi-organ contribution to lung damage, mortality, and histological findings in the WTLI and PBI rat models are very similar with pneumonitis presenting as a function of both lung and heart injury (*15*). The biggest difference in the two models is mortality in the first 21 days in the PBI model, which was ameliorated by medical management. Another difference is the late renal failure associated mortality in the PBI model. In irradiated juvenile and geriatric rats, juvenile rats were more susceptible to radiation-induced mortality, while older rats were resistant to pneumonitis, and lung-DEARE MCMs such as the angiotensin converting enzyme (ACE) inhibitor lisinopril attenuated pulmonary fibrosis (*16*).

NHP models of RILI. As with the rodent models, both WTLI and PBI have been studied in NHPs. Two important aspects of studies in larger animals are the potential for longitudinal blood draws allowing for minimally invasive monitoring, and the requirement for additional medical management, such as administration of dexamethasone to animals in respiratory distress. For WTLI NHP models, the institutional lethality curve for the female monkeys was similar to that of male animals conducted at different sites, with no significant difference in the lethal dose (LD) values (*5, 17*). Supportive care, such as dexamethasone, reduced

[1] https://olaw.nih.gov/policies-laws/phs-policy.htm.

respiratory distress, although this treatment was ineffective against severe tissue damage. Terminal tissue collection and histopathology findings in non-survivors was associated with a higher number of severe histopathological findings (*17*), and underscores the importance of secondary measurements for model refinement.

The NHP PBI/bone marrow (BM)-sparing model can differentiate between combined H-/GI-ARS, which occur within the first 50 days, and DEARE, characterized by lung, kidney and heart injury, which generally occurs after the 90-day latent period (*7*). Provision of supportive care allowed for sufficient animals to survive H-/GI-ARS yet demonstrated mortality from RILI (*7*). Non-invasive measurements of lung function, and histological examination at timed euthanasia points confirmed the progression of lung damage, and underscored similarities in lung injury irrespective of how much of the animal was shielded, suggesting that tissue damage outside of the lung may not have a great influence over lung injury (*7*).

Together, analyses of rodent and NHP RILI models indicate that both WTLI and PBI models allow for the contribution of other organ systems to lung injury, but PBI may be a closer approximation to a real life radiological/nuclear exposure. Reproducibility among different sites using similar (irradiation, species) approaches is important, and facilities are encouraged to use standard dosimetry and robust dosage-determining methods. A combined approach of mortality dose-response relationship and non-invasive measurements such as CT scan, breathing rate observations, and oxygen saturation (SpO_2) secondary endpoints allow for the tracking of disease progression and recovery. Comorbidities and age must be considered for advanced MCM development, although these studies are confounded due to longer lifespans of large mammals and lack of appropriate animal models for comorbidities.

SESSION IV

Experiences from Current Drug Development for RILI

Some challenges to lung-DEARE MCM development are the lack of validated delayed injury models; modeling clinical standard of care such as administration of antibiotics and growth factors; inconsistent outcome of medical management in different species; trigger-to-treat criterion vs. scheduled treatments; and varied response of mouse strains to irradiation. Finally, the onus to demonstrate model relevance falls on the sponsors but given high mortality due to H- and GI-ARS after PBI, the likelihood of animals surviving to 180 days postirradiation in sufficient numbers to meet statistical significance is low. Advanced development in large animals under these conditions are further complicated by the current shortage of NHPs because of the COVID pandemic.[2]

Three lung-MCMs currently under development are AEOL 10150 (Aoelus Inc), Bio 300 (Humanetics Pharmaceuticals) and IPW-5371 (Innovation Pathway). Key discussions from these sponsors interactions with the FDA are summarized here. The FDA Division of Imaging and Radiation Medicine (FDA-DIRM) invites early and often communication and encourages MCMs to be tested in patients who may benefit from the product. It is imperative that drug sponsors should define a primary commercial indication at the onset such that clinical data in related conditions (e.g., patients receiving radiation therapy) will inform about MCM safety, drug dose equivalence, and possible outcome. FDA advised that medical management must reflect standard of care in the clinics (i.e., antibiotic treatment, GF administration etc.), MCM development should have well-powered efficacy studies in two species, and efficacy data from closely related clinical indications can be supportive. Furthermore, the FDA suggested that models that isolate lung injury (e.g., WTLI) do not simulate radiological disaster exposure and have limited utility; while WTLI and ''top-up'' models are acceptable in early proof-of-concept studies, their use in pivotal studies in large mammals is not recommended. A model such as PBI/BM 5% would better suit the Animal Rule Requirement. There is a need to balance developing and refining animal models while advancing lung MCMs for approval. Sponsors should also address MOA, PD, and ensure bioavailability of the MCM at the intended route.

Development of Available Therapeutics for Analogous Pulmonary Conditions. Two pulmonary conditions analogous to RILI are idiopathic pulmonary fibrosis (IPF), and systemic sclerosis interstitial lung disease (SSc-ILD). MCMs approved for IPF treatment, development programs, regulatory considerations for these approvals, and insightful case examples of early and late phase products may provide potential MCMs for RILI. In both RILI and SSc-ILD, inflammation is prominent, with damage observable via CT (*18*). There are two drugs approved for treatment of IPF - nintedanib and pirfenidone. Nintedanib is an inhibitor of the receptors for fibroblast growth factor, platelet-derived growth factor receptor, and vascular endothelial factor. Pirfenidone has anti-inflammatory and anti-fibrotic activity, and inhibits TGFβ production and activity; pirfenidone reduced FVC decline compared to placebo control.[3] Following approval for IPF, these products are currently being tested in other pulmonary diseases such as progressive fibrosing ILD[4] and SSc-ILD.[5] Other products currently under development for IPF are Pamrevlumab, a human recombinant DNA-derived mAb that binds to connective tissue growth factor and has demonstrated efficacy in a WTLI mouse model of radiation fibrosis; autotaxin, an

[2] https://grants.nih.gov/grants/guide/notice-files/not-od-21-080.html.

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022535s005lbl.pdf

[4] NCT02999178.

[5] NCT02597933.

enzyme that cleaves lysophosphatidylcholine (LPC) producing lysophosphatidate (LPA); serum amyloid P/pentraxin 2 (PTX2), which blocks monocyte differentiation to profibrotic macrophage, and diminishes bleomycin-induced pulmonary fibrosis; JNKi, a C-Jun N-terminal kinase (JNK) inhibitor that interrupts transcription of implicated pathogenic fibrosis genes; a TGFβ siRNA that targets TGFβ1 mRNA and reduces the expression of TGFβ protein; and angiotensin receptor II blockers such as losartan, which reduce fibrosis.

SESSION V

Biomarkers of Lung Injury

Diagnostic, Predictive and Pharmacodynamic Biomarkers. A biomarker is a parameter associated with a disease/injury that can be objectively measured and evaluated to track disease progression. Biomarkers may be applied in animal models as secondary endpoints, as triggers for intervention, and/or for selection of the minimum effective dose in humans (*19*); however, at the time of publication of this article, there are no FDA-qualified biomarkers for RILI. A biomarker of lung-DEARE would ideally enable early detection of pneumonitis and fibrosis, be measurable in a readily accessible biofluid, and serve as an indicator of tissue repair, which have been identified with BIO 300 in a mouse model of RILI (*20*). Of significance, the plasma level of three of the candidate biomarkers correlated with lung injury, was also observed in an irradiated NHP model and was predictive of survival at day 180 postirradiation. Given the presence of these candidate biomarkers in human plasma, these biomarkers are feasible for clinical use, pending establishing a relationship between plasma levels of the candidate biomarkers and clinical endpoints of RILI.

Biomarkers for Predicting Onset of Chronic Conditions after Exposure to Radiation. Circulating microRNAs (miRNAs) are stable in plasma and can be sampled by minimally invasive techniques, making them attractive biomarkers for lung-DEARE to identify radiation-exposed individuals who require treatment for chronic effects such as pneumonitis or pulmonary fibrosis. Further, the profile of miRNAs differs among tissues and cell types and can be used correlate to injuries in a tissue- or organ-specific manner. In NHPs, levels of six miRNAs in a panel measured at day 2 postirradiation were predictive of the development of neutropenia on day 6, and pulmonary fibrosis, as diagnosed by lung CT at day 60. Based on rodent and NHP data, the ability of candidate miRNAs to predict late pneumonitis and lung fibrosis was evaluated in adult patients receiving radiotherapy for lung cancer. The analysis strategy comprised identification of a ~20 miRNA with the greatest predictive power and evaluation of significance for the chosen outcome of interest using logistic regression models (*21*) in normal humans. The utility of these biomarkers is evident by the strong correlation of the levels of the miRNA biomarkers in the NHP and in irradiated patients, and the potential to identify exposed patients, enabling intervention to reduce the morbidity and mortality rate.

Evidential and Validation Considerations on Qualifying Imaging Biomarkers. The NIAID-FDA Biomarker Definitions Working Group has established a compendium of harmonized terminology know as BEST (Biomarkers, EndpointS and other Tools) to facilitate biomarker development and application. Under the FDA Animal Rule, biomarkers (molecular, histologic, radiographic, or physiologic) alone should not be used as endpoints to establish efficacy (*4*). FDA has also published a template for a letter of intent to the Agency, a *Framework for Defining Evidentiary Criteria for Biomarker Qualification* (*22*), a draft guidance on *Biomarker Qualification: Evidentiary Framework* (*23*), to provide the conceptual framework described in Section 3011 of the Twenty-First Century Cures Act, entitled ''Qualification of Drug Development Tools.'' The process for biomarker development involves three stages: the letter of intent, the qualification plan, and the full qualification package. The sponsor is required to outline the biological rationale, provide data to support the biomarker's analytical performance and its clinical validation.

SESSION VI

Panel Discussion/Summary

Panel discussion between experts from academia, corporate partners, FDA, BARDA and NIAID, and the audience focused on major scientific questions in the field of RILI and sought consensus on a path forward for future research.

How can We Standardize an Animal Model that Mimics the Clinical Condition? Panelists and audience agreed on the necessity of generating an accepted standardized model that would enable sponsors to streamline and develop MCMs more effectively for RILI. The desired outcome is a model of disease that is standardized and reproducible between laboratories in terms of the time course of the disease, and the physiological impact of changes that occur at the level of the lung. Given the large variability of the course of disease between animal species, and interindividual variations, would it be feasible to use a single standardized model? The overall goal is to arrive upon a model that exhibits the features of the disease that the scientific community agrees are critical to understanding RILI (e.g., fibrosis, pneumonitis).

Another aspect of model development is the medical management of the irradiated organisms and its relevance to the standard of care used in the clinics, such as steroid treatment. While the anti-inflammatory effect of steroids is not completely understood, steroid treatment extends the duration of drug studies by prolonging survival and allows

the characterizing of the natural course of the disease, and treatment arms with and without steroid should be included in large animal models.

What Quantitative Measurements of Lung Function/ Anatomy can be Used as Efficacy Endpoints? Regarding PD biomarkers it is recommended that researchers identify the stage of the developmental and regulatory process they are in before determining study design for identifying/ selecting biomarkers for drug dose selection. For example, humans suffering from RILI exhibit inflammation, fibrosis, and radiologic indicators that can be used to assess disease severity; these measures of pulmonary function in animals could be used as endpoints for assessing drug efficacy.

All Models are Wrong… What Animal Models are Useful? Despite the inherent uncertainty of models, they are useful tools for predicting the outcome of an event provided the model is carefully tailored to the hypothesis it is intended to address. FDA provided advice on the validity of using PBI to model lung injury in humans, explaining that researchers have used a variety of partial shielding models for small animals, but guidance is less clear for NHP studies, given the serious complications from GI and hematologic injuries. For both RILI and other radiation subsyndromes, the goal is to develop a model that reliably presents all of the relevant factors involved in the human condition. Currently, the aim is to standardize a PBI model that includes multi-organ injury for small rodents and refine further prior to moving into NHPs. An approximate 5% bone marrow sparing PBI model in NHPs (2.5% in mice) is valuable because it allows scientists to evaluate the effect of a product in addressing multi-organ injury.

CONCLUSION

There are several important concepts that should be taken from the presentations and meeting discussions: 1. Sponsors should tailor their models to align with clinical experience; 2. Rodent animal models that use focal irradiation (e.g., WTLI) may be useful for exploratory studies, but the adequate and well-controlled studies to support licensure will need to include irradiation to multiple organs; 3. Refinement of small and large PBI models and consideration of other aspects of medical management and radiation exposure are critical for MCM development; 4. Use of steroids is an open question, but their use should be temporary, tapered, and indicated by pre-determined trigger; and 5. use of pulmonary function measurements, and relevant biomarkers to predict outcome of RILI and recovery is encouraged.

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