RADIATION RESEARCH **177**, 717–721 (2012)
0033-7587/12 $15.00

DOI: 10.1667/RR2881.1

COMMENTARY

Development and Licensure of Medical Countermeasures to Treat Lung Damage Resulting from a Radiological or Nuclear Incident

Andrea L. DiCarlo,[a,1] Isabel L. Jackson,[b] Jui R. Shah,[a] Christine W. Czarniecki,[a] Bert W. Maidment[a] and Jacqueline P. Williams[c]

[a]*Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland;* [b]*Duke University Medical Center, Durham, North Carolina; and* [c]*University of Rochester Medical Center, Rochester, New York*

DiCarlo, A. L., Jackson, I. L., Shah, J. R., Czarniecki, C. W., Maidment, B. W. and Williams, J. P. Development and Licensure of Medical Countermeasures to Treat Lung Damage Resulting from a Radiological or Nuclear Incident. *Radiat. Res*. 177, 717–721 (2012).

Due to the ever-present threat of a radiological or nuclear accident or attack, the National Institute of Allergy and Infectious Diseases, Radiation Medical Countermeasures Program was initiated in 2004. Since that time, the Program has funded research to establish small and large animal models for radiation damage, as well as the development of approaches to mitigate/treat normal tissue damage following radiation exposure. Because some of these exposures may be high-dose, and yet heterogeneous, the expectation is that some victims will survive initial acute radiation syndromes (e.g. hematopoietic and gastrointestinal), but then suffer from potentially lethal lung complications. For this reason, efforts have concentrated on the development of animal models of lung irradiation damage that mimic expected exposure scenarios, as well as drugs to treat radiation-induced late lung sequelae including pneumonitis and fibrosis. Approaches targeting several pathways are under study, with the eventual goal of licensure by the United States Food and Drug Administration for government stockpiling. This Commentary outlines the status of countermeasure development in this area and provides information on the specifics of licensure requirements, as well as guidance and a discussion of challenges involved in developing and licensing drugs and treatments specific to a radiation lung damage indication.

INTRODUCTION

The United States White House Office of Science and Technology Policy has rated understanding radiation-induced late effects, including pulmonary complications, as a top priority research area (*1*). To address this and other research needs in the area of radiation-induced damage and health effects, the Department of Health and Human Services (DHHS) has tasked the National Institute of Allergy and Infectious Diseases (NIAID) with the responsibility to identify and develop new medical countermeasures for use in the event of a radiological or nuclear accident or attack. In individuals exposed to high doses of radiation who survive the acute radiation syndrome (ARS), late effects such as pulmonary complications are expected. Therefore, along with continuing efforts to develop medical countermeasures targeted to hematopoietic or gastrointestinal complications, NIAID is funding studies to develop medical countermeasures to mitigate late lethality and morbidities, including radiation-induced pulmonary damage. There are currently no medical countermeasures in the strategic national stockpile to mitigate/treat radiation damage to the lungs (*2*). Therefore, there is a critical need for the development of models and treatment approaches. Availability and stockpiling of medical countermeasures for lung injury will increase medical management options to treat casualties that may present after a radiation incident.

The primary goal of NIAID's lung program is the development of medical countermeasures to mitigate and/or treat radiation-induced pneumonitis and/or chronic lung sequelae such as fibrosis with the ultimate goal being licensure by the U.S. Food and Drug Administration (FDA) under current regulations commonly referred to as the FDA Animal Rule (*3*). To this end, NIAID held a workshop on April 19–20, 2010 to discuss recent advances in the field, and to provide a forum for an open discussion about research needs and paths forward for the development of medical countermeasures for a radiation lung-damage indication (available online at http://dx.doi.org/10.1667/RROL04.1). This commentary briefly touches on the current status of the field of countermeasure development for this lung indication,

[1]Address for correspondence: DAIT, NIAID, NIH, 6610 Rockledge Drive, Room 5301, Bethesda, MD 20892; e-mail: cohena@niaid.nih.gov.

along with an overview of the data that were presented and key points from a discussion session held during the meeting.

Radiation Effects in the Lung

The lung has long been recognized clinically as being highly radiosensitive, resulting in its consideration as a dose-limiting organ in many radiation therapy protocols. Because of this sensitivity, radiation-induced lung injury is of significant medical concern, not only with respect to localized radiotherapy-related exposures, but also for its potential role following radiation accident scenarios. These might include exposure from a nuclear detonation or from a radiological dispersion device, which could result in inhalation of radioactive particles. As supportive care protocols have improved, individuals surviving ARS have ultimately succumbed to a multiple organ dysfunction syndrome, with pneumonitis and/or pulmonary fibrosis playing a prominent role (*4*). For example, following the Chernobyl incident, seven patients were diagnosed with pneumonitis and, of those, two died. Of a subset of six patients that died later, all had some degree of respiratory disorder (*5*).

Principal radiation-induced normal tissue events in the lung are an acute phase alveolitis/pneumonitis and a late chronic pulmonary fibrosis (*6*), with multiple lung-related symptoms being expressed as part of injury progression. Following the initiating radiation injury, progression to late lung disease involves a complex network of cellular processes and interacting signals (*7*). During the acute phase, inflammation is the predominant histological and physiological feature (*6*), culminating in the pneumonitic and/or fibrotic phases (*7*). Classically, prevention of normal tissue late effects has focused on pre-treatment, including free radical scavengers such as amifostine (*8*). However, this approach has failed to gain significant headway in the clinic, and pre-treatment protocols have limited relevance in a mass-casualty exposure scenario. Another widely accepted target for mitigating strategies for radiation-induced lung injury has been inflammation. Clinical evidence suggests that limiting the inflammatory reaction may be a reasonable approach, given beneficial effects seen following glucocorticosteroid drug administration (*9, 10*). However, in general, these approaches have a poor track record for decreasing long-term injury (*11*). General classes of drugs currently under study within NIAID's program for mitigation of radiation-induced lung damage include anti-oxidant drugs (*12, 13*), statins with anti-inflammatory properties[2] (*14*); oxidized glutathione variants (*15*), ACE inhibitors[3,4] (*16, 17*), and nutraceuticals[5] (*18, 19*). Other novel approaches include drugs to enhance mucociliary clearance of inhaled radionuclides (*20*), and a substance P analog (*21*).

Animal Models and Development of Mitigators for Radiation-Induced Lung Damage

It is generally accepted that the FDA Animal Rule licensure pathway will require proof of efficacy in large-animals models as well as in rodents (*22*). For this reason, animal model development is being pursued in several species, including mice, rats, canines and non-human primates (NHPs). With regard to selection of strain, some researchers have noted that certain mouse strains may be more predictive of the human lung radiation response than other strains. For example, the C57BL/6J strain may not be the best model of lung injury due to an observed development of pleural effusions. This pathology, while not widely observed in humans, was noted in patients who received accidental radiotherapy overexposures (*23*). At issue is that these effusions are normally not the cause of death in humans (whose symptoms can be resolved with steroid treatment). However, they can be the cause of death in small animal models. An excellent overview on mouse strain differences in lung effects and potential animal model limitations to mimic human lung syndromes is available (*24*). Rats are also under study for radiation-induced lung injury, since their larger size allows for greater ease of manipulation, including achieving clearer computed tomography (CT) scanning. Because medical countermeasures will also be needed for use in children, development of pediatric mouse models of lung damage is being undertaken, and animal age appears to play an important role in the outcome of the exposure (*25*). In addition to rodent models of radiation exposure, larger animals, such as canines and NHPs, are being developed for potential use as models of the human pulmonary response[6]. Pig models may also be representative of radiation-induced damage to the human lung due to the structural similarity of pig lungs to those of humans (*2*). In any model selected, careful consideration of an end point (e.g., pneumonitis or fibrosis) should be made in the context of the chosen animal.

As part of a large-scale nuclear or radiological event, it is likely that the majority of victims will experience a total body (TBI), albeit heterogeneous, exposure. However, in the absence of supportive care, external TBI, delivered at levels necessary to cause late lung damage, would be acutely lethal. To more effectively model expected scenarios, several researchers are using high-dose TBI

[2] M. Medhora *et al.*, Efficacy of structurally different angiotensin converting enzyme (ACE) inhibitors for mitigation of radiation pneumonitis. Presented at the Fifty-sixth Annual Meeting of the Radiation Research Society, 2010.

[3] E. R. Jacobs *et al.*, Angiotensin converting enzyme (ACE) inhibitors mitigate pulmonary fibrosis in rats. Presented at the Fifty-sixth Annual Meeting of the Radiation Research Society, 2010.

[4] C. Chen *et al.*, Triptolide reduces radiation-induced cytokines in lung inflammation model. Presented at the Fifty-sixth Annual Meeting of the Radiation Research Society, 2010.

[5] J. P Williams *et al.*, A combined therapeutic approach to pulmonary mitigation following a radiological event. Presented at the Fifty-sixth Annual Meeting of the Radiation Research Society, 2010.

[6] Z. Vujaskovic *et al.*, Variations in mast cell hyperplasia in the irradiated lungs of different mouse strains, rats and non-human primates. Presented at the Fifty-sixth Annual Meeting of the Radiation Research Society, 2010.

exposures, relying on bone marrow transplants to minimize mortality resulting from hematopoietic complications. Other researchers have adopted high-dose exposure protocols, in which only a part of the animal is irradiated (partial-body irradiation, PBI). A drawback with some of these models is the potential absence of hematopoietic and/or gastrointestinal damage, which might affect the progression of radiation-induced pulmonary damage. To address this issue, several models are under development in which animals either have 5% shielding of their bone marrow[7], or are exposed to a sub-lethal TBI radiation exposure with an additional, localized ''top-up,'' high-dose radiation exposure to the thorax (*26*). Still other investigators are developing ''two-hit'' models, in which radiation exposure is delivered concomitantly with other stressors (such as skin burns or infection) as a combined injury (*27*).

Because government guidance dictates that medical countermeasure delivery from the stockpile will likely not occur within hours or even days after an incident, dose regimens beginning at times >24 h to 72 h post-exposure represent appropriate testing windows for drugs to treat radiation effects, and investigators are strongly encouraged to consider testing using even greater administration delays. Only drugs licensed by the FDA for any indication can be stockpiled. Drugs can be released as therapies for radiation injuries only if they are FDA-approved for a radiation indication or through issue of an emergency use authorization by the FDA (*28*). In either of these pathways, it is important that data be obtained in appropriate, Good Laboratory Practice (GLP)-compliant animal models, as per FDA's Animal Rule (*3*). Because the ultimate goal of NIAID's program is licensure of a drug to treat late radiation-induced lung complications following exposure during a radiation incident, efforts have focused on developing animal models that would be acceptable for licensure via FDA's Animal Rule pathway. This pathway is utilized for ''approval of new drugs when human efficacy studies are not ethical or feasible'' (*22*). In contrast to traditional drug development licensure, this pathway requires: (1) a reasonably well-understood mechanism of radiation damage; (2) that effects of radiation exposure and medical countermeasure mitigation are demonstrated in at least one animal species expected to react with a response predictive of humans; (3) animal study outcomes that are clearly related to the desired benefit in humans; and (4) data on pharmacokinetics (PK) and pharmacodynamics (PD) to allow selection of an effective dose in humans. It is critical to link together data obtained in each animal model and show that the selected models are appropriate representations of the damage observed in humans. It must also be shown that amelioration of damage by the drug in the model is predictive of the response observed in humans. For example, if the mechanism of action of a particular treatment in the animal model is through inhibition of a particular pathway in a cell or tissue, then that pathway must also exist in humans, must be affected similarly by radiation damage, and must be modified by the drug in the same fashion. Precisely how this requirement will be implemented by the FDA in practice is still unclear. Although the Animal Rule has been implemented in the U.S., it does not currently have an equivalent in most countries. However, the European Medicines Agency has issued guidelines on a regulatory procedure for the ''Granting of a Marketing Authorization under Exceptional Circumstances'' [Article 14 (8) of regulation (EC) NO 726/2004] that might be applicable in some countries (*29, 30*). This approval can be used when a sponsor is ''unable to provide comprehensive data on the efficacy and safety under normal conditions of use''. Additional information on considerations for investigators pursuing licensure for a radiation indication (including who to contact at the FDA) is discussed elsewhere (*31*).

Whatever animals are selected for study, it is critical to standardize the models and validate them for their ability to detect medical countermeasure efficacy. Validation should include comparing proposed new treatments to current standards of supportive care, and perhaps testing the new treatment concurrent with administration of what would be expected care in a mass-casualty scenario. For example, dexamethasone is used clinically to treat lung injury (*32*), and in the case of radiation-induced damage, could be used off-label by a physician. Therefore, researchers might consider including this standard therapy concurrently, especially in larger animal models of radiation lung damage. Whether supportive care is needed, and to what extent, is especially important for certain models of radiation-induced lung damage (e.g., the 5% shielded model), since animals must survive multiple syndromes before manifesting lung injury. Only discussions with the FDA can delineate the animal care protocol that should be employed for development of a particular medical countermeasure. It is also important to precisely define radiation exposure parameters, and to ensure that the radiation dose delivered to the animals is accurate. Other factors, such as time of day of irradiation, anesthesia, use of acidified water, and food composition can also affect radiation responses. Because lung damage can result from internal contamination (from fallout) and/or external exposure (from prompt radiation), depending on the proposed mechanism of action of the medical countermeasure, it may be important to consider if a mitigators/treatment will work for lung injury caused by both routes of radiation exposure. Finally, it is critical to identify appropriate end points (primary and secondary) to assess efficacy of lung medical countermeasures.

FDA requires evaluation of end points that indicate clinical benefit, which for many indications is survival.

[7] T. Shea-Donohue *et al*., An acute radiation syndrome (ARS) nonhuman primate (NHP) research platform: prolonged gastrointestinal (GI) dysfunction observed in NHPs surviving the acute heme and GI syndromes. Presented at the Fifty-fifth Annual Meeting of the Radiation Research Society, 2009.

Generally, an improvement in survival of 25–30% is desirable in a drug for which licensure for this indication is being sought. It is, however, important to note that use of a survival end point is sometimes problematic for researchers, especially in large animals, due to Institutional Animal Care and Use Committee concerns. Reduction of major morbidity by the medical countermeasure may represent another possible end point. To date, FDA's stance has been that ''Primary study end points, which should be specifically discussed with the review division, generally are the enhancement of survival or prevention of major morbidity'' (*22*). The dose response for these end points should be explored fully and established. Although secondary end points can provide useful information about the animal model, and the activity of the product as studied in the animal model, ordinarily, only primary end points can serve as the basis of approval. Determination of major morbidity in the lung is a difficult clinical end point, and improvements in ''quality of life'' of affected patients are challenging to quantify in humans, and even more so in animal models. Therefore, it is important to show clinically-relevant treatment outcomes if a survival end point is not possible. For example, human lung damage is often assessed by CT, so similar scans of irradiated animals might be warranted to relate those findings to a clinically-relevant outcome. Lung compliance and/or respiratory rate could also represent surrogate end points. A more thorough consideration of potential end points can be found elsewhere (*26*). Further studies are still needed to better understand the impact of age, gender and immune competency on lung sensitivity to radiation exposure, as well as responses to therapeutics. There is also still a need to further validate existing models for radiation damage to the lungs, and to better understand the mechanisms responsible for the radiation damage as well as cellular and organ responses to the injury. For this reason, NIAID plans to continue to fund studies in these areas.

REFERENCES

1. Pellmar TC, Rockwell S. Priority list of research areas for radiological nuclear threat countermeasures. Radiat Res. 2005; 163(1):115–23.
2. Stone HB, Moulder JE, Coleman CN, Ang KK, Anscher MS, Barcellos-Hoff MH, et al. Models for evaluating agents intended for the prophylaxis, mitigation and treatment of radiation injuries. Report of an NCI Workshop, December 3–4, 2003. Radiat Res. 2004; 162(6):711–28.
3. Food and Drug Administration. New drug and biological drug products: evidence needed to demonstrate effectiveness of new drugs when human efficacy studies are not ethical or feasible. Fed Regist. 2002; 67:37988–98.
4. Fliedner TM, Dörr HD, Meineke V. Multi-organ involvement as a pathogenetic principle of the radiation syndromes: a study involving 110 case histories documented in SEARCH and classified as the bases of haematopoietic indicators of effect. BJR Suppl. 2005; 27:1–8.
5. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Report to the General Assembly, Annex J: Exposure and Effects of the Chernobyl Accident. Sources, Effects and Risks of Ionizing Radiation. 2000.
6. Travis EL, Down JD, Holmes SJ, Hobson B. Radiation pneumonitis and fibrosis in mouse lung assayed by respiratory frequency and histology. Radiat Res. 1980; 84(1):133–43.
7. Rubin P, Johnston CJ, Williams JP, McDonald S, Finkelstein JN. A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis. Int J Radiat Oncol Biol Phys. 1995; 33(1): 99–109.
8. Vujaskovic Z, Feng QF, Rabbani ZN, Samulski TV, Anscher MS, Brizel DM. Assessment of the protective effect of amifostine on radiation-induced pulmonary toxicity. Exp Lung Res. 2002; 28(7): 577–90.
9. Sekine I, Sumi M, Ito Y, Nokihara H, Yamamoto N, Kunitoh H, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. Radiother Oncol. 2006; 80(1): 93–7.
10. Magana E, Crowell RE. Radiation pneumonitis successfully treated with inhaled corticosteroids. South Med J. 2003; 96(5): 521–4.
11. Moulder JE, Robbins ME, Cohen EP, Hopewell JW, Ward WF. Pharmacologic modification of radiation-induced late normal tissue injury. Cancer treatment and research. 1998; 93:129–51.
12. Yakovlev VA, Rabender CS, Sankala H, Gauter-Fleckenstein B, Fleckenstein K, Batinic-Haberle I, et al. Proteomic analysis of radiation-induced changes in rat lung: Modulation by the superoxide dismutase mimetic MnTE-2-PyP(5+). Int J Radiat Oncol Biol Phys. 2010; 78(2):547–54.
13. Vujaskovic Z, Batinic-Haberle I, Rabbani ZN, Feng QF, Kang SK, Spasojevic I, et al. A small molecular weight catalytic metallo-porphyrin antioxidant with superoxide dismutase (SOD) mimetic properties protects lungs from radiation-induced injury. Free Radic Biol Med. 2002; 33(6):857–63.
14. Williams JP, Hernady E, Johnston CJ, Reed CM, Fenton B, Okunieff P, et al. Effect of administration of lovastatin on the development of late pulmonary effects after whole-lung irradiation in a murine model. Radiat Res. 2004; 161(5):560–7.
15. Townsend DM, Pazoles CJ, Tew KD. NOV-002, a mimetic of glutathione disulfide. Expert Opin Investig Drugs. 2008; 17(7): 1075–83.
16. Ward WF, Molteni A, Ts'ao CH. Radiation-induced endothelial dysfunction and fibrosis in rat lung: modification by the angiotensin converting enzyme inhibitor CL242817. Radiat Res. 1989; 117(2):342–50.
17. Ghosh SN, Zhang R, Fish BL, Semenenko VA, Li XA, Moulder JE, et al. Renin-Angiotensin system suppression mitigates experimental radiation pneumonitis. Int J Radiat Oncol Biol Phys. 2009; 75(5):1528–36.
18. Su Y, Yang S, Xiao Z, Wang W, Okunieff P, Zhang L. Triptolide alters mitochondrial functions. Adv Exp Med Biol. 2007; 599:139–46.
19. Para AE, Bezjak A, Yeung IW, Van Dyk J, Hill RP. Effects of genistein following fractionated lung irradiation in mice. Radiother Oncol. 2009; 92(3):500–10.
20. Muggenburg BA, Boecker BB, Hahn FF, McClellan RO. Lung lavage therapy to lessen the biological effects of inhaled 144Ce in dogs. Radiat Res. 1990; 124(2):147–55.
21. An YS, Lee E, Kang MH, Hong HS, Kim MR, Jang WS, et al. Substance P stimulates the recovery of bone marrow after the irradiation. J Cell Physiol. 2011; 226(5):1204–13.
22. Food and Drug Administration. Guidance for Industry: Animal Models — Essential Elements to Address Efficacy Under the Animal Rule. In: Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), editor: Office of Communications, Division of Drug Information, FDA; 2009.

23. International Atomic Energy Agency. Accidental Overexposure of Radiotherapy Patients in Bialystok. Vienna. 2004.

24. Sharplin J, Franko AJ. A quantitative histological study of strain-dependent differences in the effects of irradiation on mouse lung during the early phase. Radiat Res. 1989; 119(1):1–14.

25. Johnston CJ, Hernady E, Reed C, Thurston SW, Finkelstein JN, Williams JP. Early alterations in cytokine expression in adult compared to developing lung in mice after radiation exposure. Radiat Res. 2010; 173(4):522–35.

26. Williams JP, Brown SL, Georges GE, Hauer-Jensen M, Hill RP, Huser AK, et al. Animal models for medical countermeasures to radiation exposure. Radiat Res. 2010; 173(4):557–78.

27. Johnston CJ, Manning C, Hernady E, Reed C, Thurston SW, Finkelstein JN, et al. Effect of total body irradiation on late lung effects: Hidden dangers. Int J Radiat Biol. 2011; 87(8):902–13.

28. Food and Drug Administration. Draft Guidance: Emergency Use Authorization of Medical Products. In: Office of Counterterrorism Policy and Planning, editor: Office of Counterterrorism Policy and Planning (HF-29), Office of the Commissioner, FDA; 2005.

29. Committee for Medicinal Products for Human Use. Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances pursuant to Article 14 (8) of Regulation (EC) No 726/2004. London: European Medicines Agency; 2005.

30. Druckman M. Food and Drug Policy Forum. Should Congress create stronger incentives to develop vaccines and other medical countermeasures against pandemic influenza and bioterrorism. Washington, DC: Food and Drug Law Institute; 2011.

31. DiCarlo AL, Poncz M, Cassatt DR, Shah JR, Czarniecki CW, Maidment BW. Medical countermeasures for platelet regeneration after radiation exposure. Report of a workshop and guided discussion sponsored by the National Institute of Allergy and Infectious Diseases, Bethesda, MD, March 22–23, 2010. Radiat Res. 2011; 176(1):e0001–15.

32. Azoulay E, Canet E, Raffoux E, Lengline E, Lemiale V, Vincent F, et al. Dexamethasone in patients with acute lung injury from acute monocytic leukemia. Eur Respir J. 2011.