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Building the Strategic National Stockpile Through the NIAID Radiation Nuclear Countermeasures Program

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Abstract

The possibility of a public health radiological or nuclear emergency in the United States remains a concern. Media attention focused on lost radioactive sources and international nuclear threats, as well as the potential for accidents in nuclear power facilities (e.g., Windscale, Three Mile Island, Chernobyl, and Fukushima) highlight the need to address this critical national security issue. To date, no drugs have been licensed to mitigate/treat the acute and long-term radiation injuries that would result in the event of large-scale, radiation, or nuclear public health emergency. However, recent evaluation of several candidate radiation medical countermeasures (MCMs) has provided initial proof-of-concept of efficacy. The goal of the Radiation Nuclear Countermeasures Program (RNCP) of the National Institute of Allergy and Infectious Diseases (National Institutes of Health) is to help ensure the government stockpiling of safe and efficacious MCMs to treat radiation injuries, including, but not limited to, hematopoietic, gastrointestinal, pulmonary, cutaneous, renal, cardiovascular, and central nervous systems. In addition to supporting research in these areas, the RNCP continues to fund research and development of decorporation agents targeting internal radionuclide contamination, and biodosimetry platforms (e.g., biomarkers and devices) to assess the levels of an individual's radiation exposure, capabilities that would be critical in a mass casualty scenario. New areas of research within the program include a focus on special populations, especially pediatric and geriatric civilians, as well as combination studies, in which drugs are tested within the context of expected medical care management (e.g., antibiotics and growth factors). Moving forward, challenges facing the RNCP, as well as the entire radiation research field, include further advancement and qualification of animal models, dose conversion from animal models to humans, biomarker identification, and formulation development. This paper provides a review of recent work and collaborations supported by the RNCP.

Keywords

radiation; nuclear; medical countermeasures; dosimetry; animal models; mitigators; treatment

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INTRODUCTION

The Radiation Nuclear Threat

After the attacks of September 11, 2001, the growing threat of terrorism has become a primary national security issue. While many subsequent plots of terrorism have been thwarted in this country and around the world, incidents like the April 15, 2013 bombing in Boston, Massachusetts, highlight the prospects of a possible direct threat within the United States, requiring expedient government intervention.

The notion that terrorists may use unconventional means, including weapons of mass destruction, has gained ground in part due to incidents such as the 1995 Sarin chemical weapon attack on the Tokyo subway system and the 2001 biological attacks in New York, Washington, and Florida, with lethal anthrax spores delivered through the postal system. The number of known terrorist organizations with global reach, the threat of domestic terrorism, and the exponential rise of information transfer via social media has increased the possibility that more attacks with chemical, biological, radiological, or even nuclear weapons could easily occur on American soil, thus making the need for preparedness a necessity that demands attention.

Exposure of sizable segments of the population to ionizing radiation could occur through contamination of food or water with radioactive material, intentional placement of radiation sources in public locations, or detonation of a radiological dispersal device (or a “dirty bomb”) that spreads radioactive material over a populated area and attacks on nuclear power plants or high-level nuclear waste storage facilities. The worst-case scenario would be the detonation of a nuclear explosive device, which, in addition to causing enormous destruction from blast and heat, would produce an intense burst of gamma radiation and large quantities of radioactive fallout.

To respond to these threats, the U.S. Government, through a special congressional appropriation, has tasked the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) to fund programs in basic and translational biomedical research to develop radiation medical countermeasures (MCMs) to counter radiological and nuclear threats in order to protect public health. In 2004, congressional appropriations funded NIAID to establish the Radiation Nuclear Countermeasures Program (RNCP) within the Division of Allergy, Immunology and Transplantation (DAIT). The ultimate goals of RNCP are to expedite the research, identification, development, and licensure of candidate MCMs to treat the biological damage resulting from exposure to radiation and save lives in a public health emergency.

In 2005, NIAID published the *NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats* [National Institutes of Health, 2005; http://www.niaid.nih.gov/topics/radnuc/program/Pages/StrategicPlanning.aspx]. This document, developed with input from a Blue Ribbon Panel of scientific experts in the field, describes the Institute's priorities. It details the required research that will lead to new and effective medical countermeasures to assess, diagnose, and treat civilians exposed to radiation, and mitigate its harmful effects to the greatest extent possible. Following the guidance set forth in the plan and in the more recent *Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats Progress Report: 2005–2011 and Future Research Directions: 2012–2016* (http://www.niaid.nih.gov/topics/radnuc/Documents/radnucprogressreport.pdf), NIAID continues to work closely with U.S. Department of Health and Human Services (HHS) agencies (such as the Biomedical Advanced Research and Development Authority (BARDA), and the Food and Drug Administration (FDA) and the Department of Defense (DoD) to prioritize research and focus development activities using available resources.

One aspect that makes the development of radiation/nuclear MCMs challenging is the inability to test the efficacy of potential countermeasures in clinical studies. Because of this, the approval path set forth by the FDA for radiation/nuclear MCMs will follow the "Animal Rule" (21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07-8923.pdf). The Animal Rule was designed to assess the safety and efficacy of drugs or biologics when testing them in humans is not ethical or feasible. Approval under the Animal Rule requires demonstration of efficacy in well-characterized animal model(s) as well as understanding pharmacokinetics and/or pharmacodynamics of a given treatment, such that an effective human dose can be selected. To support this path of approval, the RNCP mission includes the characterization of relevant animal models, including an understanding of the mechanism of radiation injury as well and defining primary endpoints (mortality or major morbidity) and secondary endpoints that can elucidate the mechanism by which a product exerts its effect.

PRODUCT DEVELOPMENT INITIATIVE

Multielement Program

The core component of the RNCP is the support and development of basic research to expand the fundamental knowledge of the mechanism of injury caused by ionizing radiation—from the molecular level to systemic. Complementary to this is the translational research piece that sets into motion the transfer of this fundamental knowledge into a fully developed product and takes into account all possible radiation insults to the hematopoietic, gastrointestinal (GI), immune, and pulmonary systems, as well as skin, cardiovascular, and the renal and central nervous systems.

The RNCP has several mechanisms by which investigators can gain access to funding, research and development resources/capabilities, and product development and regulatory pathway guidance for the development of MCMs for radiation and nuclear injury.

Centers for Medical Countermeasures Against Radiation (CMCR)

The CMCR, a keystone of the RNCP program, was established to support a network of specialized research institutions that interact collaboratively to meet the goals of the strategic plan. Currently, seven CMCRs receive NIAID funding. The CMCRs support 24 scientific projects and 36 cores, including 22 scientific cores, 7 administrative, and 7 pilot project cores. Among the research areas addressed by the CMCRs are:

- Innate and adaptive immune system enhancement/reconstitution postradiation exposure.
- Mechanisms of radiation injury and therapy at the systemic, organ, cell, and molecular levels.
- Identification/verification of potential countermeasure targets.
- Mechanisms of secondary responses that mediate, exacerbate, or ameliorate damage and disease resulting from external or internal radiation exposure (such as inflammation and oxidative stress).
- Long-term effects, such as cancer and fibrosis.
- The development of new animal models and in vitro assays to test and evaluate promising countermeasures.

While most of the funds from NIAID cover “in-house” research projects, a portion of the CMCR budgets is set aside to support pilot projects, conducted by qualified investigators from the radiation research community at large according to an application and approval process set forth by each participating institute. More information on participating institutes can be found at: http://www.niaid.nih.gov/topics/radnuc/funding/Pages/awardees.aspx.

Among the major contributions made to date by the CMCR program has been the development of a variety of animal models such as rodent and canine platforms for GI acute radiation syndrome (GI-ARS), nonhuman primate (NHP) models for hematopoietic acute radiation syndrome (H-ARS), and rat and mouse models of renal, pulmonary, and brain injury. Testing in these models has provided a greater understanding of how radiation affects gene and protein expression as well as the metabolome, and also assisting in identification of promising radiation/nuclear MCMs. For example, these MCMs include antioxidant mimetics to reduce chronic oxidative stress and delay pulmonary tissue injury, inhibitors of mitochondrial peroxidase activity, and modulators of hematopoietic stem cell growth, renewal, and regeneration.

SUPPORTING BASIC RESEARCH

Inter-/Intraagency Agreements

Established in 2005, the interagency agreement between NIAID and the Armed Forces Radiobiology Research Institute (AFRRI) funds research in several areas related to the challenges encountered following radiological or nuclear events. These include:

1. Screening of countermeasures to prevent, mitigate/treat radiation injuries.

2. Automation of dicentric assay.
3. Development of animal models to study mechanisms and screen countermeasures to mitigate/treat radiation combined injury.
4. Development of animal models to study mechanisms and screen countermeasures to mitigate/treat gamma/neutron mixed field injury.
5. Development of the Göttingen minipig as a model for both H-ARS and GI-ARS, as well as a potential pediatric animal model.

The NIAID-funded screening program at AFRRI has performed toxicity studies, dose optimization, time optimization for postirradiation exposure, optimum route of administration, and efficacy of postirradiation exposure (24 h and beyond). They have administered 55 single candidate MCMs and three combinations of candidate MCMs on survival in CD2F1 male mice at lethal dose LD90/30 and LD70/30 levels of radiation. Promising drugs are evaluated for postexposure efficacy in an NHP model.

Medical Countermeasures Against Radiological and Nuclear Threats Consortium (MCART)

Another key component of the RNCP program is the Radiation Nuclear MCM Product Development Support Services contract awarded to the University of Maryland School of Medicine (UMSOM) in 2005 and renewed in 2010 (http://www.niaid.nih.gov/topics/radnuc/funding/Pages/awardees.aspx). Under the product development contract, UMSOM established the MCART, which encompasses a number of departments within the School of Medicine as well as subcontractors who bring radiation and radionuclide expertise and other product development capabilities. One of MCART's functions is to develop/characterize animal models of radiation injury. Accordingly, MCART has had success establishing total body irradiation dose-response ranges and survival curves for H-ARS and GI-ARS in mice and in lung whole-thorax irradiation [Booth et al., 2012a; Jackson et al., 2012; McGurk et al., 2012; Plett et al., 2012], and in NHPs [Farese et al., 2012; MacVittie et al., 2012a] for H-ARS and radiation-induced lung injury. MCART investigators have also demonstrated that, in the context of supportive care comparable with what is expected in a real-life radiation/nuclear event, reducing mortality-related infection, dehydration, and blood loss would significantly improve postradiation patient survival. Keeping their focus on simulating a realistic scenario, MCART investigators are also currently developing partially-bone-marrow-shielded NHP and rodent models for multiorgan syndrome studies [Booth et al., 2012b; MacVittie et al., 2012b].

A second key role of the MCART consortium is to provide a spectrum of product development support services and capabilities, including efficacy studies as well as preclinical, nonclinical, Investigational New Drug (IND) enabling, and early clinical safety studies required by the FDA for countermeasure licensure. Promising MCM candidates identified by the RNCP are evaluated in a screening process to confirm efficacy. If successful, they undergo evaluation for dose optimization and route/schedule of administration. More rigorous testing, such as toxicology, pharmacology, and safety studies, may also be performed. MCART facilities are compliant with Good Laboratory Practices (GLP) and are able to perform nonclinical safety studies and GLP-compliant pivotal animal

efficacy studies for radiation exposure in their facilities. MCART animal models allow for testing of a range of compounds for efficacy in mitigating the hematological, respiratory, and GI syndromes. Of note, a GLP study of the biologic, filgrastim (a prescription granulocyte colony-stimulating factor), in an animal model demonstrated a 38% increase in survival compared with control [Farese et al., 2013]. The data from this study were recently evaluated by the FDA and were also the subject of an FDA Advisory Committee meeting. The Advisory Committee voted 17:1 that these data, along with the known human efficacy safety data, were sufficient to show that filgrastim was reasonably likely to benefit patients exposed to radiation in a radiological/nuclear incident.

Grant and Contractual Funding Mechanisms

NIAID supports funding of Small Business Innovation Research (SBIR) grants for product development activities specific to radiological and nuclear medical countermeasures, leading to IND or Investigational Device Exemption submission packages to the FDA. The SBIR opportunity has standard and ongoing receipt dates, and usually remains active for 3 years from the date the announcement is released. The SBIR mechanism allows the fostering of research in key areas of unmet need where early discovery is critical. The current NIAID SBIR—PA-12–044 (Phase I [R43] and Phase II [R44]; http://www.niaid.nih.gov/topics/radnuc/program/Pages/Opportunities.aspx) supports nonclinical and preclinical product development activities to advance new MCMs toward Phase I clinical trial safety studies, GLP animal model pivotal efficacy studies, and FDA licensure. NIAID uses this Program Announcement to encourage the development of products that: mitigate and/or treat ARS and/or the delayed effects of radiation exposures; eliminate internal radionuclide contamination (decorporation); or accurately determine individual radiation exposure levels (biodosimetry). This SBIR provides a unique opportunity to investigators and developers for funding: Phase I studies are eligible for $300 000 per year for up to 2 years ($600 000 maximum) and Phase II studies are eligible for $1 million per year for up to 3 years ($3 million maximum).

NIAID has used other granting and contracting mechanisms such as Requests for Applications (RFAs), Requests for Proposals (RFPs), and Broad Agency Announcements (BAAs) to target the development of MCMs for specific organ systems and radiation injuries. One of the successes of these approaches is the identification of orally bioavailable forms of diethylenetriaminepentaacetate (pentetate) and other novel decorporation agents that have demonstrated initial in vivo radionuclide decorporation efficacy. These projects have advanced to the IND-enabling stage, and developers have held pre-IND meetings and discussions with the FDA [Cassatt et al., 2008; Maidment et al., 2008]. In addition, the Challenge Grant mechanism (RC1) was also successfully used by the RNCP to solicit research in the areas of radiation-induced damage to the bone marrow, GI tract, lung, and skin. In addition, grant awards in the area of radiation-combined injury have resulted in the development of multiple animal models of combination injuries (radiation with other trauma, such as burn, wound, and head injury), which would be anticipated following a radiological or nuclear incident [DiCarlo et al., 2008].

BAAs to fund mid-stage research and development are NIAID-DAIT-NIHAI2013166: *Development of Medical Countermeasures to Enhance Platelet Regeneration and Survival Following Radiation Exposure from a Radiological/Nuclear Incident*, and BAA-NIAID-DAIT-NIHAI2012147: *Development of Medical Countermeasures to Mitigate or Treat the Gastrointestinal Acute Radiation Syndrome after a Nuclear or Radiation Incident*, which are intended to support the translational development of already identified, promising MCMs to mitigate and/or treat radiation-induced thrombocytopenia and GI damage when administered at least 24 h after radiation exposure. It is anticipated that research and development studies awarded from these BAAs will advance MCMs toward submission of an IND application and eventual approval from the FDA under the FDA Animal Rule.

EXPANDING RESEARCH CAPACITY

Forging Collaborations

The RNCP actively seeks interagency collaborations across the U.S. Government and seeks international collaboration opportunities as well. NIAID has developed interagency agreements or memoranda of understanding with the AFRRI (mentioned above), and the National Cancer Institute [Maidment et al., 2008]. These efforts are expanding, and NIAID has recently established or is in the process of establishing partnerships with other institutes within NIH. A successful collaboration with the National Institute on Aging was also established to study radiation exposures in elderly populations, and the RNCP continues to co-fund cooperative agreements with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on the isolation and characterization of GI stem cells.

The RNCP engages in a number of international activities. It supports a bi-national research program conducted by the Radiation Effects Research Foundation in Hiroshima and nine other groups (four in Japan and five in the United States) on the long-term effects of radiation exposure and aging on the human immune system. NIAID also supports collaborations for the Bundeswehr for Radiobiology in Germany to evaluate data from radiation accident victims. NIAID has recently established a letter of intent to collaborate with the Institut de Radioprotection et de Surete Nuclaire in France. Other ongoing international activities include membership in the Global Health Security Initiative and the World Health Organization’s Radiation Emergency Medical Preparedness Assistance Network.

MAKING IT TO THE FINISH LINE

Working Closely with the FDA

While NIH/NIAID is charged with the research and development of radiation/nuclear countermeasures, BARDA, like NIH part of the U.S. Department of Health and Human Services, manages advanced development and procurement programs for vaccines, drugs, therapeutics, and diagnostics for chemical, biological, and radiation/nuclear threats. Working together, NIAID and BARDA help to move promising drug candidates through the pipeline. The end goal is to obtain FDA approval and licensure of these drug candidates to include in the Strategic National Stockpile (SNS). The recent FDA Advisory Committee results

represent a significant step forward in the pathway toward obtaining licensure for new radiation nuclear MCMs for a public health emergency indication.

CONCLUSION

The growing threat of terrorism worldwide and within the United States has become a national security issue. A strategic plan set forth by NIAID details the required research necessary to develop new and effective radiation/nuclear medical countermeasures that assess, diagnose, and treat civilians, and to save lives. The initiative to develop products for this purpose is led by NIAID's RNCP. There are several mechanisms by which drug candidates can be either evaluated and tested for efficacy (through a NIAID-supported program such as MCART or AFRRI) or by providing funds investigators (through CMCR pilot grants, SBIR grants, RFAs, RFPs, and BAAs) to support their own drug development plans.

NIAID has progressed significantly in this initiative since the start of the RNCP in 2005. RNCP continues to work with investigators across the United States and around the world, with the mutual goal of MCM development. Working closely with other agencies, including DoD, BARDA, and the FDA, the RNCP facilitates the progress of promising drug candidates through the drug development pipeline. RNCP's mission will not be complete until the SNS is reflective of the solutions necessary to counteract radiological and nuclear threats to protect public health.

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