UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES BIODOSIMETRY AND RADIOLOGICAL/NUCLEAR MEDICAL COUNTERMEASURE PROGRAMS

Mary J. Homer^{1,*†}, Robert Raulli^{1,†}, Andrea L. DiCarlo-Cohen^{2,†}, John Esker^{1,†}, Chad Hrdina^{3,†}, Bert W. Maidment^{2,†}, Brian Moyer^{1,†}, Carmen Rios^{2,†}, Francesca Macchiarini^{2,†}, Pataje G. Prasanna^{4,†} and Lynne Wathen^{1,†}

¹Biomedical Advanced Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, US Department of Health and Human Services, 330 Independence Ave., SW, Room G644, Washington, DC 20201, USA

²Radiation Nuclear Countermeasures Program, Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services, 5601 Fishers Lane, Rockville, MD 20892-9828, USA

³Medical Utilization and Response Integration, Division of Medical Countermeasure Strategy and Requirements, Office of Policy and Planning, Office of the Assistant Secretary for Preparedness and Response, US Department of Health and Human Services, 330 Independence Ave., SW, Room G644, Washington, DC 20201, USA

⁴Radiation Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute; National Institutes of Health, US Department of Health and Human Services, 9608 Medical Center Drive, Room 3W230, MSC9727, Bethesda, MD 20892-9727, USA

*Corresponding author: mary.homer@hhs.gov

The United States Department of Health and Human Services (HHS) is fully committed to the development of medical countermeasures to address national security threats from chemical, biological, radiological, and nuclear agents. Through the Public Health Emergency Medical Countermeasures Enterprise, HHS has launched and managed a multi-agency, comprehensive effort to develop and operationalize medical countermeasures. Within HHS, development of medical countermeasures includes the National Institutes of Health (NIH), (led by the National Institute of Allergy and Infectious Diseases), the Office of the Assistant Secretary of Preparedness and Response/Biomedical Advanced Research and Development Authority (BARDA); with the Division of Medical Countermeasure Strategy and Requirements, the Centers for Disease Control and Prevention, and the Food and Drug Administration as primary partners in this endeavor. This paper describes various programs and coordinating efforts of BARDA and NIH for the development of medical countermeasures for radiological and nuclear threats.

INTRODUCTION

Protection of citizens from a multitude of national health security threats continues to be a high priority for the U.S. Government. Threats from chemical, biological, radiological, and nuclear (CBRN) agents (e.g. weapons that could be used to kill or injure a large number of people) as well as emerging infectious diseases (EID) (e.g. 1918–19 influenza pandemic outbreak) are urgent areas requiring development of strategies, medical countermeasures, policies and plans. The Department of Health and Human Services is the lead agency in this endeavor through a Federal, multi-agency, coordinating body termed the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE). The PHEMCE is charged with protecting

the civilian population from potential adverse health impacts through the use of medical countermeasures (MCM), which are medicines, devices, or other medical interventions that can lessen the harmful effects of these threats^(1, 2).

The PHEMCE's goals as provided in the 2012 PHEMCE Strategy and Implementation Plans are to

- (1) identify, create, develop, manufacture, and procure critical MCMs;
- (2) establish and communicate clear pathways to facilitate MCM development and use;
- (3) develop logistics and operational plans for optimized use of MCMs at all levels of response; and
- (4) address MCM gaps for all sectors of the American civilian population. The various PHEMCE MCM mission components and responsible PHEMCE partners are shown in Figure 1. The PHEMCE members work closely together to enable mission synergy and development of MCMs.

[†]The contents of this article represent the personal views of the individual authors and do not necessarily express the opinions or policies of the US Department of Health and Human Services or its components.

A significant confounder in the development of MCMs has been the lack of investment and interest by large pharmaceutical companies, so one key aspect of the PHEMCE in the development of new MCMs is the provision of funding to bridge the need for financial resources between early pre-clinical studies showing efficacy and advanced licensure activities. Consequently, fulfilling the PHEMCE mission will require comprehensive portfolio management over time and balanced investments in consideration of the long-term sustainability of the Enterprise. Coordination of product development pathways and the MCM development pipeline across Federal agencies becomes crucial in this balancing process so that support of MCM development is one cohesive and comprehensive effort rather than potentially redundant research and development activities occurring throughout the U.S. Federal Government.

The Office of the Assistant Secretary for Preparedness and Response in HHS is responsible for the public health and emergency medical preparedness and response missions outlined in Emergency Support Function #8 (ESF-8) of the National Response Framework (NRF) and leads management of the PHEMCE. Within ASPR, the Biomedical Advanced Research and Development Authority (BARDA) is tasked with advanced development and procurement of medical countermeasures for the Strategic National Stockpile and works closely with counterparts at the NIH (NIAID leads the MCM development effort for Rad/Nuc MCMs) and Department of Defense (DoD) to ensure a robust development pipeline of MCM candidates. Also within ASPR are other critical aspects of managing the PHEMCE such as development of policies, strategic plans, product requirements, and emergency operations. The primary development of MCM requirements and utilization plans within ASPR is performed by the Division of Medical Countermeasure Strategy and Requirements (MCSR)⁽³⁾.

This paper covers the strategy and overview of two programmatic areas of the radiological/nuclear MCM product development programs within HHS – development of therapies to treat injuries resulting from a radiological event and development of biodosimetry assays and platforms for mass casualty events. Programs at BARDA and NIH/NIAID cover both areas.

OVERALL STRATEGY FOR RADIOLOGICAL/NUCLEAR MEDICAL COUNTERMEASURE DEVELOPMENT

The HHS objective for Radiological/Nuclear MCM development is to provide solutions for the key remaining gaps for two types of radiological incidents – Radiological Dispersal Device (RDD) and Improvised Nuclear Device. The Improvised

Nuclear Device (nuclear denotation) is the higher consequence threat and therefore, the treatment gaps for this type of incident are the highest priority. Radiation exposure injuries are complex by themselves but with a nuclear blast, these will be further complicated as they are combined with other types of injuries such as trauma, blast, and thermal burn. HHS strategy is predicated on prioritizing finding treatments for those injuries appearing first.

The hematopoietic subsyndrome of acute radiation exposure (H-ARS), specifically, neutropenia (loss of neutrophils) has been the primary focus since the inception of the programs, and with the U.S. Government purchase of cytokines last year using funds appropriated through Project Bioshield,⁽³⁾ a major milestone for the Strategic National Stockpile was met. However, the hematopoietic condition still of great concern is thrombocytopenia – which will be a primary, future, short-term treatment target along with the subsyndrome of next greatest consequence – gastrointestinal (GI) injury. Other organ systems of interest that are affected by radiation exposure include the immune, pulmonary, cutaneous, renal, and central nervous systems.

The development and management of emergency medical countermeasures is coordinated through the PHEMCE (Figure 1). NIH/NIAID and BARDA are funding agencies that provide funding or provide product development capabilities or IND-enabling data to companies and research agencies/programs to develop MCMs that can meet HHS objectives. NIH/NIAID is responsible primarily for discovery and early development activities. Optimally, NIH/NIAID would manage a program through completion of a Phase I clinical study before the program would be ready for the BARDA portfolio. BARDA's mission is advanced development, licensure, and procurement of medical countermeasures. After initial procurement, the Centers for Disease Control and Prevention (CDC) manage MCMs in the Strategic National Stockpile. The FDA is involved throughout the product development path to make sure regulatory requirements are met.

The MCM development program works within the framework of the FDA drug approval process. The development of radiation/nuclear MCMs is particularly challenging due to the inability to test the efficacy of potential countermeasures in clinical studies due to ethical concerns. FDA's regulations concerning the approval of new drugs when human efficacy studies are not ethical or feasible are codified in 21CFR 314.600⁽⁴⁾ for drugs and 21 CFR 601.90⁽⁵⁾ for biological products, also commonly referred to as the 'Animal Rule'⁽⁶⁾. The Animal Rule regulatory approval path is the regulatory path adopted for development of radiation/nuclear MCMs. Approval under the Animal Rule requires an understanding of the mechanism of action of the MCM,

US HHS RAD/NUC MCM DEVELOPMENT PROGRAMS

Figure 1. PHEMCE mission components and partners⁽²⁾.

demonstration of efficacy in well-characterized animal model(s) as well as understanding pharmacokinetics (PK) and/or pharmacodynamics (PD) of a given treatment such that an effective human dose can be selected. In addition, the nature of the injury caused by the damaging agent (in this case, radiation) must also be reasonably well understood. To support this path of approval, the HHS MCM development programs include animal model characterization, elucidation of mechanisms of radiation injury and defining primary endpoints (mortality or major morbidity) and secondary endpoints (e.g. blood cell profile) for drug efficacy, human safety studies, pivotal animal efficacy studies as well as animal toxicology and PK/PD studies.

The development and licensure of one product is usually the result of a large input of potential candidates at the discovery phase and gradual attrition as the candidates move through the regulatory path and meet or do not meet scientific and regulatory milestones. Additionally, the investment required increases as the product moves towards licensure. Coordination through the PHEMCE allows HHS to maximize investments, leverage each agency's efforts, and ensure the products being developed are consistent with the needs of all the agencies that may use them.

Concept of operations for a nuclear detonation response

HHS uses modeling of many scenarios to assist in planning and prioritization. Based on assessments of

probability versus impact, HHS uses a scenario or summary of scenarios as a basis to develop a concept of operations (CONOPS), and set requirements for diagnostic and therapeutic capabilities. The concept of operations becomes an essential component of product development as it is crucial to anticipate the manner and conditions in which a product will be used. The federal government outlines, in several publicly available documents, a concept of operations named the RTR System, for Radiation TRIage, TReatment, TRansport (Figure 2)⁽⁷⁻⁹⁾. The purpose of the RTR CONOPS is to support medical care following a nuclear detonation, by characterizing the blast, organizing the response, and efficiently deploying personnel and material to the detonation locale, and as appropriate to support medical centers and treatment network centers (such as the Radiation Injury Treatment Network) receiving patients from the detonation incident.

The flow of the RTR system is from the field, through RTR sites, to assembly centers, medical centers and evacuation centers, and then to national care centers with capacity to absorb patients from the detonation locale. RTR1 sites are established near the blast zone and collect and triage victims with primarily mechanical and burn trauma as well as prompt radiation exposure from the blast. RTR2 sites are positioned near the perimeter of the fallout zone and collect and triage individuals with primarily radiation exposure from the fallout, some with injuries associated with the blast. RTR3 sites are

Figure 2. Diagram of the Radiation TRIage, TRreatment, TRansport System^(3, 5).

established outside the damage zone and receive individuals who have limited injuries due to the location of victims outside of the blast and fallout zones. From triage at these sites casualties are disposed to medical centers or assembly centers, and may be treated, sheltered, and transported to evacuation sites for disposition outside the locale of the blast to capable, intact expert medical facilities throughout the nation.

MCMs for the spectrum of care

The spectrum of care within the RTR CONOPS can be viewed as two phases of medical response

- (1) field care (approximately within 72 h) and
- (2) definitive care (approximately after 72 h).

Field care is focused on initial stabilization and triage (RTR sites) of casualties of the detonation and fallout, whereas the definitive care component is focused on the medical management (medical centers and expert care centers) of casualties after they have been introduced into the health care system, e.g. admission or discharge from an emergency department into inpatient or outpatient care. Field care will be focused on primarily stopping and

managing hemorrhage and exsanguination, pain management, stabilization of fractures, laceration repair, administration of fluids and antibiotics, and decontamination, as well as initiation of MCMs to address the hematopoietic subsyndrome (H-ARS) of acute radiation syndrome (ARS). Medical countermeasures for utilization of each phase in the spectrum of response must be tailored to the end user needs for that phase (Figure 3). Field care MCMs should be easy to use (e.g. topical, oral, etc.), should have a high therapeutic index (do no harm to patients if mistakenly administered, due to limited diagnostics, and concerned citizens who may receive interventions unnecessarily), and be easily stored, deployed and distributed. A critical function in the field care phase will be point-of-care biodosimetry capabilities, which do not currently exist – this is a high priority for development and focus for HHS programs.

The definitive care phase of patient management will involve delivery of therapeutic interventions such as medications and surgical procedures and will focus on maintenance of blood counts, functional recovery of injuries, provision of fluid and nutrition and patient monitoring for future manifestations of radiation injury. Biodosimetry capabilities to process large

US HHS RAD/NUC MCM DEVELOPMENT PROGRAMS

Figure 3. MCMs and the spectrum of care.

numbers of patient samples with greater specificity to identify dose received is a priority area for development for this treatment phase. Definitive care products may require expertise to administer and may be intravenous, surgically applied, etc. In the definitive care setting, a lower therapeutic index is acceptable due to the ability to administer a diagnostic process (better diagnostics and patient monitoring) to more effectively identify patients who will benefit from an intervention. Storage requirements for MCMs may also be more restrictive, such as cold storage, etc. as they can be accommodated by the health care infrastructure.

BIODOSIMETRY PROGRAM

HHS has actively supported research and development efforts in biodosimetry. The goals of BARDA's biodosimetry program are to

- develop radiation biodosimeters that are able to accurately assess the absorbed dose of ionizing radiation to an individual between 24 h and 7 days post-exposure,
- facilitate obtaining regulatory approval from the United States Food and Drug Administration for such technologies, and
- enhance the capability of the United States Government to respond quickly to a radiological incident and assist in the treatment of exposed individuals.

Radiation biodosimeters may help to identify individuals requiring urgent medical assessment, optimize resource allocation, reassure anxious individuals, improve risk assessment for delayed or late effects of radiation exposure, identify specific tissue/organ injuries and monitor the effects of treatment. A

variety of biodosimetry technologies that are currently being developed in the US by funding through various government agencies are at different levels of technological maturity and have recently been reviewed⁽¹⁰⁾. Funding for more basic focused research in the context of accidental radiation exposures is provided through NIAID with clearly defined applied objectives. BARDA's biodosimetry program began in 2009 to support advanced development of promising biodosimetry technologies.

It is unlikely that a single biodosimetry method would have all the critical attributes for assessing the absorbed dose and an integrated biodosimetry system is necessary. Therefore, the BARDA program is currently funding two complementary categories of biodosimetry technologies:

- A Point-of-Care test for a quick triage of an exposed population based on a biological dose above or below 2-Gy to determine risk of developing ARS. This test is designed to be administered by a person with little or no medical training in a field hospital, tent or triage station. The point-of-care device is expected to be able to screen up to a million individuals for determining a cohort at-risk for developing ARS. Ideally, results would be available in less than 15 min after the sample is collected with little or minimal sample processing. The intent of this assay is to separate the individuals with radiation-related medical needs from the 'concerned citizens' who may not need specific treatment.
- A laboratory-based high-throughput assay to quantitatively assess an estimate of the absorbed dose by an individual. The system being developed is capable of assessing the absorbed dose in the range 0.5–10 Gy with a better precision

compared to the point-of-care devices. This system is expected to be able process up to 400 000 samples per week with high degree of laboratory automation. The time to obtain results after sample collection would ideally be less than 8 h. The result of this assay will be used in conjunction with signs, symptoms and hematology to empower the health care provider with additional information on dose and distribution of dose within the body, and enable better management of an irradiated individual.

Desired product attributes for the above two categories of biodosimetry technologies are provided in Table 1. Clearly, the number of individuals exposed and radiation doses received will depend on several variables, which include geographical location of exposure (urban vs. rural, shielded vs. unshielded etc.), population density, weather (radionuclide plume, wind direction, etc.), and many other confounders⁽¹⁰⁾. This will determine the number of subjects who need screening with these biodosimetry tests.

Currently six groups are involved in the advanced development of biodosimetry technologies with BARDA funding. The various technologies being developed by these groups are based on radiation-induced changes in protein expression, DNA damage, electron paramagnetic resonance (EPR), and genomics. The proteomic and genomic groups have discovered and developed radiation-responsive panels of biomarkers using murine and non-human primate (NHPs) models demonstrating dose-effect and time-course relationships as well as feasibility of platform migration for point-of-care use. Dose assessment algorithms have been already developed using pre-clinical models and are now being tested in cancer patients undergoing radiotherapy for their ability to correctly assess dose.

BARDA's biodosimetry program extensively uses the NHP model system because the 'intended use' population is not available for actual testing of the technologies. As a result, BARDA's development partners are evaluating whether the result obtained by a given biodosimeter is accurate in the NHP

model and the biomarkers' ability to correctly predict the absorbed dose in exposure scenarios of above or below 2-Gy whole-body irradiation. In addition, these groups are also evaluating if the response pattern of the biomarker panel is similar between NHPs and human patients when undergoing fractionated irradiation for bone marrow transplantation, providing an avenue for validation. The effect of most-likely confounding conditions in real case scenarios of accidental radiation exposures such as burn and trauma as well as age, gender, and disease demographics are also being tested on these biomarker panels to ensure their successful utilization in an incident. The biodosimetry technologies are now in the product development phase, where biomarkers, platforms, dose assessment algorithms, and software are being rigorously tested using dose-blinded samples. Thus BARDA's efforts in advanced development of biodosimetry technologies directly support the national preparedness and planning for a nuclear and radiological incident, which has global relevance.

NIAID PROGRAM: COMPONENTS AND STRATEGY OF PROGRAM

The Radiation Nuclear Countermeasures Program (RNCP) within the Division of Allergy, Immunology and Transplantation (DAIT) of the National Institute of Allergy and Infectious Diseases (NIAID) of NIH is charged with developing a program to expedite the identification, research, development and licensure of candidate MCMs to mitigate the sequelae of biological damage caused by exposure to high doses of radiation in a public health emergency. The RNCP established their program in 2004 with funds from a special Congressional appropriation. Priorities of the RNCP are aligned with the Strategic and Implementation Plans of PHEMCE and with the BARDA program within HHS.

NIAID's RNCP research priorities for the development of MCMs were originally described in the NIH Strategic Plan and Research Agenda for

Table 1. Product attributes of Point of Care Devices and High Throughput Devices being developed at BARDA.

Product attributes	Point-of-care device	High-throughput device
CONOPS	Field Use/Triage	Hospital or Dose Assessment Center/Assist Treatment
Type of result	Qualitative	Quantitative
Operating Dose Window	POS = > 2-Gy	0.5–10-Gy (1 Gy discrimination)
Ease to use	Integrated components	High degree of automation
	Minimal or no sample preparation	
Number of patients	Up to a million in a week	Up to 400 000/week
Time to obtain results	15–30 min/sample	Up to 24h
Processing	Batch	Batch

Medical Countermeasures against Radiological and Nuclear Threats⁽¹¹⁾.

A report on the progress of this program has also been published, *Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats Progress Report: 2005–2012 and Future Research Directions: 2012–2016*⁽¹²⁾.

The NIAID RNCP continues to work closely with HHS/BARDA, FDA and the Department of Defense (DoD) to update research priorities and develop future strategies within its funding capacity and research and development mission.

Elements/mechanisms employed

The goal of the NIAID RNCP is to support the development of basic research that leads to an understanding of the molecular and systemic mechanisms of ionizing radiation injury. A translational research component is also employed that facilitates the transfer of this fundamental knowledge into the development of mature and successful MCM products. Biodosimetry and decorporation of radionuclides are also research areas within the RNCP mission.

Several mechanisms are in place within the NIAID RNCP, by which investigators can gain access to funding, research and development resources and capabilities, as well as product development and regulatory pathway guidance. Elements of the program are described below:

Centers for Medical Countermeasures against Radiation (CMCR)

Funding to the Centers for Medical Countermeasures against Radiation (CMCR) supports a network of specialized research institutions that collaborate to meet the goals of the strategic plan. Among the research areas addressed by the CMCRs are:

- Innate and adaptive immune system enhancement/reconstitution post-radiation exposure
- Mechanisms of radiation injury and therapy at the systemic, organ, cell, and molecular levels
- Identification/verification of potential MCM 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 fibrosis
- Development of new animal models and assays to test and evaluate promising countermeasures
- Identification of biomarkers for radiation injury as well as assays and biodosimetry devices to triage individuals with regards to the dose of radiation that they have received individuals

A portion of the CMCR budget has been designated to support innovative pilot projects in the radiation research community. Each participating institute oversees their own application/approval process. More information on participating institutes can be found at: <http://www.niaid.nih.gov/topics/radnuc/funding/Pages/awardees.aspx>.

The CMCR program has made major contributions to the field, which includes the development of a variety of small and large animal models such as mouse, canine and non-human primate (NHP) platforms for GI-ARS, rodent and NHP models for H-ARS, and rat and mouse models of renal, pulmonary, and brain injury. These models have provided a wealth of information regarding gene and protein expression as well as metabolomic changes in response to radiation exposure, and the identification of promising new MCMs.

Supporting basic research – inter/intra-agency agreements

NIAID has provided funding through an Inter-Agency Agreement with the Armed Forces Radiobiology Research Institute (AFRRI) to support:

- screening of medical countermeasures to prevent, mitigate/treat radiation injuries;
- automation of the cytogenetic dicentric assay;
- development of rodent and non-human primate models to study mechanisms and screen countermeasures to mitigate/treat radiation combined injury;
- development of rodent models to study mechanisms and screen countermeasures to mitigate/treat gamma/neutron mixed field injury; and
- development of the Göttingen minipig as a model for both H-ARS and GI-ARS as well as a potential pediatric animal model.

The drug-screen program performs toxicity studies, dose optimization, time optimization for post-irradiation exposure, optimum route of administration, and efficacy of post-irradiation exposure (24 h and beyond).

Product development support services contract

Another component of the RNCP program is the Radiation and 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, the UMSOM established the MCMs against Radiological and Nuclear Threats Consortium (MCART), which includes a number of departments within the

University's School of Medicine and subcontractors, who bring radiation and radionuclide expertise as well as other product development capabilities. One of MCART's functions is to develop/characterize animal models of radiation injury. MCART has established radiation lethal dose survival curves for murine H-ARS and GI-ARS as well as lung whole-thorax irradiation^(13–16) and in non-human primates (NHPs)^(17, 18) for H-ARS and radiation-induced lung injury. MCART investigators have demonstrated that administration of supportive care can significantly improve post-radiation survival through the reduction of mortality-related infection, dehydration and blood loss. MCART investigators have developed partially-bone-marrow-shielded NHP and rodent models for multi-organ syndrome studies^(19, 20) in order to simulate a public health radiation emergency scenario.

The Product Development Support Services Contract also provides capabilities that include efficacy studies, pre-clinical, non-clinical, 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 warranted, further dose optimization and route/schedule of administration studies are conducted. Toxicology, pharmacology, safety, ADME, and PK/PD studies may also be performed. MCART facilities are compliant with Good Laboratory Practices (GLP) and are able to perform non-clinical safety studies and GLP-compliant pivotal animal efficacy studies for radiation exposure in their facilities. MCART animal models have been developed to study hematological, respiratory and GI syndromes. Of note, a GLP study of the biologic, filgrastim (Neupogen[®] (Amgen) or granulocyte colony-stimulating factor (G-CSF), in an NHP model demonstrated a 38% increase in survival compared to control⁽²¹⁾. The data from this study was evaluated at an FDA Advisory Committee meeting and voted 17:1 that these data, along with the known human efficacy and safety data were sufficient to show that filgrastim was reasonably likely to benefit patients exposed to radiation in a radiological/nuclear incident. That Committee vote led to recent (March 2015) FDA approval of Neupogen[®] (filgrastim) to treat adult and pediatric patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome). Neupogen[®] (filgrastim) was approved by FDA based on studies in animals (under the Animal Rule), as studies in humans could not be ethically conducted, and was developed for the indication with support and collaboration from the NIAID. Neupogen[®] (filgrastim) is the first FDA-approved medical countermeasure for ARS. Follow-on studies with Neulasta[®] (pegylated G-CSF) have also

demonstrated efficacy (increase d survival) in a large animal, post-radiation exposure administration study sponsored by the NIAID.

Grant and contractual funding mechanisms

NIAID's RNCP also supports Small Business Innovation Research (SBIR) grants for product development activities specific to radiological and nuclear medical countermeasures, leading to Investigational New Drug (IND) or biodosimetry devices leading to Investigational Device Exemption (IDE), 510 K, or PMA submission packages to the FDA. The SBIR opportunity has standard and ongoing receipt dates, and remains active for three years from the date the announcement is released. The current NIAID SBIR PA-125-065 (Phase I [R43] and Phase II [R44]; <http://grants.nih.gov/grants/guide/pa-files/PA-15-065.html>) supports non-clinical and pre-clinical product development activities to advance new MCMs towards Phase I clinical trial safety studies, GLP animal model pivotal efficacy studies, and U.S. FDA licensure. This Program Announcement encourages the development of products to mitigate and/or treat ARS and/or the delayed effects of radiation exposures; eliminate internal radionuclide contamination (decorporation); and the development of tools to accurately determine individual radiation exposure levels (biodosimetry). Phase I awards are eligible for \$300 000 per year for up to 2 years (\$600 000 maximum) and Phase II awards 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 support 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 (DTPA; 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^(22, 23). The Challenge Grant (RC1) and Grand Opportunities Grant (RC2) mechanisms were 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. Cooperative agreements (U01) and NIH Research Grants (R01) have also been

utilized to add to the RNCP portfolio of funded studies. Both organ-specific MCMs, as well as predictive biodosimetry (to assess likelihood of damage to specific organ systems after radiation exposure, and thus, better predict possible late effects) awards have been made using these mechanisms.

Recent BAAs issued by the RNCP to fund mid-stage research and development are

- (1) NIAID-DAIT-NIHAI2013166: *Development of Medical Countermeasures to Enhance Platelet Regeneration and Survival Following Radiation Exposure from a Radiological/Nuclear Incident,*
- (2) NIAID-DAIT-NIHAI2012147: *Development of Medical Countermeasures to Mitigate or Treat the Gastrointestinal Acute Radiation Syndrome after a Nuclear or Radiation Incident,* and
- (3) NIAID-DAIT-NIHAI2014001: *Development of Medical Countermeasures to Mitigate and/or Treat Radiation-Induced Lung Injury after a Radiological/Nuclear Incident*

These contracts are intended to support the translational development of already identified, promising MCMs to mitigate and/or treat radiation-induced thrombocytopenia, GI and lung damage, respectively, 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.

Other collaborations with the NIAID RNCP

RNCP has also developed inter-agency agreements or memoranda of understanding the National Cancer Institute (NCI; 22) with expanding efforts in conjunction with the National Institute on Aging (NIA), National Institute of Heart, Lung and Blood (NHLBI), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). NIAID also supports international collaborations. A bi-national research program conducted by the Radiation Effects Research Foundation (RERF) in Hiroshima and nine other groups (four in Japan and five in the USA) work together to study the long-term effects of radiation exposure and aging on the human immune system. A collaboration with the Bundeswehr Institute for Radiobiology (BIR) in Germany allows for the evaluation of data from radiation accident victims. In addition, the NIAID RNCP has recently established a formal collaboration with the Institut de Radioprotection et de Sécurité Nucléaire (IRSN) in France for the use of cell therapies for radiation injury. Other ongoing international activities include partnership in the Global Health Security Initiative (GHSI) and the World Health Organization's Radiation

Emergency Medical Preparedness Assistance Network (WHO-REMPAN).

Accomplishments

NIAID's RNCP multi-faceted program has been successful with recent accomplishments in the MCM development arena that include:

- An FDA Advisory Committee meeting that voted 17-1 that Neupogen[®] (filgrastim) treatment is reasonably likely to produce survival benefit in humans exposed to radiation during a public health emergency incident. This led to the label extension of Neupogen[®] (filgrastim) to treat H-ARS.
- The completion of a Neulasta[®] (PEG-G-CSF, PEG-filgrastim) efficacy study through RNCP's Radiation Nuclear MCM Product Development Support Services contract awarded to the University of Maryland School of Medicine (MCART) demonstrating a 46% survival increase in a non-human primate (NHP) model of H-ARS.
- The opening of a new pre-Investigational New Drug (p-IND) for Neulasta[®] (PEG-filgrastim) by the RNCP.
- The identification of >150 early stage candidate MCMs for further testing.
- The awarding of two contracts for the development of MCMs for GI-ARS, two contracts for thrombocytopenia associated with H-ARS, and two contracts for mitigation of radiation-induced lung injury.
- The expansion of RNCP's GLP rodent radiation testing facilities (University of Maryland and the Armed Forces Radiobiology Research Institute – AFRRRI).
- The initiation of rodent and minipig pediatric animal model development.
- The filing of a candidate oral decorporation agent IND and receipt of FDA approval to proceed.
- The establishment of a formal collaboration with IRSN (Paris, France) on clinical use of mesenchymal stem cells for ARS and exploration of non-clinical evaluations predictive of product potency.

Path forward: areas of interest for discovery and early research

Because the RNCP has been tasked with early MCM development, the list of candidate approaches under study within the program is large, and includes (but is not limited to)

- Leukocyte growth factors
- Anti-inflammatories
- Anti-oxidants
- Anti-apoptotics

- Thrombopoietin receptor agonists
- Platelet factor-4 inhibitors
- HSC expansion/niche stimulation
- Toll-like receptor agonists
- HSC regenerative growth factors
- Stem and progenitor cells therapies and enhancers
- Cell cycle inhibitors
- Lysophosphatidic acid analogs
- Nuclear factor (NF)-kB inhibitors
- Macrophage phenotype switching
- Inhibition of the ceramide pathway
- Angiotensin converting enzyme (ACE) inhibitors
- Radionuclide chelators

BARDA PROGRAM: COMPONENTS AND STRATEGY OF PROGRAM

BARDA's mission is advanced development, licensure, and procurement of medical countermeasures. The BARDA Strategic Plan⁽²⁴⁾ outlines five goals to accomplish its mission that are aligned to the PHEMCE Strategic Plan:

- (1) An advanced development pipeline with medical countermeasures and platform technologies to address unmet public health needs.
- (2) A capability base to provide enabling core services to medical countermeasure innovators.
- (3) Agile, robust and sustainable US manufacturing infrastructure capable of rapidly producing vaccines and other biologics against pandemic influenza and other emerging threats.
- (4) Responsive and nimble programs and capabilities to address novel and emerging threats.
- (5) A ready capability to develop, manufacture and facilitate distribution of medical countermeasures during public health emergencies.

To accomplish this mission in the radiological/nuclear threat space, BARDA initiated its advanced research and development program in 2006. From its inception BARDA's Rad/Nuc program has worked to establish the necessary infrastructure and scientifically informed regulatory framework to allow products to proceed in the developmental pipeline. Advanced development efforts are focused on identifying new candidates that demonstrate promising survival efficacy as well as looking for already licensed products in fields such as oncology and autoimmunity where appropriate injury analogies for radiation injury can be found. Secondary endpoints specific to the aspect of radiation injury being treated are also critical in evaluating candidates.

Elements/mechanisms employed

BARDA employs a wide array of mechanisms to empower and fund institutions and agencies in the

development of MCMs. Contracts, grants, cooperative agreements, and other transactional authorities can all be used to provide funding to non-governmental entities. For advanced research and development efforts, BARDA has several Broad Agency Announcements (viewable on the Federal Business Opportunities website) with several submission dates through the calendar year. For late stage development, licensure and procurement activities, BARDA may use Project Bioshield funding. To date, the Radiological/Nuclear program has awarded over 20 contracts for advanced research and development and two recent Project Bioshield procurement contracts.

Interagency agreements and memoranda of understanding are used for work between federal agencies. Comprehensive transparency and understanding of efforts across government are promoted through regular portfolio sharing activities and co-management of programs with mutual interest across government agencies. Often, efforts on contracts are co-funded by partner agencies to leverage limited budgets (e.g. DoD may pay for prophylactic efficacy arms for the Warfighter in an efficacy study funded by BARDA). In addition, BARDA funds government laboratories to provide infrastructure support, model development and MCM testing functions.

Less formal public/private partnerships are also critical for the success of the BARDA program. Along with NIAID, BARDA also works closely with partners on international activities such as the Global Health Security Initiative (GHSI) and the World Health Organization's Radiation Emergency Medical Preparedness Assistance Network (WHO-REMPAN). Collaboration and participation in exercises and conferences with the Radiation Injury Treatment Network (RITN), part of the federally funded National Marrow Donor Program (NMDP) are proving essential for the BARDA program as well as PHEMCE efforts in radiological/nuclear preparedness. Additional end user engagements inform many aspects of preparedness, from market research on available resources to usability issues associated with a specific product. Future efforts will include an increasing emphasis on end user engagement to enhance our efforts in radiological/nuclear preparedness and MCM development.

BARDA organization and core services

The BARDA organization provides the expertise needed throughout the product development pathway to assist our development partners with advice and support needed for the development of a given product. Moreover, additional mechanisms and support networks have been created within each expertise area/division to provide core services and enable

efficiency and focus within a specific development area (Figure 4).

The Clinical Studies Network (CSN) provides the infrastructure to conduct and analyze clinical studies according to GCP under BARDA's direction. The network has the capability to provide the full range of clinical services required to plan and execute clinical studies and can support USG-contracted companies and internal programs.

Both the Centers for Innovation in Advanced Development and Manufacturing (CIADM) and the Filling and Finishing Manufacturing Network (FFMN) were established in response to difficulties in producing, filling and finishing vaccine during the H1N1 pandemic flu of 2009. The CIADM is a group of US-based, biopharmaceutical manufacturing facilities that support advanced development and manufacturing of MCMs. The FFMN is a network of existing facilities that are pre-qualified under contract to fill and finish biologicals and drugs for USG-contracted manufacturers. Services include formulation, lyophilization, vial fill and finish, labeling and packaging, storage and distribution. Both the CIADM and FFMN are available to support Rad/Nuc portfolio companies that do not or will not have pharmaceutical manufacturing capability in house. They could also provide surge capacity in emergencies.

BARDA also created the Non-clinical Development Network (NDN) that established contracts with qualified vendors. When an animal model needs development or a product needs testing in an established model, the Network can issue a task order to the qualified vendors to complete the work.

The qualified vendors can be organized as a consortium of laboratories to develop standardized robust and reproducible models – similar to the MCART organization under NIAID.

Using this multi-faceted approach allows BARDA to address product development issues throughout the continuum of the development process. At the beginning of the continuum, the approach includes the development of animal models to further define natural history and that are suitable for testing MCM efficacy. Once appropriate models are well-defined, they can be used to investigate the potential of commercial, licensed products for use as MCMs. Additionally, development of novel leads that advance through NIAID and DoD programs also falls within this phase of the program continuum. Through the later developmental stages through procurement, we have established comprehensive infrastructure to perform clinical trials, stood up rapid and flexible bulk manufacturing facilities, established fill/finish capabilities and developed a vendor managed inventory strategy that reduces or eliminates the need to replenish expired drug in the stockpile. The effort has created an orthogonal pharmaceutical infrastructure that can develop novel leads or insert advanced candidates into the process at any stage of development. The overall strategy and plan also emphasizes the need for innovation, flexibility, multi-purpose and broad-spectrum applicability, and long-term sustainability in any development effort.

Animal models

The availability of appropriate animal models has been an ongoing hindrance to progress for development of MCMs for radiation exposure. Early efforts to evaluate MCMs in the Radiological/Nuclear arena demonstrated that there was a critical need for robust, reproducible animal models. Inter-laboratory differences in species and strains, radiation source and geometry, general conditions and especially variations in supportive care and euthanasia criteria play important roles in the degree of survival of irradiated animals. Thus, animal model development, efficacy testing and optimization of use of products are key functions for the BARDA Radiological/Nuclear portfolio. The qualified NDN vendors can be organized as a consortium of laboratories to develop standardized robust and reproducible models and protocols. Currently, BARDA is finalizing the development of a mini-pig H-ARS model with such a consortium. The approach was to harmonize the methodology as closely as possible between laboratories, realizing that there would be differences in the irradiation methodologies. The results would be compared. The model will eliminate the need to have in-program contractors spend resources to develop animal models on their own. The

Figure 4. BARDA organization: core services.

standardization of animal models also allows for better portfolio management, allowing direct comparisons in the same model to determine the MCM opportunity with the greatest value. The ultimate intent would be to obtain model qualification from the FDA. Additional plans moving forward include the development of a GI-ARS mini-pig model and large animal models for pulmonary delayed effects of acute radiation exposure (DEARE).

A major mandate from the legislation that established BARDA is to develop MCMs that can treat vulnerable populations. Future plans in the animal model program, in conjunction with NIAID efforts, include the development of pediatric, geriatric and in utero models in multiple species. The approach will be similar to that of the mini-pig H-ARS model, where Task Orders were used to create a consortium to develop the model.

Repurposing of commercially available, FDA licensed products

To offset the time and costs of developing novel MCMs from discovery through approval, BARDA plans to create a prioritized registry of FDA-licensed and commercially available drugs with potential to treat the various ARS sub-syndromes. The registry will be based on a number of criteria that will include prior published studies showing MCM efficacy, therapeutic index, and market penetration among others. The repurposing strategy for drugs on the registry will be based on Food, Drug and Cosmetic Act regulation 505(b)(2) that could allow leveraging of prior developmental research not performed by the applicant for approval of new drug indications (or other changes) from previously approved drugs. Through this approach, BARDA may be able to reduce the cost and time required for approval and to achieve preparedness in a reasonable time frame compared to new chemical entity development paths.

With sufficient efficacy and other supporting data, drugs can also be repurposed as MCMs and may be used under an EUA during a declared public health emergency. Using Project Bioshield funds, BARDA has procured Neupogen® (filgrastim) and Leukine® (sargramostim), colony-stimulating factors (CSF) that stimulate the production of neutrophils from bone marrow for the purpose of treating neutropenia associated with radiation exposure. Neupogen® (filgrastim) received licensure in March 2015 under the Animal rule to increase survival in patients acutely exposed to myelosuppressive doses of radiation. For unlicensed products, licensure of the indication is the ultimate goal; however, these products could be used under EUA until that goal is met. Emergency use authorization can be issued if one of four types of determinations is met.⁽²⁵⁾ Recent amendments to

the Pandemic and All-Hazards Preparedness Reauthorization Act also allow issuance of an EUA for preparedness purposes before a CBRN emergency occurs if the statutory criteria are met.⁽²⁵⁾ Advanced research and development efforts are targeted at ensuring that robust data on MCMs exist to support the issuance of an EUA.

As an example, SOM230, or pasireotide, is a drug originally developed by Novartis to treat Cushing's Disease and was recently approved in the US for that indication. SOM203 is a somatostatin analog that decreases pancreatic secretions with the potential to reduce the degree of autodigestion in the radiation-damaged gut wall. SOM230 is already in the BARDA portfolio and is potentially repurposable as an 'animal rule' approval candidate. Another early stage repurposing candidate is the drug beclomethasone, which is a potent anti-inflammatory steroid that has limited ability to penetrate tissue. Originally developed as an inhaled drug for treatment of asthma, the drug would be given orally to protect the GI lining from radiation-induced inflammation. The limited tissue penetration of the drug could limit its absorption into the bloodstream and thus the immunosuppressive effects observed when steroids are given systemically. Current task order efforts within the NDN include the testing of probiotics and omeprazole in mouse efficacy models of GI-ARS. Future efforts will focus on the drug registry and recently approved drugs with promising profiles.

Other current repurposing efforts include products that could be in use in the oncologic setting, such as an IL-12 product and a hematopoietic stem cell product, both to treat neutropenia.

One of the most obvious and promising repurposing efforts revolves around the use of blood, blood products, or products that can mitigate the need for blood products to treat explosion/blast-associated trauma and the hematological syndrome of ARS. Even a 2-Gy radiation dose can result in significant reductions in neutrophil count and severe neutropenia. Thrombocytopenia is also a clinical manifestation of radiation exposure. An obvious treatment strategy is to transfuse the patient with blood or platelets to counter the reduction in cell count. The problem with this approach is that a mass casualty event such as an Improvised Nuclear Device (IND) explosion will likely rapidly deplete the supply of blood (particularly platelets) and resupply will not likely occur in time to properly treat the injured. BARDA has been working on the advanced development of blood products that can be put into general emergency use, stored and/or stockpiled for a mass casualty event. Dried plasma would be ideally storable under refrigerated conditions and easily transported at room temperature to a field hospital or triage site and reconstituted in minutes. Plasma could help radiation-exposed individuals maintain

hydration and the plasma clotting factors could counter clinical manifestations of thrombocytopenia to some degree.

Another product that BARDA is developing is a lyophilized platelet derivative known as Thrombosomes. Platelet concentrates are generally in short supply and platelets can only be stored for 5 days before expiry. Thrombosomes would ideally be stored at room temperature and could be easily stockpiled or, if significant commercial success is achieved, can be managed through a vendor managed inventory (VMI). If product development is successful, Thrombosomes could serve as a hemostatic treatment for severe hemorrhagic wounds and also as a treatment for those presenting with radiation-induced thrombocytopenia.

Vendor managed inventories

BARDA is strategically committed to a sustainable MCM capability. We have adopted a VMI strategy to counter the expense of replacing drugs in the stockpile upon expiry. This strategy requires the vendor have a sufficient market presence from which they could create a bubble in the inventory for the USG to claim in an emergency. The bubble of inventory allows for expiry to be carefully managed such that the inventory flows to the commercial market with the USG managed inventory supply never expiring. Thus, the necessary countermeasures are available from the vendor on demand. This strategy eliminates the need to replace expired drugs in the stockpile and has been applied to BARDA's procurement of Neupogen® (filgrastim) and Leukine® (sargramostim). Under these respective VMI agreements, the products are acquired and remain in the possession of the manufacturers in vendor-managed inventory until they are needed by the USG. The companies continue to meet their commercial demand while maintaining the USG supply. Moving forward, this strategy will be used whenever feasible for radiological/nuclear MCMs.

BARDA accomplishments

The procurements of Neupogen® (filgrastim) and Leukine® (sargramostim), intended to treat neutropenia associated with radiation exposure, represent significant milestones in the nation's preparedness for radiological/nuclear threats. HHS awarded contracts in September 2013 totaling \$194 M to sanofi-aventis (Bridgewater, NJ) and Amgen USA Inc. (Thousand Oaks, CA) to procure the cytokines and fund the vendor managed inventories. The establishment of a major vendor managed inventory for the Strategic National Stockpile also represents a significant achievement and leveraging taxpayer dollars.

The advanced research and development portfolio currently includes 14 programs to develop MCMs to address H-ARS (neutropenia and thrombocytopenia), GI-ARS, pulmonary injury due to acute radiation exposure, and decorporation. The contracts, inclusive of all options, represent a potential government investment of over \$530 M and include activities through Phase 3 clinical trials.

Through the use of the BARDA Non-clinical Development Network, another step of critical importance is the development of a standardized, robust and reproducible mini-pig H-ARS model. This will greatly increase BARDA's capability to test candidates for efficacy against the hematopoietic effects of acute radiation exposure, and may smooth the regulatory pathway for Animal Rule approvals.

Additional accomplishments include several awards that have expanded our understanding of ARS injury to hematopoietic, cutaneous, and GI systems, pulmonary injury due to radiation exposure. Several MCMs programs have been able to progress towards licensure with BARDA support and funding.

Finally, moving forward, the BARDA program will continue to support advanced development of promising candidates for radiation injury, seek viable MCM candidates within the existing commercial space of licensed products, and develop our understanding of radiation injury through model development and biomarker identification for all aspects of radiation injury but with a focus on hematopoietic and GI injury in the short term. Ideally, all animal models developed by BARDA will eventually be submitted to the FDA's Drug Development Tools and Models review panel for validation of the model.

CONCLUSION

The HHS Radiological and Nuclear Countermeasure Development programs have been developed and implemented to ensure that appropriate MCMs are available to counter nuclear or radiological threats. The PHEMCE ensures that these programs are coordinated across the US Federal government and maximize opportunities for cooperation and leveraging of resources. The HHS programs are multi-faceted and allow for development of MCMs starting at any stage of maturity through coordination of the portfolios at NIAID and BARDA. Future efforts will include continued advanced development of promising candidates, procurement of MCMs and establishment of additional VMIs, comprehensive development of animal models and identification of additional biomarkers. NIAID and BARDA, along with other government agencies, will continue to work together and across government to achieve the critical public health emergency objectives of safe, effective medical

countermeasures and biodosimetry methods that will further our nation's preparedness against radiological and nuclear threats.

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