Chapter XXXII
The NIAID/CMCR Program Mission Relative to All the Chapters

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In 2004, the National Institute of Allergy and Infectious Diseases (NIAID) was directed by the United States Department of Health and Human Services (HHS) to develop a robust research program on behalf of the National Institutes of Health (NIH). The stated goal of this program was to accelerate the development and deployment of radiation/nuclear medical countermeasures (MCMs) for eventual procurement and placement in the Strategic National Stockpile (SNS). On October 14, 2004, the NIH convened an expert panel to review the "NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats". This strategic plan and research agenda outlined a flexible, collaborative, and comprehensive NIH research and product development program focused on medical therapies and diagnostics to counter radiation injury. As a follow-up in 2012, the NIAID released a progress report entitled: "Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats Progress Report: 2005-2011 and Future Research Directions: 2012-2016".

Since inception of the program, NIAID-sponsored activities have focused on funding research on MCMs and biodosimetry devices to be used in mass casualty a radiation/nuclear incident involving improvised nuclear devices or radiological dispersal devices. These kinds of approaches would also be important in identifying and treating radiation-exposed populations following an accident, such as at a nuclear power facility. Specific areas of program interest have focused on development of animal models and MCMs for the mitigation and/or treatment of potentially-lethal, acute radiation syndrome (ARS) and/or the delayed effects of acute radiation exposure (DEARE). Affected organ systems from radiation exposure include the hematopoietic, gastrointestinal (GI), cutaneous, pulmonary, renal, cardiovascular and/or central nervous system compartments of the body. Radiation combined injuries (radiation plus other trauma) are also an area of emphasis. It is also important to understand the level of radiation exposure that a patient may have received (biodosimetry) and the potential health impacts of that exposure to the different organ systems (biomarkers and organ-specific, predictive biodosimetry), so these areas of research are also encouraged. More information on the RNCP's role in advancing the state of the science in all of these topic areas is detailed below.

ABOUT THE PROGRAM

The NIH/NIAID Radiation and Nuclear Medical Countermeasures Program (RNCP) supports early- to mid-stage research to develop medical products that mitigate or treat injuries that can result from radiation exposure (Figure 1). In addition, NIAID program staff are available to offer valuable scientific, technical, and regulatory guidance on the process of taking a research idea from its inception through the complex

process of product development and licensure. The research priority areas of the program are to develop the following:

1) Drugs to mitigate and/or treat radiation injury to the body:
    a. Must be effective when administered 24 hours or later after radiation exposure (see Concept of Operations section below);
    b. Need to be safe and easy to give to large numbers of people, including children, the elderly, and those with underlying diseases;
    c. With a route of administration amenable to a mass casualty radiation incident (e.g. subcutaneous, intramuscular, topical, transdermal, oral are preferred to intravenous);
    d. Preferably have broad activity and long shelf life (e.g. room temperature preferred to cold storage).

2) Biodosimetry methods or devices that are:
    a. Minimally invasive (e.g. finger-stick of blood is preferred as opposed to venipuncture);
    b. Capable of identifying and measuring absorbed radiation dose due to internal and/or external radiation exposure;
    c. Able to rapidly and accurately distinguish people who need treatment from those who do not in both a field use (e.g. tent or gymnasium) and/or definitive care setting (e.g. hospital or trauma center)

3) Drugs to remove radioactive materials from the body (decorporation agents)
    a. Should be effective when administered at 24 hours or later after internalization of the isotope;
    b. Ideally able to remove more than one form of radioactivity (e.g. actinides, lanthanides);
    c. Mechanism of action could involve blocking uptake of the radioactivity into sensitive organ compartments by physical means (e.g. inducing coughing to remove inhaled particles via mucociliary clearance).

Research Funding Mechanisms. Since the first grant and cooperative agreement awards were made in 2005, the RNCP has provided important funding to the radiation biology community, as well as to other investigators studying injuries similar to those caused by radiation exposure. This has included researchers in areas including, but not limited to oncology, hematology, pulmonology, dermatology and gastroenterology. It is the multi-disciplinary nature of the program that has enable the program to have many successes. When the program was started, there was no concerted effort to fund the development of these approaches, so there were a number infrastructure updates, as well as recruitment and education efforts that needed to be addressed to ensure a robust research community. From 2005-2016, the RNCP released 22 Funding Opportunity Announcements, and more solicitations come out each year. The RNCP supports a variety of basic research and discovery projects, and has made use of a number of different funding mechanisms to provide research dollars for the academic and industry communities. These have included grants (R01, R21, RC1, R33, R34, R43, and R44), cooperative agreements (U01, U19) and contracts (N01). Generally, the more basic research has been funded with grant awards, the intermediate development of drugs and biodosimetry approaches has utilized cooperative agreements, and the more advanced development has been funded using contracts. The exception has been the RNCP's use of Small Business Innovation Research (SBIR) funding. Using NIH program announcements (PAs) dating back to

2009 (current announcement is PA-15-065), more than 50 awards have been made to small business concerns developing devices and MCMs for radiation injury.

In order to track all the studies that have been done with program funding, a previously-developed database has been substantially modified and updated to be easily searchable, allowing RNCP staff to easily access data on historical MCM and biodosimetry testing within the program. The database contains detailed information on the over 300 candidate MCMs that have been tested to date across each of the RNCP program elements. This database continues to be modified and improved, and currently includes information on evaluations and results, data on product development, and radiation injury sub-syndrome (organ) indication.

The Centers for Medical Countermeasures against Radiation Consortium (CMCRC). The centerpiece of the NIAID funding efforts since 2005 has been the Centers for Medical Countermeasures against Radiation Consortium (CMCRC) program. Initial funding of these cooperative agreements led to the establishment of eight centers. Re-competitions in 2010 and 2015 resulted in awards being made to seven and four centers, respectively. Each of the currently-awarded (2015-2020) CMCRCs has its own scientific areas of expertise and range of projects it supports. For example, the Columbia University CMCRC focuses on the research and development of high-throughput radiation biodosimetry and dose assessment. In addition, Columbia is home to the CMCRC-wide Opportunity Funds Management Core, which oversees the Centers' pilot project and product development initiatives. The University of California—Los Angeles (UCLA) CMCR focuses heavily on screening, identification and *in vivo* testing of mitigators. Home to Product Development and Radiation Dosimetry Cores, the UCLA group provides important expertise to all of the CMCRC. The Pittsburgh CMCR has concentrated on the role of mitochondria and oxidative stress in mediating radiation injury, as well as different modes of radiation-induced cell death the Pittsburgh CMCRC and also houses the Coordinating Consortium Core for the CMCRC, which oversees a number of administrative activities for the consortium. Finally, the center at Duke University is investigating a number of novel MCMs, based on mechanisms of action targeted by radiation exposures. Also highlighted within the Duke Center is the Non-Human Primate (NHP) Core, housed at Wake Forest University. Serving as a "retirement home" for aging, previously-irradiated monkeys and age-matched, unirradiated NHPs, the animals' health status are closely watched and evaluated through periodical tissue sampling and radiological assessments, including x-rays and computed tomography (CT) scans. The NHP Core also maintains a sample bank of more than 3,000 NHP tissues, which are available to both NIAID-funded investigators, as well as outside groups.

The CMCRCs have also identified areas of common interest and/or complementary expertise, leading to ongoing collaborations across the network of CMCRCs. Such collaborations are facilitated by RNCP program officers and have contributed to the sharing and advancement of common goals. In addition to helping establish a sense of shared mission, CMCRC interactions have resulted in a number of scientific collaborations outside of the Centers as well.

Product Development Support Services (PDSS) for Industry. Extensive interactions with companies through the RNCP's Advanced Drug Development Program have added to the portfolio, in terms of potential MCMs. Working in close partnership with industry, the RNCP contributes critical resources, services, and expertise to the discovery and development of MCMs. The objectives are to lower the opportunity costs and reduce the barriers to entry for companies interested in working in this area and to accelerate translational progress toward a mature product with an improved chance of Food and Drug

Administration (FDA) approval, by providing goal-oriented stewardship of promising projects. In many ways, the RNCP functions as a ‘‘virtual pharmaceutical firm,’’ coordinating the early and mid-stage development of a wide array of radiation/nuclear-focused approaches. Through a PDSS contract, the RNCP carries out many activities that can accelerate the development of a drug for a radiation indication. Perhaps most important to all areas for MCM development has been the development, by PDSS contractors, of a number of critical small and large animal radiation injury models for testing MCM effectiveness.

The current contract – awarded in 2016 to SRI, follows on the impressive work of two prior contracts to the University of Maryland's Medical Countermeasures against Radiological Threats (MCART) Consortium. The current and past contracts have provided a number of scientific services to investigators whose products showed promising results, and have resulted in three special issues of Health Physics, outlining the models developed and testing done by MCART. Contract activities have included independent confirmation of product efficacy in well-validated, small and large animal models of GI, hematopoietic, and lung syndromes resulting from radiation exposure; toxicological, pharmacological, and drug candidate synthesis/stability studies to gather data that can assist investigators in their applications for additional sources of funding; pivotal animal-model studies of efficacy; studies conducted under Good Laboratory Practices standards in small and large animal models as required by the U.S. FDA Animal Rule for product licensure; and additional studies to enable companies to advance products toward FDA licensure. More detailed information on this contract can be found elsewhere in this online resource (see Chapter XXXV, authored by Dr. David Cassatt, NIAID).

CONCEPT OF OPERATIONS

Given the nature of the expected radiation public health emergency scenarios, the RNCP has placed certain limitations on the kinds of studies that would be important to the mission of the program. For example, in a mass casualty incident, the following factors must be considered:

Timing of MCM Administration – Since it is anticipated that it will take time for the government to determine the nature of a mass casualty incident, access the site, assess the nature of the injuries sustained (e.g. the dose of radiation received) and mobilizes treatments from the SNS, it is anticipated that few drugs would be available to be provided to the injured within the first 24 hours after the incident. For this reason, the NIAID has elected to focus their funding of biodosimetry and treatment approaches that are not initiated until 24 hours or later after radiation exposure. Furthermore, drugs that require only one or a few treatments could be prioritized over those with complicated dosing regimens.

Route of Administration of the Treatment – This consideration translates into the need for formulations of products and/or improvements to existing products for civilian populations, that can be easily administered in a mass casualty scenario either by first responders or self-administered; (e.g. via oral, subcutaneous, trans-cutaneous, intramuscular or inhalation routes). Although it may be possible for intravenous treatments to be administered, these routes would be more difficult to provide in a field-setting, and might be best considered as a definitive care treatment (to be provided in a hospital setting at a later time point).

Treatment Provided with Incomplete Biodosimetry – Because it may not be possible to precisely know the dose of radiation received, and the degree of biological injury resulting from the exposure, it will be important that the treatments administered are exceedingly safe. There is a distinct possibility that people

who were not adversely affected by the radiation exposure might be provided with drug, so the safety profile of any compound considered for government acquisition must be strong.

Special Populations (Pediatrics, Geriatrics Immunocompromised or Co-Morbidities – Overall, the focus of the program is on testing of MCMs in adult animal models of radiation injury (both males and females); however, it is a specific interest of the program to insure that dosimetry methods are appropriate for all ages and pre-existing conditions. It is also critical that MCMs be safe and efficacious in these same populations. For these reasons, testing of candidate approaches in animal models that are representative of pediatric and/or geriatric human populations is encouraged.

Nature and Complications of Expected Casualties – Because a radiological or nuclear incident could involve explosions and fire, the RNCP also funds work to both develop models of radiation combined injuries (RCI), as well as test the efficacy of MCMs in those models. RCI is defines as radiation exposure concomitant with burn, wound, hemorrhage, infection/sepsis or other physiological trauma. In 2006, the RNCP initiated a collaborative work with the Armed Forces Radiobiology Research Institute (AFRRI) to identify promising MCMs and characterize cytokine profiles in a representative model of RCI. In 2007, to further accelerate work on RCI, the RNCP developed a targeted solicitation and awarded 10 Phase I exploratory/developmental research grants in this area. In addition, the nature of the radiation exposure could include neutron and beta radiation exposures, in addition to gamma, so several aspects of the program involve testing MCMs under these exposure conditions. Finally, given the recent FDA approval of Neupogen® and Neulasta® (see Regulatory section below), it is important to understand the ability of any new and/or existing therapeutic products to enhance efficacy in the presence of other expected medical management standards of care, such as antibiotics and/or growth factors.

Shelf Life and Storage Conditions – Due to the expense and complication involved in stockpiling an MCM, long shelf-lives (>1 year) are preferred, as well as room-temperature storage. This could necessitate the development of a lyophilized formulation of a drug. Although refrigerator, freezer and liquid nitrogen storage may be possible, these are not preferred, given the potential limited access to electricity and the challenges associated with stockpiling. Other government agencies involved in the procurement of MCMs are also implementing vendor-managed inventory programs as a way of solving challenges of drug expiry.

Multi-Utility (Multi-Syndrome/Multi-Organ) – To further leverage the government's investment in a particular MCM or biodosimetry device, the RNCP encourages studies to determine the usefulness of the approach in other CBRN situations: for example, the use of a drug for treatment of both radiation and chemical injuries; or a drug that can successfully improve survival from more than one form of radiation injury (e.g. hematopoietic and GI).

Importance of Other Clinical Indications for MCMs. One of the most important features of the NIAID program is that it has been deliberately constructed to develop products with commercial markets as radiation countermeasures. The strong preference is to work with companies that are aiming at commercial markets; while simultaneously seeking a biodefense indication. The basis for these efforts are twofold. First, MCMs with multi-use potential provide authorities with greater flexibility where stockpiling is concerned, making the development, management, and maintenance of stockpiles more affordable. Second, products with efficacy in treating or mitigating radiation injury in an emergency setting are likely to confer similar benefits and may have application in a cancer setting. Physician familiarity with a drug will also make them more comfortable using it for irradiated victims. For products not currently being tested for such indications, demonstrating efficacy in the emergency setting potentially opens up new (and related) commercial markets.

Thus, the most desirable approaches are those that have another indication already in place, which are then re-purposed for use in a radiation mass-casualty setting.

REGULATORY: LICENSURE CONSIDERATIONS

Translational research for MCMs can be accelerated by addressing regulatory challenges proactively, and this approach has been a central point of the RNCP since its inception. Over the past 12 years, the program has cultivated important connections with the FDA regulatory agencies (Center for Drugs Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices for Radiological Health (CDRH)), in order to improve the communications between the agencies, and thereby increase the speed with which approval of MCMs and biodosimetry devices for radiation injury can be achieved.

FDA Animal Rule. The FDA's regulations concerning the approval of new drugs or biological products when human efficacy studies are neither ethical nor feasible are known as the ''Animal Rule'' (21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products). This path to FDA approval is applicable to MCMs, and it is vitally important that everyone involved in MCM development be aware of and understand these regulations. The Animal Rule states that FDA will rely on evidence from animal studies to provide substantial evidence of effectiveness only when all of the following four criteria are met:

1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;

2. The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;

3. The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and

4. The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

If all of these criteria are met, it is reasonable to expect the effectiveness of the drug in animals to be a reliable indicator of its effectiveness in humans.

The FDA and government funding agencies, along with companies trying to license MCM products, are learning together how to operate in this comparatively new and challenging licensure framework. RNCP staff frequently communicate with investigators about the animal rule and work collaboratively to anticipate and mitigate regulatory challenges, and the RNCP has cosponsored several workshops specifically focused on regulatory issues. In addition, the RNCP and CDER, FDA interface in many informal, scientific forums, where background information on animal models of different radiation injuries are discussed.

Advanced Drug Development Activities. The RNCP funds a number of advanced drug development efforts that are critical elements leading to the submission of an Investigational New Drug Application (IND) to the FDA. Examples of activities funded to date include:

- Efficacy studies to optimize formulation, dose, and dose scheduling;
- Good Laboratory Practice (GLP) pilot and pivotal animal drug efficacy study protocols;
- Drug product current Good Manufacturing Practice (cGMP) manufacturing scale-up and stability studies;
- GLP toxicology and pharmacology safety studies;
- Pharmacokinetic (PK), pharmacodynamic (PD) and absorption, distribution, metabolism, and excretion (ADME) studies;
- GLP analytical method development for efficacy studies and product characterization;
- Preparation of IND packages for FDA submission

In addition to the need for complete animal studies to support animal rule licensure of and MCM by the FDA, human, phase I safety studies are also required. The RNCP does have mechanisms available through NIH program announcements to fund both clinical trial planning activities (PAR-16-272 (R34); https://grants.nih.gov/grants/guide/pa-files/PAR-16-272.html) and clinical trial implementation (PA-16-269 (R01); https://grants.nih.gov/grants/guide/pa-files/PAR-16-269.html).

The RNCP has also supported development and regulatory review of animal models and protocols to test MCMs through submission to the FDA's Animal Model Qualification Program (AMQP - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284078.htm). Once FDA has indicated that a given model is suitable in a specific instance, descriptions of the model can be made available, removing the major burden of developing these models and protocols from our corporate partners. The RNCP has submitted a nonhuman primate model of hematopoietic acute radiation syndrome for FDA consideration through this process.

In addition, companies can receive, based on priority and available resources, expert regulatory support and guidance from NIAID/NIH staff within the DAIT Office of Regulatory Affairs (ORA). ORA staff have relevant, in-depth knowledge and firsthand experience in guiding projects through the appropriate FDA pathways, including Animal Rule. To date, several RNCP corporate partners have received such assistance to help develop their compounds for the radiation indication.

Recent RNCP Regulatory Successes – Working closely with the ORA, RNCP staff and their funded contractors (MCART) were instrumental in the 2015 label-extensions granted to Amgen by the FDA for the use of Neupogen® (filgrastim) and Neulasta® (pegfilgrastim) to treat casualties in the wake of a radiological or nuclear incident. These approvals have paved the way for use of these already-stockpiled drugs in the wake of a radiological or nuclear incident, without the need for an Emergency Use Authorization (EUA), and has elevated their use to an expected standard of care in a mass casualty, radiation public health emergency. This approval by the FDA was based on large animal efficacy protocols supported by NIAID funding. In those GLP studies, both growth factor-based drugs improved survival when administered 24 hours after radiation exposure in NHPs. In addition, based on pre-clinical safety and efficacy studies in rodents that were funded by the NIAID, the FDA has cleared an IND for a company that plans to carry out human safety and pharmacokinetic studies on a novel, oral radionuclide decorporation agent. This drug, known as Hydroxypyridinone (HOPO) binds to a greater range of internalized radionuclides than existing stockpiled agents. In addition, its ability to remove radionuclide contamination appears to be superior to what is already available, and its route of administration (oral as opposed to intravenous for existing drug) allows for greater ease of use in a mass casualty situation. The oral formulation is also more appropriate for use in pediatric and geriatric populations. The RNCP and

ORA continue to work with other groups that have had successfully interactions with the FDA – further increasing the probability of more drug licensures for a radiation indication in the future.

COLLABORATIONS

The RNCP staff works closely with agencies and institutions across the U.S. Government, foreign governments, and non-governmental agencies (Figure 2).

NIH-Wide Activities have included shared funding activities and other interactions with:

- National Cancer Institute (NCI) – Since 2005, past and current funding of intramural (bench scientist) NCI investigators have focused on specific research, ranging from identification, characterization, and validation of safe and effective radiation/nuclear medical countermeasures, development of biology-based diagnostic assays or biomarkers to assess cellular and tissue damage following exposure to ionizing radiation and addressing other scientific areas with strong programmatic relevance, such as radiation epidemiology and radionuclide decorporation. The RNCP has also cultivated excellent collaborations with NCI extramural program staff in the Radiation Research Program (RRP).
- National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) – co-funding of the Intestinal Stem Cell Consortium (ISCC) since 2009– the mission of this consortium is to advance the understanding of intestinal epithelial stem cell biology during development, homeostasis, injury (including radiation exposure), regeneration and disease. The RNCP provides support for one project and part of the coordinating center for the program, as well as pilot project funds.
- National Institute on Aging (NIA) – past and current interactions have included cooperating on projects to benefit both Institutes' goals of advancing the study of immune-senescence from the natural process of aging and radiation exposure and its amelioration in prevention and intervention therapies. Past RNCP-funded projects have focused on how ionizing radiation and natural aging affect a person's ability to respond to vaccination and the ability of the immune system to respond to vaccination and cause inflammation, which is a hallmark of immune aging.
- National Heart Lung and Blood Institute (NHLBI) - While fibrogenesis is an essential process in normal wound healing, aberrant and relentless collagen deposition in vital organs such as heart, lung, kidney, and bone marrow can lead to debilitating symptoms, organ failure, and injuries from insults such as ionizing radiation. Together with the NHLBI, the RNCP will fund studies to look at the development of fibrosis in different organ systems following radiation exposure.

HHS-Wide Activities have included constant and successful interactions with other sister agencies:

- Biomedical Advanced Research and Development Authority (BARDA) - The RNCP and BARDA collaborate closely to speed the development process. For example, both agencies participate in ''tech watch'' meetings with academic or corporate investigators to learn about compounds under development and provide feedback related to government requirements. Both groups assist one another in policy development, program evaluation, and the technical review of new proposals. In several cases, NIAID and BARDA have also co-funded research awards. As these examples illustrate, the RNCP and BARDA have built close links on several different levels, in both the MCM and biodosimetry arenas, which highlights their shared mission. Through these collaborations, BARDA learns about promising products early in the development pipeline and NIAID learns about BARDA's needs and requirements. These links help to prepare our industry partners for the transition of a project from one federal agency to another. For example, on a relatively limited budget, 17 investigators, groups, or companies that received

critical seed funding or other support from the radiation countermeasures program have gone on to receive funding from BARDA for further development of specific products. Finally, the RNCP has previously co-sponsored a meeting with BARDA to bring together funded investigators from both programs. This meeting provided a forum for researchers and companies to share best practices in terms of moving drugs forward in the licensure process.

- The Assistant Secretary of Preparedness and Response (ASPR) – interactions have been primarily with staff in Division of Medical Countermeasures Strategy and Requirements (MCSR). MCSR leads the civilian MCM requirements process, which recommends approaches needed to mitigate radiation threats and determines stockpiling goals by assessing what will be needed and what can be effectively utilized in an emergency. The RNCP has worked with MCSR to develop Product-Specific Requirements (PSRs) for radiation casualty care.

- FDA – Interactions with the FDA have included both informal scientific research forums, as well as attendance at formal pre-Investigational New Drug (pIND) meetings, at the invitation of groups and companies funded by the NIAID. In addition, as mentioned in the Regulatory sections above, the RNCP has been working with the FDA's AMQP group on qualification of an NHP model for hematopoietic ARS. Recently, the RNCP has initiated funding for FDA bench scientists, who are engaged in research that is relevant to the NIAID mission.

- Centers for Disease Control (CDC) – The HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) identified the CDC as the organization with the responsibility to develop and maintain bioassays capable of determining the levels of exposure and/or internal contamination with radionuclides. CDC has developed capabilities to measure levels of internal contamination with a variety of radionuclides in urine samples. Interactions with the CDC have included serving together on government-wide integrated project teams (IPTs) as coordination of funding on radionuclide assays awarded by the NIAID.

Other Government, Non-HHS Interactions have involved a number of different agencies and non-government groups:

- Department of Defense (DoD) - DoD interactions have included consultations with other defense agencies that have funded radiation MCM research and development. These have included the Joint Program Executive Office (JPEO), the Defense Threat Reductions Agency (DTRA), and the Defense Advances Research Project Agency (DARPA). However, the most involved and long-standing RNCP collaboration with the DoD has been with the Armed Forces Radiobiology Research Institute (AFRRI).

    - AFRRI – Established in 2005, the Inter-Agency Agreement (IAA) between the NIAID and AFRRI funds research in several areas related to the challenges encountered following radiological or nuclear events. These have included: 1) screening of MCMs to prevent, mitigate/ treat radiation injuries; 2) automation of the cytogenetics dicentric assay; 3) development of animal models, study of mechanisms, and screening of MCMs for radiation combined injury; 4) development of animal models, study of mechanisms, and screening of MCMs for gamma/neutron mixed field injuries; and 5) development of adult and pediatric Gottingen minipigs as an ARS model. To date, over 100 MCMs have been screen by AFRRI utilizing NIAID funding.

- National Aeronautics and Space Administration (NASA) – although formal interactions are currently being negotiated directly with NASA, informal collaborations between the NIAID and NASA have been ongoing since 2005. NASA established the National Space Biomedical Research Institute (NSBRI) as a non-profit scientific partnership to engage academic, industrial and government researchers and educators and the resources of the nation's leading biomedical research institutions to provide solutions to reduce the significant health risks associated with human space travel and long-duration spaceflight. NSBRI has identified the development of effective MCMs against radiation as a programmatic priority. In recognition of their overlapping missions, the RNCP and NSBRI signed a Memorandum of Understanding (MOU) in 2007 that is still in effect today, which outlines research areas of mutual interest. This MOU states the intention of both institutions to communicate openly and coordinate research in these common interest areas. Although to date, budget limitations have prevented the development of joint programs, RNCP and NSBRI program managers have assisted each other in the review of grants and contracts and participate in each other's program meetings.

Interactions with Non-Government Domestic Organizations, although limited in scope, have been an important part of the RNCP strategy to advance the science on understanding of radiation injuries.

- Radiation Injury Treatment Network (RITN) – The RITN is a cooperative effort of the National Marrow Donor Program and the American Society for Blood and Marrow Transplantations. Their goals are to educated practitioners about their potential involvement in the response to a radiation incident, in providing expertise and treatment to injured patients. The RNCP has coordinated with the RITN since 2010, and most recently, has co-sponsored several workshops that are of interest to both groups. In 2015, meetings were co-sponsored with RITN on Medical Management of Radiation Casualties, and Late Effects of Radiation Injury

- National Academy of Sciences (NAS) – Since 2008, the RNCP has been a player in the planning and implementation of the Annual Beebe Scientific Research Symposiums. Providing both funding as well as expertise serving on organizing committees, the RNCP's role has been an important one in advancing the science and mission of the NAS.

International Collaborations - The RNCP is also engaged in a number of international activities.

- Global Health Security Initiative (GHSI) - The GHSI provides a forum for countries to discuss and coordinate efforts to prepare for and respond to the threats of CBRN terrorism and pandemic influenza. The GHSI was formed in October 2001 and includes Canada, the European Union, France, Germany, Italy, Japan, Mexico, the United Kingdom, and the United States, with WHO serving as an expert advisor. RNCP staff participate in all WG meetings and have given presentations about RNCP activities.

- World Health Organization's Radiation Emergency Medical Preparedness Assistance Network (WHO-REMPAN) - Established in 1987 to fulfill WHO's responsibility under the two international conventions on Early Notification and Assistance. RNCP's participation meetings since 2006, has allowed the program to increase its profile internationally, enabled networking between RNCP program managers and colleagues and peers abroad, and provided an international forum to communicate program priorities. The RNCP provides financial support for Biennial Meeting and expert consultations in Geneva on radiation MCM stockpile development and the harmonization of clinical treatment protocols for patients with ARS.

- Radiation Effects Research Foundation (RERF) in Hiroshima, Japan – RERF is a binational Japan–U.S. scientific organization dedicated to studying the health effects of atomic bomb radiation for peaceful purposes. RERF's long-term follow-up of atomic bomb survivors provides unparalleled opportunities to study the effects of atomic bomb radiation on human populations. RNCP financial support of the RERF has consisted of contract funding between the RERF and U. S. domestic universities to explore atomic bomb survivors who are being tracked through the RERF Lifespan Study. Specifically, studies have focused on the immune responses of these survivor populations to influenza vaccinations.

- Institut de Radioprotection et de Sûreté Nucléaire (IRSN) – Having interacted with the IRSN, based outside of Paris, France since 2008, in 2014, the NIAID mutually developed and signed a Statement of Intent to Collaborate with the organization. Outlined in the document is the desire to strengthen and develop research cooperation in the area of radiation/nuclear defense. This includes hematopoietic- and GI-ARS, as well as damage to the skin as radiological burn and combined injuries such as thermal burn and/or other wounds. Also of interest are studies directed toward determining late effects of radiation injury and research into the identification of biomarkers of radiation damage, and the development of assays and devices to determine radiation dose received by an exposed individual (in order to triage large populations of potentially-exposed citizens). The RNCP has followed up with the IRSN several times since the agreement was signed – most notably co-sponsoring a European meeting on the use of cellular therapies to treat radiation injury.

- Institute of Nuclear Medicine and Allied Sciences and the Bhabha Atomic Research Center in India – RNCP staff have served as members of a delegation to Delhi, India to participate in the Indo-U.S. Workshop "Medical Countermeasures for Radiation Injury: Current and Evolving Technologies" and to meet with Indian scientists, academicians, and policy makers. This meeting resulted in publication of a special issue of the Indian Journal of Radiation Research in 2009.

SCIENTIFIC OUTREACH

Over the years, the NIAID has held more than 35 scientific meetings, in order to identify research gaps in radiation studies, and share findings from its funded investigators. Topic areas have included, but are not limited to biodosimetry and radiation dosimetry, MCMs for immune reconstitution, platelet regeneration, lung, GI and RCI, radiation-induced vascular injury and immunosenescence, special populations, medical management, and late effects. Annual update meetings have also been held for the CMCRC and U01 funded programs, as well as conferences to bring together FDA scientists and groups seeking licensure. These meetings, held both at the NIAID offices, as well as locations across the U.S., have featured data presentations from leading investigators in the field, and have been attended by researchers, government program partners and companies developing approaches with importance for the RNCP mission space. Many of these meetings resulted in published reports, and RNCP scientists have been instrumental in the publication of other important manuscripts, ranging from policy papers and program overviews to original research (See RNCP Staff Publications below).

In addition, since 2005, the RNCP has provided financial support to more than 25 meetings and conferences. These include but are not limited to the sponsoring symposia, poster session and young investigator travel to meetings such as the Radiation Research Society (RRS), European Radiation Research Society (ERRS), the National Academy of Sciences Beebe Symposiums, International Congress

on Radiation Research (ICRR), Gordon Research Conferences, the Environmental Mutagen Society, the American Statistical Association, and BioDosEPR Meetings.

In summary, the RNCP has made substantial progress since its inception in 2004. The past 12+ years have seen over 300 MCMs tested, interactions with nearly 200 companies, transition of MCMs and biodosimetry approaches to advanced funding, improvements to radiation infrastructure – both in terms of facilities and trained investigators, and more than 20 funding opportunities made available for the research community. The future of the RNCP and the science that it supports continues to look hopeful, as government, academic and industry partners continue to work together to advance research of relevance to the needs and requirements of a radiation incident medical response.

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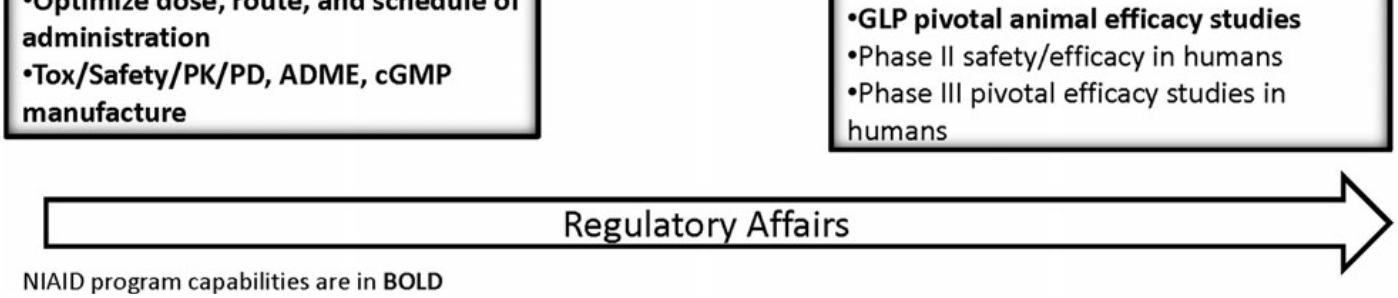

Regulatory Affairs

NIAID program capabilities are in **BOLD**

International Collaborations
Global Health Security Initiative (GHSI)
REMPAN/WHO
International Symposia
Institut de Radioprotection et de
Sûreté Nucléaire (IRSN)

Contracts
Product Development Support &
Animal Model Development
Oral Forms of DTPA
Radiation Effects Research Foundation (RERF)
GI, Lung and Platelet MCMs

Figure 2: A Sampling of REAC/TS Collaborative Efforts with Other Organizations