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NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases





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In 2004, the U.S. Department of Health and Human Services tasked the National Institute of Allergy and Infectious Diseases (NIAID) to develop a strategic plan and research agenda to guide all activities of the National Institutes of Health (NIH) to develop medical countermeasures against possible terrorist attacks involving radioactive materials. Prior to this, no Federal agency had the mission to develop such products for civilian populations. **The NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats** is the subject of the present report and builds upon and extends NIAID's activities in the biodefense arena.

Currently, relatively few medical treatments are available to counter radiological and nuclear threats, and most of those in development will need extensive preclinical testing before they can be evaluated for licensure. Radiological and nuclear threats to the nation are complex, encompassing the detonation of conventional explosives combined with radioactive materials ("dirty bombs"), placement of radioactive sources in public locations, contamination of food and water supplies, attacks on nuclear reactors or sites where radioactive materials are stored, or, in a worst case scenario, the detonation of a nuclear explosive device. Notably, only a small number of radiation countermeasures have been entered into the Strategic National Stockpile (SNS), the purpose of which is to facilitate emergency deployment on a national scale. Many more such agents are needed, based on the range of options that could be employed by terrorists, the need for urgent intervention following radiation exposure, and the medical complexities of acute and chronic radiation injury.

In developing this Strategic Plan and Research Agenda, NIAID engaged experts from other Federal agencies, academia, and industry. The resulting plan builds extensively upon prior and ongoing efforts of the NIH and other Federal agencies, including the Food and Drug Administration, the Centers for Disease Control and Prevention, the Department of Defense Armed Forces Radiobiology Research Institute, and the Department of Energy-affiliated National Laboratories.

Funding for this important program is provided through a special Congressional appropriation to the Office of Public Health Emergency Preparedness in the Department of Health and Human Services and is not part of the annual NIH budget. Depending on progress toward specific milestones and future availability of funds, it is likely that this document will be reviewed periodically and modified as necessary.

Elias A. Zerhouni, M.D.
Director, National Institutes of Health

Anthony S. Fauci, M.D.
Director, National Institute of Allergy and Infectious Diseases
National Institutes of Health

INTRODUCTION

Over the past decade, and especially since September 11, 2001, the growing threat of terrorism has become a primary national security priority. There has also been increased awareness that terrorists might employ unconventional tactics and weapons, including weapons of mass destruction. Indeed, the 1995 attack on the Tokyo subway system with Sarin involved a chemical weapon, and the 2001 attacks in New York, Washington, and Florida with a highly lethal preparation of anthrax spores delivered through the mail involved a biological weapon. The number of known terrorist organizations with a global reach and the increased rate of proliferation and transfer of technical information through the Internet raise the possibility that more attacks with chemical, biological, radiological, or even nuclear weapons may occur in the years to come.

Several terrorist threat scenarios could result in segments of the population being exposed to ionizing radiation. These include: contamination of food or water with radioactive material, placement of radiation sources in public locations, detonation of a radiological dispersal device (often referred to as an RDD or a “dirty bomb”) that spreads radioactive material over a populated area, and attacks on nuclear power plants or high-level nuclear waste storage facilities. The worst scenario would be the detonation of a nuclear explosive device which, in addition to causing enormous destruction from blast and heat, would produce an intense burst of gamma radiation and large quantities of radioactive “fallout.”

To respond to these threats, the Federal government is committed to increasing the availability of medical countermeasures that could be used in the aftermath of an attack involving the release of radioactive material. The mission of the National Institutes of Health (NIH) is to conduct basic and translational biomedical research to improve public health. Within NIH, the National Institute of Allergy and Infectious Diseases (NIAID) is the lead institute for the development of medical countermeasures against infectious agents that might be used in a terrorist attack and for research on immune homeostasis and immune reconstitution. For these reasons, the Department of Health and Human Services (DHHS) has tasked NIH, and NIAID, in particular, with developing a robust research program to accelerate the development and deployment of new medical countermeasures for radiation exposure.

To guide the research program, NIAID has developed the **NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats**, presented here. This document is limited to research that will lead to new and effective medical countermeasures to assess, diagnose, and treat civilians exposed to radiation and to mitigate the harmful effects of such exposure to the greatest extent possible. Issues such as remediation methods and environmental detection technologies will be addressed by other agencies, including the Department of Defense (DOD) and the Department of Homeland Security (DHS).

The Plan and Agenda are each divided into four sections: a) bioassays and tools for biodosimetry; b) basic and translational research on the mechanisms of radiation injury, repair, and restoration leading to the identification and characterization of new therapeutics; c) immediate product development of promising therapies; and d) infrastructure to support the necessary research. This document is intended to unify and strengthen the research community focused on these areas, promote increased collaboration, and facilitate transition from research to product development. NIH will work closely with DHHS to prioritize the research and development activities in this ambitious agenda within the resources available and as one component of the larger national biodefense research agenda.

Scientific Background

Radioactivity and Radiation. The number of protons in the nucleus of a given element is always the same; a carbon atom, for example, always contains 6 protons. Individual atoms of a given element, though, can have different atomic masses because they contain different numbers of neutrons; atoms of a single element with different atomic masses are called isotopes. Most isotopes are stable, and remain in one form virtually indefinitely. Radioactive isotopes, however, are unstable and more easily break down into other elements.

When a radioactive atom decays, it releases radiation. This radiation can be in the form of electromagnetic radiation, typically high-energy x-rays or even higher-energy gamma rays, or it can be in the form of particles, typically either alpha particles (composed of two neutrons and two protons) or beta particles (an electron or positron). Neutrons, which are uncharged particles, are produced in the decay of very heavy radioactive isotopes, such as uranium-235.

Radiation released from radioactive material is *ionizing*, which means that it can strip electrons from compounds with which it interacts, including living tissue. The more atoms in a given mass of material that decay each second, the higher the material's radioactivity; the unit of radioactivity is the Curie, equivalent to 37 billion atomic disintegrations per second.

Radiation Dose. Ionizing radiation can damage living tissue with which it interacts, especially by disrupting cellular DNA. Radiation dose is measured in terms of how much energy is absorbed per kilogram of material, given by the scientific unit called the Gray (Gy). The equivalent dose includes an adjustment of the absorbed dose to reflect differences in the relative harm different kinds of radiation do to biological tissue. Alpha particles, for example, are weighted by a factor of 20 over gamma rays. Equivalent dose is measured in the unit called the Sievert (Sv). A third dose measurement, called the effective dose, is further adjusted based on the sensitivity of the specific tissue that received the radiation; effective dose is also given in Sieverts. Older terms corresponding to the Gray and the Sievert are the RAD and the REM, respectively; 100 RAD equals 1 Gray and 100 REM equals 1 Sievert.

Many factors affect the extent of injury a person might receive from exposure to a radioactive material, such as the type of radiation and whether the radiation is localized to a specific part of the body. The length of time over which the dose is received is also significant. Exposure to a large amount of radiation over a short time is generally more harmful than exposure to a smaller amount over a longer time, even if the total dose is the same.

The physical state of the material can be significant as well. Because alpha particles cannot penetrate clothing, the outermost layer of dead skin, or a few inches of air, alpha-emitting radioactive materials do little damage if they remain outside the body. If these materials are ingested or inhaled, or enter through a wound, they can quickly deliver a highly significant dose of radiation. Of note, a finely powdered radioactive material that is readily inhaled or ingested, or spread over a wide area of skin can be far more dangerous than if delivered in a form that results in only a localized exposure. X-ray, gamma, and neutron radiation readily penetrate tissue and the dose at a given depth depends on the energy of the radiation and length of exposure. Finally, some radioactive elements tend to concentrate in certain tissues and can be difficult to remove; radioactive strontium, for example, concentrates in bone and radioactive iodine collects in the thyroid gland.

Health Effects of Ionizing Radiation. The effects of external radiation on the body may appear within minutes or develop many years after exposure; higher doses produce symptoms more quickly. In the case of whole-body exposure to high doses of radiation, doses greater than one Gray (1 Gy) can result in early, transient nausea and vomiting. At doses between approximately 1 Gy and 6 Gy, damage to the hematopoietic system will result in immunosuppression and infection, and bleeding and anemia will begin weeks after exposure. Without appropriate therapy, death may result within 60 days. Appropriate medical care could enable the majority of patients to survive. At doses higher than 6 Gy, significant damage to the gastrointestinal tract might result in prolonged severe nausea, vomiting, diarrhea, ulceration of the intestinal mucosa, and systemic infection leading to sepsis. Death may occur within the first two weeks and most victims will die within 60 days. At very high doses of more than 20 Gy the central nervous and cardiovascular systems will be acutely damaged and no known medical interventions can prevent death, which may occur within two days. Doses of radiation lower than approximately 1 Gy would produce no short-term effects, although symptoms may appear within weeks or months of exposure. Very low doses are unlikely to produce any clinically important symptoms other than late-presenting symptoms related to an increased risk of cancer.

Radiological Threat Scenarios. Terrorists might use radiation and radioactive materials in an attack in many different ways, with outcomes that vary widely in severity. Terrorists could conceal a gamma or x-ray emitter in a public place to expose people to radiation, or place radioactive materials in food or water supplies. However, these actions would be unlikely to cause large numbers of medically significant exposures. Explosion of an RDD would spread

radioactive material over a wide area. The threat from such a device would depend on the material used; in most cases, it is believed that few people would receive a high dose of radiation, although many people could be contaminated internally or externally. Terrorists might also attempt to attack a nuclear reactor or high-level waste repository in order to release radioactive material and contaminate a large geographic area.

By far the worst scenario would be the detonation of a nuclear explosive device. To accomplish such an act, terrorists would have to obtain an already manufactured military weapon or enough fissile material—either plutonium or highly enriched uranium—to make an “improvised nuclear device.” A nuclear explosion releases heat energy sufficient to destroy large portions of a city plus an immediate burst of gamma radiation; highly radioactive products of the fission reaction would also spread over a large geographic area as “fallout” that would continue to expose survivors.

STRATEGIC PLAN

Because threat scenarios involving radiation and radioactive materials vary, both in severity and in the kind of radiation involved, not all threats can be addressed simultaneously. Thus, the approach to the strategic planning process used to develop this document has been to identify the critical gaps in knowledge and capabilities, and then to set goals for the development of medical countermeasures that could be broadly applied in many situations.

Radiobiology research has been undertaken by a variety of Federal agencies. The Department of Energy (DOE) has a limited research effort focused on low-dose radiation. The National Aeronautics and Space Administration (NASA) supports research on radiation exposure at high altitudes and during space travel. The Armed Forces Radiobiology Research Institute (AFRRI), part of the DOD, supports a research and development program for medical countermeasures for radiological and nuclear threats to military forces. NIAID conducts a great deal of research on immunology, including research with adult bone marrow stem cells, transplantation, and immune reconstitution. This research is very relevant because ionizing radiation can cause immunosuppression, and hematopoietic cells are easily damaged by radiation. The National Cancer Institute (NCI) maintains an active radiation oncology program, and thus has extensive clinical expertise in radiobiology. However, there has been no program within a Federal civilian research agency dedicated to the development of medical countermeasures to be used by civilians in the event of exposure to radiation.

NIH, primarily through NIAID, has invested heavily over the past three years in research and development programs for new medical countermeasures against infectious agents and toxins. In late 2001, NIAID began a comprehensive strategic planning process to guide the NIH biodefense research program. After extensive discussions with researchers from academia, industry, and other Federal agencies, NIH developed three key documents to guide its biodefense research program: the **NIAID Strategic Plan for Biodefense Research**, the **NIAID Research Agenda for Category A Agents** (covering agents that pose the gravest threat to human health, such as those that cause smallpox, anthrax, botulism, and plague), and the **NIAID Research Agenda for Category B and C Agents** (for agents whose biological properties make them more difficult to deploy or less likely to cause widespread harm than Category A agents). The present report, **NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats**, builds upon a similar planning process.

■ Strategic Planning Process

In 2004, the HHS Office of Public Health Emergency Preparedness charged NIH with designing and implementing a national research program for the development of medical countermeasures appropriate for civilian use that can be used against radiological and nuclear

attacks. Based on its research mission spanning immune homeostasis and infectious diseases, and its recent experience with rapidly planning and expanding the biodefense research program, NIAID was given the role of coordinating the overall NIH effort and ensuring participation of other NIH Institutes and Centers.

Meetings convened in recent years by the White House Office of Science and Technology Policy (OSTP), the Homeland Security Council, the Radiological/Nuclear Threat Countermeasures Working Group, NIAID, and NCI identified deficiencies in the knowledge base related to radiological injury in humans and in the availability of effective medical countermeasures for civilians; these meetings include:

- Biodosimetry: Current and Evolving Technologies (NIAID, February 2005)
- Animal Models of Radiation Injury, Protection, and Therapy (NIAID, May 2004)
- Hematopoietic Stem Cell Expansion and Immune Reconstitution (NIAID, May 2004)
- Models and Procedures for Evaluating Radioprotectors (NIAID, May 2003)
- Radiobiology Research – Expert Panel Review (NIAID, December 2003)
- Radiological/Nuclear Threat Countermeasures Working Group (OSTP/Homeland Security Council, 2003)
- Making the Nation Safer: The Role of Science and Technology in Countering Terrorism (National Academy of Sciences, June 2002)
- Molecular and Cellular Biology of Moderate Dose Radiation and Potential Mechanisms of Radiation Protection (NCI, December 2001)
- Modifying Normal Tissue Damage Post-Irradiation (NCI, September 2000)

Based on information assembled from these meetings and other sources, the NIAID Office of Biodefense Research and the NIAID Division of Allergy, Immunology and Transplantation jointly prepared a draft strategic plan with input from NCI. On October 14, 2004, NIAID convened a meeting of the “Blue Ribbon Panel on the NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats.” Panelists with expertise in radiobiology and the health effects of ionizing radiation were selected from academic institutions and research laboratories. Representatives of the DHHS, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), NIAID, NCI, the National Heart, Lung and Blood Institute, the National Institute of Environmental Health Sciences, DOD, DOE, DHS, NASA, and the OSTP also participated in the meeting. The panel was asked to provide NIH with specific advice and recommendations on immediate and long-term research goals in each of four major areas set forth in the draft plan:

- I. Basic and translational research
- II. Radiation biodosimetry
- III. Focused product development for radiological medical countermeasures
- IV. Infrastructure for research and product development

Panelists discussed the current state of science in each of the four areas listed, identified gaps in knowledge critical for the development of radiological and nuclear medical countermeasures, and identified shortfalls in radiobiology research. Comments from panel members at the meeting were then incorporated into the final version of the document.

The resulting research strategy is limited in scope to medical countermeasures that could be used with civilians exposed to ionizing radiation or radioactive materials. It does not address environmental/ambient radiation detector systems, physical protection, radiological surveillance, environmental contamination and remediation, or patient management, nor it address the psychological impact or public communications problems that would follow a radiological or nuclear incident; these issues will be addressed separately by the DHS, DOD, the DHHS Office of Public Health Emergency Preparedness, and other Federal agencies.

The ultimate purpose of the plan is to organize and coordinate NIH efforts to accelerate development of new diagnostic tests and patient assessment tools, as well as drugs and therapies that can facilitate recovery following exposure to ionizing radiation. Drugs that protect only if given prior to radiation exposure also fall within the scope of the program, although such agents would be used primarily by first responders and remediation workers. The Strategic Plan is intended to be a flexible, collaborative, and comprehensive guide for the NIH research and product development program focused on medical therapies and diagnostics to counter radiation injury; the accompanying Research Agenda describes the mechanisms by which NIH intends to meet these goals.

I. Basic and translational research

Basic and translational research will improve our understanding of the mechanisms of radiation injury and will accelerate the discovery, development, testing, and licensure of promising products to prevent and treat radiation exposure.

Tissues that are most sensitive to the acute effects of high doses of whole-body radiation are those with rapid cellular turnover, such as bone marrow, the lining of the gastrointestinal tract, and skin. Radiation-induced pulmonary injury can also be clinically significant; experience from Chernobyl and elsewhere has shown that individuals who survive initial hematopoietic and gastrointestinal injury may develop therapy-resistant pulmonary failure 2–3 months after exposure. The kidney and liver are also radiation-sensitive, but clinically important injury to these organs is generally not apparent until months to years after exposure. Radiation-induced carcinogenesis is not organ specific, although the incidence varies somewhat from organ to organ; hematopoietic tissue, thyroid, and breast are common sites of radiation-induced malignancies.

The health effects of low level radiation exposure that does not result in clinical symptoms are not well understood, in part because such effects are difficult to measure. It is clear, however,

that low level exposure may cause serious disorders many years later, including cancer, chronic renal failure, pneumonitis, and fibrosis.

To identify and develop products that can serve as medical countermeasures to radiation exposure, an increased understanding of the mechanisms by which radiation causes injury is needed. Research areas of interest include the mechanisms of radiation injury at the systemic, organ, cell, and molecular levels, with particular focus on the hematopoietic, gastrointestinal, immune, pulmonary, renal, reproductive, and nervous systems, and skin; mechanisms of secondary responses that mediate, exacerbate, or ameliorate damage; as well as identification and characterization of methods to minimize short- and long-term effects.

Research and development activities in this area will be coordinated within the NIH, and with appropriate Federal agencies, academic research institutions, and private industry. A cooperative network of research centers will be established to ensure efficient and comprehensive communications and synergistic research and development efforts.

NIH Goals for Basic and Translational Research

Immediate Goals:

- Understand the effects of different levels of radiation exposure, with special emphasis on the moderate dose range.
- Define the mechanisms of radiation injury, including secondary responses and multi-system injury.
- Determine mechanisms of protection, mitigation, and treatment.
- Identify appropriate hierarchical animal models.

Long-Term Goals:

- Understand radiation injury at the molecular and cellular level, including the role of inflammation, neuroimmune interactions, endothelial injury, and other factors that influence the pathophysiological manifestations of radiation injury.
- Identify new drug candidates and accelerate the transition from candidate to product.
- Continue to support research on long-term effects of radiation exposure, including epidemiological and longitudinal medical studies of individuals exposed to radiation.

II. Radiation biodosimetry

Biodosimetry quantifies radiation exposure, providing the biological information necessary for medical decision making. Because the majority of assessment activities will take place

in an acute care or emergency care setting, methods are urgently needed for rapid dose assessment of a large number of individuals within a short period.

After a terrorist incident involving civilians, medical personnel will have to rapidly identify people who have been exposed to radiation, and assess the type and dose of radiation each person received. They will need to assess uptake of radioactive material by ingestion, inhalation, or contamination of wounds, identify the isotope, and determine where it might be sequestered in the body. With this information in hand, medical authorities will then estimate the likelihood that the exposure would result in serious health consequences, and decide on treatments that might mitigate short- and long-term health effects.

Although specialized technologies are currently available to assess radiation exposure in small numbers of individuals, rapid-screening tools are not yet available to evaluate radiation exposure in larger populations. Research to identify biomarkers of radiation exposure, including those that could be revealed by proteomic and genomic technologies, is under way but has not yet come to fruition. Non-invasive technologies such as dental electron paramagnetic resonance are also promising. Relatively low cost hand-held devices for patient evaluation are urgently needed, as are simple assays suitable for screening and assessment in local hospitals and clinics.

NIH Goals for Biodosimetry

Immediate Goals:

- Support rigorous quality assurance/quality control studies of current leading biodosimetry technologies to validate their use.
- Increase the speed and efficiency of current assays to determine radiation doses received due to internal or external contamination with radioactive material.

Long-term Goals:

- Develop new bioassays that can provide rapid and accurate radiation dose assessments, enabling optimal triage and medical management.
- Develop biodosimetry tools and assays to evaluate radiation-related injury and the recovery process in different physiological systems.
- Develop and validate methods to estimate radiation dose and future risk following exposure to radioactive material by various routes, including inhalation, ingestion, skin contact, or contamination of wounds.

III. Focused product development for radiological medical countermeasures

The development of medical countermeasures capable of preventing or treating radiation injury is the major component of this NIH strategic plan. NIH research on medical countermeasures to radiation exposure will be significantly enhanced by the Project BioShield Act of 2004, which provides incentives and funding mechanisms to develop and make available drugs and vaccines to protect against chemical, biological, radiological, or nuclear attack.

Under most threat scenarios involving civilian exposure to radiation, pharmacological or physical protection will not be possible for primary victims. Protection may be feasible for first responders and remediators entering an area contaminated with radioactive material by administration of radioprotective medications that can limit radiation injury without diminishing performance capabilities.

Because many civilians might be exposed in an attack involving radiation, the development of therapeutic countermeasures to treat civilian victims after radiation exposure has occurred is a high priority. Promising candidate compounds must be moved expeditiously through development, licensure, and stockpiling. Currently, the Strategic National Stockpile (SNS), a national repository of vaccines, antibiotics, antitoxins, chemical antidotes, and other essential materials needed for the medical response to a terrorist attack, includes only a limited number of medications specific for radiation exposure.

Three general categories of products are needed. (1) Radioprotectants, such as scavengers that help prevent injury from radiation-induced free radicals and other reactive species: Many such candidate drugs must be given before radiation exposure to achieve meaningful levels of protection. Radioprotectant drugs may also have a role following internal contamination to reduce the effects of ongoing exposure to ionizing radiation. Prophylactic agents also include compounds that are not directly cytoprotective, but enhance radiation tolerance of critical tissues; such agents might increase cellularity in target cell compartments or increase the expression of mediators that reduce the extent or severity of radiation injury. (2) Radiation mitigators that reduce the potential severity of the injury: This class includes agents that can eliminate radioactive material that has been incorporated into the body and thereby minimize internal radionuclide exposure as well as agents that minimize the adverse health effects of radiation exposure, accelerate tissue recovery, or enhance repair processes. (3) Radiation therapeutics that are given after overt symptoms develop to reduce pathophysiological radiation effects, facilitate tissue recovery or repair, or reverse fibrosis and other late effects.

NIH Goals for Focused Product Development

Immediate Goals:

- Initiate studies under the FDA Animal Efficacy Rule to expand the label indications for licensed products that are effective in preventing or treating radiation injury.
- Facilitate the development of products that are already in the clinical testing stage for other indications and that can prevent or treat radiation injury.
- Support research on promising compounds that are currently in preclinical development.

Long-term Goals

- Identify and develop new drugs to prevent or reduce the severity of radiation-induced damage and to treat irradiation casualties.
- Develop drugs that will prevent long-term consequences, such as mutagenesis or fibrosis.

IV. Infrastructure for research and product development

In order to carry out the research outlined in this Strategic Plan, the development of required expertise, as well as modernization and expansion of the research infrastructure will be necessary. In addition, because human studies on controlled radiation exposure are not feasible, animal studies are a crucial part of product development. Specific requirements include large-animal irradiation and animal husbandry facilities that can safely care for animals during and after radiation exposure; special attention must be given to laboratory worker safety, animal welfare, and radioactive waste disposal in such facilities as well as to the need to meet Good Laboratory Practices (GLP) for licensure studies under the FDA Animal Rule.

NIH Plans for Infrastructure for Research and Product Development

Immediate Goals:

- Establish a collaborative research network focused on the identification and development of medical countermeasures to radiation exposure.
- Promote integration and collaboration in radiobiology research and training among government organizations, academia, and private industry.
- Support centralized facilities for efficient, carefully standardized testing and validation of new products.

Long-term Goals:

- Attract a new generation of scientists in radiobiology research and radiation chemistry through training and mentoring programs.
- Support bioinformatics and specialized technology centers for radiobiology research.

RESEARCH AGENDA

The Strategic Plan sets out long- and short-term goals for each of four areas relevant to the development of medical countermeasures for exposure to radiation and radioactive materials. The Research Agenda is intended to provide additional guidance for how these goals will be achieved. It takes into account research priorities, specific research opportunities, and available funding. As such, the Research Agenda is more likely to be adapted to changing conditions and opportunities than is the Strategic Plan.

The Research Agenda is divided into the same sections as the Strategic Plan. Each discusses the state of the science relating to that section, and outlines some of the steps that will be taken to achieve the goals listed in the Strategic Plan.

I. Basic and translational research

Current Status of Basic and Translational Research

The creation and acquisition of new and effective medical countermeasures for radiation injuries among the civilian population will require basic research to expand the knowledge base, as well as translational research to begin the transformation of fundamental knowledge gained into product development. Fortunately, a significant research base already exists. The DoD has had a longstanding interest in the health effects of ionizing radiation on military personnel, and has sought ways to protect its forces from radiation and radioactive material released by nuclear weapons; however, funding for these research efforts has declined since the end of the Cold War. Several civilian government agencies support longitudinal epidemiologic studies to assess long-term health risks to x-ray technicians exposed to low-dose radiation, civilians exposed to nuclear weapons test fallout, survivors of Hiroshima and Nagasaki, and subpopulations near Chernobyl, Ukraine. These studies will provide essential knowledge for the long-term follow up of individuals who are exposed to radiation as the result of a terrorist incident. NIAID, NCI, and other agencies within DHHS currently support research on the molecular and cellular aspects of low- and moderate-dose radiation exposure. Although this research has focused largely on therapeutic uses of ionizing radiation, the results and programs can be adapted to the development of countermeasures.

Research Agenda for Basic and Translational Research

The NIH will establish a research centers program called Centers for Medical Countermeasures against Radiation that will serve as a network of specialized research institutions working collaboratively to meet the goals of the Strategic Plan in basic and translational research. Examples of research areas to be addressed include:

- Innate and adaptive immune system enhancement and reconstitution.
- Mechanisms of radiation injury and therapy at the systemic, organ, cell, and molecular levels; and identification and verification of potential targets for countermeasures for radiation injury.
- Mechanisms of secondary responses that mediate, exacerbate, or ameliorate damage and disease resulting from external or internal radiation exposure in different tissues.
- Long-term effects, such as cancer and fibrosis.
- New animal models and in vitro assays to test and evaluate promising countermeasures.

II. Radiation biodosimetry

Current Radiation Biodosimetry Technology

In the aftermath of an incident in which a significant number of civilians are exposed to radiation or radioactive materials, health authorities will need to be able to rapidly identify individuals who are contaminated externally with radioactive material, have incorporated radioactive material into their bodies, or have been exposed to medically significant doses of radiation. Detecting radioactive contamination is the easier task, because powerful technologies for detection and quantization of even small amounts of radioactive materials already exist. For example, Geiger counters or doorframe/portal monitors can detect the presence of many radioactive materials and can thus help to identify individuals who must be decontaminated immediately after any necessary medical stabilization of trauma or burn injury. Monitoring of blood or urine samples for radioactivity also can be used to reveal the presence of internalized radioactive material.

Although radioactive material can be detected with instruments, assessment of the dose of radiation a person has already received, such as from gamma radiation released by the detonation of a nuclear device, is more difficult. Radiation exposure can be assessed through clinical history, signs, symptoms, and laboratory tests such as lymphocyte counts and dicentric chromosome assays. These methods are not currently adequate for a mass-casualty scenario as signs and symptoms can be misleading and laboratory tests are time-consuming and expensive.

Research Agenda for Radiation Biodosimetry

NIH plans to pursue the goals in this research area primarily through a research centers program. Examples of research and development areas to be addressed in these centers include:

- Off-the-shelf products, such as computer-run robotic systems to automate current biodosimetry assays.

- New biodosimetry devices and techniques.
- New biomarker assays.

III. Focused research and product development

Current Status of Radiation Protectants and Prophylactic Agents

Some drugs currently available or in pre-licensure clinical trials appear to protect tissue against radiation-induced injury. Amifostine, a free radical scavenger, is the only drug currently licensed as a radioprotectant. Its use is limited to cancer radiation therapy and chemotherapy because in its approved formulation, it is unsuitable for first responders due to incapacitating side effects. Its use in the general population is also untenable because of its side effects, the need for intravenous administration, and the need to administer it one hour prior to radiation exposure. Limited data suggest that lower doses might be useful in reducing the long-term effects of radiation exposure, such as mutagenesis and carcinogenesis. Other potential radioprotectants include Tempol, a drug that is currently in clinical trials as a topical radiation protector to prevent hair loss during cancer radiotherapy; a steroid that enhances survival shortly after radiation exposure in a mouse model; and antioxidants, such as vitamin E analogs, isoflavones, and benzylsulfone analogs.

Cytokines and growth factors, particularly those of the hematopoietic system, can also protect against radiation-induced injury, in part by increasing tissue cellularity and thus ensuring a larger number of surviving cells. Granulocyte-macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) are used to partially reconstitute the immune system in cancer patients after destruction of the bone marrow during cancer treatment, and may be effective both as radioprotectants and radiation-injury mitigators.

Some drugs are known to prevent uptake of specific radioactive isotopes. Potassium iodide (KI), for example, can block radioactive iodine uptake by the thyroid. Radioactive iodine is present in waste from nuclear reactors and in fallout from nuclear weapons, and is used for diagnostic and therapeutic purposes. To be effective, KI must be taken several hours before or shortly after exposure to radioactive iodine; it is only 7 percent as effective when given 24 hours after exposure. KI does not protect against radioactive isotopes other than iodine, and does not remove radioactive iodine once it has entered the thyroid. KI tablets are currently in the SNS and efforts are underway to produce a liquid/oral formulation suitable for young children. Aluminum hydroxide limits the uptake of strontium-90, a radioactive isotope that is also found in radioactive waste and fallout, but it must be given immediately after the radioactive material is internalized in order to be effective.

Still other compounds accelerate excretion of specific radioactive materials. Prussian blue, a pigment recently licensed for use as a radioprotectant under the brand name Radiogardase,

enhances the excretion of cesium and thallium; radioactive cesium is found in spent nuclear fuel and waste, in nuclear fallout, and is widely used for medical purposes.

Chelating agents, such as calcium diethylenetriaminepentaacetate (Ca-DTPA) and zinc diethylenetriaminepentaacetate (Zn-DTPA), promote the excretion of the radioactive transuranic elements such as plutonium, americium, californium, and curium produced by nuclear explosives and nuclear reactors. Ca- and Zn-DTPA are currently in the SNS, but must be administered intravenously and usually require multiple doses, limiting their utility in a mass-casualty setting. In addition, Ca-DTPA is not considered safe for children or pregnant women; the data on Zn-DTPA are insufficient to determine safety in these populations.

Other drugs have shown some ability to help heal radiation-induced injuries. Certain cytokines and growth factors, for example, may facilitate faster recovery of cell populations damaged by radiation; GM-CSF and G-CSF are used to partially reconstitute the hematopoietic and immune systems in cancer patients and others after myeloablation or intensive chemotherapy. G-CSF is included in the SNS, but only for emergency use under an Investigational New Drug (IND) application and with the informed consent requirements as generally applied to investigational agents.

Keratinocyte growth factor facilitates recovery in epithelial tissues and shows promise for use in radiation injury. Radiation-induced damage of the gastrointestinal tract results in breakdown of the epithelial barrier, thus causing diarrhea, inability to properly absorb nutrients, hemorrhage, bacterial translocation, and increased susceptibility to infection. While post-exposure infection and sepsis are major causes of mortality, little information is available regarding the antibiotics most likely to be useful in managing such infections; proper antibiotic selection may be critical in maintaining the appropriate intestinal flora when there is denudation of the mucosa. Compounds that have a trophic effect on the gut epithelium (e.g., growth factors and intestinal peptide hormones), enhance the mucosal immune system (e.g., beta glucan), or minimize epithelial barrier breakdown or the consequences thereof (e.g., octreotide) may also be effective in pre-exposure prophylaxis or post-exposure mitigation. A combination of pentoxifylline and tocopherol has shown early promise in treating radiation fibrosis, as have angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers.

Ideally, products will be easily administered, safe for repeated doses, have a long shelf life, and be inexpensive to manufacture. With the exception of products intended for patients undergoing radiation therapy, efficacy testing of these products cannot be ethically carried out in humans. Therefore, such products will be licensed as radiation countermeasures only after meeting stringent requirements under the FDA animal rule.

Research Agenda for Focused Product Development for Radiological Medical Countermeasures

The NIH will provide support services to facilitate and accelerate product development research conducted by academia, industry, and Federal laboratories. One goal of this support is to enable academic and industry scientists to more quickly bring their products to the acquisition stage under Project Bioshield. Examples of such services include the support of:

- Animal efficacy and toxicity studies, including studies of large animal models.
- Preclinical pharmacokinetics and pharmacodynamics.
- Activity screening and early development of radioprotectant drugs and post-exposure mitigation/treatment regimens.
- Development of new product formulations and limited cGMP manufacture.
- Regulatory services.
- Development of new animal models to provide mechanistic, safety, and efficacy data to support FDA approval of new products for human use.

IV. Infrastructure for research and product development

Current Infrastructure for Radiation Countermeasures Research

AFRRI has served as the lead agency for research in radiation biology for the operational and medical support of the DOD services. The relative importance of radiobiology research waned over the past decade, however, and no Federal agency has ever had primary responsibility for the development of radiation countermeasures for the civilian population, whose needs are significantly different from those of the military. Thus, the current cadre of investigators conducting research into medical countermeasures for radiological injury is small, the infrastructure to support such research is inadequate, and only a few small training programs in the radiological health sciences exist. Moreover, the physical infrastructure and other support (e.g., biostatistical services, GLP-certified facilities) are limited for high-quality basic and translational research and are particularly lacking for development and licensure of experimental dosimetry and radiological countermeasures.

Agenda for Radiation Countermeasure Research Infrastructure Enhancement

The primary mechanism to support infrastructure enhancement will be the Centers for Medical Countermeasures against Radiation program, which will help to expand both physical and human infrastructure devoted to radiation countermeasures research. Examples of support to be provided by the research centers program, as well as other programs in this area, include:

- Training in radiation health-related sciences.
- Assay development projects.
- Animal model development.
- Preclinical testing of promising products (toxicity, pharmacokinetics, efficacy).
- Laboratory renovations and special equipment.

CONCLUSION

The **NIH Strategic Plan and Research Agenda for Medical Countermeasures against Radiological and Nuclear Threats** outlines support for: a) basic and translational research on the mechanisms of radiation injury, repair, and restoration; b) bioassays and tools for radiation biodosimetry; c) focused product development with an immediate emphasis on those products that are currently candidates for Bioshield procurement and on longer-range development of promising radioprotectants, radiation mitigators, and radionuclide eliminators; and d) expanded and enhanced infrastructure necessary to conduct this research and product development agenda. The plan and agenda will strengthen and unify the research community focused on these areas, promote increased collaboration, and facilitate transition from research to product development.

The NIH will work closely with DHHS to periodically update and prioritize the research and development activities in this agenda and to ensure its integration as a key component of the larger national biodefense research agenda.

BLUE RIBBON PANELISTS

S. James Adelstein, MD (CHAIR)

Paul C. Cabot Distinguished Professor of Medical Biophysics
Laboratory for Experimental Nuclear Medicine
Harvard Medical School
Boston, MA

Seymour Abrahamson, PhD

Professor Emeritus of Genetics and Zoology
Department of Zoology
University of Wisconsin - Madison
Madison, WI

Joel S. Bedford, D.Phil.

Professor
Department of Radiological Health Sciences
Colorado State University
Fort Collins, CO

William Bernhard, PhD

Professor of Biochemistry and Biophysics
Department of Biochemistry and Biophysics
University of Rochester School of
Medicine and Dentistry
Rochester, NY

Mark W. Dewhirst, DVM, PhD

Gustavo S. Montana Professor of Radiation Oncology
Professor of Pathology and Biomedical Engineering
Duke University Medical Center
Durham, NC

Ronald E. Goans, MD, PhD, MPH

Senior Medical Consultant
Clinical Associate Professor
MJW Corporation
Tulane University School of Public Health
and Tropical Medicine
Clinton, TN

David J. Grdina, PhD

Professor
Department of Radiology and Cell Oncology
University of Chicago
Chicago, IL

Raymond Guilmette, PhD

Team Leader
Radiation Dose Assessments
Los Alamos National Laboratory
Los Alamos, NM

Frederick T. Harper, PhD

Senior Scientist
High Consequence Assessment and
Technology Department
Sandia National Laboratories, New Mexico
Albuquerque, NM

Martin Hauer-Jensen, MD, PhD

Professor of Surgery and Pathology
Department of Surgery
Arkansas Cancer Research Center
University of Arkansas Medical Sciences
Little Rock, AR

Joshua Lederberg, PhD

Raymond and Beverly Sackler Foundation Scholar
The Rockefeller University
New York, NY
Although unable to attend the Blue Ribbon panel meeting, Dr. Lederberg provided guidance and direction in the development of this strategic plan and research agenda.

Sara Rockwell, PhD

Professor of Therapeutic Radiology and
Pharmacology and
Director, Office of Scientific Affairs
Department of Therapeutic Radiology
Yale University School of Medicine
New Haven, CT

Elizabeth Travis, PhD

Mattie Allen Fair Professor of Cancer Research and
Associate Vice President for Academic Affairs
Experimental Radiation Oncology
UTMD Anderson Cancer Center
Houston, TX

Kenneth W. Turteltaub, PhD

Division Leader
Biodefense Division
Lawrence Livermore National Laboratory
Livermore, CA

Irving Weissman, MD

Professor
Department of Pathology
Stanford University School of Medicine
Stanford, CA

PARTICIPANTS

NON-FEDERAL

Richard Hatchett, MD

Fellow in Clinical Oncology
Division of Clinical Oncology
Department of Medicine
Duke University Medical Center
Durham, NC

FEDERAL/MILITARY

Department of Defense

Colonel David G. Jarrett, MD, FACEP

Director
Armed Forces Radiobiology Research Institute
Department of Defense
Bethesda, MD

William F. Blakely, PhD

Team Leader
Armed Forces Radiobiology Research Institute
Department of Defense
Bethesda, MD

Terry Pellmar, PhD

Scientific Director
Armed Forces Radiobiology Research Institute
Department of Defense
Bethesda, MD

Department of Energy

Noelle Metting, PhD

Senior Radiation Biologist
Office of Science/BER
Department of Energy
Washington, DC

Department of Health and Human Services

Jerome Donlon, MD, PhD

Acting Director
Office of Research and Development Coordination
Office of the Assistant Secretary for
Public Health Emergency Preparedness
Department of Health and Human Services
Washington, DC

John Carney, PhD

Senior Technical Advisor
Office of Research and Development Coordination
Office of the Assistant Secretary for Public Health
Emergency Preparedness
Department of Health and Human Services
Washington, DC

Marissa Miller, DVM, MPH

Senior Advisor
Office of Research and Development Coordination
Office of the Assistant Secretary for Public Health
Emergency Preparedness
Department of Health and Human Services
Washington, DC

William Hummer, MS, MT(ASCP)

Senior Project Officer
Office of Research & Development Coordination
Office of the Assistant Secretary for Public Health
Emergency Preparedness
Department of Health and Human Services
Washington, DC

Centers for Disease Control and Prevention

Armin Ansari, PhD, CHP

Health Physicist
Radiation Studies Branch, EHHE, NCEH
Centers for Disease Control and Prevention
Atlanta, GA

Food and Drug Administration

Larry W. Cress, MD

Medical Officer
Division of Counter-Terrorism,
Center for Drug Evaluation Research
Food and Drug Administration
Rockville, MD

CDR Michael A. Noska, MS

Senior Health Physicist
Radiation Programs Branch Division of
Mammography Quality and Radiation Programs
Center for Devices and Radiological Health Food and
Drug Administration
Rockville, MD

CAPT Mary E. Purucker, MD, PhD

Director
Division of Counter-Terrorism
Center for Drug Evaluation and Research
Food and Drug Administration
Derwood, MD

Alla Shapiro, MD, PhD

Division of Counter-Terrorism
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

Cheryl Turner RN, BS

Regulatory Health Project Manager
Division of Counter-Terrorism
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

***National Institute of Allergy
and Infectious Diseases***

Anthony S. Fauci, MD

Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Jessica Benjamin

Health Specialist
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

David Cassett, PhD

Product Development Specialist
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Christine Czarniecki, PhD

Chief, Regulatory and Industry Affairs
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Patrice M. Holtz, RN, MBA

Chief, Operations and Management
Office of Clinical Applications
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Carole Hudgings, PhD

Office of the Deputy Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Theresa Lawrence, PhD

Acting Director, Office of Policy Analysis
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Jane Lockmuller, MS

Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Priti Mehrotra, PhD

Scientific Review Administrator
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Lori Mulligan, MPH

Biodefense Project Manager
Office of Biodefense Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

M. Faraz Nasser, PharmD, PhD

Program Officer, Basic Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Diane L. Pfeifer, RN

Health Specialist/Nurse Consultant
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Helen Quill, PhD

Chief, Basic Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Narayani Ramakrishnan, PhD

Program Officer
Basic Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Daniel Rotrosen, MD

Director
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Stefani T. Rudnick, PhD

Scientific Review Administrator
Division of Extramural Activities
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Ernest. T. Takafuji, MD, MPH

Assistant Director of Biodefense Research
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Nancy Volkers, MA

Science Writer
Fairfax, Vermont

National Cancer Institute

George A. Alexander, MD

Program Director
Radiation Research Program
National Cancer Institute
National Institutes of Health
Bethesda, MD

C. Norman Coleman, MD

Director
Radiation Oncology Sciences Program
Center for Cancer Research
National Cancer Institute
National Institutes of Health
Bethesda, MD

James A. Deye, PhD

Program Director
Radiation Research Programs,
DCTD,
National Cancer Institute
National Institutes of Health
Bethesda, MD

Martha Linet, MD, MPH

Chief
Radiation Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Rockville, MD

Steven L. Simon, PhD

Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Rockville, MD

Helen B. Stone, PhD

Health Science Administrator
Radiation Research Program
National Cancer Institute
National Institutes of Health
Bethesda, MD

National Heart, Lung, and Blood Institute

Pothur Srinivas, PhD, MPH

Health Science Administrator
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, MD

***National Institute of Environmental
Health Sciences***

Dennis Lang, PhD
Deputy Director
Division of Extramural Research and Training
National Institute of Environmental Health Sciences
National Institutes of Health
Research Triangle Park, NC

Department of Homeland Security


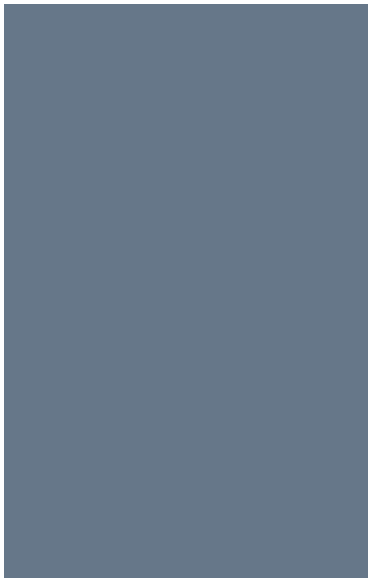
Aileen M. Marty, MD, FACP
Director of Operational Readiness and
Mission Support
Office of WMD Operations & Incident Management
Immediate Office of the Under Secretary
for Science and Technology
Department of Homeland Security
Washington, DC

***National Aeronautics and
Space Administration***

Walter Schimmerling, PhD
Program Scientist for Radiation Protection
NASA Headquarters
White House Executive Office of the President
Washington, DC

Rajeev Venkayya, MD
Director for Health and Biodefense
Homeland Security Council
Executive Office of the President
The White House
Washington, DC

Jason Boehm, PhD
AAAS/NTI Global Security Fellow
Office of Science and Technology Policy
Executive Office of the President
The White House
Washington, DC



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases
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