



NIAID
BIODEFENSE
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NIAID Strategic Plan for Biodefense Research

2007 Update



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

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National Institute of Allergy and Infectious Diseases Strategic Plan for Biodefense Research – 2007 Update

Introduction

Biological weapons in the possession of hostile states or terrorists, as well as naturally occurring emerging and reemerging infectious diseases, are among the greatest security challenges to the United States. Consequently, developing effective medical countermeasures to mitigate illness, suffering, and death resulting from emerging/reemerging diseases or the deployment of biological weapons is central to the United States government's mission to protect and ensure the welfare of its citizens. The National Institute of Allergy and Infectious Diseases (NIAID), NIH, DHHS, has a significant responsibility to support this mission.

The [NIAID Strategic Plan for Biodefense Research](#) was published in 2002 and was followed by two research agendas, one for Category A agents and another for Category B and C priority pathogens. This early plan focused on the importance of basic research, as well as applying that basic research to developing products such as diagnostics, therapeutics and vaccines. It also highlighted specific scientific gaps associated with priority pathogens. The plan and agendas acknowledged the importance of working with partners in the private and public sectors and collaborating with other agencies and organizations to ensure that the fruits of basic research would be rapidly translated into products. The principles on which these documents were based continue to hold true.

NIAID also recognized that developing new medical countermeasures for biodefense and emerging infectious diseases is associated with specific challenges. For example, the basic biology and pathogenesis of threat agents are often not well understood. Many target pathogens must be handled under high level biosafety conditions that require specialized facilities and training. The regulatory path to licensure for biomedical countermeasures often requires demonstrating efficacy in appropriate animal models, many of which have yet to be developed. Finally, many of the target pathogens do not pose public health risks outside of their use as weapons, especially within the United States, thus, to date, there has not been a significant commercial market for products developed to treat diseases caused by these microbes.

This updated Strategic Plan for Biodefense Research builds upon the successes and investments of the first plan and accompanying research agendas; it is consistent with the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy for Chemical, Biological, Radiological and Nuclear Threats, the HHS PHEMCE Implementation Plan, and the Homeland Security Presidential Directive (HSPD)-18, which outline strategies for identifying medical countermeasure requirements and establishing priorities for their research, development, and acquisition. These successes and investments include advances in understanding the biology of specific pathogens and the host's immune response; construction of new biocontainment laboratory facilities; professional training in biosafety and biocontainment; and establishment of critical research resources and infrastructure that support applied science and advanced product development. Although the focus of this updated Strategic Plan continues to be on basic research and its application to product development, there is a shift from the current "one bug-one drug" approach toward a more flexible, broad spectrum approach. This approach involves developing medical countermeasures that are effective against a variety of pathogens and toxins, developing technologies that can be widely applied to improve classes of products, and establishing platforms that can reduce the time and cost of creating new products. The broad spectrum strategy

recognizes both the expanding range of biological threats and the limited resources available to address each individual threat.

NIAID as a Partner in National Biodefense Efforts

NIAID's role in developing medical products to counter bioterrorism and emerging and reemerging infectious diseases is part of a larger national strategy, involving many agencies. The Department of Homeland Security (DHS) is responsible for determining which biological agents pose the highest threat to U.S. national security. The Department of Health and Human Services (HHS) then assesses the potential public health impact of each of the highest priority threats and establishes medical countermeasure requirements for each agent. Overall responsibility for coordinating research, development, acquisition, storage, maintenance, deployment, and guidance for using biodefense products also rests with HHS. The recently established Biomedical Advanced Research and Development Authority (BARDA), operating within HHS, has specific responsibility to facilitate collaboration between U.S. government agencies, relevant biopharmaceutical companies, and academic researchers; support advanced research and development of medical countermeasures; and promote innovation to reduce the time and cost of countermeasure development. The final acquisition of countermeasures for the Strategic National Stockpile is then provided for by Project BioShield.

NIAID's Strategic Plan for Biodefense Research supports the national biodefense strategy. As such, the Institute will continue to support basic and applied research, product development, and technology development for biological threats based on national priorities for medical countermeasures. Furthermore, NIAID will continue its direct collaborative efforts with other Federal agencies, academia and industry as part of the larger HHS strategy. For example, NIAID coordinates all NIH-supported activities aimed at the development of medical countermeasures for biological, chemical, radiological, and nuclear threats.

Characterizing Biological Threats

Homeland Security Presidential Directive (HSPD)-18, released in early 2007, outlines strategies for medical countermeasure research, development, and acquisition, and frames the spectrum of biological threats in four distinct categories:

- **Traditional Agents** -- naturally occurring microorganisms or toxin products with the potential to be disseminated to cause mass casualties. Examples: *Bacillus anthracis* (anthrax) and *Yersinia pestis* (plague).
- **Enhanced Agents** -- traditional agents that have been modified or selected to enhance their ability to harm human populations or circumvent available countermeasures. Example: Drug-resistant pathogens such as extensively drug-resistant (XDR) TB or multidrug-resistant (MDR) plague.
- **Emerging Agents** -- previously unrecognized pathogens that might be naturally occurring and present a serious risk to human populations. Tools to detect and treat these agents might not exist or be widely available. Example: Severe Acute Respiratory Syndrome (SARS) or avian influenza.
- **Advanced Agents** -- novel pathogens or other biological materials that have been artificially engineered in the laboratory to bypass traditional countermeasures or produce a

more severe or otherwise enhanced spectrum of disease. Example: Multidrug-resistant anthrax.

These designations expand on the traditional classifications of Category A, B, and C agents because they address the fact that future threats are likely to be unanticipated and ill-defined. While appropriate and effective for the highest priority traditional threats, such as smallpox and anthrax, developing medical countermeasures using a conventional “one bug-one drug” approach will rapidly prove unsustainable as the list of threats increases to include enhanced, emerging, and advanced agents. Responding to traditional and new types of threats will require the capability to rapidly identify unknown or poorly defined agents, quickly evaluate the efficacy of available interventions, and develop and deploy novel treatments to prevent or mitigate medical consequences and the subsequent impact on society. This Strategic Plan update will address how NIAID will focus future efforts to prevent and respond to traditional and novel threats.

Research Achievements: Priming the Biodefense Product Pipeline

Developing products that can protect against potential biological threats is an integrated process that includes basic and applied research, and advanced product development. Basic research is critical to efforts to develop interventions against bioterrorism. It lays the groundwork by generating new and innovative concepts based on studies of pathogen biology and host response. Applied research builds on basic research by validating concepts in model systems, and testing them in practical research settings. Successful candidates move into advanced product development, where they are manufactured and evaluated for safety and efficacy in animals and humans according to strict guidelines and regulations.

In recent years, NIAID has greatly expanded its basic and applied research portfolio for Category A, B and C pathogens and toxins. The Institute has established a comprehensive infrastructure with extensive resources that support all levels of research. This has created a solid base for transitioning to a strategy that embraces multiple broad spectrum concepts. Examples of this infrastructure include the following. (For a complete list of NIAID resources, visit www.niaid.nih.gov/research/resources.)

- Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases – ten centers, located nationwide, provide resources and communication systems that can be rapidly mobilized and coordinated with regional and local systems in response to an urgent public health event. (www.niaid.nih.gov/research/resources/rce)
- Cooperative Centers for Translational Research on Human Immunology and Biodefense further knowledge of human immune responses against infectious pathogens and elucidate molecular mechanisms responsible for both short-term immunity and long-term immune memory. The ultimate goal of these eight centers is to translate research on immunity to infection into clinical applications to protect against bioterrorist threats.
- National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs) – 2 NBLs and 13 RBLs are available or under construction for research requiring high levels of containment and are prepared to assist national, state and local public health efforts in the event of a bioterrorism or infectious disease emergency. (www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/resources/NBL_RBL)
- Expanded Vaccine and Treatment Evaluation Units – multiple sites allow for more extensive clinical trials capacity and expertise. (www.niaid.nih.gov/factsheets/vteu.htm)

- The Biodefense and Emerging Infections Research Resources Repository offers reagents and information essential for studying emerging infectious diseases and biological threats. (www.beiresources.org)
- Genomics and proteomics centers include the Microbial Sequencing Centers, the Pathogen Functional Genomics Resource Center, the Bioinformatics Resource Centers, and the Biodefense Proteomics Research Centers. (www.niaid.nih.gov/research/topics/pathogen)
- The *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense resource provides screening of potential therapeutics and the development of *in vivo* animal efficacy models for evaluating drugs and vaccines. (www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/resources/invitro)
- The Immune Epitope Database is a public database that provides information on all published antibody and T-cell epitopes for Category A, B and C pathogens and their toxins, and also provides state-of-the-art epitope analysis tools. (www.immuneepitope.org)
- The NIH Tetramer Facility provides custom major histocompatibility complex (MHC) class I and class II tetramers for detection and characterization of host T cell responses to infectious agents. (http://research.yerkes.emory.edu/tetramer_core/index.html)

NIAID has actively engaged academia and industry through a variety of grants and contracts in order to advance research and product development for biodefense. In addition, the Institute has supported a number of biodefense workshops and multiple training opportunities ranging from basic introductory courses to two-year fellowships to provide professional training in biosafety and biocontainment. These programs are available through the National Biosafety and Biocontainment Training Program (www.nbftp.org), the RCEs, and NIAID Institutional Training Grants (www.niaid.nih.gov/ncn/training/default_training.htm). Close collaboration and communication with other government agencies (e.g. Department of Defense [DoD], HHS, Centers for Disease Control and Prevention [CDC], and the U.S. Food and Drug Administration [FDA]) have been critical components of NIAID's biodefense activities. NIAID will continue to expand these activities as appropriate.

Next-Generation Research: Filling the Pipeline

Developing medical countermeasures against a finite number of known or anticipated agents is a sound approach for mitigating the most catastrophic biological threats. Responding to enhanced, emerging, and advanced agents, however, demands new paradigms that will allow for more rapid and cost-effective development of countermeasures. Now that NIAID, in collaboration with other agencies, has established a solid framework of research and product development resources for biodefense, the time is ripe for transitioning to new approaches that will provide the flexibility required to meet the challenges of non-traditional threats. NIAID has identified three "broad spectrum" strategies to underpin a more responsive biodefense capability. These strategies -- broad spectrum activity, broad spectrum technology and broad spectrum platforms -- are described below.

Broad Spectrum Activity

Broad Spectrum Activity is a characteristic that enables a particular product to mitigate biological threats across a wide range or class of agents. Multiplex diagnostics possessing broad spectrum activity will rapidly differentiate a variety of common and lesser-known pathogens in a single clinical sample, identify drug sensitivities, and determine how a sample pathogen is related to known pathogens. Vaccines demonstrating broad spectrum activity include cross-protective and

multiple component vaccines. Cross protective vaccines induce an immune response against constant components of a microbe, and therefore are effective against pathogens that evolve or “drift” naturally or deliberately. A universal influenza vaccine is an example of a cross-protective vaccine. Multiple component vaccines include, within a single vaccine, elements that protect against viruses or microbes that are different, but usually closely related. An example of a multiple component vaccine is a hemorrhagic fever vaccine that contains elements of Ebola, Marburg, and Lassa viruses.

There are a number of traditional threats for which safe and effective treatments are either non-existent, of limited usefulness, or susceptible to emerging antimicrobial resistance and genetically engineered threats. A limited number of anti-infectives with broad spectrum activity directed at common, invariable, and essential components of different classes of microbes could potentially be effective against both traditional and non-traditional threats. This approach would allow a small number of drugs to replace dozens of pathogen-specific drugs. Additionally, strategies to overcome antibacterial resistance could extend the clinical utility of existing broad spectrum anti-infectives and have immediate benefits. Treatments that target host immune responses have the potential to be effective against multiple diseases. These immunomodulators reduce morbidity and mortality by controlling responses that contribute to disease (e.g. cytokine storms) or non-specifically activating the host’s natural immune defenses to induce a faster, more potent protective response.

Broad Spectrum Technology

Broad Spectrum Technology refers to capabilities -- such as temperature stabilization or delivery method -- that can be engineered into a wide array of existing and candidate products. Developing countermeasures that will be useful in responding to future threats represents a major challenge, given the capabilities that these products must possess. They should be safe and effective against multiple pathogens in people of any age and health status. To be appropriate for storing in the Strategic National Stockpile, the products should be suitable for long-term storage at room temperature, have simple compact packaging, be easily delivered in a mass casualty setting, confer protection with limited dosing, and have single dose delivery devices that can be self-administered. Added to these factors is the potential need to produce additional quantities with little notice, requiring manufacturers to take the costly step of keeping production facilities on standby.

Broad Spectrum Platforms

Broad Spectrum Platforms are standardized methods that can be used to significantly reduce the time and cost required to bring medical countermeasures to market. For example, a proven monoclonal antibody fermentation and purification method can be applied to rapidly develop any therapeutic monoclonal antibody, avoiding lengthy development work. Other examples of platform technologies include screening systems, *in vitro* safety testing, expression modules, manufacturing technologies, and chemical synthesis designs. The potential to rapidly apply such platform methods to developing new countermeasures will considerably shorten and streamline the process.

Future Directions

NIAID will implement a Research Agenda that supports these three broad spectrum approaches for developing new drugs, vaccines, devices, and diagnostics for emerging infectious diseases and biodefense. As such, basic and applied research and product development will focus on the following strategies.

Basic Research

- Expand basic microbiology and immunology research to support the broad spectrum activity approach.
- Use genomics and bioinformatics tools to model complex molecular pathways that can predict common pathogen and host targets. Move toward a systems biology approach in which discrete knowledge about pathogens and hosts is integrated into a comprehensive picture of the full host-pathogen interface.
- Promote discovery and development of natural anti-microbial proteins, such as defensins.
- Expand research on anti-infective resistance mechanisms and develop approaches to overcome them.
- Advance understanding of the innate and adaptive immune systems to target design and development of next generation adjuvants for vaccines or new therapeutics.
- Improve understanding of cellular and molecular pathways to identify new targets for vaccines and therapeutics.

Applied Research and Product Development

- Encourage development of multiplex diagnostics and broad spectrum vaccines and drugs.
- Expand *in vitro* and *in vivo* screening resources for drugs and vaccines against high priority pathogens.
- Develop animal models to support drug and vaccine efficacy studies.
- Offer a broad array of preclinical services, including pharmacology and toxicology to characterize and evaluate candidate products.
- Devise novel delivery systems and temperature stabilization technologies for vaccines and drugs.
- Evaluate immunomodulators as adjunct treatment along with traditional anti-infective therapy.
- Evaluate novel adjuvants to increase potency of vaccines and reduce number of doses required for maximum protection.
- Create formulations that improve bioavailability and allow for multivalent drugs and vaccines
- Develop universal expression frameworks for drugs (e.g. RNAi; monoclonal antibody frameworks).
- Establish manufacturing platforms (e.g. microwave technology for chemical synthesis) for rapid and cost-effective production of therapeutics and vaccines for human use.
- Expand clinical trial capabilities for evaluation of new drugs.
- Design adaptive diagnostic systems that allow for simple and rapid incorporation of additional targets.
- Develop new classes of antibiotics.

As NIAID focuses on these key biodefense research and development activities, the Institute will continue to support training in biosafety and biocontainment as needed to ensure that research staff have the necessary tools and training to safely conduct biocontainment research.

Implications of Biodefense Research for Other Diseases

The large investment in biodefense research and product development will significantly benefit other areas of medicine. Many of the organisms under study and a host of other emerging infectious diseases and drug-resistant microbes are significant public health threats, both within the United States and in other parts of the world. Research on microbial biology and pathogenesis will enhance understanding of these and other naturally occurring infectious diseases. Advances in developing diagnostics, vaccines, and therapeutics with broad spectrum activity will have direct

relevance to many naturally occurring diseases, as well as spin-off benefits for developing other broad spectrum products. Broad spectrum technologies that improve product stability, potency, and ease of use will benefit many classes of new diagnostics, vaccines, and therapeutics, regardless of the disease target. The most obvious gain will be for interventions to prevent, diagnose, and treat major killers such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and reemerging diseases. This is especially important in countries where public health infrastructure cannot support delivery of products that require a cold chain, multiple doses of a vaccine, or advanced diagnostic equipment. Broad spectrum platforms have the potential to reduce time and cost of developing new products for many medical conditions. Basic research on host defenses will greatly enhance our understanding of the molecular and cellular mechanisms of the innate immune system and its relationship to the adaptive immune system, and lead to improvements in treatment and prevention of immune-mediated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases. Finally, improved understanding of mechanisms of regulation of the human immune system will have positive spin-offs for diseases such as cancer, immune-mediated neurological diseases, and allergic and hypersensitivity diseases, as well as for preventing rejection of transplanted organs.

Conclusion

The nation must be ready to protect its citizens with safe and effective treatments against potential biological threats. NIAID, in collaboration with other government agencies, will continue to play a significant role in this mission. Through NIAID's support of basic and applied research, advanced product development, and research resources, much progress has been made in developing countermeasures for some of the highest threat pathogens. It is clear, however, that time and resources cannot sustain a "one bug-one drug" approach for the long term. The new broad spectrum strategy and supporting Research Agenda will focus on developing countermeasures that act against multiple agents, as well as technologies and platforms that can improve the quality of products and shorten the time and cost of development. NIAID's product development infrastructure, biocontainment facilities, and research resources will be used to evaluate the most promising products, technologies and platforms through preclinical and clinical development.

This approach will most effectively utilize the strengths of NIAID and its stakeholders in the national biodefense preparedness effort. It will also provide enormous benefits to many other areas of biomedical research and development and truly usher in 21st century medicine for future generations.

For More Information

HHS Public Health Emergency Medical Countermeasures Enterprise Strategy for Chemical, Biological, Radiological and Nuclear Threats, Federal Register/Vol. 72, No. 53/ Tuesday, March 20, 2007/Notices
(www.hhs.gov/aspr/barda/documents/federalreg_vol72no53_032007notices.pdf)

HHS Public Health Emergency Medical Countermeasures Enterprise Implementation Plan for Chemical, Biological, Radiological and Nuclear Threats, Federal Register/Vol. 72, No. 77/ Monday, April 23, 2007/Notices
(<http://a257.g.akamaitech.net/7/257/2422/01jan20071800/edocket.access.gpo.gov/2007/pdf/E7-7682.pdf>)

Homeland Security Presidential Directive – 18
(www.whitehouse.gov/news/releases/2007/02/print/20070207-2.html)

NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats
(www.niaid.nih.gov/about/overview/planningPriorities/RadNuc_StrategicPlan.pdf)

NIAID Biodefense Research
(www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense)

NIAID Category A, B, and C Priority Pathogens
(www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PDF/Cat.htm)

NIAID Biodefense Research Agenda for CDC Category A Agents
(www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PDF/biotresearchagenda.pdf)

NIAID Biodefense Research Agenda for CDC Category A Agents, 2006 Progress Report
(www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PDF/CatA_2006.pdf)

NIAID Biodefense Awards, FY 2006
(www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/funding/FY2006+Awards/2006.htm)

NIAID Current Funding Opportunities in Biodefense
(www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/research/funding)