NIAID
BIODEFENSE
Preparing Through Research

NIAID Strategic Plan for Biodefense Research

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Host Response

To develop potent, safe, and effective vaccines, accurate diagnostics, and immunotherapeutics against microbes that can be used as bioterrorist agents, it is critical to improve our understanding of the complex parameters of innate and adaptive immunity. Because most potential bioterrorist agents would infect via the respiratory or oral routes, the plan includes specific studies on mucosal immunity at these sites. Crosscutting, multidisciplinary research will facilitate translation of the considerable body of basic knowledge that exists into vaccines, passive therapies, and diagnostic methods focused on bioterrorist agents. In the same way, new discoveries of immunologic principles or applications will help ensure a robust pipeline of improved or novel products.

Goals

- Expand the understanding of and ability to modify the innate and adaptive immune response to Category A, B, C, and D organisms by
  - Defining specialized innate and adaptive immune mechanisms used by the respiratory and/or oral-gastrointestinal systems
  - Mapping the protective epitopes for each agent, their respective toxins, and pathogenic factors using computational methods, genomics, proteomics, structural biology, and immunochemistry
  - Applying computational methods to model and predict immune responses
  - Refocusing basic immunology projects to include responses against potential bioterrorist agents
  - Expanding studies on host/pathogen interactions
- Facilitate clinical research on human immunology that will assist in identifying targets within innate and adaptive immune pathways by
  - Defining interactions between innate and adaptive immune systems
  - Discovering new recognition and signaling molecular pathways involved in innate immunity
  - Assessing relevant immune polymorphisms within the population

- Develop a comprehensive catalog of the variations in human immunologic responses

Vaccines

Vaccines are one of the most successful public health measures. The key features of vaccines to be developed for civilian use against bioterrorism agents will include the rapidity by which an immune response can be elicited, whether the vaccine can modulate the clinical course of an exposed person, the safety of the vaccine in all segments of the population, and the ease of administration or use. Because of the high public health concerns associated with these pathogens, smallpox and anthrax vaccine development will remain the highest priority.

Goals

Develop and test vaccine candidates for civilian bioterrorism threats with an immediate emphasis on the licensure of new generation smallpox and anthrax vaccines by

- Expanding the infrastructure for clinical testing and evaluation to rapidly test the new generation anthrax and smallpox vaccines under development
- Establishing a centralized immunology laboratory to develop and validate tests required for licensure of smallpox and anthrax vaccines
- Supporting the continued development of newer generation smallpox and anthrax vaccines with emphasis on increased safety and timely response
- Understanding and preventing complications of smallpox vaccine such as eczema vaccinatum and vaccinia gangrenosa
- Developing animal model capability and providing the required standardization and validation, including challenge of nonhuman primates, that will be necessary for licensure of smallpox and anthrax vaccines
- Identifying, prioritizing, and supporting the development of vaccines for other high-priority agents of potential bioterrorism
- Developing animal model capability and providing the required standardization and validation for development of vaccines against other select organisms

- Developing cell-culture-based approaches for viral vaccine development
- Developing improved vaccine approaches by focusing basic research interests to expand knowledge on
    - Potential targets for vaccine design
    - Vaccine delivery systems
    - B- and T-cell protective responses
    - Adjuvant development based on innate immunity
    - Potential regulation of the innate immune system as a primary defense
    - Differences in the innate and adaptive immune systems of human neonates, infants, pregnant women, immunocompromised populations, and the elderly (including genetic polymorphisms) that may influence responses to vaccines, both general and specific
- Ensuring manufacturing capacity for all delivery vehicles, vectors, and types of vaccines
- Expanding preclinical toxicology capability needed for vaccine development

Therapeutics

The development of new anti-infectives and immunotherapies, including antitoxins, and the screening of existing therapeutic agents to determine whether they have activity against select agents of bioterrorism remain a top priority. Although it has been shown that many of the bacterial agents in categories A, B, C, and D are sensitive to a number of antibiotics, licensure of these products for use in humans will require additional information. In addition, the underlying concern about the ease of development of antimicrobial resistance will factor into our need to increase this category of options. There are currently no antivirals or antisera licensed for use against smallpox and no antitoxin or other antisera licensed for use against anthrax. One antiviral, cidofovir, which is under IND for use as a backup to vaccinia immune globulin (VIG) in the setting of vaccinia immunizations and as a potential therapy in smallpox outbreaks, requires hospitalization during administration. VIG, which is required for the evaluation of smallpox vaccine candidates, is in extremely limited supply. The need to develop

and license a cadre of validated antimicrobials, alternatives to existing immunotherapies, and antitoxins, with a focus on smallpox and anthrax, will receive the highest priority.

Goals

Increase the number of licensed antimicrobials, immunotherapeutics, and antitoxins available for responding to select agents of bioterrorism through accelerated screening of new and existing agents by

- Expanding capacity for *in vitro* and *in vivo* evaluation of antimicrobials, immunotherapeutics, and antitoxins
- Developing a replacement to existing VIG
- Establishing additional agent-specific high-throughput screens
- Developing the animal model capability, including BSL-4 challenge on nonhuman primates and providing the required validation of animal models that will be necessary for licensure of new therapeutics for anthrax and smallpox
- Identifying, prioritizing, and supporting the development of other therapeutic interventions for specific agents
- Synthesizing, if needed, active lead compounds in sufficient quantities for preclinical pharmacokinetics, animal model efficacy, mechanisms of action, and toxicology studies
- Developing the animal model capability and the validation and standardization needed to assess efficacy
- Establishing required safety and pharmacokinetics data needed for licensure of new compounds
- Focusing basic research interests to expand knowledge on
    - Potential targets for therapeutic intervention
    - Discovery, characterization, optimization, and development of monoclonal and polyclonal antibodies

- Discovery and development of soluble receptors and mediators of the innate immune system as effective immunotherapeutic agents
- Differences in immune systems of human neonates, infants, pregnant women, immunocompromised subpopulations, and the elderly (including genetic polymorphisms), which may impact immunotherapeutics

Diagnostics

One of the hallmarks of a successful bioterrorist agent is clinical misdiagnosis or delayed diagnosis. The ability to rapidly identify the introduction of a bioterrorist agent into the civilian population will require highly sensitive, specific, inexpensive, and easy-to-use diagnostic tools located at primary care institutions. Ideally, these tests could also evaluate the possible spectrum of antimicrobial resistance and be connected to a central database. Centralized confirmatory testing also should be expanded to include routine evaluations of positive samples for weaponization, genetic profiling, and bioengineered properties. The theoretical ability to design and develop such assays exists. For example, we have microchip-based platforms, which could contain thousands of microbial signature profiles that are either nucleic acid or protein based. Identification of the microbial signatures is ongoing. If bioterrorism-based diagnostics could be combined with other more common and routine diagnostic needs, the value of these diagnostics to primary care institutions would ensure interest and use.

Goals

Expand interest and direction in the development of highly sensitive, specific, inexpensive, and easy-to-use tools for clinical diagnosis of potential agents of bioterrorism by

- Emphasizing this research interest
- Focusing genomic and proteomic analysis on identification of microbial signatures
- Providing standards for validation and comparison of potential products

Research Resources

The lack of routine clinical importance, and thus the absence of scientific and clinical expertise associated with the microbes, is another hallmark of a successful bioterrorist agent. The ability to develop the tools and interventions needed in a public health emergency will require the attention of the scientific community to these areas. The development of centralized sources of generalized as well as specific expertise in bioterrorism areas, such as *in vivo* and animal model development, production of standardized and validated reagents and tests, expertise in the development and humanization of antibodies, bioinformatics, diagnostic validation, and vaccine production (GLP/GMP pilot lots), will be required to speed the development of new generation products.

Goals

Expand the development of general and specific research resources to assist in the rapid development of new tools and interventions for use in bioterrorism by

- Developing 6 to12 regional Centers of Excellence for Bioterrorism and Emerging Diseases Research
- In addition to general capabilities, each center would develop a specialized expertise of importance to product development. Suggested areas of applied research emphasis include diagnostic development and validation, small- and large-animal model development, assay development and validation, immunotherapeutics, and host/pathogen interactions
- Encouraging and developing relationships between academia and industry
- Developing a centralized research reagent repository for standardized reagents that could be centrally controlled and accessed by appropriate investigators
- Developing BSL-3/4 capability at Centers of Excellence for Bioterrorism and Emerging Diseases Research
- Providing sufficient nonhuman primates to complete the testing and analysis of the therapeutic and vaccine products that are developed
- Expanding research training opportunities
- Expanding NIH clinical and basic research capabilities

Implications of Biodefense Research for Other Diseases

The positive spinoffs for other diseases that will result from the large investment in research on Biodefense will be substantial. First, many of the organisms in question and a host of other emerging infectious diseases and drug-resistant microbes are significant public health threats in endemic areas, especially in the developing world. Basic and translational research aimed at them will have direct and obvious benefit to the people threatened by them in nature. Second, research on microbial biology and pathogenesis of these organisms will enhance understanding of other more common and naturally occurring infectious diseases, both in the United States and around the world. Third, advancements in the arena of diagnostics, therapeutics, and vaccines will improve our ability to diagnose, treat, and prevent major killer-diseases, such as malaria, tuberculosis, HIV/AIDS, and a spectrum of emerging and reemerging diseases. Fourth, basic research 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 the treatment and prevention of immune-mediated diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases. Finally, improved understanding of the mechanisms of regulation of the human immune system will have positive spinoffs for diseases such as cancer, immune-mediated neurologic diseases, and allergic and hypersensitivity diseases, as well as for the prevention of rejection of organ transplantation.

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