Trilateral Seminar on R&D Policies Related to Emerging and Re-emerging Infectious Diseases

D − Plenary Session III: *Products and Technologies*

Invited Presentations

Panelist Presentations

Strategies for Developing New Vaccines to Combat Emerging Infectious Diseases

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Overview

In the history of combating infectious diseases, vaccine immunization has been the most successful and the cost-effective solution to control the spread of infectious diseases. Vaccination has the potential to produce major changes in disease epidemiology by its direct effects on those who are vaccinated, and by strengthening the herd immunity of those who are unvaccinated. The evaluation of a newly developed vaccine is a long-term study. It should cover the mechanisms of the vaccine developed, the duration of the immune responses being induced, the extent to which a vaccine reduces disease transmission, and its potential to generate herd immunity. In addition, the program of immunization is a key issue to address in order to achieve successful control of the disease.

These requirements sometimes cannot be met when there is an epidemic of emerging infectious disease. Then, one should rely as far as possible on the experience and data from the use of established vaccines which share similarities with the vaccines that need to be developed. Vaccine development is not just a matter of pure scientific research in microbiology or immunology. Besides, not all the enterprises involved are capable of producing vaccines. Vaccines are a special type of biological product to be used in healthy adults or children for preventing diseases, and there are many requirements to be fulfilled prior to a candidate vaccine being approved for clinical trial. One of the strategies for developing vaccines for emerging infectious diseases is therefore to support basic and applied research projects in those vaccines already in use whose characteristics may have implications for the development of vaccines against forthcoming emerging infectious diseases, e.g. respiratory diseases or sexual transmitted diseases. It is inappropriate to concentrate support only on newly described infectious diseases, while neglecting the refinement of vaccines against old ones. Someday, we may even find that the “old” infectious diseases generate new problems. Another point is that it is unwise to spread the funding across a broad range of institutions that have had no previous experience in vaccine research or production. This should be avoided especially when the resources are limited. To solve the problems between not enough government funding and the reluctance of companies to invest money for new vaccine

development, one solution is to select the most appropriate projects for funding and the other is to set up bridges connecting applied research projects with small scale production and pilot clinical trials.

An important characteristic shared by emerging and re-emerging infectious diseases is that the microbes which cause these diseases have usually developed new biological properties. Either the antigenicity or the immunogenicity of a familiar microbe has been changed significantly; or a novel species/type of microbes has emerged. As these microbes cannot be recognized, neutralized or eliminated by the host immune responses, endemics or epidemics may occur. To control the emerging/re-emerging diseases, vaccines that are to be developed should consist of the newly emerged microbial antigens. It should be possible for vaccines to be produced rapidly in large quantity, and they must be proved safe for mass vaccination before they can be licensed by the regulatory administration. Currently, there are different types of vaccines in use, or under clinical trials, or in preparation: 1) inactivated or attenuated microbial vaccines; 2) recombinant protein vaccines; 3) nucleic acid vaccines; 4) peptide-based vaccines; 5) conjugated vaccines; and 6) several types of therapeutic vaccines. Injection is the major route for vaccine delivery, but mucosal (oral and intranasal) delivery has also been employed in preventing certain respiratory and enteric infections.

To combat emerging diseases, aside from well-established vaccines, we would like to share our thoughts with you on some new strategies for developing novel types of vaccines. Only biological products for active immunization against new emerging diseases are presented here.

Vaccines for Stimulating Innate Immune Responses

If we encountered a new biological agent that had not been characterized, it would not be possible to develop a specific vaccine against this microbial infection. A vaccine that stimulated innate immune responses might be considered for emergency use to block a disastrous outbreak. The aim of using such nonspecific vaccines is to improve the innate immunity in the population and build nonspecific but effective barriers against the spread of microbes. For instance, plasmid DNA, CpG, and poly IC are good stimulants to induce innate immune responses in hosts. In practice, this type of vaccine has not yet been studied for its effect in blocking microbial transmission in the population, and it is therefore worthwhile to support studies on employing this type of vaccine in experimental animal infections. To develop this type of vaccine, the following studies are to be encouraged: 1) studies on the effects of using CpG or DNA etc in preventing the spread of different types of infections in groups of animals; 2) studies on the effects of different types of innate immune

response stimulants against bacterial or viral infections in animals, especially in newborns and aged animals; and 3) studies on the effects of delivering CpG/DNA, poly IC via different routes to control the spread of infections among individuals.

To give an example, we have studied the mechanisms of CpG inducing cytokines by intradermal injections in mice. The non-specific immune stimulating effects have been ascribed via toll-like receptors. Toll-like receptors are a newly recognized receptor family found in vertebrates and they are crucial important mediators of innate immune recognition. In a study using the BALB/C mice, Liu et al have compared the expression levels of toll-like receptor 9(TLR9) induced by intradermal injections using a plasmid containing CpG motifs (AACGT) (CpG1668), a plasmid containing the sequence of a negative control (CpG1668 gc) and normal saline only. Results showed that TLR9 mRNA could be induced in the skin of the mice by intradermal injections using either normal saline or plasmid CpG.. The latter also increased the expression of mRNAs for proinflammatory cytokines, such as IL-1, IL-6 IL-12 and TNF-alpha (Liu et al, Immunology 2003, 110:341-347). This shows that using products that induce innate immunity could contribute to an approach to developing a non-specific "all round" vaccine, available when necessary, to combat an emerging infection.

Inactivated "First-Aid" Microbial Vaccine against Acute Emerging Infectious Diseases

The idea behind a "first-aid" vaccine is to develop an inactivated microbial vaccine or vaccine-like biological product for immediate prevention during an outbreak of acute emerging infectious disease. Once the etiology of the emerging disease has been identified, and this microbe can be grown or propagated in cultures to a high concentration, inactivation of the specific microbe with a well-established traditional method would be able to produce "first-aid" vaccine within a short period of time. A "first-aid" vaccine would preferably be used topically, i.e. intranasally or by spray. By this delivery route the risk of side-effects might be less than from parenteral injections.

To develop this type of vaccine, the following studies might be encouraged: 1) methods for inactivation that can be used in different families or genera of bacteria or different families of viruses; 2) Effective methods for mucosal delivery of vaccines; 3) Methods for effective induction of mucosal immunity in mammalian animal models that would not lead to anaphylaxis or delayed hypersensitivity; 4) Adjuvants that can enhance local immunity; and 5) Efficient and simple assays for measuring local and systemic immune responses.

As an example, in the SARS-CoV outbreak, we cultured the virus in liter quantities and used formaldehyde for inactivation, following the inactivation protocols of influenza virus. After inactivation, the virus was inoculated onto cells and was passaged three times to confirm full inactivation. This took about six to eight weeks. The inactivated virus was then used in combination with different adjuvants for intranasal immunization of mice. Not only were neutralizing antibodies detected in mice that were immunized with the inactivated SARS-CoV with adjuvants such as CpG or PEG, but also IgA was detected in the tracheal-lung wash of the mice (Qu et al, 2005, Vaccine 23:924-31). This suggests that when the microbe responsible for an outbreak has been identified, topical use of "first- aid" inactivated vaccines could be considered. It might be effective for preventing the spread of the disease and could be used with least risk from mass immunization.

Antigen Presentation-Modifying Vaccines against Persistent Emerging Infectious Diseases

Persistent viral infections such as viral hepatitis B, hepatitis C, and HIV are prevalent in many countries, and novel genotypes or recombinant mutants are emerging. Because the hosts are unable to develop effective immune responses to clear the antigens, one may interpret these persistent infections as showing immune tolerance by the hosts against the microbes or their specific antigens. The idea is to modify the pathway of antigen processing and presentation of the microbial tolerogen to convert it into immunogen. This can then be recognized by the hosts as non-self, inducing effective host immune response. Antigen presentation-modifying vaccines can be prepared using antigen-antibody complex, or combined with-an antigen specific DNA (triple complex). In this type of triple vaccine, the antigen can be presented both through the endogenous and exogenous pathways. That is, the antigen-antibody complex can be ingested by the antigen presenting cells and be processed through the exogenous pathway while the specific DNA incorporated in the complex being ingested together with the antigen-antibody complex can be expressed in the antigen presenting cells and the expressed protein can thus be processed via the endogenous pathway. By this means, effective humoral and cellular immune responses can be induced. To develop this type of vaccine, studies of the following might be encouraged: 1) the mechanisms of antigen processing and presentation when the antigen is complexed to its antibody; 2) the processing of triple complex; 3) the immunogencity of this triple complex in animal models; and 4) the therapeutic effects of complexes versus viral persistent infections.

An HBsAg-anti-HBs (purified hepatitis B surface antigen and HBIG, Immunoglobulin against hepatitis B surface antigen) complex intended as a therapeutic candidate for viral hepatitis B patients has proved to be ingested more efficiently by the dendritic

cells or macrophages than HBsAg alone. Besides, this complex could modify the surface markers of dendritic cells. Modulation of HBsAg presentation and processing has also been shown to stimulate T lymphocytes and increased production of Th1-type cytokines in HBsAg positive transgenic mice. After being licensed by the Chinese SFDA for clinical trials, yeast-derived HBsAg-HBIG complex (YIC) is currently under phase two B clinical trial. A phase II A clinical trial showed that YIC is a promising therapeutic vaccine candidate. (Wen et al, J Gen Virol, 1994, 75(pt2): 335-9; Wen et al, Int Rev Immunol 1999, 18 (3): 251-8; Zheng et al, Vaccine 2001, 19:4219-4225; Zheng et al, J Viral Hepatitis, 2004, 14: 217-224; Xu et al, Vaccine 2005, 23:2658-2664). This type of vaccine aims at modification of the presentation of the toleragen and is an approach that might be considered for treating other microbial persistent infections than hepatitis B.

Summary

In summary, I have touched on some novel approaches to vaccine development against both emerging acute infections and persisting ones. These approaches may stimulate immune responses both non-specifically and specifically. I have touched on the preparation of “first aid” vaccines by conventional methods and described some novel vaccine approaches using microbial DNA or CpG, and using complexes of microbial antigens and hyperimmune globulin against them. In each case experimental animals, willing volunteers, and far-sighted funders are needed. These conditions must both precede and anticipate a future fruitful outcome.

Security and Intellectual Property Constraints on Emerging Infectious Diseases Research*

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Introduction

Since the bioterrorist anthrax attack in the United States following the events of 9/11/2001[1], there has been a heightened concern about access to research results that could provide somebody intent on causing injury and death through bioterrorism with information that would simplify his or her ability to obtain or engineer suitable infectious agents or their toxins. In this context it seems reasonable to: 1) restrict access to agents; 2) control research of potential relevance; and/or 3) censor presentations or publications of this research. Balanced against these concerns is the concept of academic freedom, and the belief that information made available is part and parcel of the scientific method to challenge or verify research findings in the search for scientific "truth." Where does the balance lie?

Another constraint on the openness of science is the system of patenting and licensing of intellectual property (IP). Since the passage of the Wydler-Stephenson and Bayh-Dole Acts of the U.S. Congress in 1980, which permit government and university scientists to patent their inventions and discoveries based on research funded by the public sector, there has been a sharply increasing trend to do so and to license the IP to commercial ventures and collect licensing and royalty income. University technology licensing and transfer offices have aggressively pursued these arrangements. However, on the other side of the coin is the famous response of Jonas Salk to the question why he had not patented his polio vaccine: "Would you patent the sun?" This has particular relevance to the public good content of work supported by public funding. Between the behavior of university technology transfer offices and the stance of Salk there is a middle ground where protection of IP is balanced by the stake of the public in supporting the work leading to IP[2]. Where does the balance lie?

And now in the post 9/11 era we must ask where and how the two interests, security and autonomy of research, are to be balanced. This paper will explore these issues.

Security and Academic Freedom: Balancing Legitimate Social Goals in a Time of Crisis

The debate between security and freedom is not a new one in the United States. As early as 1759 Benjamin Franklin wrote: "*They that can give up essential liberty to obtain a little safety deserve neither liberty nor safety*."[3] The newly formed Association of American University Professors (AAUP) took a different perspective in 1918, referring to security and academic freedom during World War I and coming down hard in support of security over academic freedom.[4] Commenting on this stance during the World War II, a committee of the AAUP reflected that the Association had "responded to our country's entry into the war by appointing a special Committee on Academic Freedom in Wartime. That committee's report was imbued with a spirit of jingoism, as the Association was eager to dispel any suspicion of a want of patriotic fervor on the part of the young academic profession."[5] This report went on to add the following comments.

- "As war in its second year becomes the accepted routine of American life, rather than a confused departure from the ways of peace, the decision of AAUP to hold fast to its fundamental principles has been justified."
- "Freedoms lost are difficult to regain."
- "Academic freedom is one facet of intellectual freedom; other aspects of that larger concept - freedom of speech, freedom of the press, and freedom of religion - are among the avowed objects for which this war is being fought."
- "It would be folly to draw a boundary line across the area of freedom."

The AAUP had cause to review their position in the wake of 9/11 and the need to once again attempt to strike a balance between security and academic freedom issue, which had once again become a dominant theme. There was also considerable pressure from the US government to weigh in favor of security, in effect meaning increased control and censorship. The Association reported in 2004[6] as follows:

- "Historically, the government's domestic arsenal in times of crisis has included three weapons: secrecy, surveillance, and suppression."
- "The need to maintain secrecy of certain critical military information is indisputable, as is the imperative to gather information about an enemy's actions and plans."
- "The law has long criminalized 'giving aid and comfort' to the enemy, which entails, for example, trading with or providing financial support to the enemy."
- "Confined within proper bounds, such measures need not pose a threat to civil liberties in general or to academic freedom in particular."

The report noted that the boundaries are most likely to blur in the "passion of war" especially among those who "may be properly zealous for its successful prosecution." Without sufficient public scrutiny surveillance is often extended to lawful activity,

political dissent is suppressed, and there is a serious infringement on the "robustness of debate upon which democracy depends." The report addresses a baseline assumption underlying the more draconian responses that security and freedom are in such a state of inherent tension that balance is not possible and there must be a tilt towards one or the other extreme, depending on the prevailing circumstances. Thus, in the post-9/11 period in the U.S there have been attempts to: 1) categorize and restrict some research as "sensitive" and therefore subject to control; 2) implement strict export control laws and select agent regulations; 3) limit the publication of research findings; 4) prohibit certain foreign nationals from collaborating with US researchers and receiving education and training in US universities; and (5) restrain faculty free speech. The question then becomes the degree to which these approaches are applied.

However, the very assumption that balance is not possible and tilt is required is challenged by the writers of the AAUP report. They note:

- "The free exchange of scientific data − for example a component of a deadly toxin − may well help to equip a terrorist group with a means of mass destruction. But that same openness may better equip researchers to produce the means of preempting or neutralizing that very threat."
- "Secrecy can impede the pace of scientific discovery for good as well as for ill."

We should neither be naïve about terrorism nor so idealistic that we believe the default position among scientists is Hippocratic−first do no harm−for not everybody in science inherently wants to do good. This brings the debate back to the question of balance, and there are basically four ways to approach it:[7] 1) continue the current method of classification of research results because new restrictions will only hurt scientific progress while the actual usefulness of research results to terrorists is limited; 2) revert to self-regulation by scientists using an "Asilomar-like" process to develop consensus (e.g. as used for recombinant DNA); 3) rely on publishers to scrutinize articles for data with potential security ramifications and refuse to publish those papers; and/or 4) mandate review by federal funding agencies, either before funding or publication, as a centralized federally based option.

A group of journal editors has thoughtfully addressed these issues.[8] They have stated the following:

1. "We must protect the integrity of the scientific process by publishing manuscripts of high quality, in sufficient detail to permit reproducibility. Without independent verification, a requirement for scientific progress, we can neither advance biomedical research nor provide the knowledge base for building strong biodefense systems."
2. "We recognize that the prospect of bioterrorism has raised legitimate concerns about the potential abuse of published information, but also

recognize that research in the very same fields will be critical to society in meeting the challenges of defense."

3. "Scientists and their journals should consider the appropriate level and design of processes to accomplish effective review of papers that raise such security issues."
4. "On occasion an editor may conclude that the potential harm of publication outweighs potential societal benefits. Under such circumstances, the paper should be modified or not be published. Journals and scientific societies can play an important role in encouraging investigators to communicate results of research in ways that maximize public benefits and minimize risks of misuse."

The responsibility to do responsible science and to publish responsibly is a compact among scientists and publishers. Ultimately, we must promote the ethics of science itself to find the right balance, and not revert to a position of mindless censorship, while remaining alert to the possibility of harm being done.

Intellectual Property Management: Finding the Balance between Protection and Dissemination of and Access to Information

The Global Forum on Health Research[9] estimates there has been a slow but steady rise in research and development (R&D) expenditures in health over the past several years, from around $84 billion in 1998 to nearly $106 billion in 2001. The percentage of R&D funding from the private for-profit sector has also been steadily increasing, reaching nearly 50 percent of the total by 2001, while the support from the public sector has been slowly diminishing, to 43 percent of the total in 2001. The table below shows that 97.5 percent of this investment comes from the high income countries, with just about 44 percent from the United States. What is noteworthy is that 2.5 percent of the total is being invested by transitional developing countries. This represents a major growth area for these countries, and it is a reasonable expectation that this will grow substantially over the next several decades and potentially change the picture of R&D spending in health.

Table: Private for profit health research spending, US $, millions

Country	Total $ Billions	% of Total
Global Total	$51,230	100%
USA	22,502	43.9%
Japan	7,726	15.1%
United Kingdom	4,534	8.9%
Germany	3,375	6.6%
France	2,370	4.6%
Switzerland	1,374	2.7%
Sweden	1,304	2.5%
Total HIC	49,885	97.4%
China	262	0.5%
India	141	0.3%
Transition	182	0.4%
Other LMIC	$760	1.5%
Total LMIC	$1,345	2.6%

Source: GFHR estimates based on data from OECD, national sources and pharmaceutical associations

The magnitude of these investments serves as a backdrop for the increasing public attention to global disparities in health − AIDS, tuberculosis, and malaria in particular. This is in large part due to greater coverage in the media and the interest of major entertainment figures such as Bono and Angelina Jolie. There is, at the same time, increasing public exposure to controversies stemming from IP and trade issues (TRIPS) and globalization, and the WTO, IMF and World Bank are becoming household names, extensively covered by the media and vilified in public by advocacy groups for the poor. The media most often portray the players in polar terms, for example the rich vs. poor, or big pharma vs. sick people, or insensitive bureaucracies vs. caring charitable relief organizations and non-governmental organizations (NGOs). While these stories gain attention they are at best simplistic views that obscure many of the underlying issues and at worst create barriers to solutions. In reality, perceptions of intellectual property and what it does, or does not do, vary depending on the perspective the viewer. Thus patents are − or are not − the problem; the profit based industry controls IP, guarantees high prices, and prevents universal access or is the source of new innovation in health products; poor countries are either the victims of the system or they suffer because they fail to implement and enforce laws to protect IP; and industry reaps great profits at the expense of the poor, or health product development is an uncertain, risky, and inherently costly endeavor, sustained only when there can be a reasonable profit margin, whatever is meant by the operative word “reasonable”.

IP laws in the United States were revised in 1980 because the Congress was concerned that IP generated from federally supported research was owned by the government and was not being applied. In fact, at the time less than 5 percent of government patents vs. 25-30 percent of private sector patents were being applied and developed into products. Congress was also concerned that if something were not done to spur commercialization of discovery the United States would "fall behind" other countries in technology and market dominance. A major barrier was the unwillingness of the responsible government agencies to grant exclusive licenses for commercial development, apparently because they were interested in "protecting the public interest." Companies complained that even the non-exclusive licensing process was "excruciatingly slow" and that different policies were applied by each agency. Together, the Bayh-Dole and Stephenson-Wydler acts of 1980 created a uniform licensing system for all federal agencies, reduced the steps needed to grant licenses, and provided incentives for industry to invest risk capital in product commercialization from federal patents. Universities and small business government contractors, as well as government scientists, were permitted to receive title to inventions derived from federal support and grantees and contractors were allowed to license the technology developed under these patents for use by small business and private industry. Independent analyses conclude that the law increased technology transfer from researchers to private industry, improved government patenting/licensing processes, and has facilitated the introduction of products that improve the health and well-being of the public. Royalties received by academic institutions engaged in technology transfer have grown by 20-30 percent annually, which is usually taken as proof of the application of IP to product development and marketing. Yet, despite these benefits, most university technology transfer offices have licensed few or no commercialized products and typically operate at a loss, unless they have a "blockbuster" piece of IP. Many products also remain too expensive for those in need to purchase them, for example the elderly in the U.S. and the majority in developing countries.

To protect the public against non-use or unreasonable use of inventions, especially to insure access to life saving products, these acts retained for the government the rights to a non-exclusive, nontransferable, irrevocable, paid-up license to practice for or on behalf of the United States everywhere (otherwise known as a "compulsory license"), and to require the patent holder or licensee to grant use rights to another user, with due compensation, under special circumstances, for example the lack of use within an agreed-upon time frame, or unmet special health or public safety needs (so called "march-in" rights). Neither provision has been implemented. In October 2001, with the anthrax bioterrorist act in the United States still unfolding and limited supplies of the drug of choice, ciprofloxacin (Cipro®), Senator Schumer of New York asked the Department of Health and Human Services to seek a stockpile of Cipro sufficient to treat 10 million people. This was far greater than the supply or of the capacity of the company to produce it in a timely manner and would have required a compulsory license to generic manufacturers to meet the request. However, a few days later the department decided

against this course, in part because at the same time, the Government of Canada had decided to break Bayer's patent and this threat apparently was sufficient pressure to change the dynamics of the situation. According to Bayer itself, "…we reached agreements with the two governments intended to ensure adequate supplies of Cipro while preserving our existing patent rights, we cannot assure you that these or other governments would not impose compulsory licensing in the future in response to renewed or increased bioterror attack..." In order to ensure that sufficient antibiotics will be available from U.S. governmental stockpiles, and in addition to donating four million tablets, Bayer has entered into an agreement with the U.S. government to supply up to 300 million tablets, the first 100 million tablets to be delivered by the end of 2001 at a price of $0.95 per tablet."[10] A similar agreement was reached with the Canadian Government and compulsory licensing in North America was avoided.

Government march-in rights have been formally tested once, in 1997, when CellPro petitioned the National Institutes of Health (NIH) to use a Johns Hopkins University stem-cell separation method because they claimed they were unable to negotiate a license with the university. CellPro's petition argued that Hopkins and its licensee failed to commercialize the technology in a timely fashion and that public health and safety needs were not being met. CellPro then used the technology without permission and was sued and found guilty of willful infringement on the Hopkins patent. NIH rejected the CellPro petition on the grounds that most IP is pre-product and a minor part of total IP, and because it was not possible to adequately define what a "timely" manner meant. To this day, both universities and industry remain concerned that march-in will undermine licensing rights under Bayh-Dole, and that each petition for march-in will prompt a full-blown legal process, with major time and financial burdens for all concerned with these costs ultimately being passed on to the public.

While the two clauses are still debated by IP specialists and still provoke anxiety in both academia and the private sector, a new twist was potentially introduced by the Supreme Court in June 2005 when it ruled that local governments may force property owners to sell their property under the principal of eminent domain when the goal is to promote private economic development so long as the officials decided it would benefit the public, even if the property is not blighted and the new project's success is not guaranteed. Very quickly the state of Vermont and the District of Columbia readied legislation that would allow them to issue compulsory drug licenses to patent holders under the eminent domain process in order to drive down prices in their respective jurisdictions. The respective jurisdictions would then contract with a generic manufacturer to produce the drug, paying the drug company a "reasonable royalty" on each sale (4 percent was proposed). The contention was that the competition would facilitate the "public good" by offering State residents cheaper drugs.

In effect, the problem of IP has become the same problem as the security and academic freedom conundrum: that is, finding the right balance between the preservation of IP as a

reward for exceptional work, marked by the issuance of a patent and a licensing agreement and as an incentive to do better, with the desirability of advancing the "public good." In the case of IP, a large majority of university technology transfer offices have licensed few or no significant commercialized products, and typically operate at a loss, unless they happen to own a blockbuster piece of IP. In addition, many products remain too expensive for those in need to purchase them, even in the United States.

Summary:

As the emerging/re-emerging infectious diseases problem continues to evolve, with the potential for new problems to arise as a result of natural events or by the determined effort of some to genetically engineer organisms to do harm, and as pressure on government to act to protect the public, there is an increased need for research, information and, at times, restriction of the open access to new information. In every case a balance must be struck between government concerns for secrecy and the academic need for openness. The two are not compatible unless made to be so by vigilant citizens on both sides of the equation. Equally as pressing is the problem of balancing intellectual property and the costs of commercial development of new drugs and medical technology with the need of the public for affordable products. In the private pharmaceutical industry model which exists in the United States and virtually all the world's rich countries, the public assumes the financial risk inherent in drug and medical device research and development, and risk, investment and profit figure in the pricing models. When the products are life-saving, and at risk of being priced out of access to the poor in developing countries, a new model is necessary in which R&D occurs in an environment of cooperation and mutual benefit for industry and the public, including those in poor developing nations, for example, tiered pricing or technology transfer and local manufacture. Excessive stridency will not work and could be highly counterproductive.

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Technology for Identification of emerging and re-emerging pathogens

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Emerging Infectious Diseases

- Having been identified in China
- Having possibility being transferred from other countries into China;
- Un-known emerging infectious diseases in future

The importance of Detection

- The occurring and spreading of emerging and re-emerging infectious diseases is testing how effective our diagnosis and surveillance is performed.
- If the diagnosis or surveillance fails to address the needs of public and policy-makers, it is likely that there will be loss of confidence.

Current problems

- It is difficult to detect or identify emerging pathogens in a country where the reliable method, technology or experienced personals is not available.
- Detection such events relies on good data collection, comparative background data, reference pathogen strains or materials, diagnostic serum.

Keys

- One of the keys to deal with emerging infectious diseases globally is developing the collaboration, technology exchange and information sharing among involving countries.

Global Efforts to Deal with Emerging Infectious Diseases

- Technology transfer for detection of emerging infectious disease
- Workshop for training personal
- Reagents and materials
- Technology sharing in field of emerging infectious diseases

Trilateral Seminar on R&D Policies related to Emerging and Re-emerging Infectious Diseases

Session III: Products and Technologies

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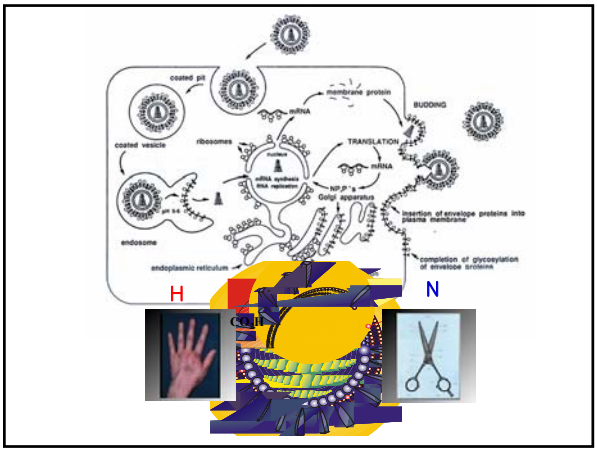
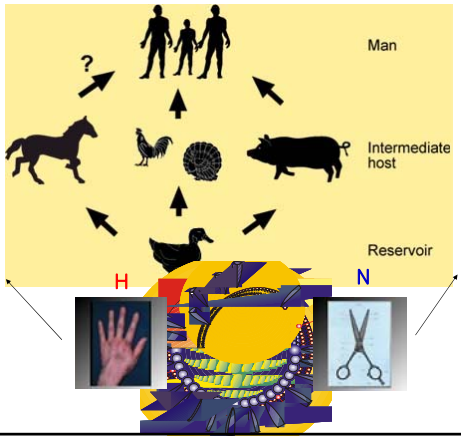
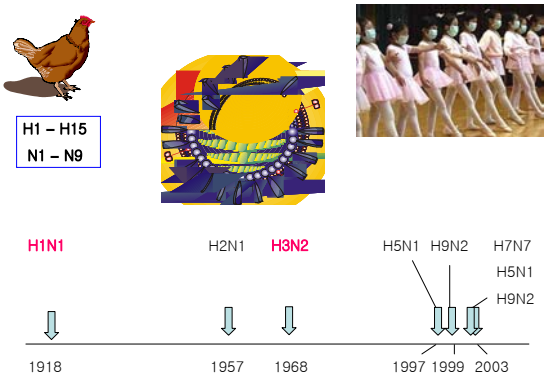
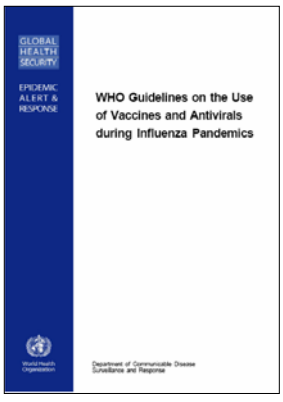






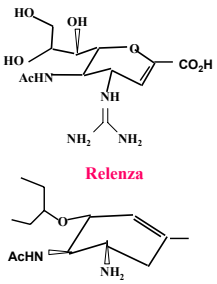


Therapeutic Intervention

Vaccine Development

Pandemic Preparedness: Stockpiling of Antivirals

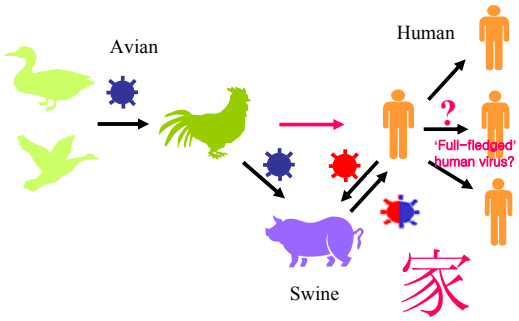
Neuraminidase



Relenza

TamiFlu

Transmission of Avian Influenza to Human



Pandemic Preparedness: Global Aspects

Antivirals: Stockpiling of TamiFlu

Vaccines: 1) Broad spectrum, needle-free vaccine

2) Dose - sparing strategy: Adjuvants

3) Cell-culture vaccine

4) Recombinant vaccine:

Genomic vaccine with other viral components

Pandemic Preparedness: Korean Perspective

Contingency plan for vaccine shortage

- Independent vaccine production facility
- Cell culture production facility (Celltrion; CMO)
- Independent vaccine strain (warning from 1997 HK AI)

1) A/Leningrad/134/17/57 (H2N2)
B/USSR/60/69
2) A/Ann Arbor/6/60 (H2N2)
B/Ann Arbor/1/66 FluMist
3) A/X-31(H3N2) virus (PR8/34 H1N1 backbone)
B/Yamagata & B/Lee

Global Planning of Pandemic Preparedness

- Global economic impact by avian influenza pandemic: 200 billion US$ (World Bank estimate); 300 billion US$ (Asia Development Bank ADB estimate).
- WHO issued revision of Global Influenza Preparedness Plan (May 2005). WHO estimates 500 million cases of infection with 2-7 million death in case of pandemic.
- USA: President George Bush submitted an R&D expenditure plan of 7.5 billion US$ for avian flu pandemic (Oct. 2005)
- President Bush urges in UN summit conference to establish International Partnership on Avian and Pandemic Influenza (IPAPI) (Sept., 2005)
- China: Allocated 2 billion Yuan (about 250 million US$) for pandemic preparedness plan (Oct. 2005).
- Thailand: Avian influenza pandemic preparedness fund (100 million Bat) for southeast Asian countries (Oct. 2005).

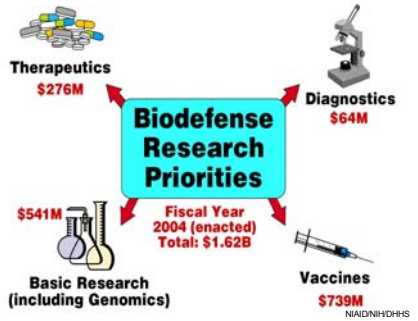
Plan for E&RE Pathogens: Korea vs US

- Vaccine Production Facility: 10 million US$ (Green Cross-GSK)
- Strategies on Emerging and Re-emerging Viruses (SERV) (0.5 million US$) (2004-2005)
- Pandemic Influenza Research Grant (0.3 million US$) (Dec. 2005)
- Bio- and Chemical Terrorism Grant (1 million US$/yr)(2002 -2007)

Project Bioshield: 5.6 billion US$

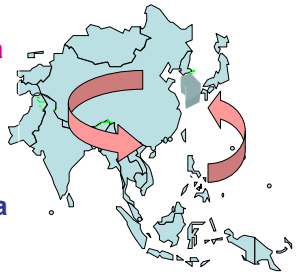
Avian flu pandemic: 7.5 billion US$

Project Bioshield



The Pandemic Influenza Consortium, Korea (PICK)

for the Prevention and Control of Pandemic Influenza in the Asia Pacific Region



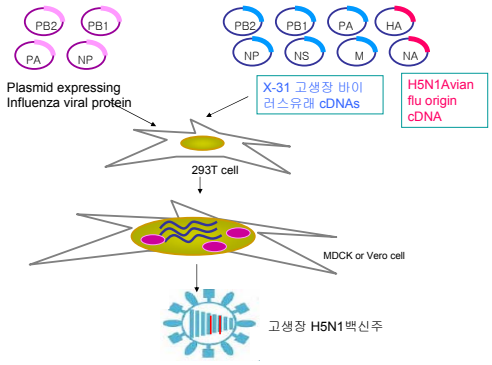
Budget: 500 million US$

Duration: 5 yrs

Project Goal 1: Development of high-yielding H5N1 vaccine strain

- ***Strategic Objective: Development of reverse genetic methodology, generation of high-yielding genetically engineered H5N1 vaccine strain and method for rapid analysis of the genetic composition of vaccine virus***
- *Deliverable:* High yielding H5N1 vaccine strains suitable for mass production in embryonated eggs and animal cell culture

Establishment of reverse genetic system uptake using cDNA transfection and production of H5N1 vaccine strain



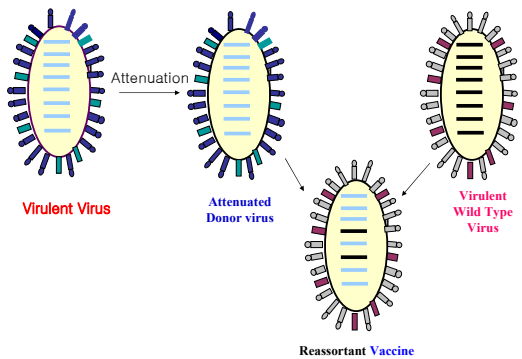
Project Goal 2: Recombinant and Genetic Vaccine

- ***Strategic objective: Combination of M2 or NP proteins with HA/NA as new protective antigens***
- Rationale:
  - M2 protein has been recently identified as a component of influenza virion. NP (nucleoprotein) is an internal viral protein, and in contrast to surface antigens, maintains high degree of homology among various influenza subtypes, and is known to provide strong CTL (Cytotoxic T lymphocyte) response.
  - The inclusion of these proteins, in addition to the classic HA/NA antigen, is expected to induce higher and cross-protective immunity among different influenza subtypes.

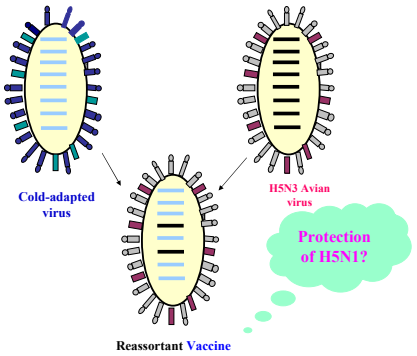
Project Goal 3: Development of "needle free" vaccine for mass immunization

- ***Development of fast-acting nasal spray type live attenuated avian influenza vaccine suitable for mass immunization***
- Rationale:
  - Live attenuated induces mucosal immunity on the respiratory tract and the secretory IgA class antibody provides the first line of defense against the infecting virus.
  - Live attenuated H5N1 vaccine could be delivered as nasal spray with minimal medical guidance and therefore suitable for mass immunization in time of pandemic.
  - Live vaccine stimulates innate immune responses that provides immediate protection and broad-spectrum immunity.

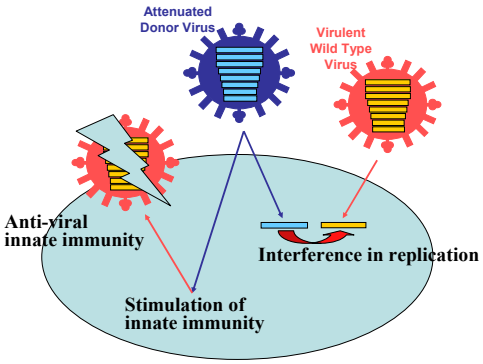
Live Vaccine Candidates by Reassortant Formation



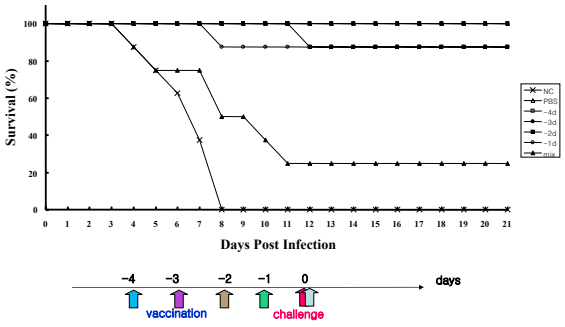
Live Vaccine Candidate for Avian Influenza



Immediate Protection & Broad Spectrum Immunity: Innate Immune Response by Live Vaccine



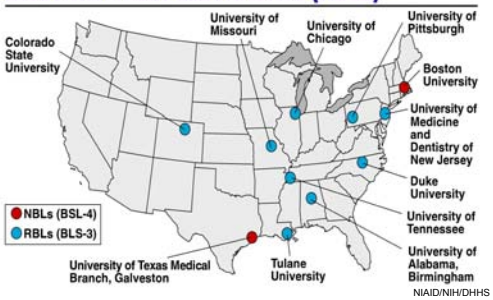
Early Protection and Potential Therapeutic Effects: Protection from New Caledonia Strain



Project Goal 4: Research Infra-structure

- Vaccine Center of Excellence (VCE)
- Regional Biocontainment Laboratory BSL3 level (RBL)

NIAID-Supported National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs)



NIAID/NIH/DHHS

http://www.bepast.org/

Center for Biologic Counterterrorism and Emerging Diseases
MedStar Health Group Washington, DC

Disease Information

Anthrax
Avian Influenza
Botulism
Hemorrhagic Fever
MDR Tuberculosis
Monkeypox
Pandemic Influenza
Plague
S A R S
Smallpox
Tularemia
West Nile

Pandemic Influenza

Sin Nombre/ Hantaan

Acronyms for ~ 40 Category A, B, & C Potential Bioterrorism Diseases

Category A: "BE PAST"

Category B: "BEWARE OF GERMS"

Category C: "HINT: YEAR(S) TO COME"

B: Botulism
E: Ebola (VHFS)

P: Plague
A: Anthrax
S: Smallpox
T: Tularemia

http://www.bepast.org/

Center for Biologic Counterterrorism and Emerging Diseases
MedStar Health Group Washington, DC

- Updates
- 2005-11-24: WHO - Influenza Pandemic Threat page
- 2005-11-17: WHO - Cumulative H5N1 cases in humans as of November 17 2005
- 2005-11-23: Bloomberg - China's New Bird Flu Outbreaks Take Total to 25
- 2005-11-02: References to Masks or N-95 Respirators in the HHS Pandemic Flu Plan
- 2005-11-22: New York Times - US bans some Canadian poultry
- 2005-11-21: Reuters - Romania confirms H5N1 virus in Danube delta poultry
- 2005-11-18: Reuters - U.N. to set up bird flu early warning system
- 2005-11-08: Dagens Nyeter - First Photos of Avian Flu Virus
- 2005-11-02: HHS - National Influenza Pandemic Plan
- H5N1 Influenza: The Pandemic Threat

Conclusion

- Secure R&D funds from competing activities (bioterrorism or stem cell research)
- All we want is that pandemic does not occur at all.
- Strategy to minimize the opportunity cost
- Avian influenza does not respect national borders and international collaboration is most essential.

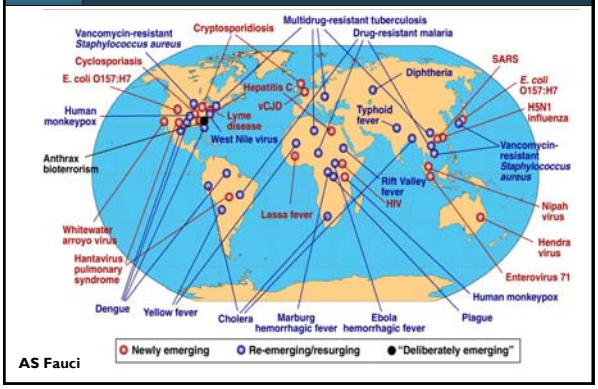
Global Emerging and Re-emerging Infectious Diseases Research: The Emerging Infectious Diseases and Biodefense Network in the USA

Mark S. Klempner, MD

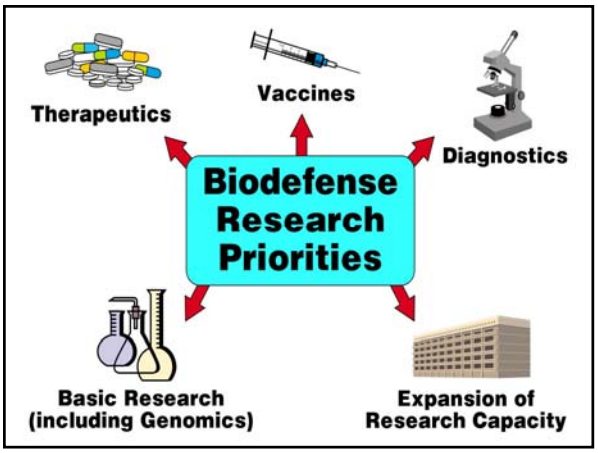
Boston University
Associate Provost for Research

Director, National Emerging Infectious Diseases Laboratories (NEIDL) Institute

GLOBAL EXAMPLES OF EMERGING AND RE-EMERGING INFECTIOUS DISEASES



AS Fauci



Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs)

- RCE Network established in 2003
- 10 centers (8 funded in 2003, 2 in 2005)
- >150 research projects; >100 pilot projects
- $350M total funding over 5 years
- ~90 publications as of July, 2005 on Category A, B and C pathogens, host immunity, countermeasure development

NIAID Regional Centers of Excellence (RCEs)

- Basic research to understand category A, B, and C agents
- Interdisciplinary research
- Translational research leading to the identification of new drugs, vaccines and diagnostics
- Training of new researchers
- Developmental research projects
- Research for National emergency responders

NIAID CATEGORY A, B & C PATHOGENS

Category A
- Bacillus anthracis (anthrax)
- Clostridium botulinum
- Yersinia pestis
- Variola major (small pox) and other pox viruses
- Francisella tularensis (tularemia)
- Viral hemorrhagic fevers
  - Arenaviruses
    - LCM, Junin virus, Machupo virus, Guanarito virus
    - Lassa Fever
  - Bunyaviruses
    - Hantaviruses
    - Rift Valley Fever
  - Flaviruses
    - Dengue
  - Filoviruses
    - Ebola
    - Marburg

Category B
- Burkholderia pseudomallei
- Coxiella burnetii (Q fever)
- Brucella species (brucellosis)
- Burkholderia mallei (glanders)
- Ricin toxin (from Ricinus communis)
- Epsilon toxin of Clostridium perfringens
- Staphylococcus enterotoxin B
- Typhus fever (Rickettsia prowazekii)
- Food and Waterborne Pathogens
  - Bacteria
    - Diarrheagenic E.coli
    - Pathogenic Vibrios
    - Shigella species
    - Salmonella
    - Listeria monocytogenes
    - Campylobacter jejuni Yersinia enterocolitica)
  - Viruses
  - Protozoa
    - Cryptosporidium parvum
    - Cyclospora cayatanensis
    - Giardia lamblia
    - Entamoeba histolytica
    - Toxoplasma
    - Microsporidia
- Additional viral encephalitides
  - West Nile Virus
  - LaCrosse
  - California encephalitis
  - VEE
  - EEE
  - WEE
  - Japanese Encephalitis Virus
  - Kyasanur Forest Virus

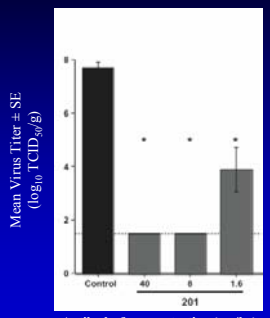
Category C Emerging infectious disease threats such as
- Nipah virus and additional hantaviruses.
- Tickborne hemorrhagic fever viruses
  - Crimean-Congo Hemorrhagic fever virus
- Tickborne encephalitis viruses
- Yellow fever
- Multi-drug resistant TB
- Influenza
- Other Rickettsias
- Rabies
- Severe acute respiratory syndrome-associated coronavirus (SARS-CoV) (Note: SARS-CoV added August 30, 2004)

SARS

MAb to SARS

- 3/03 SARS Agent identified
- 5/03 NIH supports MBL to discover protective MAb
- 9/03 MBL identifies binding domain for SARS and neutralizing antibody
- 5/04 Identify MAb that protects mice from SARS
- 10/04 Announce MAb effectively treats SARS in animal model

SARS CoV Replication in Mouse-Lungs



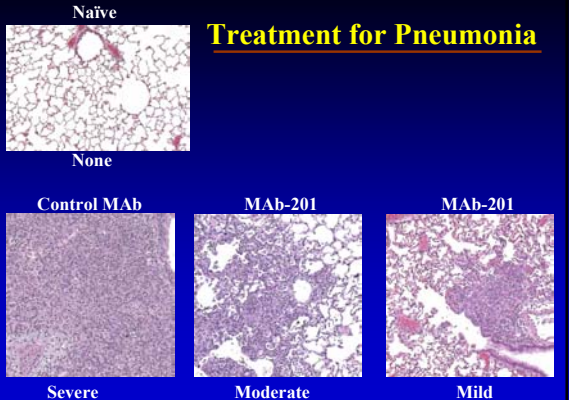
*p value <0.05

PROPHYLAXIS

SARS MAb as Treatment

- **Laboratory of Infectious Diseases, NIAID, NIH**
  - Anjeanette Roberts · Elaine Lamirande
  - Kanta Subbarao · Leatrice Vogel
- **Comparative Medicine Branch, NIH**
  - Jadon Jackson
- **University of Massachusetts Medical School & Massachusetts Biological Laboratories**
  - Donna Ambrosino · Thomas Greenough
  - William Thomas · Gregory Babcock
  - John Sullivan
- **Infectious Disease Pathology Activity, CDC**
  - Jeannette Guarner · Sherif Zaki
  - Norman Hayes

Treatment for Pneumonia



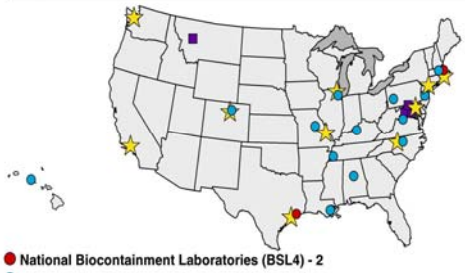
NIAID Regional Biocontainment Laboratories (RBLs)

- 13 RBLs (9 funded in 2003, 4 in 2005)
- ~$260M total funding from NIAID; institutions provided matching funds
- Design, construct, and commission state-of-the art BSL-2/3 laboratories, and research and administrative support space
- Complement & support research activities of the RCEs
- Available to assist national, state, and local public health efforts in event of bioterrorism or infectious disease emergency

NIAID National Biocontainment Laboratories (NBLs)

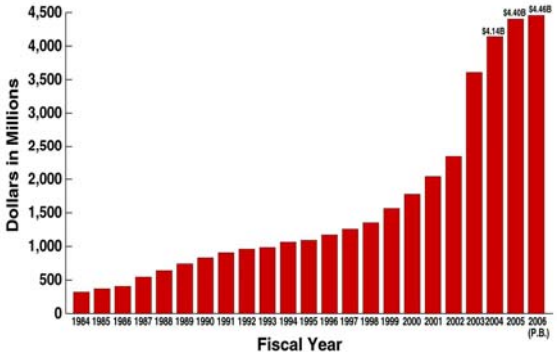
- 2 NBLs, funded in 2003
- ~$240M total funding from NIAID; institutions provided matching funds
- Design, construct, and commission state-of-the art BSL-2/3/4 laboratories, and research and administrative support space
- Complement and support research activities of the RCEs
- Available to assist national, state, and local public health efforts in event of bioterrorism or infectious disease emergency

Expansion of Biodefense Research Capacity

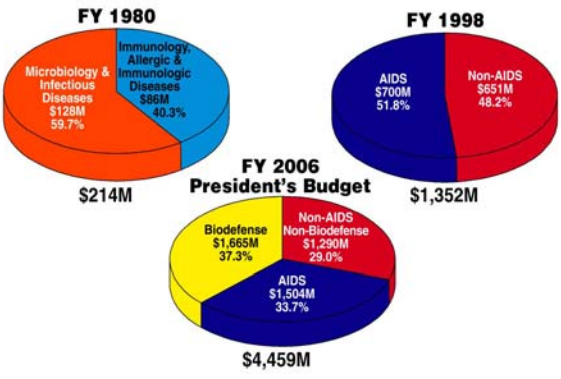


- National Biocontainment Laboratories (BSL4) - 2
- Regional Biocontainment Laboratories (BSL3) - 13
- Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research - 10
- New NIH Facilities - 4

NIAID Funding History, 1984-2006 (P.B.)



The Evolution of the NIAID Budget



The NEIDL Institute's Mission

- Basic and clinical research on emerging infectious diseases, including category A, B, and C agents aimed at developing diagnostic tests, treatments and vaccines to promote the public's health.
- To provide training in these areas of research.
- To support a national response in the event of a biodefense emergency.
- To establish a research facility with the highest attention to community and laboratory safety and security.

National Emerging Infectious Diseases Laboratories at Boston University Medical Center

NATIONAL EMERGING INFECTIOUS DISEASES LABORATORIES (NEIDL)

Located within BioSquare Phase II Development Area.

Building Area: 195,000 sf.

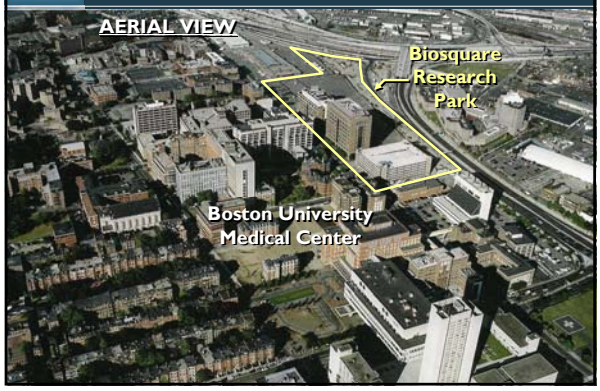
7 floors / 111 ft

Building setback 150' from Albany Street.

Begin Construction 1st Qtr 2006

Occupy 3rd Qtr 2008

PROJECT LOCATION



NEIDL Cores

Research Cores

1. Aerobiology Core BSL-3
2. Aerobiology Core BSL-4
3. Animal Core BSL-3
4. Animal Core BSL-4
5. Bioinformatics Core
6. Biomolecule Production Core for BSL-3
7. Biomolecule Production Core for BSL-4
8. Cell and Tissue Imaging Core
9. Clinical Research Core
10. Genomics/Microarray Core
11. High throughput Screening Core
12. Immunology Core
13. Insectarium Core BSL-3
14. Insectarium Core BSL-4
15. Proteomics/Mass Spectrometry Core
16. Specimen Processing Core
17. Training Simulator Core
18. Whole Animal Imaging Core
19. Collaborative Research Core #1
20. Collaborative Research Core #2

Operations Cores

1. Management/Administration Core
2. Community Relations Core
3. Emergency Response and Planning Core
4. Environmental Health and Safety Core
5. Facilities Core
6. Information Technology Core
7. Materials Management Core
8. Occupational Health Core
9. Security Core
10. Telecommunications Core

BOSTON MEDICAL CENTER

Global Issues For The Emerging Infectious Diseases and Biodefense Network in the USA

Safety Standards
Construction Standards
Research Priorities
Collaborative Research Projects
Collaborative Funding
Global Stockpiles:Where? Under What Auspices?
Distribution: Oversight and Logistics