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Final
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May 18, 1999

Qs and As on NIH Response to the AVAC report, "Eight Years and Counting"

Q. What is the NIH response to the report?

A. Developing an AIDS vaccine is a priority for us all and AVAC should be commended for its rigorous advocacy for research and development of an AIDS vaccine.

Q. Where are we on developing an AIDS vaccine?

A. This Administration has responded aggressively to the significant threat posed by HIV/AIDS with increased attention to research, prevention and treatment. Significant progress has been made in the federal vaccine effort: Since May 18, 1997, when President Clinton challenged the nation to commit itself to the goal of developing an AIDS vaccine within the next ten years, a number of important steps have been taken to help fulfill this commitment, including:

- Doubling the funding for AIDS vaccine research since FY 1995. NIH plans to spend \$194 million on AIDS vaccine efforts in FY 1999, up 30% from FY 1998.
- A dedicated research center for AIDS vaccine research at NIH is being established.
- As of May 1999, NIH-supported researchers had evaluated 27 vaccine candidates and 12 adjuvants (substances incorporated into a vaccine that boost specific immune responses to the vaccine) in more than 3,000 volunteers in 49 phase I/II clinical trials.
- Three key leaders have been appointed to help shepherd the aggressive federal efforts.
- In June 1998, FDA approved the first large-scale efficacy trial of an AIDS vaccine in the United States.
- Continued high-level international collaboration and outreach to scientists, pharmaceutical companies, and patient advocates to maximize the involvement of both private and public sectors in the development of an AIDS vaccine.

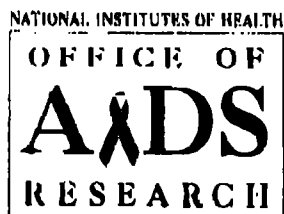
Q. Are we on track for an AIDS vaccine within the next decade?

A. Federal research programs are fully committed to developing a safe and effective AIDS vaccine. While we can't always predict where the science will take all partners in this important effort, we have put into place research, development and

management strategies to seize the most promising advances and translate them expeditiously into potential products, including:

- New initiatives have been launched to enhance opportunities for vaccine discovery and to help move vaccine concepts from basic research through clinical trials with the goal of increasing the number of new, innovative and promising vaccine concepts flowing through the pipeline.
- Three key leaders have been appointed to help shepherd the aggressive federal effort.
- Several scientific advances in basic immunology and new vector development have greatly enhanced our research efforts.
- More than 3,000 non-HIV -infected volunteers have enrolled in 52 NIAID-supported preventive vaccine studies involving 27 vaccines.
- In June 1998, FDA approved the first large-scale efficacy trial of an AIDS vaccine in the United States. The trial for AIDSVAX will include at least 5,000 volunteers from the U.S., Canada and Europe and will last up to five years. A separate Phase III trial of AIDSVAX in Thailand will enroll 2,500 volunteers.

While considerable progress has been made, progress cannot simply be measured by the number of products passing specific milestones because quality of vaccine products is much more important than the number tested. Since advancement of new candidate vaccines into phase 1 trials is an important milestone in vaccine research, we envision periodic review, at least yearly and with input from the AIDS Vaccine Research Committee, of potential candidates that might be considered for high priority advancement to phase 1 trials.

**FACSIMILE TRANSMISSION****DATE:** 11/14/97**TO:** Todd Summers**PHONE:** 202-632-1090**FAX:** 202-632-1096**FROM:** Bonnie Mathieson, Ph.D.
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Fax: (301) 496-4843**SUBJECT:** _____**TOTAL NUMBER OF PAGES INCLUDING THIS COVER SHEET:** 3
(If total number of pages have not been transmitted, please call 301-496-4564)**REMARKS:**

Why a Push for an HIV/AIDS Vaccine Now? What has changed?

There is no single breakthrough but rather a series of scientific findings and advances over the past 2 years that have convinced investigators to be more optimistic about the possibility of an effective vaccine to prevent HIV infection.

1. **BEFORE:** By genetic sequence it was known that **HIV-1 is highly variable**, particularly in the proteins at the surface of the virus. There are at least 7 major variant families of HIV-1 and viruses from every infected individual are unique. It was feared that this high degree of variability might be an unsurmountable obstacle and would require hundreds or thousands of variants for vaccine design.

NOW: Scientists have shown that both the serum antibody arm and the cellular arm of the immune system which recognize differences between strains of HIV, also recognize similarities that were not previously predicted. New computer models and data from virus targeting in cultures suggest that a vaccine designed for the world might be possible with only a few components.

2. **BEFORE:** Because most transmission of HIV-1 is by sexual (mucosal) exposure and many early attempts to test vaccines against other sexually transmitted diseases had failed, it was felt that it would be more difficult to protect against virus entering the body through mucosal surfaces. Furthermore, animal models for vaccines were primarily tested by challenging them with virus injected directly into the bloodstream and these vaccines were only partially successful.

NOW: Recent animal experiments with SIV, the related virus from monkeys, HIV in chimpanzees, and recombinant SIV-HIV (SHIV) viruses tested in monkeys suggest that it may be easier for vaccines to protect from virus exposure at mucosal sites than from direct blood exposure because mucosal surfaces have several built-in defense systems that either help to limit the actual number of virus particles that get through the initial barrier and/or the immune system is more effective at limiting the replication and initial spread of virus from these sites.

3. **BEFORE:** Scientists thought that a vaccine would have to prevent ANY virus from infecting someone; this is referred to as "sterilizing immunity".

NOW: Several animal experiments with "live vector" vaccines that activate the cellular component of the immune system have shown that even if the animals become infected, they are able to control the virus. This results in animals that either are able to eventually clear the virus or reduce the virus to undetectable levels and remain healthy without drug therapy. Also there is strong evidence that HIV-infected individuals who naturally are able to effectively control virus load without drug therapy become long-term non-progressors.

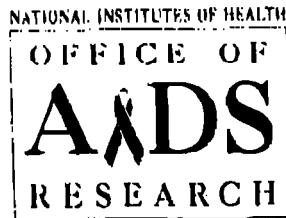
4. **BEFORE:** HIV can be shown to prefer to grow either in macrophages or in T cells. The first virus that can be isolated from infected cells in the blood is often the type that grows in macrophages, so scientists thought that it would be important to focus the design of vaccines to selectively prevent HIV-1 from infecting macrophages.

NOW: Recent animal experiments with SIV, SHIV and HIV indicate that it is very difficult, if not impossible, to transmit infection with solely macrophage-tropic viruses via mucosal routes. Whereas, it is possible to mucosally transmit viruses when they grow easily in T cells. Recent data from scid mice with human blood cells also suggest that differences in the growth rates for the macrophage-tropic viruses and T-tropic virus may explain why macrophage-tropic viruses are seen first.

5. **BEFORE:** Because HIV (and SIV) can be "hidden" inside cells like a Trojan horse, it was thought that it would be critical to design vaccines to protect against infection by "cell-associated" virus. Further, it was proposed that this might be the most effective way to transmit HIV.

NOW: Repeated attempts in animal models to transmit infection via sexual routes of exposure with infected cells have only rarely succeeded even at 1000X the cell dose required to infect by direct injection into blood. Those few transmissions may be attributable to virus shed from the infected cells. In addition, the natural differences between cells (histocompatibility type) from different individuals may play a role to prevent infection in individuals that are heavily exposed to HIV infection. Whereas, depending on the mucosal site exposed, cell-free virus from almost every stock tested can be shown to be transmitted with equivalent or slightly less efficiency than injection of the virus into the blood stream.

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5/29/97

**FACSIMILE TRANSMISSION**

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REMARKS:

*Todd —
I don't see why they
are being so secretive —
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need for survey —*

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of comments —*

*are you any closer
Helen*

*Editorial Review # 2***AREA OF EMPHASIS:****Vaccines****Status:****Overview**

Developing a vaccine or vaccines that are safe and effective in preventing HIV infection in exposed individuals is a major public health priority in the national and international effort to combat this pandemic. HIV disease continues to have a major impact on public health worldwide, and its spread is projected to increase through the year 2000 and beyond. The United Nations Joint Programme on AIDS (UNAIDS) has estimated that about 8,500 people become infected with HIV daily, of which 90 percent are in the developing world. If current trends persist, the rate of new infections will remain relatively stable in Europe and North America but will expand and devastate parts of Latin America, Africa, and Asia.

In the United States alone, more than 600,000 persons have developed AIDS, and as many as 850,000 are believed to be infected with HIV-1. The demographics of newly reported AIDS cases has been shifting to an increasing proportion in women, adolescents, and minorities. Even with the reduced number of AIDS deaths in the past year, it is estimated that there are 40,000 to 60,000 new infections occurring annually in the United States. New data indicate that trends for reduced risk of

infections in homosexual populations may have reversed, particularly in young men, with the unsubstantiated belief that new drug combinations would provide a cure.

Finding effective means to control the human, social, and economic costs of HIV/AIDS represents one of the highest public health priorities. Behavioral interventions remain a critical component in preventing the spread of HIV, and delivery of effective drug therapy will decrease the number of AIDS deaths in the near term in the United States. These activities alone will not be sufficient to contain the epidemic, and vaccines may be the only cost-effective way to prevent HIV infection worldwide. Therefore, an affordable, safe, and effective vaccine that is also easily delivered and acceptable to various populations at risk is urgently needed.

To address the obstacles and facilitate HIV vaccine development, NIH has stepped up support for a broad program encompassing basic, preclinical, and clinical vaccine research on candidate vaccine products. To this end, the AVRC, headed by Dr. David Baltimore, has been established to increase the focus on new strategies for discovery and development of a safe and effective HIV vaccine. The AVRC identified three specific areas of basic research that were needed to support more effective vaccine research. These areas were understanding the structure and function of HIV envelope (env) protein; improvement of animal models to understand correlates of immune protection; and understanding the

1997

mechanisms of directing antigen processing *in vivo*. A new program of 2-year "innovation" grants were awarded through NIAID in FY 1998 to encourage active support of these specific research areas. In addition, a cross-institute NIH Vaccine Laboratory effort has been initiated by focused staff discussions, and joint vaccine research will be funded through NIAID and NCI intramural programs beginning in FY 1998.

In parallel, NIH supports research on risk factors and other preventive interventions that will form an essential foundation for vaccine trials, in collaboration with other Federal agencies, local communities, industry, and international organizations.

Goals for a Preventive Vaccine

The goal of preventive vaccines is to slow and eventually end the HIV pandemic and to protect the individual from HIV infection and/or disease. Protective efficacy against HIV infection can be measured by a range of clinical and virological endpoints. Desirable goals of vaccination are to induce immune responses that quickly clear or reduce incoming virus and infected cells and, if HIV is established, to control viral replication and maintain a low viral load, thereby preventing disease progression and transmission. It may be unrealistic to expect an HIV vaccine to completely prevent HIV infection. Optimally, the vaccine-induced immune response would be capable of clearing virus and virus-infected cells. Thus, limited replication might occur

at the site of entry, but disseminated infection would be prevented.

Control of viral replication, even if the virus is disseminated, could maintain a low viral load and/or reduce viral shedding, thereby preventing secondary spread of the virus to others. Vaccine-induced diminution in viral load also might be correlated with prevention or delay in disease progression; a correlation between low virus load and long-term nonprogression has been observed in both epidemiologic investigations and animal studies of pathogenesis and vaccines. Efficacy of vaccines in preventing established infection can be determined relatively early in the conduct of a vaccine trial by viral culture or PCR. However, assessment of long-term control of viral replication, or immunosuppression and disease progression, which may be critical for assessing efficacy, will make the conduct of efficacy trials more complex. This will be particularly true in populations with access to the highly effective multiple-drug therapeutic regimens early in the course of infection.

enzyme
reaction

Vaccine efficacy may also be influenced by the dose of infecting virus and by the site or route of exposure. For example, a vaccine may protect against a low dose of virus at a mucosal site of sexual exposure but not protect against a large inoculum acquired intravenously. Alternatively, a vaccine may protect against exposure to virus intravenously but not protect against spread of HIV infection from an established

mucosal site. Vaccine strategies therefore may need to be tailored for route of HIV exposure and may require combination approaches to optimize protection.

Various strategies for stimulating a protective immune response against HIV infection are being explored through basic research, animal models, and clinical trials. There are many inherent uncertainties, not only in the identification of the immune responses required for protection against HIV infection or disease but also in the vaccine designs and strategies needed to induce such protective responses. Thus, multiple conceptual and practical approaches to development of candidate vaccines are being pursued at the preclinical level, with prioritization into small Phase I trials and additional selection and prioritization of candidates for further clinical study. Conducting small clinical trials affords the opportunity to return to the laboratory and refine those candidates that prove less than optimally immunogenic and permits rapid incorporation of vaccine improvements. Vaccines also may serve as immunomodulators to improve immune function and diminish HIV disease progression particularly in recently infected individuals and may potentially prevent transmission from mother to fetus or from one infected adult to another.

Basic Research Relevant to Vaccine Development

Basic research on HIV and the immune system provides crucial information required for the development of vaccine

candidates. These efforts, however, are complicated by many unique aspects of HIV infection, including an unprecedented degree of antigenic variation. There are at least two major groups of HIV-1 (M and O), with each exhibiting several major genotypic subtypes (clades). Virus from one clade (B) predominates in the United States. However, there is extensive variation within a single clade and even in a single individual. This variation has been shown to affect recognition by and escape from both humoral and cellular immune responses. Vaccines capable of eliciting an immune response to a broad spectrum of antigenic specificities or to highly conserved epitopes will thus be required to protect against HIV infection.

Recent information suggests that antibodies (humoral immunity) from some infected individuals are able to effect broad neutralization of HIV subtypes. This suggests common epitopes, possibly related to the receptors and coreceptors of the virus that are expressed on widely divergent subtypes of HIV. In addition, recent data from both HIV-infected and HIV vaccine volunteers indicate that cytotoxic T cells also are able to recognize epitopes from widely divergent HIV.

The NIAID-sponsored HIV variation project is investigating the rate and magnitude of both genetic and antigenic variation in HIV and related retroviruses. The findings from this project will help determine the impact of such variation on strategies for developing potential AIDS vaccines.

*Recent information
reported @
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suggests this
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The nature of the immune response needed to protect against HIV infection or to ameliorate established infection is poorly understood because much still needs to be learned about immune responses, in general, and those relevant to protection from viruses with the potential to establish latency in infected cells, in particular. In this context, a great deal of new information will be necessary if one is to create vaccines that will be effective against a virus such as HIV that replicates within cells, specifically targets and destroys cells of the immune system, and can spread by cell-to-cell transmission. This includes knowledge concerning (1) the factors that regulate the induction of cytotoxic T cells that destroy virus-infected cells of various types, (2) the factors that determine whether effector immune responses that occur to key antigens are amplified rather than ~~tolerized~~ or deleted responses, (3) the factors that establish immunologic memory responses to antigens of interest so that protection is persistent, (4) the identity, source, regulation, and mechanism of action of cytokines or chemokines that affect, directly or indirectly, viral replication and persistence, (5) the signaling events that result in productive T-cell activation or interfere with responsiveness, (6) the role of antibodies in reducing virus load and/or controlling the spread of infection, (7) the mechanisms by which antibodies function to neutralize HIV and related viruses, (8) the role of antibody-dependent killing of infected cells, and (9) the interaction of humoral and cellular immune responses at mucosal sites to effectively contain viral infection.

Vaccine Strategies

Currently, NIH researchers are pursuing a multipronged approach for the development of HIV vaccines including traditional approaches such as the incorporation of killed viruses in known adjuvants and the development of attenuated viruses. There are serious concerns about the safety of these approaches that remain unresolved, but studies in animal models on killed and attenuated virus vaccines may help to reveal the correlates of immune protection and the requirements for an effective vaccine. However, the unique problems posed by HIV suggest a need for increased efforts to design novel approaches. Several being pursued include the use of synthetic viral peptides, recombinant proteins, and virus-like particles (VLPs). In addition, live recombinant vectors, vaccines composed of copies of the virus genome incorporated into the genomes of highly immunogenic but non-disease-producing carrier viruses such as vaccinia and avipox, are being studied. Other vaccines under evaluation in animal studies (e.g., adenovirus or poliovirus vectors) exhibit efficient delivery of antigens to selected compartments of the immune system, such as the mucosal area, where specialized immune responses particularly relevant to preventing entry of HIV are needed.

One area of emphasis is the design of more complex synthetic vaccine candidates capable of inducing both cellular and humoral immunity. This involves identifying segments of the HIV glycoprotein envelope and internal proteins, such as Gag and RT,

Is this really correct? Where? Who? How much?

gag RT

that induce immune-targeted helper T cells and cytotoxic T lymphocytes (CTLs). Another approach is the development of genetically engineered, noninfectious HIV mutants that lack the viral RNA genome or are crippled in such a way that the virus is unable to infect yet contains a full complement of HIV antigenic proteins, which can assemble ~~potentially into more authentic~~ as VLPs, against which a protective response can be generated. VLPs can be produced in genetically engineered cell lines to decrease safety concerns.

One promising new approach to eliciting cell-mediated and humoral immune responses utilizes the direct injection of "naked" DNA encoding HIV antigens into muscle or other accessible tissues. Animals injected with DNA construct for the HIV *env* gene produced CTLs and humoral responses specific for the HIV envelope and produced antibodies that neutralized certain infectious HIV isolates *in vitro*.

These studies of potential vaccine candidates need to be expanded to include a far wider group of molecular, bacterial, and viral vectors and to include strategies that address the problems of intracellular HIV and viral latency. Nearly all of the first-generation vaccines that have reached evaluation in human volunteers were based on laboratory-adapted isolates of HIV that are more easily neutralized than macrophage-tropic primary HIV strains that are isolated early after infection in many individuals. Second-generation vaccines based on primary HIV isolates are just entering early research testing. Finally,

combination approaches, sometimes referred to as "prime plus boost" strategies, need to be explored more fully to enhance the responses induced by only a single type of vaccine approach.

HIV/Chimpanzee Model

Some strains of HIV-1 can infect chimpanzees, thereby establishing an animal model to evaluate vaccines and infection with HIV-1. However, infections with most HIV isolates have not been accompanied by development of disease. After incubation periods exceeding 7 years, several chimpanzees have shown signs of immune suppression and AIDS. HIV-1 from the affected animals may have become adapted to chimpanzee cells and developed a higher pathogenic potential.

In vaccine studies utilizing the HIV/chimpanzee model, native or recombinant HIV *env* proteins and virus vectors carrying HIV protein genes have induced both cellular and humoral immunity. In addition, studies of *env* product vaccine candidates as well as more complex HIV vaccine strategies with recombinant adenovirus vectors or HIV DNA have shown efficacy in preventing HIV infection in chimpanzees. Hyperimmune anti-HIV immunoglobulin (HIVIG) and several monoclonal antibodies to envelope protein also have been evaluated for safety and potential to prevent HIV infection in chimpanzees under experimental conditions. Chimpanzees with persistent but apparently "attenuated" HIV infection have been exposed to other HIV isolates

Can't that be determined?

from the same or different clades in an attempt to learn whether immune responses that were not capable of clearing the initial infection were, nonetheless, capable of combating a new strain. Thus, infected chimpanzees may provide a valuable resource for studying cross-reactive immune responses. NIH supports chimpanzee colonies and programs that evaluate vaccine candidates and products for passive immunity in this animal model. The importance of using more pathogenic-virus challenge stocks and routes of exposure that more closely approximate naturally occurring HIV strains has been appreciated, and new stocks are in development or being tested both for strains found in the United States and elsewhere.

Macaque Models

Key developments for various vaccine approaches have resulted from studies using SIV. The importance of this model rests with both the genetic relatedness of SIV to HIV and the AIDS-like syndromes that develop in several species of SIV-infected macaques. The higher viral load and disease endpoints, which have not been demonstrable in the chimpanzee model, are very important for vaccine development. Different SIV isolates provide virus/host interactions that exhibit different degrees of virulence reflecting the spectrum of HIV infections that occur in humans. More importantly, in addition to sterilizing immunity to prevent infection, macaque models permit investigation of vaccine effects that may be more realistic goals for

initial human vaccines—protection against disease and vaccine modulation of viral replication. Experimental vaccines analogous to those being developed for clinical trials as well as other novel approaches are being evaluated in this model.

To date, vaccine approaches based on live attenuated SIV have exhibited the greatest degree of efficacy and provide opportunities for defining correlates of immune protection. Concerns for safety, particularly in infants, must be resolved before progress can be made with an attenuated HIV-vaccine approach. However, studies of attenuated AIDS vaccines in animal models may provide genetic constructs with improved safety for development of live-vector vaccines or VLPs, i.e., genetically “killed” vaccine approaches.

Chimeric viruses (SHIV) made by replacing the *env* gene (and other selected genes) of SIV with any of a variety of HIV-1 *env* genes show increased promise for vaccine evaluation in macaques. SHIV viruses infect and persist in macaques, and recent animal-adapted constructs have induced CD4 cell depletion, AIDS, and death. Vaccines containing HIV *env* components that are intended for human use can now be tested for immunogenicity and efficacy in macaques in a disease model. SHIV constructs that infect efficiently via the mucosal route and incorporate genes for *env* protein from non-clade-B HIV are being developed to evaluate vaccine-induced protection against divergent HIV isolates.

The pig-tailed macaque, *Macaca nemestrina*, which is susceptible to infection with selected stocks of HIV-1 and HIV-2, and baboons, which can be infected with some isolates of HIV-2, continue to be studied. HIV-2 stocks have been developed that induce AIDS-like disease in *M. nemestrina* and baboons.

Other Animal Models

Human immune system tissues have been successfully transplanted into mice with SCID to create a system for testing vaccine candidates or components of the human immune response to HIV vaccines. While a wide range of viral isolates can be tested, incomplete repopulation with human lymphoid stromal cells and low numbers of repopulating human lymphoid cells have presented major limitations to use of this system.

Feline immunodeficiency virus (FIV) isolates that are pathogenic for cats now exist, and a vaginal transmission model recently has been developed. Its convenience and relatively low cost might make it an attractive model for analysis of biomedical agents to block transmission, such as microbicides. Vaccine experiments with cross-strain protection have been performed in this model and its relevance as an animal disease make this an attractive model for further vaccine studies.

Equine infectious anemia virus (EIAV) may provide a unique model to investigate the relevance of vaccine-induced enhancement

of lentivirus disease as well as escape from protective humoral immunity.

Vaccine Development

NIAID has established HIV Vaccine Working Groups, which include representatives drawn from intramural scientists at NIH, NIH-sponsored extramural scientists, and community constituency groups, to assist in the scientific coordination and planning of NIAID efforts in targeted areas of vaccine design and correlates of immunity. The National Cooperative Vaccine Development Groups (NCVDGs) for the discovery and development of vaccine candidates will be competitively renewed as Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) grants in FY 1998 and FY 1999. The scope of the work may be extended in these awards to include early human clinical testing. Research teams comprising scientists from industry, academia, and Government collaborate to develop and test novel experimental HIV vaccine concepts in laboratory and animal models.

Several adjuvants such as immune-stimulating complexes (ISCOMs), muramyl tripeptide, Quil A or QS 21, liposomes, and MF59 have been studied in macaques for their ability to stimulate humoral and cellular responses as well as to provide protection against virus challenge with candidate vaccines. These as well as other adjuvants have now been studied in human clinical trials with HIV *env* vaccines with limited success. Novel approaches to

induce effective antigen presentation for both humoral and cellular immunity, as well as durable functional immune responses, are still urgently needed. Use of cytokines (delivered either as proteins, as DNA, or in vectors) to modify and focus the type of immune responses is an extremely active area of research in both mice and macaques.

Collaborative Mucosal Immunity Groups (CMIGs) initiated studies focused on induction and assessment of regional mucosal immune responses to HIV in human subjects as well as nonhuman primate models. Studies in this area are now open to competitive renewal and remain critical for prevention of infection in the worldwide pandemic.

Cooperation with Industry

Industrial partners will play an essential role in development of HIV vaccines and other biomedical interventions to prevent infection. Factors that affect the participation and collaboration of industrial partners need to be addressed. These include not only economic, legal, and regulatory issues but also scientific ones. Vaccines need to prevent HIV infection not only in the United States but worldwide. Collaborations must be established to provide relevant clinical isolates and information for the preparation and testing of such vaccines. Moreover, to facilitate the development of safe and efficacious vaccines, mechanisms should be adopted to promote further utilization of information generated from relevant animal models. Currently, few vaccine developers are

pursuing the SIV/macaque models partly because of the need to develop unique reagents and methodologies and the extensive resources required. Collaborative programs between industrial, governmental, and academic agencies are needed to evaluate the comparative efficacy of parallel vaccine approaches against HIV and related retroviral models.

Vaccines and Immune Intervention Against Perinatal HIV Transmission

The ACTG 076 trial has demonstrated that transmission of HIV from mother to infant can be significantly reduced by use of a ZDV regimen given to HIV-infected pregnant women and their newborn infants. However, the complex ACTG 076 regimen is not practical for most of the developing world, where the largest proportion of HIV infection among women and children exists. An ideal regimen would be given once or only for a limited period of time, easily administered, nontoxic to mother and child, and inexpensive and have potential to prevent postpartum transmission via colostrum or breast milk.

The mechanism of the ZDV effect is not known, but initial studies indicate that ZDV therapy was associated with only a modest decrease in maternal RNA copy number, and that reduction in RNA level by ZDV explained only part of the observed treatment effect. Other studies have suggested that the presence of autologous or broadly reactive neutralizing antibody in HIV-infected women may be associated with lower rates of HIV transmission to

their infants. An active immune response of newborn infants to HIV has also been suggested to be effective in averting perinatal transmission by studies reporting detection of HIV-specific cellular immune responses in some uninfected infants born to HIV-infected women. Additionally, several investigators have reported the rare occurrence of apparent clearance of HIV infection in perinatally exposed infants.

Thus, vaccines capable of stimulating the mother's and/or infant's immune response or passive immunity therapies may be capable of reducing perinatal transmission. Like hepatitis B, the use of active, passive, or active/passive strategies to reduce transmission has the highest potential for reducing mother-to-child transmission in developing countries.

Clinical studies targeted toward developing active or passive immunization strategies to prevent perinatal HIV transmission were conducted at 49 PACTG sites funded by NIAID and NICHD and four NIAID-funded AIDS Vaccine Evaluation Group (AVEG) sites and are being conducted at one international site through grant support. HIVIG product and trials support for the passive immunity studies was also provided through NHLBI. The PACTG trial of HIVIG (ACTG 185) was halted because with full implementation of the 076 regimen in a much broader group of pregnant women in that trial the rate of HIV infection dropped to less than 5 percent, thus requiring more than 1,000 mother-infant pairs in each study arm to complete the trial.

Vaccine Clinical Trials

To date the NIAID-supported AVEG has conducted or initiated 29 Phase I and II trials with 19 different candidates.

Significant progress has been made in the evaluation of vaccine candidates developed by manufacturers. For example, all vaccine candidates tested to date in Phase I trials have been shown to be safe and well tolerated. Phase I trials involving HIV-seronegative individuals have shown that (1) the majority of vaccines induce binding antibodies; (2) moderate titers of neutralizing antibody directed toward homologous and heterologous laboratory strains of HIV-1 are produced; (3) neutralization of virus in assays employing standard phytohemagglutinin (PHA)-stimulated blasts has not been detected; and (4) the duration of the neutralizing response in some trials has been maintained for up to 2 years in up to 50 percent of the individuals in the trial. In addition, recent studies testing recombinant poxvirus vaccines, including vaccinia-gp160, canarypox-gp160, and canarypox-env, gag, protease, with or without a subsequent recombinant gp120 subunit booster vaccine, have been shown to induce strong CD8+ CTL responses in a proportion of the volunteers; those boosted with recombinant env proteins also make neutralizing antibodies to laboratory-adapted HIV isolates and to some primary isolates. Studies of a recombinant canarypox vector with HIV env, gag, and protease is proposed for testing in Uganda to determine whether individuals of different genetic backgrounds will respond as well as volunteers in the

United States and France. More complex vaccinia and canarypox vectors incorporating portions of *pol* and *nef* are now under study. Peptide vaccine candidates that might provide products for boosting specific immune responses to internal core proteins (gag) and ~~env~~^{env} are under study. In addition, particulate vaccines are of high interest, and the first of these, Ty-p24 VLPs, is being tested parenterally with and without adjuvant and with mucosal administration. Additional studies are planned with other vaccine candidates for mucosal administration.

Phase II Clinical Trials

NIH is now completing followup of Phase II trial with gp120 vaccine candidates that enrolled uninfected at-risk individuals. Antibody responses did not differ between higher and lower risk populations, and associated studies found that most participants understood the elements of the trial and did not systematically alter their risk behavior as a result of participation in the trial. A second Phase II trial has begun to further explore the combination of recombinant canarypox (containing genetic copies for *env*, gag, protease) and boosting with a different recombinant envelope.

Preparation for Efficacy Trials of HIV Vaccines and Biomedical Prevention

Research required to prepare for clinical evaluations of potential vaccine candidates in efficacy trials is being performed in several domestic and international areas with populations at risk of HIV infection.

As candidate vaccines become ready for efficacy trials, it will be important to have identified populations who remain at risk for HIV infection after counseling and risk-reduction measures have been implemented and who are willing to participate in the trials. Characterizing the circulating viral strains and risk factors, learning how to effectively reduce risk behaviors, and gaining the support of the communities (and, as applicable, governments) will take considerable time and effort. In preparation for implementation of efficacy trials, investigators participating in the HIVNET are determining the incidence of HIV in populations such as IDUs, gay/bisexual men, and individuals attending STD clinics, in the United States and several international sites, who may participate in future vaccine trials. In addition, risk behavior and the impact of risk reduction efforts are being assessed. Investigators are obtaining virus from individuals who recently seroconverted to ensure that vaccines genetically match virus strains now circulating. Close collaboration has been established and continues between the HIVNET and the PHE AIDS International Training and Research Program (AITRP) to train local investigators and develop necessary laboratory skills and infrastructure for international vaccine efficacy trials and trials of other interventions. These trials provide opportunities for fundamental research to increase understanding of HIV transmission and disease progression.

NIH also plans to study innovative strategies for prevention or reduction of

sexual and perinatal HIV transmission through the domestic and international epidemiologic and vaccine preparedness cohorts already in place. Using this infrastructure, NIAID-supported investigators are studying prevention strategies, such as STD diagnosis and treatment to reduce susceptibility to and transmission between sexual partners, targeted chemical and mechanical barrier methods, behavioral interventions, methods for reducing perinatal exposure to maternal HIV-infected blood and secretions, and simple relatively inexpensive pharmacologic or immunologic interventions to reduce mother-to-child transmission of HIV.

Additional Basic Research Resources

The NIH supports a program to develop and standardize immunologic and virologic laboratory assessments of AIDS vaccines in primates. In addition, NIH supports an AIDS vaccine reagent project for clinical analysis and preclinical vaccine development.

NIAID supports the AIDS Research Reagent and Reference Program, which provides an extensive repository of materials useful in basic and applied research for vaccine development.

Daniel,
Please fax to Reserch Comm.
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Director, Vaccine Research Center

The National Institute of Allergy and Infectious Diseases and the National Cancer Institute, National Institutes of Health (NIH) are recruiting for the position of Director, Vaccine Research Center (VRC). The VRC's goal is the development of an effective HIV vaccine through the integration of modern Immunological science with a detailed understanding of HIV and of the mechanisms of the pathogenesis of HIV infection. The VRC will develop existing and new immunogens and vectors and may undertake entirely new approaches to vaccination. The Director will have responsibility for directing a multidisciplinary research program ranging from basic and clinical immunology and virology through vaccine design and production of an HIV vaccine. Applicants must have earned an M.D. or doctorate degree in biomedicine, virology, immunology or related field and have experience with HIV/AIDS, vaccine development and outstanding stature and reputation in the scientific community in the areas of immunology and/or virology. Further qualifications include: experience as a scientific research administrator in the virological, immunological and/or clinical aspects of infectious diseases in a laboratory and/or clinical research setting and knowledge of medical research operations within the Federal Government, universities and non-profit research institutions, industry, and in an international setting. Annual salary range up to \$148,400. Recruitment bonus up to 25% of base pay may be available. Persons interested in this position may call Dr. John McGowan, Deputy Director, NIAID at (301) 496-9677. For more information on the application process, please contact Lynn Hellinger at: 301-496-9686.

Applicants should submit either a curriculum vitae or resume by August 29, 1997, to:

Ms. Lynn C. Hellinger, Director
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Developing Vaccines against HIV: Options for Accelerated Progress

Richard T. Mahoney

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INTRODUCTION

The development of a vaccine against HIV will require the successful completion of many steps including basic research, animal trials, clinical trials, regulatory agency licensure, production, and establishment of distribution systems. As Fields has persuasively argued, basic research should be the highest priority today.¹ But it is also important to ensure that the process for developing a vaccine against HIV is well managed—from start to finish. Various management systems are available, and they have different capabilities. The development of an HIV vaccine will require the participation of private industry; so far, however, private industry has accorded low priority to the development of an HIV vaccine, especially one for developing countries. A recent assessment carried out by Widdus reports that only about \$25 million per year is being spent on developing vaccines against HIV.² The development of a single new vaccine entails investment on the order of \$200 million to \$300 million.

THE SPECIAL ROLE OF THE PUBLIC SECTOR

The public sector must take the lead in ensuring that there is an effective management system for the development of an HIV vaccine—especially for a vaccine to be used in developing countries. (The *public sector* is defined as governments, interna-

tional multigovernmental agencies, universities, and nonprofit agencies. The *private sector* is all those companies whose primary goal is commercial gain.) Although the private sector can take initiatives (for example, forming industrial consortia) the public sector should take the most important steps. The public sector controls most of the funding for science, controls the regulatory process, sets priorities for public health interventions, cares for most of the unvaccinated who become ill, and buys and delivers the vaccines. With respect to public health and, in particular, vaccines, the public sector is best poised to facilitate the creation of market opportunities to which the private sector can and will respond.

So far, progress in developing an HIV vaccine has been slow. While it is true that lack of basic knowledge has inhibited development, it is also probably true that lack of funding and commitment by the private sector has contributed to this slow pace. The problem is not that the private sector is callous to the needs of developing countries or that it has turned its back on the need for an HIV vaccine. The private sector has been the major producer of products such as vaccines and contraceptives that have done so much to benefit developing countries. The problem is that the public sector has not properly organized itself and established the appropriate conditions to allow industry to do what it can do: manufacture high-quality, safe, effective vaccines in cost-efficient ways.

SPECIAL REQUIREMENTS FOR SUCCESS

Certain "standard" requirements must be met for successful development of vaccines: establish-

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ment of appropriate regulatory processes, construction of production facilities, development of appropriate clinical trial protocols, and creation of effective immunization programs for delivery of the vaccine. These are by no means simple tasks, but they have been done in the past. It is likely that no fundamentally new systems will be needed to meet these requirements for HIV vaccines. In addition to these standard requirements, there are three "special" requirements for successful development of vaccines against diseases that affect the developing world: (1) ensuring that promising laboratory discoveries enter the product-development process; (2) ensuring mobilization of the dispersed capabilities for vaccine research and development; and (3) ensuring procurement of these vaccines (that is, ensuring that a market exists). It is likely that new systems will be required to meet these special requirements. It is this need to establish new systems that distinguishes special requirements from standard requirements.

ENSURING THAT PROMISING LABORATORY DISCOVERIES ENTER THE PRODUCT-DEVELOPMENT PROCESS

A study carried out by the U.S. National Academy of Sciences Institute of Medicine (IOM) reported that the large pharmaceutical companies have reduced basic research on vaccines for both childhood and adult vaccines.³ These companies prefer to obtain their leads from academia or from small biotechnology companies that, in turn, get their leads from academia. Many biotechnology firms are started by academicians who wish to commercialize their discoveries: their goal is to bring a product to market that will be profitable. This system is fairly efficient in bringing potentially profitable laboratory discoveries to the product-development stage. However, under this system, laboratory discoveries that relate to vaccines for use in the developing world are assigned low priority. With respect to vaccines that only the developing world will use, industry consistently says "the public sector will have to pay all the costs."

In the case of HIV, it has been found that the strains of HIV prevalent in developing countries differ from those appearing in developed countries. Different vaccines may be required for the various strains. One goal is to develop a multivalent vaccine that will be equally effective against all strains of

HIV and in all people. This is a long-term goal that will be reached in incremental steps. Looking at industry's current priorities, it appears that one of the first steps will be the development of a vaccine that is effective against a strain that is not prevalent in developing countries. How does one get industry to accord higher priority to strains that are prevalent in the developing world?

A critical bottleneck in developing new vaccines is production of pilot lots of vaccine according to good manufacturing practices (GMPs). A facility must be certified by an independent regulatory authority that it is capable of producing vaccines according to certain high standards (GMPs) before pilot lots produced in that facility can be used in clinical trials. Because there are not enough facilities to do this work, a large backlog exists. As stated in the IOM report, "The end result of the shortage of vaccine pilot production facilities is considerable delay (sometimes years) in producing pilot batches of required vaccine."⁴ This bottleneck even has an effect on vaccine manufacturers in the private sector. All other things being equal, companies will put the potentially most profitable vaccines first in the pilot-production waiting line.

MOBILIZING DISPERSED CAPABILITIES

Vaccine research and development is carried out in hundreds of laboratories, public and private, in more than 10 countries.⁵ These laboratories have varying capabilities, priorities, financial resources, relationships with the private sector, policies for protection of intellectual property, and other conditions. Experience has shown that, although it is possible to bring most of the key players together in a single room to discuss a particular goal for vaccine development, it is very difficult to have all those players leave the room in agreement on a coordinated management strategy for reaching that goal. This dispersion of capabilities has certain advantages, such as facilitating competition. It also helps ensure that more than one approach will be taken to problem solving, thus helping to avoid "placing all the eggs in one basket." The World Health Organization (WHO) has been tirelessly addressing this issue with respect to HIV vaccines; the organization has convened a number of meetings seeking to reach agreement on the standard requirements for success—especially establishment of scientific research priorities, design of clinical

trials, development of regulatory requirements, and design of immunization programs. However, WHO cannot impose its findings on member states—much less on firms in the private sector.

Another effect of the dispersion of vaccine research, development, and manufacture is the need to assemble intellectual property rights (IPRs) before a vaccine can be sold. IPRs include patents, trademarks, copyrights, trade secrets, and knowledge. Unlike the vaccines currently used in childhood immunization programs, vaccines of the future will be controlled by an extensive web of IPRs. This requirement to assemble IPRs is one of the most daunting requirements for public vaccine research and development programs. Most agencies do not have an effective system for carrying out the required work. Commonly the agencies are staffed by scientists, who turn to lawyers who have little previous formal training in IPRs. In industry, these licenses are put together by business specialists who integrate scientific, legal, market, production, and regulatory issues into each license. The scientist-lawyer teams of the public sector are not trained to carry out this integration. One of the main problems public agencies face is that they will not be the eventual manufacturer of the product, so they cannot fully anticipate how the licenses need to be structured. The development of an HIV vaccine will likely face these same difficulties. Because of the dispersed nature of the vaccine enterprise, it will not be possible to have a single supranational agency that will hold, either directly or through license, all relevant IPRs for an HIV vaccine.

ENSURING VACCINE PROCUREMENT

Development of the market. What makes the HIV vaccine market for developing countries different from other vaccine markets (such as measles)? To create a market for HIV vaccines, two things must be done: create market demand (the desire to purchase) and create market power (the ability to purchase). In the coming years, while scientists are struggling to find the keys to unlock the secrets of an HIV vaccine, it will be necessary to ensure similar or better progress in the development of the market. If we believe there will be an acceptable HIV vaccine at some future time, we need to create a well-developed market so that the private sector will be willing to invest. Levin puts it this way:

"The discovery of an effective AIDS vaccine will not be the beginning of the end. It will only be the end of the beginning."⁶ Developing the market will not be easy because it involves many unexplored issues. In the case of an HIV vaccine, the total number of potential users is probably great. However, many people do not perceive the population at risk to be the general population; they see it instead as a smaller subset, of which they are not a member. Some individuals will want the vaccine, but "want" does not necessarily translate into a firm decision or ability to obtain the vaccine. These people will weigh their individual risks and benefits carefully and will give lower weight in their risk-benefit equation to the good of others. Many potential users will be affected by their ability to pay. If they cannot pay, but still want the vaccine, then someone else must pay. These issues—particularly as they relate to developing countries—need to be examined while the vaccine is being developed, and not afterwards. These issues need to be addressed in a comprehensive management plan.

The two-tier market. The public sector buys vaccines for immunization programs in developing countries at greatly reduced prices, compared to the prices at which the vaccines are sold in the private sector. For example, hepatitis B vaccine is sold in Korea for about \$8 per dose, while the same manufacturers sell the vaccine to the international public sector for about \$0.60 per dose. Companies sell vaccines at two levels based on several rationales: they have excess capacity, and using the excess capacity lowers their average production cost per dose so that sales in the private sector are more profitable; marketing and sales costs for the public sector are low; they believe sales in the public sector will generate goodwill; and they have a sincere concern for better public health. The most important factor is the existence of excess capacity beyond what is needed to meet the demand in the private sector. That excess capacity exists because of the relative ease of manufacturing the vaccines or increased production to meet additional orders. (This excess capacity does not counterbalance the absence of capacity for production of test lots of vaccine mentioned above. Facilities dedicated to the production of existing vaccines and flexible facilities for prototype production are two different types of production centers.)

A vaccine against HIV will probably sell for many dollars per dose in developed countries, which will be beyond the capabilities of developing countries or donor agencies. Thus, a two-tier market will be necessary for HIV vaccines, just as it is necessary for other vaccines in developing countries.

The public sector can implement certain policies to help ensure a two-tier market where it might not naturally evolve. These policies include: tax credits for investing in production capacity; widespread, favorable publicity for manufacturers that supply HIV vaccines to developing countries; and effective management of IPRs. Several public-sector organizations, including the Program for Appropriate Technology in Health (PATH),⁷ that develop products and obtain patents on promising technologies, have implemented licensing policies that permit a private-sector licensee to sell a product in the private (commercial) sector at any price the licensee can; however, the price to the public sector (governments, philanthropies, public service agencies) must be lower than the private-sector price. For example, PATH has licensed a company to manufacture a single-use, prefilled syringe that PATH developed. The company is free to set the price to the private sector, but the public-sector price must be lower. This policy provides a substantial savings for the public sector—in the case of the syringe, greater than 25 percent.

MANAGEMENT SYSTEMS

In considering management systems, it is instructive to review the successful effort to develop a vaccine against polio. The following summary is based on information provided by Dr. F. Robbins, who won the Nobel Prize for his research on the polio virus. Polio vaccine research and development was sponsored principally by the National Foundation for Infantile Paralysis, which was the only major sponsor of virology research in the United States in the late 1930s and much of the 1940s. It raised funds primarily through public appeals (the March of Dimes) and also received funds from wealthy donors. At first, these funds were used to sponsor basic research. The foundation often sponsored research on virology not directly related to the polio virus. Only when clear leads had been identified did the foundation allocate funds for vaccine development. The founda-

tion's research program was guided by an external advisory committee of outstanding scientists. When the vaccines became available for human trials, the foundation helped develop guidelines and provided the financial support for large-scale trials. The Salk vaccine, which emerged from this effort, was not patented. Nor was Robbin's technology for tissue culture. Several companies increased their scale of production from the laboratory methods developed by the researchers. One of these companies, Cutter, experienced difficulty in achieving complete viral inactivation. "As a result, new requirements were introduced for safety testing along with a filtration step. With these relatively modest changes, the problem was solved, and no untoward reactions from the inactivated vaccine have since been observed."⁸

Several observations can be made about this stupendous success:

- The foundation was the dominant force. It controlled the money and could determine the strategies and priorities for the field.
- Governmental regulation of vaccine manufacturing and clinical trials was limited. The foundation developed the regulations for clinical trials.
- Because the vaccines had no associated patents, many companies were able to establish production.
- The foundation used private funds, so it had great flexibility in spending.

The most important point is that a coordinated management plan was possible because a single agency was guiding most of the work, and other agencies (such as the U.S. Food and Drug Administration) did not have clear rules about vaccines. It seems unlikely that this exact model could be employed today. As noted above, vaccine research and development is too dispersed to be coordinated by a single agency unless that agency is endowed with very significant resources.

SYSTEMS CURRENTLY EMPLOYED

The public sector currently uses three systems for HIV vaccine development: investigator-initiated research programs, directed-contract research programs, and codevelopment agreements.

Investigator-initiated research programs. Most basic research is funded through investigator-initiated programs. The results of investigator-initiated research are translated into products through a process of licensing. Most universities have a "technology transfer" office that is responsible for licensing. This structure of collaboration between public and private sectors is probably the most common. For example, a licensing agreement for HIV vaccines has been signed by Harvard University Medical School and Therion Biologics Corporation of Cambridge, Massachusetts. They are seeking to develop a live, attenuated (genetically modified) HIV vaccine. In this case, Harvard completed early development work and applied for a patent on the prototype vaccine. Harvard licensed the patent to Therion, a relatively small biotechnology firm that plans to conduct further applied research studies leading to clinical trials.⁹ Production of a prototype vaccine for clinical trials will be subcontracted. Because Therion does not have capabilities for vaccine production or marketing, it will most likely have to license its product to a larger vaccine company, if the project proves promising. Some national medical research agencies such as the U.S. National Institutes of Health (NIH) have policies controlling the nature of the licenses that can be granted. These controls may call for a favorable price and guaranteed access for the public sector.

Directed-contract research programs. There are many examples in the public sector of directed-contract programs, such as WHO's Tropical Disease Research Program and its Human Reproduction Program. These programs operate by identifying priorities for product development (such as a malaria vaccine). They hire scientists with relevant expertise and empower these scientist-administrators to design development programs.

Outside technical advisory committees, usually made up exclusively of scientists from the public sector, are assembled to help in design and oversee the programs. The scientist-administrators are provided a budget to contract with research and development agencies from both private and public sectors to carry out various components of the product-development program.

Co-development agreements. In a codevelopment agreement, a public research and development institution joins forces with a private company. They

agree to share in the tasks necessary to commercialize a particular product. WHO has signed many codevelopment agreements, including agreements for the development of vaccines. NIH uses cooperative research and development agreements for vaccine development.¹⁰

NEW SYSTEMS THAT COULD BE EMPLOYED

There are three new types of management systems that could be employed for research and development of an HIV vaccine: finished-product procurement, not-for-profit institute, and consultative groups. The common denominator of these new systems is that they provide a way for the public sector to construct comprehensive management plans in which industry has a well-defined role. To be successful, the management plans would have to address each of the essential requirements discussed above (ensuring that promising discoveries enter the product-development process, mobilizing dispersed capabilities, and ensuring vaccine procurement).

Finished-product procurement. The finished-product procurement system is straightforward and is often employed by the military. For example, "We want 1,000 tanks that will travel up to 100 mph, over sand, in temperatures up to 60 degrees centigrade, and fire up to 2,000 rounds per minute." Such a tank may not exist, and the bids include the cost of research and development. The finished-product (or military-procurement) system has been considered for the HIV Vaccine Development Superfund.¹¹ Clearly, the finished-product procurement system will be less effective when the desired product is in the early stages of research, and it will be most effective when proven product prototypes have been developed. Further, this system requires a clear knowledge of the desirable specifications for the final product. Can specifications be accurately defined for an HIV vaccine today? With respect to vaccines for developing countries, implementation of this system would require sufficient funds not only to cover all research and development costs, but also to construct and maintain the production facility and to purchase the vaccine for a fixed period of time. Is it too early in the process of developing an HIV vaccine to implement this system?

Not-for-profit institutes. In this model, the public sector decides that there is a compelling public need for the development of certain products and that no single private company could or would undertake the work. The public sector establishes a mission-oriented agency. Examples are Airbus Industry and the Manhattan Project. Recently the IOM recommended establishing of a national vaccine authority to undertake, in collaboration with private industry, the development and production of new vaccines for children as a part of the new worldwide children's vaccine initiative (CVI):

In the committee's view, the development of new and improved [children's] vaccines is unlikely to occur unless there is an entity that has the mandate to manage and oversee the process from beginning to end. Because the private sector alone cannot sustain the costs and risks associated with the development of most CVI vaccines, and because the successful development of vaccines requires an integrated process, the committee recommends that an entity, tentatively called the National Vaccine Authority (NVA), be organized to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of global public health need.¹²

A common denominator of these not-for-profit institutes is that they are designed to undertake research and development, but they rely on private industry for production and marketing. These institutes assume most of the risk of early product development. One of the strengths of these institutes is that they can manage the product-development process from start to finish, much as private industry does. Even though they may not actually execute each step of the process, they maintain a constant involvement as the product moves toward distribution. This ongoing involvement reflects their concern with the ultimate use of the product and not just with a single stage of the process. Undertaking the work under one roof, they seek to assemble the required IPRs, and they seek to protect the interests of the public sector, including ensuring that the public-sector market will be served.

Consultative groups. A consultative group is composed of multilateral agencies, bilateral donors, specialized agencies, industry, academia, and others. For example, the Consultative Group on International Agricultural Research (CGIAR) is a

highly successful system for encouraging the development and dissemination of new crops, fertilizers, irrigation systems, and other technologies important for agriculture. It meets twice each year: once to review technical and strategic issues, and once to review financial requirements and to provide donors an opportunity to make pledges of support. The CGIAR coordinates support for a number of agricultural research institutes throughout the world. Each institute has a special area or areas of expertise, including rice, wheat, maize, irrigation, and so forth. The CGIAR operates through a secretariat at the World Bank. Each institute prepares budget proposals. The secretariat screens the proposals to ensure that they fit within an overall strategy approved by the consultative group. In addition, the proposals are reviewed by the Food and Agricultural Organization for technical merit. The secretariat then recommends to the consultative group the funding to be received by each institute. The CGIAR allocates over \$200 million per year.

For a vaccine-development consultative group, industry would have to be directly involved in designing the management plan to be overseen by the consultative group. The new United Nations AIDS program may provide the basis for an HIV-vaccine-development consultative group.¹³

DISCUSSION

CURRENT MANAGEMENT SYSTEMS

The existing management systems (investigator-initiated research programs, directed-contract research programs, and codevelopment agreements) have their strengths, but they have weaknesses, too. These weaknesses may help explain why little progress has been made toward development of vaccines for developing countries. All of the existing systems are strong in transferring laboratory findings to industry when these findings are the basis for a product with a promising commercial market. In fact, this is the main objective of these systems. However, all of the systems have faced difficulties in transferring findings that relate to development of products to be used almost exclusively in developing countries. For example, both the Human Reproduction Program and the Tropical Disease Research Program at WHO have had

numerous arrangements with private industry for vaccine development. Some of these arrangements have faced difficulties because of the reluctance of the partners from the private sector to invest heavily in the product. The antifertility vaccine, which probably could enjoy a market among the well-to-do, serves as an example. WHO has struggled to find a partner from the private sector that will accept a product license and assume responsibility for production of pilot-scale batches, development of the vaccine into a commercial entity, and liability. In general, the public sector has lacked the resources to push development of these vaccines. For example, the budgets for these WHO programs have generally not exceeded \$30 million per year. Because these budgets cover a wide range of products, no more than a few million dollars can be allocated to any one product.

Over the years, directed-contract research programs have faced many challenges. The most difficult challenge has been to take a product concept from the very early stages of research all the way through to a finished product. This has led many of these programs to focus increasingly on the later stages of product development. The Tropical Disease Research Program has recently been reorganized for just this purpose. The Human Reproduction Program established a downstream program a few years ago and gave it the largest budget of all the Human Reproduction Program's activities.

Certain aspects of these directed-contract research programs may limit their capability to develop products as rapidly as private industry can:

- One of the greatest challenges faced by these programs is inadequate funding. With much higher levels of funding, the success rate would certainly be greater.
- These programs are often administered by former academic scientists, who tend to identify the additional research that can be done on a product rather than to pass the product along to the next stage of development.
- The scientist-administrators and the members of the external advisory committees, also predominantly from academia, have limited experience in the product-development process.
- The organizations that house these programs have struggled to determine how and whether

they should own patents, assume licenses, deal with liability, and so forth. Clear guidelines have yet to be identified.

These directed-contract research programs have many strengths. In particular they have been successful in substantially expanding research capacity in developing countries. They have also performed excellent multicentered studies of existing products to document their performance in a variety of settings.

The existing management systems are weak in facilitating the assembly of IPRs. A license agreement almost always deals with only one piece of intellectual property. Take, for example, a scientist who discovers an antigen that provokes neutralizing antibodies in experimental animals; if the antibody is produced most efficiently using a proprietary method owned by a third party, the licensee for the antibody will have to obtain rights from the third party. All structures are generally weak in taking account of the dispersed nature of the research and development community. The parties to an agreement often find themselves in competition with other groups, rather than helping to synthesize the work of a number of groups. They have a particular product lead to which they are committed, and they will work hard for its success. Although competition and product champions are important in the development process, the management systems described here have little capability to bring together disparate resources that might be valuable in achieving a successful project.

In summary, current public-sector systems of vaccine development have not been as successful as desired. They are best at implementing tactics, but they face difficulties in formulating and implementing a strategic plan that covers activities from product conception to product use.

POSSIBLE NEW SYSTEMS

The finished-product procurement system, the not-for-profit institute, and the consultative group all take a more strategic, comprehensive (start-to-finish) management approach to vaccine development than the models that are currently in use. Successful implementation of these systems requires a comprehensive management strategy, from basic research to vaccine program implementation.

The problem with the finished-product procurement system is that the HIV vaccine is not sufficiently developed to make it possible to "order" a finished product. There are also problems with the approach used with not-for-profit institute: first, it cannot harness a sufficiently wide range of capabilities; second it would take time to form the institute or to expand an existing institute to sufficient size and capability.

The consultative-group system seems most attractive. Its greatest asset is its ability to mobilize a wide range of capabilities. It could work with both the public and private sectors, help assemble IPRs, and make provisions for a two-tier market through licensing and other approaches. A well-designed consultative-group system would be likely to obtain the confidence of the donor community, which would make more funds available. The major problem is getting various power centers to agree to participate in a consultative group and thereby subjugate some of their decision-making authority to a higher body. A specific difficulty will be to obtain agreement on a system of effective management of IPRs. Without such a system, it is unlikely that the needs of developing countries, particularly the need for a two-tier market, can be met. A consultative-group system could be managed by WHO, the World Bank, or a new entity—perhaps affiliated with an existing agency—formed specifically for this purpose. The recently formed United Nations AIDS program may be able to fill this role.

CONCLUSION

The existing systems for developing a vaccine against HIV should continue to be employed and receive greater levels of funding. They can make important contributions. However, if the goal is to help control AIDS with an HIV vaccine as quickly and effectively as possible, it will be necessary to implement a more comprehensive management system. It is our belief that the most appropriate system to accelerate development of an HIV vaccine is the consultative-group model. The great advantage of this system is that it provides a means to develop a coherent, strategic management plan.

ACKNOWLEDGEMENTS

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The contributions of Dr. Jane Rowley and Dr. Seth Berkley of the Rockefeller Foundation, Dr. Peter Carpenter of the Vision and Values Institute, Steve Brooke and Sara Tift of PATH, and Edgar Sheller are gratefully acknowledged.

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1. B.N. Fields, "AIDS: Time to Turn to Basic Science," *Nature* 369 (12 May 1994): 95-96.
2. R. Widdus, Global Programme on Vaccines and Immunization, World Health Organization, Geneva, Switzerland, personal communication with the author, 1994.
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7. PATH is an international, nonprofit, non-governmental agency that is concerned with improving the health of women and children. It has an energetic research and development program, funded in large part by the U.S. Agency for International Development. The program has developed various technologies including a rapid-dip-strip diagnostic procedure for HIV-1 and HIV-2, which is now widely used in health programs in developing countries.
8. F. Robbins, personal communication with the author, February 1994; and F. Robbins, "Polio Historical," in *Vaccines*, ed. S. Plotkin and E. Mortimer (Philadelphia, Penn.: W.B. Saunders, 1988), 102-3.
9. "Worldwide Agreement for AIDS Vaccine Technology Signed," *CDC AIDS Weekly* (29 March 1993): 4.
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Director, Vaccine Research Center

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THE SPECIAL ROLE OF THE PUBLIC SECTOR

The public sector must take the lead in ensuring that there is an effective management system for the development of an HIV vaccine—especially for a vaccine to be used in developing countries. (The *public sector* is defined as governments, interna-

tional multigovernmental agencies, universities, and nonprofit agencies. The *private sector* is all those companies whose primary goal is commercial gain.) Although the private sector can take initiatives (for example, forming industrial consortia) the public sector should take the most important steps. The public sector controls most of the funding for science, controls the regulatory process, sets priorities for public health interventions, cares for most of the unvaccinated who become ill, and buys and delivers the vaccines. With respect to public health and, in particular, vaccines, the public sector is best poised to facilitate the creation of market opportunities to which the private sector can and will respond.

So far, progress in developing an HIV vaccine has been slow. While it is true that lack of basic knowledge has inhibited development, it is also probably true that lack of funding and commitment by the private sector has contributed to this slow pace. The problem is not that the private sector is callous to the needs of developing countries or that it has turned its back on the need for an HIV vaccine. The private sector has been the major producer of products such as vaccines and contraceptives that have done so much to benefit developing countries. The problem is that the public sector has not properly organized itself and established the appropriate conditions to allow industry to do what it can do: manufacture high-quality, safe, effective vaccines in cost-efficient ways.

SPECIAL REQUIREMENTS FOR SUCCESS

Certain "standard" requirements must be met for successful development of vaccines: establish-

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ment of appropriate regulatory processes, construction of production facilities, development of appropriate clinical trial protocols, and creation of effective immunization programs for delivery of the vaccine. These are by no means simple tasks, but they have been done in the past. It is likely that no fundamentally new systems will be needed to meet these requirements for HIV vaccines. In addition to these standard requirements, there are three "special" requirements for successful development of vaccines against diseases that affect the developing world: (1) ensuring that promising laboratory discoveries enter the product-development process; (2) ensuring mobilization of the dispersed capabilities for vaccine research and development; and (3) ensuring procurement of these vaccines (that is, ensuring that a market exists). It is likely that new systems will be required to meet these special requirements. It is this need to establish new systems that distinguishes special requirements from standard requirements.

ENSURING THAT PROMISING LABORATORY DISCOVERIES ENTER THE PRODUCT-DEVELOPMENT PROCESS

A study carried out by the U.S. National Academy of Sciences Institute of Medicine (IOM) reported that the large pharmaceutical companies have reduced basic research on vaccines for both childhood and adult vaccines.³ These companies prefer to obtain their leads from academia or from small biotechnology companies that, in turn, get their leads from academia. Many biotechnology firms are started by academicians who wish to commercialize their discoveries: their goal is to bring a product to market that will be profitable. This system is fairly efficient in bringing potentially profitable laboratory discoveries to the product-development stage. However, under this system, laboratory discoveries that relate to vaccines for use in the developing world are assigned low priority. With respect to vaccines that only the developing world will use, industry consistently says "the public sector will have to pay all the costs."

In the case of HIV, it has been found that the strains of HIV prevalent in developing countries differ from those appearing in developed countries. Different vaccines may be required for the various strains. One goal is to develop a multivalent vaccine that will be equally effective against all strains of

HIV and in all people. This is a long-term goal that will be reached in incremental steps. Looking at industry's current priorities, it appears that one of the first steps will be the development of a vaccine that is effective against a strain that is not prevalent in developing countries. How does one get industry to accord higher priority to strains that are prevalent in the developing world?

A critical bottleneck in developing new vaccines is production of pilot lots of vaccine according to good manufacturing practices (GMPs). A facility must be certified by an independent regulatory authority that it is capable of producing vaccines according to certain high standards (GMPs) before pilot lots produced in that facility can be used in clinical trials. Because there are not enough facilities to do this work, a large backlog exists. As stated in the IOM report, "The end result of the shortage of vaccine pilot production facilities is considerable delay (sometimes years) in producing pilot batches of required vaccine."⁴ This bottleneck even has an effect on vaccine manufacturers in the private sector. All other things being equal, companies will put the potentially most profitable vaccines first in the pilot-production waiting line.

MOBILIZING DISPERSED CAPABILITIES

Vaccine research and development is carried out in hundreds of laboratories, public and private, in more than 10 countries.⁵ These laboratories have varying capabilities, priorities, financial resources, relationships with the private sector, policies for protection of intellectual property, and other conditions. Experience has shown that, although it is possible to bring most of the key players together in a single room to discuss a particular goal for vaccine development, it is very difficult to have all those players leave the room in agreement on a coordinated management strategy for reaching that goal. This dispersion of capabilities has certain advantages, such as facilitating competition. It also helps ensure that more than one approach will be taken to problem solving, thus helping to avoid "placing all the eggs in one basket." The World Health Organization (WHO) has been tirelessly addressing this issue with respect to HIV vaccines; the organization has convened a number of meetings seeking to reach agreement on the standard requirements for success—especially establishment of scientific research priorities, design of clinical

trials, development of regulatory requirements, and design of immunization programs. However, WHO cannot impose its findings on member states—much less on firms in the private sector.

Another effect of the dispersion of vaccine research, development, and manufacture is the need to assemble intellectual property rights (IPRs) before a vaccine can be sold. IPRs include patents, trademarks, copyrights, trade secrets, and knowledge. Unlike the vaccines currently used in childhood immunization programs, vaccines of the future will be controlled by an extensive web of IPRs. This requirement to assemble IPRs is one of the most daunting requirements for public vaccine research and development programs. Most agencies do not have an effective system for carrying out the required work. Commonly the agencies are staffed by scientists, who turn to lawyers who have little previous formal training in IPRs. In industry, these licenses are put together by business specialists who integrate scientific, legal, market, production, and regulatory issues into each license. The scientist-lawyer teams of the public sector are not trained to carry out this integration. One of the main problems public agencies face is that they will not be the eventual manufacturer of the product, so they cannot fully anticipate how the licenses need to be structured. The development of an HIV vaccine will likely face these same difficulties. Because of the dispersed nature of the vaccine enterprise, it will not be possible to have a single supranational agency that will hold, either directly or through license, all relevant IPRs for an HIV vaccine.

ENSURING VACCINE PROCUREMENT

Development of the market. What makes the HIV vaccine market for developing countries different from other vaccine markets (such as measles)? To create a market for HIV vaccines, two things must be done: create market demand (the desire to purchase) and create market power (the ability to purchase). In the coming years, while scientists are struggling to find the keys to unlock the secrets of an HIV vaccine, it will be necessary to ensure similar or better progress in the development of the market. If we believe there will be an acceptable HIV vaccine at some future time, we need to create a well-developed market so that the private sector will be willing to invest. Levin puts it this way:

"The discovery of an effective AIDS vaccine will not be the beginning of the end. It will only be the end of the beginning."⁶ Developing the market will not be easy because it involves many unexplored issues. In the case of an HIV vaccine, the total number of potential users is probably great. However, many people do not perceive the population at risk to be the general population; they see it instead as a smaller subset, of which they are not a member. Some individuals will want the vaccine, but "want" does not necessarily translate into a firm decision or ability to obtain the vaccine. These people will weigh their individual risks and benefits carefully and will give lower weight in their risk-benefit equation to the good of others. Many potential users will be affected by their ability to pay. If they cannot pay, but still want the vaccine, then someone else must pay. These issues—particularly as they relate to developing countries—need to be examined while the vaccine is being developed, and not afterwards. These issues need to be addressed in a comprehensive management plan.

The two-tier market. The public sector buys vaccines for immunization programs in developing countries at greatly reduced prices, compared to the prices at which the vaccines are sold in the private sector. For example, hepatitis B vaccine is sold in Korea for about \$8 per dose, while the same manufacturers sell the vaccine to the international public sector for about \$0.60 per dose. Companies sell vaccines at two levels based on several rationales: they have excess capacity, and using the excess capacity lowers their average production cost per dose so that sales in the private sector are more profitable; marketing and sales costs for the public sector are low; they believe sales in the public sector will generate goodwill; and they have a sincere concern for better public health. The most important factor is the existence of excess capacity beyond what is needed to meet the demand in the private sector. That excess capacity exists because of the relative ease of manufacturing the vaccines or increased production to meet additional orders. (This excess capacity does not counterbalance the absence of capacity for production of test lots of vaccine mentioned above. Facilities dedicated to the production of existing vaccines and flexible facilities for prototype production are two different types of production centers.)

A vaccine against HIV will probably sell for many dollars per dose in developed countries, which will be beyond the capabilities of developing countries or donor agencies. Thus, a two-tier market will be necessary for HIV vaccines, just as it is necessary for other vaccines in developing countries.

The public sector can implement certain policies to help ensure a two-tier market where it might not naturally evolve. These policies include: tax credits for investing in production capacity; widespread, favorable publicity for manufacturers that supply HIV vaccines to developing countries; and effective management of IPRs. Several public-sector organizations, including the Program for Appropriate Technology in Health (PATH),⁷ that develop products and obtain patents on promising technologies, have implemented licensing policies that permit a private-sector licensee to sell a product in the private (commercial) sector at any price the licensee can; however, the price to the public sector (governments, philanthropies, public service agencies) must be lower than the private-sector price. For example, PATH has licensed a company to manufacture a single-use, prefilled syringe that PATH developed. The company is free to set the price to the private sector, but the public-sector price must be lower. This policy provides a substantial savings for the public sector—in the case of the syringe, greater than 25 percent.

MANAGEMENT SYSTEMS

In considering management systems, it is instructive to review the successful effort to develop a vaccine against polio. The following summary is based on information provided by Dr. F. Robbins, who won the Nobel Prize for his research on the polio virus. Polio vaccine research and development was sponsored principally by the National Foundation for Infantile Paralysis, which was the only major sponsor of virology research in the United States in the late 1930s and much of the 1940s. It raised funds primarily through public appeals (the March of Dimes) and also received funds from wealthy donors. At first, these funds were used to sponsor basic research. The foundation often sponsored research on virology not directly related to the polio virus. Only when clear leads had been identified did the foundation allocate funds for vaccine development. The founda-

tion's research program was guided by an external advisory committee of outstanding scientists. When the vaccines became available for human trials, the foundation helped develop guidelines and provided the financial support for large-scale trials. The Salk vaccine, which emerged from this effort, was not patented. Nor was Robbin's technology for tissue culture. Several companies increased their scale of production from the laboratory methods developed by the researchers. One of these companies, Cutter, experienced difficulty in achieving complete viral inactivation. "As a result, new requirements were introduced for safety testing along with a filtration step. With these relatively modest changes, the problem was solved, and no untoward reactions from the inactivated vaccine have since been observed."⁸

Several observations can be made about this stupendous success:

- The foundation was the dominant force. It controlled the money and could determine the strategies and priorities for the field.
- Governmental regulation of vaccine manufacturing and clinical trials was limited. The foundation developed the regulations for clinical trials.
- Because the vaccines had no associated patents, many companies were able to establish production.
- The foundation used private funds, so it had great flexibility in spending.

The most important point is that a coordinated management plan was possible because a single agency was guiding most of the work, and other agencies (such as the U.S. Food and Drug Administration) did not have clear rules about vaccines. It seems unlikely that this exact model could be employed today. As noted above, vaccine research and development is too dispersed to be coordinated by a single agency unless that agency is endowed with very significant resources.

SYSTEMS CURRENTLY EMPLOYED

The public sector currently uses three systems for HIV vaccine development: investigator-initiated research programs, directed-contract research programs, and codevelopment agreements.

Investigator-initiated research programs. Most basic research is funded through investigator-initiated programs. The results of investigator-initiated research are translated into products through a process of licensing. Most universities have a "technology transfer" office that is responsible for licensing. This structure of collaboration between public and private sectors is probably the most common. For example, a licensing agreement for HIV vaccines has been signed by Harvard University Medical School and Therion Biologics Corporation of Cambridge, Massachusetts. They are seeking to develop a live, attenuated (genetically modified) HIV vaccine. In this case, Harvard completed early development work and applied for a patent on the prototype vaccine. Harvard licensed the patent to Therion, a relatively small biotechnology firm that plans to conduct further applied research studies leading to clinical trials.⁹ Production of a prototype vaccine for clinical trials will be subcontracted. Because Therion does not have capabilities for vaccine production or marketing, it will most likely have to license its product to a larger vaccine company, if the project proves promising. Some national medical research agencies such as the U.S. National Institutes of Health (NIH) have policies controlling the nature of the licenses that can be granted. These controls may call for a favorable price and guaranteed access for the public sector.

Directed-contract research programs. There are many examples in the public sector of directed-contract programs, such as WHO's Tropical Disease Research Program and its Human Reproduction Program. These programs operate by identifying priorities for product development (such as a malaria vaccine). They hire scientists with relevant expertise and empower these scientist-administrators to design development programs.

Outside technical advisory committees, usually made up exclusively of scientists from the public sector, are assembled to help in design and oversee the programs. The scientist-administrators are provided a budget to contract with research and development agencies from both private and public sectors to carry out various components of the product-development program.

Co-development agreements. In a codevelopment agreement, a public research and development institution joins forces with a private company. They

agree to share in the tasks necessary to commercialize a particular product. WHO has signed many codevelopment agreements, including agreements for the development of vaccines. NIH uses cooperative research and development agreements for vaccine development.¹⁰

NEW SYSTEMS THAT COULD BE EMPLOYED

There are three new types of management systems that could be employed for research and development of an HIV vaccine: finished-product procurement, not-for-profit institute, and consultative groups. The common denominator of these new systems is that they provide a way for the public sector to construct comprehensive management plans in which industry has a well-defined role. To be successful, the management plans would have to address each of the essential requirements discussed above (ensuring that promising discoveries enter the product-development process, mobilizing dispersed capabilities, and ensuring vaccine procurement).

Finished-product procurement. The finished-product procurement system is straightforward and is often employed by the military. For example, "We want 1,000 tanks that will travel up to 100 mph, over sand, in temperatures up to 60 degrees centigrade, and fire up to 2,000 rounds per minute." Such a tank may not exist, and the bids include the cost of research and development. The finished-product (or military-procurement) system has been considered for the HIV Vaccine Development Superfund.¹¹ Clearly, the finished-product procurement system will be less effective when the desired product is in the early stages of research, and it will be most effective when proven product prototypes have been developed. Further, this system requires a clear knowledge of the desirable specifications for the final product. Can specifications be accurately defined for an HIV vaccine today? With respect to vaccines for developing countries, implementation of this system would require sufficient funds not only to cover all research and development costs, but also to construct and maintain the production facility and to purchase the vaccine for a fixed period of time. Is it too early in the process of developing an HIV vaccine to implement this system?

Not-for-profit institutes. In this model, the public sector decides that there is a compelling public need for the development of certain products and that no single private company could or would undertake the work. The public sector establishes a mission-oriented agency. Examples are Airbus Industry and the Manhattan Project. Recently the IOM recommended establishing of a national vaccine authority to undertake, in collaboration with private industry, the development and production of new vaccines for children as a part of the new worldwide children's vaccine initiative (CVI):

In the committee's view, the development of new and improved [children's] vaccines is unlikely to occur unless there is an entity that has the mandate to manage and oversee the process from beginning to end. Because the private sector alone cannot sustain the costs and risks associated with the development of most CVI vaccines, and because the successful development of vaccines requires an integrated process, the committee recommends that an entity, tentatively called the National Vaccine Authority (NVA), be organized to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of global public health need.¹²

A common denominator of these not-for-profit institutes is that they are designed to undertake research and development, but they rely on private industry for production and marketing. These institutes assume most of the risk of early product development. One of the strengths of these institutes is that they can manage the product-development process from start to finish, much as private industry does. Even though they may not actually execute each step of the process, they maintain a constant involvement as the product moves toward distribution. This ongoing involvement reflects their concern with the ultimate use of the product and not just with a single stage of the process. Undertaking the work under one roof, they seek to assemble the required IPRs, and they seek to protect the interests of the public sector, including ensuring that the public-sector market will be served.

Consultative groups. A consultative group is composed of multilateral agencies, bilateral donors, specialized agencies, industry, academia, and others. For example, the Consultative Group on International Agricultural Research (CGIAR) is a

highly successful system for encouraging the development and dissemination of new crops, fertilizers, irrigation systems, and other technologies important for agriculture. It meets twice each year: once to review technical and strategic issues, and once to review financial requirements and to provide donors an opportunity to make pledges of support. The CGIAR coordinates support for a number of agricultural research institutes throughout the world. Each institute has a special area or areas of expertise, including rice, wheat, maize, irrigation, and so forth. The CGIAR operates through a secretariat at the World Bank. Each institute prepares budget proposals. The secretariat screens the proposals to ensure that they fit within an overall strategy approved by the consultative group. In addition, the proposals are reviewed by the Food and Agricultural Organization for technical merit. The secretariat then recommends to the consultative group the funding to be received by each institute. The CGIAR allocates over \$200 million per year.

For a vaccine-development consultative group, industry would have to be directly involved in designing the management plan to be overseen by the consultative group. The new United Nations AIDS program may provide the basis for an HIV-vaccine-development consultative group.¹³

DISCUSSION

CURRENT MANAGEMENT SYSTEMS

The existing management systems (investigator-initiated research programs, directed-contract research programs, and codevelopment agreements) have their strengths, but they have weaknesses, too. These weaknesses may help explain why little progress has been made toward development of vaccines for developing countries. All of the existing systems are strong in transferring laboratory findings to industry when these findings are the basis for a product with a promising commercial market. In fact, this is the main objective of these systems. However, all of the systems have faced difficulties in transferring findings that relate to development of products to be used almost exclusively in developing countries. For example, both the Human Reproduction Program and the Tropical Disease Research Program at WHO have had

numerous arrangements with private industry for vaccine development. Some of these arrangements have faced difficulties because of the reluctance of the partners from the private sector to invest heavily in the product. The antifertility vaccine, which probably could enjoy a market among the well-to-do, serves as an example. WHO has struggled to find a partner from the private sector that will accept a product license and assume responsibility for production of pilot-scale batches, development of the vaccine into a commercial entity, and liability. In general, the public sector has lacked the resources to push development of these vaccines. For example, the budgets for these WHO programs have generally not exceeded \$30 million per year. Because these budgets cover a wide range of products, no more than a few million dollars can be allocated to any one product.

Over the years, directed-contract research programs have faced many challenges. The most difficult challenge has been to take a product concept from the very early stages of research all the way through to a finished product. This has led many of these programs to focus increasingly on the later stages of product development. The Tropical Disease Research Program has recently been reorganized for just this purpose. The Human Reproduction Program established a downstream program a few years ago and gave it the largest budget of all the Human Reproduction Program's activities.

Certain aspects of these directed-contract research programs may limit their capability to develop products as rapidly as private industry can:

- One of the greatest challenges faced by these programs is inadequate funding. With much higher levels of funding, the success rate would certainly be greater.
- These programs are often administered by former academic scientists, who tend to identify the additional research that can be done on a product rather than to pass the product along to the next stage of development.
- The scientist-administrators and the members of the external advisory committees, also predominantly from academia, have limited experience in the product-development process.
- The organizations that house these programs have struggled to determine how and whether

they should own patents, assume licenses, deal with liability, and so forth. Clear guidelines have yet to be identified.

These directed-contract research programs have many strengths. In particular they have been successful in substantially expanding research capacity in developing countries. They have also performed excellent multicentered studies of existing products to document their performance in a variety of settings.

The existing management systems are weak in facilitating the assembly of IPRs. A license agreement almost always deals with only one piece of intellectual property. Take, for example, a scientist who discovers an antigen that provokes neutralizing antibodies in experimental animals; if the antibody is produced most efficiently using a proprietary method owned by a third party, the licensee for the antibody will have to obtain rights from the third party. All structures are generally weak in taking account of the dispersed nature of the research and development community. The parties to an agreement often find themselves in competition with other groups, rather than helping to synthesize the work of a number of groups. They have a particular product lead to which they are committed, and they will work hard for its success. Although competition and product champions are important in the development process, the management systems described here have little capability to bring together disparate resources that might be valuable in achieving a successful project.

In summary, current public-sector systems of vaccine development have not been as successful as desired. They are best at implementing tactics, but they face difficulties in formulating and implementing a strategic plan that covers activities from product conception to product use.

POSSIBLE NEW SYSTEMS

The finished-product procurement system, the not-for-profit institute, and the consultative group all take a more strategic, comprehensive (start-to-finish) management approach to vaccine development than the models that are currently in use. Successful implementation of these systems requires a comprehensive management strategy, from basic research to vaccine program implementation.

The problem with the finished-product procurement system is that the HIV vaccine is not sufficiently developed to make it possible to "order" a finished product. There are also problems with the approach used with not-for-profit institute: first, it cannot harness a sufficiently wide range of capabilities; second it would take time to form the institute or to expand an existing institute to sufficient size and capability.

The consultative-group system seems most attractive. Its greatest asset is its ability to mobilize a wide range of capabilities. It could work with both the public and private sectors, help assemble IPRs, and make provisions for a two-tier market through licensing and other approaches. A well-designed consultative-group system would be likely to obtain the confidence of the donor community, which would make more funds available. The major problem is getting various power centers to agree to participate in a consultative group and thereby subjugate some of their decision-making authority to a higher body. A specific difficulty will be to obtain agreement on a system of effective management of IPRs. Without such a system, it is unlikely that the needs of developing countries, particularly the need for a two-tier market, can be met. A consultative-group system could be managed by WHO, the World Bank, or a new entity—perhaps affiliated with an existing agency—formed specifically for this purpose. The recently formed United Nations AIDS program may be able to fill this role.

CONCLUSION

The existing systems for developing a vaccine against HIV should continue to be employed and receive greater levels of funding. They can make important contributions. However, if the goal is to help control AIDS with an HIV vaccine as quickly and effectively as possible, it will be necessary to implement a more comprehensive management system. It is our belief that the most appropriate system to accelerate development of an HIV vaccine is the consultative-group model. The great advantage of this system is that it provides a means to develop a coherent, strategic management plan.

ACKNOWLEDGEMENTS

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NOTES

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2. R. Widdus, Global Programme on Vaccines and Immunization, World Health Organization, Geneva, Switzerland, personal communication with the author, 1994.

3. V.S. Mitchell, N.M. Philipose, and J.P. Sanford, eds., *The Children's Vaccine Initiative: Achieving the Vision* (Washington, D.C.: Institute of Medicine, National Academy Press, 1993), 116-18.

4. Ibid.

5. World Health Organization, *Global Investment in Children's Vaccine Research and Development: Results of a Survey*, 2nd ed. (Geneva: World Health Organization, Children's Vaccine Initiative, May 1994).

6. M.A. Levin, "The Day After an AIDS Vaccine is Discovered: Management Matters," *Journal of Policy Analysis and Management* 12, no. 3 (Summer 1993): 438.

7. PATH is an international, nonprofit, non-governmental agency that is concerned with improving the health of women and children. It has an energetic research and development program, funded in large part by the U.S. Agency for International Development. The program has developed various technologies including a rapid-dip-strip diagnostic procedure for HIV-1 and HIV-2, which is now widely used in health programs in developing countries.

8. F. Robbins, personal communication with the author, February 1994; and F. Robbins, "Polio Historical," in *Vaccines*, ed. S. Plotkin and E. Mortimer (Philadelphia, Penn.: W.B. Saunders, 1988), 102-3.

9. "Worldwide Agreement for AIDS Vaccine Technology Signed," *CDC AIDS Weekly* (29 March 1993): 4.

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Background

- A 1996 landmark review of the NIH AIDS program by a panel of experts recommended that NIH restructure and reinvigorate its AIDS vaccine research program, with leadership from non-government scientists. As a result of the so-called "Levine Report", named after its chairman, Dr. Arnold Levine of Princeton, NIH has increased its budget for AIDS vaccine research and established the AIDS Vaccine Research Committee (AVRC), a panel of distinguished scientists, chaired by Dr. David Baltimore. The AVRC will serve as a scientific advisory group for the new Vaccine Research Center (VRC).
- The new VRC is only a part of the vaccine development challenge. Another NIH effort is a new grant program administered by the NIAID to encourage new and novel approaches to AIDS vaccine research. Grant awards, totaling approximately \$6 million, will be made later this year. In addition, NIH and other Administration officials are working with industry to find ways to overcome the formidable obstacles that have discouraged industry from continuing its investment in the development of AIDS vaccine. Further, President Clinton has said that at the summit of industrialized nations in Denver in June he will enlist other nations to join the U.S. in a worldwide effort to develop an AIDS vaccine.
- A safe and effective AIDS vaccine is a global public health imperative. More than 29 million men, women, and children around the world have been infected with HIV. More than 3 million of these infections occurred in just the past year, with nearly 95 percent in the poorest parts of the world. Without an effective vaccine, AIDS will soon overtake tuberculosis, malaria, and measles as the leading infectious cause of death in the world.

* Commencement Address, Morgan State University, Baltimore, MD, May 18, 1997.

** The NIH intramural program is the in-house NIH research effort, staffed with government scientists, primarily located on the 300 acre NIH campus in Bethesda, Maryland.

May 23, 1997

Lerine Mtg.

- Sandy Lerine -

- PACITA Rec
- not interested in pushing science
- concerned about

- Varanus -

- WIT will host ^{convene} semi-annually

- Scott

- not what PACITA rec'd.
- wanted WIT to coordinate

Sandy

Todd

Arnold V

Tary F.

Don B.

Don F.

Seth B.

Scott H.

Helen M.

Sandra L.

{ Phase II - 3 addit'l products may be added
Baltimore Comm to advise Vace Ctr

Tom - see charts +)

NIH HIV Vaccine Research

**Handouts for Meeting
at
Office of National AIDS Policy**

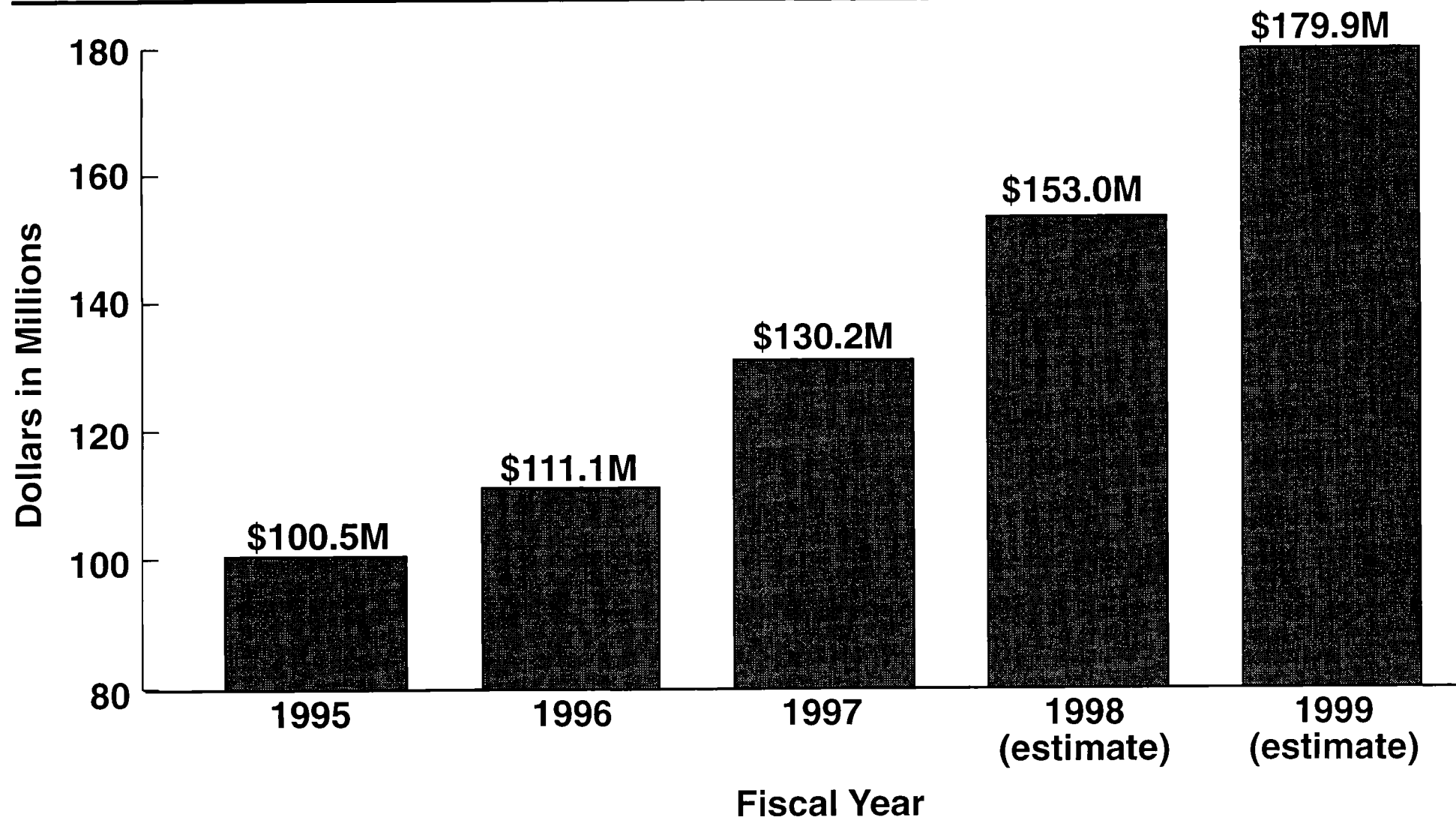
**Old Executive Office Building
Room 472
Tuesday, May 12, 1998**

National Institutes of Health HIV Vaccine Development, 1998

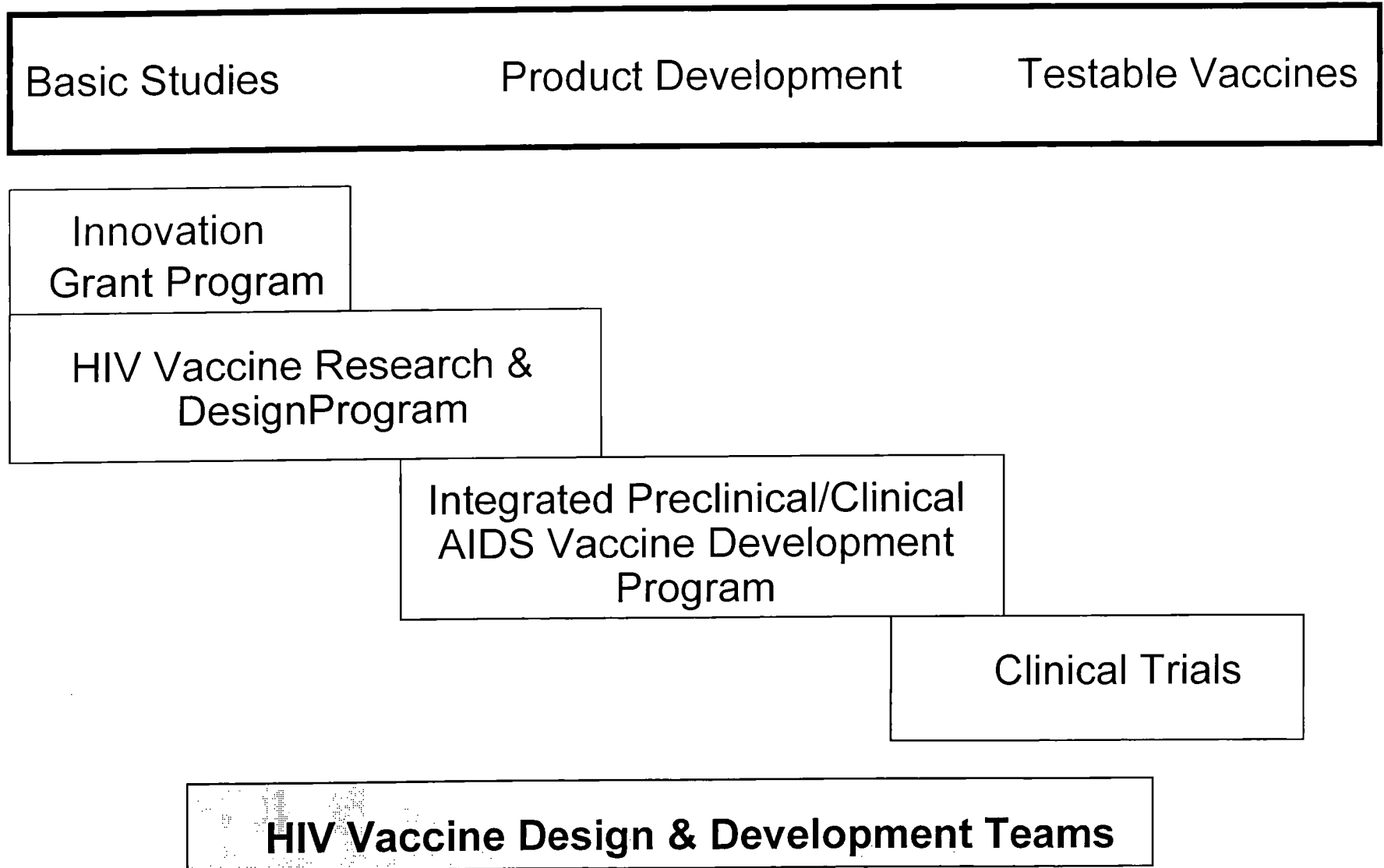
- **Selective increase in research resources for HIV vaccine development**
- **Innovation Grants and other programs to spur vaccine discovery**
- **Targeted grant programs to facilitate vaccine development**
- **Creation of an NIH Vaccine Research Center**
- **Invigoration of clinical trials program**
- **Plan for canarypox/gp-120 intermediate-size trial**

NIH AIDS Vaccine Funding

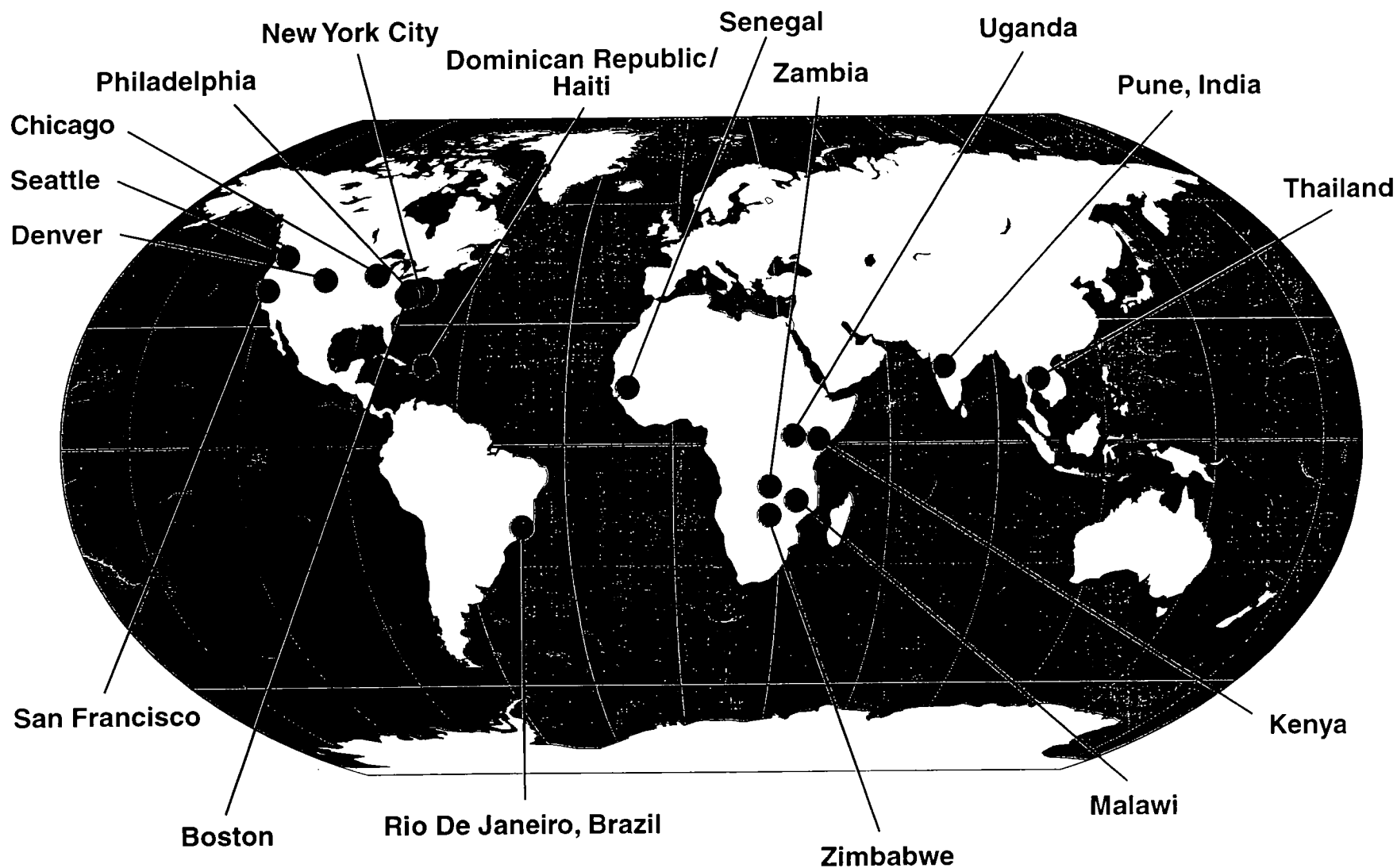
FY 1995-FY 1999



Vaccine Discovery & Development



NIAID-Sponsored Domestic and International HIV Vaccine and Prevention Sites



Vaccine Concepts

- **Recombinant Subunits – gp120, gp160, p24**
- **Live Vectors – poxviruses (vaccinia, avipox), non-pox vectors (adenovirus, salmonella, BCG, poliovirus)**
- **Peptide Epitopes – V3 epitopes, CTL/Th epitopes, particles (Ty-gag, HIV gag), others**
- **Pseudovirions**
- **DNA immunization**
- **Whole-killed**
- **Live attenuated**

Phase II Prime-Boost HIV Vaccine Trial (AVEG 202/HIVNET 014)

- **vCP205 (live-attenuated canarypox carrying HIV genes)
vs. vCP205 + SF-2 rgp120 (Chiron)
vs. Placebo**
- **Immunization at 0, 1, 3, 6 months**
- **420 volunteers in 12 U.S. cities
360 high-risk
60 low-risk**
- **To date, CTL in approximately one-third of vaccinated individuals**

Prime-Boost Development Timeline – May 5, 1998

AVEG/HIVNET Studies

Vector Comparison Study

Boost Comparison Study

Vector GMP Production

Intermediate Sized Trial

Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q3
1998				1999				2000				2001				2002	

Prime-Boost Development Plans

■ Phase II Study

- Complete analysis and gather additional safety and immunogenicity data on participants at low and high risk for infection**
- Assess pilot test procedures used in the study**

■ Vector Comparison Study

- Evaluating three potential products to determine which product produces the maximal breadth and depth of immune response**

Prime-Boost Development Plans

(continued)

■ Boost Comparison Study

- Designed to determine:
 - Which regimen maximizes the neutralizing antibody response to "native" HIV
 - If primary or tissue culture isolates should be used
 - Whether multiple immunogens or a single immunogen is needed

■ Intermediate Sized Trial

- Purpose - feasibility study to identify products/regimens that show no efficacy versus those with plausible efficacy
- 1500-2000 volunteers per arm
- Endpoint: kinetics of infections in those volunteers who become infected

Innovation Grant Program

Total Applications 133

Scientific Areas	Funded
Antigen Processing (Formulations)	19
Antigen Processing (Vectors)	19
Animals Models	8
Envelope Studies	12



National Institutes of Health Vaccine Research Center

- **Discussion of the NIH VRC concept initiated among Drs. Varmus, Paul, Fauci, Klausner and selected ICD directors**
- **Oval office meeting with President Clinton in December, 1996**
- **President Clinton announced NIH VRC at Morgan State University, Baltimore in May, 1997**

National Institutes of Health Vaccine Research Center (continued)

- **Joint venture of the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Diseases (NIAID)**
- **National search underway for director**
- **Goal of VRC: to stimulate multidisciplinary research in basic and clinical immunology and virology, leading to HIV vaccine design and production**

National Institutes of Health Vaccine Research Center (continued)

- **Estimated funding, FY 1998: \$12.5 million
(\$6.25M from NCI, \$6.25M from NIAID)**
- **Currently a "Center Without Walls" involving core
of NIH scientists with expertise in immunology,
virology and vaccine development**

National Institutes of Health Vaccine Research Center (continued)

- **50,000 gross square-foot facility to be constructed on NIH campus**
- **Estimated completion date: 2000**
- **\$16.9 million for construction in FY 1998 budget**
- **Approximately 125 staff**
- **Mix of BL-2 and BL-3 laboratories**

National Institutes of Health Vaccine Research Center (continued)

- **VRC will integrate modern immunological science with:**
 - **HIV pathogenesis**
 - **Development of immunogens and vectors**
 - **New approaches to vaccination**

Examples of NIH Role in Vaccine Development

Rabies (human diploid cell culture)

Pneumococcal polysaccharide

Hib conjugate

Typhoid (live oral attenuated)

DTP acellular

DTP whole cell + Hib conj. polysaccharide

Varicella zoster, live-attenuated

Inactivated Influenza A

Rotavirus

Measles, mumps and rubella

Meningococcal polysaccharide

Hepatitis B

Hepatitis A

Adenovirus type 4 and 7

Influenza, cold adapted

Pasteur-Merieux

Lederle, Merck

Lederle, Merck, Connaught, Pasteur-Merieux

Swiss Serum and Vaccine Institute

Connaught, Lederle

Connaught, Lederle

Merck

Connaught, Lederle, Wyeth, Parke-Davis

Wyeth-Lederle

Merck

Connaught

SKB, Merck

SKB, Merck

Wyeth

Aviron

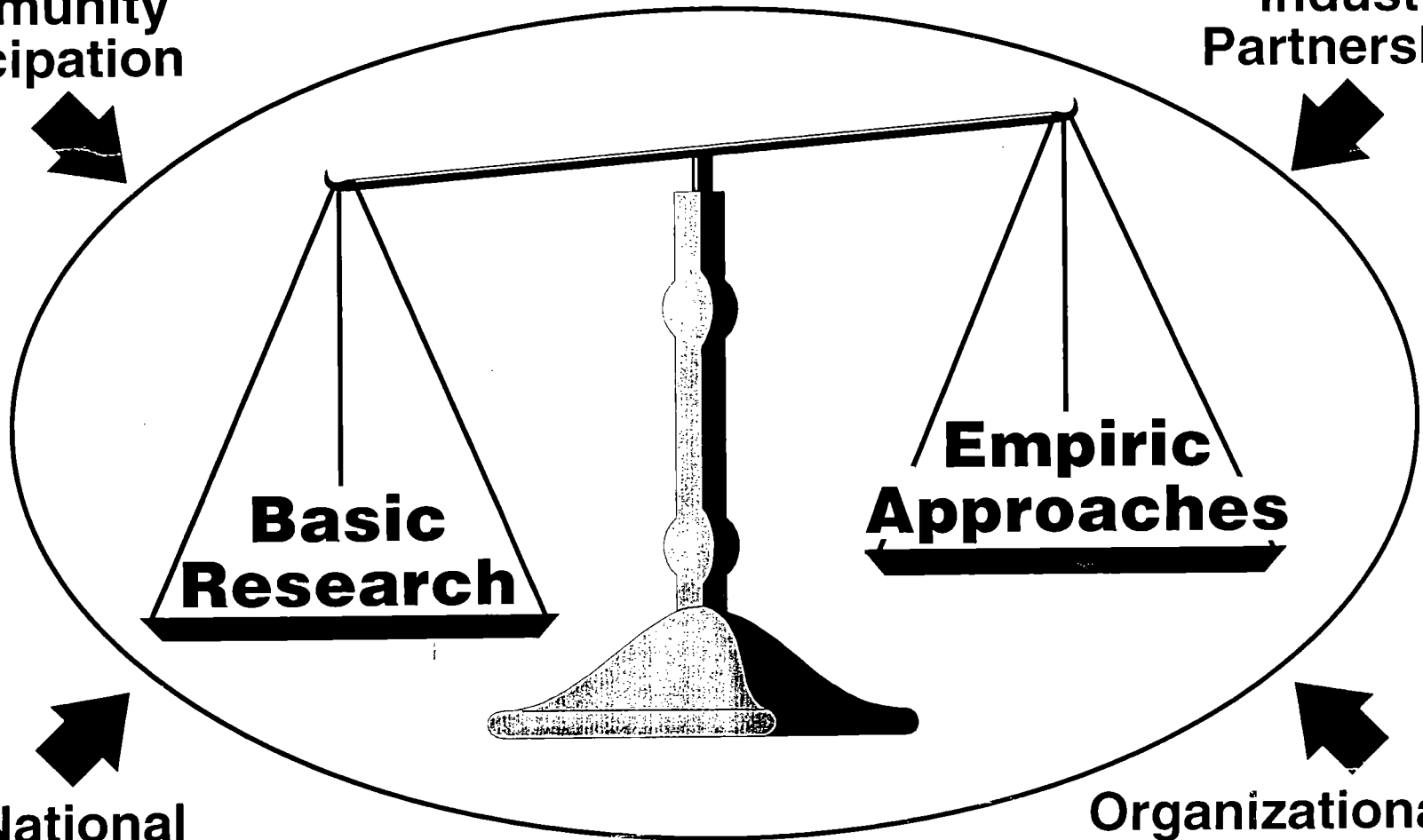
Ongoing Collaborations/Interactions

- **NIH HIV/AIDS Vaccine Coordinating Committee**
- **Interdepartmental HIV/AIDS Vaccine Plan**
- **Currently working with 9 vaccine companies**
- **UNAIDS (e.g. genetic variation; workshops; committees; ethics)**
- **DoD/WRAIR**
- **Vaccine meetings (e.g. NCVDG meeting)**
- **Scientific workshops**

A Balanced Approach to the Development of an HIV Vaccine

Community
Participation

Industry
Partnerships



The National
Institutes
of Health

Organizational
Collaborations
(e.g. DOD, WHO, etc)

HIV Vaccine Design and Development Teams

Goal:

Advance vaccine concepts to the product stage via a focused, development-based approach

Approach:

Identify and support consortia of scientists with development experience from industry and/or academia that have 1) identified a promising vaccine concept, and 2) envisioned a product amenable to targeted development



HIV Vaccine Design and Development Teams

The competing Teams will be evaluated for:

- Soundness of the scientific rationale of the vaccine concept
- Plausibility of development to a product within the timeframe
- The design and development plan describing the proposed process for taking the concept through to the product stage
- How the Team will redefine goals and milestones as the project matures
- Expertise and development experience of the Team, including how additional members or subcontractors will be selected based on the emerging scientific directions of the project
- Plans for obtaining "intellectual property" assurances, and procedures that will be used to resolve legal issues that arise within the Team
- Infrastructure, resources, and facilities to accomplish the project



HIV Vaccine Trials Network: Concept

Purpose:

Develop a comprehensive, integrated, and multidisciplinary program of HIV vaccine research leading to the identification of a safe and efficacious HIV vaccine(s)

Objective:

Establish a highly coordinated group of clinical and bench researchers charged with addressing fundamental research questions in the course of conducting HIV clinical vaccine research



HIV Vaccine Trials Network: Concept

Proposed Structure

- HVTN leadership would define scientific agenda
- Capacity to conduct phase I/II clinical research in developed/developing countries
- Opportunity to engage, directly or through collaborations, in basic laboratory research for the purpose of furthering HIV vaccine development efforts
- Inclusion, as part of the scientific agenda, the research and logistical efforts deemed necessary for phase III trials



HIV Vaccine Trials Network: Concept

Examples of clinical research opportunities

- Expansion of human immunology research
- Evaluation of impact of viral and host genetic diversity in the development of an HIV vaccine



HIV Vaccine Trials Network: Concept

Examples of Phase III opportunities/needs

- Conduct research on clinical trial methodology including efficacy trial design
- Develop strong and ongoing community outreach/education on vaccine activities
- Develop input system for community needs/issues
- Define and conduct research which will ensure readiness and success of large efficacy trials

