BILL & MELINDA GATES foundation

BACKGROUNDER
NEW GRANTS TO ACCELERATE HIV VACCINE DEVELOPMENT

The Bill & Melinda Gates Foundation has provided 16 grants totaling $287 million over five years to establish an international network of HIV vaccine discovery consortia, supported by central laboratories and data analysis facilities. The goal of this new network is to overcome major scientific obstacles facing HIV vaccine research, and accelerate the development of an effective vaccine that could help bring the global AIDS epidemic under control.

The grants bring together more than 165 investigators from 19 countries to design and evaluate novel vaccine candidates capable of eliciting immune responses believed to be critical for protection against HIV. As new vaccine candidates are created, grantees will test the vaccines using standardized protocols, share data in real time, and compare results so that the most promising vaccine approaches can be quickly prioritized for further development, including clinical trials in humans.

The 16 grants, known collectively as the Collaboration for AIDS Vaccine Discovery, include:

- *Vaccine discovery consortia:* Eleven grants establish large-scale vaccine discovery consortia to pursue a range of innovative strategies for designing an effective HIV vaccine:
    - *Neutralizing antibodies:* Five consortia will focus on designing vaccine candidates capable of eliciting effective neutralizing antibodies against HIV
    - *Cellular immunity:* Six consortia will focus on overcoming significant shortcomings with current vaccine candidates designed to elicit effective cellular immunity
- *Central facilities:* Five grants establish central facilities to support comparative evaluations of the vaccine candidates created by the discovery consortia. These include three laboratory networks for evaluating the immune responses elicited by vaccine candidates, a research specimen repository, and a data and statistical management center.

These grants target new resources to research priorities identified in the Scientific Strategic Plan of the Global HIV Vaccine Enterprise, an international alliance of researchers, funders, and advocates dedicated to accelerating HIV vaccine development by implementing a shared scientific plan. The Enterprise plan, developed by 140 scientists worldwide and published in the February 2005 issue of *PLoS Medicine,* outlines six priority areas: vaccine discovery, laboratory standardization, manufacturing, clinical trials capacity, regulatory capacity, and intellectual property. (The Enterprise plan is available at medicine.plosjournals.org, and additional information about the Enterprise is available at www.hivvaccineenterprise.org.)

Following are descriptions of each of the 16 grants.

VACCINE DISCOVERY CONSORTIA

Neutralizing Antibodies

Five grants establish large-scale vaccine discovery consortia to address one of the biggest scientific obstacles currently facing HIV vaccine development: designing novel vaccine candidates capable of eliciting effective neutralizing antibodies.

Virtually all licensed vaccines are believed to work, at least in part, by stimulating the immune system to produce neutralizing antibodies that bind to vulnerable regions on the infection-causing agent – much like a lock and key. But traditional approaches for eliciting effective antibodies have mostly failed for HIV. A major challenge is that HIV has a high level of genetic variability, and an effective vaccine will need to elicit antibodies that can neutralize a broad range of HIV strains.

The five grants focused on neutralizing antibodies include:

- **Vaccines to Neutralize HIV-1**

  Lead investigator: Robin Weiss, University College London
  Grant amount: $25.3 million

  One potential approach for the design of an HIV vaccine that elicits effective neutralizing antibodies is to "work backwards" – first isolate and characterize the types of antibodies that can neutralize a broad range of HIV strains, and then use these antibodies to identify the regions of HIV that are targeted, and incorporate the regions into the design of vaccine candidates. However, only a handful of broadly neutralizing HIV antibodies have been identified to date, and Dr. Weiss's consortium will mount a large-scale effort to identify additional types of neutralizing antibodies. The investigators will isolate a large number of monoclonal antibodies from humans and animals, screen them for the ability to neutralize HIV, and use the best antibodies to design new vaccine candidates. The consortium of scientists working in the U.K., Netherlands, Germany, France, Switzerland, and the U.S. will combine expertise in antibodies, molecular structures, and immune responses to vaccines.

  Discovery of Novel HIV Neutralizing Epitopes and Their Optimal Presentation Though Computational Design of Small Protein Immunogens

  Lead investigator: Leo Stamatatos, Seattle Biomedical Research Institute
  Grant amount: $19.4 million

  Traditionally, vaccines that elicit antibodies against viruses have been constructed from inactivated or weakened versions of the viruses themselves (for example, the polio vaccines), or from parts of the viruses such as surface proteins (for example, the hepatitis B vaccine). But these approaches have been mostly unsuccessful for HIV, and in order for an HIV vaccine to elicit effective neutralizing antibodies, it may be necessary to engineer entirely new molecules. One of the approaches to be explored by Dr. Stamatatos's consortium involves using state-of-the-art computer design techniques to manufacture synthetic molecules consisting of key regions of HIV incorporated into non-HIV structures called "protein scaffolds." These molecules would then be delivered in a vaccine to trigger immune responses. To help provide the massive computing power necessary to conduct this project, the consortium will partner with the Rosetta@home project, which allows individuals around the world to donate their personal computer's idle time to run research calculations over the Internet.

- **Broadly Reactive Neutralizing Antibodies: Novel Strategies for Vaccine Design**

  Lead investigator: Barton Haynes, Duke University
  Grant amount: $15 million

  Previous studies by Dr. Haynes and colleagues have suggested that the immune system is naturally capable of producing effective antibodies against HIV, but suppresses these antibodies from being generated. The investigators hypothesize that critical areas on HIV's outer coat mimic a person's own "self" molecules, and the immune system therefore does not attack HIV with effective antibodies – a phenomenon known as immune tolerance. The consortium's goal is to identify vaccine strategies to "switch on" the immune system's ability to make effective antibodies against HIV, either by interrupting immune tolerance, or by making altered versions of the outer coat of HIV that can stimulate different but effective antibodies. As part of this research, the consortium will collaborate with scientists in Zambia to study a less virulent type of HIV, called HIV-2. By understanding how antibodies are more easily able to neutralize HIV-2, the investigators hope to uncover new strategies for effective vaccine design.

- **The V3 Loop: A Conserved Structure of gp120 That Can Induce Broadly Neutralizing Antibodies Against HIV-1**

  Lead investigator: Susan Zolla-Pazner, New York University School of Medicine
  Grant amount: $8.4 million

  Dr. Zolla-Pazner and her consortium will explore the use of the V3 region of HIV for vaccine design (V3 is short for "third variable loop" of the outer viral coat). Although this region of HIV has been shown to stimulate antibodies, the antibodies are not effective against a broad range of HIV strains, because the V3 region has a very high level of genetic variability. These investigators propose that certain areas on the V3 region are actually "structurally conserved" across HIV strains, and that if this structural conservation were properly understood, the information could be used to design novel vaccine candidates that elicit effective neutralizing antibodies against different HIV strains. In addition to studying the V3 region of HIV strains circulating in developed countries, the consortium has established international collaborations to study HIV strains from Africa and South Asia.

- **Allogenic HIV Vaccine Strategy Utilizing Innate and Adaptive Immunity**

  Lead investigator: Thomas Lehner, Kings College London
  Grant amount: $5.6 million

  Currently licensed vaccines for infectious diseases are designed to stimulate immune responses against proteins of the infectious organisms. However, epidemiological and experimental studies have suggested that harnessing immune responses involved in rejecting tissue transplants – that is, foreign tissue types called HLA proteins – may be an effective means of preventing HIV infection. This is because when HIV replicates inside human cells, selected human proteins become incorporated in the virus, and become potential targets for an anti-HIV immune response. Dr. Lehner's consortium will focus on designing vaccine candidates based on human HLA proteins that can stimulate immunity against HIV.

Cellular Immunity

In addition to neutralizing antibodies, an effective HIV vaccine may need to induce cellular, or T-cell, immunity. Cellular immunity and neutralizing antibodies work in concert – while antibodies

bind to viruses to prevent them from infecting cells, cellular immunity locates and destroys infected cells.

Six grants establish large-scale consortia to address critical challenges in designing vaccine candidates capable of eliciting strong and long-lasting protective cellular immune responses against HIV. To date, several HIV vaccine candidates designed to elicit cellular immunity have been tested in clinical trials, although all have significant shortcomings.

The six grants focused on cellular immunity include:

- **Novel Recombinant Adenovirus and Mycobacteria Vector-Based Vaccines for HIV-1**

  Lead investigator: Norman Letvin, Harvard University and Beth Israel Deaconess Medical Center
  Grant amount: $18 million

  Optimization and Efficacy of a Transcutaneous "Stealth" Adenovirus Vector Vaccine for Mucosal Protection Against HIV

  Lead investigator: Steven Patterson, Imperial College London
  Grant amount: $9.2 million

  The consortia supported by these two grants will work in parallel to address a potentially major shortcoming of the leading vaccine approach for eliciting cellular immunity to HIV, called adenovirus type 5 (Ad5) vectored vaccines. While Ad5-vectored vaccine candidates have been shown in early clinical trials to elicit relatively strong and long-lasting cellular immunity against HIV, they may be ineffective in developing countries. These vaccine candidates use Ad5 as a vector, or "carrier," to transfer inactive genetic material from HIV into human cells and stimulate an immune response to HIV. However, many people in developing countries have been exposed to Ad5 in its naturally circulating form (it causes common respiratory and intestinal infections), and have developed a pre-existing immunity to it, which could render Ad5 less effective as a carrier virus. The Patterson and Letvin consortia will use different approaches to try to circumvent pre-existing immunity to Ad5 by designing vaccines based on less prevalent serotypes of adenovirus (for example, Ad35 and Ad41), to which few people are likely to have been exposed. They will also develop polymer-coated shields to "hide" adenovirus vectors from pre-existing immunity.

  Dr. Patterson's consortium will also focus on testing a system for delivering an HIV vaccine by skin patch, which would be more practical for developing countries than a needle-based vaccine. And in addition to adenovirus-based vaccines, Dr. Letvin's consortium will study the use of modified versions of the bacteria that cause tuberculosis (recombinant BCG and recombinant *Mycobacterium smegmatis*) as potential vectors for HIV vaccines.

- **Poxvirus T-Cell Vaccine Discovery Consortium**

  Lead investigator: Giuseppe Pantaleo, Centre Hospitalier Universitaire Vaudois
  Grant amount: $15.3 million

  Dr. Pantaleo's consortium will focus on improving HIV vaccine designs based on poxvirus vectors. The use of poxvirus-based vaccines is supported by extensive pre-clinical and clinical experience (one of the poxviruses is a modified version of the vaccinia virus that was successfully used to eradicate smallpox), and evidence suggests that poxvirus vector vaccines could be significantly improved in their ability to stimulate

cellular immune responses. The consortium will focus on making improvements to three poxvirus vectors that have been used in HIV vaccines – MVA, NYVAC, and ALVAC. The investigators will also develop new immunologic tests and strategies to help better determine how the results of animal studies should guide decisions about which poxvirus candidates are most promising to move forward into human clinical trials. The ultimate goal of the consortium is to advance the most promising new poxvirus vaccine candidate into Phase I clinical trials by the end of the grant period.

- **T-Cell Vaccine Research and Development Consortium**

  Lead investigator: Timothy Zamb, International AIDS Vaccine Initiative
  Grant amount: $23.7 million

  Dr. Zamb's consortium will study a range of novel viral vectors for their potential use in HIV vaccines. The investigators will focus on viral vectors that have been identified as promising, but have not been adequately pursued – including hybrid viruses and vectors derived from reoviruses, adeno-associated virus, and Newcastle Disease virus. Vaccine candidates created by the consortium will be tested in large-scale animal studies, with the results rank-ordered so that the most promising vaccine designs can be prioritized for human clinical trials.

- **Harnessing Dendritic Cells and Innate Immune Activation Signals to Guide HIV-1 Vaccine Development**

  Lead investigator: David Ho, Aaron Diamond AIDS Research Center,The Rockefeller University
  Grant amount: $24.7 million

  Dr. Ho's consortium will attempt to design HIV vaccine candidates that specifically target dendritic cells, a part of the immune system that is believed to play an important role in enhancing both antibody and cellular immune responses. The investigators will develop vaccine candidates that include protein, virus-like particle, and viral vector constructs that specifically bind to the surface of dendritic cells. In addition, the consortium will study the use of chemicals called glycolipids, which activate immune cells that stimulate dendritic cells. Although glycolipids have been used to treat cancer, they have never been studied in humans to improve the immune responses elicited by vaccines.

- **Harnessing Innate Immunity to Enhance the Immunogenicity of HIV Vaccines**

  Lead investigator: M. Juliana McElrath, Fred Hutchinson Cancer Research Center
  Grant amount: $30.1 million

  For decades, vaccine developers have added substances called adjuvants to vaccines in order to increase the potency of the immune responses they elicit. Although adjuvants often make vaccines more effective, very little is understood about how they actually work. Dr. McElrath's consortium – which includes scientists from academia, biotechnology, and industry with broad expertise in the development and testing of adjuvants – will use both laboratory and animal studies to explore the molecular pathways by which adjuvants enhance cellular immune responses. The consortium will compare multiple existing and novel adjuvants to try to understand their mechanisms of action, and evaluate novel adjuvants in clinical trials to determine the best ways to use them in combination with HIV vaccines. Because adjuvants are not specific to any one vaccine, the information obtained from these studies could be widely applicable to the use of adjuvants with other types of vaccines.

CENTRAL FACILITIES

Five grants will create central facilities to support the vaccine discovery consortia described above. These facilities will help consortia members share data in a timely manner, and use standardized protocols and benchmarks to compare results.

The five grants for central facilities include:

- **Comprehensive Antibody Vaccine Immune Monitoring Consortium**

  Lead investigator: David Montefiori, Duke University
  Grant amount: $31.5 million

  Comprehensive T-Cell Vaccine Immune Monitoring Consortium

  Lead investigator: Richard Koup, Dale and Betty Bumpers Vaccine Research Center, U.S. National Institutes of Health
  Grant recipient: Foundation for the National Institutes of Health
  Grant amount: $33.3 million

  Dr. Montefiori will establish an international network of laboratories to evaluate neutralizing antibody responses elicited by HIV vaccine candidates created by the vaccine discovery consortia, and Dr. Koup will establish a complementary network of laboratories to evaluate cellular immune responses. Testing procedures and equipment will be standardized across the laboratories, so that studies of vaccine candidates in both animals and humans can be compared against common benchmarks. In addition to standardizing testing, the central laboratories will conduct research to develop new, more accurate immune monitoring tests, and will provide training and the transfer of technology to laboratories in developing countries. Regional laboratories will be strengthened in selected developing countries, and will be expected to play a critical role in the future conduct of large-scale human trials of HIV vaccine candidates in these countries.

- **Mouse Immunology Laboratory**

  Lead investigator: Phil Greenberg, University of Washington
  Grant amount: $10 million

  Many of the vaccine discovery consortia focusing on cellular immunity will conduct initial tests of new vaccine candidates in animals. Dr. Greenberg is establishing a network of laboratories to improve methods for using mouse studies to evaluate the cellular immune responses elicited by vaccine candidates. This will help investigators make comparative evaluations of vaccine candidates, determine improvements that can be made to candidates, and help identify the most promising candidates for further testing in animals and humans.

- **Consortium on Global HIV Vaccine Research Cryorepository**

  Lead investigator: Hagen Von Briesen, Fraunhofer-Institut für Biomedizinische Technik
  Grant amount: $7.5 million

  Dr. Hagen Von Briesen will establish a state-of-the-art specimen repository where samples obtained from tests of vaccine candidates can be stored in controlled low-temperature conditions, for long-term preservation and for sharing among collaborating laboratories. The facility will also conduct research to develop novel techniques for preserving research samples.

- **Vaccine Immunology Statistical Center**

  Lead investigator: Steven Self, Fred Hutchinson Cancer Research Center
  Grant amount: $9.9 million

  Dr. Self will establish a standardized central repository for storing, comparing, and sharing statistical data generated by the animal and human studies of HIV vaccine candidates conducted through these grants. The repository will include a web-based interface that will provide researchers with real-time, secure access to data. The center will also provide consultation on study design and biostatistics for all of the vaccine discovery consortia and central laboratories. Statistical data analysis will be conducted through the Statistical Center for HIV/AIDS Research and Prevention based at Fred Hutchinson Cancer Research Center.

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