

INVOKING THE ENTERPRISE

In a June 27, 2003 Science magazine Policy Forum, Richard Klausner, Executive Director for Global Health at the Bill & Melinda Gates Foundation, along with twenty-three additional authors (including Chris Collins, then Executive Director of AVAC) address “The Need for a Global HIV Vaccine Enterprise.”

By coincidence, that issue of Science also features a ravishing cover illustration of how Myosin V carries biochemical cargo within cells by taking nanometer-size steps along actin filaments, placing “one foot over another”—a lesson in biochemical tightrope walking that might be taken to heart by the twenty-four authors and the loose organization developed since then to make such an enterprise a reality.

Their thesis is that there is still a need for a high-quality collaborative AIDS vaccine research system that goes well beyond the high-quality—but separate—research projects that we have today.

- The world awaits the development of an effective preventive vaccine.
- Transferring concepts for HIV-1 vaccines into clinical applications has lagged.
- There is an urgent need to create and systematically evaluate more candidate vaccines, and the pace of development of new AIDS vaccine candidates needs to be accelerated.
- The best engine for solving major scientific challenges in AIDS vaccine research is the creativity of individual scientists working together in multidisciplinary problem-solving consortia, adequately resourced and linked to vaccine development capabilities.
- Thus, a well-coordinated global enterprise does not exist and must be created.

This case has been made by many over the course of the epidemic, but never before with such unanimity or from such well-funded and well-placed principal authors. Therein lies its appeal and its power. That and a certain sense of fatigue and frustration with the scientific community’s level of uncertainty after more than a decade of hard work.

The importance of the four-page article cannot be overestimated. It signals a new level of collaboration and a call to radically increase planning, funding and cooperation in the long-term effort to develop an effective AIDS vaccine. Because of the prominence of the Gates Foundation in global health and its demonstrated willingness to use its wealth to put major new resources into projects it supports, many hope that this declaration heralds a new, higher level of activity and progress commensurate with the overwhelming importance of this issue.



Perhaps drawing on Klausner’s experience as former Director of the National Cancer Institute—where large cooperative medical research consortia are common—the article cites the model of acute lymphocytic leukemia (ALL), where cure rates improved eight to ten fold, to 80–100 percent, through a coordinated and iterative program of preclinical developments. That kind of gradual advance required a centralized coordinated clinical trial and laboratory evaluation system, and substantial medical and political support. Because of the scope and toll of the HIV pandemic, however, the article recommends a much faster and better-funded response.

The inescapable fact that there is still this need after more than a decade of work and hundreds of millions already invested seems unassailable. Yet, the promise of big and desperately needed new investments across the AIDS vaccine board has generated lively and contentious public and private comment in the ensuing months while work has proceeded under the informal auspices of the Gates Foundation to move what is now known as “the Enterprise” forward.

AVAC believes that the key to success of this enterprise will be if its sponsors remain unsatisfied with incremental improvements across the field—and instead strike a balance of exploratory and developmental research with bold funding decisions that finance genuine gaps in the current programs. That would truly energize the effort, not just inside the small world of AIDS vaccines research, but for the outside world as well.

The all-star team

To begin to understand the Enterprise, it helps to first take a look at the original authors. Seven are listed before the names go alphabetical:

- Klausner and Helene Gayle of the Bill & Melinda Gates Foundation.
- Seth Berkley, President of the International AIDS Vaccine Initiative (IAVI).
- Four leaders from the National Institutes of Health (NIH) and its programs:
Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID);
Larry Corey, Principal Investigator of the NIH-funded HIV Vaccine Trials Network (HVTN);
Gary Nabel, Director of the Vaccine Research Center (VRC); Barton Haynes, Chair of the
AIDS Vaccine Research Working Group (AVRWG).

Additional luminaries include: David Baltimore, former AVRWG Chair and Harold Varmus, former NIH Director; Julie Gerberding, director of the Centers for Disease Control and Prevention (CDC); Michel Kazatchkine, director of the French Agence Nationale de Recherches sur le Sida (ANRS);

Peter Piot, Director of the Joint United Nations Programme on HIV/AIDS (UNAIDS); Jose Esparza, then Director of the World Health Organization (WHO) HIV Vaccine Program who has since moved to the Gates Foundation to work on this project; and a wide range of scientific and international leaders in the field. In fact, the list of authors and their affiliations fill more than five column inches of Science small print.

Thus, this is a wide-ranging group headed by the leaders of the largest and most influential AIDS vaccine development programs in the public sector. If this group says there's a need for a Global HIV Vaccine Enterprise, that's saying something. These are the very people we've entrusted with developing such a vaccine, and the very people who have the power and resources to influence it most.

A loose but grand structure is proposed

In the article, the authors say they hope to prompt an international dialogue about options to achieve the goal of developing a safe and effective AIDS vaccine in the shortest time possible by defining basic principles for the Enterprise. The authors present a number of ideas:

- AIDS vaccine development centers.
- Vaccine science consortia.
- Development of dedicated HIV-1 vaccine manufacturing capacity.
- Establishment of standardized preclinical and clinical laboratory assessment.
- Expansion of an integrated international clinical trials system.
- Optimizing interactions among regulatory authorities.
- Coordinating international AIDS vaccine development.

The authors invoke the Human Genome Project model, saying that the time is right for the major scientific and product-development leaders, and stakeholders involved in the global AIDS vaccine development enterprise to come together in an analogous way—with particular attention to international aspects and with full participation of the developing world where the pandemic rages.

With the caveat that this enterprise should consider multiple structural models to accomplish its goals, the authors propose developing a road map for this new Global HIV Vaccine Enterprise that 1) prioritizes the scientific challenges and product development efforts, 2) sets a rapid implementation plan, and 3) identifies the resources needed. That work is now underway.

Progress to date: brave new world

In August 2003, the authors invited about sixty key researchers to a retreat at Airlie House in Virginia to further develop the enterprise concept. There, five working groups defined their portion of the Enterprise, two co-chairs were identified for each group, and a coordinating committee was announced (see page 50). A report and terms of reference for making the blueprint were made available to participants so they could continue their work.

The Airlie House meeting was a way to get further input from experts in each of six areas—vaccine discovery, product development, measurements, manufacturing, clinical trials capacity, and global regulatory and licensing—share those ideas, and begin to explore what initiatives would move the field forward. The retreat stated a “moral commitment” of participants to work in alliance and participate in implementation of a strategic plan. It also began to vet a set of ideas for initiatives that could fundamentally transform what people are able to accomplish themselves and together. This is exciting stuff for those who advocate for an AIDS vaccine.



Now work is underway to elaborate and hone the working groups’ ideas into specific proposals and initiatives that can be agreed upon—defined well enough to be achievable in predictable time frames, yet open ended enough to be amenable to the scientific process of change and development. Not a Manhattan Project, not a man-on-the-moon drive, not an empire building exercise. Something more like the Human Genome Project, whose members have been advising and consulting with the group. A kinder, gentler form of big science.

Not terribly long after the publication of this report we can look forward to an articulated plan with state-of-the-art scientific goals, programmatic recommendations, and—everyone hopes—a new influx of funds and activities. That, after all, is what the original article (and all this work) calls for.

Invoking the Enterprise

While all this has been going on, a number of individuals have mentioned or talked about the Enterprise publicly and from varying angles. Though nothing has been formally announced, these invocations give a good indication of the machinations and adjustment inherent in such an endeavor—and the sense of apprehension and importance it evokes.

First, Anthony Fauci. In his plenary and press conference on AIDS Vaccine Policy and Science at the Vaccines 2003 Conference in New York last September, Fauci unveiled the new government AIDS vaccine collaboration, Partnership for AIDS Vaccine Evaluation (PAVE). Also announced were inter-agency agreements among the US Department of Health and Human Services agencies, which, Fauci

said, would in turn embrace other public and private sector partners that he specifically and particularly included as “an important component of the recently proposed Global HIV Vaccine Enterprise.” This complex, ungrammatical, and somewhat contradictory relationship of including and being included illustrates the ambiguities of how the largest investor in AIDS vaccine research and development, the biggest most powerful government in the world, and the largest private foundation funded by the world’s richest man are engaging with each other.

Next up was Klausner, invited to speak to the HIV Vaccine Trials Network at its October full group meeting in Seattle. In a way, it was the mirror image of Fauci’s speech. The Gates Foundation Global Health Executive Director, first author of the Enterprise vision, was presenting it to a group of government investigators and sites already engaged in a variety of clinical trials of private industry and public/private/academic product-development partnerships. Clearly the HVTN participants had concerns about the inclusiveness of the Enterprise, since it is largely a top-down effort to remake AIDS vaccine research and development. Klausner spoke with enthusiasm about how the work of clinical networks could be enhanced, and how more and better products could be developed with feedback from clinical trials while feeding into them—another complex two-way relationship.

The Conference on Retroviruses and Opportunistic Infections at San Francisco in February was the next opportunity to continue the public discussion about the yet largely undefined Enterprise. This meeting draws researchers and clinicians who are more involved in HIV disease progression and treatment and more sanguine about AIDS vaccines. There are always a number of vaccine sessions, however, and the two most prominent invoked the Enterprise, which at this stage was being developed behind closed doors.

Ronald Desrosiers of the New England Regional Primate Research Center at Harvard Medical School, whose arguments have been described in earlier chapters of this report, took to the podium and delivered a sharp critique of the AIDS vaccine field. Desrosiers is, in fact, an active and valuable member of the Enterprise planning group; as is Susan Buchbinder, head of HIV programs at the San Francisco Health Department, who gave a balancing plenary at the same meeting on the lessons learned and future directions of AIDS vaccine efficacy trials—the other end of the so-called research and development pipeline. She concluded her talk by invoking the Enterprise with a doctored picture from *Star Trek*. She expressed hopes that it would help make iterative, mid-size efficacy trials an integral part of product screening, refinement and scientific development—as an alternative to larger, hit-or-miss licensing trials more appropriate for a more mature field.

Then most recently, and a full eight months after the original article, Science published two letters from eminent, non-contributing European scientists responding to two very different aspects of the original

Enterprise piece. The Nobel-winning immunologist, Rolf Zinkernagel from the Institute of Experimental Immunology in Zurich, flat-out states that we have no idea how to make a vaccine against a group of diseases that includes HIV—so an influx of investment would serve no purpose “if current accepted paradigms are not drastically changed,” which is not unlike Desrosiers’ perspective. Even more extremely, Zinkernagel proposes that this is such a long-term scientific task that the epidemic needs to be controlled by behavioral, therapeutic and epidemiological means. A similar argument was made by Chip Schooley at the Conference on Retroviruses in a talk on the future of antiviral therapy subtitled, “What If There Is No Vaccine?” In fact, a new clinical trial is even testing use of the anti-viral tenofovir as a prophylactic medication.

Hans Wolf from the University of Regensburg, Germany, takes issue with the need for a new enterprise at all. He describes the efforts of the European Commission to organize AIDS vaccine research and development and proposes that the United Nations serve to coordinate existing efforts.

Apparently, no good idea goes unopposed—and the buffeting that the proposed Enterprise is undergoing may be a sign of its vitality. Yes, the authors reply, “the development of an HIV vaccine is one of the most complex scientific challenges that modern biomedical research is confronting.” Yes, success “will depend on the ability of all,” and yes, they are “delighted that this international dialogue is taking place.”

AVAC’s history with the Enterprise

Chris Collins, then Executive Director of AVAC, was asked to sign on to the Enterprise article and had input on its final form. He also attended the Airlie House meeting. Immediately following, AVAC formally made the following points to the organizers:

As a citizen’s advocacy group, AVAC believes several additional points are particular concerns, offered in the spirit of collaboration and with our offer to help in any way we can. Our thoughts fall into three categories: the social context, leadership on clinical trials, and engaging industry. We discuss them in this order because we believe the social context and clinical trials will be the keys to introducing new products down the road and maintaining and enhancing public and private interest and support.

- 1. The social context.** Success in AIDS vaccine research is sure to require sustained public support for research as well as recruitment and retention of volunteers for years to come. Attention to the social context is crucial. AVAC believes at least four principles are important to success: fostering high standards for clinical research, leaving tangible benefits for communities, involving civil society and operating with an appreciation of global access issues.
- 2. Leadership on clinical trials.** Clinical research on current promising products needs to be accelerated even as the (AIDS vaccine) enterprise is breathing new life into product development. The practical

and scientific benefits of obtaining efficacy data on cellular immunity mediated vaccines as soon as possible cannot take second place while we hunt for a more perfect vaccine. Like the Salk and Sabin controversy, this would be a waste of scientific energy and credibility.

One deficit in the field is relative lack of pressure—from the public, politicians, public health leaders, and sometimes scientists—to run efficacy trials. The Enterprise can remind the world about the risk-reward of clinical research in this field and the need to take decisive actions in order to get results. The Gates Foundation is known for its pragmatic approach to health emergencies and, in the case of AIDS vaccines, support of genuinely iterative efficacy trials is the most immediate and practical current activity.

3. Engaging industry. Industry representatives have emphasized the potentially crucial convening role of the Enterprise as a place to discuss assay and other research standardization that can make data more comparable across the field. That would be an excellent entry point for further collaboration. Also there is the concept of the Enterprise itself: if it is positioned as a visible global leader in health research, the Enterprise can produce public relations benefits for companies that participate.



The Enterprise as envisioned would bring much needed collaboration, energy, attention and resources to AIDS vaccine research. AVAC encourages the Enterprise to also make a contribution on the policy, legal and regulatory issues involved in moving forward.

AVAC invokes the Enterprise

We at the AIDS Vaccine Advocacy Coalition would now like to invoke the Enterprise ourselves by making the following additional points:

- If we really want to get an AIDS vaccine faster, this kind of cooperation and influx of funds has to happen.
- Its success will require giving up some autonomy on the part of each and every organization involved, and in pulling new researchers, ideas and energy into the system.
- The entire AIDS vaccine (small E) enterprise needs to reestablish its sense of urgency similar to what we've recently witnessed for SARS, avian flu, and BSE.
- The AIDS vaccine enterprise needs to acknowledge and take account of its place and proportion in relationship to other AIDS control and global health efforts. The Gates Foundation Global Health program is the ideal convener for such a sea-change among vaccine researchers.
- The role of private money needs to be tempered with public, academic and consumer input.

In March, AVAC talked with Helene Gayle who has direct responsibility for the project at the Gates Foundation. She says that every meeting toward the Enterprise gives “the sense that this is so necessary” and she’s very pleased that it is energizing the scientific community about the overwhelming importance of this issue.

We can look forward to a fall announcement of the Enterprise plan. If it’s a compelling plan, is a platform for sharing, and there’s a sense it can accelerate the effort, it will be impossible to ignore the Gates Foundation and others who have already joined into the process. Now more than ever, especially in the face of current doubts and uncertainties, such an enterprise is necessary. Courage, verve and legitimate optimism are the order for the day.

Stay tuned.

THE GLOBAL HIV VACCINE ENTERPRISE STEERING COMMITTEE	
Michel Kazatchkine <i>Agence Nationale de Recherches sur le Sida (ANRS)</i>	William Makgoba <i>University of KwaZulu-Natal</i>
Richard Klausner, Helene Gayle, José Esparsza¹ <i>Bill & Melinda Gates Foundation</i>	Mark Walport <i>The Wellcome Trust</i>
Seth Berkley, Emilio Emini² <i>International AIDS Vaccine Initiative (IAVI)</i>	Eric Lander <i>Whitehead Institute/ National Human Genome Research Institute</i>
Anthony Fauci, Edmund Tramont, Peggy Johnston <i>US National Institutes of Health (NIH)</i>	Peter Piot <i>UNAIDS</i>
ENTERPRISE WORKING GROUPS AND CO-CHAIRS	
PRODUCT DEVELOPMENT	REGULATORY/LICENSING/IP
Emilio Emini², IAVI	Gladys Monroy, Morrison & Forester LLP
Gary Nabel, NIH-VRC	Helen Rees, University of the Witwatersrand
MANUFACTURING ISSUES	CLINICAL TRIALS CAPACITY
Gordon Douglas, NIH-VRC	Nzeera Ketter, IAVI
Jerald Sadoff, Aeras Global TB Foundation	Judith Wasserheit, HVTN
LABORATORY STANDARDIZATION	<i>HVTN – HIV Vaccine Trials Network</i>
David Montefiori, Duke University	<i>NIH – US National Institutes of Health</i>
Giuseppe Pantaleo, University of Lausanne	<i>IAVI – International AIDS Vaccine Initiative</i>
	<i>VRC – Vaccine Research Center</i>
	¹ Formerly of the WHO-UNAIDS HIV Vaccine Initiative
	² Formerly of Merck & Co.