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The Future of HIV Vaccine Research and the Role of the Global HIV Vaccine Enterprise

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¹Global HIV Vaccine Enterprise

Abstract

Purpose of review—This review covers the role of the Global HIV Vaccine Enterprise (the Enterprise), an alliance of independent organizations committed to development of a safe and effective HIV vaccine. It discusses the history, impact on the field and future directions and initiatives of the alliance, in the context of recent progress in HIV vaccine research and development.

Recent Findings—Significant progress has been made in the field since the release of the 2005 Scientific Strategic Plan (The Plan) of the Enterprise. Over the last year, the Enterprise embarked on an impact assessment of the 2005 Plan and the development of the 2010 Plan. Enterprise Working Groups identified key priorities in the field, several of which are discussed in this review, including: changing the nature, purpose and process of clinical trials; increasing and facilitating data sharing; and optimizing existing and attracting new resources.

Summary—This is an important moment in HIV vaccine research. New clinical trial and laboratory results have created new opportunities to advance the search for an HIV vaccine and reinvigorated the field. The Enterprise will publish its 2010 Scientific Strategic Plan this year, providing a framework for setting new priorities and directions, and encouraging new and existing partners to embark on a shared scientific agenda.

Keywords

Global HIV Vaccine Enterprise; Scientific Strategic Plan; Data Sharing; Clinical Trials

Introduction

This is an important moment in HIV vaccine research. The result of the trial in Thailand (RV144), showing for the first time that a vaccine can confer protection (albeit limited) against HIV acquisition, has provided an important proof of concept that a vaccine against HIV is a possibility [1**]. In addition, it comes at the same time as a steadily increasing flow of important laboratory results, including new insights into the human immune response to HIV and the virus's attempt to evade it, technological advances that have facilitated the isolation of broadly neutralizing antibodies against HIV, the demonstration in non-human primates of the critical role of CD8⁺ effector memory T cells in conferring protection, detailed insights into the role of the mucosa both as a physical and immunological barrier to HIV infection, and novel strategies for vaccine design based on the evolutionary analysis of viral sequences in infected individuals (Fig. 1). Together, these clinical and laboratory advances have created new momentum and a new optimism in the field. In the context of this fundamentally changed

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landscape, this article will discuss the origins, past contributions and future role of the Global HIV Vaccine Enterprise (the Enterprise, www.vaccineenterprise.org) (Fig. 2).

The Global HIV Vaccine Enterprise

The Enterprise is a voluntary alliance of independent organizations committed to working together to accelerate the development of a preventative HIV vaccine. The creation of the Enterprise in 2003 was an unprecedented response to the daunting scientific challenges of developing an HIV vaccine.

Despite 27 years of international effort to control the HIV epidemic, HIV/AIDS continues to pose the greatest health challenge facing humanity today. Approximately 33 million people are living with HIV worldwide and since the beginning of the epidemic in 1981, 25 million people have died of AIDS. Sub-Saharan Africa remains the region most heavily affected by HIV, accounting for 67% of all people living with HIV and AIDS related illness remain a leading cause of death worldwide [12].

Various strategies are being pursued to prevent transmission and/or acquisition of the virus, including behavioral interventions and education, microbicides, pre-exposure prophylaxis, and treatment as prevention [13]. Vaccines are recognized as the most cost-effective and highest-impact public health intervention to control a wide variety of viruses and bacteria and thus, developing a safe and effective vaccine against HIV must be one of our greatest public health priorities. However, HIV has proven to be a difficult adversary, with a remarkable combination of strategies for both suppressing and evading the host immune response. Its extraordinary genetic diversity, the complex properties of its envelope glycoprotein, and its unique ability to infect and induce the death of the cells in the human immune system (CD4+ T helper cells) required for an effective immune response, have together posed unprecedented challenges for vaccine development.

In 2002, the overall landscape of HIV vaccine research reflected traditional and largely successful approaches pursued in other fields of infectious disease research: multiple governmental and philanthropic organizations from around the world were independently funding basic and translational research efforts, largely pursued by individual investigators. However, frustrated by the pace of progress, a group of leaders met in 2003 to discuss the best and fastest way forward. Out of those discussions emerged a proposal to create a global alliance tasked with catalyzing and overseeing a more coordinated approach to HIV vaccine research and development [14]. The need for creation of such a structure, termed the Global HIV Vaccine Enterprise, stemmed from a shared view that the strength of existing efforts was largely limited to single investigator approaches to fundamental vaccine research and that the field would benefit from the development of a high-level shared vision of the best way forward. While the insights and discoveries of independent investigators are necessary for driving progress in the field, there was a growing appreciation that such efforts alone were not sufficient. For example, the collaborative efforts required to move basic vaccine concepts along a path towards clinical testing, product development and licensure are typically beyond the scope of any single investigator. Furthermore, the changing nature of biomedical research itself was driving fundamental changes in how science was organized more broadly.

Given these considerations, there was broad enthusiasm for the need to create the Enterprise, not as a new organization, but as an alliance of independent organizations committed to accelerating the development of a preventive HIV vaccine through the implementation of a shared strategic plan, mobilization of additional resources, and greater collaboration among HIV vaccine researchers and funders worldwide. The founding members of the Enterprise included The Bill & Melinda Gates Foundation (The Gates Foundation), the European Commission (EC), the French National Agency for Research on AIDS (ANRS), the

International AIDS Vaccine Initiative (IAVI), the US National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), the Wellcome Trust, and the World Health Organization (WHO) – United Nations Joint Programme on HIV/AIDS (UNAIDS). Enterprise stakeholders now include funding agencies, research organizations, non-government organizations, pharmaceutical and biotech companies, international agencies, and individual scientists supported by different programs that have been launched or realigned to target the research priorities of the shared Scientific Strategic Plan.

The Enterprise Scientific Strategic Plan

The Scientific Strategic Plan (the Plan), developed by the Enterprise Council, the body charged with guiding the directions and activities of the alliance, presents opportunities to advance HIV vaccine research and development (R&D) through approaches that require increased global collaboration, thus building on and complementing critical contributions from individual researchers. While the Plan is not prescriptive in nature, the vision of the Enterprise assumes shared accountability of members for implementing the Plan's high level goals and priorities. In addition, other stakeholders involved in controlling the HIV epidemic and more directly in HIV vaccine R&D are encouraged to align their activities with the Plan. In particular, the Enterprise aims to increase the engagement and commitment of industry partners in HIV vaccine research and development to ensure that their expertise is harnessed effectively.

In 2005, the Enterprise published its first Plan [15]. The culmination of a broad consultative process, the Plan identified six priority areas and emphasized the need for greater collaboration both amongst funders and researchers. Aligned with and supporting both the specific and overall themes of the Plan, several new research initiatives were started, including the Center for HIV/AIDS Vaccine Immunology (CHAVI) established by NIAID, and the Collaboration for AIDS Vaccine Discovery (CAVD), a compendium of 18 consortia, established by The Gates Foundation. The CHAVI collaboration has brought together 91 researchers from 9 countries and 43 institutions to understand the early events that follow acute HIV infection. The resources available to the collaboration have allowed large-scale projects that could not have been achieved by individual laboratories or small collaborations, especially without the easy access to samples from shared cohorts. Besides the many scientific projects underway in CAVD, the collaboration includes a set of shared core facilities, which provide validated standardized assays and methods to the field. The expertise of these facilities ranges from statistical analyses to mouse immunology and antibody assays. To support collaboration, WHO-UNAIDS and AVAC, hosted by the Enterprise, formed a Coordinating Group and a Communications Sub-group to prepare for the release of HIV vaccine efficacy trial results. These structures now serve as fora for greater dialogue between different funders and researchers (Fig.2).

Since 2005, HIV vaccine research has changed fundamentally, both in how it is organized, the science being undertaken and most importantly, recent discoveries (Fig. 1). As noted in the introduction and Figure 1, new laboratory and clinical results are charting new directions for exploration and providing new momentum for the field. It was in the context of this changing landscape that the Enterprise embarked on an evaluation of the impact of the 2005 Plan and development of the 2010 Plan. Similar to the process used in development of the 2005 Plan, the perspectives of the scientific community on major challenges in the field were gathered through discussions of the Enterprise Science Committee, five Working Groups and consultations at major conferences, involving over 400 scientists in the process. Finally, as this is the Strategic Plan of the Enterprise Council, Council has discussed the Plan several times during the process and provided individual inputs into the final Plan. While the opinions on where the field needs to go next varied widely and the diversity of issues was quite broad, some common themes did emerge.

Rethinking the Centrality of Clinical Trials

Enterprise Working Groups members, from across widely different areas of HIV vaccine research, agreed that now was the time to fundamentally rethink the purpose, nature and organization of clinical trials. As in many other areas of health research, basic discovery and clinical research on HIV vaccines are largely performed as separate activities, funded by different mechanisms and carried out by investigators with different backgrounds and training. The integration of fundamental and clinical research has sometimes been referred to as 'translational research'. However, this term connotes a process whereby groups working separately come together at appropriate moments to discuss opportunities to translate the results from one field to another. This process is intrinsically inefficient as it assumes that one knows when an appropriate moment has arrived, and for clinical efficacy trials, it precludes the necessary pre-trial planning of what hypothesis should be tested, and what immunological and virological assays should be carried out, from which tissues and at what time points. While these issues were discussed to a certain degree before the start of the Step and RV144 trials, many questions about the results of these efficacy trials are now being addressed in post-hoc analysis of available clinical samples, provided to the global scientific community through a peer-review process. The process of providing specimen access is novel and commendable; however, one important lesson from this process has been an appreciation of the critical importance of the laboratory and epidemiological analysis to understand the clinical efficacy data. Without that analysis, there is no opportunity of acquiring insights into the signatures or correlates of protection, of discerning whether the vaccine elicited an immune response that exerted any selection pressure on the virus, and what the impacts were of other parameters, such as circumcision, gender, risk behavior, etc to response. At the same time, it is recognized that robust scientific enquiry as an integral part of human trials requires additional resources and will increase the complexity of trial design and the importance of community engagement.

A common view that emerged from the Working Groups that have been discussing the 2010 Plan was that clinical trials represent a unique opportunity to gain insights into the mechanisms of immunological protection against HIV, and to define the relevance of a variety of immune responses to vaccine efficacy in humans. In short, human clinical trials should be viewed both as an integral and necessary part of scientific exploration, as well as the only definitive way of advancing promising vaccine candidates along a development pathway. This scientifically-enriched approach to human trials requires integrated teams of researchers that include investigators with both laboratory and clinical trials expertise.

The centrality of human efficacy trials to the discovery and development process has other important implications. As stressed by the Working Groups, it has become critical that the field undertake more efficacy trials. Since HIV was discovered, there have only been four large-scale human efficacy vaccine trials of three different vaccine concepts [1*,16,17], a number that is now viewed as insufficient to explore diverse vaccine concepts in humans, and certainly does not reflect the urgency of the epidemic. The need for an increase in the number of trials has at least two implications: first, we need to identify efficiencies in the timelines involved in conducting trials. Currently, efficacy trials span a period of at least seven years from concept to initial results. And second, efficiencies and increased resources must be found to cover the high costs of undertaking large-scale, scientifically-enriched efficacy trials.

Data Sharing

Clinical trials with a robust laboratory component generate enormous amounts of data which, if mined fully, can yield important insights into vaccine immunogenicity and efficacy, as well as the relative importance of various behavioral, genetic, and biological risk factors for acquisition. In order to take maximum advantage of this valuable data, the Working Groups

stressed the importance of quality, relational, open-access databases. Recent progress in high-throughput data collection has led to the creation of multiple databases with a diversity of deposition protocols, file formats, and metadata terms. These databases are managed and mostly maintained by data-producers. The limitations of existing systems include the inability to compare datasets obtained independently, the lack of cross-reference between different data sets and data types, and the frequent lack of access to data. Development of common standards for data deposition and shared tools for data analysis would tremendously facilitate the discovery and development process. Several Enterprise partners have started dialogues to facilitate the coordinated approach of data access and deposition and these efforts will receive more attention in the near future.

Optimizing Existing and Attracting New Resources

The objectives outlined above will not be reached without optimizing the use of existing and attracting new resources. Currently, financial support for HIV vaccine research and development primarily comes from a very limited number of funders. Many countries and regions of the world possess significant human, scientific and financial resources that could be focused to help address the global HIV epidemic. One goal of the Enterprise and its Scientific Strategic Plan is, therefore, to provide a mechanism through which new partners can be engaged and can maximize the impact of their contributions. By developing a comprehensive picture of the global effort, the Plan identifies key gaps and opportunities where additional attention is needed. Thus, the Plan provides a vehicle both to attract new resources and to ensure that their impact has the most benefit.

Regional Initiatives

For this reason (amongst others), the Enterprise is supporting the development of regional initiatives whose goals are to consolidate and mobilize local resources, and build critical mass. One such initiative is the African AIDS Vaccine Program (AAVP), which was formed with the support of several Enterprise partners, including the WHO-UNAIDS, the Canadian International Development Agency (CIDA) and IAVI. AAVP aims to build capacity within four centers of excellence established throughout the African continent. Alignment of AAVP priorities with the Enterprise Plan provides the framework for significant contributions of African scientists to the global effort. It also serves as a powerful advocacy tool both for strengthening commitment of African governments and for increasing local community involvement in all aspects of HIV vaccine research and development. Finally, the spirit of collaboration fostered by the values of the Enterprise promotes sharing of resources within African scientific networks and exchange of information and human resources between the North and the South. A similar initiative is currently under development for Asia, where the AIDS Vaccine Asia Network (AVAN) aims to bring together scientists across Asia and capitalize on the rapidly growing scientific potential in the region.

New Minds, New Ideas

In addition to the regional initiatives, the Enterprise has launched the New Minds, New Ideas initiative to nurture and attract young and early career investigators as well as investigators from other fields. The goals of this initiative are to raise awareness of the importance of young scientists to the field and to suggest strategies for addressing the exceptional challenges young scientists are currently facing on the path to becoming independent researchers. The increasingly multidisciplinary nature of biomedical research is one of the challenges facing young investigators as it requires a very diverse array of expertise, ranging from basic immunology to clinical trial design and computational analysis. Multidisciplinary team research is transforming biomedical science, so that even the concept of independence itself is currently undergoing change. Team science and consortia are becoming the norm and

especially so in the HIV vaccine field. This changing landscape raises multiple questions about attribution of credit, mentorship, and career opportunities for young scientists within these multidisciplinary teams. First and foremost, these challenges have to be recognized by established researchers in the field, whose guidance and mentorship is essential to ensure that scientific excellence is maintained in the future. The Enterprise, in collaboration with OCTAVE, is launching a series of multidisciplinary training workshops as part of its New Minds, New Ideas Initiative.

Concluding Remarks

This is an extraordinary time in HIV vaccine research. New concepts for vaccine design are emerging from many different directions. And these novel ideas for vaccine design are surfacing at the same time as the results of RV144 have provided proof of concept that it is possible for a vaccine to confer protection against HIV infection. In addition, powerful new technologies from other areas of biomedical research are creating new opportunities for vaccine design and analysis. The convergence of these three streams has important implications for the future of the field: science without the possibility of vaccine-induced protection is tantalizing but ultimately of no public health value, while the proof of concept demonstration that a vaccine can confer limited protection is only of value if there is the possibility of improving on the results of the RV144 trial. It is the role of the Enterprise—that is the organizations and individuals who form the alliance—to ensure that this special moment is not lost and that we capitalize to the fullest on the opportunities that lie ahead.

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Figure 1. Examples of recent progress in HIV vaccinology

a) Mosaic sequences encompassing a wide array of virus sequences are exhibiting increased breadth and depth of responses, two key features of a desirable immunogen, in NHP trials [2*]. Preclinical studies of an MVA-based HIV vaccine candidate demonstrate efficient antigen presentation and some antiviral effect [3*]. b) Approaches tested in non-human primates (NHPs) show protection against SIV challenge [4*,5*]. c) The results of RV144 demonstrated a modest protection (31%) against acquisition of HIV [1*]. d) Analysis of the Step vaccine candidate shows a sieve effect on breakthrough viruses, suggesting that the vaccine was able to induce immune responses targeting the incoming virus [6*]. e) Analyses of viral sequences following acute infection show that one or a few viruses usually establish infection[7]. f) Different adjuvants induce increased mucosal protection through induction of both innate and adaptive immunity [8*]. g) Discovery of additional broadly neutralizing antibodies (Nabs) with new epitope targets suggest novel approaches for rational immunogen design [9*]. h) Systems biology approaches have begun to provide insights into the mechanisms and signatures of protection after vaccination and the signatures of progression to AIDS[10*,11*].

Figure 2. Timeline of Enterprise development stages from conceptualization to implementation