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Organizing the HIV Vaccine Development Effort

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Abstract

Purpose of Review—Describe and compare the diverse organizational structures and funding mechanisms applied to advance HIV preventive vaccine research and development, to help explain and inform evolving infrastructures and collaborative funding models.

Recent Findings—Based on models that have been tried, improved or abandoned over three decades, the field seems to have settled into a relatively stable set of diverse initiatives, each with its own organizational signature. At the same time, this set of organizations is forging cross-organizational collaborations, which promise to acquire newly emergent beneficial properties.

Summary—Strong motivation to expedite HIV vaccine R&D has driven a diversity of customized and inventive organizational approaches, largely government and foundation funded. While no one approach has proven a panacea, the field has evolved into a constellation of often overlapping organizations that complement or reinforce one another. The Global HIV Vaccine Enterprise, a responsive, rapidly evolving loose infrastructure, is an innovative collaboration to catalyze that evolution.

Keywords

HIV vaccine; HIV prevention; funding; clinical trials; Global HIV Vaccine Enterprise

Introduction

Since the end of World War II, the governments of industrialized countries have purposely emphasized funding fundamental research, leaving the majority of product development to private companies. That division of expertise and responsibilities has led to unprecedented medical progress, pharmaceutical success and beneficial health outcomes.

However, the impetus to translate basic discoveries into clinically relevant medicines depends largely on perceived risk and potential profit for the private sector. In-depth knowledge of the pathogen and immune responses do not guarantee that a vaccine approach tested in the preclinical studies will be safe, efficacious and practical in humans. This well-known gap--the product development “valley of death”--is especially large for HIV vaccines due to multiple scientific challenges and the very high bar of cost, human resources, and time for efficacy testing of candidates (1,2). A successful HIV vaccine will require severely

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tiered pricing to have a public health impact in areas where the epidemic is most destructive, which adds uncertainty about whether a private company will be able to recoup its research and development costs. As a result, the vast majority of the U.S. \$8.5 billion invested in HIV vaccine R&D between 2000 and 2011 has come from public and philanthropic sources (3).

The Challenges of making a preventive HIV vaccine engender organizational creativity

In spite of the acknowledged urgent need for industry involvement, a majority of basic researchers who want to translate their immunological ideas into candidate constructs are championing their candidates through clinical trials on their own, with limited industry engagement and with primarily public funding. To understand why that approach is challenging, it is helpful to accentuate the fundamental differences in the organization of research from the organization of development.

Research and innovation are by nature unorganized without being dis-organized (having their own internal logic and processes). Well-refined but pliable systems of grant applications, grant making, reporting, publishing and re-granting are based on the inherently flexible approach of inquiry-driven experiments adapting to and being shaped by emerging data. Even when specific vaccine development objectives are stated in a grant application, investigators have latitude to change plans. The possibility of negative or unexpected outcomes is accepted. Despite strict rules of scientific process, scientists take pride in being inquiry driven and fundamentally un-organizable.

Vaccine development is traditionally the purview of companies, or organizations, like the military, that need to produce vaccines they can bring to market or deploy in a timely way. Product development is an art and science of its own, differing fundamentally from academic research. The required expertise focuses on manufacturing and product delivery; flexibility is sacrificed for the sake of consistency; decision-making is consolidated, decisive and driven by milestones, risk/benefit analyses, and implementation considerations; regulatory and intellectual property challenges of the development process go beyond anything encountered by an academic researcher.

In HIV vaccine development, industry has compelling reasons to be cautious with investments. Developing a vaccine has already proven to be difficult, resource-intensive (cost and labor), time-consuming, and without guarantee of return on investment even if the research is successful. As a result, the field of HIV vaccines has been unfortunate to suffer the loss of not just the financial backing provided by industrial partners, but perhaps more importantly, the expertise, perspective, and incentives of vaccine developers.

Evolving organizational infrastructures

The standard model of academic research, which relies on grants and publishing, is not providing strong enough incentives for collaboration or rapid information exchange, which are necessities in moving the research agenda forward at a pace commensurate with the extent and human cost of the epidemic.

Since the 1980s, funders have stepped up by funding innovation, by making larger, targeted grants, and by designing and funding diverse organizations of researchers, labs, institutions and companies, while straining to maintain support of investigator-initiated research in the face of flat funding and rising costs (3,4).

An early organizational innovation was the creation of the Military HIV Research Program (MHRP) in 1986. While centered in the US, MHRP adopted or developed research sites in several African countries and in Thailand, engaging local governments, scientists and communities in a collaborative international network in the spokes and hub model shown in Figure 1. This work paid off two decades later by providing MHRP with the expertise and knowledge of realities on the ground required to conduct the 16,000-person RV144. MHRP also served as a model of integrating immunology, virology and clinical research globally that has increasingly been used by other organizations.

Established in 1996, IAVI was an early public-private partnership that brought together diverse expertise to make development agreements with scientists and biotech, do preclinical research and clinical evaluation, and advance the cause of developing an HIV vaccine (5). IAVI can be viewed as a vertical organization, aiming to support every level and stage of HIV vaccine R&D. It is funded by a variety of international donors – philanthropic, governmental and industry. In 2002, IAVI launched its Neutralizing Antibody Consortium (NAC), another innovative organizational model which brings together scientists working on this challenge from a wide variety of institutions as an interest group that works together on top of members' individual affiliations.

In 2000, DAIDS-NIH awarded a grant to the Fred Hutchinson Cancer Research Center to serve as the core for the worldwide HIV Vaccine Trials Network (HVTN). However, it is much more than a network of trial sites, as it includes a core laboratory program to perform assays on samples from clinical trials, and a center for data storage and statistical analysis (SCHARP). The integrated structure streamlined clinical research, consolidated and advanced clinical expertise, facilitating cross-study comparisons of immune responses to candidate vaccines.

Also in 2000, the Vaccine Research Center (VRC) was established, also meant to shepherd vaccines from initial concepts to proof of efficacy, but funded with intramural resources by the National Institute of Allergy and Infectious Diseases (NIAID) (and originally the National Cancer Institute). Ideally, products developed by the VRC would be taken over privately through technology transfer agreements, but industry's role would be receiving the efficacious vaccine, optimizing and scaling up manufacturing processes, and developing capacity to deploy the vaccine, perhaps with advanced marketing arrangements.

The call for a Global HIV Vaccine Enterprise, conceived in 2003 (6), led to development of a field-wide Strategic Plan (7) first published in February 2005. That plan set the stage for the creation of two large consortia, the Collaboration for AIDS Vaccine Discovery (CAVD) by the Bill & Melinda Gates Foundation, and the Center for HIV/AIDS Vaccine Immunology (CHAVI) by NIAID. Those collaborative structures focused on pre-developmental research while providing the benefits of increased data sharing, joint

research, information exchange, and large studies impossible for researchers funded by regular grants.

The large organizations described above are all making substantive contributions to the field, often working together or in complementary ways. They have certain characteristics, some of which are also shared with past programs: cooperative agreements, partnership across organizations and disciplines, and substantial governmental or philanthropic funding. Each of the organizations has also benefited from an identity and strong leadership as much as from collaboration.

A final organizational example is Europrise, funded by the European Commission's sixth Framework, which was a consortium to bring together EU scientists and vaccine developers to embrace a coordinated approach to HIV prevention research (vaccines and microbicides) from 2007 to 2012. The newly inaugurated seventh Framework shifts to multi-disease funding for scientists to work with European vaccine and biotech companies, ending Europrise funding in hopes that it has become self-supporting. EDCTP, the European/Developing Country Clinical Trials Program, however, continues to support clinical collaborations in Africa.

Other approaches that have or haven't been tried to date

A number of models have been proposed to facilitate HIV vaccine research and development. Since early in the epidemic there were calls and experiments with different project concepts, such as the following (with signal examples):

- a Manhattan-like or Human-Genome-like project (never feasible);
- an Über committee (the NIH-wide AVRC “Baltimore Committee”);
- global organization through normative agency (WHO/UNAIDS VAC*);
- bench to clinic projects (NIH Integrated Preclinical/Clinical Vaccine Development*);
- large immunogen development consortia (two CHAVI-ID*);
- product development partnerships (IAVI-Gates Foundation*);
- public/private partnerships (NIAID design and development teams; the recently established French Vaccine Research Institute*);
- bilateral collaboration (US Military and Government of Thailand*);
- regional initiatives (AAVP for Africa; AVAN for Asia,*
- national initiatives (CHVI, Canada;* CAVI, China;* SAAVI, South Africa)

Those examples with *s still exist. Figure 1 uses cartoons to illustrate some of their similarities, and their very real and consequential differences.

Organizing Clinical Trials

While human trials are the best source of relevant data on immunogenicity and efficacy of HIV vaccines, the “1-2-3” phase model for clinical trials is not ideal for inquiry-driven exploration by academically-oriented researchers. This obstacle led early on to field-wide adoption of the “proof of concept,” phase 2b trials, which are moderately sized (except for RV144, which was conducted in 16,000 participants in lower risk general population) to give a reasonable probability of demonstrating a statistically significant efficacy outcome. As such, these efficacy trials are true experiments. Lately, experimental medicine trials are under consideration to accelerate, advance and make the earliest stages of clinical research more efficient (Figure 2). These small trials would be used to test several slightly-different versions of an immunogen to better understand the factors that influence immune responses. Thus, the objective of these trials is not to choose one of the products to advance on the path to licensure, but to interrogate the human immune system and to allow more rational immunogen design in the future.

The field has conducted five efficacy trials in the past 30 years. More recent trials involved more collaborators and funding has shifted from private to public (Table 1). Largely because the RV144 Thai trial demonstrated partial efficacy, its follow up program, the Pox Protein Public Private Partnership (P5), is bringing together an even larger group of stakeholders from industry, funding, and clinical research. P5 has laid out a multi-trial program with a development track and a research track for phase 2b and 3 efficacy trials in Southern Africa and Thailand.

Umbrella Organization: the Global HIV Vaccine Enterprise

The Global HIV Vaccine Enterprise (Enterprise) is an innovative alliance of independent agencies committed to accelerating the development of an HIV vaccine. While members of this unique collaboration of the world's leading HIV vaccine research funding, policymaking, advocacy and stakeholder organizations relinquish none of their power to make decisions independently, their leaders work together through mutual coordination, collaboration, knowledge-sharing, and resource optimization. Critical information is exchanged, and common issues or needs are identified and addressed strategically through regular Funders Fora and common projects.

An original, defining task for the Enterprise was to create and maintain a Scientific Strategic Plan for the entire HIV vaccine R&D endeavor. The first plan was created in 2005 (7) and updated in 2007 (8,9); and a second complete plan was developed and released in 2010 (10). Though plans were useful, contributors realized that a more flexible approach to adapt to the changing needs of the field would be more vital. Therefore, in place of bi-annual Scientific Plans, the Enterprise Board charged its Secretariat (established in 2009) with creating real-time customizable mechanisms, to facilitate interactions among the funders of HIV vaccine research and strategic programs that convene and allow major players to identify and respond to unresolved and emerging field-wide problems or needs as they are recognized. The Enterprise Funders Program and Strategic Convening initiative were born out of this direction.

In July 2012, the Secretariat created *Timely Topics in HIV Vaccines* to identify the most strategic needs of the field from an open call for ideas, as well as from internal proposals and funder-initiated projects. Engaging multiple and diverse stakeholders, the Secretariat is facilitating consultations and developing solutions to tackle these issues. In 2013, the Enterprise Secretariat is working on more than ten such projects. The first Timely Topics have been successful and well-received.

The Global HIV Vaccine Enterprise name and provenance lend credibility and field-wide support to the small Secretariat, while the contributions of partners drive its agenda and activities. The intent of this loose, but committed collaboration with some dedicated organizational support is to make a significant additive contribution toward making the search for an HIV vaccine more strategic, inclusive, effective and all-encompassing.

Conclusions

With all the wisdom, talent and effort already invested, there remain many unresolved, new, and yet-to-be faced challenges, which necessitate the coming together of many diverse stakeholders and the growing trend toward co-funding. At a landmark funders' meeting in 2012 organized by the Enterprise, a dozen of the top HIV vaccine R&D funders confirmed that, with the range of projects and their cost in today's economic environment, no single funder can move ahead alone.

Collaboration may be the wave of the future, but unaffiliated scientists with innovative hypotheses can only take a novel concept so far with traditional funding. Some do benefit from the several initiatives designed to move candidates forward, but there will always be a competitive factor to those, with favorites, trends, and blind alleys. The traditional traits of the scientific profession will always be needed: independence, inquiry, diversity of opinion and approach, willingness to take risks or work outside the mainstream, and dogged hard work in the face of many set-backs and complications. Since one cannot know where answers will come from, a robust mixture of approaches, and hence organizations, must continue to be nurtured and supported.

Perhaps the biggest obstacle to moving forward rapidly through large collaborative structures is the widening circle of parties who need to be involved. When big decisions take months or years, the possibility of smooth, let alone expedited, development becomes hugely problematic. While we may not have the resources, efficiencies and discipline of a private company, we need to work collectively to emulate that capability while still retaining the benefits of group and public process.

History and experience show that a generation of dedicated individuals has learned how to pull together in better ways. It may, however, take the next generation to outgrow us and demonstrate new thinking and greater flexibility. Those future leaders must be recruited, encouraged and given opportunities to step into leadership roles. Scientists who mature in collaborative environments are taking a broader, cross-disciplinary view more easily; increasing the chances for breakthrough discoveries.

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Key Points

- The challenges of developing a preventive HIV vaccine engender organizational creativity
- Clinical testing of HIV vaccines includes increased focus on the discovery research as compared to the standard licensure track
- Multiple collaborative structures, both formal and informal, permeate the current HIV vaccine field

Figure 1.

Schematic cartoons of the types of organizational structures devised to accelerate HIV vaccine research.

a) Traditional grants portfolio: funders provide a landscape of stand-alone grants of various sizes, each focused on a particular scientific area of inquiry. b) Ad hoc consortia: researcher-initiated ad hoc consortia are self-assembling structures formed around a common question, topic or technology of interest. Such ad hoc consortia differ in their degree of project coordination/governance, but can be formalized with well-defined structures, dedicated funding, and intellectual property agreements, e.g. IAVI's Ab Consortium. c) Funder-initiated consortia: these structures bring multiple researchers together around a common research agenda via virtual structures governed by a centralized coordinating and decision-making committee and common facilities, e.g. CHAVI-IDs. d) Dedicated research organizations: formal structures, like the public-private partnership IAVI or the NIAID-funded VRC, which enable streamlined decision-making, focus research on specific questions, and often bring researchers physically together. e) Spoke-and-wheel network: CAVD projects funded by the Gates Foundation, bring together several grants by linking them into a larger network via a number of central service facilities (CSF) to standardize assays, with common policies to facilitate information sharing. f) Cross-funder collaborative project: Collaborative structures don't have to be limited by a single funder, as exemplified by Europrise, which brought together projects funded by European Commission and the Gates Foundation.

Figure 2.

Alternative clinical trial models: a) traditional sequential testing of safety, followed by expected activity, followed by efficacy; b) because correlates of protection for HIV infection are not known, testing for activity is not useful in the absence of efficacy data. Phase 2b trials are large enough to establish proof of concept and hypothesis generation from correlates analysis; c) in experimental medicine trials hypotheses about immunogenicity would be explored quickly by testing multiple versions of a candidate vaccine in small groups of volunteers. There have also been efforts to design adaptive trials with various combinations of the above specified in advance.

The trend for sponsoring and funding Vaccine Efficacy Trials demonstrates movement toward public-private partnerships or fully public projects in lieu of industry-driven development. With the exception of the candidate vaccines for HVTN 505 developed by NIH Vaccine Research Center, Vaccine Development is still largely the purview of private companies.

Table 1

Preventive HIV Vaccine Efficacy Trials ¹									
Title: Period	VAX 004 1998–2003	VAX 003 1999–2003	HVTN 502 (STEP) 2004 – 2009	HVTN 503 (Phambili) 2006–2009	RV144 2003–2009 WRAIR	HVTN 505 2009 –2013	P5 ² Development Track Southern Africa Planned for 2015–2016	P5 Development Track Thailand Planned for 2015–2016	
Sponsor ³	VaxGen	VaxGen	Merck	NIH-DAIDS and SAAVI	U.S. Army Surgeon General: WRAIR	DAIDS-NIAID	P5 Consortium, NIH-DAIDS	P5 consortium, US Army Surgeon General/WRAIR	
Funding	Predominantly private	Predominantly private	Private	Public	Public/Private partnership	Public	Public/Private/Philanthropic collaboration		
Vaccine Developer	Private (VaxGen, nowGSID)	Private (VaxGen, nowGSID)	Private (Merck)	Private (Merck)	Private (Sanofi Pasteur and GSID)	Public (VRC/NIAID/NIH)	Private, 2 companies (Sanofi Pasteur and Novartis)		
Study Countries - Sites	61 sites in 3 countries	17 sites in Thailand	34 sites in 8 countries	5 sites in South Africa	55 sites in Thailand	21 sites in US	TBD: Approximately 25 sites in several Southern African countries	TBD: Thailand	
Other Collaborators		<ul style="list-style-type: none">• Bangkok Metropolitan Authority• Mahidol University• Thai Ministry of Public Health	<ul style="list-style-type: none">• HVTN		<ul style="list-style-type: none">• Thai Ministry of Public Health• Mahidol University• U.S. Army: AFRIMS, MHRP, WRAIR	<ul style="list-style-type: none">• HVTN	<ul style="list-style-type: none">• NIH-NIAID• Gates Foundation• HVTN• Sanofi Pasteur• Novartis	<ul style="list-style-type: none">• NIH-NIAID• Gates Foundation• US MHRP• Sanofi Pasteur• Novartis	

¹ Information for the Table has been collected from <http://www.clinicaltrials.gov> and/or official trial websites, then confirmed by Principal Investigators.

² Abbreviations: GSID: Global Solutions for Infectious Diseases (formerly VaxGen); HVTN: HIV Vaccine Trials Network; MHRP: Military HIV Research Program; NIH: US National Institutes of Health; NIH-DAIDS: Division of AIDS, NIH; NIH-NIAID: National Institute of Allergy and Infectious Diseases, NIH; P5: Pox Protein Public-Private Partnership; NIH-VRC: Dale and Betty Bumpers Vaccine Research Center, NIH; SAAVI: South Africa AIDS Vaccine Initiative; WRAIR: Walter Reed Army Institute of Research

³ We use U.S. Federal Drug Administration's definition of sponsor: "Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization." 21 CFR 312.3(a)