

## Solving the Enterprise Equation

### When is a whole greater than the sum of its parts?

Every year since the Global HIV Vaccine Enterprise was first proposed in 2003, the *AVAC Report* has devoted some of its pages to considering the role and responsibilities of that entity. We've done this as both the Enterprise and the field have changed—and this year is no exception. In this article, we report on how the Enterprise is regarded by a wide range of stakeholders and on how it might improve and expand its mandate. We heard both recognition of contributions and ambivalence and caution amongst many stakeholders. This divided sentiment represents something of a catch-22 for the organization: its added value is not yet completely convincing, therefore it can't draw full buy-in from the people and organizations it's meant to convene. As a member of the Enterprise, AVAC's hope is that this input—along with attention to some of the key issues we've raised in previous years (see box at right)—can help strengthen it for us all.

January 2009 marks the one-year anniversary of Alan Bernstein's leadership as executive director of the Global HIV Vaccine Enterprise secretariat. As we discuss in the previous pages, it's been a year of new insights from vaccine science, renewed emphasis on innovation and discovery research, and expanded appreciation of the scientific contributions from the Step study (see page 32). There have been interesting research findings from teams spanning the globe, including ones working through the NIH-funded CHAVI consortium, the Bill & Melinda Gates Foundation-funded CAVD, the HVTN, and IAVI, along with work funded by European entities like the French ANRS and the European Commission.

With the engines of research chugging along, what does the Enterprise look like in 2009? How relevant and/or responsive is it to the current times? For those looking for a take-home message, we'll say this: there's some good news but also

many places where we find stasis—a sense of “here we are again”—in situations that have not changed since last year's *Report*. Most significant, we're concerned that it's still unclear whether the Enterprise in 2009 has the influence to accelerate and activate conversations between funders and scientists that will lead to swift action in critical directions.

Many of the 20-plus people interviewed for this piece\* focused on the need for an entity that could influence spending, organization, and scientific priorities.

The key roles envisioned for the Enterprise can only be accomplished through collective work. AVAC remains committed to supporting the Enterprise through our participation in various Enterprise-related activities. Our goal with this article is to help catalyze conversation and contribute to setting the Enterprise on a sustainable course.

\* We aimed for diversity and included scientists, donors, funders, policy makers, advocates, US-, Africa-, and Europe-based respondents, scientists working in “big science” consortia and those working in smaller laboratories, clinical trialists and basic scientists. We had one or two respondents, sometimes more, in each category—enough to get a qualitative sense of differing perspectives, though obviously in small numbers.



## AVAC's Quick Take on the Enterprise

AVAC has been involved with the Enterprise from its beginning in 2003, and we have provided updates and recommendations in each of our annual reports since then. In 2005, we identified eight issues that needed to be addressed. Below we've reprinted those key recommendations and updated them. They're broad and ambitious, and many of them could not be accomplished in the single year that the Enterprise secretariat has had an executive director and staff. But they're still targets and there's both progress in some areas and indications of the Enterprise falling short in others.

- 1. Communicate frequently and transparently.** More information, more opinions, more leadership. We'd like to see the Enterprise communicating with stakeholders about emerging issues on a more regular basis, and not just through periodic letters. On the other hand, the meeting reports and minutes posted on the website are useful resources and demonstrate a commitment to transparency.
- 2. Set policies for sharing and coordination of data and technology.** Work here is ongoing; we're eager to hear reports in the coming year.
- 3. Ensure the ability to take risks.** As we discuss in the main article, there's a time for caution and a time for provoking discussion, and we look forward to even more of the latter to balance the former in Enterprise activity.
- 4. Bring new investigators into the search.** This has been a particular area of strength, evidenced by investments in the development of the New Minds, New Ideas initiative to address the need for young and early career investigators, and efforts to build bridges to systems biology. The key now is to set metrics for measuring progress and to update the field on what's working and what's falling short.
- 5. Make the Enterprise truly global.** Commitment to African and Asian regional networks, and on the 2008 AIDS Vaccine Conference in South Africa has helped the Enterprise strengthen global ties. Now the challenge is to get more developing country scientists to the table for scientific deliberations in addition to discussions of geography-specific issues.
- 6. Involve civil society in a meaningful way.** Much more needs to be done here, and the Enterprise needs to be clear about its goals. Is developing country civil society involvement a priority? Is input on scientific issues, such as the Strategic Plan, a priority as the secretariat has stated? If not, that's alright. If so, what's the plan for ensuring the scientific literacy that's needed for meaningful community involvement? Clear expectations and commitments are needed either way.
- 7. Take on the politics and ethics of clinical trials.** This hasn't happened yet. From HVTN 505 to plans for what AIDS vaccine trials might look like if there's benefit from PrEP, there are many issues where the Enterprise can and should play a critical leadership role.
- 8. Establish realistic milestones and a process for monitoring progress.** We look to these as an integral part of the Scientific Strategic Plan and will expect the Enterprise to provide status reports on an ongoing basis.

We posed the same four questions to all of our interviewees:

1. Describe your involvement with the Enterprise to date.
2. What are some of the places where Enterprise-related activities have added value to the field?
3. Are there specific areas where the Enterprise could either change what it's doing or add new areas of expertise to further fulfill its mission?
4. What are your expectations of how Enterprise leadership might or should cause both the overall field and your specific organization to look different a year from now?

When asked to describe their involvement, interviewees had a broad range of answers. Some had been involved with the Enterprise since day one; others, only recently. Some felt a strong affiliation with the entity in its first years when it was steered by an interim secretariat based at the Gates Foundation in Seattle. For other people,

the strongest tie was a conversation or consultation with Dr. Bernstein.

But for everyone there was a sense of engagement and interest in the Enterprise. Whether tempered by optimism or frustration or a little of both, a sense of investment was conveyed by every interviewee.

The Enterprise was originally conceived as the whole of the field, united in a loose, additive structure that would speed the identification of an effective AIDS vaccine. In 2004, the Enterprise was all of us. In 2009, with the New York office, an expanding staff, and the leadership of Dr. Bernstein, it looks more like an independent entity.

As the interviews revealed, if the Enterprise that belongs to all of us is going to succeed, then the Enterprise secretariat must continue to nurture the whole—all of us working toward an AIDS vaccine—while maintaining a clear identity as one of its parts. This is a tall order, perhaps nearly impossible, as several of the interviewees pointed out. But this is, by definition, an ambitious field.

### Contributions to date

Five years ago, the Enterprise was proposed to address frustrations of stakeholders and spectators of the AIDS vaccine effort about the lack of coordination across the major scientific players. There were nearly 50 vaccine candidates, many of which were highly similar, in various stages of clinical development. There was no mechanism for making field-wide “go/no-go” decisions. Assays being used to evaluate candidates were not standardized, making it impossible

“We’re now working to strengthen long-term capacity for phase II/III trials of HIV vaccine candidates in Uganda and Malawi through a collaboration among the UVRI, MRC/UVRI Uganda Research Unit on AIDS, IAVI, the Malawi-Liverpool-Wellcome Trust Clinical Research Program and World Fish. Screening and enrollment of a population cohort among four fishing communities is already underway in Masaka and Wakiso districts, Uganda. Also, we plan to continue with vaccine preparedness studies (funded by IAVI) that we’ve been doing since 2003, in addition to conducting a pilot study to evaluate the safety of daily and intermittent dosing of pre-exposure prophylaxis (PrEP).”

*Dr. Anatoli Kamali, Principal Investigator, Medical Research Council/Uganda Virus Research Institute Research Unit on AIDS, Uganda*



## Major Contributions of the Enterprise

- Historically, a galvanizing and catalytic force for funding decisions on major programs and for scientific agenda-setting based on a shared plan
- Increased coordination and communication among scientists
- Leadership on involvement of young and early career investigators
- A neutral voice representing “good science”

to compare some candidates. There were also major gaps, such as funding for manufacturing capacity, and concerns about clinical trial capacity being exhausted in the near future, as multiple vaccine, microbicide, and other prevention trials launched across the globe.

Today the world looks different, and many of our interviewees credited the Enterprise for some of these changes, particularly around resource allocation for specific areas identified in its Scientific Strategic Plan, the first version of which was published in January 2005. Both the CAVD initiative and CHAVI were created with the explicit goal of addressing areas identified in the plan. The Gates Foundation also initiated a collaboration with the Canadian HIV Vaccine Initiative on vaccine manufacturing capacity, in line with a gap identified in the plan. The European and Developing Countries Clinical Trials Partnership was seen as part of the solution to some of the clinical trial capacity issues identified in the plan.

This success is the result of a sense of the scientific community’s endorsement of the plan and, by extension, of the Enterprise and a close alignment of donor decision-making with the plan. The very existence of the Enterprise made it possible for donors and scientists to develop and execute a joint vision.

Looking specifically at contributions made since Dr. Bernstein assumed leadership, interviewees repeatedly mentioned the sense of being listened to and commended. Dr. Bernstein’s commitment to understanding the priorities and concerns of stakeholders throughout the field. This was often coupled with a sense that, as a cancer researcher, Dr. Bernstein has brought a fresh perspective. One interviewee said, “Alan is trying to make the point that we can’t fall into the trap of specific dichotomies: big versus small science; primate versus bench versus human trials. He’s advocating for a harmonious development of ideas and cross-fertilization. It is reassuring that there is an entity that is a voice for ‘good science.’”

“The Enterprise has become the spokesperson for the whole field,” said another interviewee. “It has a much higher profile than it has had in the past. I think he [Dr. Bernstein] is a thought leader. In the year that he’s been there, he’s made contact with pretty much everybody at all continents and all levels. He’s been promoting the young investigator angle. I think it’s been a very positive thing ... time will tell what [the] impact will be.”

Several others mentioned the “New Minds, New Ideas” initiative, which has convened a committee of young and early career investigators to craft and execute an advocacy strategy aimed at addressing



### Areas for Improvement and Expansion

- Timely publication of the updated Scientific Strategic Plan in early 2010
- Expand scientific leadership on strategically selected issues
- Demonstration of the ability to facilitate donor-scientist communication that impacts the course of the field

some of the needs and priorities of the next generation of scientists. The committee members have brought high energy to this nascent initiative, to which the Enterprise has given a platform and legitimacy. It's a strong example of how the Enterprise can use its convening function to catalyze activity on a specific issue that has long-term relevance and consequences for the field.

The Enterprise has also had some success in expanding participation of scientists outside the US and Europe. Under Dr. Bernstein's leadership, the Enterprise has worked with the African AIDS Vaccine Programme and with Asian stakeholders to increase coordination and capacity. Such regional efforts can have an impact, particularly if they're well-structured and focused on strategic goals. Looking forward, the Enterprise should ensure that its scientific convening work reflects this commitment to diversity, by bringing African, Asian, and Latin American researchers to forums where they remain underrepresented.

### Areas for change or expansion at the Enterprise

Interviewees who cited the Scientific Strategic Plan as a success of the Enterprise also identified it as an area for change and expansion. How is this possible? In large part because an updated version of the entire plan hasn't been published since 2005. However, in this interval, reports on Enterprise-convened meetings on humoral, innate, and mucosal immunity have been published. Also in 2008, IAVI published its biennial *AIDS Vaccine Blueprint* "as a founding partner of the Global HIV Vaccine Enterprise." This valuable report hoped "to stimulate discussion among all stakeholders..." We hope that IAVI will continue to produce strategic plans detailing its singular approach to dovetail with an Enterprise-initiated field-wide drafting process.

In *AVAC Report 2008* and *2007*, we called for an updated plan to help organize and orient the field and to reaffirm the role of the Enterprise. Dr. Bernstein and his team have launched a process of updating the plan that highlights some of the strengths and challenges of the organization. The sense among our interviewees is that the plan update is overdue, in part because the field has shifted so much since 2005.

On the plus side, we've heard praise for how topics of interest are being parsed and assigned to specific working groups. We have also heard a sense of impatience with the pace of this work. Deliberation is important, but so is decisiveness.

Stakeholders will need to support the Enterprise secretariat in moving as quickly as possible to produce a hard-hitting

quality Scientific Strategic Plan. We hope that the goal of publication by early 2010 will be met, so that the updated plan might guide the possible NIH re-funding of CHAVI and the next steps for CAVD.

The ability, or lack thereof, of today's Enterprise to catalyze conversations among scientists, funders and donors was raised by several people we spoke with. These interviewees said that the response to the revised Scientific Strategic Plan would help them gauge whether the Enterprise in 2009 had the influence to accelerate and activate conversations between funders and scientists necessary to turn the plan's recommendations into reality.

Major funding initiatives were closely tied to the last Scientific Strategic Plan. Some interviewees characterized CAVD and CHAVI as the "carrots" that brought stakeholders together under the Enterprise umbrella. They questioned whether coordination would continue without these incentives. "I think it's going to be very challenging for Alan to make sure that the Enterprise is recognized as the entity that is going to propose new directions that all the other people in the field are going to support," said one interviewee.

Another interviewee said, "Decisions were made at the Gates Foundation to create the secretariat and to have distance from it, and at that point the air came out of the balloon."

For their part, the funders we interviewed stressed the importance of the first Scientific Strategic Plan in validating their decisions and looked to the updated plan to provide similar guidance. This is another reason why the updated plan

must be as strong as possible, with every effort taken to guard against the dilution—and pork barrel proposals—that can creep into a document that's written by consensus.

The plan is a key component of Enterprise leadership, but it's not the only vehicle for guiding the field. Although the Enterprise has convened expert working groups on key scientific issues; there was a sense that the Enterprise could wield its scientific leadership and convening role in additional, useful ways. Several respondents would like to see the Enterprise take on specific, time-sensitive issues that could be resolved or refined by small meetings, with recommendations and Enterprise-led follow-up on deliverables.

"While we wait for the draft of the scientific plan, are we willing to say that there are no issues that have come up in the last year and a half that you wouldn't want to have discussion on?" said one interviewee. Some also mentioned that a senior staff member or advisory group with expertise in the AIDS vaccine field could help to catalyze and convene these discussions.

Donor-scientist dialogues that have measurable outcomes would help affirm and solidify that the Enterprise under Dr. Bernstein's leadership can serve as a bridge-builder between donors and scientists. "One thing the Enterprise could try to do is try to convince donors and investigators that they may not have the solution on their own," said one interviewee. "If you want to get a good strategy—a heterologous prime-boost for example—you need to get groups that have different [components] working together."

This type of action might bring clarity to the Enterprise's overall identity. Many stakeholders sounded as unsure of what the Enterprise is going to do next as about what its perceived influence will allow it to do. We heard statements like, "The Enterprise is whatever Alan wants it to be," "I view the impact of the Enterprise as ahead of us," and "It [the Enterprise] hasn't done much of anything yet." Some raised questions about its relevance today as opposed to five years ago and said that perhaps the field had built a structure that it wasn't actually willing to use.

#### If the Enterprise does its job, what's changed a year from now?

The fourth and final question in our interview imposed an artificial time frame on the Enterprise. Many of the things that Dr. Bernstein and his team are working on won't show dramatic changes in 12 or even 24 months. It will take time to see if the New Minds, New Ideas initiative leads to lasting change via programs and initiatives that improve the outlook for new investigators and whether young and early career investigators enter AIDS vaccine research from other fields and/or commit to it as a long-term career path. A year from now

"Our planned work on microarray analysis of responses to yellow fever vaccine is very exciting to the staff. There's a lot of interest in using systems biology to understand how the immune system works in response to vaccines. With yellow fever vaccine, we know it works but we don't know how it works, so we're going to look at how the immune genes switched on when people get the vaccines. This was done in North Americans and we're repeating it here in Uganda."

*Dr. Pontiano Kaleebu, Principal Investigator, Uganda Virus Research Institute-International AIDS Vaccine Initiative Vaccine Program, Uganda*

may be too early to evaluate the influence of the Scientific Strategic Plan in full because major funders like NIH and the Gates Foundation may not have indicated their specific plans for funding beyond CHAVI and CAVD, respectively.

Still, we decided to ask about measures of progress, if not success, and will use the answers to guide our analyses this time next year.

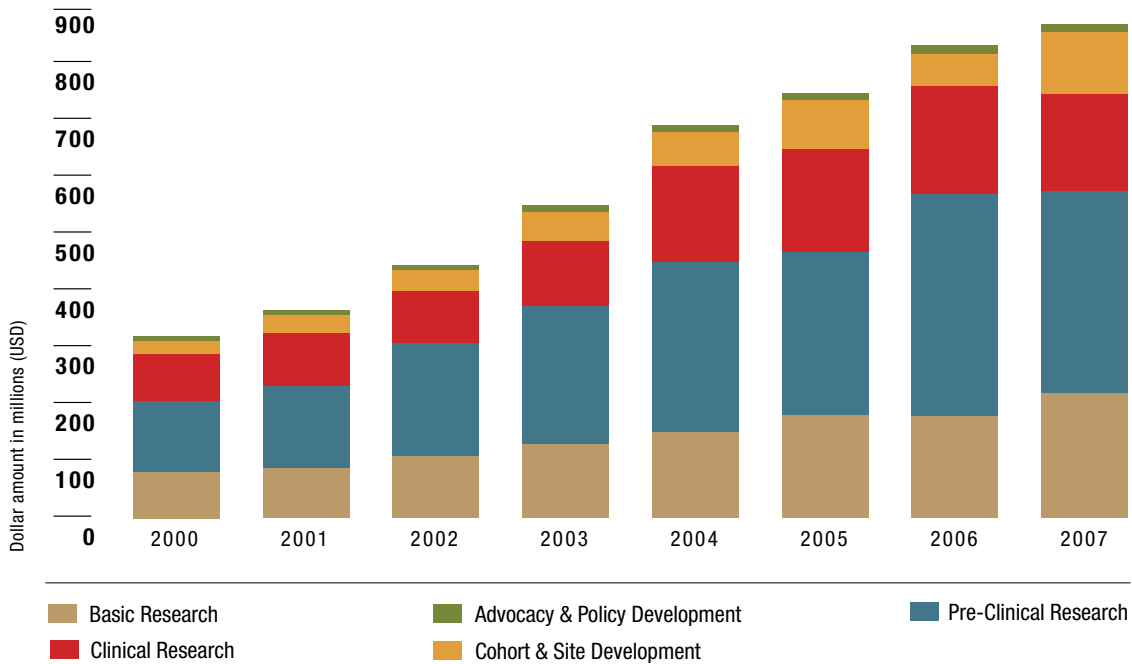
For many interviewees, the greatest portion of the worth of the Enterprise will be measured by the degree to which the Scientific Strategic Plan:

- Reflects clear, bold thinking for the field—as opposed to watered-down consensus, which some interviewees feared might come from the drafting-by-committee process; and
- Guides subsequent funding decisions by donors. (One interviewee proposed measuring added value by the answer to the question: "Do the funders and donors fundamentally embrace this as the way of doing business?")

Expanded scientific leadership on specific gaps would be another metric of success. This work would complement the ongoing work on "enabling environment"—related issues like young investigators and systems biology. A year from now we'll ask: are there one or two scientific issues that the Enterprise has taken on with strategic consultations between funders and scientists that led to actionable recommendations—with funding suggestions, milestones, metrics of progress, and success?

We heard varying opinions on whether the work described above necessitates filling the Director of Science position that's been posted and vacant for nearly a year. It's a hard position to fill. Scientists with

Figure 2 Annual Public and Philanthropic Investments in Preventive HIV Vaccine R&D from 2000 to 2007\*



\* Based upon a subset of total expenditures for which allocations could be calculated.

Source: HIV Vaccines and Microbicides Resources Tracking Working Group. Sustaining the HIV Prevention Research Agenda: Funding for Research and Development of HIV Vaccines, Microbicides and other New Prevention Options, 2000-2007. 2008. Available at: [www.hivresourcetracking.org](http://www.hivresourcetracking.org).

the depth of experience in the AIDS vaccine field that would serve the job well might not want to leave the lab. But there are other options for building the senior scientific leadership at the Enterprise: make the position a rotating seat to attract working scientists for a sabbatical year or develop a small core team of advisors, each monitoring a different topic.

Overall, a year from now, progress would be an Enterprise that's operating on two tracks: the all-of-us Enterprise that captures the big picture in the Scientific Strategic Plan and then works to execute its goals; and the secretariat-level leadership track, in which Dr. Bernstein and the New York office offer problem-solving resources and more rapid responses to emerging

issues. With all of this, we'll be looking for as much clarity on roles, responsibilities, and measurable outcomes as possible.

We end with the reminder—that we take to heart as well—that the Enterprise isn't solely the responsibility of the people working in the secretariat office in New York. It continues to belong to all of us. Progress and success are collective responsibilities.

As one interviewee said, "The community as a whole should decide the top five things that need to get done by the end of 2010 and agree on how to measure success. What do we want from *our* Enterprise?" 🌟