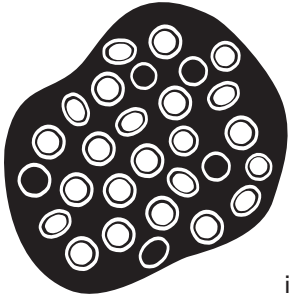


DATELINE **2009**

LOCATION **A major European city**



Dr. Delaware looks over her notes one last time. The presentation she is preparing for is an important one. As leader of a team of independent expert auditors, she has been asked by the Global HIV Vaccine Enterprise to monitor the progress of some of the major funding initiatives directed towards AIDS vaccine research in 2005-2006. For the past three years, she and her team, which includes Nobel laureates and experts from vaccinology, immunology, AIDS and other disciplines, have been able to review the budgets, data and workplans of the grantees and consortia who set out, in 2005, to answer some of the questions that have foiled the field for twenty years.

It has been a hard job by definition. The questions themselves defied easy answers and could not be molded to traditional series of interim milestones. In some instances, the milestones that were set turned out to be irrelevant; and more than once, Dr. Delaware's team recommended that the overall plan be revised and restructured with an eye to focusing on other more readily answerable questions essential to AIDS vaccine design.

Some unpredicted findings moved the field forward, as they appeared to lend themselves to swift development of candidates that could move into clinical trials.

And it has been her task to monitor all of this, to measure progress through meaningful targets, and to keep an eye on the "prize" of novel candidates moving into trials, without pursuing a full "pipeline" for its own sake.

She stacks her papers one more time. Would the field even care about her recommendations? Where potential candidates were emerging, would industry add its resources? Would the array of collaborators and consortia be willing to revisit their ways of working in the service of the field yet again?

I hope so, she thinks as she walks out the door.

01. AIDS Vaccine Science, Strategy and Action: The State of the Field, the Stakes for the Future

I. STATE OF THE FIELD

Since its inception in 2003, the Global HIV Vaccine Enterprise has been viewed as a critical, defining element of the field's current approach to developing an AIDS vaccine. And as we look back over the past year, we focus first on what this collaborative entity has—and has not—achieved.

We start at the top: the executive position at the Enterprise secretariat. Here, the news is disappointing. In August, the Enterprise coordinating committee and Dr. Adel Mahmoud made it known that the forthright former Merck executive Dr. Mahmoud would not be taking the job (see opposite).

And so, three years after the initial article which conceived of an over-arching framework for the field, and 18 months after the publication of the Enterprise Scientific Strategic Plan, the Enterprise will be starting over in its search for a leader. This is a setback for the field, as we discuss below. And AVAC looks to the Enterprise to re-commence the search, including a swift and transparent process of reviewing the job description to ensure that it captures the roles, responsibilities and skill set needed for this entity, at this time. Acting director Jose Esparza phrased it well when he posed the question, “Does the Enterprise need a scientific leader? An ambassador? A scientific administrator?”

The Enterprise coordinating committee must answer these questions and fill the position. But we also note that as it starts the search anew, it is not starting from the same point.

In 2005-2006, two major funding initiatives began to develop agendas, plans and budgets in ways designed to execute specific parts of the shared scientific strategic plan.

Last year, the Center for HIV/AIDS Vaccine Immunology (CHAVI) was funded by the US National Institutes of Health (NIH) with a seven-year grant that aims to provide more than US\$300 million, US\$15 million of which was designated for its first year. Then in June, the Bill & Melinda Gates Foundation launched the Collaboration for AIDS Vaccine Discovery (CAVD), which provides a total of US\$287 million to 16 principal investigators over the next five years.

Both of these funding streams could have emerged and been committed without the existence of the Enterprise—and very well may have. Yet both funders credit the pre-existence of the scientific strategic plan and the principles for coordination laid out therein as having influenced these initiatives. The collaborative structures and scientific goals of CHAVI and CAVD have a common point-of-reference; and the grant-making work for each was done with an eye toward avoiding duplication, according to individuals who participated in the process.

CHAVI, for example, has already started a multi-level effort to gain a better understanding of the early immunological events that follow infection. By learning what the immune system does in the first weeks after infection and why these responses are insufficient to control infection the group hopes to shed more light on the kinds of immune responses that would be

In last year's AVAC Report, we anticipated that the Enterprise would advance into operational reality when its first executive director was to be appointed. We identified eight concrete tasks that should be the focus of the new director from the first day:

- 01 Communicate frequently and transparently.
- 02 Set policies for sharing and coordination of data and technology.
- 03 Ensure the ability to take risks.
- 04 Bring new investigators into the search.
- 05 Make the Enterprise truly global.
- 06 Involve civil society in a meaningful way.
- 07 Take on the politics and ethics of clinical trials.
- 08 Establish realistic milestones and a process for monitoring progress.

We were excited in March of this year when it was finally announced that Adel Mahmoud would be the chief executive of the Enterprise. Shortly after the announcement, Mahmoud met with the AVAC board and staff, and we were impressed. He displayed a command of the challenges, a bold willingness to address them and a commitment to ignite and fuel new scientific innovation. Mahmoud said he wanted to look at ideas that had not been explored and challenge scientists to work together more collaboratively.

At the time of his appointment, he said: "My job will be to help Enterprise partners realize the vision of the scientific plan—to identify timelines and milestones, track progress, and keep us on course to reach our ultimate goal."

The recent announcement that Mahmoud would not take up his position in September is, therefore, a disappointment.

While the Enterprise partners continue to do important work individually, and are showing signs of willingness and ability to work together in new ways, leadership matters.

In fact, it may matter more than ever. In the absence of an executive director, the Enterprise has achieved some advances, including:

- Publication of a scientific plan that lays out major issues and begins to articulate a way forward (and that now needs to be updated)
- Commitments from new funding initiatives from the Gates Foundation and the NIH that support collaborative work in the highest priority areas of vaccine discovery and laboratory standardization
- Additional Enterprise-related funding announcements from Germany, Russia and Switzerland which show promise of making the efforts more global

(continued on page 12)

Leadership is needed to take these initiatives to the next level. The Enterprise still needs an updated, more concrete plan, with specific timelines and milestones and a process to monitor progress, achieve accountability, and modify directions accordingly.

In the absence of a director, the Enterprise may find itself in danger of losing momentum, as it seeks to establish itself as an entity deserving of funding; and the individual players—who are collaborating now—may not agree on how best to measure progress and ensure that the new money is being spent in the best way possible.

An executive director does not have to monitor progress directly, but having someone in this role—part constructive critic, part cheerleader, part champion—will strengthen the overall endeavor and send a clear signal to multiple audiences about the importance of this undertaking.

New ventures frequently have start-up challenges—especially one like the Enterprise which has, as its core mission, a new way of doing business. And the fact that new events have taken place during the year that we were waiting for Dr. Mahmoud may help refine the job description for the next search, which we are told is already underway.

This is a critical juncture, then, for the Enterprise and its members. The ongoing search for a leader should continue with all due speed; and critical Enterprise-related activities like re-constituting working groups should happen even before the position is filled.

If this happens, then the delay—while disappointing—will have been a learning opportunity, and not a major setback for the field.

protective. This effort includes EuroCHAVI, a study of samples from progressors and non-progressors provided by several European collaborators.

Meanwhile, CAVD grants include suites of inter-linked funding for “Discovery Consortia” aimed at developing better T-cell and antibody-inducing vaccines.

And in what may turn out to be the most critical part of this initiative, the Gates Foundation provided US\$92.2 million out of the total to a set of central facilities, including a data and statistical analysis center, a mouse immunology laboratory, and laboratories for evaluation of antibody and T-cell responses.

Laboratory standardization was one critical element mentioned in the Enterprise plan, since the inability

to compare results hinders progress, and can lead to duplication.

This kind of activity would appear to embody the principle that the Enterprise is whatever its members do. And it could prompt the question: if all this happened in a year without a “head,” is there still a need for an executive director at the Enterprise secretariat?

AVAC’s answer is *Yes*. Here are three reasons why.

01. Because there are other, still-neglected areas that require attention.

How do we ensure that, as the field redoubles its efforts to answer fundamental questions, there is a clear path from scientific discoveries to vaccine candidates? The answer lies in attending to *all* six of

the Enterprise's priority areas: not just vaccine discovery and laboratory standardization, but also product development and manufacturing, clinical trials capacity, regulatory issues, and intellectual property issues.

Working groups on these issues have been convened and have conducted preliminary gap analysis. But more intensive work is needed. The groups should be reconstituted and given more specific assignments to address, so that they can develop clear plans to address clinical trial capacity, intellectual property (taking into account work already done by CHAVI and CAVD) and other arenas.

Engagement with industry partners is also of paramount importance and should receive attention both on these groups and in cross-cutting analysis and evaluations of the Enterprise.

Of course, ad-hoc working groups can convene themselves, issue reports and even hold cross-cutting meetings to discuss shared agendas. But this process would be greatly facilitated by a body that has authority, respect and a mandate to oversee the entire process with a respected individual as its spokesperson and head.

02. **Because the Enterprise is still far from global.**

In our 2005 memo, we urged the new Enterprise ED to make the Enterprise truly global. This has not happened yet. None of the principal investigators for CAVD are from developing countries (although there are many collaborators from the developing world). Bringing in expertise and unique perspectives from countries in Africa, Asia, Eastern Europe, Latin America and the Caribbean is of vital importance. The search for an AIDS vaccine must include scientists and communities from countries where the epidemic is spreading fastest.

This is not an overnight process: making the Enterprise global means making investments in training, research funding and capacity building for scientists and clinicians from the developing world. We know that creating these opportunities is essential to addressing the health care human resource crises in these countries. The Enterprise and its ED have a critical role to play in fostering these initiatives.

03. **Because monitoring and oversight are essential.**

As we look at the past year's activities, we see that there is a new level of organization in the field. In addition to the work that will continue in individual laboratories, ad-hoc collaborations, and pre-existing consortia like the IAVI Neutralizing Antibody Consortium (NAC), there are two new entities, which have their own rules of order, engagement and collaboration.

CHAVI and CAVD are focused on pre-clinical vaccine discovery efforts, including exploration of basic scientific questions that continue to challenge the field (see page 16), and funding for central facilities to support them.

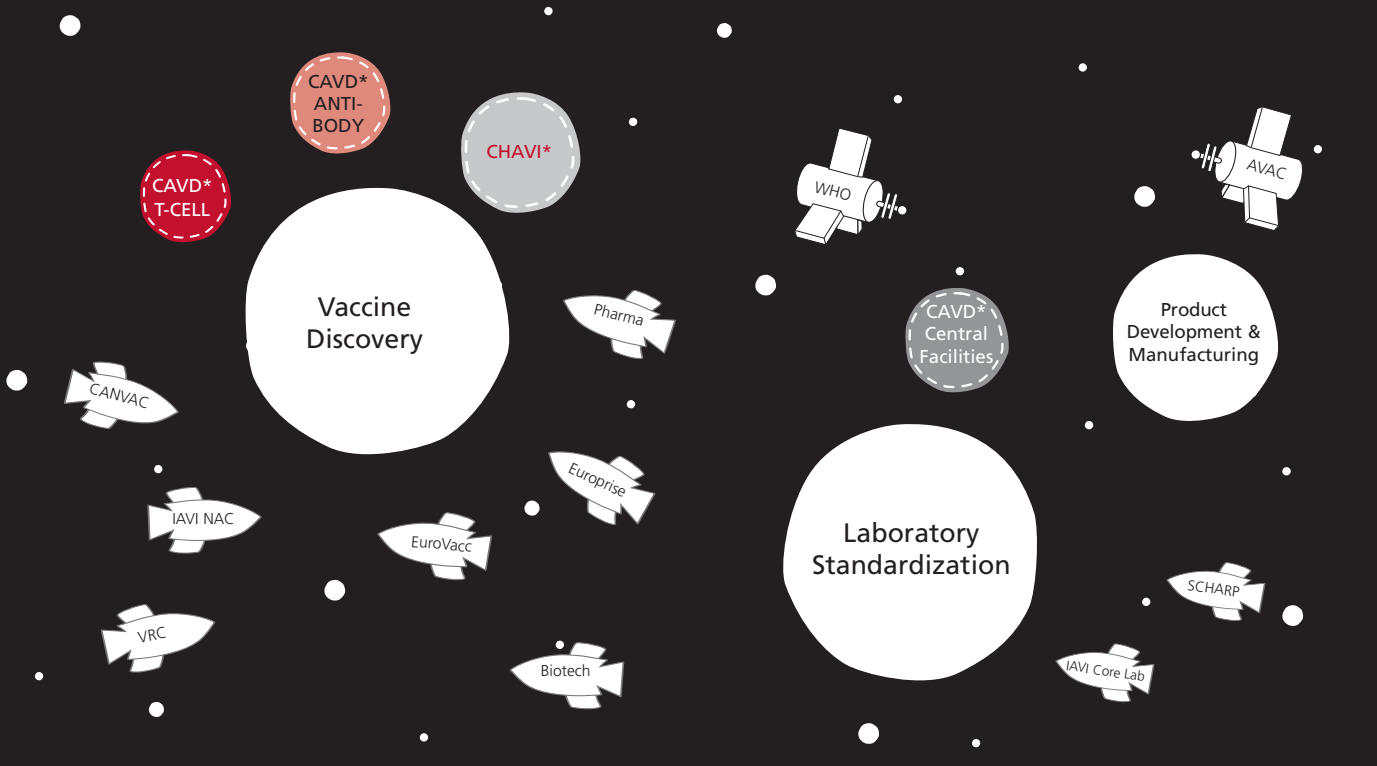
These initiatives are in their early days. They are, at the moment, *opportunities* for change. The evidence of their effectiveness, in terms of helping the field work more swiftly and efficiently than it has in the past, is still to come.

The Enterprise secretariat and, in particular, its leader can play a critical role in evaluating this evidence when it emerges over time.

There is a need for independent monitoring by an entity with high scientific caliber and a grand perspective on the field as a whole to monitor progress and determine whether money is being well spent, productive collaborations are being launched, and duplication is eliminated, while also harnessing strategic competitiveness.

This was a critique of the scientific strategic plan itself: that it lacked milestones, defined targets and timetables. We know that milestones have not always worked in the past. But defined targets need to be there: what are the answerable questions? How are they being re-framed as new data emerge from one quarter or another?

The Enterprise leadership should be in a position to provide this oversight; and it is dangerous to think that the field can now do without it.



MAKING SENSE OF THE NEW ENTERPRISE “COSMOLOGY”

What’s going on in this corner of the sky? The six “planets” in the graphic above are the focus areas identified in the Global HIV Vaccine Enterprise Scientific Strategic Plan. CHAVI and CAVD work plans are specifically linked to these areas. Since they are the first initiatives to be connected to the Enterprise from their inception, they are represented as moons in the orbit of the Enterprise.

But the universe did not begin with the Enterprise. A wide array of projects and initiatives has been launched over the past decade or more. We’ve highlighted some of these projects—represented as rocket ships—and show how their trajectories relate to the Enterprise focus areas. As busy as this graphic looks, there is still work to be done: clinical trials capacity, product development, manufacturing, regulatory issues and

intellectual property issues are still being addressed by individual entities, without the coordination that has been brought to bear on vaccine discovery and standardization.

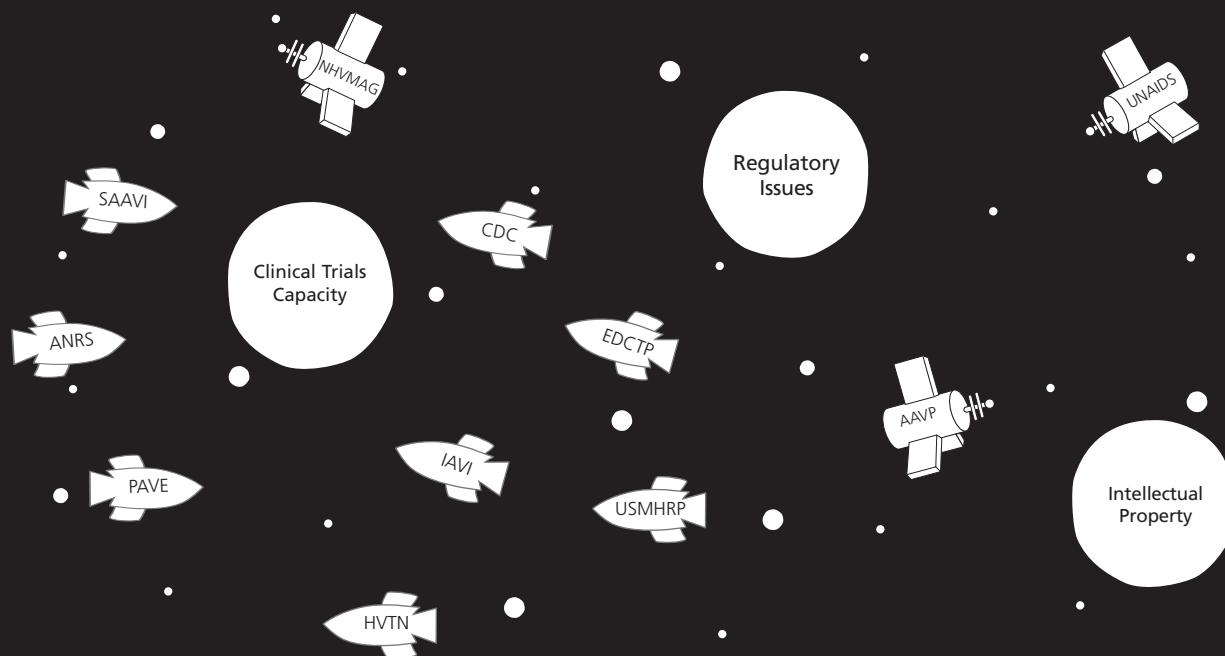
It’s also important to remember that there are other critical elements of the AIDS vaccine universe which do not feature in the Enterprise cosmology at all—including social and behavioral science, policy formulation, advocacy, strategic linkages with other prevention research arenas, preparing for future access and expanded community involvement. We’ve included some of the groups doing advocacy work in as satellites because these entities monitor, transmit information to multiple audiences, and have an important role to play in evaluating and informing the work of the Enterprise and the field at large.

KEY

**2005-2006 New funding*

- AAVP** African AIDS Vaccine Programme
- ANRS** Agence Nationale de Recherches sur le SIDA
- AVAC** AIDS Vaccine Advocacy Coalition
- CANVAC** Canadian Network for Vaccines and Immunotherapeutics
- CAVD** Collaboration for AIDS Vaccine Discovery
- CDC** Centers for Disease Control
- CHAVI** Center for HIV/AIDS Vaccine Immunology
- EDCTP** European and Developing Countries Clinical Trials Partnership
- Europrise** European Vaccine/Microbicide Enterprise
- EuroVacc** European Vaccine Effort Against HIV/AIDS

- HVTN** HIV Vaccine Trials Network
- IAVI** International AIDS Vaccine Initiative
- NAC** Neutralizing Antibody Consortium
- NHVMAG** Nigerian HIV Vaccine and Microbicide Advocacy Group
- PAVE** Partnership for AIDS Vaccine Evaluation
- SAAVI** South African AIDS Vaccine Initiative
- SCHARP** Statistical Center for HIV/AIDS Research and Prevention
- UNAIDS** Joint United Nations Programme on HIV/AIDS
- USMHRP** US Military HIV Research Program
- VRC** Vaccine Research Center
- WHO** World Health Organization



NEW ENTERPRISE-RELATED FUNDING STREAMS

CENTER FOR HIV/AIDS VACCINE IMMUNOLOGY (CHAVI) www.chavi.org

Vital statistics: Established in July 2005. US\$300 million over seven years from the US National Institutes of Health, support 80 investigators at 35 institutions worldwide in Year 2.

Overall goal: To define the enabling technology for HIV vaccine development by determining correlates of protective immunity at mucosal surfaces in acute HIV-infected (AHI), and exposed uninfected (EU) individuals.

Specific initial studies: (1) Determine the molecular and virologic characteristics of the transmitted virus; (2) Define the genes that determine viral load levels in AHI individuals; (3) Define the genes that determine protection; (4) Define the genes that determine protection in EU and AHI individuals; (5) Determine T cell, B cell and innate immune responses to the transmitted virus at the mucosal surface in AHI and EU individuals; (6) Develop vectors and adjuvants that are capable of inducing protective immune responses to the transmitted virus at mucosal surfaces. Use data from studies 1-6 to design and test novel immunogens for induction of optimal mucosal anti-HIV immune responses.

COLLABORATION FOR AIDS VACCINE DISCOVERY (CAVD) www.cavd.org

Vital statistics: Launched in July 2006. US\$287 million over five years from the Bill & Melinda Gates Foundation. Funding will support 16 research consortia, with more than 165 investigators from 20 countries.

Overall goal: 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.

Specific initial studies: The 16 grants are organized into eleven vaccine discovery consortia (five neutralizing antibodies discovery consortia and six cellular immunity discovery consortia) and five central laboratory and statistical service facilities. The neutralizing antibody consortia include grants for novel vaccine design using HIV-2, synthetic molecules incorporating key regions of HIV into protein "scaffolds," research on additional types of neutralizing antibodies in animals and humans; as well as studies of the V-3 loop region of HIV, and innate and adaptive immunity. The cellular immunity consortia include grants to optimize existing strategies, such as pox virus and adenovirus vectors; as well as studies of candidates which target dendritic cells, and adjuvants to enhance T-cell vaccine performance. Central facilities include three laboratory networks for evaluating the immune responses elicited by vaccine candidates, a research specimen repository, and a data and statistical management center.

WHAT DOES AN EFFECTIVE AIDS VACCINE NEED TO DO?

The broad consensus—based on fundamental principles of vaccinology as well as years of observations of long-term non-progressors, highly-exposed persistently seronegative individuals, and non-human primate studies—is that an effective AIDS vaccine will need to stimulate two key types of immune responses.

The first type is responses that induce broadly-neutralizing antibodies, which are capable of binding to HIV and blocking it from infecting target cells. To be effective, these antibodies must be able to neutralize different HIV strains.

The other type is cell-mediated immune responses, which can destroy cells that have already been infected with HIV, effectively eliminating the viral “factories” that drive infection.

We know what we need in theory. But we still don’t know how to determine whether we’ve found it. The search for “correlates of protection” (measurable indices of whether or not a candidate is effective) and “surrogate markers” (early clinical endpoints—markers of disease progression), continues, and without this information it is difficult to answer this question, or the one that follows directly from it, below.

HOW DO WE BUILD VACCINES THAT CAN DO WHAT WE NEED THEM TO DO?

The ultimate goal is a vaccine or vaccine combination that induces broadly neutralizing antibodies and potent cell-mediated immunity against HIV. So how do we do this? The answer is still: we are not sure. We do not know how many antigens need to be in the vaccine. Should there be multiple antigens (i.e., a range of synthetic fragments of HIV genetic material)? Is there an optimal number? What types of vaccine designs will optimize both the potency and longevity of the induced immune response, since we want to develop vaccines that provide lasting protection, ideally for years after the immunizations have been delivered? Antigens are one piece of this; vectors and adjuvants are also critical; and the field still lacks information about optimal forms of various vectors that have been tested extensively in various Phase I trials; likewise there is still a tremendous amount to be learned about how to use adjuvants to the best advantage in AIDS vaccine design.

WHAT, EXACTLY, DOES THE VACCINE TARGET “LOOK” LIKE?

We know, in broad strokes, that an ideal vaccine needs to induce immune responses that block HIV from infecting cells and destroys cells that have already been infected. But HIV has a tremendous amount of genetic variability, and there is some indication that the strains that are transmitted most frequently have some specific traits that may make them more efficient at establishing infection. What are these defining traits exactly? Should a vaccine be targeted against the viruses? How relevant is this for prevention of infection in injection drug users?

II. STATE OF THE SCIENCE

Everything that we've talked about so far falls under the rubric of science management. That's one part of the picture. The other part, of course, is the science itself. When we look back over the past year's developments it isn't a matter of seeing what CHAVI or CAVD did—and it never will be. Exciting breakthroughs can come from anywhere, and frequently emerge from individual scientists who have gone out on a limb, exploring possibilities that are left unexplored, by their peers.

Continuing importance of mucosal immunology; and a continuing lack of validated assays to measure it

Last year we called for expanded research on mucosal immunology. There is more attention being paid; CHAVI has added a mucosal immunology discovery team, led by Robin Shattock of St. George's Hospital Medical School at the University of London. The findings of researchers like Daniel Douek (Vaccine Research Center) have provided further rationale for this area of inquiry.

This year, for example, Douek reported on preservation of central memory cells in the gut mucosa of a group of 10 men who received post-exposure prophylaxis with ARVs after exposure to HIV. Three of the men had evidence of anti-HIV antibodies in their blood but no sign of infection, and Douek hypothesizes that preservation of gut mucosal immune responses may be an indicator of protection against HIV.

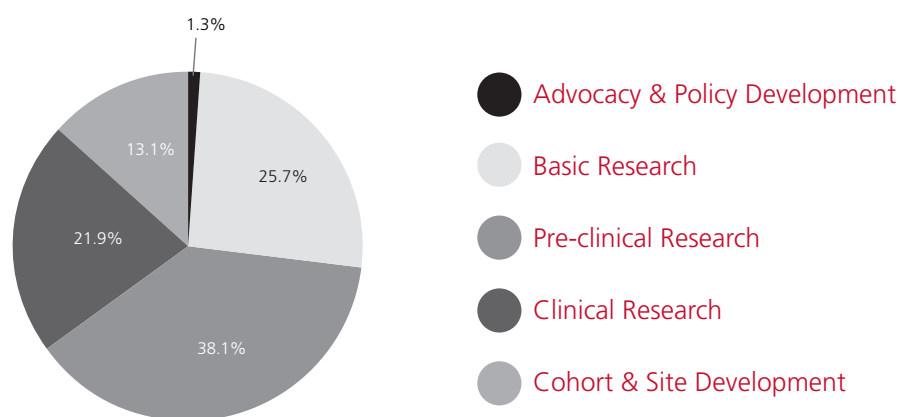
Biopsies such as those used in Douek's study are invasive, complicated and unfeasible for large-scale trials and the field has yet to identify a reliable surrogate marker for mucosal immune responses. We welcome the ongoing interest in developing mucosally-targeted interventions and learning more about immune events at the mucosa. **We urge that this work continue with an additional emphasis on developing practical assays to measure mucosal immunity in the field.**

Central memory cells as correlates of protection

At scientific meetings and in journals Norman Letvin (Beth Israel Deaconess Medical Center) and Douek

FIGURE 2

NON-COMMERCIAL FUNDING ALLOCATIONS FOR PREVENTIVE HIV VACCINE R&D BY CATEGORY IN 2005



Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Adding It All Up: Funding for HIV Vaccine and Microbicide Development, 2000 to 2005*, August 2006, www.hivresourcetracking.org.

presented data suggesting that central memory T-cells could be a correlate of protection. Memory T-cells are a subset of the immune repertoire that mounts the most rapid responses to invading pathogens. As their name suggests, they are the keepers of the immunologic “memory” of diseases that have been encountered before. Central memory cells, when triggered, can rapidly begin dividing to fight the disease if it reappears.

Memory T-cells have a specific “phenotype” thought to be indicated by particular receptors on the cell surface. Past HIV vaccine trials have looked at vaccine-induced HIV-specific T-cells overall, but have not looked at memory cells in particular. Letvin has presented data suggesting that HIV-specific memory T-cells could potentially be used as a measure of vaccine protection by measuring cells with these receptors. However these measurements require new and expensive technology.

These data have prompted excitement: VRC head Gary Nabel says that the Partnership for AIDS Vaccine Evaluation (PAVE), the collaborative effort

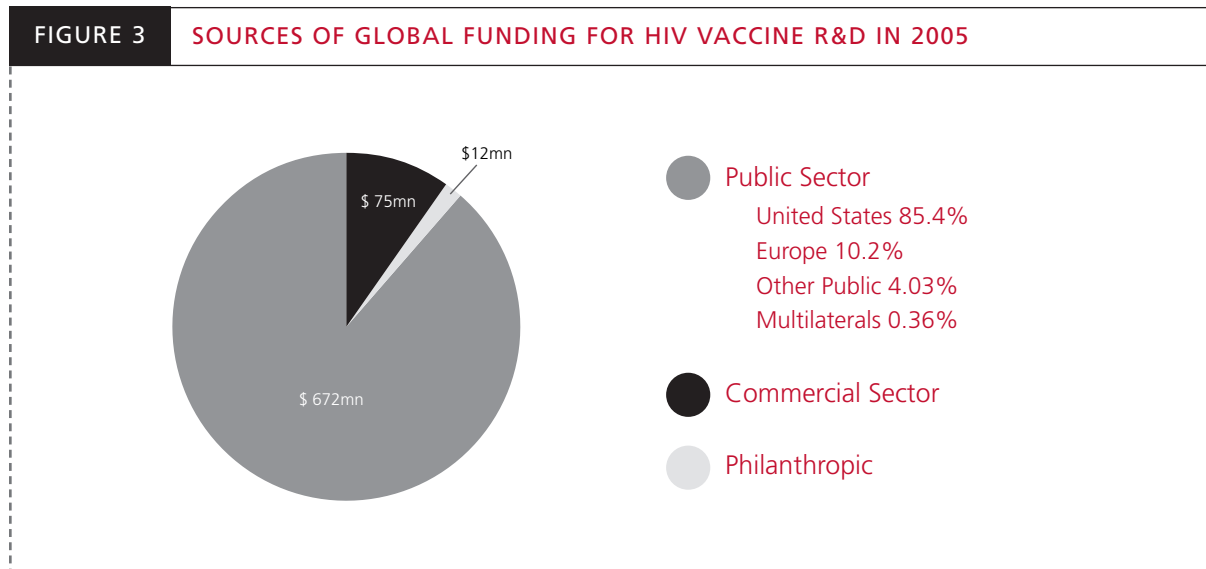
currently evaluating the VRC’s DNA-Adenovirus based combination, is considering using central memory T-cells as a correlate of protection in the planned test-of-concept study known as PAVE 100.

As intriguing as these findings are, there are still many unanswered questions. Can an assay that measures memory in the peripheral blood (as opposed to the mucosa) be developed and validated for widespread use, given that mucosal memory—which is harder to measure—may be the determining factor?

In the next year, as the PAVE 100 protocol is finalized, we call for expert consultation about the potential benefits and challenges of using memory cell responses as a correlate of protection—including analysis of how these data should be collected in other trials and over time.

New approaches to adjuvants and enhancing immune responses

Data presented this year from ongoing work on toll-like



Source: HIV Vaccines and Microbicides Resource Tracking Working Group, *Adding It All Up: Funding for HIV Vaccine and Microbicide Development, 2000 to 2005*, August 2006, www.hivresourcetracking.org.

- In 2005, total global investment in preventive HIV vaccine R&D was approximately US\$759 million.
- Between 2000 and 2005, public and the philanthropic investments more than doubled from US\$327 million to US\$684 million.
- During the last six years, European funders have increased their commitment to preventive vaccine R&D three-fold from US\$23 to US\$69 million. In 2005, R&D continued to grow outside of the US and Europe with contributions from countries such as Brazil, Canada, India, South Africa and Thailand totaling US\$27 million.
- The public sector, particularly in developing countries where trials are planned or are underway, provides considerable non-financial support through staff and facilities. These non-cash contributions are not trivial and have grown considerably over the last six years.
- In 2005, R&D expenditures were predominately on basic and pre-clinical research, which accounted for approximately 64% of the funds spent. In comparison, support for clinical trials accounted for 22%, cohort and site development 13%, and advocacy and policy development 1%.
- As of July 31 2006, preliminary public sector and philanthropic commitments for 2006 equaled US\$781 million, a 14% combined increase for these two sectors over 2005. This increase may not be sustained in subsequent years, as it reflects significant new investments by the Bill & Melinda Gates Foundation and the US National Institutes of Health.
- Although investment in preventive HIV vaccines increased in 2005, the Global HIV Vaccine Enterprise estimates that US\$1.1-US\$1.2 billion is needed annually to speed the search for a safe, effective HIV vaccine.

receptors (TLR) and dendritic cells suggests that targeted stimulation can increase the immune response. Given that HIV also targets dendritic cells (which stimulate TLRs), it remains to be seen whether this will be a useful strategy for fighting HIV infections. Juliana McElrath (Fred Hutchinson Cancer Research Center) is leading a team from industry, biotechnology and academia that, with support from CAVD, will seek to develop and understand the mechanism of these specific biological signalling mechanisms, which could be used with a variety of vaccines.

In the next year, we look to see evidence that promising findings from adjuvant research feed into design of next generation products, with safety, regulatory, and intellectual property issues for new potential adjuvants addressed promptly.

New targets for neutralizing antibodies

Neutralizing antibodies (NAb) that block the activity of HIV remain one of the most elusive goals in the search for an AIDS vaccine. This year's scientific conferences focused on the potential target area

TABLE 1	ANNUAL INVESTMENTS IN PREVENTIVE HIV VACCINE R&D BETWEEN 2000 AND 2005 (current US\$ millions).						
	*The 2006 estimates represent disbursements and firm commitments made as of July 31, 2006.						
	2000	2001	2002	2003	2004	2005	2006
PUBLIC SECTOR							
US	272	314	376	463	516	574	663
Europe ^A	23	32	39	44	57	69	26
Other ^B	10	12	21	24	28	27	10
Multilaterals	2	2	2	2	2	2	2
Total public	307	359	436	532	602	672	704
PHILANTHROPIC SECTOR							
Total philanthropic	20	7	112	15	12	12	77
Total non-commercial investment	327	366	548	547	614	684	781
COMMERCIAL SECTOR							
Pharmaceutical companies	-	-	-	-	59 (range 47-71)	64 (range 52-76)	
Biotechnology companies	-	-	-	-	9 (range 7-11)	9 (range 9-13)	
Total commercial	-	-			68 (range 54-82)	75 (range 61-89)	
Total global investment^C					682	759	

^A This figure includes funding from the European Commission

^B Other includes all national public sector funding apart from funding from the US and Europe

^C Commercial sector investments were estimated for selected years in the series

known as the membrane-proximal external region (MPER) of gp41 (an area of HIV that is instrumental in docking on and infecting cells). Monoclonal antibodies that bind to conserved epitopes in the MPER neutralize primary HIV isolates from different clades. At the Conference on Retroviruses and Opportunistic Infections, Michael Zwick (Scripps Research Institute) was among the speakers who discussed MPERs and narrowed down the specific epitopes in the region that induce potent antibodies. Like other NAb-inducing sites, MPERs may be “masked” by the outer coating of lipids that surrounds HIV. Another potential drawback is that these antibodies

may be poly-specific, meaning that they could bind to targets other than HIV, causing an auto-immune reaction in the body. Barton Haynes (Duke University) has received grants from CHAVI and CAVD to pursue separate but related projects in this area.

With multiple laboratories working on MPERs, this area of research is an ideal test case for the field’s ability to work collaboratively and additively, sharing information and avoiding redundancy. In the next year, we will look to outputs from the various groups to measure both scientific progress and process within the field.

III. THE STAKES FOR THE FUTURE

Fundamentally speaking, the stakes for the future are exactly the same as they have ever been: an AIDS vaccine is an essential tool for slowing the spread of this epidemic and failure to act swiftly, efficiently and in harmony will be measured in a heartbreaking toll of lives.

But as always there are new forces at work, and so we can also say this. In the next one to two years, the soundness of the vision behind CHAVI, CAVD and the Enterprise will be tested. It cannot fairly be tested in terms of the numbers of scientific breakthroughs or new candidates that emerge in 10, 12 or 18 months. These are long-term problems and one of the strengths of the new grants is that they do not have unrealistic timeframes for the results.

Nevertheless, the strength of the vision can still be measured by the field's ability to pose answerable questions; to assign well-funded, well-resourced teams to tackle these questions; to minimize duplication of efforts between these teams; and to ensure that there is rapid sharing of data, scientific platforms, and reagents across the field as needed and where appropriate.

It will also be measured by the progress that the Enterprise secretariat makes towards articulating its role and finding the appropriate structure and staff.

Now is the time to use this opportunity—without delay. The prolonged hiring process sends a signal of disorganization about the field to outside observers and potential allies. The job for all of us, including AVAC, is to continue to communicate clearly with

multiple constituencies about the state of the science, the organizational structures that have been proposed to make it work better, and, most importantly, the pace of progress towards our ultimate goal of changing the face of the epidemic forever.

With this in mind, AVAC commits to:

- Critical analysis of CAVD and CHAVI funding looking at transparency of granting procedures; duplicative versus additive funding; and optimizing of linkages across programs and consortia where possible and needed
- Work in collaboration with developing country scientists and initiatives including AAVP, SAAVI and others to develop a concrete proposal for achievable targets for increasing developing country leadership in new and existing consortia in the field
- Hold the Enterprise secretariat and its members accountable for proceeding swiftly with organizational activities in other critical areas including regulatory, intellectual property, clinical trials capacity, manufacturing process development and scale-up
- Work with the Enterprise to ensure that the job description of the Enterprise executive director is reassessed, that a transparent process is put in place to select a new slate of ED candidates and that the position is filled with deliberate urgency
- Serve as an active partner and, where needed, a leader in engaging civil society in dialogues about the direction, scope and vision of the Enterprise

TABLE 2

TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (AUGUST 2006)

PROTOCOL #	START DATE	SPONSOR, FUNDER, DEVELOPER	TRIAL SITE(S)
PHASE III			
RV 144	Oct-03	USMHRP, MoPH Thailand, Aventis, Vaxgen	Thailand
TEST-OF-CONCEPT			
HVTN 502/Merck 023	Dec-04	DAIDS, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica
PHASE II			
IAVI A002	Nov-05	Children's Hospital of Pennsylvania, Columbus Children's Research Center, Indian Council of Medical Research, National AIDS Control Organization, Targeted Genetics Corp.	South Africa, Uganda, Zambia
HVTN 204	Sep-05	DAIDS, HVTN, VRC, Vical, GenVec	US, Brazil, South Africa, Haiti, Jamaica
ANRS VAC 18	Sep-04	ANRS, Aventis	France
PHASE I/II			
RV 172	May-06	NIH, WRAIR, VRC	Kenya, Uganda, Tanzania
C060301	Feb-04	FIT Biotech, IAVI	Finland
PHASE I			
VRC 011	Apr-06	NIAID, VRC	US
HVTN 065	Apr-06	DAIDS, HVTN, VRC, GeoVax	US
IAVI D001	Feb-06	IAVI, Therion	India
HVTN 064	Jan-06	DAIDS, HVTN, Pharmexa-Epimmune	US, Peru
HVTN 068	Feb-06	DAIDS, HVTN, VRC	US
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, WRAIR	Sweden
IAVI V001	Nov-05	IAVI, NIAID, VRC	Rwanda, Kenya
RV 158	Nov-05	WRAIR, NIH	US, Thailand
HVTN 063	Sep-05	DAIDS, HVTN, Wyeth	US, Brazil
HVTN 060	Aug-05	DAIDS, HVTN, Wyeth	US, Thailand

VACCINE(S)	# OF VOLUNTEERS	CLADE
Prime: canary pox viral vector with <i>env</i> and <i>gag-pol</i> Boost: Env protein (gp120 subunits)	16,402	B, A/E
Adenovirus vector with <i>gag, pol, nef</i>	3,000	B
AAV2 (adeno-associated virus type 2) vector with <i>gag, pol, ΔRT</i>	91	C
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	480	B A, B, C
5 lipopeptides with CTL epitopes from <i>gag, nef, pol</i>	132	B
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	324	B A, B, C
DNA vaccine with <i>nef, rev, tat, gag, pol, env</i> , CTL epitopes	28	B
DNA vaccine with <i>gag, pol, nef + env</i> or Adenovirus vector with <i>gag, pol + env</i>	60	A, B, C
Prime: DNA plasmid with <i>gag, pro, RT, env, tat, rev, vpu</i> Boost: Modified vaccinia Ankara (MVA) vector with <i>gag, pol, env</i>	120	B
Modified vaccinia Ankara (MVA) with <i>env, gag, tat-rev, nef-RT</i>	32	C
Recombinant protein vaccine with <i>gag, pol, vpr, nef</i> and DNA vaccine with protein containing T-helper epitopes from <i>env, gag, pol, vpu</i>	120	B
Adenovirus vector with <i>gag, pol + env</i> or DNA vaccine with <i>gag, pol, nef + env</i> followed by adenoviral boost	66	B A, B, C
Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, and pol</i> to volunteers from HIVIS 01	38	A, E
Prime: DNA vaccine with <i>gag, pol, env</i> Boost: Adenovirus vector with <i>gag, pol, env</i>	104	A, B, C
Modified vaccinia Ankara (MVA) viral vector with gp160, <i>gag</i> and <i>pol</i>	48	A, E
Prime: Genevax Gag-2692 +/- IL-15 DNA Boost: Genevax Gag-2692 + IL-12 DNA or IL-15 DNA	120	B
Prime: Genevax Gag-2692 +/- IL-12 DNA adjuvant Boost: DNA plasmids with <i>gag</i> or RC529-SE and GM-CSF with <i>env, gag, nef</i>	156	B

TRIALS OF PREVENTIVE HIV/AIDS VACCINES WORLDWIDE (AUGUST 2006) *continued*

PROTOCOL #	START DATE	SPONSOR, FUNDER, DEVELOPER	TRIAL SITE(S)
HVTN 054	Apr-05	DAIDS, HVTN, VRC	US
VRC 008	Apr-05	NIAID, VRC	US
N/A	Mar-05	Changchun BCHT, Guangxi CDC	China
HIVIS 01	Feb-05	Karolinska Institute, Swedish Institute for Infectious Disease Control, Vecura	Sweden
EuroVacc 02	Feb-05	EU, Imperial College London, UK MRC Clinical Trials Unit, EuroVacc	UK, Switzerland
N/A	Feb-05	St. Jude, NIH	US
RV 156	Jan-05	NIAID, HVTN, VRC, USMHRP, Makerere U.	Uganda
IAVI C002	Jan-05	IAVI, ADARC	US
HVTN 059	Oct-04	HVTN, SAAVI, Alphavax	US, South Africa, Botswana
HVTN 055	Sept-04	DAIDS, HVTN, Therion	US, Brazil
HVTN 056	Apr-04	DAIDS, HVTN, Wyeth	US
HVTN 050/Merck 018	Jan-04	NIAID, HVTN, Merck	Thailand, Brazil, Haiti, Puerto Rico, South Africa, US, Malawi, Peru
HVTN 049	Dec-03	DAIDS, HVTN, Chiron	US
HVTN 044	Dec-03	DAIDS, HVTN, VRC	US
IAVI A001	Dec-03	Columbus Children's Research Center, Indian Council of Medical Research, National AIDS Control Organization, IAVI, Targeted Genetics	Belgium, Germany, India
B011; RV 138	Jul-02	WRAR	US

KEY

ABL Advanced BioScience Laboratories
 ADARC Aaron Diamond AIDS Research Center
 ANRS Agence Nationale de Recherches sur le Sida (France)
 DAIDS Division of AIDS
 HVTN HIV Vaccine Trials Network
 IAVI International AIDS Vaccine Initiative
 MoPH Ministry of Public Health
 NIAID National Institute of Allergy and Infectious Diseases

NIH National Institutes of Health
 SAAVI South African AIDS Vaccine Initiative
 UMMS University of Massachusetts Medical School
 USMHRP United States Military HIV Research Program
 VRC Vaccine Research Center
 WRAR Walter Reed Army Institute for Research
 ZEHRP Zambia Emory HIV Research Project

VACCINE(S)	# OF VOLUNTEERS	CLADE
Adenovirus vector with <i>gag, pol + env</i>	48	B A, B, C
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	40	B A, B, C
Prime: DNA vaccine Boost: recombinant adenovirus vector	49	C
Intramuscular or intradermal injections of plasmid DNA. with HIV genes <i>env, rev, gag, and RT</i>	40	A, B, C
Vaccinia vector with <i>gag, pol, nef, env</i>	40	C
Recombinant HIV-1 multi-envelope DNA plasmid vaccine with <i>env</i>	6	A, B, C, D, E
Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>		B A, B, C
Modified vaccinia Ankara (MVA) vector with <i>env/gag-pol, nef-tat</i>	48	C
VEE (Venezuelan equine encephalitis) vector with <i>gag</i>	96	C
Prime: Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, tat, rev, nef, pol</i> Boost: Fowlpox viral vector (FPV) with same genes as prime	150	B
Conserved CTL epitopes from <i>gag, nef</i> and helper T epitopes from <i>env, gag</i> in adjuvant (RC329-SE), with or without cytokine (GM-CSF)	96	B
Adenovirus vector with <i>gag</i>	435	B
Prime: DNA vaccine with <i>gag, env</i> attached to microparticles Boost: Env protein (oligomeric gp140) + adjuvant (MF59)	96	B
DNA vaccine with <i>gag, pol, nef + env</i> with or without cytokine (IL-2) adjuvant	70	B A, B, C
AAV2 (adeno-associated virus type 2) vector with <i>gag, pol, ΔRT</i>	50	C
Canarypox viral vector with <i>env, gag, pol</i>	36	B