



SCIENCE SNAPSHOT: QUICK TAKES ON NEXT STEPS IN THE SEARCH FOR AN AIDS VACCINE

This year's AVAC Report heads to press in a flurry of editorials and articles opining, often gloomily, about the possibility of finding an AIDS vaccine. Much of this mainstream media coverage was prompted by the NIH Vaccine Summit which was billed as the first step in reorienting the US government's spending and priorities in the post-STEP era.

AVAC hopes and anticipates that there will be concrete changes coming out of the Summit and related meetings to be held in the coming months, and that organizations like IAVI (see page 41), Europrise and the Global HIV Vaccine Enterprise will contribute to an even broader discussion and set of shared activities.

Over the coming year, AVAC will track what's been suggested and see what's actually come from these more recent conversations, as well as take a closer look at what's coming out of the "big science" consortia like CAVD (the multi-million-dollar Gates Foundation initiative), the IAVI consortia on neutralizing antibodies and replicating vectors, and the NIH-funded CHAVI. Each of these has promised broader, well-funded and more systematic approaches to some of the field's most intractable scientific challenges. As they approach two to three years of activity, we can fairly start to look at what CHAVI and CAVD teams have delivered thus far. One challenge is figuring out how to evaluate and monitor such discovery efforts, since they don't

lend themselves as readily to milestones or signal achievements, which are the most straightforward metrics of success.

These are quite complex topics, so we've decided to publish the results of that work in a separate in-depth report during the coming year, before our next annual report. For this Report, we decided to put together a brief snapshot of some of the most important or intriguing suggestions that have emerged from those efforts. It's an eclectic and admittedly incomplete list, which we'll be able to revisit more systematically in the future.

ORGANIZING FOR FUTURE WORK

- Standardize assays in emerging areas: single-cell proliferation, mucosal immunity, viral suppression.
- Fund and coordinate more systematic animal-model work with the goals of: meeting the need for a wider range of well-characterized antigens, immunogens and challenge viruses; standardizing where appropriate; addressing animal shortages and funding issues for primate facilities; and working, where possible, toward agreement about which models are useful for which types of questions. There also needs to be further exploration and some level of resolve in the ongoing debate over using animal models as a gatekeeper for advancing candidates into clinical trials.



- Define a suite of human discovery trials that would be most valuable for moving the field forward, and which would support several parallel approaches to key challenges or questions.
- Use an annual meeting such as the October AIDS Vaccine conference in Cape Town for a public, town hall-style forum to review the scope of ongoing work and assess implications and gaps. Some questions, prompted by the March summit, include: What do primate researchers and Phase I clinical trialists need to do to optimize each other's work? What are human discovery studies yielding in terms of insights for product development? What are new insights into immunogen design—and is the field acting on them? Such a meeting should be linked to responsive funding. If a “natural” collaboration emerges that needs additional support, there should be a pool of funds for the group to draw on.
- Make sure that each funding entity does most what it does best. NIH, AmfAR, the Gates Foundation, IAVI and others have strengths and “sweet spots” when it comes to fueling different types of research such as investigator-initiated, innovation-oriented or orphan projects. There doesn't need to be turf carved out, but it would help for entities to play to their strengths and collaborate so that no corner is overlooked.

- CHAVI, CAVD and other consortia like IAVI's groups could productively be more systematic, strategic and open about how they assess progress. Going “forward to basics” means recognizing that the clear, measurable milestones of product development simply don't apply here. Given the unpredictability of discovery-based work, it's far from clear what the best criteria are for evaluating success, especially since repeated failure may even be a good measure of potential future success.

EXPANDING THE OVERALL EFFORT

- Follow the outcomes of the Europrise example, which is creating a PhD “school” that trains graduate students and places them in laboratories of participating Europrise scientists, so that outreach to young scientists starts early.
- Look for novel funding incentives that would support young scientists' work in established scientists' laboratories. Can grants to seasoned investigators have plus-ups or designated budget lines for new scientists? Perhaps more important, cultivate independence by strengthening funding structures for first-time or R01-naive investigators.

AREAS FOR NEW OR INTENSIFIED INVESTIGATION

- “Immunogens, immunogens, immunogens”: Where are the antibody-inducing immunogens? What types of inserts should be used in vaccines





to induce effective immune responses? What can be learned about immunogen design by studying human responses to proven vaccines?

- Continue work on defining what constitutes an effective T-cell response and on standardizing measures of this. This work should consider T-cell qualities like memory phenotype, proliferative ability, *in vitro* control of HIV replication, homing to mucosal tissues, interaction with innate immunity, and support for B-cell immunity.
- Probe B-cell regulation: HIV-positive people don't generate neutralizing antibodies in real time against their virus. Instead, antibodies isolated at any given time point can neutralize virus isolated from the same person at earlier timepoints. Viral genetic variability means that HIV is always one step ahead of naturally-generated antibodies. So researchers are beginning to ask whether this delay reflects not only the molecular trickery HIV uses to hide Env from the immune system, but perhaps also something about the B-cell immune response itself. Are the right kinds of neutralizing antibodies actually made, but the cells that produce them switched off? Might it be possible to manipulate B-cells to be better responders to HIV? Might that manipulation occur at the site of infection? At Keystone, Quentin Sattentau

(Oxford University) presented data on stimulating antibodies through vaginal delivery of adjuvants and antigens. Other insights may come from an ongoing clinical study on neutralizing antibody responses in HIV-infected people with certain B-cell defects. More complete answers will take extensive research into how antibodies against HIV are made and how these pathways are regulated—research that's beginning, but still sorely needs expertise from researchers already expert in B-cell regulation.

- Don't rest with the current definition of polyfunctionality. As Rafick Sekaly wrote in a recent article¹: "The term polyfunctionality might also imply more than just the induction of CD8+ and CD4+ cells that produce multiple cytokines; it could also reflect an integrated immune response that includes different types of T cells (Th1 and Th2), B cells, and other innate immune cells, including dendritic cells and natural killer (NK) cells."
- Look at factors that may increase T-cell resistance to HIV infection. For example, the VRC has data showing that production of MIP-1 beta by CMV-specific memory CD4 T cells is associated with greatly reduced susceptibility to HIV. Can this type of response be preferentially induced with an HIV vaccine candidate?

¹ Rafick-Pierre Sekaly, "The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development?" *The Journal of Experimental Medicine* 205, no. 1 (2008), <http://www.jem.org/cgi/content/short/205/1/7>.

TIME FOR THE ENTERPRISE TO EXPAND ITS IMPACT

For each of the past three years, AVAC has devoted a portion of its annual report to addressing the executive director of the Enterprise—before one had been identified, after the first candidate was offered the position, and then again as the search continued. Our core recommendations remain the same since we first published them in 2005:

1. Communicate frequently and transparently.
2. Set policies for sharing and coordination of data and technology.
3. Ensure the ability to take risks.
4. Bring new investigators into the search.
5. Make the Enterprise truly global.
6. Involve civil society in a meaningful way.
7. Take on the politics and ethics of clinical trials.
8. Establish realistic milestones and a process for monitoring progress.

Our sense of urgency has only intensified with the appointment of Alan Bernstein as the inaugural director at the beginning of the year. As he finds his bearings and conducts the necessary “listening tour” and introductory meetings, we have been impressed with his openness and honesty. We look to him now to articulate the critical milestones for the rest of 2008 and beyond.

We need an updated scientific plan; we need a convening entity that uses the members’ professed “moral” commitment to collaboration to its best advantage. We hope the Enterprise will not become sidetracked by issues of fundraising, but instead focuses on better use of existing resources. And there’s still a lot of work to be done around building scientific and clinical-trials literacy as a foundation for real community engagement. Here, too, the Enterprise has a critical leadership role to play.

- Hone understanding of *in vivo* neutralization. For HIV and most other viruses, neutralization is defined (and measured) by an antibody’s ability to block virus from entering (and then replicating in) cultured cells. But for HIV, it’s emerging that neutralization and protection don’t necessarily go hand-in-hand: several new studies have found antibodies that protect macaques against the simian immunodeficiency virus (SIV), but don’t neutralize virus in the standard laboratory test. So the issue of defining the right responses takes on a new twist: what, exactly, defines a protective antibody? If classical neutralization isn’t the whole story, does it need to block virus from crossing the mucosal layers that line the genital tract—a key step in sexual transmission? Or block virus transmission from one type of cell to another? Over the next year, CHAVI researchers will systematically look at which of four antibody functions (or which combination) is most relevant to protection in macaques—one first step in answering this important question.
- Increase complementarity of Phase I and discovery studies in humans and trials in non-human primates, so that data from either discipline informs the other in real time, and so that there’s information on a given question coming from both non-human primates and humans.



THE SEARCH CONTINUES. IT MUST.

What's the best way to end a Report from a year that's been by turns disappointing, frustrating, heartbreaking and inspiring—in terms of individual and collective ability to face difficult situations?

With appreciation.

For the integrity, honesty, and faith that so many different stakeholders have brought to these difficult times.

These stakeholders range from volunteers who, on learning that the STEP and Phambili trials would halt immunizations, asked, “When is the next trial?” to senior scientists like the University of Alabama’s Beatrice Hahn who made clarion calls for funding the next generation, to the study nurses at sites from Cape Town to Lima to San Francisco who explained difficult data and disappointing news to participants.

Appreciation, too, to leaders who reiterate to skeptics near and far that the search for an AIDS vaccine cannot, under any circumstances, be abandoned. Dazon Dixon Diallo, Tony Fauci, Zackie Achmat, Glenda Gray and many, many others around the world have been stalwart on this front throughout this year.

To you and many other stakeholders, we say: Thank you. The search continues.

ABOUT AVAC

Founded in 1995, the non-profit AIDS Vaccine Advocacy Coalition (AVAC) seeks to create a favorable policy and social environment for accelerated ethical research and eventual global delivery of AIDS vaccines and other HIV prevention options as part of a comprehensive response to the pandemic. This work is guided by the following principles:

- Translate complex scientific ideas to communities AND translate community needs and perceptions to the scientific community.
- Manage expectations.
- Hold agencies accountable for accelerating ethical research and development.
- Expand international partnerships to ensure local relevance and a global movement.
- Ensure that policy and advocacy are based on thorough research and evidence.
- Build coalitions, working groups and think tanks for specific issues.
- Develop and widely disseminate high-quality, user-friendly materials.

AVAC FOCUSES IN FOUR PRIORITY AREAS:

1. Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction and use of AIDS vaccines and other HIV prevention options.
2. Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial and access processes.
3. Monitor HIV prevention research and development and mobilize political, financial and community support for sustained research as part of a comprehensive response.
4. Build an informed, action-oriented global coalition of civil society and community-based

organizations exchanging information and experiences.

A major part of AVAC's work is to translate complex scientific ideas to communities through the development and wide dissemination of high-quality, user-friendly materials. In addition to our annual Report, which analyzes progress in the field and makes recommendations for actions in the coming year, AVAC publishes the *AIDS Vaccine Handbook*, maintains the AIDS Vaccine Clearinghouse (www.aidsvaccineclearinghouse.org) and PrEP Watch (www.prepwatch.org) as comprehensive and interactive sources of information on the internet, and publishes *Px Wire*, a quarterly update on HIV Prevention Research (www.pxwire.org).

We also manage the Advocates' Network, an electronic network for organizations and individuals interested and involved in AIDS vaccine and HIV prevention research advocacy. Please join us by visiting <http://aidsvaccineclearinghouse.org/network.htm> or e-mail avac@avac.org.

For more information about AVAC's programs and publications or to become a Member, please contact us at:

Physical: 119 West 24th Street, 7th Floor,
New York, NY 10011

Mailing: 101 West 23rd Street, Suite 2227,
New York, NY 10011

Phone: +1 212 367 1279

Fax: +1 646 365 3452

E-mail: avac@avac.org

Internet:
www.avac.org / www.aidsvaccineclearinghouse.org
/ www.prepwatch.org / www.pxwire.org

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FOR MORE INFORMATION, PLEASE CONTACT:

AIDS Vaccine Advocacy Coalition	<i>Phone:</i> +1 212.367.1279
101 West 23rd Street #2227	<i>Fax:</i> +1 646.365.3452
New York, NY 10011	<i>Email:</i> avac@avac.org
USA	<i>Internet:</i> www.avac.org

