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VACCINE ISSUE
INTERVIEW WITH JON COHEN

SEARCHLIGHT

NEWS FROM AIDS RESEARCH ALLIANCE

A NATIONAL LEADER IN FAST-TRACK AIDS RESEARCH

VISION

AIDS Research Alliance (ARA) envisions a future in which HIV and its effects on health are eliminated, and new infections are prevented.

MISSION STATEMENT

AIDS Research Alliance (ARA) exists to develop a cure for HIV/AIDS, medical modalities to prevent new infections and better treatments for those living with HIV.

AREAS OF BUSINESS

The core areas of the AIDS Research Alliance (ARA) non-profit business model include:

1. Independent clinical research, without regard to profit.
2. Clinical trials for innovative anti-HIV technologies and treatments, and for vaccine, microbicide and other biomedical prevention research.
3. The development of treatments for HIV-related conditions.
4. Collaborations and strategic partnerships with other scientific organizations (including academic institutions, biotech and pharmaceutical companies, and governmental agencies).

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THE SEARCH FOR AN HIV VACCINE

Where are we?

The search for an HIV vaccine began in earnest 23 years ago, two years after the discovery that HIV causes AIDS. While progress has been made, we do not yet have a vaccine. Nor it is apparent that a vaccine will be discovered in the near future. However, the situation is not as grim as it looks. It took 105 years to discover a vaccine for typhoid, 92 years for influenza, 89 years for pertussis, 47 years for polio, and 42 years for measles. Thus, from a purely historical perspective, there is reason to be hopeful.



Thirty-four HIV vaccine candidates are now in the pipeline. That's the good news. The bad news is that all of these candidates are based on the same hypothesis—that a vaccine can confer partial protection by eliciting a cell-mediated response. If that is false, all the candidates in the pipeline will fail and vast resources will have been wasted.

The Global HIV/AIDS Vaccine Enterprise, spearheaded by the Bill and Melinda Gates Foundation is an alliance of scientists targeting critical areas of HIV vaccine research. The Enterprise Strategic Plan, published in January 2005, seeks to overcome the obstacles to HIV vaccine research by an organized, managed, and systematized international effort targeted on the design and clinical evaluation of novel HIV immunogens.

Despite the Plan's emphasis on coordination and collaboration, it acknowledges that "the major difficulties encountered in the development of an HIV vaccine are scientific, not organizational". Questions have been raised about some of these difficulties, including which HIV antigens and host immune responses are required for eliciting protective immunity? Is mucosal immunity beneficial? Which vaccine designs are most effective at stimulating mucosal immunity, and how best are these responses assessed? Can the robust protection conferred to monkeys by live-attenuated SIV vaccines be mimicked by vaccine designs that do not have the safety risk of live-attenuated approaches?

Then there is the critical issue of funding. The Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise estimates that the \$682 million currently invested per year in vaccine research must be *doubled* if we are to meet the challenge of developing a vaccine in our lifetime. Currently, we spend less than 1% of total health product funding on HIV vaccine research.

Nonetheless, we at ARA are not discouraged. We are optimistic about the Global HIV/AIDS Vaccine Enterprise Strategic Plan because it represents a platform that will energize and sustain HIV vaccine research. In addition, we like the Enterprise's research model, which is remarkably like our own. AIDS Research Alliance began in 1989 as a collaboration of individual physicians who shared

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Coverage of the 13th Conference on Retroviruses and Opportunistic Infection (February 5-8, 2006)

High HIV prevalence and incidence among African-American men who have sex with men (MSM) in Baltimore^[1]

Between June 2004 and April 2005, Sifakis and colleagues of the John Hopkins School of Public Health examined HIV prevalence (percentage of HIV positive people), incidence (number of people that become infected with HIV per year), and risk behaviors among 1,013 men who have sex with men (MSM) residing in the Baltimore metropolitan area. The study revealed an alarmingly high incidence (9% *per year*) and prevalence (32%) of HIV infection among the study group. HIV prevalence and incidence were higher among African American MSM (45.6% and 15.4% *per year*, respectively) compared to other ethnic groups. In addition 63.5% of African Americans were unaware of their HIV status. These results indicate an urgent need to improve prevention and education efforts geared specifically toward African American MSM.

Pre-exposure Prophylaxis (PrEP) with antiretroviral agents prevent rectal transmission of SIV^[2]

Despite the positive impact of antiretroviral medications in decreasing the rate of progression to AIDS and death among HIV positive patients, and considerable success in reducing the price of drugs in developing countries, the pandemic continues to outpace all efforts to contain it. It is evident that HIV cannot be stopped without effective prevention strategies. Several studies are investigating the use of antiretroviral drugs to prevent sexual transmission of HIV. Investigators from the Center for Disease Control (CDC) in Atlanta investigated whether a two-drug combination of tenofovir (TDF) and emtricitabine (FTC) could protect rhesus macaques from rectal transmission of SHIV, a simian immunodeficiency virus altered so that it expressed the HIV-1 envelope. Six macaques received a subcutaneous injection of TDF (22 mg) and FTC (20 mg) *per kg* once daily; six control animals received no drugs. All animals were subjected to weekly rectal exposures with a low dose of SHIV (3×10^5 virus particles). Infection was monitored by checking the fluid part of the blood for antibodies to the virus and blood cells for virus using PCR amplification of sequences of two SHIV proteins, gag and pol. Four of 6 (67%) control animals became infected after 4 virus exposures. In contrast, none of the 6 animals treated with TDF/FTC were infected even after 10 additional virus challenges. It is noteworthy that the dose of TDF used in these experiments is comparable to that approved for humans. This study demonstrates that pre-exposure prophylaxis with antiretrovirals may be an effective strategy for preventing sexual transmission of HIV in human.

Early antiretroviral therapy is beneficial in restoring mucosal CD4+ T cells^[3]

The current measures of success of the antiretroviral drug regimen HAART are an increase in the CD4+ T cell

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NEWS AND VIEWS

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count and a decrease in the number of virus in peripheral blood. However, recent studies demonstrated that the Gut-Associated Lymphoid Tissue (GALT) plays an important role in HIV infection as an early site for viral replication and severe depletion of CD4+ T cells. Current guidelines recommend that HAART should be started when CD4+ T cells fall below 350 cells/mm³. To investigate the clinical benefits of initiating HAART when a patient is first infected (acute infection) *versus* later (chronic infection), Guadeloupe and colleagues at the University of California, Davis, analyzed restoration of CD4+ T cell count and function in GALT of HIV positive patients initiating HAART during acute *versus* chronic infection. The rate of CD4+ T cell restoration in GALT with HAART treatment in acutely infected patients was significantly higher than that observed in chronic HIV infected patients ($p=0.012$). Using microarray, a powerful slide-based molecular analysis technique, the investigators found in the GALT of recently infected individuals treated with HAART a decrease in proteins involved in inflammation and an increase in protein signals for cell growth, and cell to cell interactions critical for an immune response. They also saw higher levels of CD4+ T cells expressing markers for functional mature T cells (CD11a, CCR5, and CXCR4) in GALT of primary patients as compared to GALT in chronic infected individuals. Furthermore, acutely HIV infected individuals had stronger HIV-specific killer (CD8+) T cell responses in both GALT and blood. These results indicate that beginning HAART during primary HIV-1 infection was more effective in restoring and maintaining mucosal CD4+ T cells and suppressing viral load than initiation of HAART during chronic HIV infection. The authors also suggest that monitoring disease progression in both lymphoid tissue and peripheral blood provides a more accurate assessment of the efficacy of HAART.

Merck's HIV-1 integrase inhibitor^[4]

Despite significant progress in understanding of the life cycle of the Human Immunodeficiency Virus (HIV) and the development of anti-HIV drugs, there is no single medication or combination of medications that is able to eliminate or cure HIV. Therapy failure is generally due to the emergence of resistance and the toxicities associated with the long-term use of antiviral drugs. There is a pressing need for the development of new, potent, antiretroviral compounds with different resistance profiles or with novel mechanisms of action. MK-0518 was developed by

Merck as a potent inhibitor of integrase, an enzyme necessary for integration of the genetic material of HIV into the cell's DNA. Grinsztejn and colleagues reported the preliminary results of the first multi-center, double-blind, randomized study to evaluate the safety and efficacy of MK-0518, as compared to placebo in patients receiving an optimized drug regimen based on the patient's drug resistance profile (OBT). One hundred and thirty-two patients who failed combination antiretroviral therapy with documented resistance were randomized to four groups (placebo, MK-0518 at 200, 400, or 600 mg twice daily). Because Atazanavir (ATV) increases the plasma concentration of MK-0518, each group was divided into 2 sub-groups: (A) patients receiving Optimized Background Therapy (OBT) without ATV, and (B) patients receiving OBT with ATV. At week 8, 63% to 67% of patients receiving MK-0518 had undetectable plasma viral load (<50 copies/ml) as compared to 8% in the placebo group. There was no significant drug-related toxicity in any group. Since it is difficult to achieve suppression of viral replication in patients with multiple drug resistance, MK-0518 may represent an important new class of drugs.

Exposure to protease inhibitors increases the risk of heart attack^[5]



In this observational study of more than 23,400 HIV-infected individuals (11 cohorts in Europe, Australia, and the United States), investigators asked if the risk of heart attack associated with long term use of different classes of HAART increased over time. Two different models were

used to assess the association of heart attack with years on HAART, and with years on Protease Inhibitors (PI) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI), separately. This large study showed that a HAART regimen-containing PI increases the relative rate per year of heart attack by about 1.16 (1.10 to 1.23, $p=0.0001$) after adjusting for other cardiovascular risk factors. The relative rate of heart attack per year for a NNRTI-containing regimen is 1.05. The increase in the risk of heart attack with PI containing regimens appears to be due, in part, to an increase in the level of lipids in the blood (dyslipidemia). In contrast, HAART regimen-containing NNRTI did not increase the risk of heart attack.

Gilead's HIV-1 integrase inhibitor⁶¹

The antiviral activity and safety of GS-9137, a new integrase inhibitor developed by Gilead, was evaluated in a prospective, randomized, double-blind, placebo-controlled monotherapy study in 40 treatment-naïve and previously treated HIV-1 infected individuals. Patients were randomized into 6 groups (GS-9137 at 200, 400, 800 twice daily, 800 mg once daily, or 50 mg boosted with 100 mg ritonavir or placebo). Over the 10-day period, all groups showed a significant decrease in their plasma viral load as compared

to placebo. There were no significant side effects. Therefore, GS-917 is sufficiently safe and potent to warrant further studies.

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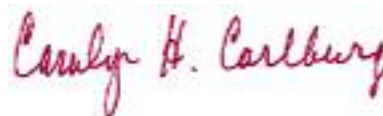
MESSAGE FROM THE CEO

continued from page 2

research data with one another. Since then, our research program has been centralized at one facility, where we conduct independent research in several critical areas aimed at better treating and preventing the spread of HIV/AIDS. Our *modus operandi* is to work with other scientific organizations on a contractual and collaborative basis, which allows us to leverage limited resources.

We see a role for ARA in the Global HIV/AIDS Vaccine Enterprise Strategic Plan. The Enterprise promotes openness and cooperation, a strategy that has allowed us to survive and excel. We are ideally positioned to carry out clinical trials of vaccine candidates identified by Enterprise scientists and collaborators. Indeed ARA joined UCLA in the recent re-competition for funding through the HIV Vaccine Trials Network. If we are successful, ARA will become the site for the Vaccine Trial unit.

Currently, ARA is the only nonprofit in the United States to be *in-licensed* by NIH to develop a drug for the treatment of HIV. To date, we have conducted clinical trials for 11 of the 27 drugs currently used in the treatment of HIV. Thus, we believe that we have a contribution to make and a role to play. The Global HIV/AIDS Vaccine Enterprise Strategic Plan presents us with the opportunity to do what we do best, and inspires the hope that ARA will be around as long as it takes to rid the world of HIV/AIDS.



Carolyn H. Carlburg, J.D.
Chief Executive Officer

STILL SHOOTING IN THE DARK?

Jon Cohen, science journalist, assesses the state of HIV vaccine development and funding



Photo by Malcolm Linton

In March, ARA sat down with Jon Cohen, author of the critically acclaimed **Shots in the Dark: The Wayward Search for an AIDS Vaccine** (Norton, 2001 ISBN 0-393-32225-4), and veteran science journalist who covers HIV/AIDS research for Science Magazine. With the funding of HIV vaccine grants by the Gates

Foundation in the wings, and the international and national commitments to HIV vaccine research increasingly in the news from the formation of the Center for HIV/AIDS Vaccine Immunology (CHAVI) and the Global HIV/AIDS Vaccine Enterprise, it seemed a good time to ask this long-term observer of the field for his sense of where we are, and if he is optimistic about the future. We were not disappointed.

Q. Do you think the prospect for an HIV/AIDS vaccine has improved or worsened since you published *Shots in the Dark*?

A. While the scientific barriers to the development of an HIV vaccine remain the same and a breakthrough insight is still missing, there have been significant improvements in our understanding of the immune system's response to the virus. We also now realize that the early infection takes place in the gut and understand how the virus destroys immune system cells in the gut, but I see no vaccines under development that exploit that understanding. People are talking about it, but nothing yet. I am convinced that a vaccine is possible because of the abundant evidence that the immune system can control the virus. Chimps in the

wild carry a virus similar to HIV yet remain symptom-free. We know that some high risk humans are repeatedly exposed to the virus yet remain well. Their resistance may be genetic, for example, because of the absence of a key receptor. But the genetic difference does not account for all of the people who are repeatedly exposed, yet do not become detectably infected. That has to be due to an immune response; we just don't know what that is.

Q. Since your book was published, the focus has shifted from humoral immunity to cell mediated immunity. But now researchers speak of the need to elicit an antibody response to prevent HIV entry. Do you think a vaccine that generates only cell mediated immunity might provide protection?

A. There is no reason to speculate. The current Merck/HVTN trial of the adenovirus based vaccine with three viral proteins (Gag-Pol-Nef) is a well designed trial that will answer the question whether cell mediated immunity will lead to control of the virus, either by preventing infection or resulting in a low viral load in people who become infected. This approach will not lead to sterilization, or complete absence of the virus, but may provide a useful vaccine.

Q. Several groups have run simulation analyses that suggest that a partially effective vaccine used by some percentage of at-risk populations would be useful in some settings, for example in Africa. How relevant do you think these simulations are?

A. These analyses support the idea that reducing the number of people who become infected with a partially effective vaccine would reduce the number of HIV/AIDS cases. We know from other viral infections and other vaccines, such as the first polio vaccine, that herd immunity, which

reduces the pool of virus in the community, reduces infection. The first Salk vaccine was taken by 70% of the population and was 70% effective, yet between 1955 and 1961 polio dropped in the US by 90-95%. There is no reason to believe that HIV would be different. We know that once HIV enters a community it is slow to spread. And we know from recent studies that the virus is not that good at establishing an infection. So reducing the pool of virus in a community has a good chance of reducing infection.

Q. How has the pool of Gates funding changed the scientific landscape— for better or worse?

A. It is too soon to know. The Gates Foundation has not announced who will receive funds in response to its Request for Proposals (RFP) submitted under the Scientific Strategic Plan of the Global HIV Vaccine Enterprise. The three RFPs are: The Design of Immunogens that Induce Broadly Reactive Neutralizing Antibodies, The Design of Immunogens that Induce Persistent High Levels of Cell-mediated Immunity, and Standardization and Development of Laboratory Assays to Comparatively Measure the Immunogenicity of HIV Vaccine Candidates in Pre-clinical and Clinical Trials. The impact of the Gates funding will depend upon whether the Enterprise proves itself able to manage the scientific collaborations effectively. Putting serious money behind answering the questions identified by the Enterprise may well move the field, if it is managed well.

Q. Do you think that using immunologic surrogate endpoints, such as the level and durability of an immune response for Phase IIb trials, will help or hinder identifying the best vaccine candidates?

A. It is inevitable that as we move forward better surrogates will be developed. The surrogates that we use today are best guesses and perhaps we will reject a useful vaccine candidate using these endpoints. There is another problem with surrogate endpoints that comes from how the trials are done. Most vaccine trials enroll high risk individuals and within this population there are likely some people who have developed a protective immune response. That's why they are not infected. But we don't know what that baseline immunity is and how to measure it. The critical questions about these correlates of immunity need to

be understood and they are not being addressed. For example, the current tenofovir pre-exposure prophylaxis trials going on in half a dozen countries around the world are enrolling such high risk individuals. There will be some people in these studies who do become infected and we need to compare the immunity in the people receiving the drug who become infected with the people receiving the drug who don't, and to try to understand the differences. I know of only one lab that is doing this. This is a missed

“The impact of the Gates funding will depend upon whether the Enterprise proves itself able to manage the scientific collaborations effectively.”

opportunity. I am not a Pollyanna. This trial may or may not succeed. Things in science fail, but failing to exploit all that can be learned from such a trial means we are not learning as much as we can from the study. Gilead, the company that makes tenofovir, is only providing the drug; the study is funded by the Gates Foundation, the NIH and the CDC. They are not funding the kind of studies I am talking about, but it should be done. Progress in science often comes from looking at problems not just head on, but from the side. Another observation that makes this intriguing is that in monkey studies with antiretroviral drugs, protection is seen long after the drug has been stopped. What happens when the drug comes along and partially kills the virus? Is that weakened virus essentially an attenuated vaccine? Understanding the correlates of immunity in both the human drug prophylaxis trials and the primate study settings may provide deep insights about what baseline immune response is protective and may provide better surrogate markers.

Q. Should some of the money allocated to vaccines be diverted to other strategies that may be more rapidly developed, such as microbicides?

A. There should be money for such strategies, but taking money away from the effort to find a vaccine doesn't make sense. While developing a microbicide may or may not be easier to achieve than a vaccine, it is important to find out. There should be money enough for both.

Q. Do you think the Global HIV/AIDS Vaccine Enterprise, which in its Scientific Strategic Plan seems to echo a number of your suggestions, will be able to bring enough of the players on board in deeds and not just words, both public and private, NGO and governmental, to speed the development of a vaccine?

A. The approach is definitely an improvement on the way things were done in the past, relying only on individual investigator initiated grants. The Enterprise has developed a rational, targeted scientific plan. A key aspect of the Enterprise is the requirement that scientists work together, sharing insights and findings. I am convinced that scientists can work together and share data. You see it in companies all the time and we saw it work in the Human Genome Project, where the data were made available on public web sites very quickly. The key will be whether the Enterprise can, as a virtual entity, manage scientific collaborations that are virtual centers. How will the Enterprise hold the groups to their timelines and milestones? This remains to be seen. I don't see a strong leader in place to make these things happen. Perhaps what is needed is a non-scientist like Basil O'Connor, an attorney who provided the strong leadership that resulted in the first polio vaccine. What is needed for the HIV vaccine effort is someone who is such a leader, a great champion of the cause, who understands the science, the politics, and the media. Another concern I have is the need not only for scientific transparency but also financial transparency so that everyone can see how the funds are being distributed and spent. The Global Fund does that in

“A key aspect of the Enterprise is the requirement for scientists to work together, sharing insights and findings.”

its management of awards to support delivery of care to people with HIV/AIDS in many countries. You can go to its web site and see exactly who received the money and how it was spent. The Enterprise is a virtual organization and I think we need to see transparency and aggressive accountability, with the organization constantly giving itself report cards.

Q. Finally, do you remain hopeful that an effective HIV vaccine will be found?

A. As I said earlier, there is abundant evidence that it can be done, especially from the observations about SIV infected chimps and repeatedly exposed humans who remain healthy. Yes, the key scientific insight is missing, but everyone will know when that insight occurs that it is the key. Look at what happened when people stumbled onto the

“Perhaps what is needed is a non-scientist like Basil O'Connor, an attorney who provided the strong leadership that resulted in the first polio vaccine.”

observations about the co-receptor and how things just took off. You can speculate about where the insight for the vaccine will come from. I could imagine it coming from something like plasmoid dendritic cells, mucosal immunity, the innate immune system, all kinds of ideas. Maybe the answer will come through a biological systems approach. These massive screens to look at protein-protein interactions, gene-gene interactions, should be applied to the HIV virus and how it interacts with cells and the whole organism. Systems biologists are now developing tools to understand what they call *interactomes*, the protein interaction networks of cells and entire organisms. If these methods, that are really the extension of the Human Genome Project, of annotating the genome by understanding the complex interactions of the products of genes under different conditions could be applied to HIV, then maybe we would achieve that key breakthrough. I would like to get these very smart people interested in working on HIV.

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HOW DOES THE US FUND HIV VACCINE RESEARCH?

Funding for HIV vaccine research and development comes from three sectors, the public sector (national and international government agencies), philanthropic organizations and the commercial sector of pharmaceutical and biotechnology companies. The public sector is far and away the largest source of funding, accounting for nearly 90% of the US\$682 million investment in vaccine research in 2004. The largest single source of funding is the US National Institutes of Health. In 2004 the NIH accounted for US\$452 million, or 75% of the total public sector investment. To put these numbers in a larger context, the per capita US public sector investment in a preventative HIV vaccine in 2004 was between \$1.50 and \$2.00, or 0.4% to 0.5% of our gross domestic product. Only Ireland invests a comparable per capita amount.

Within the NIH, the National Institute of Allergy and Infectious Diseases (NIAID) has the primary responsibility for HIV vaccine Research and Development, historically providing funding through investigator initiated R01 grants, as well as targeted grant and contract funding for vaccine design, development, manufacturing, animal testing, and evaluation of promising candidates in non-human primates.

BY BERNICE SCHACTER, Ph.D.

Bernice Zeldin Schacter, Ph.D., is a biotechnology consultant and freelance writer with over twenty-five years experience in biomedical research and research management, both in academia and the pharmaceutical industry. Her extensive writings have covered immunology, pharmaceutical research, medical genetics and drug development.



In 1999 NIAID established the HIV Vaccine Trials Network (HVTN), an international collaboration of scientists and institutions whose goal is to accelerate the search for a preventative HIV vaccine by sharing trial results and facilitating parallel, concurrent testing. The HVTN is composed of more than two dozen research institutions worldwide, coordinated from its headquarters at the Fred Hutchinson Cancer Research Center in Seattle, Washington. HVTN consolidated NIAID's long-standing research program, which until 1999 was carried out by the

U.S.-based AIDS Vaccine Evaluation Group (AVEG), focused on early-stage testing of vaccine candidates, and the HIV Network for Prevention Trials (HIV NET), focused on domestic and international trials of HIV vaccines and other prevention strategies.

In 2004, President Bush, in addition to endorsing the Global HIV/AIDS Vaccine Enterprise, announced plans to establish a second HIV Vaccine Research and Development Center in the US. In July 2005, the NIAID awarded a seven-year grant to a consortium of academic institutions led by Dr. Barton Haynes of Duke University to establish the Center for HIV/AIDS Vaccine Immunology (CHAVI). The first year's funding was US\$15 million. Total funding could reach US\$300 million. CHAVI investigators will undertake fundamental research directed at tackling major scientific obstacles that hinder HIV vaccine design and development. CHAVI's goals were established in response to recommendations by the Global HIV Vaccine Enterprise. CHAVI investigators will collaborate, develop and share novel research resources; engage non-CHAVI researchers; and contribute in a direct and meaningful fashion to the successful devel-

opment of an efficacious and globally applicable HIV vaccine. While the over-arching goal of CHAVI to help transform HIV vaccine research in the U.S. into a more cooperative and collaborative system is laudable, there is the concern that with its ability to engage and fund non-CHAVI investigators, CHAVI could lead to scientific orthodoxy and become a bottleneck for the flow of funding for new ideas.

The Bill and Melinda Gates Foundation is the largest philanthropic funder of HIV vaccine R&D, accounting for US\$123 million of the US\$166 million of the philanthropic investment between 2000 and 2004. With its commitment to provide up to US\$360 million over the next five years, through the Global HIV/AIDS Vaccine Enterprise, the Gates Foundation will continue to play a major role in funding research on an HIV/AIDS vaccine.

The total commercial investment in a vaccine in 2004 was estimated to be US\$68 million, down from US\$99 million in 2002, due to the completion of VaxGen's Phase III

trials of its candidate vaccine, and the company's shift from work on HIV vaccines to vaccines on bioterror agents. Merck's 2004 investment in HIV vaccine R&D was US\$10 million.

The current level of funding makes it clear that reaching the \$1.2 billion in yearly funding that the Enterprise estimates is needed will require greater urgency and a commitment from all sectors.

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PROSTRATIN UPDATE

The *phorbol ester* prostratin, used in Western Samoa as an ethnobotanical treatment for viral hepatitis, was isolated at the National Cancer Institutes (NCI) in 1992. Prostratin increases the expression of viral products from latently infected cells such as U1 and ACH-2 cell lines. It also inhibits the replication of HIV-1 and prevents viral spread. Prostratin represents a distinct subclass of Protein Kinase C (PKC) activators, and does not promote the development of tumors. The lack of tumor promotion by prostratin, coupled with its ability to up-regulate latent HIV-1 provirus expression, are important features that could be exploited as an effective therapy to target latent reservoirs for patients on Highly Active Antiretroviral Therapy (HAART).

In March 2001, AIDS Research Alliance in-licensed prostratin from the National Institutes of Health (NIH), and is moving prostratin through the drug development pipeline. In 2001, AIDS Research Alliance was awarded an NIH grant under the DART program (NIH-DART) to perform pre-clinical studies for prostratin. A complete account of these studies is available in previous issues of "Searchlight". In July 2005, AIDS Research Alliance signed an agreement with Covance Laboratories, Inc. to conduct the remaining pharmacokinetic and toxicology studies of prostratin.

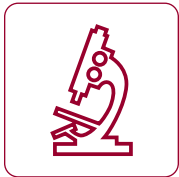
Covance is in the process of conducting two studies, using ³H-prostratin (prostratin labeled with the radioactive form of hydrogen, ³H):

- Quantitative whole body autoradiography of rats following oral administration of ³H-prostratin (to determine where in the body prostratin accumulates).
- In vitro metabolism of ³H-prostratin in rat, monkey, and human primary hepatocytes (to learn how different species break down prostratin).

Currently, we are waiting for the results of these experiments.



WORKING TOWARD AN EFFECTIVE HIV/AIDS VACCINE



The human immunodeficiency virus (HIV) is a global cause of morbidity, mortality, disability, associated health care costs, and loss of productivity. The latest report from the World Health Organization (WHO) indicates that, in

2005, an estimated 49 million people, mostly adults, were living with HIV/AIDS worldwide, - 95% of them in developing countries. The development of a safe, effective, and affordable vaccine for protection against HIV is thus a major priority for the biomedical community, since such a vaccine would be an important addition to the existing array of prevention strategies and could profoundly improve global public health.

As a result of the global effort to develop an effective HIV vaccine, more than 34 vaccine candidates in 19 countries are currently in the early phases of human clinical trials. Yet 23 years after the discovery of the virus, a safe and effective preventative HIV vaccine remains elusive. Some delay can justly be blamed on inadequate funding, lack of political commitment, and the disinterest of pharmaceutical companies. But even if we could vanquish these obstacles, major scientific challenges remain.

The modern science of immunology grew out of the common belief that people who had recovered from an infectious disease were protected from getting the same disease again. In ancient Greece, it was known that only those who had recovered from the plague could nurse the sick because they would not contract plague a second time. Unfortunately, there is no population that has been cured of AIDS and no immune system parameters have been identified that correlate with protection from this disease. However, there are at least two examples that sug-

gest that partial natural protection occasionally occurs. First, a small percentage of commercial sex workers who are continuously exposed to HIV remain uninfected. Secondly a few HIV infected individuals remain symptom-free for long periods of time (long-term non-progressors). Several studies are underway to understand the reasons for this protection and to identify immunologic markers that may be used to guide vaccine development.

The extensive genome variation of HIV isolates results in variation in the sequences of the amino acids that make up the proteins of the virus. Since proteins are generally the targets of a vaccine, these variations make it difficult to design a vaccine that would protect against all or even most HIV infections, thus posing a considerable barrier to vaccine development. Variation in HIV arises both as a result of mutations introduced by the error-prone enzyme, reverse transcriptase, that copies the viral genome within an infected cell, and by recombination between different viral strains (19). The rapid replication of HIV-1, *in vivo*, which produces up to 1010 new virus particles *per day* (18), also results in the rapid generation of sequence variants. Based on the analyses of HIV-1 nucleotide and amino acid sequences, HIV-1 isolates have been grouped into 9 major (M) subtypes (designated A through I), and a tenth outlier (O) (8). Variation of the amino acid sequences of the HIV envelope, the protein covering the virus, may exceed 30%. The high genetic variability allows the HIV virus to escape from the control of a specific immune response. Also, rapid spread of newly appearing HIV variants and several recombinant viruses have been observed in different parts of the world. This variation and changeability of HIV renders the development of a universal HIV vaccine extremely problematic (22).

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THE IMMUNE RESPONSE TO HIV INFECTION

The goal of all vaccination is to induce specific, long lasting immunity to an infectious bacterium or virus, and thus provide long-lasting protection from infection. To understand the challenges of developing an HIV vaccine, it is important to understand the normal immune responses

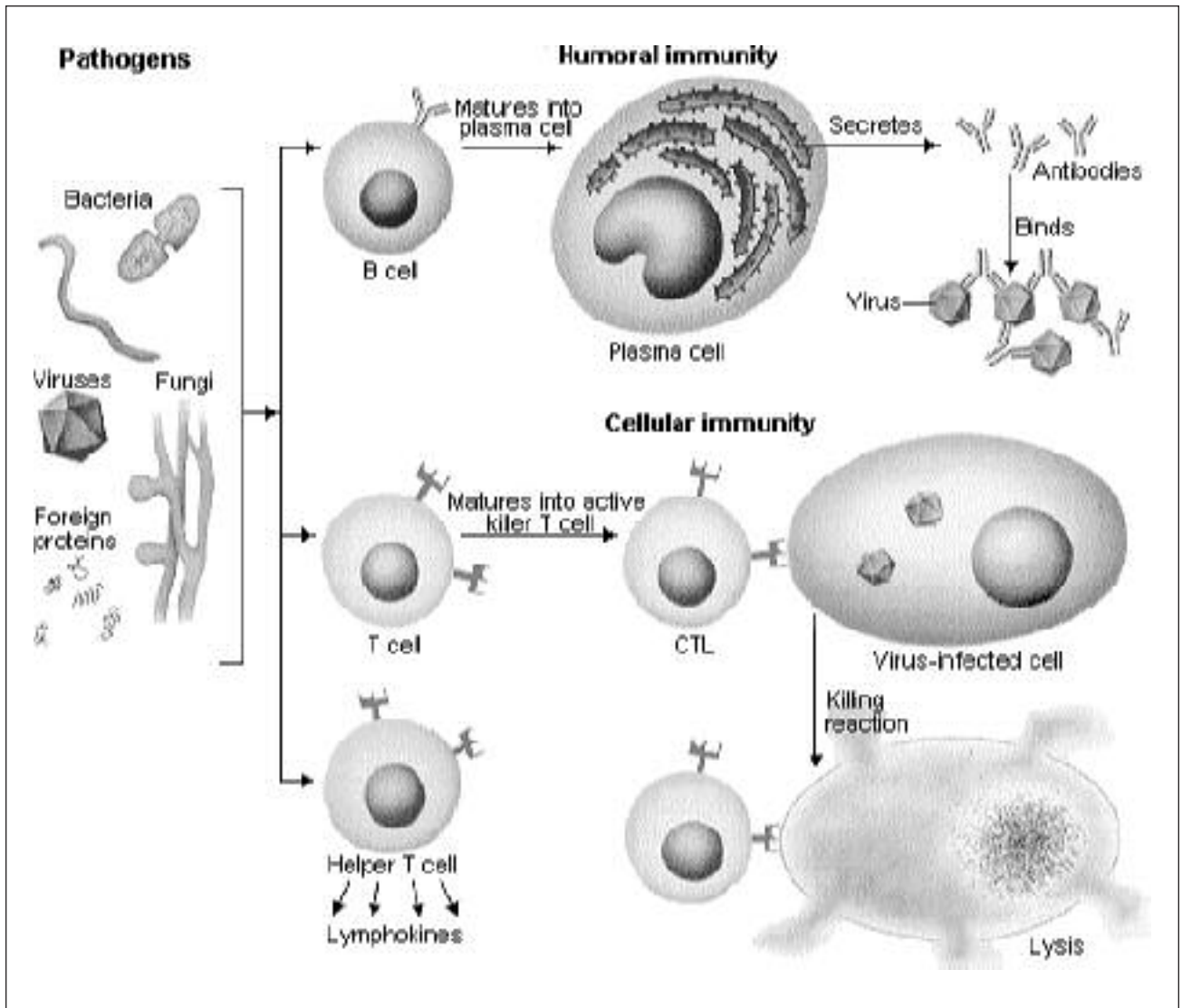


Figure 1. The adaptive immune response to pathogens. Antibodies trap and eliminate virus and the cellular immune response generates cytotoxic (cell killing) lymphocytes that kill virus infected cells.

to a viral infection. The primary role of the immune system is the discrimination between self and non-self. The fundamental purpose of recognition of non-self is to protect against invading micro-organisms (e.g. virus, bacteria), chemical agents, or other foreign substances. To eliminate non-self agents, the immune system has an armamentarium of methods that can trap, lyse or kill biologic agents or foreign cells. Some cells of the immune system can ingest foreign materials and thus kill invaders.

Immunity against viral infection is mediated by a combination of immune system proteins called antibodies and immune system cells, including but not limited to

CD4 + T lymphocytes. The antibody response is also called a humoral immune response. (Figure 1.). The immune response begins with the recognition by CD4 + T lymphocytes of viral proteins displayed on the surface of specialized cells that break down the viral proteins into small pieces. CD4+ T cell recognition activates production of specific antibodies by another type of lymphocyte called a B- lymphocyte, and also generates cytotoxic (cell killing) CD8+ lymphocytes (cellular immunity). Cytotoxic T cells recognize pieces of virus protein on infected cells, and kill the infected cells, thus stopping virus production. Once T and B cells have been exposed to a foreign antigen,



they produce memory cells that remember past encounters with the piece of viral protein and can stimulate faster, stronger immune responses to a subsequent challenge with the same virus and prevent new infection. Antibodies that bind a virus envelope or capsid protein, and block the virus from attaching to and entering a cell, are called neutralizing antibodies. The humoral immune response generated by some vaccines may provide not only long lived but immediate protection resulting from the presence of neutralizing antibodies in the blood for many years.

In acutely infected HIV individuals, a dramatic burst of viral replication occurs within a few weeks of viral exposure. In the following weeks, viral replication decreases due to a partially successful antiviral immune response. In these individuals, an antibody response can only be detected several weeks after the partial containment of viral replication. These antibodies have a weak ability to suppress viral replication because HIV has developed multiple mechanisms to protect it from antibody binding and neutralization (9, 23).

An HIV neutralizing antibody works either by binding to the envelope at the surface of the virion and inhibiting viral attachment or by binding after the virion attachment event and inhibiting the fusion/entry process (17). HIV uses a three protein envelope complex containing two types of glycoproteins, the gp120 and gp41, for fusion to its target cells. The envelope complex provides the virus with a protective shield, consisting of a loop of variable amino acid sequences and many protein bound carbohydrates (the surface of HIV envelop is covered by carbohydrates) that prevent binding of the antibody (3, 4).

Despite these defense mechanisms, several studies have found that primary virus isolates from different genetic subtypes can be neutralized by potent neutralizing antibodies (e.g. b12 and 2G12). Also, injection with neutralizing antibodies (passive immunization) can prevent establishment of chronic infection in chimpanzees inoculated with Simian Immunodeficiency Virus (SIV) (3, 7, 12). Thus, neutralizing antibodies may play an important role in vaccine design and could block infection by cell-free virus. Structure analysis of several potent neutralizing antibodies generated in the laboratory from B lymphocytes from HIV infected individuals, such as b12, 2G12, and 4E10, have demonstrated the remarkable adaptation by the antibody molecule to counter the HIV immune evasion tactics (4). Careful analysis of complexes of these antibodies and viral proteins will provide

important insight for the design of a vaccine capable of eliciting a potent humoral response against HIV.

The importance of the cellular immune response in the containment of HIV infection is supported by studies of humans and non-human primates. High levels of virus-specific CD8+ T cells are predictive of good clinical status for HIV infected individuals (16). The early suppression of HIV replication in acutely infected individuals coincides with the emergence of HIV-specific CD8+ T cell responses (11). The most conclusive experimental data on the role of cellular immune response in the control of immunodeficiency virus infection is shown in SIV infected monkeys. Monkeys depleted of CD8 lymphocytes by administration of a monoclonal anti-CD8 antibody and then infected with SIV never controlled viral replication, and died with an accelerated disease progression (20). These accumulating data suggest that an HIV vaccine that elicits high-level cell-mediated immunity may provide protection.

HIV transmission may occur by both cell-free and cell-associated viral particles. Because cell-free virus can only be eliminated through binding to neutralizing antibodies, and cell-associated virus can only be controlled by cell-mediated immune responses, a vaccine may have to elicit both types of immune responses (humoral and cell-mediated) to suppress viral replication and prevent escape of the virus from immune control (2, 23).

NOVEL APPROACHES FOR DEVELOPMENT OF AN AIDS VACCINE

Traditional strategies for vaccination are not proving useful in protecting against the HIV virus. Strategies such as live attenuated (weakened) virus, inactivated (not infectious) virus, and recombinant proteins have safely protected humans against a variety of viral infections. Because of safety issues, these strategies are not likely to be useful for vaccination against HIV.

Many viruses can be mutated so that they remain infectious, but lose their ability to cause disease (are not pathogenic). Such attenuated virus preparations have provided safe and effective protection against small pox, measles, and polio. Large deletions made in nonstructural genes of SIV resulted in elimination of early but not late pathogenic consequences of infection in adult monkeys. This triggered serious concerns about the safety of an attenuated HIV vaccine and abandonment of this approach (1, 6). Yet understanding the mechanism of pro-



tection of a live attenuated SIV may provide important insights for development of an effective vaccine. The International AIDS Vaccine Initiative (IAVI) has established a consortium to elucidate mechanisms of protection conferred by live attenuated SIV vaccine in monkeys (10).

Inactivated virus provides effective immunity in humans against influenza and polio. Inactivated virus has also provided effective immunity in monkeys against infection with SIV, but the duration of the protection was quite short (14). There is little hope that this type of approach will ultimately prove useful because inactivated viruses fail to elicit antibodies that neutralize diverse HIV isolates and cannot elicit a CTL response.

Recombinant and highly purified viral protein was proven to be efficacious and safe in the successful hepatitis B vaccine. Two recently concluded efficacy trials of VaxGen, a genetically engineered version of the HIV surface protein gp120, failed to demonstrate any protection against HIV infection (5, 14).

Because of the limitations of traditional vaccine strategies against HIV, investigators have been exploring novel approaches for the development of an effective HIV vaccine. Most of these approaches are based on a vaccine consisting of protein or DNA delivered by a live virus unable to cause disease or direct the production of more viruses. One example currently being tested is Merck's vaccine candidate, in which adenovirus, related to the cold virus, is used as a vehicle or vector both to carry HIV genes and to enhance the effectiveness of the vaccine. (See Box 1 for vaccine research at ARA. For a complete list of candidate vaccines, please visit www.iavi.org.)

All currently available infectious disease vaccines provide sterilizing immunity (complete protection) through generation of strong neutralizing antibody responses. To date, there is no immunogen capable of producing a potent neutralizing antibody against diverse HIV isolates. Most current HIV vaccine candidates are designed to stimulate strong cell-mediated immune responses to HIV. Therefore, it is unlikely that any currently available vaccine would provide complete protection against HIV infection. But, vaccines that do not attain complete protection can still be useful. Such a vaccine could prevent or limit viral replication and confer important clinical benefits in humans. In addition, several modeling studies suggest that a vaccine with 50 percent efficacy and 10 years duration of protection supplied to 65 percent of all adults could reduce HIV incidence by 25 to 60 percent, depending on the context and stage of the epidemic (21).

FUTURE DIRECTIONS

The ultimate goal of an HIV vaccine is to develop protection independent of the route of transmission, i.e. how the virus gets into the body. This is a challenging task since it is possible that the route of transmission (by sexual transmission or by contaminated blood products) will have an impact on the efficacy of a vaccine. In addition, the efficacy of a vaccine might vary depending on different types of sexual exposure (anal *versus* vaginal exposure). It is crucial to investigate the immune responses in the mucous membranes, such as those of the rectal and vaginal canals, induced by AIDS vaccine candidates in diverse populations.

BOX 1: PAST AND CURRENT HIV VACCINE TRIALS AT AIDS RESEARCH ALLIANCE

- VaxGen
- Merck trivalent adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in healthy volunteers
- Merck trivalent adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in people at low-risk of HIV infection
- Merck trivalent adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in people at high-risk of HIV infection
- Merck trivalent adenovirus serotype 5 and 6 HIV-1 gag/pol/nef vaccine in healthy volunteers



It is now well established that after infection, the primary site of SIV or HIV replication is in Gut-Associated Lymphoid Tissue (GALT), which results in a rapid, profound depletion of primary CD4+ cells. Furthermore, it has been shown that SIV infects and destroys resting memory CD4+ T cells in GALT and in other lymphoid tissues, causing considerable depletion of the CD4+ effector arm of the immune system (13, 15). A successful immunization strategy may also need to suppress HIV replication and subsequent depletion of CD4+ T cells in GALT and other mucosal compartments, through induction of a strong mucosal immune response. Therefore, efforts should be directed to the development of a HIV vaccine targeting the mucosal compartment.

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ERRATUM

Searchlight December 2005

In the article entitled, "Microbicides offer hope as HIV prevention tools that are under individual control (by Marjan Hezareh, Ph.D.)," the legend for Figure 1 should read: Estimated percent of adults (age 15-49) living with HIV who are women, by region.

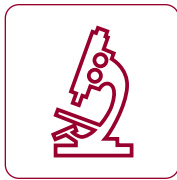
RESEARCH & CLINICAL TRIALS AT ARA

STUDY & INDICATION	DESCRIPTION	STATUS
<p>PRE-CLINICAL & BASIC RESEARCH</p> <p><i>AIDS Research Alliance (ARA)</i></p>	<p>The pre-clinical study of prostratin, an anti-HIV drug targeting viral reservoirs.</p>	<p><i>Study Ongoing</i></p>
<p>NEW INVESTIGATIONAL TREATMENT FOR HIV-ASSOCIATED NEUROPATHIC PAIN</p> <p>Pregabalin A0081066</p> <p><i>Pfizer</i></p>	<p>This trial investigates the efficacy and safety of pregabalin (<i>versus</i> placebo) in the treatment of neuropathic pain in HIV positive volunteers.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>NEW INVESTIGATIONAL TREATMENT TO DECREASE ABDOMINAL FAT ACCUMULATION</p> <p>TH9507 (Growth Hormone)</p> <p><i>Theratechnologies Inc.</i></p>	<p>This study assesses the efficacy and safety of TH9507, a human growth hormone releasing factor analog, in HIV positive volunteers with excess abdominal fat accumulation.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>NEW INVESTIGATIONAL TEST TO MEASURE RESISTANCE TO ANTI-HIV DRUGS</p> <p>HIV SpectraPoint</p> <p><i>SpectraDigital Corporation</i></p>	<p>This study investigates the efficacy of an <i>in vitro</i> diagnostic device, <i>HIV SpectraPoint</i>, in HIV positive volunteers with prior resistance to antiretroviral medications.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>INVESTIGATIONAL SUPPLEMENT FOR TREATMENT OF DIARRHEA</p> <p>Microbial Food Supplement</p> <p><i>AIDS Research Alliance (ARA)</i></p>	<p>This study investigates the safety and efficacy of <i>Bifidobacterium infantis</i> therapy in the treatment of HIV-1 associated diarrhea.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>INVESTIGATIONAL HIV-1 VACCINE</p> <p><i>Major Pharmaceutical Co.</i></p>	<p>This study investigates the safety, tolerability and efficacy of an investigational HIV-1 vaccine in healthy volunteers at <u>higher risk</u> of HIV infection.</p>	<p><i>Enrollment & Study Ongoing</i></p>

RESEARCH & CLINICAL TRIALS AT ARA

STUDY & INDICATION	DESCRIPTION	STATUS
<p>NEW INVESTIGATIONAL REGIMEN FOR HIV-POSITIVE VOLUNTEERS FAILING HAART-CONTAINING REGIMEN</p> <p>BMS A1424128</p> <p><i>Bristol-Myers Squibb</i></p>	<p>This study evaluates 150L substitution among treatment-experienced HIV positive volunteers who have failed Highly Active Antiretroviral (HAART) regimens containing Atazanavir (ATV).</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>NEW INVESTIGATIONAL ANTI-HIV DRUG</p> <p>Investigational Integrase Inhibitor</p> <p><i>Major Pharmaceutical Co.</i></p>	<p>This study compares the safety and activity of an investigational integrase inhibitor in combination regimens with 2 approved antiviral drugs, compared to a standard 3 drug combination in antiretroviral-naïve, HIV-infected volunteers.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>NEW INVESTIGATIONAL ANTI-HIV DRUG</p> <p>Investigational Integrase Inhibitor</p> <p><i>Major Pharmaceutical Co.</i></p>	<p>This study compares the safety and activity of an investigational integrase inhibitor in combination regimens with optimized background treatment, compared to optimized background therapy alone in antiretroviral-experienced, HIV-infected volunteers with documented resistance to one of the antiretroviral drugs in each class.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>NEW INVESTIGATIONAL PROTEASE INHIBITOR</p> <p>TMC114</p> <p><i>Tibotec</i></p>	<p>This study compare the efficacy, safety and tolerability of TMC114/RTV <i>versus</i> LPV/RTV in treatment-experienced HIV-1 infected volunteers.</p>	<p><i>Enrollment & Study Ongoing</i></p>
<p>INVESTIGATIONAL HIV-1 VACCINE</p> <p><i>Major Pharmaceutical Co.</i></p>	<p>This study investigates the safety, tolerability and efficacy of an investigational HIV-1 vaccine in healthy volunteers <u>at low risk of HIV infection.</u></p>	<p><i>Enrollment & Study Ongoing</i></p>

INNATE AND ACQUIRED IMMUNITY



A major function of our immune system is to provide defense from disease-causing organisms (pathogens). Over time, two broad immune response systems have evolved, providing protection with increasingly complex interactions of cells, proteins, antibodies and other molecules both within each system as well as between systems. These two broad immune responses are called innate and acquired immunity.

INNATE IMMUNITY

Most encounters with micro-organisms do not result in disease due to the activity of the innate immune system. This system¹ recognizes and responds immediately to various pathogens. The majority of microbes that manage to cross our external barriers of skin, mucus, cilia, acid or basic conditions are usually eliminated by *innate immune mechanisms*, which begin immediately, indeed within minutes, upon pathogen entry. This system is present in all members of the animal family from worms on up and consists of pre-existing defenses.

These responses are not tailored to any one pathogen. Fortunately, many pathogens share molecular structures not present in the host organism. These shared structures are called Pathogen-Associated Molecular Patterns or PAMPs. Most PAMPs are polysaccharides (linked sugar molecules) or nucleotides (genetic material) not found in host cells. Several examples are molecules present in the flagella, (the whip like structure used for movement of some bacteria), parts of the wall of gram positive bacteria (peptidoglycan), and the endotoxin of gram negative bacteria (also known as Lipopolysaccharide or LPS). The double stranded RNA genetic material of many viruses is another PAMP recognized by cells of the innate immunologic

system. To respond to these non-specific markers of pathogen invasion, the host innate immune system has developed Pattern Recognition Receptors or PRRs that recognize their complementary PAMPs. These ready-made receptors², both secreted and on the surface of immune system cells, provide a fast, broad and non-specific response to pathogen invasion, including the triggering of an inflammatory response that attracts additional cells that engulf and destroy the invading organism. PRRs may be part of larger molecules secreted into the blood and lymph fluid to coat the pathogen, making it attractive to phagocytes, the white blood cells that engulf pathogens. PRRs themselves may be secreted in saliva or blood. PRRs on the surface of some immune system cells trigger the cells to ingest the trapped pathogen or to secrete molecules (cytokines like interferon) that can begin an inflammatory response. The cells of the innate immune system include macrophages (widely distributed throughout all tissues), blood monocytes, granulocytes (basophil, eosinophils, neutrophils), and $\gamma\delta$ T-cells³ Only if the inflammatory process is unsuccessful in eliminating the pathogen will the adaptive immune system be activated, a process which requires several days to produce specifically directed effector cells that can produce antibodies or kill cells.

The genes that encode the innate responses' PRRs are derived directly from the host DNA. Because the innate immune system has no "memory" of its interaction with the pathogen, if the identical pathogen is encountered again, the same response, rather than a quicker and augmented response, is elicited.

ACQUIRED IMMUNITY

The acquired immune system is present in vertebrate (skeletonized) and higher animals and represents a pathogen-specific and tailored response to infection. The response of the acquired immune response is slow, taking days to weeks to develop. A key process in the generation

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of acquired immunity is the processing and presentation of antigens, the specific pieces of pathogens recognized by the acquired immune system. This concept must be understood in order to understand acquired immunity.

ANTIGEN PROCESSING AND PRESENTATION

To get the acquired immune response started, the pathogen must encounter a docking protein, a receptor, with a fairly narrow range of specificity. As entire pathogens are usually too large for the recognition process, they must be broken down into manageable pieces. The initial step is called antigen processing and presentation. In brief, certain cells are “experts” in breaking down pathogen molecules (usually proteins) into small pieces and displaying them on their surface in combination with other immune molecules. The several types of professional cells that do the processing and presenting are known collectively as “antigen presenting cells,” or APCs. The combination of the presented antigen with the immune molecule signals the immune system that pathogens are present. The cells that dock with the antigen loaded APCs are triggered to increase their number and become equipped to fight the pathogen. Many of the APCs are the cells of the innate immune system, so that the two systems interact to support the function of the acquired immune system.

The primary cells involved in acquired immunity are B cells and T-cells (both T-helper and cytolytic, cell killing cells). The B cells, T helper and T cytolytic cells, recognize different kinds of substances as foreign antigens and antigen presentation to each is different.

B-CELLS

B-cells produce immunoglobulins (antibodies) and are simpler to understand. B cell receptors are the same immunoglobulins that the cells are genetically programmed to produce and secrete, but are attached to the surface of the cell. Recognition of the foreign antigen by the receptor causes the B-cell population to increase in number and change into large lymphoblasts that then become either plasma cells (antibody factories secreting large numbers of antibodies), or small, long lasting memory cells which are able to provide a more rapid and robust response to future infections by the same pathogen. It is the “memory” function that helps distinguish innate from acquired memory. Along the way from B-cells with recep-

tors on their surface, to more mature plasma cells, mutations⁴ in the DNA instructions for the antibody structure allow the response to “mature” to produce antibodies that are better at binding to the foreign antigens. Thus, the antibodies can gain in specificity. B-cells produce antibodies against soluble antigens such as proteins, polysaccharides (the large carbohydrates that coat many pathogens), nucleic acids, some lipids, and occasionally, and usually detrimentally, small chemicals that can attach to host proteins and lead to allergic reactions.

T-CELLS

T-cells usually recognize peptides, small pieces of proteins. A single protein from a pathogen will become, after fragmentation, multiple small peptide fragments that can have overlapping sections. This increases the chance that a T-cell will recognize some part of the protein and respond.

But T-cells “recognize” antigens bound to the APC in a pocket of one of two classes of host molecules, termed Major Histocompatibility (histo=tissue) Complex (MHC) molecules because they are part of the “self/non-self” recognition system of the immune system. The class of the MHC presenting the antigen and the type of T-cell involved are tied to the types of pathogens targeted. Host cells infected with pathogens, such as viruses growing inside them, must be destroyed to prevent viral production. Cells which display virus antigens on their class I MHC molecules set up these virus-producing cells to be destroyed by cytolytic T-cells. Bacteria usually grow outside of host cells. Bacteria are taken up by APCs that can display the processed antigens on class II MCH molecules. This attracts the helper T-cells that once activated, assist the antibody producing B-cells to produce blood antibodies against the bacteria.

RELEVANCE TO VACCINES

The purpose of a vaccine is to set up or prime the acquired immune system to respond rapidly with an amplified response from its “memory” rather than from scratch. If the innate system cannot contain the pathogen⁵, or if there is unacceptable disease or risk of death (as in many childhood diseases), or if the acquired immune system is needed for reinforcement of the innate system and must be primed and ready to do its job, a vaccine (prevention rather than treatment) is the preferred method of decreasing morbidity and mortality. The acquired immune system is the traditional target for vaccines since



only this system has a memory function, allowing it to be primed for more rapid response. In the search for an HIV vaccine, we may need to consider how the cells and proteins of both innate and acquired immune systems reinforce and interact with one another. Manipulating the innate system may have a role in designing a more effective vaccine candidate to which the acquired immune system can respond.

FOOTNOTES

1. Innate immunity also encompasses such protections from infection such as the skin barrier, mucus production in nasal and bronchial passages, stomach acidity, the cilia in the lungs that constantly sweep mucus upwards from the lung bronchi, and various anti-microbial and antiviral compounds secreted in blood, saliva, tears and other secretions. In addition, there are natural antibiotics such as lysozyme, anti-microbial peptides, and defensins that work via other mechanisms. Here, we are using innate immunity to refer primarily to blood cells, effectors, and other factors commonly thought of as immunologically based.

2. Among the PRRs identified are the toll-like receptor family (at least 9 members identified so far), pentraxins, and mannose binding lectins.
3. The science of Gamma-Delta T-cells is rapidly evolving with recognition of an expanded role of these cells as innate cells, but also antigen-presenting cells working with the acquired immune system.
4. The production in the body of all the potential antibodies and specific T-helper and cytolytic T-cells would require DNA that exceeds by far the DNA information for the entire organism. The ability to produce the needed extensive repertoire of antibodies and specific cells is due to an elegant and effective system of systematically producing mutations and intentional cutting and splicing variations of the DNA that codes for the T-cell receptor. Thus, as cell populations expand, these immunological cells can produce subtle variations on their originally programmed T-cell receptors. Those that match a pathogen best are selected for expansion. After the pathogen is vanquished, some of these cells remain as long-lived memory cells, ready to again expand in the face of the same or similar pathogen. A discussion of this elegant process is well beyond the scope of this scientific concept.
5. Some pathogens easily escape the innate immune system. Among these are the bacteria that cause gas gangrene and tetanus, both from the clostridium family of bacteria.



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CARY STEVENS JOINS BOARD OF DIRECTORS



The ARA Board of Directors is pleased to welcome its newest member, architect Cary Stevens. Board Chair Bruce W. Cochran, Esq., who worked with Cary last year on the ArtSeen Executive Committee, said, "Cary's enthusiasm for ArtSeen helped in making the event such a wonderful success. The talent and new spheres of influence that he brings to ARA will help us in our

quest for pushing for better HIV treatments."

Cary, along with his late companion Edward Judd, began their longtime support of AIDS Research Alliance in connection with their love of the arts. They were early and generous supporters of *Focus on AIDS*, a photography benefit that ARA co-produced from 1987-2002. It was a natural leap from supporting ArtSeen to supporting the organization. Cary's volunteer work afforded him the opportunity to work closely with the agency. "Through my involvement, I've learned how this small organization

has a large impact on the way HIV research is being conducted. Having survived a number of personal losses to AIDS, I appreciate how important it is to advance the scientific understanding of HIV."

Cary is a graduate of UCLA and Cal Poly Pomona, where he earned a Master of Architecture Degree, graduating with honors. Since 1987, he has been a partner in the Architectural firm Landa Stevens Partnership, whose projects include single family residential and commercial projects primarily in Southern California, from Santa Barbara to the Palms Springs area. In addition, the firm has completed projects in the Bay area, New York, Connecticut, and the Bahamas. Landa Stevens has many celebrity clients, has been featured in dozens of publications, and has received numerous design awards. Currently, Cary and his business partner, Sharon Landa, are developing independent, single-family custom residential projects.

Cary, a second-generation native of Los Angeles, currently shares his life with physician Allen "Buddy" Green. "Both Buddy and I welcome this opportunity that I have to assist AIDS Research Alliance reach its goal of ending this epidemic. My new position on the board will give me the opportunity to make a difference."



COMMUNITY FORUM: ARA OUTREACHES INTO CYBERSPACE



ARA announces the launch of our new Internet recruitment strategy for the Merck preventative HIV vaccine study (STEP Study) for high risk study volunteers. After other STEP Study sites (Boston, San Francisco,

Seattle) reported great success with their own Internet strategies (approximately 20% of all study volunteers in Seattle contacted the clinic due to Internet advertising), ARA decided to develop its own.

Traditionally, ARA has sent study announcements to patients on our mailing list, posted fliers at AIDS Service Organizations (ASOs), staffed booths at gay pride and public health events, given community presentations, and advertised in local magazines in order to recruit study volunteers and to educate the community. These methods have worked quite well, resulting in ARA's reputation of being a top study enroller. Indeed, ARA was the 3rd highest enroller for the AIDS VAX vaccine study, the first Phase III vaccine study, and ARA was the top enroller for the more recent Capsaicin neuropathy study.

But we recognize that the Internet has become the most important method of communication of our time.

BY MICHELLE SIMEK & MARTELL RANDOLPH

Michelle Simek is the Community Educator at AIDS Research Alliance and is in charge of the Outreach Department. Ms. Simek, a Certified HIV Counselor and AIDS Treatment Advocate, serves on the Board of Directors of Women at Risk, and represents AIDS Research Alliance on the Women's Caucus on HIV/AIDS Los Angeles County.

Martell Randolph is a Recruitment Specialist at AIDS Research Alliance. She also works with the California Microbicides Initiative (CAMI), serves as a member of the UCLA Care Center's Community Advisory Board, the AIDS Treatment Activist Coalition (ATAC) and its Drug Development Committee (DDC), and the Women's Caucus on HIV/AIDS Los Angeles County.

Thus, ARA has begun conducting Internet outreach for the STEP Study, a study of an experimental HIV vaccine for high risk volunteers, as well as continuing our traditional outreach methods. ARA's new Internet Outreach Program, overseen by Simek, seeks to educate the commu-



nity about the potential that HIV vaccines hold as well as encourage volunteers to become involved in HIV vaccine research. This new strategy provides direct access to populations at high risk of HIV infection - men who have sex with men (MSM).

ARA was fortunate to find Ryan Murphy, a pre-medical student and a committed volunteer. Ryan wanted to volunteer for ARA because of his concern about rising HIV infection rates and his dedication to ending the AIDS epidemic. As ARA's new Chat Room Intern, Ryan has already logged 120 hours on the project. Several nights a week, he logs on to popular MSM websites and disseminates information about HIV, ARA's work, the STEP study, and he refers HIV- men who are interested in vaccine studies to the clinic for screening. He also receives inquiries from HIV+ men who are looking for AIDS treatment trials and refers them to ARA's clinic, where we are enrolling for HIV/AIDS treatment trials. Overall, community feedback about ARA's new outreach intervention has been positive, says Ryan. "I get a lot of good comments from men in the community who are happy to see ARA's presence on these [hookup] websites." Currently, he is logging on to www.manhunt.net, www.craigslist.org, and www.adam4adam.com. So far, this program has generated over 300 web inquiries. ARA appreciates Ryan's contribution and dedication on behalf of The Internet Outreach Program. ARA also thanks Shaun Lord, Health Liaison at www.manhunt.net, for generously donating both a web banner and a free web account for this program.

In order to fully staff this program, ARA is in need of a second Chat Room Intern. If you are interested in volunteering, please contact Michelle Simek at msimek@aidsresearch.org, or at 310/358-2423.

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REVOLUTIONS: CYCLING FOR RESEARCH



On July 22, 2006, AIDS Research Alliance (ARA) and Crunch Fitness join forces to host the second annual *Revolutions: The 2006 Cycling Event*. With the help of our sponsors, ARA will turn a fun and exciting day into a powerful response to the HIV/AIDS pandemic. Every dollar raised will go to HIV/AIDS research and education.

Celebrity Spin® Instructors will lead *Revolutions* participants at Crunch Fitness, a world-renowned gym in Southern California. There will be four outdoor cycling classes (30 minutes each), with live DJs spinning music and sweeping views of the Sunset Strip and Hollywood Hills inspiring the riders to “go the distance.” Participants have the option of signing up for a single class or as many as they can handle! Friends and family, as well as members of the media, will be on hand to cheer on the *Revolutions* riders. Our team of volunteers and Sponsors will make sure that enough food and drinks will be on hand throughout the event.

By signing up to participate in this thrilling event, each *Revolutions* rider will raise \$250 to help fund much needed AIDS research projects. There is a \$25 registration fee (this fee counts toward the fundraising goal). As an added bonus, participants will receive incentive gifts,



including gift bags and opportunities to win fantastic prizes that have been provided by sponsors such as Best Western and Walt Disney Parks and Resorts. The more money a participant raises, the more opportunities there are to win!

It is not too late to be a part of this exciting event. We are still recruiting riders, and it does not matter if you spend 5 days a week in the gym or feel out of shape or are unsure how to fundraise. As long as you have a desire to make a difference in the lives of people living with HIV/AIDS, we will make sure that you are prepared.

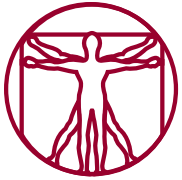
We hope you will become a part of our team. There are many heroes living in our community who have powerful stories to share about survival and courage. Join them, share your own story, make some new life-long friends, and contribute to our search for a cure.

To find out how to become a rider or volunteer, contact Jessica Patterson at 310-358-2423, or email her at jjpatterson@aidsresearch.org.



Photos provided by Crunch Fitness

ARA'S INSTITUTIONAL REVIEW BOARD: PROTECTING THE RIGHTS OF CLINICAL TRIAL PARTICIPANTS



ARA's Institutional Review Board (IRB) is a panel of outside experts and community members that ensures that every study participant who volunteers for an experimental study is protected by the standards set by the United States Government, the International Conference on Harmonization (ICH) Guideline; and the Declaration of Helsinki.

As ethical overseers, this volunteer panel is a critical – and legally mandated – part of our research program. IRB members review study protocols and the required informed consent forms to determine whether there is full disclosure to study participants and that the process for each study is ethical. They look critically at such issues as whether the potential risks of a study exceed the potential benefits; whether clinical investigators use appropriate research designs; and whether they are vigilant in protecting the right of participants, including their freedom to withdraw from a study at any time.

When the Pure Food and Drug Act was passed in 1906, there were no uniform rules regulating the ethical use of humans in research. In December 1946, an American military tribunal held criminal proceedings against German physicians for forcibly conducting medical experiments on thousands of concentration camp prisoners. The outcome of that trial, the Nuremberg Code, established many of the basic principles governing the ethical conduct of research involving humans. It holds that it is “absolutely essential”



D. Mark Arnold, R.N.

to have the voluntary consent of the human subject undergoing any experimentation.

Unfortunately, the Nuremberg Code was sometimes ignored. A particularly shocking example is the Tuskegee Syphilis Experiment (1932-1972) in the state of Alabama that enrolled four hundred low-income African-American males diagnosed with syphilis to be monitored for 40 years, to determine the natural progression of the disease. To ensure that the men were denied treatment – an increasingly difficult task given the discovery and widespread use of penicillin to cure the disease in 1943 – the men's names were disclosed to local physicians, draft board doctors and Protection of Human Subjects (PHS) venereal disease eradication programs, all of whom did their best to make sure none of the men received antibiotic treatment. By the end of the experiment, 28 of the men had died directly of syphilis, 100 were dead of related complications, 40 of their wives had been infected, and 19 of their children had been born with congenital syphilis.

In 1974, the U.S. Department of Health, Education, and Welfare, stung by public outcry when a journalist exposed the Tuskegee experiment, raised to regulatory status the NIH “Policies for the Protection of Human Subjects.” Among other things, the new regulation required that an independent committee – an IRB – evaluate all human research studies carried out at any institution to protect the rights of human subjects. ARA could not conduct its research program without its IRB. They give their time freely, without compensation, other than the personal satisfaction of knowing that they are a part of the search for a cure for this disease. We salute all of our IRB members, with special thanks to Dr. Stephen L. Fefferman, who is stepping down as IRB Chair after tirelessly serving in that capacity since 1998. We also welcome the two newest members of ARA's IRB, D. Mark Arnold, R.N. and Richard Lapin, M.D.

Mark, a Registered Nurse, currently works in the Intensive Care Unit at Cedars-Sinai Hospital. At Cedars, as well as Glendale Memorial Hospital, he spent a number of

continued on next page



Richard Lapin, M.D.

years specializing in HIV care, including caring for HIV patients diagnosed with psychiatric disorders. Mark has volunteered for numerous community projects, including coordinating care for “Strength for the Journey,” a yearly summer retreat for under-served HIV/AIDS patients. Mark states, “the research that ARA is doing is very exciting, and this will be a great chance for me to learn more about what is available for our patients and what is coming in the future.”

Richard is a Board-Certified Hospitalist Physician, currently working at the UCLA Center for Health Sciences. Richard received his Master of Public Health in Epidemiology degree from UCLA. After a number of years in the field, he felt that he would have a greater impact on the AIDS crisis as a physician. He returned to school to earn a Doctorate in Medicine from the Albert Einstein College of Medicine, Yeshiva University. A native of Baltimore, Richard has been treating HIV+ patients since the late '90s. His background in HIV care, HIV epidemiology, racial differences in the use of HIV therapies, and treatment algorithms will be invaluable to the IRB's mission.

ARA's new IRB chair, Dr. Seymour Young, stated “Mark and Richard both bring a wealth of knowledge and a deep sense of compassion to the IRB. We are lucky to have them join our mission to safeguard the health of clinical trial participants.”



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