Industry Investment in HIV Vaccine Research

An Investigation by the AIDS Vaccine Advocacy Coalition

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AVAC Is

The AIDS Vaccine Advocacy Coalition (AVAC) was founded in December 1995 to advocate for the development of a safe, effective, and accessible HIV vaccine. It seeks to promote increased funding and investment in HIV vaccine research by government agencies, private industry and non-governmental organizations; to identify barriers to the development of a vaccine; and to increase public awareness about the need for a well funded, coordinated HIV vaccine research program. It seeks to promote increased HIV vaccine advocacy efforts by community-based organizations and increased awareness about HIV vaccine development among AIDS-affected communities. It is committed to the principle that funds for HIV vaccine research are not to be taken from basic HIV research, drug development or prevention efforts.

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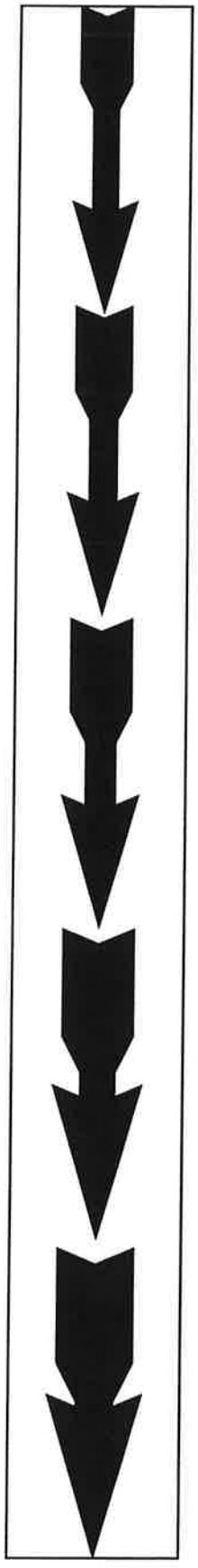

Five Steps to a Vaccine for HIV

Vaccine Research: Scientists working in university, government and some pharmaceutical/biotech company labs study immune response in humans and animals, and experiment with a variety of traditional and new approaches for stimulating immune responses that might confer protection from HIV. This conceptual research focuses on answering scientific questions and identifying approaches that could be used to design a candidate vaccine (in contrast to "basic" research, which seeks to answer fundamental scientific questions without regard to a potential application).

Product Development: Pharmaceutical and biotech companies construct experimental vaccines and adjuvants (substances that enhance the immunogenic properties of a vaccine) which can then be tested in the laboratory and in animals in order to predict and improve their safety and potential immunogenicity in humans. (Immunogenicity is the product's ability to elicit immune responses.) Results from earlier human trials can also be used to develop improved products. Though government funded researchers traditionally focus on more fundamental research, public health agencies could choose to fund or do product development

Human (Clinical) Trials: Many different candidate HIV vaccines are already in initial human trials.

Phase I trials involve a small number of (usually low risk) volunteers and are designed to identify a product's safety and immunogenicity, and to set appropriate dosage and schedule of administration. If deemed successful, larger numbers of low and higher risk volunteers are recruited for Phase II trials, which provide more extensive testing of safety and immunogenicity.

Phase III trials involve thousands of high risk volunteers and are the only trials large enough to test the actual efficacy of a vaccine (its effectiveness in preventing infection or disease). Lately, Intermediate Sized Trials have been proposed which involve smaller numbers of volunteers than Phase III trials but are large enough to identify partial efficacy before undertaking a full scale efficacy trial. No HIV vaccine candidate has yet entered an Intermediate or Phase III trial.

Licensing: If an efficacy trial clearly demonstrates the safety and efficacy of a vaccine, the manufacturer can apply to the Food and Drug Administration (FDA) for licensing of the product for sale in the United States. The World Health Organization and each country would also consider approving the product for distribution.

Distribution: Cost, portability, ease of administration and access to health care are issues that will effect who ultimately receives an approved HIV vaccine. These important issues should be considered and resolved while a potentially licensable vaccine is still in testing.

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Executive Summary

A safe, effective and affordable vaccine is the best hope to bring the AIDS epidemic under control. There is widespread belief among scientists that development of such a vaccine is possible. Yet, fifteen years into the epidemic, the AIDS vaccine research effort faces extraordinary hurdles. These include: inadequate funding, insufficient focus on the scientific roadblocks, lagging industry investment, few candidate vaccines in the pipeline, little urgency among affected communities and a lack of leadership in the overall effort.

A series of interviews with industry scientists and leaders were conducted by the community-based AIDS Vaccine Advocacy Coalition (AVAC). In total, researchers and leaders from 23 companies with active or once-active HIV vaccine programs were interviewed. The interviews, conducted in confidence, attempted to examine the major incentives and disincentives to private investment in HIV vaccine development.

Overall, according to the industry scientists, the current HIV vaccine effort is a patchwork of efforts, not the aggressive, well-funded and coordinated international strategy that is required. Though the current picture is discouraging, it need not remain so. A number of particularly urgent needs were identified. These include: providing more resources for HIV vaccine research, focusing on the key scientific roadblocks, actively encouraging investment by large pharmaceutical companies, insuring effective and accountable leadership in the HIV vaccine effort, and increasing commitment to the HIV vaccine effort by community-based organizations.

State of Industry Research and Development

On a worldwide basis, private industry investment in HIV vaccine development is extremely limited. Biotech and pharmaceutical company interest in HIV vaccine development is extremely low. Private financing favors surer investments. The U.S. government, which carries the weight of facilitating and financing the worldwide effort, has centered its research in one division of one institute of the NIH. The Executive Branch and Congress provide relatively little support. Opportunities for expanded private/public partnerships and inter-company collaboration are being overlooked. In terms of the number of companies with active programs, the actual funds and staff being devoted, and the number of approaches being pursued, the overall picture is quite discouraging. Only a handful of companies have reasonably secure programs of any size.

In fact, of the five leading global vaccine manufacturers, only two (Pasteur-Merieux-Connaught and Chiron) have broad based HIV vaccine programs that are pursuing a number of approaches. Merck & Co. has what appears to be a substantial program, but, after earlier discouragement, it is currently focused on only a single approach. The remaining two companies (SmithKline Beecham and Wyeth Lederle) have insignificant HIV vaccine programs. The smaller biotech companies have programs that are largely limited to a single scientific approach. While these programs must be actively supported, there is no reason to believe they will continue if the approach being pursued proves unsuccessful. In short, very few companies are making a sustained, comprehensive investment in HIV vaccine development.

To date, industry investment has focused largely on the subunit approach – gp160, gp120 or other HIV proteins. Other approaches being pursued include DNA vaccines (also known genetic immunization), live vector strategies and peptide vaccines. Overall, HIV DNA vaccines appear to be the single approach which has attracted significant private investment capital. A few HIV vaccine approaches are being studied in combination. One notable example is the ALVAC canary pox vaccine, manufactured by Pasteur-Merieux Connaught, used in combination with a gp120 vaccine, produced by Chiron, as a boost. Unfortunately, this NIAID-facilitated collaborative effort is the exception rather than the rule.

Obstacles to Private Sector Investment

Questions about the scientific feasibility of making an HIV vaccine, given current knowledge, emerged as by far the most important reason for limited private sector investment in the field. Defining and addressing such questions must be a responsibility of both government and industry. In addition to its traditional role as funder of exploratory science, government must support research that seeks to answer specific scientific questions which, when answered, will nourish private sector efforts. Other commonly noted reasons for limited industry involvement include liability concerns and the opportunity costs of HIV vaccine research compared to development of other products with a shorter and more certain development timeline. Interestingly, smaller biotech companies viewed liability concerns as a significantly greater worry than large pharmaceutical companies. The threat of price controls and concerns about market size did not emerge as major constraints.

Incentives to Private Sector Investment

Direct funding from government to stimulate HIV vaccine research efforts was the most widely supported potential strategy to increase private sector scientific research. Faced with difficulty in obtaining private financing and significant scientific uncertainty, it is not surprising that direct contracting from government is attractive to industry. This idea has appeal because it would allow government to identify gaps in research and strategically fill those gaps by utilizing private sector expertise as well as investigator initiated research. It is also a model which has some precedent in the United States and abroad.

Other potential government actions receiving broad support from industry leaders and researchers were: tax deductions and credits for HIV vaccine development costs, better coordination of research efforts, assistance in securing animal models, and guaranteed purchase of approved vaccines. The need for leadership in the overall HIV vaccine research effort was consistently cited by industry researchers. An increase in the priority given the development of an HIV vaccine by government and the public at large was proposed as a potential influence on internal company funding decisions, even absent other incentives.

This report and the recommendations that follow are an attempt to fully engage private sector resources in the effort to develop an HIV vaccine. Working in partnership, industry, government, community based organizations, and the public have the potential here and now to save literally tens of millions of lives.

Recommendations

The essential ingredients to develop an HIV vaccine already exist: scientific expertise, private and public investment capability, research infrastructure, thousands of individuals interested in participating in trials, and a history of developing and delivering vaccines which can halt devastating epidemics. What is missing in this effort is the vision, the leadership and the commitment of governmental, corporate and institutional resources.

To be sure, development of an HIV vaccine faces a complex set of challenges. There is no simple solution. We therefore propose a package of recommendations directed at the most important stakeholders: the U.S. government, private industry, and the public at large. Each recommendation addresses a different aspect of the problem; together, they seek to unite scattered efforts into a well-funded, well-focused, and effective effort. These recommendations are designed to be a starting point, to be built upon by other organizations committed to the development of a safe, effective, and affordable HIV vaccine.

Five Key Recommendations

Five key steps would lay the foundation for making significant advances in HIV vaccine research and development. They are:

- **Increased government funding for HIV vaccine research:** The President and Congress should significantly increase funding to the National Institutes of Health (NIH) for HIV vaccine research. These funds should be managed by the Office of AIDS Research. The NIH should pursue multiple scientific approaches in HIV vaccine research. NIH leadership must be accountable for effectively advancing efforts in AIDS vaccine research. If NIH does not take up this critically important responsibility within a fixed period of time, authority and funds for the task should be placed elsewhere.

- **Targeted scientific research to stimulate industry investment:** Additional funds should be targeted to answer key scientific questions which now act as impediments to private sector investment in HIV vaccine development. Investigator-initiated research must also be encouraged by developing a peer review mechanism with the broad expertise and continuity to evaluate vaccine related proposals. Direct funding and other incentives to public and private researchers must be used to fill gaps in research.

- **Expanded commitment by large pharmaceutical companies:** Large pharmaceutical companies, particularly those with extensive vaccine programs, must significantly expand their commitment to HIV vaccine development. The commitment of substantial corporate resources and personnel by specific companies was largely responsible for recent advances in HIV treatment. Similar commitments are now needed in HIV vaccine development. Leading vaccine manufacturers, such as Merck & Co., SmithKline Beecham, and Wyeth-Lederle must recognize their responsibility to worldwide public health and make the development of a safe and effective HIV vaccine a corporate priority at the highest level.

- **Increased commitment by affected communities:** Community-based and national AIDS organizations must commit themselves to assigning staff to advocate for HIV vaccine research. HIV vaccines must become a central part of the AIDS advocacy agenda.

- **Expanded public leadership:** The President must make the development of a safe, effective and inexpensive vaccine by the year 2007 a national priority. The President should meet with reputable leaders in the pharmaceutical and biotech industries to urge them to increase their investment in HIV vaccine development and assure the removal of roadblocks to such research. The Vice-President should be responsible for implementing and monitoring specific actions.

Additional Recommendations

The remaining recommendations fall into four categories: government, industry, affected communities/American public, and collaborative efforts.

To Government:

- **Enact liability legislation:** The President and Congress should work together to develop legislation insuring that concerns about liability claims do not inhibit investment by private industry in HIV vaccine development. Such legislation must balance the needs of industry and those who are vaccinated.

- **Promptly Implement OAR recommendations:** The NIH Office of AIDS Research recommended in the Levine Committee Report that "a restructured trans-NIH vaccine research effort ... with leadership and oversight provided by distinguished, non-government scientists" be established. This must be implemented without delay.

- **Encourage inter-company collaboration and recognize existing efforts:** Companies that are presently investing in HIV vaccine development, despite the limited investment outlook, need to be publicly recognized and supported. The NIH must work closely with these companies to provide support whenever appropriate. Companies must be encouraged to cooperate and work together to develop combinations of approaches to HIV vaccine development. Government is uniquely positioned to bring together the research and development efforts of companies, research institutions and individual scientists.

- **Increase assistance in securing animal models:** The NIH must undertake additional efforts to insure that industry scientists are able to obtain sufficient numbers of appropriate animals to conduct ongoing research.

To Industry:

- **Increase support for vaccine research:** Leading pharmaceutical and biotech companies should provide support for HIV vaccine research. Each pharmaceutical and biotechnology company with an approved HIV-related therapy or diagnostic product should either invest in its own HIV vaccine development program, another company's vaccine program, or dedicate a percentage of HIV-AIDS revenues to independent efforts such as those of the International AIDS Vaccine Initiative (IAVI).

- **Maintain commitment to HIV treatment:** Industry can use its resources and expertise to develop and market preventive as well as therapeutic approaches to fighting the HIV pandemic. The two approaches must go hand in hand.

- **Share industry expertise:** Top company scientists involved in all aspects of HIV and vaccine research, particularly pathogenesis, immunology, adjuvants, assay development and animal studies should be encouraged to work with other researchers involved in HIV vaccine development. Companies should consider lending individual scientists on a part-time or temporary basis to cooperative HIV vaccine research efforts.

To Affected Communities and the American Public:

- **Increase awareness of and commitment to HIV vaccine development:** The American public must be brought into the effort to develop a safe and effective HIV vaccine. A broad-based campaign must be undertaken by community-based organizations working in concert with elected officials to make the development of an HIV vaccine a national and international priority.

To Stakeholders Working in Collaboration:

- **Create investment incentives for HIV vaccine research:** Working together, the financial investment community, pharmaceutical and biotech companies, insurance and healthcare companies, research institutions, community advocates, and government officials must develop alternative vehicles to generate resources for HIV vaccine research and development. Options include tax-free or tax-deferred investment funds for HIV vaccine development, government-backed bond offerings, or specifically earmarked revenues from consumer product companies or charities.

- **Assure access to approved vaccines:** Public support for HIV vaccine development must not become a giveaway to industry. When public funds are allocated for research, development and clinical trials conducted by private companies, assured access to the vaccines produced from such research should be addressed in the funding negotiations.

Key Principles

Finally, two key principles are essential to ensuring an ethical, sustainable and ultimately successful HIV vaccine research effort.

- **Maintain aggressive research effort in HIV prevention and treatment:** While new funding for HIV vaccine research is necessary, it must never come at the expense of research into HIV treatments or behavioral risk reduction efforts, including biomedical interventions to reduce perinatal transmission and microbicide research. Government's role in supporting basic HIV research must continue and not be compromised.

- **Address international access issues:** The governments of the U.S. and of other nations, international assistance agencies, and industry should begin laying the groundwork for securing broad international access to an HIV vaccine, once available, by establishing an advisory structure to address liscencing and access issues.

Together, these recommendations can help to harness private and public sector resources and expertise to meet the urgent need for an HIV vaccine. As with any public project, partnership, planning, coordination, and leadership are critical. Working in collaboration, industry, government, affected communities, and the public have the potential here and now to save literally tens of millions of lives.

Introduction

It is customary to begin discussions of the need for an HIV vaccine with a recapitulation of the latest epidemiological horrors. In the twelve years since the virus was first identified, the epidemic has shifted, spread, become a full international pandemic and decimated populations in many parts of the world.

Still, there are some reasons to be hopeful. Dramatic advances in HIV treatment, using powerful new combinations of therapies, have been reported. Research has demonstrated that AZT can significantly reduce HIV transmission to newborns. And novel health intervention programs appear to have reduced the rate of new infections in countries such as Thailand.

Nevertheless, the need for an HIV vaccine has never been greater. Worldwide, over five million men, women and children have already died from HIV disease. Already, over 21 million people have been infected with the virus, more than 90 percent of these in developing countries. An additional 8,000 people are infected every day. By the year 2000, an estimated 40 million people will be infected with HIV. Because of the epidemic, average life expectancy is declining not only throughout Africa, but also, for the first time this century, among men in New York City. Among gay men in San Francisco, life expectancies are 45 years. In the United States, 40,000 to 80,000 people will be infected every year, one in four of whom are 22 years old or younger. Moreover, even the well-publicized advances in AIDS treatment require expensive therapies which are unavailable to most of the world's HIV-infected individuals, and also to some in the U.S..

The original urgency attending the development of an HIV vaccine dissipated long ago. Minimal resources are now being invested in HIV vaccine research. The Rockefeller Foundation estimates that, in 1993, a total of only $160 million was spent worldwide on all HIV vaccine research and development. The NIH, the world's leading funder of biomedical research, reports that it spent $111 million on HIV vaccine research in 1994. Yet, a closer look by the AIDS Research Program Evaluation Working Group (the Levine Committee) discovered that much less, about $89 million, was actually spent. Even this figure is inflated, since much of the funding goes to the maintenance of cohort studies. In reality, less than $40 million per year is likely being spent on HIV vaccine-related research by the NIH.

Private industry possesses much of the expertise needed to develop and produce vaccines. In fact, few believe that an HIV vaccine can be produced without the active involvement of industry. It is therefore extremely troubling that only a handful of companies are actively attempting to develop an HIV vaccine. A number of the world's large vaccine manufacturers invest very little to HIV vaccine development. In evaluating current HIV vaccine research efforts, the Levine Committee warned that

> *"Without a strong stimulus from NIH that includes much needed basic information, the waning private sector interest in an HIV vaccine may vanish altogether."*

One result of this limited investment of resources: there are few candidate vaccines in the pipeline. While 268 new therapies have received FDA approval to enter clinical trials for HIV or HIV- related conditions, only 17 HIV vaccines have reached such a stage. The NIH Trials-A data-

base includes 118 trials sponsored by either government agencies or industry. Of these, only 9 were preventive vaccine trials.

The lack of interest in HIV vaccine research extends well beyond government and industry. AIDS organizations have, at this point, done little in the area. Very few of these groups have even placed vaccines on their lobbying agenda.

Ironically, while government, industry and affected communities continue to focus little attention on HIV vaccine research, there is growing conviction among scientists that a vaccine is possible. But according to our interviews of industry researchers and leaders, the research pathways to an HIV vaccine are not clear at this time. In other words, the scientific optimism that currently exists has yet to be translated into a commitment of research funds and investment capital.

Few believe that an HIV vaccine can be developed without the active involvement and substantial investment of private industry. What is needed to vitalize and coordinate public and private sector expertise to meet the growing urgency for an HIV vaccine? Who is investing in vaccine research and who is not? Why, and why not?

This report is an assessment — based on confidential interviews with industry scientists and leaders — of major incentives and disincentives to private investment in HIV vaccine research. In total, researchers and leaders of 23 companies with active or once-active HIV vaccine programs were interviewed. The report also provides industry perspectives on the various steps that have been proposed for government action to remove impediments to HIV vaccine development. In addition, a concise, detailed summary of current HIV vaccine research programs at seventeen pharmaceutical and biotech companies in the United States, Canada, and Europe is included.

We began this study with the intent of determining the incentives and disincentives to private sector investment in this field. We discovered that some answers were quite clear and many more were not so simple. We also discovered a great deal of passion and commitment among the researchers we spoke with, particularly at companies where HIV vaccine development is a priority. Unfortunately, at most companies, priorities lie elsewhere.

We believe that our recommended actions can improve the current investment environment and significantly advance the overall HIV vaccine effort. In this way, the dire epidemiological predictions included in so many of these reports may yet be proven wrong.

AIDS Vaccine Advocacy Coalition

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I. SURVEY BACKGROUND

A. Related Efforts on HIV Vaccines

We began with a number of assumptions and theories about obstacles to industry involvement that have currency in the field: liability risk, market failure, marketing uncertainties, large research and development costs with uncertain timelines, limited funding sources, and questionable scientific feasibility. Some or all of these have been attributed as reasons for companies leaving or not entering the field. A number of other efforts have examined these issues. Listed below are some noteworthy examples:

- In the fallout from the 1994 decision not to put gp120 vaccines into field trials in the U.S., **NIAID's Division of AIDS** has concluded that industry needs assurance that there are predetermined scientific milestones that will be the standard for each vaccine to advance into government supported efficacy trials.

- The **Congressional Office of Technology Assessment** completed a study, *Adverse Reactions to HIV Vaccines: Medical, Ethical, and Legal Issues*, as background for legislation that would protect and encourage vaccine developers *(see below)*.

- **Representative Pete Stark** of California drafted legislation in 1992 for government to set up a liability fund like the Children's Vaccine Initiative to address liability concerns.

- The **International AIDS Vaccine Initiative (IAVI)**, sponsored by The Rockefeller Foundation, has been launched to support targeted research directed at scientific areas that have not received attention, are riskier than industry has undertaken so far and that are directed toward the developing world. IAVI's mission is also to encourage the creation of "a more enabling environment for private investment in HIV vaccine development."

- The **NIH Office of AIDS Research** proposed appointing a panel of distinguished outside scientists to oversee NIH HIV vaccine research with an eye toward a more open, focused, and balanced program throughout the National Institutes of Health.

- **Vice President Albert Gore** met with the heads of pharmaceutical and biotech companies in 1996 to identify ways to facilitate development of HIV vaccines and therapeutics.

- Several other groups, such as the **Albert B. Sabin Vaccine Foundation, Genenvax,** the **Global Vaccine Development Foundation**, and the **President's Commission on AIDS** have proposed forms of fundraising or public investment to stimulate HIV vaccine development.

- **California legislation** passed in 1986 provided direct funding, liability protection, guaranteed purchasing, and other incentives to California-based companies working on HIV vaccine research (Assembly Bills 2404 and 4250).

- Proposals have been made to encourage a groundswell of public donations or additional government largesse for HIV vaccine research, modeled on the March of Dimes effort formed by the Infantile Paralysis Foundation to fight polio. Several organizations, including the **Until There's A Cure Foundation, VACT UP**, and **Marathon of Mothers**, have proposed such a model.

B. Relevant Publications

- **Adverse Reactions to HIV Vaccines: Medical, Ethical and Legal Issues:** Published by the now defunct **Congressional Office of Technology Assessment** in Fall 1995, this report outlined possible incentives for increasing investment in HIV vaccine development. These included: tax deductions or credits; expanded access to pre-clinical non-human animal models; expanded patent protection; mechanisms for increased collaboration and information sharing among vaccine researchers; simplification of collaborative arrangements between government and industry researchers; expedited FDA review of license applications; guaranteed purchases of vaccine supplies by government; and international harmonization of national vaccine licensing standards.

- **The Rockefeller Foundation's IAVI Reports:** The Rockefeller Foundation has published reports based on three international meetings. The first report, *Accelerating the Development of Preventive HIV Vaccines for the World: Summary Report and Recommendation of an International Meeting,* followed a meeting held in Bellagio, Italy in March, 1994. The second report, *Accelerating the Development of Preventive HIV Vaccines for the World: Summary Report of an International Ad Hoc Scientific Committee* (also sponsored by the Foundation Merieux), was based on a meeting held in Paris, France in October, 1994, that focused on the scientific roadblocks to a vaccine. The third report, *The International AIDS Vaccine Initiative (IAVI): Financial and Structural Issues,* was based on a meeting held in New York City, in August, 1995. A report on *Intellectual Property Rights Issues and HIV Vaccine Development* will be published by IAVI in early 1997.

- **HIV/AIDS Vaccine Research and Development Strategy and Opportunity:** Published by **NIAID** in November, 1995, this paper outlined the agency's four main strategies to foster investment in HIV vaccines. These included: maintaining scientific programs that integrate "fundamental research and empiric development"; developing "more and better-defined partnerships between NIAID and industry"; identifying "scientific opportunities that will accelerate HIV vaccine research and development and determine resource requirements to fully exploit them"; and strengthening "linkages with communities and other public or private organizations working in the field."

- **The next steps toward a global AIDS vaccine:** Published in *Science* (266:1335-1337, Nov. 15, 1994), **Wayne Koff's** article called for "increased government funding of diversified global vaccine strategies, tax incentives for HIV vaccine development, guaranteed purchase of an established quantity of the licensed HIV vaccine to ensure a reasonable return on investment, orphan drug categorization and assistance with patent protection, and exclusion of HIV vaccines from broad pharmaceutical price control legislation."

- **Why AIDS vaccine development is taking longer than it should:** Published in *Current Issues in Public Health* (I:181-185, 1995), this article by **Donald Francis** called for a government role in "correcting the imbalance of value given to prevention versus therapy," forming more partnerships with industry, and urged "a social movement demanding an AIDS vaccine."

C. Survey Methodology

We wanted to find out what industry thought of the issues raised by these reports. The obvious way to do this was to ask.

As an independent group with contacts in many companies, we hoped to get frank answers by talking to key scientists and program managers who are struggling to maintain or expand their company's vaccine efforts, individuals from companies that have dropped out of the field, and directors of research at companies that maintain only a very low level of activity, despite having large HIV treatment research or non-HIV vaccine programs.

We began each interview by asking for a detailed description of the HIV vaccine program at the interviewee's company *(see section IV)*. We then asked: "What problems, scientific or otherwise, does your company faced in its HIV vaccine work?" Interviewees were then asked about the relative importance of the following previously identified obstacles to HIV vaccine research: 1) liability concerns, 2) perception of a "limited consumer market" for an HIV vaccine, 3) fears about demands for subsidized pricing of a vaccine, 4) opportunity costs of vaccine development relative to development of drugs, 5) questions about scientific feasibility of an HIV vaccine at this time. At the end of this section, each interviewee was asked to rank the potential problems in order of importance. All answers have been pooled and are unattributed.

Interviewees were also asked to suggest what government might be able to do to assist in the development of an HIV vaccine and to discuss the relative importance of a variety of hypothetical government interventions. (Numbers cited in parenthesis indicate the number of interviewees giving a particular response, followed by the total number who directly answered that specific question.) Interviewees were not asked about the politics of the field or about leadership issues. Nevertheless, these issues were raised again and again.

We guaranteed our interviewees anonymity. We accepted that the people we

interviewed were not speaking officially for their companies, but were reporting on the business aspects and scientific dynamics of the field as they understood them.

D. Companies/Research Institutions Interviewed

Companies with HIV vaccine programs that were interviewed:

Apollon
Auragen
Bristol-Myers Squibb
British Biotech
Cel-Sci Corp./Viral Technologies
Chiron
Genentech/Vaxigen
Immune Response Corp.
Immuno AG/Baxter International
Merck & Co.
MicroGeneSys
Pasteur-Merieux Connaught
SmithKline Beecham
Therion Biologics
United Biomedical, Inc.
Virus Research Institute
Wyeth-Lederle Vaccines and Pediatrics

Other companies or institutes that were interviewed:

Acrogen
Chiron-Viagene
Immunization Products, Ltd.
MedImmune, Inc.
The Salk Foundation
Walter Reed Army Institute for Research (WRAIR)

II. Survey Results: Obstacles and Impediments

A. What Industry Sees As The Challenges

Not surprisingly, each company had problems with its vaccine program. Generally, these were reflections of the company's culture and mission, its chosen approach, or an unexpected outcome along the way. The main challenges or obstacles identified were: the sheer difficulty of answering the scientific questions—particularly correlates of protection and immunity, dealing with multiple strains and a mutating virus, financial difficulties for the smaller biotechs, politics and leadership, and social challenges (at least 6:12). Larger pharmaceutical companies were more troubled by the scientific (7:7) and social/political issues (4:7). The smaller companies were more concerned about short-term financing and ability to bring their products forward.

Based on our interviews, we would rank the obstacles in order of importance, as follows:

1. Science
2. Liability
3. Investment cost/development priorities
4. Pricing a later issue
5. Market size not an issue

In virtually every case, when a company terminated or completely refocused their program, unimpressive scientific results, often with loss of backing from corporate partners, was cited as the primary problem (6). In all of these cases, the companies had limited, single approach or single product programs dependent on partners or outside financing. The partners were usually large companies who invested with a specific interest in future product rights.

We found it interesting, and a bit inspiring, that scientists from the few companies with well-funded, comprehensive HIV vaccine programs all cited ethical responsibility and commitment to the public health as a major reason for their company's investment. These factors, according to the researchers, in some way influenced or overrode strict economic or competitive business decisions.

In many questions, there was a striking similarity in the answers given. In other questions, answers closely correlated with the size of the company or appeared to be the result of a unique experience in a company's development program. Below we summarize the responses and give a flavor of the strength and sentiment of the responses by quoting typical, particularly vehement or insightful comments.

B. Specific Obstacles/Impediments

In order of importance:

"Scientific challenges are the real hurdle."

1. Scientific feasibility of an HIV vaccine at this time

By far the most universal response had to do with the imperfect state of science for this endeavor at present and for the foreseeable future. This is a risky long term enterprise, especially when there is no consensus on what approaches are most promising, or what immunity will be required to prevent infections or disease progression.

"There's no very clear direction in terms of scientific knowledge. It's very difficult to design a strategy."

The most strongly emphasized scientific problems, aside from the overall difficulty of the task, were quite general: a need for information from efficacy trials, disarray in the field, and no clear development pathway. Only one of our interviewees who has a new, high technology approach expressed the opinion that ultimate feasibility might be a problem (1:19), saying "it is possible that HIV will not yield," perhaps referring only to that approach. The rest firmly believe and act as if an HIV vaccine is possible, achievable, and well worth working on.

"Lawyers say we can't get our clients to give you money because of potential liability."

2. Liability concerns

In terms of liability concerns, there were significant differences in perspective between large pharmaceutical and smaller biotech companies. Among the pharmaceuticals, the general feeling was that this was an area to be addressed but a less significant concern that others, with only one company (1:8) calling it "important". However, among smaller biotechs, liability concerns were considered significantly more important (7:10), with three calling it very or most important.

"This type of legislation would be an incentive."

3. Opportunity costs of vaccine development relative to development of drugs

We didn't frame this question broadly enough, but the answers broadened it for us. Each type of program has its own funding bind. For wealthy companies with other profitable products the greatest financial need seems to be for funding (multi-million dollar) efficacy trials. Tax breaks or patent/marketing incentives would have the most value for those companies. The largest companies with ongoing vaccine programs see their work as competing with other vaccine projects rather than with their drug development programs.

"There will be a groundswell of support once there is a good product."

Smaller companies with single focus programs generally never have enough financing and always need support. They could use money for funding basic and targeted research but are reluctant to give up control or go through complicated grant writing or oversight requirements from government. There is also high risk and dubious promise in many small company programs, not always clearly represented in their fundraising appeals.

"The average vaccine R&D period is 12 years. Unless investors can be committed, it's very difficult."

Potential sources of support are many and varied, but the high risk long term nature of the investment has definitely hindered private investment in the field.

"We don't know about funding in the long haul; we're OK in the short haul."

4. Fears about demands for subsidized pricing of a vaccine

Answers to this problem ranged from predictions of a low profit margin and potential price controls (important, 8:17), to less important (5:17), to not important (4:17). An underlying reason given or implied was that this issue is a concern down the road, and not as pressing as other obstacles (3 comments).

"Some investors view HIV investment as a very difficult field."

5. Perception of "limited consumer market" for HIV vaccine

The answers to this question came as a surprise. Only 4 of 18 interviewees said projected market limitations were important, and several (4) flatly contradicted this assumption, saying that they believed this statement was simply untrue, that there would ultimately be a very large market for an effective HIV vaccine.

"In negotiations with potential partners, [price controls are] more of a problem for them than for us."

C. Ranking Specific Obstacles/Impediments

Most interviewees did not give a ranking of the potential problems. The primary ones mentioned by more than one company were: science (4), legal and liability issues (3), the need for more different approaches and strategies (2), and size and cost of trials (2).

"This perception [of a limited market] is completely wrong. We don't base our scientific considerations on marketing considerations. They are based on science or public health."

Other notable topics raised in our interviews included:

- The need for an empirical approach and clinical efficacy trials versus the need to pursue a rational approach with adequate basic scientific knowledge first.
- The impact of short-term failure on smaller companies and the ability of all companies to maintain a long term commitment.

- The government's ability to quickly change strategies given changes in scientific knowledge and technologies, and political aspects of getting government attention and support.
- A clearer process by which government officials make decisions about vaccine research directions.
- Public awareness about the need for vaccines and the state of research.

"If a vaccine of reasonable efficacy can be made, it will be a multi-billion-dollar product."

In short, the answers run the gamut. As three people said, more or less delicately, "they're all damned important." We believe that no potential problem should be discounted if it is important for some potential players. It would make sense, however, to expend more effort in the most important areas and to focus on addressing them first.

"If something works and you can produce it reasonably, you can sell it."

We should note that these are the opinions of individuals in industry who are scientists, not marketing or legal experts in their companies. Academic scientists supported by competitive grants or targeted contracts, government scientists, politicians, and activists would almost certainly identify some different obstacles in different priorities. These answers only point toward what those most involved in industry say might stimulate or improve their companies' participation. We should also note that some of these individuals have a strong stake in how their product or company is presented. In the words of one individual we interviewed, "there's a lot of hype and hot air in this field". Clearly, people speak from their unique perspectives in both industry and non-industry settings.

These priorities also do not consistently reflect received wisdom or the message of groups and individuals lobbying for one sort of direct action or another, especially for government action by individuals who believe strongly in particular plans or products. They do argue that initiatives like those of OAR and IAVI are well conceived, and that something similar to Congressman Stark's proposal should be revived. It is our belief, and hope, that as scientific questions are answered, investment will follow.

III. Survey Results: What Industry Wants from Government

A. A Question of Leadership

A substantial share of the expertise to develop, produce and distribute vaccines lies with private pharmaceutical and biotech companies. But government researchers and health officials have equally important, multiple responsibilities in the pursuit of an HIV vaccine.

Publicly funded researchers and labs have classically provided the basic scientific research which allows private efforts to pay off. Government can also fund clinical trials of HIV vaccines. But the public sector must also help create an investment climate which will harness private sector expertise. Publicly funded incentives can be an opportunity to address equity issues when these incentives are negotiated as part of a package which includes price breaks or other guarantees to expand access to vaccines by at-risk, low income and uninsured populations.

"Government needs to provide value. It needs to declare this is a major priority like going to the moon."

Many are looking to government to provide scientific leadership on vaccine research, and to mobilize communities for vaccine trials. And government could choose to play a more active role in the actual design and development of vaccine products.

"What government can do is to support the idea that an HIV vaccine can be developed by bully pulpit."

Our final set of questions asked what steps government could take to increase private sector investment in vaccine research and development. Again, our questions were based on ideas suggested in earlier writings.

B. What Government Should Do

Our first question was an attempt to get a reading of respondents' ideas before they were prompted with specifics. It was the most open ended: "What can government do to help?" We received a variety of responses, most often clustering around the ideas of: providing public funds, economic incentives for research, and improving the investment climate (11); doing basic scientific and immunological research (6); providing leadership (4); and broadening the focus of research beyond protein envelope approaches (4).

The need for direct government funding was heard from

"Provide confidence. Show that the government is really serious."

"The problem is not so much in the institutions. No one has come along with leadership, and that's the missing ingredient."

large and small companies alike. An employee of a major pharmaceutical told us that, "given all the disincentives for industry to do something...the emphasis for pubic funding becomes more acute." From an employee at a smaller biotech, "For us, the only source for money for this comes from the US government. The investment community, where we get most of our capital, venture capital, institutional investors, view the scientific risk and long term nature of the development program as the greatest disincentive to invest. They don't want to wait around for fifteen years to see a return." An employee at another comparatively small company insisted that, "there should be some big incentives for small companies where innovative strategies are coming from. The risk is less for larger companies. I don't have a lot of empathy for large companies who can enter this area and it would be drop in the bucket." The importance of visible leadership also emerged as a recurring theme in responses to this and other questions.

C. Specific Actions

Next we asked people about the value of specific actions government might take. We asked, "How important would each of the following government actions be to increase investment in vaccine development?"

"That would be a big plus."

1. Tax deductions or credits for investments

Given that these were employees of private companies being interviewed, we were not surprised that responses tended to be supportive of this approach. Nine of 16 responding thought deductions or credits would be very or moderately helpful, two ranked their usefulness as low, and four were not sure. One interviewee said sufficient deductions and credits already exist in the United States. There were no consistent trends between large and small companies. One representative of a large pharmaceutical said tax deductions would be "good for large companies, but small companies don't have big tax bills."

"IND reviews have been as quick as they can be, but we haven't filed one recently."

2. Expedited review by FDA

Several respondents seemed to view lengthy delays in the FDA review process as an issue mostly in the past, and this suggestion received the second lowest overall support. Four of 13 responding said it was very or somewhat important; seven ranked it low in importance; and two did not know. Respondents noted that "it's sort of happened" and "it's not really a problem."

3. Creating uniform international standards for licensing

"Any standards would be appreciated."

Inconsistent, or nonexistent, standards of safety and efficacy for vaccine licensing have been named as an impediment to investment. As officials at NIAID have observed, lack of clarity about the ultimate goal is the one uncertainty business has a difficult time tolerating. Yet in our survey the concept of uniform international licensing standards received limited support. One of 14 said it would be very important; seven said somewhat important; six said it would be of little or no importance.

"Realities in each country are somewhat different...why would you have something uniform?"

4. Expanded patent protection

"That would definitely help."

Expanded patent protection would allow a vaccine manufacturer a longer period of exclusive marketing of their product, and more time to recoup their investment and show profits. Support also varied for this proposal. Two of 15 responding ranked it high; four said it would be helpful or moderately helpful; five ranked it of low importance; and four said they did not know. One interviewee worried that expanded patent protection or orphan drug status for a vaccine might be unseemly, "...a vaccine could potentially be very profitable...there's a fear of how it would look for a corporation to profit from an AIDS vaccine, for example Burroughs Wellcome and their AZT pricing...[an HIV vaccine] would be a billion dollar product, so orphan drug status doesn't make sense, but some kind of economic incentive is necessary."

"Companies are protected enough."

5. Guaranteed purchases of vaccine supplies by government

"Outside the US, guaranteed purchase would be a good idea, but not in the US."

The logic behind this approach is that companies may be concerned about the ultimate size of the market for an HIV vaccine – at least the market which could pay for the product. Guaranteed purchases would ensure a market size adequate to justify investment. But, as noted in the previous section of this report, concerns about the lack of a market for HIV vaccines may have been exaggerated, and we found only limited support for the guaranteed purchase approach. Three of 15 responding listed this as very important; four said it was somewhat important; and six ranked it of low or no importance; one said government purchase of an HIV vaccine was "expected"; and one respondent did not know. "If there is a vaccine, it will be sold," said one company representative. Another raised the concern that guaranteed government purchasing might serve as a disincentive if companies became overly concerned about the potential for price fixing by government.

"Government should commit to this effort and then everything will come."

6. International coordination of vaccine research and distribution

It's hard to argue against this idea, and it is a role that many agencies, including NIAID, UNAIDS, IAVI, OAR, and the Department of Defense, have attempted to play. Eight of 12 respondents said it would be very or somewhat important; three said it would be of little or no importance; and one did not know.

"If we didn't receive money from the government, our program would not be where it currently is."

7. Direct contracting between government and industry for specific research

This idea has appeal because it would allow government aggressively to identify gaps in vaccine R&D and strategically fill those gaps utilizing expertise in the private sector. It is also a model which has some precedent: the HIV vaccine work of Pasteur-Merieux, Connaught, Chiron, Genentech, Therion and others has benefited from direct government financing. This approach also has serious potential pitfalls: Will NIAID or another government agency identify an appropriately broad array of research, or choose to fund a more narrow range of approaches? Will public financing be used as an opportunity to secure expanded access to vaccines by low income populations, or as a give away to billion dollar multinational pharmaceuticals? Will companies with extensive vaccine expertise be interested in contract work to which strings are attached (such as subsidized pricing, or partial patent ownership by government)?

"The single greatest impediment for smaller companies is that the capital resources are not there for research and development."

Perhaps not surprisingly, the industry representatives we spoke to were far more supportive of this potential government action than any other we suggested. All 17 of those responding said this approach would be very or somewhat important; seven of those said it would be very important.

"We gain credibility with investors through these grants."

Several companies noted that past government financing by the US, France, and Canada was one of the driving forces behind current HIV vaccine research. Widespread support for this approach also begs a rather big question: if our interviewees are convinced there is a substantial market for HIV vaccines, why do they expect their work to be subsidized? And if it is, how are the fruits of that work to be shared?

"Increasing grants to academia on HIV pathogenesis to learn about what needs to be done would be money well spent."

8. Greater clarity about thresholds for moving to Phase II and III trials

This approach is a central piece of NIAID's plan to foster better relations with industry. NIAID staff are working with industry representatives to negotiate specific "milestones" which, if attained, will move different candidate vaccines to late stage

human trials. These milestones would change with scientific knowledge, but would serve as relatively stable markers for product evaluation and development. The industry staff we spoke with for this survey voiced strong to moderate support for the overall concept. Seven of 12 respondents said the idea was very or somewhat important; two said it was of low importance; one said "safety should be the threshold"; and two said they did not know. There was also praise for NIAID's current efforts to set milestones: "The effort begun in 1995 to be serious about long term plans...what they are doing is very helpful."

"Government has too often played astrologer rather than empirical evaluator."

"NIAID is pulling 'milestones' out of a hat. We'll see those thresholds change."

However, one respondent questioned the long term validity of those agreements, and several of those interviewed said the June 1994 NIAID decision not to proceed with Phase III trials of the Genentech and Chiron gp120 products had been "a damper" on industry interest.

9. Increased assistance securing animal models for research

Animals remain essential for pre-clinical testing of vaccine candidates, even though one of the frustrations of HIV vaccine research has been the lack of predictive animal model. High cost and limited availability of these animals has been noted as one impediment to research. Our survey elicited relatively strong support for greater assistance with access to animals for research. Eight of thirteen responding said this would be very or somewhat important; five ranked it of low importance. Since animal testing is considered a critical first step in assessing the safety of products before human trials, we were a bit taken aback by one interviewee who responded to our question by saying animal models are, "not needed. We can use humans. The virus is specific for humans. Why not just find volunteers from high-risk groups?"

"The Cooperative Vaccine Development Groups work well and play a major role in supporting vaccine research."

"I have had very positive experiences working with both NIH and FDA."

10. Need for changes in vaccine trial networks

Though industry representatives voiced various frustrations about working with government ("All government programs could be better managed."), when we asked a specific question about the NIAID clinical trial networks, few had complaints to voice. No one ranked reform of these programs a high priority. One of ten ranked it of medium importance; four ranked it of low importance or "OK as it is"; three did not know; one called for increased "centralization" and another said "alternative approaches" and "leadership" were needed.

"We have had nothing but a lot of help from NIH and FDA. The FDA has approached this in a very rational way."

"We would like to be more a part in the decision making in the center of research, not only to be a provider of vaccines. We also have clear thoughts about research and would like to bring these in."

"Industry should be at the table when NIH meets with WHO, and other scientific meetings."

D. The Pros and Cons of Working with Government Agencies

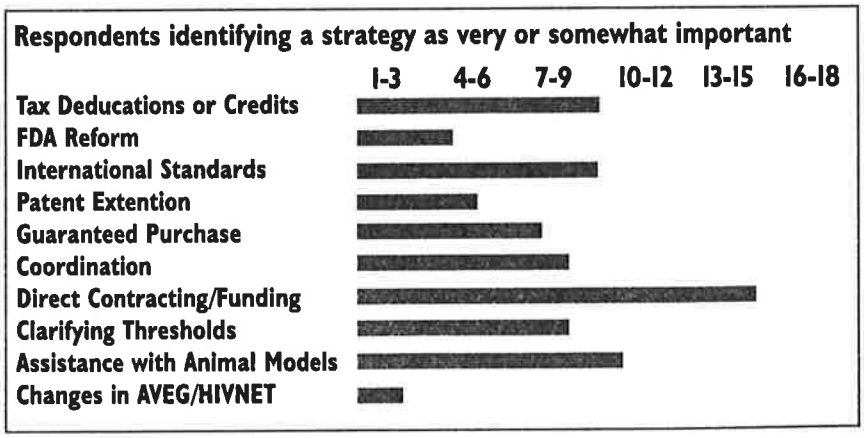
Many of the people we interviewed reported reasonably good experiences with US government agencies and several offered praise for individuals at NIH. The pros of working with government included the availability of funding, the chance to exchange information with others, the presence of knowledgeable scientists, and facilitation of primates studies and human clinical trials. One employee of a large pharmaceutical noted that, "NIH...goes to great lengths to bring people together."

Cons included dealing with a "big, slow bureaucracy," and putting up with "reporting structures and unending regulations." An employee of a large pharmaceutical argued that, "There needs to be increased authority given to lower levels [in government] to make decisions without tons of committees."

One theme that emerged was a concern that pharmaceutical companies are not included in NIH planning. Industry scientists wanted to be taken more seriously as scientists and thinkers and to be involved in decision making in a greater capacity than as mere providers of product. Again, concerns about overall leadership and a perceived lack of direction in government efforts emerged.

E. Ranking Specific Actions Government Should Take

Three interviewees reminded us of a key issue from the "obstacles" section of the interview which we neglected to include here: the need for a liability system to provide industry with some protection from lawsuits. Four others said direct contracting between government and industry was the most important idea we had listed. Additional items noted were: leadership, guaranteed purchase of vaccine, basic scientific research, and improving the investment climate.



F. Government Leadership

"We need a group whose whole focus is to make a vaccine and to interact with basic researchers. Like a think tank, with that as the whole mission and sole focus."

The responses to this question were most remarkable in the emphatic unanimity of opinion expressed about the need for increased active government leadership. Without this key ingredient, many interviewees believed the search for an HIV vaccine would be seriously impeded.

We were surprised to find most interviewees volunteering these perspectives unasked, and so will let their comments speak for themselves:

> "Government needs to bring together companies and communities and countries for clinical trials....What it takes is a person with credibility and assets to work with a company to absorb some of the financial risks...There needs to be someone who sees this as his or her job: bringing partners together, building links between companies, communities and governments. [NIAID staff] need to get out of their offices and say to companies 'we will work with you.'"

> "We don't have anyone in the entire government who has been asked to assume responsibility to get a vaccine. No one's salary or bonus depends on it. No one is on the line on this issue. No one is in charge."

> "We need someone like Jonas Salk who took it upon himself to try it out. But his problem was easy to solve. People are frustrated and an easy answer is not there."

> "It takes a person. Not a committee."

The answers to this last set of questions suggest that the efforts of NIH and other government agencies to improve working relationships with industry-based HIV vaccine researchers are appreciated, but that they do not go nearly far enough. Creation of a clinical trials network, growing clarity about thresholds for moving ahead with clinical trials, and FDA reform are beginning to have an impact. NIH's role as a funder of basic research remains essential.

But according to the industry representatives we spoke with, important deficits remain. Measures to improve investment, leadership, and the inclusion of industry in planning are necessary.

The HIV Vaccine Effort by Company

Listed in order of estimated size of overall 1996 R&D expenditures*

Company	HIV vaccine approaches in development	$$ in R&D**	$$ in Sales**
Merck & Co.	**D**	**$$$$$**	**$$$$$**
Bristol-Myers Squibb	**—**	**$$$$$**	**$$$$$**
Wyeth-Lederle (AHP)	**P, LV, D, M**	**$$$$$**	**$$$$$**
SmithKline Beecham	**S**	**$$$**	**$$$$$**
Pasteur-Merieux Connaught	**S, P, PV, LV, D**	**$$$**	**$$$**
Chiron	**S, P, LV, D, M**	**$$$**	**$$$**
Genentech / Vaxigen	**S**	**$$$**	**$$$**
British Biotech	**S**	**$**	**$**
Therion Biologics	**S, LV**	**$**	**$**
Apollon	**D**	**$**	**$**
Auragen	**D**	**$**	**$**
Cel-Sci / VTI	**P**	**$**	**$**
ImmunoAG / Baxter International	**S,WK**	**$**	**$**
MicroGeneSys	**S**	**$**	**$**
United Biomedical, Inc.	**P**	**$**	**$**
Immune Response Corp.	**—**	**$**	**$**

Vaccine Approaches:
S=subunit, P=peptide, PV=pseudovirion, LV=live vector, D=DNA, M=mucosal, WK=whole killed

*** Information from 1995 Lehman Brothers and 1995 Bioscan analyses.**

**** R&D and Sales: $$$$$: more than $1 billion,**
$$$: $100 million to $1 billion,
$: less than $100 million.

IV. Corporations with HIV Vaccine Programs

Up until now, most industry investment in HIV vaccine development has focused on a subunit approach—gp160, gp120, or other HIV proteins. Other approaches being pursued by a number of companies include DNA vaccines, live vector strategies, and peptide vaccines. We hoped to get a picture of other products in development by asking companies about the scope and extent of their HIV vaccine research and development programs. Combined, the short-overviews below speak powerfully to the disarray in the field and poor investment climate many companies face.

Apollon

Company Background: Apollon is a Malvern, PA-based privately-owned biotechnology company founded in 1992. Employing 45 people, the company is primarily focused on developing gene-based products, including DNA vaccines (trademark GENEVAX®), immunotherapeutics and other pharmaceutical products. Apollon is developing DNA vaccines for HIV, herpes infections, human papilloma virus (HPV), genital warts, hepatitis B and C, tuberculosis, T-cell mediated autoimmune diseases, and lymphoma. Wyeth-Ayerst, a division American Home Products (AHP), is a partner in the development of the HIV, herpes, and HPV vaccines.

Earlier this year, in collaboration with NIAID, Apollon began a phase I clinical trial of its HIV DNA vaccine as an immunotherapy in HIV-positive patients. A Phase I study of the vaccine in HIV-negative patients is currently enrolling, also with the support of NIAID. Apollon has also initiated a Phase I clinical trial of its DNA vaccine to treat T-cell lymphoma. Clinical studies of a herpes DNA vaccine will begin later this year and of an HPV vaccine sometime next year.

HIV Vaccine Program: Apollon's HIV vaccine program focuses entirely on the DNA approach. The candidate HIV vaccine currently in clinical trials is based on an MN strain of HIV with gp120, gp41 and *rev*. Additional proteins (such as *gag* and or *pol*) may be added to the construct. Apollon is also hoping to develop a DNA vaccine based on HIV subtype E, which could be available for testing in Thailand.

At the XI International Conference on AIDS in Vancouver, researchers reported that the company's HIV DNA vaccine was able to provide short-term protection in chimpanzees. Apollon researchers also report that early data from the Phase I study of the vaccine as an immune-therapy in HIV-positive patients suggests that it is "safe and immunogenic".

Auragen
(formerly Agracetus)

Company Background: Auragen is a Middleton, WI company focusing on development of anti-cancer therapies and research in gene delivery systems (using the company's hand held Accell® gene delivery system for DNA vaccines). The company is a wholly owned subsidiary of W.R. Grace & Co. Auragen's DNA vaccine program was previously part of Agracetus, a subsidiary of Monsanto. The Agracetus DNA vaccine program began in 1991 and is broad-based, with vaccines in development for HIV, hepatitis B, influenza, malaria, measles, dengue, and rheumatoid arthritis. Auragen's gene-gun approach (Accell®) enables DNA to be injected into the skin, in order to generate more of an immune response. The company is also working with the National Cancer Institute (NCI) to develop cancer vaccines. Auragen's HIV vaccine program is funded with a $2 million grant from the U.S. Army which began in 1994. At present, Auragen has approximately 35 employees and no licensed products.

HIV Vaccine Program: Auragen is currently testing a number of HIV DNA vaccines in different animal models. The candidate vaccines all utilize the company's gene-gun delivery system and are based on different HIV constructs including *gag*, *pol*, and gp120. As part of the delivery system, HIV DNA is placed on gold "beads" approximately one micron large. The gene gun then utilizes a cartridge to inject the bead into epidermal cells. Auragen researchers report that the company's HIV DNA vaccines generated significant immune responses in rhesus macaques. Even greater immune responses were seen in macaques when the vaccine was administered in combination with live-vector vaccines, adjuvants, or boosts of subunit vaccines. The company plans to continue testing its HIV DNA vaccines in animals, and to look for a clearly superior construct before initiating human studies.

Bristol-Myers Squibb

Company Background: Bristol-Myers Squibb is one of the largest pharmaceutical companies in the world. The company invests more than $1 billion annually in research and development of new products. Research areas include antibiotics, cancer drugs, anti-depressants, immunology, drugs for lowering cholesterol and reducing high blood pressure, and the HIV anti-viral drugs ddI and d4T. Annual sales of BMS drugs approach $8 billion.

HIV Vaccine Program: Bristol is not currently involved in HIV vaccine development. Having acquired Oncogen in 1986, Bristol acquired an HIV vaccine research program focused on developing a prime-boost combination involving a vaccinia vector and subunit envelope antigen. Phase I/II research on Bristol/Oncogen's vaccinia-gp160 product began in 1988 through the NCVDG and AVEG networks. These studies combined the vaccinia-gp160 vaccine with gp160 or gp120 products developed by MicroGeneSys, Chiron, Genentech, and

Immuno AG. While no research is currently being done on Bristol's product, the company makes the vaccinia virus available as a research reagent, and several scientists at Bristol remain involved in HIV vaccine research efforts at other sites.

British Biotech

Company Background: British Biotech is based in Oxford, UK. The company has been involved in the development of several products, including a compound to protect stem cells in cancer treatment and a range of cytokine-based treatments for wasting syndrome and as anti-inflammatory therapy.

HIV Vaccine Program: British Biotech's HIV vaccine program was focused on a vaccine called p24-VLP, a virus-like particle containing the p17 and p24 proteins of HIV. The vaccine was tested as an immunotherapy in HIV-positive patients in the United States and Europe, but results from these trials showed disappointing immunogenicity. There was no effect on HIV disease progression and the company has since halted this research. A Phase I/II trial in HIV-negative volunteers, sponsored by the NIH, has been continuing since 1995 to look at the safety and immunogenicity of p24-VLP with and without an alum adjuvant.

Cel-Sci Corporation / Viral Technologies, Inc.

Company Background: Cel-Sci, a publicly traded biotechnology company based in Alexandria, VA, was formed in 1983 and currently employs 25 people. In addition to its HIV vaccine, Cel-Sci is evaluating a diagnostic test to be used in monitoring the disease status of HIV-positive patients.

HIV Vaccine Program: The focus of Cel-Sci's HIV vaccine program is a peptide based-vaccine known as HGP-30. The product is a synthetic copy of a 30 amino acid antigenic region of the p17 core protein of HIV, administered with an alum adjuvant. Cel-Sci is currently pursuing a Phase I study of HGP-30 as an immunotherapy in HIV-positive patients. The company began Phase I studies of HGP-30 in HIV-negative volunteers in 1991 at the University of California at San Francisco and USC Medical Center, Los Angeles. In 1995, Cel-Sci initiated a booster immunization protocol in which volunteers from the first study received additional injections of the HGP-30 vaccine. Although results from these trials are disappointing, results from SCID mouse studies seemed to show that inoculation with blood cells from immunized volunteers protected mice against a different strain of HIV-1. Based on this, researchers are seeking funding to initiate a Phase II trial to gather more data on safety and immunogenicity.

Chiron

Company Background: Chiron is one of the world's leading biotechnology companies. Founded in 1981, the company employs over 7,000 people worldwide and is primarily focused on diagnostics, therapeutics (particularly oncology), opthalmics, and vaccines. Chiron Vaccines oversees a substantial vaccine research and development program. Currently in development are vaccines for Hepatitis A, herpes, influenza, CMV, whooping cough, HIV, and meningitis. The company's herpes vaccine is in Phase III studies. Chiron' s DNA vaccine program is studying HIV and hepatitis C. Based on the failure of two Phase III clinical trials, in November, 1996, Chiron halted development of a vaccine to prevent genital herpes, on which the company estimated it had spent $50 million over more than 10 years. The company also has a substantial program utilizing branched DNA technology for diagnostics, particularly in the area of HIV (Quantiplex®).

HIV Vaccine Program: Chiron has a substantial HIV vaccine effort. At one point, the company had 45 full-time researchers working on HIV vaccine research. Currently, about 16 full-time staff are involved in the program.

Much of Chiron's HIV vaccine research has focused on the envelope subunit vaccine, gp120. The company's program, which began in 1991, is now focused on developing: a gp120 vaccine, a p24 vaccine that induces CTL activity, improved adjuvants, next-generation vaccine technologies such as DNA-based vaccines, and technologies to induce mucosal immunity. Phase I/II trials of Chiron's CHO-expressed gp120 have been conducted through the AVEG network with adjuvants MF59 and MTP-PE, in combination with Bristol-Myers-Squibb's live vaccinia gp160, and in combination with Pasteur-Merieux Connaught's (PMC) ALVAC live canarypox gp160 vaccine candidate. The gp120 vaccine will also be included as a boost in Phase II studies of the ALVAC vaccine. Chiron and PMC, to their mutual credit, appear to have established a strong working relationship in developing this vaccine combination. Chiron is also developing a bivalent vaccine gp120 based on HIV subtypes E and B. Phase I/II trials of this vaccine will be initiated in Thailand, in cooperation with the Thai government and the US Army.

Other HIV vaccines in development include a p24 antigen vaccine and a range of HIV DNA vaccines. Current plans are to initiate a trial of the p24 antigen vaccine, which might be followed by studies of the vaccine as a boost for the canarypox or in combination with a gp120 vaccine. Chiron's HIV DNA program is developing constructs for core (*gag*) and envelope (gp120, gp160) proteins using intramuscular injection and the Agracetus gene gun. DNA immunizations with a gp120 plus MF59 boost have been studied in mice and guinea pigs, where strong cytotoxic T-cell (CTL) activity and moderate antibody responses were observed.

Genentech / Vaxigen

Company Background: Genentech is another of the world's leading biotechnology companies. Based in San Francisco, CA, the company is 75 percent owned by the Swiss pharmaceutical company, Roche Ltd. Licensed products developed by Genentech include human growth hormone products, gamma interferon, Pulmozyme® for cystic fibrosis, and Activase® for blood clotting products.

HIV Vaccine Program: Genentech's HIV vaccine program has focused primarily on the HIV envelope product, gp120. The company claims that it has invested in excess of $50 million on HIV vaccine development since it began its program in 1985. In 1990, Genentech scientists reported that their gp120 product protected a number of chimpanzees from challenge with HIV. In 1991, this product entered Phase I/II trials in the AVEG network, and was tested with several adjuvants. In 1992, a Phase II study with Chiron's product was begun, and in 1995, a Phase I/II study was started in Thailand. No Phase III trial has yet been initiated, although such studies were considered in 1994.

Earlier this year, Genentech announced that it was creating a new company, Vaxigen, to bring its gp120 vaccine to market. Genenetech is spinning off all but its profit-generating programs. The company said it would provide Vaxigen with $2 million in start-up costs and seek an additional $18 million in private financing for large clinical trials and new vaccine formulations. If it can raise the necessary funds, Vaxigen will initiate Phase III studies of its gp120 vaccine in the U.S., with a bivalent clade B formulation, and in Thailand with a bivalent clade B and E formulation in 1997.

Immune Response Corporation

Company Background: Immune Response Corp. is a public biotechnology company formed by the late Dr. Jonas Salk to develop HIV therapeutics and an HIV vaccine.The company recently launched a Phase III study of its therapeutic vaccine (the "Salk immunogen"), a whole killed virus with a partially deleted envelope, in HIV-positive patients.

HIV Vaccine Program: While Immune Response Corp. reports that it is interested in developing a whole-killed preventive HIV vaccine, it has no immediate plans (or funds) to do so. The company was backed by Rhone-Poulenc through a joint venture, Immunization Products Ltd., to develop the whole-killed approach. This partnership is now defunct.

Immuno AG / Baxter International

Company Background: Immuno AG is a Vienna-based international pharmaceutical company, established in the 1950s and just recently sold to Baxter

International. The company has a substantial blood plasma operation. The Immuno Group has local companies in 18 countries.

HIV Vaccine Program: Immuno AG's HIV vaccine program began in 1986. The program has been almost entirely focused on envelope gp160 vaccines. A number of gp160 trials, both in the United States and Europe, have been initiated since 1990, with some funding from the NIH. Recent results from European clinical trials of the Immuno rgp160 vaccine in HIV infected individuals found the vaccine to be safe and immunogenic, but it did not appear to affect viral load or CD4 counts. The company has decided to increase its focus on whole killed HIV vaccines. These vaccines are being developed in cooperation with the United States Department of Defense. Immuno reports that its whole-killed vaccine products are currently in animal studies. Tests in chimpanzees should begin sometime this year. Plans for human trials, possibly in Thailand, are being developed. Immuno also has a small research project on attenuated vectors expressing HIV antigens.

Merck & Co.

Company Background: Merck & Co. is the world's largest pharmaceutical company in terms of brand product sales and also in terms of total research spending. Research at Merck covers almost every area of drug technology and development. The company's vaccine program includes vaccines for Hepatitis A and B, chicken pox, MMR, and bacterial pneumonia. Merck's DNA vaccine program is in partnership with Vical, Inc. a San Diego, CA-based biotechnology company. Vical researchers pioneered DNA vaccine delivery and in 1990 demonstrated that DNA injected into mice could result in protein production *in vivo*. Merck and Vical researchers reported probable protection using a DNA influenza vaccine in animals, the first published demonstration of such protective efficacy. Merck's DNA vaccine for influenza is now in early human trials. Extensive work on DNA vaccines, backed by Merck's considerable resources, is being done in animal models for a wide range of other diseases, including tuberculosis, hepatitis B and C, herpes, HPV, and HIV. Merck's extensive HIV anti-viral development program led to the FDA-approval of the protease inhibitor Crixivan®.

HIV Vaccine Program: Merck's research on preventive HIV vaccines began with a joint venture with Repligen. The venture focused on a sub-unit V3 loop vaccine. Merck also attempted to develop a BCG-vector vaccine expressing V3 with MedImmune. Merck's current HIV vaccine program focuses on a DNA HIV vaccine. This work is still in the early preclinical research stage, and there is no investigational DNA HIV vaccine ready for human trials. Preliminary primate studies, while promising, clearly demonstrate the need to improve antibody responses.

According to the company, efforts at Merck are now being focused on learning how to generate antibody responses, specifically responses that are robust and specific enough to neutralize primary isolates. Merck researchers believe

that, because of the generic nature of DNA vaccine technology, research efforts in other vaccines may yield useful information toward the development of an HIV DNA vaccine.

MicroGeneSys

Company Background: MicroGeneSys is a Meridien, CT-based privately-owned biotechnology company focused on developing HIV vaccines and therapeutics.

HIV Vaccine Program: MicroGeneSys has focused its research and development on gp160 vaccine products. A p24 protein vaccine was also in development. All told, the company has conducted approximately 30 human studies of these products, many partially sponsored by NIAID or the U.S. Army. While these studies were conducted in HIV-positive and negative individuals, the primary emphasis was to study the vaccine as an immunotherapy. However, these studies failed to demonstrate clinical benefits. MicroGeneSys claims that it has invested a total of $60 million in HIV vaccines, $20 million of that on preventive vaccines. The company reports that it would now like to focus on preventive vaccines, beginning with studies of a gp160 vaccine used with a vaccinia vector. It hopes to start clinical trials, but needs a financial partner to fund the studies.

Pasteur-Merieux Connaught

Company Background: Pasteur-Merieux Connaught, a subsidiary of Rhone-Poulenc, is one of the world's leading vaccine manufacturers. With its purchase of Connaught, the company significantly increased the scope of its research and development. Pasteur-Merieux Connaught is developing vaccines for Hepatitis B, influenza, herpes, whooping cough, DTP, MMR, BCG, and tetanus. The company is working with Vical to develop DNA vaccines for Lyme disease, malaria, *H. pylori* bacteria, and CMV.

HIV Vaccine Program: Pasteur-Merieux Connaught's HIV vaccine program began in 1991, and includes four major areas of research. These are: an envelope (gp160) approach; a peptide approach based on a number of HIV peptides; a pseudovirion vaccine, made of non-infectious particles containing most of the viral proteins; and the ALVAC vaccine, a canary pox vector expressing some HIV antigens (now being studied with Chiron's gp120 vaccine as a boost). Three ALVAC vaccines are currently in clinical trials: vCP125 expressing gp160; vCP205 (vCP125 with *gag* and protease added) ; and vCP300 (vCP205 with *nef* and segments of *pol* added).

Studies suggest that both vCP125 and vCP205, used with a gp120 boost, can induce some cellular and antibody response. According to early data, between 25 and 50 percent of participants given vCP205 with a gp120 boost generate new cellular immune responses to HIV. The NIH is working with Pasteur-

Merieux Connaught to identify levels of immune response needed to move ahead to a large Phase III efficacy study. In the meantime, further Phase II studies will be conducted in 1997.

The pseudovirion product is awaiting approval by the FDA for human study in the US. Pasteur-Merieux Connaught reports that it is currently devoting at least 20 percent of its research efforts to HIV vaccine research. The company has invested a total of between $20 to 25 million on HIV vaccine development since it began its program. This program receives substantial support from the French government. In addition, from 1989 to 1994, Connaught received money for its peptide and particle research program from the Ontario Technology Fund, a Canadian government program.

SmithKline Beecham

Company Background: SmithKline Beecham is one of the world's ten largest pharmaceutical companies both in terms of revenues and total research spending. The company has developed leading treatments for ulcers, arthritis, elevated blood pressure, high cholesterol, depression, and a range of infectious diseases. SmithKline Beecham is also a leading vaccine manufacturer, with vaccine programs for Hepatitis A and B (already approved), herpes, influenza, and cellular whooping cough in combination with diphtheria and tetanus.

HIV Vaccine Program: SmithKline Beecham's research effort in preventive HIV vaccines began in 1985. Since 1993 it has focused primarily on developing adjuvants in combination with an envelope gp120 product. A Phase I study of the company's gp120 vaccine with a potent adjuvant is currently underway in HIV-negative volunteers. This study is being conducted in the United Kingdom in cooperation with the British Medical Research Council. The company is also studying adjuvants based on immunostimulants and an SIV envelope vaccine in primates and is developing further HIV antigens for inclusion in a vaccine.

Therion Biologics

Company Background: Therion is a Cambridge, MA-based privately-owned biotechnology company with about 28 employees. Most of the company's work is on cancer vaccines and immunotherapies. Vaccines for cancers of the colon, lung, breast, prostate, colon, and skin are all in Phase I clinical trials.

HIV Vaccine Program: Therion's HIV vaccine program has focused primarily on developing recombinant viral vectors to express multiple HIV proteins. The company claims that, so far, it has invested close to $10 million of the company's own funds on HIV vaccine development. Although in previous years HIV vaccine research constituted 60 to 70 percent of the company's research spending, it is reported that at present only about 20 percent of Therion's research funds are devoted to HIV vaccine development. Therion has received support

from NIAID for both preclinical and clinical research. The vaccines currently being tested include a vaccinia vector inserted with *env*, *gag*, and *pol* in clades B and E, currently in NIAID sponsored Phase I trials. Therion is awaiting FDA approval for further studies of this vaccine in HIV-negative volunteers. Researchers at Therion are also reportedly working on developing a macrophage tropic envelope vaccine.

Therion also owns the rights to genetically engineered live attenuated HIV vaccines developed at the New England Regional Primate Center which are now in pre-clinical animal studies. The company has no present plans to initiate human studies of a live attenuated vaccine, although it is working on developing different mechanisms to manufacture one.

United Biomedical, Inc.

Company Background: United Biomedical is a Long Island-based biotechnology company. The company, founded in 1984, employs about 85 people.

HIV Vaccine Program: United Biomedical's HIV vaccine program has focused on developing peptide products, with the most widely tested vaccine being a V3 peptide immunogen used with alum. Clinical studies of this vaccine began in 1993 and examined safety, immunogenicity, and dose scheduling. Trials of the V3 peptide vaccine were initiated in China, Thailand, and Brazil. United Biomedical also studied a lipopeptide product and a "microparticle" technology for mucosal administration, neither of which generated promising data. United Biomedical reports that it is now focusing on developing monoclonal antibodies that can neutralize a wide range of HIV isolates. The company says it will return to clinical research once it has a product that it believes is capable of doing this.

Virus Research Institute

Company Background: The Vaccine Research Institute (VRI) was formed in 1992 with a primary focus on HIV research. Founders of VRI include Max Essex, Bill Haseltine, and the late Bernard Fields. The company's main product is currently an adjuvant that is water-soluble and easily absorbed. Pasteur-Merieux Connaught is testing this adjuvant with its influenza vaccine.

HIV Vaccine Program: In terms of HIV-specific research, VRI has developed a patented chimeric SHIV virus that infects and causes disease in monkeys.

Wyeth-Lederle Vaccines and Pediatrics/American Home Products

Company Background: Wyeth-Lederle Vaccines and Pediatrics (WLVP) is a unit of Wyeth-Ayerst Laboratories, which is a division of American Home

Products Corporation (AHP). AHP is a large pharmaceutical company which invests over $1 billion annually in research and development in such areas as cancer, infectious diseases, CNS disease, and cardiovascular disease. WLVP was recently formed through the merger of Lederle-Praxis Biologicals and Wyeth-Ayerst Vaccines following the acquisition of American Cyanamid by AHP. WLVP is heavily involved in vaccine research and is developing new vaccines for herpes, respiratory syncytial virus, rotavirus, bacterial meningitis, and pneumonia to complement its existing vaccines for DTP, *H. influenzae* type b, and polio.

HIV Vaccine Program: Wyeth's HIV vaccine development includes programs in gp120 V3 peptides, recombinant adenovirus, DNA vaccines, and mucosal immunization strategies. Prototype peptide and DNA vaccines developed in collaboration with Duke University and Apollon, respectively, have been tested in HIV-positive individuals and are entering trials in HIV-negative volunteers. Mucosal immunization strategies under preclinical evaluation include the delivery of DNA vaccines in lipid cochleates and subunit vaccines in biodegradable microspheres. These efforts are being carried out in collaboration with BioDelivery Sciences and the Southern Research Institute, respectively, with partial funding obtained from NIAID.

On a worldwide basis, private industry investment in HIV vaccine development is extremely limited. The number of companies with active HIV vaccine programs, the actual funds and staff being devoted to these programs, and the number of approaches being pursued, is, overall, quite discouraging.

The successful development of an HIV vaccine will require clearer focus on the scientific challenges, stronger leadership for the research effort, and greater public and private funding.

While existing industry efforts need to be encouraged, there is little reason to believe these programs will continue if the science seems too daunting in the short-term. In short, very few companies are making a sustained and comprehensive investment in HIV vaccine development.

Meanwhile, the epidemic marches on.