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PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS

RESEARCH SUBCOMMITTEE

Achieving the Goal of an AIDS Vaccine

Passed Recommendation

Background

Approximately 40,000 people become infected with HIV in the USA each year; worldwide, 6 million new infections occur annually. Although behavioral change to reduce risk of HIV infection is a viable strategy for some, it is clear that this strategy will not work for all. Only a preventive vaccine will ultimately be successful in stopping the AIDS pandemic. Commendably, President Clinton declared the goal, in May 1997, of a successful AIDS vaccine within the next decade. However, the current federal AIDS vaccine effort is stalled in paralyzing scientific debate and bureaucratic delay.

Since late 1995, the Research Committee of the Presidential Advisory Council on HIV and AIDS has devoted significant time and effort to issues concerning the development of an AIDS vaccine. The Committee consulted with numerous experts in AIDS research and vaccinology (Appendix A), and also solicited and received written input from these and other experts (Appendix B).

The scientific issues involved in vaccine development are extremely complex and controversial, and should be addressed by existing Federal agencies. NIH has an essential role to play in elucidating the basic scientific knowledge that underlies vaccine generation. However, this is only one aspect in the complete process of vaccine development. Additional administrative and policy structures will also be required to address the myriad public policy issues which must also be resolved, both nationally and internationally to expedite development of a successful AIDS vaccine. These issues include development and implementation of mechanisms to assure the active

participation and coordination of all relevant agencies of the US government, as well as the pharmaceutical industry and the international community, where candidate vaccines must be tested for efficacy, and where the need for an effective vaccine is the greatest. The recommendations which follow concern these administrative issues, which must be planned and coordinated simultaneously with the actual generation of candidate vaccines.

Requisite participants in vaccine development

Federal agencies: The proposed restructuring of the AIDS vaccine program within NIH represents an important step in expanding the scientific leadership which will be necessary to expedite the development of candidate vaccines. The appointment of Dr. David Baltimore as Chair of the AIDS Vaccine Research Committee (AVRC), the expanded vaccine budget, and the proposed institution of a new Vaccine Research Laboratory at the NIH, can all serve to invigorate the scientific process. The appointment of a full-time Director of the Vaccine Research Lab could provide another mechanism for coordination of the vaccine development effort within NIH. However, the Council is very concerned that recent progress has been slowed substantially by the failure to appoint this individual, who must be at the highest level of expertise.

In addition to NIH, Federal agencies such as the Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), and the United States Agency for International Development (USAID) have among them extensive experience and expertise in the area of vaccine development, field epidemiology, surveillance, and the conduct of vaccine efficacy trials, especially in developing countries. It would thus seem prudent to ensure the active cooperation, collaboration and communication of all relevant federal agencies in the areas of candidate vaccine development and testing, if the President's goal is to be met. Similar recommendations were made by the Levine Commission. However, although various NIH vaccine meetings have been attended by DOD and CDC representatives, and although an informal interagency group was formed, this group does not include senior leadership, and has not met on a regular basis. Thus, it is clear that no formal process of interagency coordination has been developed or implemented. If the President's goal is to be

met, such interagency communication and coordination must occur, involving the highest levels of leadership from each agency.

Pharmaceutical and biotechnology industries: It is clear that development of a successful AIDS vaccine will also require the active involvement of the pharmaceutical and biotechnology industries, working in a coordinated manner with relevant federal agencies. The pharmaceutical industry traditionally has been a major leader in the creation and development of vaccines, and should be encouraged to participate actively in the pursuit of an AIDS vaccine. Further, eventual product development will require the infrastructure and expertise which reside primarily within the private sector of pharmaceutical and biotechnology industries. To ensure the requisite coordination of both public and private sectors, an administrative mechanism must be created. Multiple policy issues must also be addressed, in an attempt to overcome existing financial disincentives for involvement by the private sector. This may entail subsidies for targeted applied research, cooperative agreements for pilot manufacture of vaccine approaches not commercially attractive, support of phase III human efficacy trials, tax rebates, and/or patent extensions. Federal leadership will also be needed to address related issues, such as intellectual property rights, liability, and international vaccine development and purchase funds.

International community: Due to the higher prevalence of HIV/AIDS in developing nations, the majority of clinical testing for efficacy of candidate vaccines (Phase III) must be accomplished internationally. Further, the majority of AIDS vaccine use is expected to occur in nations outside the USA. It is thus apparent that mechanisms to develop true partnerships between the international community and the federal AIDS vaccine effort must begin at once, with exchange of information and full coordination of combined efforts. Agencies such as the United Nations Program on AIDS (UNAIDS), the World Bank, the International AIDS Vaccine Initiative (IAVI), and the leading developed countries (G-8), as well as those countries most affected, have critical roles to play in the final testing and implementation of an AIDS vaccine. A mechanism must be developed to provide a means for ongoing communication and collaboration among these groups, as well as the other critical constituencies listed above. Critical issues which must be addressed by these groups

include active involvement in the process by scientists living in the countries involved, assurance of scientifically and ethically appropriate field testing of candidate vaccines, and mechanisms to ensure access to vaccine product after successful field testing.

Leadership and coordination

Role of the President's Office: It is only within the Office of the President that sufficient authority exists to ensure leadership, through coordination and collaboration of all requisite constituencies, including Federal agencies, private sector, and the international community. Responsibility for this effort should rest with the Office of National AIDS Policy (ONAP). The Council, therefore, recommends that the President formally charge the Director of ONAP with developing and maintaining administrative mechanisms for accomplishing the requisite communication and coordination among all relevant parties, including assurance of the involvement of senior leadership from all constituencies. Adequate resources must be made available for this function.

Generation of a Comprehensive Federal Plan for AIDS Vaccine Development: A Comprehensive Federal AIDS Vaccine Plan must be developed and implemented. This plan must include the vision and process for vaccine development, and must also depict the specific objectives, responsibilities, strategies and outcomes for the implementation of the plan. Additional requisites of the plan should include the framework by which competing issues may be addressed, an overall work schedule, and a specific time-frame in which certain milestones are to be accomplished. The Council recommends that the process for development of this plan be organized within the Office of National AIDS Policy, working with relevant federal agencies.

Moving candidate vaccines into human trials

Differences of opinion on the appropriate time for bringing AIDS vaccine strategies into human efficacy trials result from two divergent philosophical approaches. The "basic science"

approach pursues knowledge of the underlying biological mechanisms of retroviral disease and immunity in animal models and limited human studies, in order to elucidate the protective immune response. Candidate vaccines are then designed to induce those specific responses, and only then do human efficacy trials proceed. The "empirical science" approach brings vaccines into human trials relatively earlier, if comparable vaccines were safe and effective in animals, even without a clear understanding of their biological mechanisms of action. This has been the case for many existing vaccines in current use. With the gravity of the current AIDS pandemic in the world, and the need to proceed with vaccine development as quickly as possible, the Council acknowledges that it will be necessary to test various traditional and novel vaccine design strategies in human clinical trials, even before the scientific correlates of protection have been fully deciphered. We thus advocate the simultaneous implementation of both basic and empiric scientific approaches. These parallel approaches should be recognized within the comprehensive Federal plan for AIDS vaccine development.

Summary of Recommendations:

1. Substantive involvement, coordination, and collaboration among all relevant federal agencies, the private sector, and the international community are critical to the development of an effective AIDS vaccine.

2. Federal leadership at the highest level will be required, through the Office of National AIDS Policy, ensuring that adequate resources are provided for the coordination process necessary to achieve the goal of an effective AIDS vaccine.

3. The Office of National AIDS Policy should ensure the development and implementation of a comprehensive federal plan to achieve the goal of an effective AIDS vaccine.

4. The process of defining the structure and mission of the proposed (AIDS) Vaccine Center at NIH, and the appointment of a director with the highest level of expertise, should proceed promptly.

5. The urgent need for an AIDS vaccine mandates the simultaneous implementation of both basic and empiric scientific approaches.

APPENDIX A: LIST OF INFORMANTS

The following invited individuals formally discussed AIDS vaccine issues with the Committee or the Council on one or more occasions between April 1996 and October 1997. Listing here is solely to indicate the breadth of expertise and opinion received, and does not necessarily imply agreement or endorsement with the above analyses and recommendations.

1. David Baltimore, Ph.D.
   President, California Institute of Technology
   Chair, NIH AIDS Vaccine Research Committee

2. Seth Berkley, M.D.
   Rockefeller Foundation
   President, International AIDS Vaccine Initiative (IAVI)

3. Deborah Birx, M.D.
   Director of Retrovirology
   Walter Reed Army Institute of Research

4. Dani Bolognesi, Ph.D.
   Director, Center for AIDS Research
   Duke University
   Co-Director, Human Vaccine Institute

5. Larry Brilliant, M.D.
   Founder
   Seva Foundation

6. Donald S. Burke, M.D.
   Director, Center for Immunization Research
   School of Public Health
   John Hopkins University

7. Margaret Chesney, Ph.D.
   Center for AIDS Prevention Studies
   University of California, San Francisco

8. Mary-Lou Clements-Mann, M.D., Ph.D.
   Center for Immunization Research
   School of Public Health
   John Hopkins University

9. Chris Collins
   Center for AIDS Prevention Studies (CAPS)
   UCSF & VACT-UP

10. Dino Dina, M.D.
    President
    Chiron Vaccines Corporation

11. Burt Dorman, Ph.D.
President and CEO
Acrogen, Inc.

12. Jose Esparza, M.D., Ph.D.
Chief, Vaccine Development
United Nations Programme on AIDS (UNAIDS)

13. Max Essex, DVM, Ph.D.
Professor of Virology
Chairman, Harvard AIDS Institute
Harvard School of Public Health

14. Anthony S. Fauci, M.D.
Director
NIAID, NIH

15. Richard G.A. Feachem, Ph.D.
Senior Advisor Human Development
World Bank
Board of Directors, IAVI

16. Donald P. Francis, M.D., Sc.D.
President
VaxGen, Inc.

17. David Gold, JD
AIDS Vaccine Advocacy Coalition

18. William L. Heyward, M.D.
HIV Vaccine Coordinator
National Center for HIV, STD, and TB Prevention
Centers for Disease Control and Prevention

19. Maurice R. Hilleman, Ph.D.
Director
Merck Institute of Therapeutic Research

20. Margaret "Peggy" Johnston, Ph.D.
Scientific Director
International AIDS Vaccine Initiative (IAVI)

21. John Y. Killen, M.D.
Director, Division of AIDS
NIAID, NIH

22. Wayne Koff, M.D., Ph.D.
United Biomedical, Inc.

23. Yichen Lu, Ph.D.
Senior Scientist and Manager
HIV Program
Virus Research Institute, Inc.

24. Richard T. Mahoney, Ph.D.
Director, Institutional Development
International Vaccine Institute, Seoul, Korea

25. John G. McNeil, M.D.
Director,
DOD, HIV-1/AIDS Vaccine Development Program

26. Ronald Moss, M.D.
Medical Director
Immune Response Corporation

27. Kenrad E.Nelson, M.D.
Professor of Epidemiology
School of Public Health
John Hopkins University

28. William E. Paul, M.D.
Director
Office of AIDS Research, NIH

29. Peter Piot, M.D.
Executive Director
United Nations Programme on AIDS (UNAIDS)

30. Bryan Roberts, Ph.D.
Vice President of Research
Virus Research Institute, Inc.

31. Philip K. Russell, M.D.
John Hopkins University
Founding President, Albert B. Sabin Vaccine Foundation
Board of Directors, International AIDS Vaccine Initiative (IAVI)

32. Jerald C. Sadoff, M.D.
Executive Director, Vaccine Research
Merck Research Laboratories

33. Allan Schultz, Ph.D.
Chief, Vaccine Research and Development Branch
Division of AIDS, NIAID, NIH

34. Haynes "Chip" Sheppard, Ph.D.
Cellular Immunologist
Virus Laboratory
California Department of Health

35. William Snow
ACT-UP Golden Gate
Co-founder, AIDS Vaccine Advocacy Coalition (AVAC)
Member, NIH AIDS Vaccine Research Committee

36. Sten Vermund, M.D., Ph.D.
Professor of Epidemiology
President, Gorgas Memorial Institute for Tropical and
Geographic Medicine, University of Alabama

APPENDIX B: SOURCES OF ADDITIONAL WRITTEN INPUT

In response to a public solicitation by the Research Committee for comment and opinion, the following individuals provided written input between September and December 1995 (written documentation was also received by some of the informants listed above to supplement their verbal input). Listing is solely to indicate the breadth of opinion received, and does not necessarily imply agreement or endorsement with the above analyses and recommendations.

37. Abdul K. Abbas, M.D.
Professor of Pathology
Harvard Medical School

38. Arthur J. Ammann, M.D.
Director of Research
American Foundation for AIDS Research (AMFAR)

39. Dana Cappiello
Co-Founder
Until There's a Cure Foundation

40. Scott B. Halstead, M.D.
Director, Infectious Disease Research
Department of the Navy
(Former head, Health Sciences Division, Rockefeller Foundation)

41. Norman L. Letvin, M.D.
Chief, Division of Viral Pathogenesis, Beth Israel Hospital
Professor of Medicine, Harvard Medical School

42. John Moore, Ph.D.
Staff Investigator
Aaron Diamond AIDS Research Center

43. Lendon Payne, M.D., Ph.D.
Director of Research
Virus Research Institute, Inc.

44. Kathleen Scutchfield
Co-Founder
Until There's a Cure Foundation

45. Robert T. Schooley, M.D.
Professor of AIDS Research
University of Colorado Health Sciences Center

46. Raymond E. Spier, Ph.D.
Editor of the journal Vaccine
University of Surrey, UK

47. Jonathan T. Warren, Ph.D.
Immunologist, AIDS Vaccine Evaluation Group
The EMMES Corporation

48. Peter F. Wright, M.D.
Director, AIDS Vaccine Evaluation Unit
Professor of Pediatrics, Vanderbilt University School of Medicine

Todd -
From Daniel

FYI: Next Research Subcommittee
conference call is
Wed; 3/4 10 am.

Daniel Montoya
(202)632-1096

MEMORANDUM

TO Presidential Advisory Council on HIV/AIDS
Research Committee; Vaccine sub-committee

FROM Alexandra Levine,MD

DATE March 1, 1998

INRE NEXT DRAFT OF THE RECOMMENDATIONS ON VACCINES

First, I apologize for taking so long to come up with this next draft. I have been the Attending on general medicine at LAC-USC Med Center during February, and have been TOTALLY over my head (as opposed to partially) during the month.

Anyway, the revised document is enclosed. In making the revisions, I have taken into consideration the following: (1) all comments during our conference calls; (2) the written suggestions which I received; (3) some minor changes of my own, based upon the fact that I had not seen the document for 10 days, and could look at it "fresh", in terms of word smithing.

I have underlined all of the changes, and have written notes about these changes into the margins. If you want to see a clean copy, just call my secretary, Laurie Hornor, at 213-764-3913, and she will send one out to you.

I have not included language about the "pipeline", since I just don't like the language, and since I don't really think that this adds to the strength of our arguments. Also, please note that there ARE lots of candidate vaccines inthe "pipeline", as recently shown by IAVI. I have included a copy from one of their recent publications, detailing the fact that the pipeline is NOT empty, as our earlier drafts had implied. Also, please note that these candidate vaccines do NOT include anything but vector based approaches. In other words, there are other candidates, as well, employing other approaches.

Also, please note that there are essentially FIVE recommendations within this document: (1) A mechanism must be put into place to assure the on-going communcation and cooperation of ALL relevant federal agencies, as well as private sector and international communities; (2) A vaccine coordinator should be appointed within ONAP, whose job would be to coordinate the communication, and cooperation among all constutuencies (including federal agencies, private sector, and international community); (3) The Vaccine coordinator should be responsible for developing a comprehensive federal plan concerning development of an AIDS vaccine; (4) President Clinton should get involved in the appointment of the Director of the Vaccine Research Lab at the NIH; and (5) Both classic scientific approaches as well as approaches based upon thoughtful empiricism should be employed in an attempt to develop a successful AIDS vaccine. IN THE FINAL DOCUMENT, SHOULD THESE BE SUMMARIZED AT THE END OF THE SHEET? OR, WE COULD BOLD THEM IN THE TEXT, AS WELL. Please think about how you would want to depict this.

I have NOT included the appendices A and B within this FAX, since it is too long. However, they WILL be included within the full document, which will be seen by the full Council. OK: that's it for now. Talk to you all on Wednesday at 10:00am eastern. Please fax changes or corrections to me ASAP, if you have them before Wedensday.

TOTAL PAGES FAXED = 7
including this sheet

PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS

RESEARCH SUB-COMMITTEE

Achieving the Goal of an AIDS Vaccine

DRAFT # 5: 2/28/98

Background

In the USA, approximately 100 new people are infected with HIV each day; world-wide, 16,000-17,000 new infections occur on a daily basis. Although behavioral change to reduce risk of HIV infection is a viable strategy for some, it is clear that this stragegy will not work for all. It has thus become apparent that only a preventive vaccine will ultimately be successful in stopping the AIDS pandemic. In recognition of these facts, President Clinton declared his goal of development of a successful AIDS vaccine within the next decade.

Since late 1995, the Research Committee of the Presidential Advisory Counciol on HIV and AIDS has devoted signficiant time and effort to issues concerning the development of an AIDS vaccine. The Committee consulted with numerous experts in AIDS research and vaccinology (Appendix A). and also solicited and received written input from these and other experts (Appendix B).

The scientific issues involved in vaccine development are extremely complex and controversial, and can best be addressed by existing Federal agencies, including the National Institutes of Health, the world's premier biomedical research agency. The recent re-organization of the AIDS vaccine program within the NIH, with appointment of Dr. David Baltimore as Chairman of the NIH AIDS Vaccine Research Committee, is an extremely important step in meeting the President's stated goal, as is the commitment of Dr. Harold Varmus of the NIH.

Despite the ~~newly organized~~ proposed additional vaccine effort within NIH, however, it has become apparent to the Council that an appropriate administrative structure will also be required, in order to address the myriad of public policy issues which must also be resolved, both nationally and internationally, prior to implementation of a successful AIDS vaccine program. These issues include development and implementation of mechansims to assure active participation and

coordination of all relevant agencies of the US government, as well as the pharmaceutical industry, and the international community, where candidate vaccines must be tested for efficacy, and where the need for an effective vaccine is the greatest. The recommendations which follow concern these administrative issues, which must be planned and coordinated simultaneously with the actual generation of candidate vaccines .

I CLEANS up the language, and deleted concepts which were repeated in sections which followed

Requisite participants in vaccine development

Federal agencies: The recent restructuring of the AIDS vaccine program within NIH represents an important step in defining the scientific leadership which will be necessary to expedite the development of candidate vaccines. The appointment of Dr. David Baltimore as Chair of the AIDS Vaccine Research Committee (AVRC), the expanded vaccine budget, the institution of a new Vaccine Research Laboratory at the NIH, and the active and on-going participation of senior NIH leadership including it's Director, Dr. Harold Varmus, have all served to invigorate the scientific process which will be essential to vaccine generation. The Council supports these changes with enthusiasm. The appointment of a full time Director of the Vaccine Research Lab provides another mechansim for coordination of the vaccine development effort within NIH, although recent progress has been slowed substantially by the failure to appoint this individual, who must be at the highest level of expertise. The Council recommends the direct involvment of the President in an attempt to fill the post of Director of the Vaccine Research Lab within the NIH as quickly and successfully as possible.

Repetitive of 1st page of 3rd ¶

NEW

Each has different experience & expertise

In addition to NIH, Federal agencies such as the Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), and the United States Agency for International Development (USAID) ~~have~~ offer an array of extensive experience and expertise in the area of vaccine development, field epidemiology, surveillance, and the conduct of vaccine efficacy trials, especially in developing countries. It would thus seem prudent to assure the active cooperation, collaboration and communication among all relevant Federal agencies in the areas of candidate vaccine development and testing, if the President's goal is to be met. Although the Levine Report called for such coordination; although NIH vaccine meetings have been attended by DOD and CDC representatives; and although an informal interagency group was formed, this group does not include senior leadorship, and has not met on a regular basis. It is thus clear that no formal process of interagency coordination has yet been developed or implemented. If the President's goal is to be met, such interagency communication and coordination must occur,

reference needed

involving the highest levels of leadership from each Agency.

Pharmaceutical and biotechnology industries: It is clear that development of a successful AIDS vaccine will also require the active and independent involvement of the pharmaceutical and biotechnology industries. The pharmaceutical industry has traditionally been involved in development of vaccines, and should continue to be encouraged to participate actively in the pursuit of an AIDS vaccine. Further, eventual product development will require the infrastructure and expertise which/that resides primarily within the private sector of pharmaceutical and biotechnology industries. To assure the requisite coordination of both public and private sectors, an administrative mechanism must be created. Multiple policy issues must also be addressed, in an attempt to overcome existing financial disincentives for involvement by the private sector. This may entail subsidies for targeted applied research, cooperative agreements for pilot manufacture of vaccine approaches not commercially attractive, support of phase III human efficacy trials, tax rebates, and/or patent extensions. Federal leadership will also be needed to address related issues, such as intellectual property rights, liability, and international vaccine development and purchase funds.

FROM DRAFT #1 - Suggested by Bruce

International community: Due to the higher prevalence of HIV/AIDS in developing nations, the majority of clinical testing for efficacy of candidate vaccines (Phase III) must be accomplished internationally. Further, the majority of AIDS vaccine use is expected to occur in nations outside the USA. It is thus apparent that mechansims to exchange information and to coordinate international efforts must begin at once. Agencies such as the United Nations Program on AIDS (UNAIDS), the World Bank, the International AIDS Vaccine Initiative (IAVI), and the G-7 leading ~~developed~~ developed countries have critical roles to play in the final testing and implementation of an AIDS vaccine. A mechanism must be developed to provide a means for on-going communication among these groups, as well as the other critical constituencies listed above. Critical issues which must be addressed by these groups include active involvement in the process by scientists living in the countries involved, assurance of scientifically and ethically appropriate field testing of candidate vaccines, and mechanisms to assure access to vaccine product after successful field testing.

BROUGHT DOWN from original 1st page, + also augmented the issues as well.

Leadership and coordination

Role of the President's Office: It is only within the Office of the President that sufficient

authority exists to assure coordination and collaboration of all requisite constituencies, including Federal agencies, private sector, and the international community. A Vaccine Coordinator should be appointed within the Office of National AIDS Policy (ONAP), whose role will be to develop administrative mechansims for mandatory on-going dialogue and coordination among all relevant parties. This individual will be responsible for assuring the involvement of senior leadership in all constituencies, and for addressing problems or concerns as they arise; this individual will have no fiscal responsibility. The Vaccine Coordinator will report to the Director of ONAP, and will serve in a purely administrative capacity, assuring that the appropriate constituences are in communication, and providing input to the President when problems arise. Adequate resources must be made available for this function.

Development of a comprehensive federal plan: The Vaccine Coordinator within ONAP should be responsible for drafting a comprehensive plan for assurance of a successful AIDS vaccine. This plan must include the vision and process for vaccine development, and must also depict the specific objectives, responsibilities, strategies and outcomes for the implementation of the plan. Additional requisites of the plan should include the framework by which competing issues may be addressed, an over-all work schedule, and a specific time-frame in which certain milestones are to be accomplished.

ALL NEW

Candidate vaccines to be tested

Conceptually, the development of an AIDS vaccine could proceed by means of standard scientific inquiry, or via thoughtful empiricism. Employing the standard scientific method, various hypotheses are generated and then tested. With such study, the elucidation of protective immune responses to HIV can be determined, with subsequent use of this information in the design of candidate vaccines, and eventual human testing of promising vaccine candidates. The Council also acknowledges, however, that many of the currently used protective vaccines were initially developed without a clear understanding of the basic biological mechanisms which were likely to confer protection. With the gravity of the current AIDS pandemic in the world, and the need to proceed with vaccine development as quickly as possible, the Council acknowledges that it will be necessary to test various traditional and novel vaccine design strategies in human clinical trials, even before the scientific correlates of protection have been fully deciphered. We thus advocate the simulataneous implementation of both hypothesis-driven scientific studies, as well as studies based upon thoughtful empiricism.

TRIED TO OVERCOME MY OWN BIASES - HOPE. This is more "even" and fair to both approaches (see my note)

Vector-Based HIV Vaccines Currently in Development

Vaccines in Pre-clinical Research and Development

Vector	HIV/SIV content	Developer	Status
Adenovirus	env, gag	Marjorie Robert-Guroff National Cancer Institute, USA Wyeth-Ayerst, USA	chimps/macaques
Bacille Calmette-Gureh (BCG)	env-V3 [clades B and E] CTL epitopes	Mitsuo Honda National Institute of Infectious Diseases, Japan	macaques
BCG	nef peptides	Bridgette Gicquel Institut Pasteur, France	mice
Fowlpox+DNA	env, gag	Stephen Kent Macfarlane Burnet, Australia	macaques
Herpes simplex and vaccinia	gp160	Lynda Morrison Saint Louis University, USA	mice
Herpes virus	SIV	David Knipe Harvard/New England Primate Center, USA	macaques
Herpes simplex virus	SIV gag	Ann Hill Oregon Health Sciences University, USA	macaques
Human rhinovirus	V3 peptides	Gail Ferstandig Arnold Rutgers University, USA	mice
Listeria monocytogenes	SIV gag, env	M. Murphy-Corb/Y. Patterson University of Pittsburgh, USA	macaques
Modified Vaccinia Ankara (MVA) + gp140	env, gag-pol	B. Moss, V. Hirsch NIAID, USA	macaques
MVA	env, gag, pol, tat, rev, nef	A. Fleuchaus, G. Sutter GSF Institute for Molecular Biology, Germany	macaques
MVA	env, gag, pol	Gunnel Biberfield Karolinska Institute, Sweden	macaques
MVA+DNA	Multiple genes, CTL epitopes	Andrew McMichael Oxford University, UK	macaques
MVA+Fowlpox	env, gag, pol, nef	Therion	macaques
MVA+Influenza	core, envelope proteins	Peter Palese Mt. Sinai School of Medicine, USA	macaques
Pertussis	gag, nef, V3 peptide	Nicholas Carbonetti University of Maryland, USA Institute of Human Virology, USA	mice, macaques
Poliovirus	220 amino acids of HIV	Raul Andino University of California, San Francisco, USA	macaques
Polio replicon	SIV gag, env, nef HIV env (5 clades)	Patricia Fultz University of Alabama, Birmingham, USA	macaques
Recombinant polio	peptide fragments	Jeffrey Almond University of Reading, UK	mice
Saccharomyces cerevisiae	gp160	Richard Duke University of Colorado, USA	mice
Salmonella (mucosal)	env	Ruth Berggren University of Colorado, USA	mice

Vaccines in Pre-clinical Research and Development *(continued from page 3)*

Vector	HIV/SIV content	Developer	Status
Shigella	env	David Hone Institute of Human Virology, USA	mice
Streptococcus gordonii	gp120	Simonetta Di Fabio Istituto Superiore di Sanita, Italy	macaques
Vaccinia+subunit	gag, pol, env	Shui-Lok Hu University of Washington, USA	macaques
Venezuelan equine encephalitis (VEE) replicon	env, gag gene	Robert Johnston University of North Carolina, USA	macaques

Vectors In Human Studies

Vector	HIV content	Developer	Status
Canarypox-ALVAC vCP125	env	Pasteur-Mérieux-Connaught, France	Phase I
Canarypox-ALVAC vCP205	env; gag-protease	Pasteur-Mérieux-Connaught, France	Phase I, II
Canarypox-ALVAC vCP1433	env; gag-protease; nef/pol	Pasteur-Mérieux-Connaught, France	Phase I
Canarypox-ALVAC vCP205 mucosal	env; gag-protease	Pasteur-Mérieux-Connaught, France	Phase I
Salmonella typhi (attenuated)	env, gp120	Institute of Human Virology, USA Johns Hopkins, USA	Phase I
Vaccinia	env; gag-pol	Therion, USA	Phase I
Vaccinia	25 different env constructs	St. Jude's Hospital, USA	Phase I

Candidate vaccines are made from clade B strains of HIV unless otherwise specified. The information listed above was obtained through a review of scientific articles, abstracts and NIH grants, as well as discussions with a number of researchers. It is by no means a complete list of all vector-based HIV vaccine research. To add information on ongoing research to our database, please e-mail information to: dgold@iavi.org.

RECOMBINANT VECTOR VACCINES *continued from page 2*

Another approach is to delete a portion of the genes from the vector. By deleting approximately 10-15% of the genes in the vaccinia virus, researchers have produced an attenuated vaccinia vector. A related approach is to use a vaccinia strain that was "passaged" multiple times in chicken cells so that it barely replicates in mammalian cells. This virus is known as MVA (Modified Vaccinia Virus Ankara).

Still one more approach is to cleverly alter the packaged nucleic acid of a virus so that it can only replicate once in the host. This "replicon" technology is being evaluated in primate experiments for poliovirus and at least two alphaviruses, Semliki forest virus and Venezuelan equine encephalitis virus. Finally, it is possible to bypass the vector completely and just inoculate its DNA. One of the most promising developments has been the surprising immunogenicity of so-called "naked DNA." *[Editor's note: This article does not include DNA vaccines. They will be part of a separate article in an upcoming issue.]*

Although there are many advantages to the naked DNA approach, the biological properties that are unique to the different live vectors could be the key to successful immunization. For example, vaccinia infects a wide range of cell types and generally gets cleared from the body by the immune system, while herpes viruses target the nerves and are able to persist there. Other vectors, such as those that naturally infect the oral/nasal system (adenovirus, influenza, rhinovirus) or the gastrointestinal system (salmonella, polio) mucosa could induce good mucosal immune responses. (Childhood polio vaccines are given orally, and in chimpanzees, an adenovirus-vectored HIV vaccine is being tested through intranasal administration.)

There are still many uncertainties in attempting to design viral and bacterial vectors for use in an HIV vaccine. Researchers still remain fundamentally unsure as to which HIV antigens or specific immune responses are essential for generating protective immunity. Thus, determining the exact HIV genes to incorporate into a vector-based vaccine remains a very open research question. With this in mind, it is clear that the best approach is to encourage the development of a wide variety of vector-based vaccines and move promising approaches into animal studies and well-designed human trials. ◆

Alan Schultz oversees the Pre-clinical Research Branch of the U.S. NIAID's Vaccine and Prevention Research Program.

Research CC

2/10/98

add language
high-level person

"Coordinator"

need to be specific about support staff

next Az PACHA -
small panel ?

Single presenter, w/ support of 2 other committee members
vote <u>same</u> day

MEMORANDUM

TO Daniel Montoya
White House

Members of vaccine sub-committee of Research Committee
PACHA

FROM Alexandra Levine,MD

DATE February 9, 1998

INRE DRAFT #4 OF THE DOCUMENT

I thought the call last week was VERY valuable, and I have tried to take the various comments into account on this draft.

There are two things which I did not change, and I wanted to state the "why" at this point. First, I LEFT the leadership piece toward the end, since it didn't make sense to say that this whole big piece could only be organized within the White House until we said WHAT the "whole big piece" really IS. I just think we have to define the players and the problems first, before we say that the coordination must occur, and must occur in the White House.

Second, I did not change the language on the first line of the last section on Candidate vaccines...read very carefully, and I think you will agree...the most logical approach to ASSURE a vaccine is to go, bit by bit, through all of the science, allowing the answer to one question lead you on to the next, and so forth. HOWEVER, we also state that the problem is so overwhelming that we cannot depend upon the scientific method alone, but MUST also go forward with empiricism....point is this: if you "shoot off the hip" and think you might have a home run, you very well might, and we should proceed along these lines ALSO. BUT, this type of METHOD of study does not ASSURE an eventually successful effort. Either you hit the home run, or it's an out. Then, you start all over, trying for another home run. We do NOT say that scientific method is the ONLY method to be employed. We say BOTH, which I personally believe is the only way to go. However, please read the first line very carefully---scientific method, in the long run (and that's the problem with it) IS the only way to ASSURE that you'll get there, eventually.

OK: that's it for now. Be well everyone.

10 A.M.
Conf. call
today

PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS

RESEARCH SUB-COMMITTEE

Achieving the Goal of an AIDS Vaccine

Background

In the USA, approximately 100 new people are infected with HIV each day; world-wide, 16,000-17,000 new infections occur on a daily basis. Although behavioral change to reduce risk of HIV infection is a viable strategy for some, it is clear that this stragegy will not work for all. It has thus become apparent that only a preventive vaccine will ultimately be successful in stopping the AIDS pandemic. In recognition of these facts, President Clinton declared his goal of development of a successful AIDS vaccine within the next decade.

Since late 1995, the Research Committee of the Presidential Advisory Council on HIV and AIDS has devoted signficiant time and effort to issues concerning the development of an AIDS vaccine. The Committee consulted with numerous experts in AIDS research and vaccinology (Appendix A), and also solicited and received written input from these and other experts (Appendix B).

The scientific issues involved in vaccine development are extremely complex and controversial, and can best be addressed by existing Federal agencies, including the National Institutes of Health, the world's premier biomedical research agency. The recent re-organization of the AIDS vaccine program within the NIH, with appointment of Dr. David Baltimore as Chairman of the NIH AIDS Vaccine Research Committee, is an extremely important step in meeting the President's stated goal, as is the commitment of Dr. Harold Varmus of the NIH.

Despite the newly organized vaccine effort within NIH, however, it has become apparent to the Council that an appropriate administrative structure will also be required, in order to address the myriad of public policy issues which must also be resolved, both nationally and internationally, prior to implementation of a successful AIDS vaccine program. These issues include development and implementation of mechansims to assure active participation of the pharmaceutical industry, resolution of issues such as intellectual property rights, and regulatory and liability concerns, and the involvement of the international community, where

candidate vaccines must be tested, and where the greatest quantity of vaccine will be used. Specific administrative mechanisms must be in place to assure scientifically and ethically appropriate field testing of candidate vaccines; other mechanisms will be required to assure a fully coordinated effort among all relevant agencies of the US government in collaboration with the private sector and international representatives. The recommendations which follow concern these administrative issues, which must be planned and coordinated simultaneously with the actual generation of candidate vaccines .

Requisite participants in vaccine development

Federal agencies: The recent restructuring of the AIDS vaccine program within NIH represents an important step in defining the scientific leadership which will be necessary to expedite the development of candidate vaccines. The appointment of Dr. David Baltimore as Chair of the AIDS Vaccine Research Committee (AVRC), the expanded vaccine budget, the institution of a new Vaccine Research Laboratory at the NIH, and the active and on-going participation of senior NIH leadership including it's Director, Dr. Harold Varmus, have all served to invigorate the scientific process which will be essential to vaccine generation. The appointment of a full time Director of the Vaccine Research Lab provides another mechansim for coordination of the vaccine development effort within NIH, although recent progress has been slowed by the failure to appoint this individual. The Council supports these changes with enthusiasm.

In addition to NIH, Federal agencies such as the Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), and the United States Agency for International Development (USAID) have extensive experience and expertise in the area of vaccine development, field epidemiology, surveillance, and the conduct of vaccine efficacy trials, especially in developing countries. It would thus seem prudent to assure the active collaboration and coordination of all relevant Federal agencies in the areas of candidate vaccine development and testing, if the President's goal is to be met. _ Although the Levine Report called for such coordination; although NIH vaccine meetings have been attended by DOD and CDC representatives; and although an informal interagency group was formed, this group does not include senior leadership, and has not met on a regular basis. It is thus clear that no formal process of interagency coordination has yet been developed or implemented. If the President's goal is to be met, such interagency coordination must occur, involving the highest levels of

leadership from each Agency.

Pharmaceutical industry, and regulatory agencies (FDA): It is clear that the scientific efforts of NIH and other Federal agencies must remain independent of the pharmaceutical industry in terms of the development of candidate AIDS vaccines. However, the pharmaceutical industry has traditionally been involved in development of vaccines, and should be encouraged to participate actively in the pursuit of an AIDS vaccine. Further, eventual product development will require the infrastructure and expertise which resides primarily in the private sector (pharmaceutical and biotechnology industries). To assure the requisite coordination of both public and private sectors, an administrative mechanism must be created. Multiple policy issues must also be addressed, such as intellectual property rights, financial incentives, tax rebates, subsidies for vaccine approaches not commerially attractive, patent extensions, and liability concerns.

International community: Due to the higher prevalence of HIV/AIDS in developing nations, the majority of clinical testing for efficacy of candidate vaccines (Phase III) must be accomplished internationally. Further, the majority of AIDS vaccine use is expected to occur in nations outside the USA. It is thus apparent that mechansims to exchange information and to coordinate international efforts must begin at once. Agencies such as the United Nations Program on AIDS (UNAIDS), the World Bank, the International AIDS Vaccine Initiative (IAVI), and the G-7 countries have critical roles to play in the final testing and implementation of an AIDS vaccine. A mechanism must be developed at once to provide a means for on-going communication among these groups, and among the other critical constituencies listed above.

Leadership and coordination

Role of the President's Office: It is only within the Office of the President that sufficient authority exists to assure coordination and collaboration of all requisite constituencies, including Federal agencies, private sector, and the international community. A Vaccine Administrator should be appointed within the Office of National AIDS Policy (ONAP), whose role will be to develop administrative mechansims for mandatory on-going dialogue and coordination among all relevant parties. This individual will be responsible for assuring the involvement of senior leadership in all constituencies, and for addressing problems or concerns as they arise; this individual will have no fiscal responsibility. The Vaccine Administrator will report to

the Director of ONAP, and will serve in a purely administrative capacity, assuring that the appropriate constituences are in communication, and providing input to the President when problems arise. Adequate resources must be made available for this function.

Candidate vaccines to be tested

The most logical way to assure the eventual development of a successful AIDS vaccine will be to proceed scientifically, with the generation of hypotheses, and the testing of these hypotheses by means of standard scientific inquiry. With such study, the elucidation of protective immune responses to HIV can be determined, with subsequent use of this information in the design of candidate vaccines, and eventual human testing of promising vaccine candidates. The Council also acknowledges, however, that many of the currently used protective vaccines were initially developed without a clear understanding of the basic biological mechanisms which were likely to confer protection. With the gravity of the current AIDS pandemic in the world, and the need to proceed with vaccine development as quickly as possible, the Council acknowledges that it will be necessary to test various traditional and novel vaccine design strategies in human clinical trials, even before the scientific correlates of protection have been fully deciphered. We thus advocate the simulataneous implementation of both hypothesis-driven scientific studies, as well as studies based upon thoughtful empiricism.

M2

- Why does the Council think the NIH **must** remain independent of the pharmaceutical industry in terms of candidate vaccines? Page 3

It almost sounds as if they are saying NIH should do its it research, the private sector do its own, and lets see who gets there first. At the same time they are clamoring for coordination with the private sector and within government.

- The real issue seems to be a concern that the various players are not talking with each other. Thus, why not have each Department (CDC, NIH, DOD, UNAIDS) name an AIDS coordinator who would meet quarterly with the others, in a meeting chaired by ONAP; an Interagency Task Force on Vaccine Development. Page 4

A summary of the meeting would be developed and shared with interested parties, including information about attendance. ONAP's role would be to ensure that the meeting occurs, and the summary report is developed -- no more.

This group would then issue a report every six months/year to the President on progress in meeting the 10 year goal. This position is less than an "administrative coordinator" since his/her job will be only to schedule the meetings. The Departments would still be responsible for developing the report, presenting at the meeting, etc. Non-feds would be invited to attend/present as necessary.

- the draft clearly states that they will concern themselves only with administrative issues, not scientific issues. Yet the section "candidate vaccines to be tested" deals with scientific issues., calling for both hypothesis-driven and empirical studies. Page 4

Format Issue:

I think they should state up front what their recommendation is and then follow-up with narrative explaining why it is important. They should use the recommendation/justification format so that people know what the recommendation is up front and then read the rationale.

Many of the paragraphs are awkward (last paragraph, page 1; last paragraph, page 2)

NOTE:

UNDERLINED TEXT ON THE DRAFT IS TO BE Deleted.

BOLDED TEXT IS NEW TO THIS VERSION.

DRAFT #3 - 2/4/98

PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS
RESEARCH SUB-COMMITTEE
Recommendations concerning development of an effective AIDS vaccine

In the USA, approximately 100 people are infected with HIV each day; world-wide, 8,000 to 9,000 new infections occur on a daily basis. Despite institution of multiple behavioral risk reduction strategies, it has become apparent that only a preventive vaccine will ultimately be successful in stopping the AIDS pandemic. In recognition of these facts, President Clinton declared his goal of development of a successful AIDS vaccine within the next decade.

The scientific issues involved in vaccine development are extremely complex and controversial; the Presidential Advisory Council on HIV/AIDS has neither the expertise nor the desire to address these complexities. Further, the National Institutes of Health, the world's premier biomedical research agency, is well equipped to provide the scientific focus and leadership required. The recent re-organization of the AIDS vaccine program within the NIH, under the strong leadership of Dr. David Baltimore, is an extremely important step in meeting the President's stated goal, and will, in all probability, lead to the generation of a series of scientifically valid candidate vaccines for future testing.

Despite the newly organized vaccine effort within NIH, however, it has become apparent to the Council that an appropriate administrative structure will also be required, in order to address the myriad of public policy issues which must also be resolved, both nationally and internationally, prior to implementation of a successful AIDS vaccine program. These policy issues include development and implementation of mechanisms to assure active participation of the pharmaceutical industry, to address issues such as intellectual property rights, regulatory and liability concerns, and to involve the international community, where candidate vaccines must be tested, and where the bulk of vaccine product will be used. Specific administrative mechanisms must be in place to assure

scientifically and ethically appropriate field testing of candidate vaccines, while other mechanisms will be required to assure a fully coordinated effort among all relevant agencies of the US government. The recommendations which follow concern these administrative issues, which must be planned and coordinated simultaneously with the actual generation of candidate vaccines.

Administrative leadership and coordination

Scientific (NIH): The recent restructuring of the AIDS vaccine program within NIH represents an important step in defining the scientific leadership which will be necessary to expedite the development of candidate vaccines. The appointment of Dr. David Baltimore as Chair of the AIDS Vaccine Research Committee (AVRC), the institution of a new Vaccine Research Laboratory at the NIH, and the active and on-going participation of senior NIH leadership including its Director, Dr. Harold Varmus, have all served to invigorate the scientific process which will be essential to vaccine generation. The appointment of a full time Director of the Vaccine Research Lab provides another mechanism for coordination of the vaccine development effort within NIH. The Council supports these changes with enthusiasm.

Scientific: Other Federal agencies: Aside from NIH, agencies such as the Centers for Disease Control and Prevention (CDC), Department of Defense (DOD), and the United States Agency for International Development (USAID) have extensive experience and expertise in the area **vaccine development**, of field epidemiology, surveillance, and the conduct of vaccine efficacy trials, especially in developing countries. **Since this high level of expertise currently exists, it would seem prudent to assure the active participation and coordination of these agencies in the areas of candidate vaccine development and testing, if the President's goal is to be met.** The Council agrees with the NIH-commissioned Levine Report on AIDS Vaccines, that "...in parallel with basic development and preclinical testing of a variety of vaccine candidates, it is essential to prepare cohorts within different populations well in advance of efficacy trials". It is clear that the activities of all relevant Federal agencies must be coordinated simultaneously with the scientific

efforts of the NIH. Although the Levine Report called for such coordination, although NIH vaccine meetings have been attended by DOD and CDC representatives, and although an informal interagency group was formed, this group is not comprised of senior leadership, and has not met on a regular basis. It is clear that no formal process of interagency coordination has yet been developed or implemented. If the President's goal is to be met, such interagency coordination must occur, involving the highest levels of leadership from each Agency.

Pharmaceutical industry, and regulatory agencies (FDA): It is clear that the scientific efforts of NIH must remain independent of the pharmaceutical industry in terms of the development of candidate AIDS vaccines. It is also clear, however, **that the pharmaceutical industry must also be involved in development of candidate vaccines. Further,** eventual product development will require the infrastructure and expertise which resides primarily in the private sector (pharmaceutical and biotechnology industries). Since industry **will be involved in generation of candidate vaccines, and** be called upon to further develop the more promising candidate vaccines, an administrative mechanism must be developed to assure coordination of the public and private sectors. Federal leadership will be required to address a host of essential issues, such as intellectual property rights, financial incentives, tax rebates, subsidies for vaccine approaches not commercially attractive, patent extensions, and liability issues.

International community: Due to the higher prevalence of HIV/AIDS in developing nations, **the majority of** clinical testing for efficacy of candidate vaccines (Phase III) must be accomplished internationally. Further, the majority of AIDS vaccine use is expected to occur in nations outside the USA. It if thus apparent that mechanisms to exchange information and to coordinate international efforts must begin at once, if the President's goal is to be achieved. Agencies such as the United Nations Program on AIDS (UNAIDS), the World Bank, the International AIDS Vaccine Initiative (IAVI), and the G-7 countries have critical roles to play in the final testing and implementation of an AIDS vaccine. A mechanism must be developed at once to provide a means for on-going communication

among these groups, and among the other critical constituencies listed above.

Role of the President's Office in coordination of full vaccine effort: It is only within the Office of the President that sufficient authority exists to assure coordination of all requisite constituencies, including Federal agencies, private sector, and the international community. A Vaccine Coordinator should be appointed within the Office of National AIDS Policy (ONAP), whose role will be to develop administrative mechanisms for mandatory on-going dialogue and coordination among all relevant parties. This individual will be responsible for assuring the involvement of senior leadership in all constituencies, and for addressing problems or concerns as they arise; this individual will have no fiscal responsibility. The Vaccine Coordinator will serve in a purely administrative capacity, assuring that the appropriate constituencies are in communication, providing input to the President when problems arise, and assuring that all administrative mechanisms are in place to achieve the President's stated goal of an AIDS vaccine within one decade.

Candidate vaccines to be tested

The most logical way to assure the eventual development of a successful AIDS vaccine will be to proceed scientifically, with the generation of hypotheses, and the testing of these hypotheses by means of standard scientific inquiry. With such study, the elucidation of protective immune responses to HIV can be determined, with subsequent design of appropriate candidate vaccines, and eventual human testing of promising candidates. The Council also acknowledges, however, that many of the currently used protective vaccines were initially developed without a clear understanding of the basic biological mechanisms which were likely to confer protection. With the gravity of the current AIDS pandemic in the world, and the need to proceed with vaccine development as quickly as possible, the Council acknowledges that it will be necessary to test various traditional and novel vaccine design strategies in human clinical trials, even before the scientific correlates of protection have been fully deciphered. We thus advocate the simultaneous implementation of both hypothesis-driven scientific studies, as well as studies based upon thoughtful empiricism.

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Re: Sharing Johnston feedback with Resc. Comm.

>X-Sender: dburke@phir.sph.jhu.edu
>Date: Tue, 18 Nov 1997 16:21:00 -0500
>To: Helen Miramontes <helenmm@itsa.ucsf.edu>
>From: Don Burke <dburke@phir.sph.jhu.edu>
>Subject: Re: Sharing Johnston feedback with Resc. Comm.
>
>
>Helen,
> I think you should stand firm on the issue of a comprehensive plan. I
>disagree with Pegyy - I don't think the exercise would be useless, and it
>seems clear to me that something must be done to alter present course. I do
>agree with her on the point that unless there is clear leadership that plan
>development won't get very far. But we should lay out the ideal approach
>and stick with it - and this should include a thoughtful comprehensive
>plan. Don
>**********
>Donald S. Burke, M.D.
>Director, Center for Immunization Research
>School of Hygiene and Public Health
>Johns Hopkins University
>Room 241 Hampton House
>624 North Broadway
>Baltimore, Maryland 21205
>Phone (410) 614 - 5960
>Fax (410) 502 - 6898
>email <dburke@jhsph.edu> (! Note new email address !)
>**********
>
>

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Feedback from David Sencer on Res. Comm. Document

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Montoya, Daniel (WhiteHouse ONAP)'" <Montoya_DC@a1.eop.gov>
>Cc: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>,
> "'Levine, Alexandra (PACHA)'" <hornor@hsc.usc.edu>
>Subject: Feedback from David Sencer on Res. Comm. Document
>Date: Fri, 21 Nov 1997 18:13:00 -0500
>
>
>Dear Daniel,
> I received permission from Dr. David Sencer
>to share his feedback and comments to me about the
>Research Committee's draft document with the other
>Council members. Please add this to the documents
>you are assembling and will be sharing with us in
>the briefing book or handouts.
>
> FYI, Dr. Sencer is a former director of the
>CDC (pre-AIDS epidemic) and former Commissioner
>of Health of New York City (during onset of the
>epidemic).
>
> Thanks,
> Bruce
>
> ----------
>From: David J. Sencer
>To: Weniger, Bruce
>Subject: Re: Draft PACHA AIDS vaccine document
>Date: 20 November, 1997 13:16
>
>Bruce,
>
>Thanks for the opportunity to look at your draft document.
>Let me speak only as characterized by Harvey Fineburg
>as an "able, wily bureaucrat," not as a scientist.
>
>You propose:
>To complement the Vice-President+s role, the President
>should appoint a respected and accomplished leader in
>public health/medical science as the National Director for
>AIDS Vaccine Development. This should be a full time
>position in a semi-autonomous environment sufficiently

>high in the Government hierarchy to: (1) be an advocate
>for AIDS vaccine development, (2) have fiscal authority
>over all government AIDS vaccine efforts, (3) provide
>strong leadership and coordinate all government
>organizations involved in this field, (4) maintain close
>relationships with vaccine developers in the private sector,
>and (5) martial the resources and cooperation of other
>nations, international organizations, and the philanthropic
>community.
>
>As nice and neat as that may sound, the track record for
>positions such as that is not great: "Drug Tsar" or "Whatever
>Sandy Thurman is called" or the even the President's
>Science Advisor (I don't even know the current one's name!).
>
>VP Gore has had more impact than many VP's but most of it
>has been marginal not really policy determining or more
>importantly, budget allocations.
>
>I have found that when extraagency pressures (from the
>Secretary's Office or higher) try to influence scientific priorities,
>the agencies do not respond as well as if they developed
>those priorities themselves.
>
>Interagency communication is best facilitated by the workers
>not by the bosses (Sencer's Maxim III).
>
>Dave
>
>

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Re: Feedback from David Sencer on Res. Comm. Document

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: Helen Miramontes <helenmm@itsa.ucsf.edu>
>Subject: Re: Feedback from David Sencer on Res. Comm. Document
>Date: Tue, 25 Nov 1997 14:02:00 -0500
>
>
>Helen,
> See below for the comments from David Sencer.
> Bruce
>
> ----------
>From: Helen Miramontes
>To: Weniger, Bruce; Montoya_dc@a1.eop.gov
>Subject: Re: Feedback from David Sencer on Res.
>Comm. Document
>Date: 23 November, 1997 23:20
>
>Bruce,
>
>please send these comments to me - I will put them
>together for Danile in one packet - Didn't you get my
>email from the 20th about this?
>
>helen
>
>
>+++++++++++++++++++++++++++++++
>
>Dr. Sencer is a former director of the CDC (in the
>pre-AIDS era) and former Commissioner of Health of
>New York City (during onset of the epidemic).
>
> --
>From: David J. Sencer
>To: Weniger, Bruce
>Subject: Re: Draft PACHA AIDS vaccine document
>Date: 20 November, 1997 13:16
>
>Bruce,
>
>Thanks for the opportunity to look at your draft
>document. Let me speak only as characterized by

>Harvey Fineburg as an "able, wily bureaucrat," not as
>a scientist.
>
>You propose:
>To complement the Vice-President's role, the President
>should appoint a respected and accomplished leader in
>public health/medical science as the National Director for
>AIDS Vaccine Development. This should be a full time
>position in a semi-autonomous environment sufficiently
>high in the Government hierarchy to: (1) be an advocate
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>"Whatever Sandy Thurman is called" or the even the
>President's Science Advisor (I don't even know the
>current one's name!).
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>has been marginal not really policy determining or more
>importantly, budget allocations.
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>I have found that when extraagency pressures (from the
>Secretary's Office or higher) try to influence scientific priorities,
>the agencies do not respond as well as if they developed
>those priorities themselves.
>
>Interagency communication is best facilitated by the workers
>not by the bosses (Sencer's Maxim III).
>
>Dave
>
>
>
>

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Comments from Dr. Harriet Robinson

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: Comments from Dr. Harriet Robinson
>Date: Tue, 25 Nov 1997 13:56:00 -0500
>
>
>Dear Helen,
> Comments from Dr. Harriet Robinson, a
>DNA vaccine researcher, now at Emory University
>and formerly Professor of Pathology at the University
>of Massachusetts.
> Thanks,
> Bruce
>
>+++++++++++++++++++++++++++++++++++
>
>From: Harriet.Robinson@banyan.ummed.edu
>To: bgw2@cdc.gov
>Subject: ...no subject...
>Date: 20 November, 1997 12:42
>
>Dear Bruce,
>
>Thank you for forwarding the draft analysis for
>recommendations on AIDS vaccines. In the vaccine
>development approach section: I agree about the
>importance of human trials. However, I think the
>SHIV/macaque models should not be totally discounted.
>
>Using the SHIV models one can conduct challenges that
>are graded in virulence with a number of different HIV-1
>envelope glycoproteins. These challenge allow
>determination of correlates of protection; correlates that
>can then be used as benchmarks for immune responses
>being raised in human trials.
>
>To me the ideal scenario is one where preclinical testing
>in macaque models serves to identify correlates of
>protection (which are likely to hold for HIV-1 in humans)
>with parallell human trials being used to assess
>immunogenicity in humans. The macaques can also be
>used for an initial assessment of safety and efficacy of

>novel approaches.
>
>Therefore I would not be too negative on the importance
>of continued work in the macaque models, to parallel and
>in some cases come before trials in humans.
>
>Sincerely yours,
>
>Harriet Robinson
>
>

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Peggy Johnston's comments

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: Peggy Johnston's comments
>Date: Tue, 25 Nov 1997 13:35:00 -0500
>
>
>Dear Helen,
> Here are Peggy Johnston's comments for the
>compilation.
> Bruce
>
> ----------
>From: Margaret Johnston (IAVI)
>To: Weniger, Bruce; Sam Avrett
>Cc: Helen Miramontes; Seth Berkley; Phil Russell;
>INTERNET:bkovacs@iavi.org; Hanna Sarn
>Subject: Draft PACHA AIDS Vaccine Recommendations
>Date: 18 November, 1997 12:32
>
>Bruce,
>
>In brief, here is a summary of my comments/concerns:
>
> 1. A comprehensive plan. I remain skeptical. I have
>participated creating way too many plans on paper, forced
>from on high, to believe that another plan on paper is going
>to make any difference in what the government does. A
>plan only works when the people responsible for
>implementing the plan want to implement the plan. Here is
>where #2 is important.
>
> 2. Leadership. Overall, I would encourage someone
>in the VP office to be involved. However, I think not
>realistic to think that that person would have budget
>authority over all the vaccine dollars (e.g. HHS,
>Defense, etc). The Secretaries would have to give up too
>much. That said, by virtue of being in the VP office, the
>person could weld considerable power, especially behind
>the scenes in getting people to work together, and
>in representing the US on international issues and
>non-scientific issues.
>

> 3. planning and process and goals. This comes
>across as far too much work for what will come out in the
>end, which will likely be a collection of contributions
>describing what is already ongoing and planned
>sewn together by a good writer. Perhaps what needs to
>change can be changed by #2 without going through this
>sort of "process". (take a look at the NIH OAR review
>process, report and implementation plan.....golly....so many
>hours and dollars spent, trees destroyed and for
>what? I contend there is not one change happening that
>could not have happened without leadership. Now,
>PACHA may feel that what is needed is "buy in" for
>change. And I admit that this sort of process is great at
>getting buy in even when the course of action is well
>known. I'd ask if there may be an easier and quicker way
>to get that buy in. and perhaps the person designated in
>#2 should make that call.
>
> 4. basic science research. clear and on target.
> 5. vaccine development approach. clear and on target.
> 6. product development - clear and on target.
>
> 7. phase III trials - this gets at the crux, and may be
>the only area worthy of consideration in #3 above. getting
>all the agencies to work together is key. my impression is
>that the army and the NIH already work well together, at least
>to the extent that they are working in the same countries.
>they talk alot, which is facilitated by their geographic
>proximity. What is missing is USAID and CDC to get into
>this loop. In my opinion, this will require that individuals be
>designated with the responsibility to make that communication
>happen, and to be held accountable for making it work.
>
>Thanks for the opportunity to comment. I look forward to
>continued interactions with PACHA and applaud your
>dedication, interest and efforts to get the attention this needs
>at the highest levels in the US.
>
>Peggy
>
>

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: WHO/GPV comments on vaccine document

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: WHO/GPV comments on vaccine document
>Date: Fri, 28 Nov 1997 11:48:00 -0500
>
>
>Dear Helen,
> Below are informal comments shared with me
>from WHO on the draft document. The first
>is from Peter Evans and the second from Mark Miller
>in the WHO Global Programme on Vaccines and
>Immunizations (GPV).
>
> If you bring to Washington a set of all the
>comments I have been e-mailing you, it should be
>possible to make copies for the notebooks of the
>Research Committee members.
>
> Thanks,
>
> Bruce
>
>+++++++++++++++++++++++++++++++++++
>From: millermark@who.ch
>To: Weniger; Bruce; evansp@who.ch
>Subject: Re[3]: Draft PACHA AIDS vaccine document
>Date: 27 November, 1997 11:19
>
>Bruce, response from Peter Evans, GPV Unit Chief
>Vaccine Supply and Quality
>
>Regards, Mark
>
>
>_____ Reply Separator_____
>Subject: Re[2]: Draft PACHA AIDS vaccine document
>Author: P.M. EVANS at whohq3
>Date: 27-11-97 4:28 PM
>
> Mark,
>
> Thank you for sharing the document with me and for you own

> introductory remarks.
>
> At first glance at the paper and the list of informants it would
> appear as if the science of creation is receiving high attention.
> This will give the best possible chance for people in the
> industrialised countries to receive protection at an early date.
> What is not clear is if anything different about the introduction
> is being addressed. Unless several steps are taken this vaccine
> will follow the route of other vaccines widely needed and becoming
> available in the last decade or so. The vaccine will be available
> in limited quantities at high prices to a restricted market.
> Eventually after 5 years when this high value market is saturated
> additional capacity will become available for a second tier market
> and eventually after another few years sufficient capacity will be
> installed to allow for all markets to be served. This doesn't have
> to happen this way but the paper does not give any reason to think
> that something different will happen for an AIDS vaccine.
>
> peter
>
>
> _____ Reply Separator_____
> Subject: Re: Draft PACHA AIDS vaccine document
> Author: M. MILLER at whohq2
> Date: 19/11/97 10:31
>
> Bruce,
> Thank your for sending me the draft document. I believe you
> covered most of the pertinent issues. You may wish to address some
> of the issues regarding the eventual delivery and affordability of
> a vaccine at the global level. All too often, not enough thought
> is given up front to the practical issues of delivering affordable
> public health interventions to areas with the greatest disease
> burden. I would hope that any AIDS vaccine would have the
> characteristics to be able reach the global population in a timely
> manner, unlike many other new vaccines.
>
> I will send your comments to Drs. Lee, Widdus and other GPV unit
> chiefs for further comments.
>
> Regards,
> Mark
>
>

helenmm @ itsa.ucsf.edu
11/30/97 08:19:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: David Baltimore comments for compilation

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: David Baltimore comments for compilation
>Date: Fri, 28 Nov 1997 16:57:00 -0500
>
>
>Dear Helen,
> Kindly please add Dr. Baltimore's comments
>below to your compilation for the research committee.
> Thanks,
> Bruce
>
> ----------
>From: David Baltimore
>To: Weniger, Bruce
>Cc: Carole Heilman
>Subject: Re: Draft PACHA AIDS Vaccine Recommendations
>Date: 28 November, 1997 16:30
>
>Dear Bruce,
>
>I thought I'd share with you my reaction to your draft report, even
>though
>I suspect you will hear similar things from others.
>
>Without tooting my own horn too much, I think that the vaccine program
>is
>not in such bad shape and is shaping up. While it can always use
>further
>organization, the program is not so disorganized that it needs a
>wholesale
>revamping. It certainly shouldn't be directed from the White House
>because
>many key issues are NIH issues and the capability to handle them is in
>NIH.
>Everything has to be done with an eye to ultimate industrial production
>of
>a vaccine but just where industry becomes involved is an open question
>and
>depends on its perspective on particular candidates. There are many
>ancillary issues beyond the actual production of vaccine candidates and
>they certainly do need attention but they haven't been ignored.

>
>The urgency of the situation is unquestionable but I do not believe that
>a
>Director appointed over the existing authorities, with fiscal and
>managerial responsibility over them is the answer. There is a new
>senior
>person to be appointed in DAIDS and he or she probably should have more
>national visibility than previously. There is a new OAR Director to be
>appointed and that is another opportunity to bring distinction to the
>program. Working outside or above these channels would bring
>disorganization to the process and would completely disrupt the
>integrated
>activities that now exist. It is important to remember that the AIDS
>vaccine program increasingly draws on the full resources of NIH,
>especially
>on protein structural, immunological and virological problems.
>
>There is a lot of value in having a few parallel programs so that no one
>person has purview over all decisions about directions of research. For
>instance, I disagree with some of the aims of the DOD program but I'm
>glad
>that it can pursue its ideas without asking my approval so that "many
>flowers can bloom".
>
>As your draft acknowledges, the new AIDS Vaccine Lab at NIH offers the
>opportunity to bring in someone who can mount a coordinated program on
>the
>NIH campus. I hope that such a lab will have access to the facilities
>to
>make vaccine candidates for testing so that the Director can carry a
>candidate up to the stage where industry can take it over. At the same
>time, the Lab should be independent of industry so that it can pursue
>its
>own ideas.
>
>We all agree that we need more candidates and need to get them to the
>field
>testing stage faster and in larger numbers. I believe that there are
>more
>effective ways of reaching this goal than appointing a czar. The issue
>to
>me is not primarily organization, it is the generation of vaccine
>candidates that take into account the latest information. We need to
>carry
>through testing of materials that are promising but we must also
>recognize
>that the candidates now in hand have been extensively investigated and
>that
>most knowledgeable scientists have grave doubts about their potential
>for
>efficacy. I think that we have in place a system that will generate new
>candidates over the next few years and we have to let that system work.
>
>I believe that the Presidential Council can have a positive role in the

>process of gathering and deploying the resources needed to produce a
>vaccine. It will be most effective if it takes into account the
>processes
>now in place, gives them their proper acknowledgement as effective
>elements
>of the discovery effort, looks hard at those areas of true need and
>helps
>put in place mechanisms for coping with them.
>
>Sincerely,
>
>David Baltimore
>
>
>**********
>David Baltimore
>[NOTE THE NEW ADDRESS AND NUMBERS]
>President
>California Institute of Technology
>Pasadena, California 91125
>
>Tel. 626-395-6301
>Fax 626-449-9374
>
>baltimo@caltech.edu
>**********
>
>

helenmm @ itsa.ucsf.edu
11/30/97 05:39:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Comments from Dr. Lichen Yu

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: Comments from Dr. Lichen Yu
>Date: Tue, 25 Nov 1997 18:29:00 -0500
>
>
>Dear Helen,
> Commentary from Dr. Yichen Lu, formerly
>of the Virus Research Institute, Cambridge, who
>addressed the PACHA at our April 7 panel
>discussion.
>
> Bruce
>
> ----------
>From: ylu@vrii.com
>To: bgw2@cdc.gov
>Subject: PATHA recommendations
>Date: 25 November, 1997 10:14
>
>Dear Bruce: I was happy, or rather relieved, to read the
>new draft of recommendations from the PACHA (draft 11).
>
>With the way it went in the past 6 months, I began to worry
>about the commitment of our scientific leaders to achieve
>the President's goal of an AIDS vaccine within a decade.
>
>If NIH has not yet had a comprehensive timetable as how
>to achieve the goal by now, it is then not capable of being
>the leader in this crusade.
>
>It's very unfortunate... We have to have an aggressive
>timetable for multiple phase III trials. We have to have
>multiple approaches. I like this draft and sincerely hope
>that PACHA will recommend it to the Preseident.
>
>If there is anything I can do to help, please do not
>hesitate to ask.
>
>Good luck, Bruce.
>
>Yichen

helenmm @ itsa.ucsf.edu
11/30/97 05:33:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Nara comment on draft

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: Nara comment on draft
>Date: Tue, 25 Nov 1997 17:23:00 -0500
>
>
>Dear Helen,
> Some more commentary on the AIDS vaccine
>document for your compilation.
>
> FYI, in addition to the affiliation given by
>Dr. Nara below, he is also President of the International
>Society for Vaccines and formerly a research scientist
>at the National Cancer Institute, NIH.
>
> Bruce
>
> ----------
>From: Nara, Peter
>To: 'Weniger, Bruce'
>Subject: RE: Draft PACHA AIDS vaccine document
>Date: 21 November, 1997 09:33
>
>Dear Bruce,
> Thank you for the PACHA AIDS draft document.
>I have read over the draft and found it to be a well written
>consensus of most of the meeting/think tanks I have
>been involved with over the past 10 years, which have
>included all the agencies listed in this document.
>
> This coordination has been talked about far too
>long and gone without action even longer. I believe that
>an efficient and adequate funding stream needs to exists
>for AIDS vaccine researchers with a track record to
>promote and expedite ongoing novel and high risk
>research. While I was in the government this was talked
>about, however was not practiced enough, one of the
>reasons for my moving the program to the private side.
>Now on the private side I am curious about how
>well the government will now fund novel efforts such as
>our company's.
>

> Please keep me informed about any relevent
>matters in this area in which you are involved. We have
>a novel technology with much promise; it needs however
>additional funding quickly.
>
> Best regards,
>
> Peter Nara, D.V.M., PhD
> Co-founder and Executive Director
> for Research and Development
> Biological Mimetics Inc.
> 431 Aviation Way
> Frederick, Md. 21701
>
> (301) 620-7691
> (301) 964-7223
> E-mail: nara@sri.org
>
>

helenmm @ itsa.ucsf.edu
11/30/97 05:31:00 PM

Record Type: Record

To: Daniel C. Montoya

cc:
Subject: Comments of Richard Mahoney on Draft Document

>From: "Weniger, Bruce" <bgw2@cdc.gov>
>To: "'Miramontes, Helen (PACHA)'" <helenmm@itsa.ucsf.edu>
>Subject: Comments of Richard Mahoney on Draft Document
>Date: Tue, 25 Nov 1997 14:05:00 -0500
>
>
>Dear Helen,
> See below for your compilation from Richard
>Mahoney, Executive Director of the International
>Vaccine Institute in Seoul, Korea.
> Bruce
>
> ----------
>From: Richard T. Mahoney
>To: 'Weniger, Bruce'
>Subject: RE: Draft PACHA AIDS vaccine document
>Date: 24 November, 1997 03:54
>
>Dear Bruce:
>
>I have studied the draft report and must congratulate you on an
>excellent effort. The novelty is placing responsibility in the Office
>of the Vice President. It seems like a great idea to me. I can imagine
>many resisting it because it sets a "precedent" for special interests to
>have their issues "promoted" to the VP's office.
>
>I hope it has a large impact. I'll be interested to learn what happens.
>Please keep me informed.
>
>Good luck,
>
>Rich
>
>