Vaccine Research Center
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Initial Planning Retreat
Summary

Embassy Suites at the Chevy Chase Pavilion
Washington, DC
April 16-17, 1999

Contents Page

Vaccine Research Center
Initial Planning Retreat

Minutes

April 16-17, 1999

WELCOME AND INTRODUCTION

Dr. Gary Nabel, Director of the Vaccine Research Center (VRC), at the National Institutes of Health (NIH), welcomed participants to what he hopes will be the first of many planning meetings and noted his particular appreciation that they were able to attend upon such short notice. Dr. Nabel indicated that the specific issues to be addressed represent a crucial effort that is important to him, NIH and the AIDS community. Since Dr. Nabel is newly appointed as the Director of the recently established VRC, he also wanted to convey his thanks to all those at NIH who gave him enormous support in his transition.

Dr. Nabel challenged the group to create a framework for the Center so that it meets not only short-term goals but also provides a useful model for future vaccine development. The purpose of the meeting was to build a consensus regarding plans for the development of the VRC. The meeting was divided into seven sessions, each with an assigned moderator to lead discussion and provide an overall perspective on the topic. Dr. Nabel saw the key questions as:

- What is the scope of the scientific research needed?
- What approaches can be taken to develop a successful vaccine?
- What infrastructure is needed?
- What types of researchers should be recruited?
- How can interactive researchers who will stimulate the field be targeted?

Plans for the building, now under construction and scheduled for completion by August 2000, were presented and the state-of-the-art equipment as well as the functional usefulness of the space was emphasized. For example, there will be multiple areas in which collaborators can meet to discuss and present; the cyber café chief among them. The laboratories will largely be an open architectural style with the potential to close in additional areas if needed. Ample Biosafety Level (BSL) areas (2+ and 3) will be available, and there are plans for a small-scale Good Laboratory Practices (GLP)-specified production area on the top floor, which enables incorporation of any containment needs that arise. The hallmark of the plan is the flexibility of the design since it is not yet established who will be taking up residence in the space or what specific activities will be ongoing.

SESSION I: Initial Scientific Strategies

Moderator: Dr. Dan Littman
Discussants: Drs. Dennis Burton, Ron Desrosiers, Malcolm Martin, John Moore, and Jack Nunberg

Items:
1. What are the most promising approaches for; a.) development of a CTL-based vaccine, b.) generation of broadly neutralizing antibodies, and, c.) the persistence of antigen (live-attenuated or sustained expression vectors)?
2. Should the VRC facilitate the study of immune/inflammatory mechanisms of protection in viral infection for which vaccination has proven protective? Which viruses and organisms (human vs. animal models) would be most relevant to HIV?

Item 1
Dr. Dan Littman presented an overview and noted that due to research of the past several years, there was probably general consensus that, in order to approach the production of a sterilizing immunity against HIV, a combination of good humoral responses and cytotoxic responses would be needed. He emphasized that there is good reason to hope for a vaccine since it is clear that one can get good cytotoxic responses and reduce the virus levels significantly, but the question is still how to harness that activity and why the virus cannot be eliminated.

Dr. Dennis Burton discussed the topic of whether broadly neutralizing antibodies (Abs) hold much promise for vaccine development. In general, the problem has been that Ab response to HIV infections reveals that the antigens (Ags) presented by HIV produce low antigenicity and low immunogenicity and thus would not be an effective means to developing immunity. There are some "chinks" in the armor, however, which may be utilized and will be discussed later. Generally, Dr. Burton's work shows that the Ab, when presented with HIV, probably bind to a small part of the HIV envelope protein (env). It is only the Abs that actually bind the env protein that then elicit a neutralizing response and very little of env protein is available for binding.

The CD4 binding region on HIV is the key region that binds to lymphocytes and, therefore, is thought by many to be a key target for vaccine production. However, Dr. Burton's structural studies show that the CD4 binding region on HIV is well hidden from neutralizing Abs. Thus, it may not be a prime target. Due to the minimal surfaces available for binding in the three dimensional conformation of this env protein in the intact virus, Dr. Burton speculated that there would only be a few types of Abs that would have the potential to bind env. He has isolated three and would perhaps expect only one additional non-overlapping Ab.

However, Dr. Littman noted that all of the Abs identified by investigators so far have depended on a binding assay and not a functional assay for neutralization. Thus, this could be only a small portion of what is out there, and it would be worthwhile to screen

with the newer assays where one can, in real time and with high throughput, screen for functional activity. There was agreement with this suggestion.

Dr. Burton also noted that ways need to be found to enhance immunogenicity, and that a lot of fundamental immunology needs to be done to understand how to enhance the immunogenicity by immunological manipulations. Dr. Nabel asked the extent of the efforts to date. Dr. Burton notes that no one has the mature oligomer structure to do it. If one did, then they could devise some protocols to manipulate this. There is also a need to learn more about how to manipulate the Ab response. Thus, there is a great deal of basic immunological science that needs to be pursued whether at the VRC or elsewhere.

The three Abs isolated by Dr. Burton are broadly neutralizing in the sense that they can easily neutralize 90-95% of various clade viruses. However, it still appears that a CTL response will be needed to neutralize the remaining 5-10% and produce a sterilizing type of immunity. Thus, a multivalent vaccine would be needed. Upon discussion, it appears that this is not different from what has been seen with other vaccines and although it may not appear that there is a 100% response, the combined Ab and CTL response could be effective enough to prevent disease, again as seen in other vaccines. Thus, the percent neutralization by the Ab may be able to be lower that 99-95%, but it is not known how low. In the case of polio, 1/4 or 1/8 in the patient is sufficient, but this is a highly effective neutralizing Ab.

Dr. John Moore presented research emphasizing the need to have the appropriate conformation of any Ag one tries to present, one that is closest to the native conformation. He indicated that most researchers have not, in the past, used the appropriate conformation of the env oligomer, but that he and several others are currently doing so. They should have information by the end of the year on whether this form increases antigenicity. However, an understudied area of research is to learn how to most advantageously present exogenous proteins to the immune system. This includes looking at adjuvants other than alum as well as defining other variables that might enhance presentation such that antigenicity is enhanced.

Dr. Jack Nunberg described his research, which may be a new technique to use in the search for broadly neutralizing Abs. He has looked at intermediates in the fusion of the virus and cell and finds that fusion-competent intermediates are capable of eliciting broadly neutralizing Abs.

The question was posed as to whether it would be useful for the VRC to advocate a structural approach vs. empirical approach. Participants thought the science was at a stage where one could determine some reasonable avenues to pursue, but that it is not at the stage where one can say they could move this moiety and know what to expect. The VRC could concentrate on structure, and/or it could focus on high throughput screening and test some of the ideas heard at the meeting. Dr. Johnston pointed out that in the absence of any assay that will predict immunogenicity, investigators should look at different types of designs of protein and see what they do in animals. There was much discussion again about the value of having a structure that whose conformation is well known, but still

produces low immunogenicity. It is difficult to know what to vary in order to mimic what may be seen *in vivo* and some are working on this.

The gp120 monomer binds Ab well, but again, is a poor immunogen. Questions arose about adjuvants helping in this instance, and although the AIDS Evaluation Group has tried 9-10 different adjuvants and saw no improvement of differences, they were still looking at the monomer form. Thus, one cannot just immunize with the peptides.

The mechanism of neutralization here is defined as the inhibition of virus attachment. There is a close correlation between the attachment to spikes and neutralization.

Item 2
(Discussed further in Session IV)

Dr. Nathanson noted that consideration should be given to going back and looking at existing vaccines with the more modern immunological, virological and molecular biological techniques in order to see how they work. There was strong support for this idea and discussants supported the need for a Core within the VRC that would focus on correlates of immunity.

SESSION II: Informatics and Genomics Applications for Vaccine Development

Moderator: Dr. Jeff Trent
Discussants: Drs. Louis Staudt and Ron Germaine

Items:
1. How might bioinformatics and genomics technology contribute to vaccine design, development and clinical trial design and analysis? Can vaccines be developed more predictively and less empirically?
2. What approaches might be taken to modeling the immune response to peptides based on their primary amino acid sequence?
3. Are there applications of microarray technology to the analysis of immune responses in animal models or in vaccine trials?
4. Can bioinformatics and molecular diagnostics be applied to perform more efficient surveillance for infectious agents?

Item 1
Dr. Ron Germaine noted that genomics and bioinformatics cannot yet provide answers at the same level as the chip technology, but what they can do in some instances is narrow choices down. For example, Dr. Lou Miller, working with malaria, has been working with the Library of Medicine examining sequence complexity and non-complexity. He can show relationships between regions that vary in those properties and their general immunogenicity for Ab responses. Thus, he would be able to make some generalizations about what to study next. However, research is not yet at the level where one could predict the neutralizing epitopes except to say they are in a more structured region. In the next few years, with the information gained, these approaches will achieve their potential.

Item 2
This was not addressed.

Item 3
Dr. Jeff Trent began by saying that 90% of the genome project will be completed after this year, which will provide much useful information. He presented an overview of three expression tools and their power for this technology. One technique, Sequence Analysis of Genome Expression (SAGE) developed by Dr. Bert Vogelstein, has not yet been applied in the context of virus or HIV, but this sequence-based approach has some useful tools that have recently been posted on the NCBI and NCI Web pages. Two other techniques are some of the array-based approaches which involve depositing individual cDNAs onto glass slides and Gene Chip systems which entails the photolithography approach, developing synthetic wafers either on glass or silicon surfaces by Affymetrix that use defined oligonucleotides as the hybridization template rather than cDNA. These tools, coupled with the completion of the genome sequence, will allow these expression systems to provide such information as viral sequence, mapping information, patterns of viral expression and their relationships, and time courses of expression. Thus, the real power will be looking for signature patterns in the array. There are also ways to display the information to depict what is happening, i.e., hierarchies and clusters while also

providing the ability to screen. These types of information could in turn provide insight into the natural history of a patient's infection.

Items 3 and 4

Dr. Louis Staudt proposed ways one could use these arrays broadly to look at issues of human immune responses and variations between individuals. They have created a specialized microchip called a lymphochip, which allows one to look at the expression of inactivation of all cells involved in the immune system or immune cancers. One could then see, for example, which genes are turned on or off in response to a particular cytokine. A library can then be constructed so when a patient is seen it would be possible to know what genes are turned on in this patient. Dr. Staudt has begun a project with Drs. Pat Brown and David Romanoff at Stanford examining whether peripheral blood mononuclear cells would be sensitive indicators, via the chip technology, of a variety of health problems. For example, since they know what genes should be expressed when, it would be interesting to see what happens when the patient has a cold, is exposed to an infectious agent, has sepsis, been exposed to a toxin, or has an autoimmune disorder. Thus, these data, once collected, could be used diagnostically. Family studies could also be done and one could look to see how a patient responds to an antigenic challenge. These indicators would also be useful in identifying sub-clinical responses.

SESSION III: Complementary NIH Intramural Programs

Moderator: Dr. Rick Klausner
Discussants: Drs. Tony Fauci and Michael Gottesman

Dr. Michael Gottesman noted that a compelling reason that the NIH was chosen as the site for the VRC was due to its somewhat unique and clearly extensive resources available. He listed the following resources:

People: Over 10% (~100 investigators) of the intramural scientists are involved in AIDS-related research. Seventy-five investigators attended a town meeting about the development of the VRC and this led to the formation of another Special Interest Group (there are currently over 70 on the NIH campus) focused on the topic of an HIV vaccine. These Special Interest Groups present their data, hold journal clubs, invite speakers and form collaborations among the different laboratories.

Ongoing NIH Programs:

1. Existing Vaccine programs: There are a number of laboratories studying vaccines; three were mentioned here- Drs. John Robbins' and Bob Chanock's programs have successfully developed vaccines. Dr. Lou Miller is currently working on a malaria vaccine.
2. Intramural AIDS-Targeted Anti-Viral Program (IATAP) is a grant program for intramural scientists sponsored by Dr. Gottesman's office. Most of the funds are for infrastructure for structural biology studies related to AIDS and some vaccine projects related to AIDS (i.e., NMR, crystallography, EM crystallography).
3. NIH has a formidable structural biology program with world-class NMR spectroscopists and crystallographers. There are over 11 crystallography groups with over 80 people doing crystallography. In addition, they have full-time dedicated access to Brookhaven and Argon facilities. They are currently building an EM crystallography program facility that will have state-of-the-art high voltage EM technology with investigators interested in studying viral structural proteins and membrane proteins.
4. The NCI, Frederick facility was originally built to support a variety of structural and biological modifiers programs. There is a Good Manufacturing Practices (GMP)-specified facility on site, which has made vaccines. Also, Dr. John Coffin is establishing a major program in HIV drug resistance. Dr. Larry Arthur, Director, AIDS Vaccine Program, NCI, Frederick, invited Dr. Nabel to tour the facility.
5. Protein Expression Lab (PEL) lies within NIAMS and has a mission to supply protein in large quantities, particularly AIDS-related proteins, for study in the intramural program.
6. The Pilot Plant within NIDDK has many 30 and 50-liter fermentors and is currently being renovated. Dr. Nabel has met with them to discuss ways it can be modified to best serve the VRC.

7. The Bioengineering and Physical Sciences Program within the Office of Research Services has provided many bioengineers who have been helpful in developing technologies needed for high throughput screening techniques. A collaboration with NCI produced a laser capture microdissection.
8. *In vivo* NMR center.
9. A small animal imaging center is being developed.
10. Vivarium for animal care.
11. The National Center for Biotechnology Information encompasses a wide variety of bioinformatics.
12. Clinical capabilities. A new clinical center is being built and the current clinical center has years of experience in which many important clinical trials have been conducted. Dr. Cliff Lane, Clinical Director, National Institute for Allergy and Infectious Diseases (NIAID), is a willing collaborator.
13. Proximity of Center for Biologics Evaluation and Research (CBER), FDA. CBER has enormous experience on regulation and vaccine development. In addition, CBER has a very active HIV research group that is available for consultation and collaboration.

Dr. Anthony Fauci, Director, NIAID, noted that NIH has developed vaccines in the past and possesses the capabilities to span the breadth of what is needed to develop a vaccine, from basic to clinical to scale-up of a pilot lot to do a vaccine trial and collaborate with industry to produce a final product. For example, within NIAID, Dr. Chanock's group has been successful in such efforts with hepatitis A, rhodovirus, influenza, and respiratory syncytial virus. This process was exemplary in obtaining resources from throughout the NIH without having to build it into their program. The VRC can do likewise. Additional laboratories with vaccine interests include Drs. Mal Martin, Vanessa Hirsch, and Bernie Moss.

Dr. Harold Varmus, Director, NIH, inquired as to the projected national need for primate resources for AIDS research. There are not expected to be resources at the VRC, but there are ones at Poolesville, MD and in Frederick, MD. All participants agreed that this was a critical question and a major potential problem for all of AIDS research. The primates are fast becoming depleted, especially ones with known and/or matched HLA alleles (which some participants saw as important, others less so). Many researchers currently follow the animals longer, leaving less space for new animals. Thus, there is a need for MHC-defined Rhesus monkeys as well as a need to have some system oversee that animals are used such that maximum data are retrieved from the studies. There may be a need to set priorities as to what studies can be done. NIAID supports 5 SIV vaccine evaluation units as extramural studies with 50 animals and plans to increase this to 6 studies with 75 animals. They have a committee to prioritize the studies. For the purposes of the VRC, Poolesville is underutilized. In addition, there has been successful outsourcing for other intramural laboratories' primate needs.

SESSION IV: Composition of Laboratories

Moderator: Dr. Mark Feinberg
Discussants: Drs. Neal Nathanson, Michel DeWilde, Ron Germaine, and Jon Altman

Items:
1. Given the priorities, what is an optimal mix of laboratories within the VRC with respect to basic virology, basic immunology, core laboratories, applied (technical) research, vaccine/vector production, and clinical trials?
2. To what extent should the recruitments and activities of the VRC focus on AIDS? Should other targets, such as tumor viruses, herpes viruses, TB or malaria be pursued? If so, which ones and at what percent effort? How does the initial composition of laboratories influence or limit the ability to approach other vaccine candidates in the future?
3. Review of building plan and potential activities in the VRC.

Item 1
Dr. Nathanson noted that consideration should be given to going back and looking at existing vaccines with the more modern immunological, virological, and molecular biological techniques in order to see how they work. There was strong support for this idea to be implemented within the VRC and for a Core that focuses on correlates of immunity. There was also general agreement that an essential part of this Immunology Core would be a focus on standardizing immunological assays in a meaningful and reproducible way in order to characterize human and primate immune responses to candidate vaccines. This would fill a critical need nationally and be a benefit to any other vaccine candidate for any disease.

Dr. Nathanson also suggested that it be ascertained who is at the NIH already involved in HIV/AIDS studies and who would like to participate in what manner. He thought there were many investigators who would be interested in 10-15% participation rather than 100% and that this offered a key opportunity to leverage these people into more than the space might represent. As many participants noted, this would need to be done in a manner that did not dilute the Core.

Item 2
There was unanimous agreement that the VRC should focus entirely on AIDS so that the vital effort of developing a vaccine is not diluted. Researchers working on other diseases should be considered if it is in the context of taking advantage of expertise where there is a known vaccine or have something to directly contribute to HIV research. There was a strong opinion that in order to be successful, there needed to be a focus and integrated team. It was thought that understanding HIV will provide valuable information on other diseases. Although Dr. Varmus notes that this was not called the AIDS VRC because they wanted it left intellectually open and because the building would hopefully outlast the problem of AIDS, he agreed with the HIV focus for now.

Dr. Nabel noted that where the study of HIV may open up an opportunity in some other disease model, or vice-versa, they should take advantage of that. This idea met with wide support. It was noted, at this time, HIV-2 would not be a focus in the VRC; rather, a higher priority would be given to studying different clades of HIV-1.

Regarding recruitment, there was extensive discussion about how much leeway should be allowed potential investigators to have research apart from a focus on HIV. The primary concern, again, is to not destroy the team concept. Participants were divided in opinion with some wanting variations of a very strong team forging ahead to a common goal that may not be subject to evaluation in the standard mode (i.e., published papers). Most see teamwork as necessary but more in the standard mode of individual investigators.

There is an Executive Advisory Group made up of Drs. Varmus, Fauci, Klausner, Gottesman, Nathanson, and Nabel. Dr. Varmus mentioned that this is really an Administrative Advisory Group and that he expected an Expert Advisory Group would be established which would at least include Drs. Bill Paul and Malcolm Martin (who have been advising this Vaccine Center Without Walls groups on campus) as well as some members from Dr. David Baltimore's AIDS Vaccine Research Committee. This committee would be the nucleus of the group to which Dr. Nabel wants to add intramural and extramural specialists.

Item 3

There was extensive discussion about whether the VRC should have a GLP production facility as planned. Justification for this on site facility rests on the important issues of having real time access to and control over the quality of materials needed. Many participants have had problems with access to contractors and with producing the desired products, which have sometimes been of low quality. Concerns were noted, however, by some participants that this large space may not be as useful as expected since there will often have to be down time for change over of preparations. Additionally, demand for these facilities may expand to the point where a lot of time and effort would be spent servicing other projects with little gain from the vaccine effort. However, Dr. Nabel noted that the GLP facilities would be used when other avenues were not appropriate and when they needed material quickly. It is important that they have the capacity to do so. The facility could be used in a variety of ways, thus there will be good use of space. It is intended to only produce limited quantities of materials for Phase I studies, not produce large quantities for services.

When appropriate, the VRC will use other avenues to outsource production (the NIH can facilitate this), including:

1. Use of the Frederick facilities (including its possible expansion).
2. Contracting out. The main problems of access and quality assurance can be addressed by the man-in-the-plant mode of operation where the investigator has a person working on site in the plant. Additionally, some investigators have had success once they establish a long-term relationship with a contractor (Dr. Nabel was directed to Dr. Brian Murphy regarding this). The most hopeful improvement in the contracting

path is that the FDA, two years ago, allowed contractors to produce biologics; thus, it can be expected that many companies are in the process of gearing up to do so and this will improve access and quality.
3. NIAID has put out an RFP for contracts to have the capacity to produce biologics (see notes from Session IV).

It was generally agreed that the structure of the VRC should be a strong scientific focus within the AIDS framework and there should not be an attempt to cover all areas of AIDS research. As noted above, immunology would figure prominently in this effort. It was seen that the VRC could take more risks due to the resources available and be responsive to needs in the community, but that leadership will be important to keep a team concept and foster the climate where the investigators as a group decide on what avenues to pursue together. It was agreed that the team effort should be strongly focused on getting a vaccine to market. Dr. Nabel does see that the glue will be the team and the ability to produce Phase I products will be an incentive for those who have been limited by this previously.

Recommendations regarding space issues:

1. BSL 3 space should be reviewed to see if it is sufficient. (This was determined to be sufficient given the BSL 2+ levels unless the recruited investigators desired a change).
2. The number of tissue culture hoods was questioned, but was acceptable at this time due to the flexibility to expand the number, if necessary, when recruitment is completed.
3. There is a need to have a devoted large FACS room in the BSL 3 containment room. This would require an anteroom. Use of non-human primates would require the FACS within the BSL-3 facility. Thus, at least half of the BSL-3 rooms should have a FACS sorter.
4. More FACS scanners are needed in the building.

SESSION V: Scope and Mission of the VRC

Moderator: Dr. William Paul
Discussants: Drs. Bernie Moss, Larry Arthur, and Peggy Johnston

Items
1. What is the mission statement for the VRC?
2. What are the production needs for vaccine development? Small-scale production is currently envisioned in the VRC, with large-scale production off-site. Which off-site facilities are available, and what are the lag times for large-scale production? Is this a reasonable strategy? What VRC cores can be useful both for investigators within the VRC, on the NIH campus, and elsewhere?
3. Can/should the VRC contribute to efforts to address bioterrorism? (Not discussed)

Item 1
Prior to drafting a mission statement, there was extensive discussion regarding what should be the mission of the VRC. Important gaps that the VRC could try to address include:

1. Establishing a Core for studying correlates of immunity.
2. Establishing a Core for assay and reagent development (could be within Immunology Core). In the extramural world, assay and reagent development, i.e. a pathogenic SHIV, is difficult to get funded. It could be funded as part of another grant, but it is too mundane for a grant and too creative for a contract. Thus, developing important reagents could be a national service. Development of assays is also a critical need. The VRC should have the ability to do its own "routine" assays (i.e., CTL) and should not provide this as a national service. What the VRC can do nationally is work on improving labor-intensive assays (i.e., intracellular cytokine) to make them easier. It was suggested that the VRC should develop assays and reagents not only for human studies, but also for macaque studies where the field is farther behind. Additionally, there will be personnel within the VRC to assist in the preliminary aspects of assay development such as entry into the IND (investigational new drugs) and toxicology. Dr. Fauci emphasized that NIAID has had success in these areas already over the past 20 years, thus the model is there.
3. Establishing a Core for aiding translational activities. Extramural funding is able to supply good basic research and a network of clinical trials, but it is difficult to fund the translational aspects of taking promising vaccine into clinical trials.
4. Providing program project management advice and services for the developmental and translational phase of a product. This could be included under the Translational Core. There is a need for centralized program management (or project management of the science) with to help determine when some avenue should be dropped and other avenues explored. This is important for conserving resources and helping candidates to move into Phase I trials.

5. Providing aids in drafting and helping investigators to navigate regulatory aspects. Providing workshops regarding regulatory issues where the VRC can bring all parties to the table (intramural, extramural, industry, and FDA).
6. Advancing vaccine candidates. Extensive discussion occurred on whether this should be the VRC's job. Several participants thought the VRC could bring along a few candidates, but should not try to do too many in addition to developing their own. Mr. Bill Snow advocated that the VRC pick up several candidates from elsewhere so that there would be many approaches being attempted in parallel and in different phases of development. It was the general consensus that the VRC would help to bring some outside candidates along.

Mission Statement:
Dr. William Paul presented a draft mission statement which raised several important issues. It was decided that the statement was actually a combination of mission statement, goals and a vision statement with the first and possibly second sentences being the mission statement. Concern was noted that the first sentence said the mission was to "conduct research". Other participants suggested instead it should read "conduct research and promote development" or "conduct and facilitate" research. Dr. Nabel noted they would want a mission statement that would stand the test of time, thus something like "to conduct research that facilitates development of effective vaccines for human disease". Then, in the goals section, state that the primary emphasis is HIV.

The draft mission statement mentioned the possibility that NIH would produce and market the vaccine if no commercial enterprise took it on. There was substantial discussion since it seemed that one would not want to involve the NIH in production and marketing since industry would most likely pick it up. However, discussion brought to light, that given that much of the need for an AIDS vaccine is outside of the country, there may not be a real profit and no real guarantee of return on investment. Thus, industry has no incentive. There are other options, i.e., working with the World Bank. The Public Health Act does give the government the authority to produce and sell a vaccine (probably not at a profit), if necessary, and there may be other vaccines the VRC will need to develop. Thus, it should have the option.

During this discussion, an important gap was identified; the need to study the human immune response (not just non-human primate) for candidate vaccines to decide which candidate vaccine to take to Phase I trial. Most researchers would agree that the best chance for getting an effective HIV vaccine is having a product that induces the broadest range and highest level of immune response against the virus. To move development forward, investigators need to be able to go back and forth between the lab and clinic to get the best potential product. Just as knowledge increased immensely regarding critical aspects of HIV pathogenesis by studies of small numbers of humans given potent antiviral drugs, investigators now need a mechanism to study, in detail, human responses in people who are given alternative candidate vaccines. The ability to use GLP material in small human subject trials is thus vital.

Substantial discussion revolved around whether the mission of the VRC should be as a

national resource to fill gaps, or to do the best research to develop a vaccine. Dr. Fauci notes that these are not mutually exclusive. Participants agreed, but suggested an initial decision and focus is needed in order to recruit candidates. Most agreed that it should be a research center and help nationally when appropriate and able. A minority would like to see more of a national effort.

One way to combine the visions is that there are already many questions that are not sufficiently being researched because they are difficult, but also because they require a lot of resources. For example, Dr. Ron Desrosier's attenuated viruses give the best protection, but it is not known how they work, and it is not clear that the work to do so has been mounted. Also, if the effort falls short of a sterilizing vaccine, what are the implications for those who have been immunized with partially protective vaccines? Thus, the VRC could address the questions that require a lot of resources.

Item 2

Regarding production needs, Dr. Peggy Johnston presented NIAID's current extramural efforts that would benefit the VRC. NIAID has put out a call for contracts that would develop pools of contractors for: 1) GMP manufacturing, 2) support preclinical IND-directed studies that need to be done to submit an IND, and 3) expertise in IND preparation. Products for GMP include peptides, subunit protein, DNA vectors, particle design, or whole killed and live attenuated viruses. They obtained two categories of responses: half will do whatever one wants; half will work on some specific design. Results of the bid will be known by fiscal year's end. There will be room and space to accommodate intramural needs. Expectations for lag times are not clear, but it is likely that peptides and DNA will go quickly and there will be a lot of capability to produce these; replicating vectors would be moderate lag time and have good capability for viral vectors. Recombinant proteins will be the most difficult with expertise found only in a few places, although there are some new vendors coming on the market. For small-scale products, the capabilities will be there. Dr. Johnston does not think intra- or extramural laboratories should attempt large-scale productions without the backing of industry. NIAID does expect high usage and projects will be chosen to use these facilities by a quasi-peer review committee. The contract does allow for intramural laboratories to put money into the contract and then use it as needed.

Regarding the on-site VRC facility, the overriding issues leading to a GLP facility were access and quality. Dr. Nabel also noted here that many of the activities discussed for the VRC will not actually require a lot of wet bench space (i.e., Immunology Core, regulatory aids).

Dr. Nabel asked whether a Frederick-like facility should be considered for production of vaccines in general (not at the VRC). The consensus was yes, given the lag time between getting the facility, planning and getting the facility to turn out GMP material. NIAID's extramural efforts will be useful, especially since there will be other vaccines. Dr. Larry Arthur was not sure there was room for expansion at Frederick, but thought there may be.

A recommendation was made that since the VRC production facilities are often going to

be used as a back up, it might be prudent to begin to make certain classes of arrangements now for outsourcing, especially since the production of biologics is a growing business.

SESSION VI: Clinical Interface

Moderator: Dr. Cliff Lane
Discussants: Drs. Jim Hoxie, Sam Avrett, Jack Nunberg, and Kathy Zoon

Items
1. What role should the VRC play in clinical trials, both in implementation of new trials and analyses of ongoing trials intramurally and extramurally?
2. How do we facilitate scientific collaborations with extramural industrial and academic clinical trials?
3. Should the VRC serve as a resource to analyze immunologic and virologic responses for industrial and academic clinical trials? If so, what immunologic and virologic assays should be included?
4. Are there regulatory issues that can be addressed generically for vaccine development and how can the VRC and FDA work to expedite the implementation of clinical trials?

Item 1
Dr. Cliff Lane expected the VRC to play an important role in fostering clinical trials and clinical research in general. He presented the many unique assets that the intramural environment can provide to make the trials easy to accomplish:

1. Current and new clinical center.
2. Staff physicians who are clinical investigator physicians who spend all their time in the clinic.
3. Study coordinators (nurses) provide a model service. NIAID has its own IRP, thus there is a fast turn-around on protocols.
4. Case Managers (nurses) who are familiar with the protocols.
5. Relationship between intramural scientists and industry, which has already evolved via Cooperative Research and Development Agreements (CRADAs). The Office of Technology Transfer sets the policy for interactions and has a formal mechanism for deciding each partner's responsibility while protecting intellectual property. This process works well and fast.
6. Collaboration with extramural investigators is best accomplished by cooperative agreements since they allow payment and participation in the proposal writing process. Neither of these are allowed in the grant process.
7. Support contracts present a good option to work past resources. Frederick's NCI has one in place that is very broad, i.e., studies of the immune system, and many institutes have subcontracts.
8. Proximity of CBER, which also has a vaccine research group on campus.

Item 2
Dr. Jim Hoxie noted that the extramural PI needs help in taking candidate vaccines to the clinic, i.e., translational activities of feasibility, scale up, and Phase I. The extramural PI can do this, but it requires many rounds of going back and forth to study sections. Similarly, Dr. Jack Nunberg sees the primary gap for the extramural person as the

movement of concept and development or the rapid advance to the clinic. He would see value in providing project management help similar to the model that industry uses, having a person guide the PI through the process, assays, safety, and regulations with respect to the clinical protocol.

Mr. Gonsalves noted that the Vaccine Trials Network (VTN) and the extramural clinical research community are additional resources for the VRC, and Dr. Johnston could foresee many areas where the VRC could interact with these. Two examples are: The network has the strength of being able to conduct multicenter studies and has a base of information about previous vaccines as well as a central lab and statistical and data center. The strength of the VRC is that it is able to move quickly and maybe do some small pilot studies. Thus, the interactions could grow if the vaccine tested by the VRC were promising. Then they could go onto larger trials in the vaccine network. Additionally, the VTN could assist in assay development by helping to translate VRC assays in a uniform manner. Mr. Avrett noted that the VTN also is a resource since it prepares the public for clinical trials.

Item 3
NCI's RAID Program may serve as a good model since it was developed because NCI saw that there were good candidates for therapeutics that could not go forward to trial. It has a Board of Scientific Advisors that decides which products should move forward. Then they provide the capacity to move these through GMP to Phase I. This may actually be an external resource for the VRC so that all products do not have to go through the VRC. An additional role for VRC may be to feedback into the community what has been learned from Phase I trials.

As already noted, the VRC maybe be a good place to develop new assays or improve old ones, but once that is accomplished, the VRC should not provide services for other laboratories. NIAID already has core facilities to do assays for many protocols, thus, if desired, assays could be accommodated either there or at Frederick.

Item 4
Dr. Zoon, CBER, noted that CBER was part of NIH until 1972 and has maintained close ties with the intramural community. They currently have 10 investigators doing research in HIV. Additionally, they have the practical experience of having reviewed many vaccines and dealing with clinical trials and trial design to get the most out the each trial. Trial design is a vital area since the addition of each experiment raises the cost considerably; thus to get maximum information, the trial needs to be designed with care. The VRC could take a leadership role in bringing interested parties to the table to deal with this issue as well as other regulatory ones.

SESSION VII: Critical Hurdles to Vaccine Development

Moderator: Dr. Peggy Johnston
Discussants: Drs. Michael Gottesman, Mark Feinberg, John Moore, and Ron Desrosiers

Items

1. How do we best promote collaboration among scientists within the VRC and elsewhere on the NIH campus? What mechanisms can be used to promote interactions between intramural and extramural scientists for the AIDS vaccine research effort?
2. What proportion of recruitments for the VRC should be from the intramural program vs. the extramural program?
3. How can the VRC eliminate the gaps in vaccine development?
4. Are there any modifications to the existing building plan that might be useful?

Item 1

Dr. Johnston noted that three studies of the roadblocks to AIDS vaccine development concluded that limited scientific knowledge is the major obstacle. Thus, the question of collaboration is key to addressing how to move the field ahead rapidly. Dr. Gottesman presented NIH resources and incentives for establishing collaborations since this is one of his main functions. He has found the best incentive is the science, but communication is also key. Thus, the Special Interest Groups are an important resource.

The next most important incentive is space. He urges that space be left for visiting people from extramural and intramural. It would be important for Dr. Nabel to not assign all the space and keep a Director's reserve since investigators are not anxious to give up space. Money is likewise a good incentive; thus, Dr. Nabel should also keep reserves for various possibilities. NIH has the Inter-governmental Personnel Act (IPA), which allows people to maintain their current employment (industry or academia) and come to the NIH if NIH pays their salary. This can last for four years and can work in reverse, i.e., supporting an NIH person to go out to industry or academia. Additionally, the money could support intramural people visiting at the VRC or VRC scientists visiting an intramural laboratory. The IATAP fund of money regulated by Dr. Gottesman's office also stimulates collaboration and would be appropriate for use at the VRC.

Individual scientists may collaborate with industry via the CRADA. The guiding principle with respect to consulting is that a researcher cannot have an official duty activity with industry (CRADA) and a paid consultancy. Researchers can consult with industry as long as they are not consulting in an area directly related to what they are working on in their laboratory, which is also an official duty activity. Thus, they can use their general expertise and must take leave for consulting duties.

Item 2

Recruitment for the VRC should draw mostly from the extramural community so as to increase and stimulate the pool of AIDS researchers on campus. There are ways that a PI with an NIH-funded RO1 can come to the NIH or VRC. Some of the mechanisms of

support at the NIH mentioned include:

1. Tenure: There is a tenure track similar to that for assistant professors. There is a promotion and tenure committee that considers many outside references.
2. "Whitehead-like Fellow": Although not an accelerated track to tenure, this position provides independent resources to the investigators for three years. At that time, if they are not accepted for tenure, they can take two years of funding with them to an outside position.
3. Title 42: This mechanism provides five-year renewable appointments and allows unlimited salary.
4. Staff Scientist: This position is not a permanent Civil Service position.

Item 3
The potential gaps that the VRC could address have been discussed earlier and will be summarized at the end of this report. One additional gap mentioned here was keeping the FDA appraised of emerging concepts in HIV vaccine development. Participants again emphasized the need to be able to use GLP materials in small-scale human subject studies.

Item 4
Suggested recommendations for the building were discussed in Session IV and will be summarized at the end of this report.

Dr. Johnston summarized the retreat by saying that the VRC appears to be an exciting and attractive package with a nice building, new space, and a solid leadership, open for input, which bodes well for the future success of the Center. Dr. Varmus' presence brings to light how important this Center is to the NIH. Dr. Johnston stressed that collaboration and dedication to the vaccine effort will make the Center work and that it will be important for the community to see products and concepts moving ahead.

SUMMARY

Dr. Nabel thanked the participants again and noted the excellence and breadth of comments that will be helpful in his planning. The wealth of the NIH resources, particularly in structural biology, clinical infrastructure, and basic immunology are impressive and provide a wide base of support and a variety of ways to interact. This will provide a great start. He sees three recurring themes:

1. The need for a scientific agenda with a core group of scientists who have hypothesis-driven ideas about vaccine development. Areas of need include developing approaches to utilize neutralizing Abs and CTL responses so that the vaccine will provide persistent protection.
2. The need to provide access to translation activities and understand human immune responses.
3. That there is a good opportunity to help the national effort by the VRC helping to define regulatory requirements and take the lead in eliminating unnecessary obstacles. Additionally, providing guidelines that will facilitate trials and the scientific knowledge that results. Dr. Nabel agrees it will come down to the people who come. Thus, the recruitment effort will target outstanding scientists who are collaborative and passionate about developing vaccines.

Lastly, Dr. Nabel presented a draft job description, which elicited the following recommendations:

- Emphasize the need for collaborative and goal-directed personalities.
- Add wording that will target industrial development people for the translational needs.
- Consider a separate ad targeting translational researchers and different journals.

The next meeting will include topics on the governance of the VRC and the interaction with intramural laboratories.

Dr. Varmus invited all to the Corner Stone laying scheduled for mid-May. The building will be named for Dale and Betty Bumpers who have had a long-standing interest in vaccines, distribution of vaccines and children. Dr. Varmus will keep those participants who indicated an interest in attending informed.

MAJOR RECOMMENDATIONS

Mission

The VRC should conduct research that facilitates development of effective vaccines for human disease. The VRC should be a research center that aids in the national program when appropriate and able.

Cores Needed and Gaps for the VRC to Potentially Address

1. Establish an Immunology Core to study correlates of immunity. Consideration should be given to going back and looking at existing vaccines with the more modern immunological, virological, and molecular biological techniques in order to see how they work.
2. Establish a Core for assay and reagent development (could be within Immunology Core). In the extramural world, assay and reagent development, i.e. a pathogenic SHIV, is difficult to get funded. It could be funded as part of another grant, but it is too mundane for a grant and too creative for a contract. Thus, developing important reagents could be a national service. Development of assays is also a critical need. The VRC should have the ability to do its own "routine" assays (i.e., CTL) and should not provide this as a national service. What the VRC can do nationally is to work on improving labor-intensive assays (i.e., intracellular cytokine) to make them easier. It was suggested that the VRC should develop assays and reagents not only for human studies, but also for macaque studies, where the field is farther behind. Additionally, assisting in the developmental aspects of assay development such as entry into the IND (investigational new drug) and toxicology. There will be personnel within the VRC to do this. Dr. Fauci emphasized that NIAID has had success in these areas already over the past 20 years, thus the model is there.
3. Establish a Core for aiding translational activities. Extramural funding is able to supply good basic research and a network of clinical trials, but it is difficult to fund the translational aspects of taking promising vaccine into clinical trials.
4. Help address the need to be able to study the human immune response (not just non-human primate) for candidate vaccines to decide which candidate vaccine to take to Phase I trial. The best chance for getting an effective HIV vaccine is having a product that induces the broadest range and highest level of immune response against the virus. To move development forward, investigators need to be able to go back and forth between the lab and clinic to get the best potential product. Just as knowledge increased immensely regarding critical aspects of HIV pathogenesis by studies of small numbers of humans given potent antiviral drugs, investigators now need a mechanism to study, in detail, human responses in people who are given alternative candidate vaccines. The ability to use GLP material in small human subject trials is thus vital.
5. Provide program project management advice and services for the developmental and translational phase of a product. This could be included under the Translational Core. There is a need for centralized program management (or

project management of the science) with help for determining when some avenue should be dropped and other avenues explored. This is important for conserving resources and helping candidates to move into Phase I trials.
6. Provide aids in drafting and helping investigators to navigate regulatory aspects.
7. Provide workshops regarding regulatory issues where the VRC can bring all parties to the table (intramural, extramural, industry, and FDA). Important subjects would be regulatory obstacles to trials and clinical trial design.
8. Feed back information gained from Phase I trials.
9. Advance vaccine candidates. Extensive discussion occurred on whether this should be the VRC's job. Several participants thought the VRC could bring along a few candidates, but should not try to do too many in addition to developing their own. Mr. Bill Snow advocated that the VRC pick up several candidates from elsewhere so that there would be many approaches being attempted in parallel and in different phases of development. It was the general consensus that the VRC would help to bring some outside candidates along.
10. Address research questions, which require substantial resources.
11. Keep the FDA appraised of emerging concepts in HIV vaccine development.
12. Increase non-human primate resources (not necessarily in the VRC), which are desperately needed.

Focus on AIDS

The VRC should initially focus only on AIDS so as not to dilute the effort to bring a vaccine to market. Researchers working on other diseases should be considered if it is in the context of taking advantage of expertise where there is a known vaccine or the work has something to directly contribute to HIV research. Also, where the study of HIV may open up an opportunity in some other disease model, or vice-versa, the VRC should take advantage of this. Teamwork is seen as a high priority in the effort to move the field forward.

Research Needed in the Area of AIDS

1. Additional research seeking and analyzing broadly neutralizing antibodies. All current broadly neutralizing antibodies have been identified via binding assays rather than a functional assay for neutralization. New assays are needed and high throughput technology brought to bear on this subject.
2. Finding immunogens that can elicit broadly neutralizing antibodies and performing structural studies of these.
3. Ways to enhance immunogenicity.
4. Ways to present exogenous proteins most advantageously to the immune system; looking at other adjuvants.
5. Ways to manipulate antibody responses.
6. Examine existing vaccine with newer immunological, virological, and molecular biological techniques to see how they work.
7. Use some new microarray techniques, especially for analyzing expression systems.

8. Develop several vaccine candidates at a time with some in different stages of development.

Production Needs and Options

The VRC will have GLP facilities that will be used to produce small-scale materials quickly. Other options for small-scale products:

1. Contracting out
2. NIAID's extramural contract. If the VRC contributes to the contract, they can have significant access.
3. NCI, Frederick facility.

A recommendation was made that since the VRC production facilities were often going to be used as a back up, it might be prudent to make certain classes of arrangements now for outsourcing, especially since the production of biologics is a growing business.

VRC Space Recommendations

1. BSL 3 space should be reviewed to see if it is sufficient. (This was determined to be sufficient given the BSL 2+ levels unless the recruited investigators desired a change).
2. The number of tissue culture hoods was questioned, but was acceptable at this time due to the flexibility to expand the number, if necessary, when recruitment is completed.
3. There is a need to have a large, devoted FACS room in the BSL 3 containment room. This would require an anteroom. Use of non-human primates would require the FACS within the BSL-3 facility. Thus, have at least half of the BSL-3 rooms with a FACS sorter.
4. More FACS scanners are needed in the building.

Resources

1. National Institute of Human Genome Research (NIHGR)- bioinformatics and genomics.
2. NIH AIDS-related research investigators (over 100).
3. Ongoing NIH programs.
4. Existing Vaccine programs: There are a number of laboratories studying vaccines; three mentioned were: Drs. John Robbins' and Bob Cahnuk's programs, which have successfully developed vaccines and Dr. Lou Miller who's currently working on a malaria vaccine.
5. Intramural AIDS-Targeted Anti-Viral Program (IATAP) is a grant program for intramural scientists sponsored by Dr. Gottesman's office. Most of the funds are for infrastructure for structural biology studies related to AIDS and some vaccine projects related to AIDS (i.e., NMR, crystallography, EM crystallography).

6. NIH has a formidable structural biology program with world-class NMR spectroscopists and crystallographers. There are over 11 crystallography groups with over 80 people doing crystallography. In addition, they have full time dedicated access to Brookhaven and Argon facilities. They are currently building an EM crystallography program facility that will have state-of-the-art high voltage EM technology with investigators interested in studying viral structural proteins and membrane proteins.
7. The NCI, Frederick facility was originally built to support a variety of structural and biological modifier programs. There is a Good Manufacturing Practices (GMP)-specified facility on site, which has made vaccines. Also, Dr. John Coffin is establishing a major program in HIV drug resistance. Dr. Larry Arthur, Director, AIDS Vaccine Program, NCI, Frederick, invited Dr. Nabel to tour the facility.
8. A Protein Expression Lab (PEL) lies within NIAMS and has a mission to supply protein in large quantities, particularly AIDS-related proteins, for study in the intramural program.
9. The Pilot Plant within NIDDK has many 30- and 50 liter fermentors and is currently being renovated. Dr. Nabel has met with them to discuss ways it can be modified to best serve the VRC.
10. The Bioengineering and Physical Sciences Program within the Office of Research Services has provided many bioengineers who have been helpful in developing technologies needed for high throughput screening techniques. Collaboration with NCI produced a laser capture microdissection.
11. *In vivo* NMR center
12. A small animal imaging center is being developed.
13. Vivarium for animal care.
14. The National Center for Biotechnology Information encompasses a wide variety of bioinformatics.
15. Clinical capabilities. A new clinical center is being built and the current clinical center has years of experience in which many important clinical trials have been conducted. Dr. Cliff Lane, Clinical Director, NIAID, is a willing collaborator.
16. Proximity of Center for Biologics Evaluation and Research (CBER), FDA. CBER has enormous experience on regulation and vaccine development. In addition, CBER has a very active HIV vaccine research group that is available for consultation and collaboration.
17. NIAID Vaccine-related researchers
18. Dr. David Baltimore's AIDS Vaccine Research Committee (AVRC).
19. Current and new clinical center.
20. Staff physicians who are clinical investigator physicians.
21. Study coordinators (nurses) provide a model service. NIAID has its own IRP; thus there is a fast turn around on protocols.
22. Case Managers (nurses) who are familiar with the protocols.
23. Relationship between intramural scientists and industry, which has already evolved via CRADAs. The Office of Technology Transfer sets the policy for interactions and has a formal mechanism for deciding each partner's

responsibility while protecting intellectual property. This process works well and fast.

24. Collaboration with extramural investigators is best accomplished by cooperative agreements since they allow payment and participation in the proposal writing process. Neither of these are allowed in the grant process.
25. Support contracts present a good option to work past resources. Frederick's NCI has one in place that is very broad, i.e., studies of the immune system, and many institutes have subcontracts.
26. NCI's RAID program. Designed to take good candidates for therapeutics forward by moving them through GMP and into Phase I trials.

VACCINE RESEARCH CENTER RETREAT

Embassy Suites at the Chevy Chase Pavilion
Washington, DC

April 16-17, 1999

Participant List

Dr. Rafi Ahmed
Director
Emory Vaccine Center
Emory University
Rollins Research Building, G211
1510 Clifton Road
Atlanta, GA 30322
Phone: (404) 727-3571
Fax: (404) 727-3722

Dr. John D. Altman
Assistant Professor
Department of Microbiology and Immunology
Emory University
Emory Research Center
3119 Rollins Research Center
1510 Clifton Road
Atlanta, GA 30322
Phone: (404) 727-5981
Fax: (404) 727-3659

Dr. Larry O. Arthur
Director
AIDS Vaccine Program
National Cancer Institute
Building 535, 5th floor
P.O. Box B
Frederick, MD 21702
Phone: (301) 846-1408
Fax: (301) 846-5588

Mr. Samuel H. Avrett
Executive Director
AIDS Vaccine Advocacy Coalition (AVAC)
1875 Connecticut Avenue, N.W., #700
Washington, DC 20009
Phone: (202) 265-7034 or (202) 387-5517
Fax: (202) 986-1345
Email: savrett@aol.com

Dr. Dennis R. Burton
Department of Immunology
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037
Phone: (619) 784-9298
Fax: (619) 784-8360
Email: burton@scripps.edu

Dr. Michael De Wilde
SmithKline Beecham Pharmaceuticals
SB Biologicals
Ruade l'Institut 89
1330 Rixensart
BELGIUM
Phone: 32 2 656 8334
Fax: 32 2 656 8113

Dr. Ronald C. Desrosiers
Harvard Medical School
New England Regional Primate Research Center
One Pine Hill Drive, Box 9102
Southborough, MA 01772-9102
Phone: (508) 624-8042
Fax: (508) 624-8190

Dr. William Egan
Acting Director
Office of Vaccines Research and Review

Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Building 29/B, Room 1NN01
29 Lincoln Drive
Bethesda, MD 20892
Phone: (301) 827-0655
Fax: (301) 827-0448

Dr. Anthony Fauci
Director
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Building 31, Room 7A03
31 Center Drive
Bethesda, MD 20892-2520
Phone: (301) 496-2263
Fax: (301) 496-4409

Dr. Mark B. Feinberg
Associate Director/Associate Professor
Medicine /Microbiology/Immunology
Emory University
Emory/Atlanta Center of AIDS Research
1518 Clifton Road, N.E., Room 816
Atlanta, GA 30322
Phone: (404) 727-4374
Fax: (404) 727-9853

Dr. Ronald N. Germain
Division of Intramural Research
Laboratory of Immunology
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Building 10, Room 11N311
10 Center Drive, MSC 1892
Bethesda, MD 20892-1892
Phone: (301) 496-1904
Fax: (301) 496-0222
Email: ronald_germain@nih.gov

Dr. Neil Goldman
Associate Director for Research
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Building 29, Room 5N22
1401 Rockville Pike, HFM-20
Rockville, MD 20852
Phone: (301) 827-0377
Fax: (301) 827-0440
Email: goldmann@cber.fda.gov

Mr. Gregg Gonsalves
Policy Director
Treatment Action Group
413 West 48th Street, #3F
New York, NY 10036
Phone: (212) 707-8424
Fax: (212) 777-8919
Email: ggonsalves@msn.com

Dr. Michael Gottesman
Office of Intramural Research
Office of Director
National Institutes of Health
Building 1, Room 114
1 Center Drive
Bethesda, MD 20892
Phone: (301) 496-1921
Fax: (301) 402-4273

Dr. Carole Heilman
Division of AIDS
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Solar Building, Room 2A16
6003 Executive Boulevard
Bethesda, MD 20892-7620
Phone: (301) 496-0545
Fax: (301) 402-1505

Dr. Richard J. Hodes
Director
National Institute on Aging
Building 31, Room 5C35
31 Center Drive
Bethesda, MD 20892

Phone: (301) 496-9265
Fax: (301) 496-2525
Email: hodesr@nia.nih.gov

Mr. James A. Hoxie
Professor
Medicine
University of Pennsylvania
Clinical Research Building, Room 664
415 Curie Boulevard
Philadelphia, PA 19104
Phone: (215) 898-0261
Fax: (215) 573-7912
Email: hoxie@mail.med.upenn.edu

Dr. Peggy Johnson
Assistant Director for AIDS Vaccines
Associate Director for Vaccine and Prevention Research, DAIDS
Division of AIDS
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Solar Building, Room 2A07
6003 Executive Boulevard
Bethesda, MD 20892-7620
Phone: (301) 402-0846
Fax: (301) 402-3684
Email: pj7p@nih.gov

Dr. Richard D. Klausner
Director
National Cancer Institute
Building 31, Room 11A48
31 Center Drive, MSC 2590
Bethesda, MD 20892-2590
Phone: (301) 496-5615
Fax: (301) 402-0338

Dr. David Knipe
Professor of Microbiology and Molecular Genetics
Harvard Medical School
Building D1, Room 616
200 Longwood Avenue
Boston, MA 02115
Phone: (617) 432-1934
Fax: (617) 432-0223
Email: david_knipe@ hms.harvard.edu

Dr. Cliff Lane
Office of the Clinical Director
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Building 10, Room 11S231
10 Center Drive
Bethesda, MD 20892-1894
Phone: (301) 496-7196
Fax: (301) 480-5560

Dr. Dan R. Littman
Professor and Howard Hughes Medical Institute Investigator
Skirball Institute of Biomolecular Medicine
New York University Medical Center
Howard Hughes Medical Institute
540 First Avenue, 2nd Floor
New York, NY 10016
Phone: (212) 263-7520
Fax: (212) 263-5711
Email: littman@saturn.med.nyu.edu

Dr. Malcom A. Martin
Laboratory of Molecular Biology
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Building 4, Room 315
4 Center Drive, MSC 0460
Bethesda, MD 20892-0460
Phone: (301) 496-4012
Fax: (301) 402-0226

Dr. Bonnie Mathieson
Office of AIDS Research
National Institutes of Health
Building 31, Room 4C06
31 Center Drive
Bethesda, MD 20892
Phone: (301) 496-4564

Fax: (301) 496-4843

Dr. John Moore
Staff Investigator
Aaron Diamond AIDS Research Center
455 First Avenue, 7th floor
New York, NY 10016
Phone: (212) 725-0018
Fax: (212) 725-1126

Dr. Bernard Moss
Laboratory of Viral Diseases
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Building 4, Room 229
4 Center Drive
Bethesda, MD 20892-0445
Phone: (301) 496-9869
Fax: (301) 480-1147

Dr. Gary J. Nabel
Director
Vaccine Research Center
National Institutes of Health
4520 MSRB 1, Box 0650
1150 W. Medical Center Drive
Ann Arbor, MI 48109
(temporary address until move to NIH)
Phone: (734) 763-7753
Fax: (734) 764-3596

Dr. Neal Nathanson
Director
Office of AIDS Research
National Institutes of Health
Building 31, Room 4C02
31 Center Drive, MSC 2340
Bethesda, MD 20892
Phone: (301) 496-0357
Fax: (301) 496-2119

Dr. Douglas F. Nixon
Assistant Professor/Staff Investigator
The Rockefeller University
455 First Avenue, 7th floor
New York, NY 10016
Phone: (212) 448-5010
Fax: (212) 725-1126
Email: dnixon@adarc.org

Dr. Jack H. Nunberg
Professor and Director
Montana Biotechnology Center
University of Montana
Science Complex 221
Missoula, MT 59812
Phone: (406) 243-6421
Fax: (406) 243-6425

Dr. William Paul
Laboratory of Immunology
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Building 10, Room 11N311
10 Center Drive, MSC 1892
Bethesda, MD 20892-1892
Phone: (301) 496-5046
Fax: (301) 496-0222

Dr. Robert Seder
Acting Chief, Clinical Immunology Section
Laboratory of Clinical Investigation
Division of Intramural Research
National Institutes of Allergy and Infectious Diseases
National Institutes of Health
Building 10, Room 11C217
10 Center Drive
Bethesda, MD 20892
Phone: (301) 402-4816
Fax: (301) 480-1936

Ms. Cyrena Simons
Research Facilities Coordinator
ORS
Building 1, Room 160
1 Center Drive
Bethesda, MD 20852-0158
Phone: (301) 496-8869

Fax: (301) 496-8270
Email: simonsc@ors.od.nih.gov

Mr. William Snow
AIDS Vaccine Advocacy Coalition
40 Alta Road
Berkeley, CA 94708
Phone: (510) 524-5257
Fax: (510) 524-5723

Dr. Louis Staudt
Metabolism Branch
National Cancer Institute
Building 10, Room 4N114
10 Center Drive
Bethesda, MD 20892
Phone: (301) 402-1892
Fax: (301) 496-9956

Dr. Jeffrey Trent
National Human Genome Research Institute
National Institutes of Health
Building 49, Room 4A22
49 Convent Drive
Bethesda, MD 20892-4470
Phone: (301) 402-2023
Fax: (301) 402-2040

Dr. Harold Varmus
Director
National Institutes of Health
Building 1, Room 126
1 Center Drive, MSC 0148
Bethesda, MD 20892-0148
Phone: (301) 496-2433
Fax: (301) 402-2700

Dr. Kathryn Zoon
Director
Immediate Office of the Director
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
Woodmont Office Center, HFM-1
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448
Phone: (301) 827-0548
Fax: (301) 827-0440