NIH AIDS Research Program Evaluation

DRUG DISCOVERY AREA REVIEW PANEL

Findings and Recommendations

Panel Members

Emilio Emini, Ph.D., ***Chair***
Merck Research Laboratories
Judith Feinberg, M.D., ***Executive Secretary***
Office of AIDS Research, NIH
John M. Coffin, Ph.D.
Tufts University School of Medicine
William Current, Ph.D.
Eli Lilly and Company
Alan D. Frankel, Ph.D.
University of California, San Francisco
James M. Hogle, Ph.D.
Harvard University
Brenda Lein
Project Inform
Judy Lieberman, M.D., Ph.D.
Harvard University
Richard Lynn, Ph.D.
Pfizer Inc.
Joseph M. McCune, M.D., Ph.D.
University of California, San Francisco
Manuel Navia, Ph.D.
Vertex Pharmaceuticals
John Secrist, Ph.D.
Southern Research Institute
Richard R. Tidwell, Ph.D.
University of North Carolina

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Executive Summary

The Drug Discovery Area Review Panel was charged with assessing the current NIH portfolio in the area of drug discovery and preclinical drug development, developing the goals and priorities for the next phase of AIDS research in these areas, and making recommendations to ensure that these goals and priorities will be met. The Panel specifically addressed the effectiveness, optimal focus, balance, duplication, and cooperation among NIH Institutes, Centers, and Divisions (ICDs), the role of the Government versus the private sector, and the definition of a vision for the future of NIH drug discovery research. The Panel divided its evaluation into a number of different focus areas: basic and applied research, molecular/structural studies, animal models, opportunistic infections, and the programs of two ICDs–the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI). This summary presents the general themes that arose during the review, outlines the evaluation, and provides the recommendations made in each of the areas.

General Themes

1. Mechanisms for encouraging the initial evaluation of potential lead discoveries relevant to therapeutics should be developed. The ICD staff should play a key role in ensuring appropriate contact between discoverers and potential developers. This might include providing appropriate expertise, establishing contacts, as necessary, with the private sector, ensuring rapid dissemination of new data in appropriate venues, and providing support for proof-of-concept testing in animal models and in the clinic.

2. Periodic, rigorous external scientific review and guidance is essential in a number of areas evaluated by the Panel, such as use of primate animal resources and funding of translational proof-of-concept studies for novel therapeutic approaches. Current study sections should be realigned to include appropriate expertise in these areas.

3. No database currently captures scientific information resulting from NIH-supported research. The AIDS Research Information System (ARIS) database, created to track expenditures for research projects supported in whole or in part by the AIDS budget, is incomplete with regard to fiscal accountability for individual projects and is wholly inadequate for tracking scientific progress. Such information may reside at the program staff level of various ICDs, but not in a format suitable for oversight by the Office of AIDS Research (OAR) or for implementing long-range planning and coordination of efforts among the ICDs. The NIH must develop an effective system for tracking HIV-related research that includes both intramural and extramural efforts.

A. Basic and Applied HIV Research

Evaluation

1. The basic HIV research funded by NIH has been the major success story of the war on AIDS. It serves as a leading example of high-quality virological and infectious disease research.

2. These basic research efforts have yielded a number of therapeutic approaches that are currently in various stages of evaluation.

3. No formal mechanisms exist to ensure that basic research findings are effectively translated into practical therapeutic advances through appropriate preclinical and clinical studies. It is unclear to what extent NIH fosters the interaction between the discoverers and those who might be interested in developing these discoveries. Current study sections are not constituted to provide appropriate expertise for determining the scientific merit of such "translational research."

Recommendations

1. **Support of basic and applied HIV (and all retroviral) research should be continued.**

2. **Better communication is required between the Institutes and the OAR and among the specific Institutes involved in the support of basic and applied HIV-related research.**

3. **The OAR should develop a system for identifying priority areas for NIH support and for encouraging new basic research activities. This could include the formation of a blue-ribbon panel that would meet at regular intervals to assess the state of the art in HIV basic and applied research and to recommend areas for future or continued focus. This panel would also consider the likelihood of private sector involvement in various areas of HIV research.**

4. **Investigator-initiated applications should be strongly encouraged for those areas determined to be critical research priorities. This may be accomplished by inviting key and young investigators who are not currently involved in the designated area of research (or who are involved in allied research areas) to specific workshops.**

5. **Mechanisms for encouraging the initial evaluation of potential lead discoveries relevant to therapeutics should be developed. ICD staff should play a key role in ensuring appropriate contact between discoverers and potential developers. This might include providing appropriate expertise;**

establishing contacts, as necessary, with the private sector; ensuring rapid dissemination of new data in appropriate venues; and providing support for proof-of-concept testing in animal models and in clinical trials.

B. Molecular/Structural Studies

Evaluation

1. The emphasis on a multidisciplinary programmatic approach to determining high-resolution structures of HIV-related targets has proven to be successful and has provided impressive information. This information has guided an understanding of the therapeutic potential of various targets, helped in the design of possible therapeutic agents, and provided an appreciation of the structural basis for drug resistance.

2. The diversity of funding mechanisms used to support molecular structural studies has been productive. These include investigator-initiated grants; various NIH intramural programs, such as those conducted by the NCI Frederick Cancer Research and Development Center (FCRDC) and the National Institute for Diabetes, Digestive, and Kidney Diseases (NIDDK); and program projects sponsored by the National Institute of General Medical Sciences (NIGMS).

Recommendations

1. **Continued support of structure-based designs focused on the HIV protease and reverse transcriptase (RT) should be evaluated periodically, given the commercial sector's changing interest in these targets.**

2. **Support for new structure-based inhibitor design should focus on HIV integrase and on novel approaches to other targets, such as the CD4 receptor.**

3. **Support should continue for structural studies of HIV envelope glycoproteins, regulatory proteins, response elements, and regulatory protein/response element complexes.**

4. **Use of diverse funding mechanisms, including both investigator-initiated grants and targeted initiatives, should continue.**

5. **Enhanced cooperation among ICDs for the coordination of structural studies should be ensured by OAR.**

6. **A uniform policy should be implemented on the timely deposition and release of structural coordinates determined from NIH-supported studies (including research receiving partial NIH support).**

C. NIAID Drug Discovery Programs, including the National Cooperative Drug Discovery Groups (NCDDG), the Strategic Program for Innovative Research on AIDS Therapies (SPIRAT), and the AIDS Research and Reference Reagent Program

Evaluation

1. The current NCDDG-HIV program appears to be reasonably well-targeted. Following its restructuring in 1991-92, the program appears to have been successful in enhancing both cooperation and productivity.

2. The SPIRAT program is new and it is too early to assess the productivity of this innovative, yet unproven, approach to the discovery and development of novel HIV therapeutics.

3. The NCDDG-HIV and SPIRAT programs currently emphasize the study of novel, high-risk therapeutic approaches (e.g., gene therapy, cellular immunotherapy, ribozymes) that have not been successfully implemented to date for any disease.

4. It is necessary to quickly assess the clinical feasibility and applicability of novel therapies. These assessments may be critical to eliciting private sector interest in further development. However, proof-of-concept trials for novel therapeutic approaches currently have limited possibility for funding as investigator-initiated proposals because there are no study sections with appropriate expertise. Of the current NIH developmental therapeutics programs, only SPIRAT includes support for bridging preclinical and clinical development.

5 The AIDS Research and Reference Reagent Program is a well-organized and important resource for investigators.

Recommendations

1. **The NCDDG-HIV and SPIRAT programs should continue at their current level of support. However, both programs should be evaluated in the near future to assess their productivity and recommend appropriate adjustments, in a manner similar to the review initiated prior to the renewal of the NCDDG program.**

2. **The choice of therapeutic targets for study should be guided by an expert panel, including non-Government investigators, that periodically would assess the state of the art in HIV research. Consideration also should be given to the support of programs designed to investigate therapeutic approaches that do not necessarily advance the technological frontier but may have real potential for improving the current clinical management of HIV disease.**

3. **Realignment of current study sections to include appropriate expertise to evaluate translational research may be essential for assessment of investigator-initiated preclinical and proof-of-concept clinical studies.**

4. **The AIDS Research and Reference Reagent Program is a valuable resource. NIH-funded investigators should be actively solicited and encouraged to provide, in a timely fashion, novel reagents to the program for potential use by other researchers.**

D. Animal Models

Evaluation

1. NIAID fosters work in multiple animal models, including mice (MAIDS/BM5, LCMV, SCID/HIV, transgenic), cows (BIV), horses (EIAV), cats (FIV, FeLV), sheep (type D retroviruses), rabbits (HIV), and nonhuman primates (particularly rhesus macaques, pigtailed macaques and chimpanzees) infected with SIV or HIV.

   The emphasis has been on the mouse, cat, and rhesus macaque models. These three models are also supported separately by contracts for the preclinical evaluation of anti-HIV compounds. The relevance of these models and the productivity of research in these areas has been variable.

2. The National Center for Research Resources (NCRR) supports the infrastructure and research activities of seven Regional Primate Research Centers (RPRCs). Various animal models represented at these Centers include chimpanzees, specific pathogen free (SPF) macaques, and rhesus macaques. The Centers and the available models provide a valuable resource to the research community. However, this resource is not readily available to NIH-funded investigators who are not directly affiliated with the Centers.

3. The SIV-infected rhesus macaque, generally acknowledged to be the best model for pathogenesis studies, also has considerable potential for drug discovery research. The use of SHIV recombinants is particularly attractive for drug discovery research because they are capable of infection with pathogenic consequences but retain the desired molecular targets of HIV.

4. The animal models endeavors at other ICDs, particularly the National Institute of Mental Health (NIMH), the National Institute of Child Health and Human Development (NICHD), and NCI, are focused on pathogenesis and vaccine studies. Some of these models (such as mucosal models of HIV transmission) may be useful for the evaluation of possible therapeutic agents. The quality and productivity of these efforts have been uneven.

Recommendations

1. **There remains a critical need for further development and optimization of animal models for HIV disease. This need is likely to become increasingly important in the future. Different animal models clearly will be required to meet different research needs. Some models are particularly well-suited for studies of pathogenesis, while others are useful for the preclinical evaluation of new therapeutic agents. It will be particularly important to support the development of a model that can be used for both types of studies.**

2. **NIH should strive to optimize and validate the small-animal models (e.g., various mouse and cat models) that currently appear useful for preclinical evaluation of anti-HIV compounds, to determine which (if any) of the models are predictive of efficacy and pharmacodynamic attributes in humans. Those models determined to be relevant and useful should be provided with additional infrastructure and support; support for other models should be de-emphasized.**

3. **More resources should be devoted to the development and optimization of the SIV-infected rhesus macaque model for preclinical drug evaluation *in vivo*. Additional support would be valuable for further derivation and standardization of molecularly cloned SHIV recombinants, expansion of colony size to reduce animal costs, and infrastructure for housing and research facilities.**

4. **Drug discovery research involving the chimpanzee, rabbit/HIV, and SPF macaque models has not been productive. Funds for this research should be redirected.**

5. **At this time, animal model research is sufficiently mature so that heavily directed research efforts by NIH program staff are inappropriate. Research funded in the future should be subjected to rigorous peer review. This can be facilitated by refocusing current study sections and ensuring that they have appropriate expertise; study section review is preferable to *ad hoc* reviews.**

6. **The NCRR should ensure broad access by qualified investigators to the resources provided by the RPRCs. This may be accomplished by creating independent peer review panels to evaluate proposed research projects by both Center staff and non-Center investigators seeking access to these facilities. The infrastructure for studies that are approved for implementation at a given Center (including the supply, housing, and handling of the animals; obtaining and processing of specimens) should come from the operating budget of that Center. Competitive renewal of the Center grants should include, as a measure of productivity, a description of the Center's peer review process and its success in supporting studies initiated by non-Center investigators.**

7. **Therapeutic agents that have limited effectiveness in patients with advanced HIV infection may be effective around the time of initial infection or in early**

stages of the disease. More research on both novel and conventional therapies in primate models should focus on these early time points.

E. NCI HIV Drug Discovery Program

Evaluation

1. The Panel was impressed with the logistical scope of the NCI's Developmental Therapeutics Program (DTP) effort and with the highly interactive process by which anti-HIV-1 compounds are evaluated. However, the heavy dependence of the NCI drug discovery program on the nonselective cell-based antiviral screen is problematic. Since the screen is not aimed at specific molecular targets, the entire system is driven solely by agents that yield positive activity in this assay, irrespective of the specific target that is inhibited. Many compounds that have the same target as agents already well-studied in the clinic, particularly nonnucleoside RT inhibitors, have been identified and pursued to varying degrees. As a result, the productivity of the program over the last 8 years has been limited, and the overall program is rather diffuse, in spite of the fact that day-to-day management of its many component branches, laboratories, and contractors appears to be well-integrated.

2. Of the many thousands of defined compounds and natural products that have been screened, the few that have advanced to further study represent a restricted number of antiviral mechanisms. Most of the compounds that were initially identified by the screen are nonnucleoside RT inhibitors, and one is a putative inhibitor of the viral nucleocapsid protein. Several compounds were introduced into the DTP development process at later stages following their initial identification as antiviral agents elsewhere.

3. Much of the basic research that has gone into elucidating the mode of action of these compounds has been of good quality, as has the research required to establish the mechanism-based assays needed for these studies. Yet these undertakings have not been used in a way that enhances the ability of the program to discover and study truly novel inhibitors of HIV.

4. The development of new treatment modalities for AIDS-associated malignancies appears to have received relatively scant attention from DTP efforts.

Recommendations

1. **The DTP should no longer focus primarily on the nonselective antiviral screen.**

2. **The DTP management structure should be reviewed, given its apparent inability to enhance the productivity of the AIDS drug discovery effort.**

3. **The DTP should use its core resources to support NIH-wide antiretroviral discovery efforts by providing compounds and natural products for various screening endeavors as well as medicinal chemistry, pharmacologic, and toxicologic support as needed. Ongoing review of the DTP AIDS drug discovery program should include assessment of its ability to support the overall NIH drug discovery effort.**

4. **DTP resources also should be used to support the efforts of other ICDs to develop treatments for opportunistic infections (OIs).**

5. **An external scientific advisory board should be constituted to provide guidance regarding appropriate DTP support for NIH drug discovery programs. It is not cost-effective to reproduce the considerable DTP infrastructure in other ICDs.**

6. **The operational logistics of the DTP require review and restructuring. Given the Panel's recommendations, a substantial decrease in the size and funding of the DTP's current HIV drug discovery effort may be appropriate.**

7. **Support is needed for research on developmental therapeutics for HIV-associated malignancies.**

F. Drug Discovery in Opportunistic Infections

Evaluation

1. The NCDDG-OI program has been productive, as judged by focus, quantity, and quality of publications resulting from funded projects, by the number of new investigators brought into the field, and by the successful development of a number of agents that have reached Phase III clinical trials.

2. NIAID has focused research funds, through the NCDDG-OI program and various contracts, on the opportunistic pathogens of importance in AIDS that are not considered "primary targets" by major pharmaceutical firms. The single exception appears to be the high level of funding for research on *Candida*.

3. Although the current focus on *Mycobacteria, Cryptosporidium,* and *Microsporidia* appears justified, it is unclear how decisions about pathogen focus and total amount of funding committed to OI research are being made at the program level. This is complicated by the fact that both AIDS and non-AIDS funds are used to support basic and applied research on opportunistic pathogens.

4. Although contract support for animal models and drug screening has been uncoordinated and unfocused in the past, there appears to have been some improvement in the management of these programs more recently.

Recommendations

1. **Support for the NCDDG-OI program should continue at the present level.**

2. **Even though it may be anticipated that some pharmaceutical industry support of mycobacterial research will be forthcoming, the present medical need justifies at least short-term support by NIH. However, NIAID should continue to monitor the development of new therapies (especially for *M. avium* complex) by the private sector, with the goal of redirecting funds at the appropriate time.**

3. **Support for *Microsporidia, Cryptosporidium,* JC virus, and other pathogens that have less attractive market potential should be emphasized. In general, when projecting future needs, NIH should consider where pharmaceutical industry efforts are being placed, so that Federal funds can be used to target understudied pathogens.**

4. **The selection of organisms to be studied by the NCDDG system should involve several factors, including the number of Research Project Grants (RPGs) funding research on that organism, its relative importance in the clinical management of AIDS patients, and the commitment of pharmaceutical companies to research on the organism. An external advisory group could significantly assist in determining which organisms should be studied.**

5. **The NIAID should be encouraged to periodically assess the overall value of individual contracts supporting OI research with respect to productivity, reliability, and user accessibility.**

Introduction and Methods

The Panel was constituted to provide broad representation across a range of scientific disciplines pertinent to drug discovery, including medicinal chemistry, structural chemistry, animal models, retrovirology, immunotherapy, and OIs. Panel members were drawn from both academia and industry and included community representatives. Diversity with regard to geographic location, gender, and community representation was sought (a complete list of Panel members and their affiliations can be found in Appendix G). The full Panel met four times, with the first session on April 20, 1995, and the last on November 29, 1995. In addition, five subpanel meetings were held (a complete schedule can be found in Appendix B). The final meeting included an open public session for testimony from individuals and groups wishing to have input into the review process.

The OAR AIDS Research Information System (ARIS) was queried for all research projects from 1990-1994 according to the Strategic Plan code for drug discovery, and corresponding abstracts were obtained from the Division of Research Grants (DRG) Computer Retrieval Information Systems Program (CRISP) database. This review provided the initial description of NIH-funded efforts in this area. The Panel subsequently targeted 1994 for its review as this was the most recent fiscal year (FY) for which complete data were available and because there had been significant changes in funding from prior years. The Panel was initially divided into seven subpanels: five based on the diverse areas that comprise HIV/AIDS drug discovery and two created along Institute lines because of the considerable resources devoted to drug discovery by NIAID and NCI. ARIS was searched using the following key words in titles (and abstracts, if titles were uninformative) to sort them into the subpanel areas for review:

- **Basic HIV-directed research (including immunology)**
  key words: reverse transcriptase, protease/proteinase, integrase, tat, rev, nef, gene, mechanism of action, function, catalytic, replication, cloning, inhibition, transdominant, pathogenesis, receptor, fusion, immunoregulation

- **Targeted HIV-directed research (including immunotherapy)**
  key words: assay, drug, design/construction, chemistry, synthesis, isolation, analog, derivatives, engineering, novel, delivery, vector, expression, target, inhibition, catalytic, resistance, monoclonal antibody, phosphorylated, passage, activity, mechanism of action, nucleoside, oligonucleotide, heterocyclic, binding, natural product, screening, preclinical, safety, treatment, therapy, gene therapy, technical, support, services, core laboratory

- **Basic and targeted research in OIs, including the NCDDG-OI**
  key words: names of specific OIs, HIV-directed

- **Molecular/structural studies**
  key words: molecular, structure/structural, high resolution, mapping, crystallography

- **Animal models**
  key words: animal, model, model development, *in vivo*, transgenic, transplacental plus species designations

- **NIAID drug discovery program**

- **NCI drug discovery program**

Each Panel member was assigned to two subpanels, with members' expertise matched to the areas to be reviewed; a Panel member was named to lead each subpanel at the first meeting (subpanel membership is listed in Appendix C). It was subsequently apparent that (1) the division of HIV-directed research into separate "basic" and "targeted" subpanels was artificial, and so the two were merged, and (2) there was insufficient breadth of expertise to review OI basic research, so a separate joint subpanel with the Etiology and Pathogenesis Area Review Panel was created (see Appendix C).

Written materials were requested from the six ICDs with significant intramural and/or extramural funding in the areas pertinent to HIV/AIDS drug discovery: NIAID, NICHD, NCI, NCRR, NIDDK, and NIGMS.

The Panel met with key NIH staff responsible for these programs and heard presentations focused on goals, accomplishments, gaps, funding mechanisms, and future directions. The three ICDs with smaller AIDS research portfolios were reviewed on the basis of written materials only: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Environmental Health Sciences (NIEHS), and the National Institute of Dental Research (NIDR). The Panel also made use of prior scientific and administrative reviews that had been conducted by NIH and by outside groups, e.g., the Institute of Medicine (IOM) and advocacy groups.

A number of areas reviewed by the Panel overlapped with those of other Panels. Joint subpanels with the Etiology and Pathogenesis Area Review Panel were established for the areas of animal models and basic research on OIs. For OIs, a broader range of expertise than existed in either parent Panel was needed, and 21 additional experts were named to this joint subpanel. The issue of alternative therapies was addressed by a separate *ad hoc* subpanel as well as by the Clinical Trials Area Review Panel. In the area of translational research–the transitional domain between drug discovery and clinical trials–the Drug Discovery and Clinical Trials Panels addressed the issue separately, from their own perspectives, with subsequent discussion by the two Panel chairs.

Based on its evaluation, the Panel formulated an Executive Summary of its findings and recommendations. A complete report was generated from the individual subpanel reports and was reviewed in detail at the last two meetings by the full Panel.

Evaluation

General Themes

Mechanisms for encouraging the initial evaluation of potential lead discoveries relevant to therapeutics should be developed. ICD staff should play a key role in ensuring appropriate contact between discoverers and potential developers. This might include providing appropriate expertise; establishing contacts, as necessary, with the private sector; ensuring rapid dissemination of new data in appropriate venues; and providing support for proof-of-concept testing in animal models and in the clinic.

Guidance, including periodic and rigorous scientific review, was found to be necessary in a number of areas evaluated by the Panel, such as the use of primate animal resources and funding of translational proof-of-concept studies for novel therapeutic approaches. Current study sections should be realigned to include appropriate expertise in these areas.

No database currently captures scientific information resulting from NIH-supported research. The ARIS database, created to track expenditures for research projects supported in whole or in part by the AIDS budget, is incomplete with regard to fiscal accountability for individual projects and is wholly inadequate for tracking scientific progress. Such information may reside at the program staff level of various ICDs, but not in a format suitable for oversight by the OAR or for implementing long-range planning and coordination of efforts among the ICDs. NIH must develop an effective system for tracking the progress of HIV-related research that is inclusive of both intramural and extramural efforts.

A. Basic and Targeted HIV Research Subpanel

Background

The AIDS basic science research program relevant to anti-HIV drug discovery encompasses essentially the entire NIH basic research effort. Although current useful therapeutic strategies are directed against only two specific targets—RT and protease—any aspect of virus-host interaction presents, in principle, a potential target for therapy, and quite a number have, in fact, either been tested or are currently at some stage of development. Examples of other strategies arising from basic research include soluble CD4 to interrupt the virus-receptor interaction,

glycosylation inhibition, intracellular protection (i.e., gene therapy) strategies directed against tat and rev function as well as antisense RNA and DNA and ribozymes directed against the viral genome, and "zinc finger" antagonists directed against the viral NC-RNA intermediate. Other areas of basic HIV research that are important for drug discovery include genetic variation and drug resistance.

The majority of extramural basic HIV research is supported by NIAID. Although a significant portfolio of research in fundamental non-HIV retrovirology is funded by NCI, it is not coded as "AIDS-related." Intramural basic HIV research is conducted by a number of ICDs, most prominently NIAID, but there is considerable activity in NCI, especially at the Frederick Cancer Research and Development Center (FCRDC).

Currently, the only way that the overall basic research program can be assessed is fiscally, using the ARIS database for research expenditures that have been coded as "AIDS" or "AIDS-related." No system is in place to assess the appropriateness of, or progress towards, scientific goals; thus, a review of this area, which consists almost entirely of investigator-initiated research grants and not wide-ranging programs, is problematic.

Assessment

The NIH-supported basic HIV research effort has been the major success story of the war on AIDS. It is difficult to imagine that progress in understanding HIV could have been any more rapid. Many outstanding investigators from other areas have been drawn into HIV research; as a result, it has been in the forefront of new scientific advances in virological and infectious disease research. Little needs to be done in the way of adjustments to the overall direction and management of investigator-initiated basic research. The most significant problem in this area is that the payline for grants has dropped into single digits.

Although a limited number of useful approaches has resulted from the application of basic research findings to drug development, a very large number of potential therapies (mostly technologically novel and with uncertain prospects for success) are being evaluated. Many of these strategies are directly derived from NIH-supported basic HIV research. Clearly, at least a subset of investigators conducting basic or applied research has been sensitive to translating basic findings into potential therapies. It is less clear to what extent NIH fosters this process by making useful information available to investigators, by fostering interaction between discoverers and parties who might be interesting in developing such discoveries, and by providing resources for early stages of development.

Another area that is even more clearly deficient is access to information regarding ongoing research. There is no adequate computerized database oriented to tracking scientific advances accomplished by NIH grantees. The ARIS database, created for tracking expenditures by the various coding systems, is incomplete (no intramural NCI/FCRDC projects even appear), inaccurate, and poorly organized. The

classification codes appear to be assigned arbitrarily and inconsistently from Institute to Institute. At the program office level in NIAID's Division of AIDS, staff have a good grasp of the overall grants activity, but this cannot be obtained from the ARIS or any other available database. Further, while program staff seem to maintain close contact with their grantees, communication is poor among Institutes and between the Institutes and the OAR. The end result is that no one at NIH has a complete overview of the basic research portfolio, and effective oversight and coordination at the current time would seem to be impossible.

Recommendations

1. **Support of basic and applied HIV research, as well as all retroviral research, should be continued.**

2. **Improved communication is required between the Institutes and the OAR and among the specific Institutes involved in the support of basic and applied HIV-related research.**

3. **OAR should develop a system for identifying priority areas for NIH support and for encouraging new basic research activities. This could include the formation of a blue-ribbon panel that would meet at regular intervals to assess the state of the art in HIV basic and applied research and to recommend areas for future or continued focus. This panel would consider not only the state of scientific knowledge but also the likelihood of private sector involvement in various areas of HIV research.**

4. **Investigator-initiated applications should be strongly encouraged for those areas determined to be critical research priorities related to drug discovery (e.g., drug resistance and the molecular and cellular interactions between the HIV genome, HIV proteins, and host cellular proteins). This might be accomplished by inviting key and young investigators who are not currently involved in the designated area of research (or who are involved in allied areas) to specific workshops.**

5. **Mechanisms for encouraging the initial evaluation of potential lead discoveries relevant to therapeutics should be developed. ICD staff should play a key role in ensuring appropriate contact between discoverers and potential developers. This might include providing appropriate expertise; establishing contacts, as necessary, with the private sector; ensuring rapid dissemination of new research data in appropriate venues; and providing support for proof-of-concept testing in animal models and in the clinic.**

B. Molecular/Structural Studies Subpanel

Background

The Molecular/Structural Studies Subpanel reviewed structural studies of potential macromolecular targets for structure-based design of candidate drugs for HIV infection and its complications. The Subpanel specifically focused on high-resolution structures of HIV-related targets. The focus on high-resolution studies is based on the assumption that structures determined at significantly less than atomic resolution do not provide an adequate template for drug design.

When efforts to promote structural studies were initiated in the mid-1980s, there were no well-documented sources of HIV-related proteins. Therefore, initial funding efforts were forced to relax the normal requirements for individual research awards which implicitly state that feasibility for structural studies should be documented by a demonstration that a reliable source of large amounts of pure material is available and that crystals have been obtained. Several early programs, including the NCDDGs and a targeted initiative sponsored by NIGMS, chose to emphasize programmatic approaches that promoted interactions between structural laboratories and laboratories focusing on the production and characterization of potential macromolecular targets. In the intervening years, these programs have been supplemented with individual investigator-initiated awards.

Assessment

a. Overview of the Structures Determined

The overall success of the efforts to determine HIV macromolecular structures and use of them to design potential AIDS therapeutics is most readily documented by listing the AIDS-related macromolecules whose structures are now known. These include the proteases of HIV-1 and HIV-2 (including x-ray and Nuclear Magnetic Resonance [NMR] structures of the free enzyme and numerous enzyme/inhibitor complexes), the RNAseH domain of reverse transcriptase (RT), the intact HIV RT (as the free enzyme and as complexes with nonnucleoside inhibitors), the catalytic domain of HIV integrase (INT), the HIV matrix protein (both NMR and x-ray structures), the HIV capsid protein (nearing completion), an N-terminal two-domain fragment of CD4, and a C-terminal two-domain fragment of CD4. Although not all of the structures were funded directly by NIH, most have benefited at least indirectly from NIH-sponsored efforts to characterize targets and develop efficient expression systems.

To put this work in perspective, although the emergence of HIV and AIDS is very recent, no other virus has nearly as complete characterization of both its structural and nonstructural proteins. There are several targets, however, for which structures are noticeably lacking. These include the surface glycoproteins (gp160, gp120, gp41), the regulatory proteins (tat, rev, vpr) and elements (tar), and complexes between the regulatory proteins and their response elements. These structures provide potentially novel targets for antiviral drug design. Because they presumably lack cellular homologues, appropriate agents may cause less cytotoxicity. Continued support for structural studies of these molecules should receive priority for future support.

b. Use of Structures as Templates for Inhibitor Design

Several of these structures have been used as templates for the design of inhibitors as potential anti-HIV drugs. Predictably, much of the early focus has centered on protease, the first of the viral enzymes to have its structure solved, and more

recently on RT. These two targets are homologous to targets with long histories of drug design by both classical mechanism-based and structure-based approaches. Structure-based design methods have been used to develop a number of protease inhibitors, some of which have been tested in clinical trials. Although structures have been available for a shorter time for RT, the use of these structures to design the next generation of both nucleoside-based inhibitors and inhibitors targeting the nonnucleoside site of RT may be anticipated. Although some of this work has been initiated in academic laboratories, the use of the protease and RT structures for structure-based design has moved rapidly into the commercial sector, where the ability to focus priorities of all components of the design effort (including structural biology, pharmaceutical chemistry, synthetic chemistry, *in vitro* screens, and clinical investigation) provides significant advantages over academic-based consortia. Consequently, the need for the continued priority of Federal support for drug design targeting the principal viral enzymes, especially protease, is substantially reduced. The exception may be the third—and most recently solved—enzyme structure, HIV integrase. This enzyme's function differs significantly from other traditional targets for drug design, and available leads are generally poor inhibitors. Therefore, NIH support for design of integrase inhibitors should be continued until commercial interest in the inhibitors is adequately demonstrated.

There also has been a significant amount of work focused on using the structure of CD4 to design small ligands capable of interfering with virus-receptor interactions. These efforts led to some success, but no useful drug candidates have been developed to date. These studies represent an area where traditional mechanism-based design methods are not particularly useful. Serious difficulties are associated with the design of small molecules that interfere with macromolecule interactions. These difficulties include the necessity of achieving sufficient affinity to permit competition with highly evolved macromolecule ligands and potential problems with large pools of target in a system where a stoichiometric rather than catalytic activity is targeted. The principles of these design efforts will also have clear relevance to other targets, including regulatory protein/response element recognition. With some exceptions, efforts to inhibit macromolecule/macromolecule interactions are outside the traditional focus of commercial development. Continued NIH support for these efforts in the academic sector is, therefore, strongly encouraged.

c. Funding Mechanisms

Although the programmatic goals of promoting structural studies and subsequent structure-based inhibitor design has met with obvious and readily documented accomplishments, the success of specific funding initiatives and mechanisms is much more difficult to assess. Specific funding sources for research on structures that have been completed or nearly completely characterized have included NIAID-sponsored National Cooperative Drug Discovery Groups (NCDDGs), NIGMS-sponsored program projects, intramural NIH support, NCI-sponsored research at FCRDC, and

individual investigator-initiated grants. Because structural studies are supported in a number of Institutes, it was often impossible to ascertain the total dollar figure of support and the percentage of grants that were successful in achieving a significant fraction of their goals, with the exceptions being the NIDDK intramural program, the FCRDC program, and the NIGMS program projects. The NIDDK and NCI programs are small and their structural results were readily documented. The NIGMS AIDS program projects, which were initiated by a Request for Applications (RFA) issued in 1987, continued in 1992, and to be reissued in 1997, all had structure and structure-based design components and were readily tracked. These program projects have succeeded in attracting an impressive group of investigators to the field of AIDS research. Not all of the originally funded programs were productive, although this is explained by the very early stages of HIV-related molecular research when this program was initiated. A significant percentage of the original group of programs and most of the current group appear to have made significant contributions to the field. At a time when there is a call for greater focus on individual investigator-initiated research grants, the success of this program points to the advantages of a stringently peer-reviewed, carefully-managed program in a field that is inherently multidisciplinary.

d. Guidelines Promoting Rapid Publication and Release of Coordinates

Given the considerable potential clinical implications of the molecular studies funded by NIH, it is critical that the results of NIH-sponsored studies, including the coordinates derived from crystallographic and NMR studies, be made public in a timely fashion. The economic potential of prophylactic and therapeutic agents derived from structural studies, together with investments already made by for-profit organizations in supporting these studies, has created an environment in which substantial potential economic benefits may slow the release of information, particularly the release of coordinates. In the past, most NIH-funded programs have included a stipulation that the results of structural studies—including the coordinates—must be made public, but compliance has been uneven.

The OAR should clearly define and publicize a policy for coordinate deposition, stipulating that coordinates must be deposited at the time of publication (journals have widely varying policies), the time period (if any) allowed between deposition and public release (the Protein Data Bank currently allows coordinates to be held for up to 1 year), and a workable means of enforcing compliance with the policy.

Recommendations

1. **Continued support of structure-based designs focused on the HIV protease and RT should be periodically evaluated, given the commercial sector's changing interest in these targets.**

2. **Support for new structure-based inhibitor design should focus on HIV integrase and on novel approaches to other targets, such as the CD4 receptor.**

3. **Support should continue for structural studies of HIV envelope glycoproteins, regulatory proteins, response elements, and regulatory protein/response element complexes.**

4. **Use of diverse funding mechanisms, including both investigator-initiated grants and targeted initiatives, should continue.**

5. **Enhanced cooperation among ICDs for the coordination of structural studies should be ensured by the OAR.**

6. **Timely deposition and release of structural coordinates determined from NIH-supported studies (including research receiving partial NIH support) should be implemented.**

C. NIAID Drug Discovery Program Subpanel

Background

The National Cooperative Drug Discovery Groups (NCDDGs) were established in 1986 to encourage cooperative research between academic and industry-based investigators for the discovery and development of new therapies for HIV disease and related OIs. In its early years, the NCDDG was involved in the development of RT, protease, tat inhibitors, and CD4 blockers that were subsequently evaluated in clinical trials. Early successes of the program include the development of nonnucleoside RT and protease inhibitors. However, the research programs supported by this mechanism were uneven. In 1991, an external review recommended increased allocation of resources for drug development for AIDS-associated OIs and a concomitant decrease in the total support for HIV-targeted research, in part because of the successful engagement of the pharmaceutical industry in research and development for anti-HIV agents. The reviewers recommended redirection of the HIV-related effort to novel, underexplored, or difficult targets and to new therapeutic strategies involving unconventional approaches such as gene therapies, antisense oligonucleotides, and ribozymes. In that year, the NCDDG program was reorganized into programs targeted to the treatment of HIV (the NCDDG-HIV program), and the treatment of opportunistic infections (the NCDDG-OI effort). In 1995, 13 NCDDG-HIV programs received a total of $9 million to support investigations in gene therapy (four), ribozymes (two), antisense oligonucleotide inhibitors (one), and gp120/CD4 blockers (two), RNAseH function (two), and HIV RNA function and virion assembly (two).

The Strategic Program for Innovative Research in AIDS Therapeutics (SPIRAT) was initiated in 1994 to fund late-stage preclinical development and early proof-of-concept clinical trials, with an emphasis on therapeutic approaches to HIV infection that do not involve conventional antiviral drugs. Six SPIRAT programs were funded in FY 1994, totalling $5,414,000 (two devoted to gene therapy, three to cellular immunotherapy, and one to an env-based DNA-based vaccine), and another two

were funded in FY 1995. Like the NCDDG, the SPIRAT involves academic-industry collaborations. In some cases, NCDDG-developed approaches are being evaluated in clinical trials as SPIRAT projects.

The NIH AIDS Research and Reference Reagent Program was established as a contract in 1988, to provide reference reagents to AIDS researchers in academia, industry, and Government. In 1994, 8,000 reagents were provided to 1,100 users free of charge, with NIH funds totalling $2,416,000. The current list of 700 reagents, many of them donated by independent researchers, includes laboratory strains and clinical isolates of HIV, genetic clones, and expression vectors; recombinant proteins and synthetic peptides; monoclonal and polyclonal antibodies; body fluid specimens (i.e., seminal plasma and vaginal secretions from HIV-infected subjects); reference panels for polymerase chain reaction (PCR) studies, HIV subtyping, drug resistance and viral neutralizing antibody assays; isolates of opportunistic pathogens; and drug standards.

Assessment

The NCDDG-HIV program as currently constituted appears to be well-targeted and productive. The reorganization has appropriately focused Federal resources to fill gaps in privately funded research. Initial preclinical progress in the SPIRAT program includes the development of methods to expand CD4 cells and HIV-specific CD4 cells from infected individuals to be infused for therapy, the development of nonretroviral methods for genetic transduction of CD4 cells, and the preclinical development of DNA vectors encoding other HIV gene products, ribozyme-based gene therapy, and genetically-engineered CD8 cells whose growth and function is independent of exogenous cytokine stimulation. Early progress in the clinical arena includes a Phase I trial of an env-based DNA vaccine in HIV-infected subjects, further development of T cell therapy with antiviral cytotoxic T lymphocytes (CTL) polyclonal cell lines and clones, the initiation of a trial to measure the longevity of transduced CD4 cells and of another study to investigate the infusion of Human Leucocyte Antigen (HLA)-matched allogeneic dendritic cells pulsed with HIV peptides or envelope protein, and the first demonstration of immune destruction of genetically-modified T cells. However, the SPIRAT program is fairly new, and there has not been enough time to assess its potential contributions. Both the NCDDG-HIV and SPIRAT have provided opportunities for fruitful interactions between academic and industrial researchers.

While these programs deserve continued support, certain gaps exist, primarily for research at the late preclinical/clinical interface and for early therapeutic development. A better understanding of the mechanisms of interactions between HIV gene products (especially for regulatory genes), and host genes and proteins will provide new opportunities for targeting HIV infection. Neither of the existing programs has a mechanism to support the development of therapeutic approaches that are truly at a preliminary stage. Moreover, the threshold for funding R01s in developmental therapeutics is too high, and no study section has the appropriate

expertise to review such research proposals fairly. Aside from the small number of SPIRAT programs, there is currently no mechanism outside of the AIDS Clinical Trials Group (ACTG) for small investigator-initiated proof-of-concept clinical trials, and no way for promising preclinical ideas to be developed in animal models. Although clinical evaluation of antiviral agents has probably not been hampered by the lack of Federally funded small-scale mechanisms for clinical research, more speculative and immunomodulatory approaches have not benefited from a clear mechanism for preclinical and clinical development. Further, the NCDDG and SPIRAT programs almost exclusively emphasize high-technology approaches to HIV therapy, such as gene therapy, cellular immunotherapy, and ribozymes, that have not yet been implemented successfully in the treatment of any disease.

The AIDS Research and Reference Reagent program is a well-organized and important resource for investigators.

Recommendations

1. **The NCDDG-HIV and SPIRAT programs should continue at their current level of support. However, both programs should be evaluated in the near future for productivity and appropriate adjustments, similar to the previous review and recompetition of the NCDDG program.**

2. **The choice of therapeutic targets for study should be guided by an expert panel, including non-Government investigators, that periodically evaluates the state of the art in HIV research. Consideration also should be given to the support of programs designed to investigate therapeutic approaches that do not necessarily advance the technological frontier but may have real potential for improving the current clinical management of HIV disease.**

3. **Realignment of current study sections to include appropriate expertise to evaluate translational research may be essential to the effective assessment of investigator-initiated preclinical and proof-of-concept clinical studies.**

4. **The AIDS Research and Reference Reagent program is a valuable resource. NIH-funded investigators should be actively encouraged to provide novel reagents for potential use by other researchers in a timely fashion.**

D. Animal Models Subpanel

Background

Animal models traditionally have been used for the preclinical evaluation of lead compounds, including evaluations to determine mechanism of action, biodistribution, toxicity, and efficacy. For HIV disease, particular emphasis has been placed on the development and validation of animal models that might be

applicable to these ends. In its review of the NIH AIDS Research program in 1991, the Institute of Medicine (IOM) recommended that: "… (1) the optimal role for NIH's preclinical drug development program should be to facilitate drug development by all sectors—government, academia, and private—and to develop drugs whose development is not likely to be supported by the pharmaceutical industry; and (2) NIH should develop and support a range of screening tests for anti-HIV drugs; in addition, NIAID and its Division of AIDS should expand its intramural or dedicated extramural resources for mechanism-of-action studies for anti-HIV drugs."

Assessment

To meet these goals, total NIH expenditure on "Animal Models and Related Studies" (Functional Category Code 1A5) has ranged from 4 percent in 1991 ($32 million of $805 million) to approximately 3.2 percent in 1994 ($35 million of $1.74 billion). Monies for research using animal models for preclinical drug evaluation are also coded under the category of "Drug Discovery" (Strategic Plan Code 3A), funding a total of 124 grants and contracts (or 4 percent of the 3,124 awards) made during this period. Although the Subpanel's review of retrospective work must be acknowledged as incomplete, general themes were identified within the programs of specific ICDs described below. Review of these activities indicates that productivity has been uneven and that some animal model research has involved significant direction from program staff.

NIAID. Consistent with the 1991 IOM recommendation, the Division of AIDS (DAIDS) Basic Sciences Program has fostered the development of lentivirus animal models for the study of pathogenic mechanisms and for the evaluation of novel therapeutic modalities, and the DAIDS Targeted Intervention Branch has preclinical research and development contracts that support specialized lentivirus animal model efficacy studies. Outside the purview of this Panel (but included in the total expenditures for FY 1994), DAIDS also has supported animal models for the evaluation of the safety and efficacy of various HIV vaccines (which were evaluated by the Vaccine Research and Development Area Review Panel). Multiple animal models are supported, including mice (MAIDS/BM5, LCMV, SCID/HIV, transgenic), cows (BIV), horses (EIAV), cats (FIV, FeLV), sheep (type D retroviruses), rabbits (HIV), and nonhuman primates (e.g., rhesus macaques, pigtail macaques, and chimpanzees infected with SIV or HIV), with emphasis on mouse, cat, and rhesus macaque models. Under competitively bid contracts, the latter three models were also separately supported for the preclinical evaluation of anti-HIV compounds.

NIMH. The Institute's animal model studies have focused on lentiviral infection of the central nervous system (CNS). Much of the funded work has been carried out as a program project at the Scripps Research Center that was initiated in 1986 after a competitive process. This program sponsors research on transgenic mouse models of gp120 neurotoxicity, FIV-induced early CNS abnormalities in cats, and neuropsychological testing in SIV-infected rhesus macaques.

NICHD. The Institute's animal model studies have focused on the mechanism and prevention of genital transmission (of SIV in rhesus macaques), with the monies divided between contracts and grants. Much of the scientific direction apparently emanates from NICHD program staff using the Contraceptive Research and Development Program (CONRAD), a contract used to "jump start" work in the field.

NCRR. The Comparative Medicine Program supports the research activities of seven Regional Primate Research Centers (RPRCs), including activities to develop and optimize animal models for AIDS, and provides infrastructure support for the generation and maintenance of animal colonies and their facilities. Each of the Centers is designed to serve the needs of a given geographic region of the country. There is no uniform mechanism to provide non-Center investigators access to RPRC resources. If access is granted, funds for animal support usually must be provided by the non-Center investigator's grants, which frequently are not large enough to support the high costs of working with animals.

Recommendations

1. **There remains a critical need for further development and optimization of animal models for HIV disease. This need is likely to become increasingly important in the future. Different animal models clearly will be required to meet different research needs. Some models are particularly well-suited for studies of pathogenesis, while others are useful for the preclinical evaluation of new therapeutic agents. It will be particularly important to support the development of a model that can be used for both purposes.**

2. **NIH should strive to optimize and validate the small-animal models (e.g., various mouse and cat models) that currently appear useful for preclinical evaluation of anti-HIV compounds in order to determine which (if any) of the models are predictive of efficacy and pharmacodynamic attributes in humans. Those models determined to be relevant and useful should be provided with additional infrastructure and support, while support for other models should be deemphasized.**

3. **More resources should be devoted to the development and optimization of the SIV-infected rhesus macaque model for preclinical drug evaluation *in vivo*. Additional support for further derivation and standardization of molecularly cloned SHIV recombinants, expansion of colony size to reduce animal costs, and infrastructure for housing and research facilities would be valuable.**

4. **Drug discovery research involving the chimpanzee, rabbit/HIV, and SPF-macaque models has not been productive. These funds should be redirected.**

5. **Animal models research is sufficiently mature to make heavily directed research efforts by NIH program staff inappropriate. Research funded in the future should be subjected to rigorous peer review. This can be facilitated by**

refocusing current study sections and ensuring that they have appropriate expertise; study section review would be preferable to *ad hoc* reviews.

6. **The NCRR should ensure broad access by qualified investigators to the resources provided by the RPRCs. This may be accomplished by creating independent peer review panels to evaluate proposed research projects by both Center staff and non-Center investigators seeking access to these facilities. The infrastructure for studies that are approved for implementation at a given Center (including the supply, housing, and handling of the animals; obtaining and processing specimens) should come from the operating budget of that Center. Competitive renewal of the Center grants should include, as a measure of the Center's productivity, a description of its peer review process and its success at supporting studies initiated by non-Center investigators.**

7. **Agents that have limited effectiveness in patients with advanced HIV infection may be effective around the time of initial infection or in early disease. More research in primate models on both novel and conventional therapies should focus on these early time points.**

E. NCI Developmental Therapeutics Program Subpanel

Background

The NCI drug discovery program, which focuses on drug development for cancer and AIDS, is an enormous endeavor largely situated within the Developmental Therapeutics Program (DTP) of the Division of Cancer Treatment. The overall DTP budget for FY 1995 is $53.7 million, of which 52 percent is attributed by the NCI as expenditures for AIDS-related projects. The proportion of AIDS-related expenditures varies among the individual intramural and extramural branches involved in this program and ranges from 23 percent to 100 percent (a breakdown is given in Appendix E). A small amount of funds to support investigator-initiated grants are coded as AIDS-related drug discovery and are disbursed independently of the DTP.

a. Structure

At the time of the Subpanel's review, the DTP was divided into a series of intramural laboratories and extramural branches (see Appendix E). The DTP is divided between the main campus in Bethesda, where the intramural laboratories of Biological Chemistry, Medicinal Chemistry, and Molecular Pharmacology are located, and FRCDC, where the laboratories of Drug Discovery Research and Development and Pharmaceutical Chemistry are located. The extramural efforts largely involve contractor-performed activities. The two primary FCRDC contractors, Science Applications International Corporation (SAIC) and Applied Bioscience Laboratories (ABL), provide services and basic research for the Antiviral Evaluations Branch,

the Information Technology Branch, the Biological Testing Branch, and the Natural Products Branch. Non-FCRDC contractors also provide services for these branches. In addition, non-FCRDC contractors are used exclusively by the Drug Synthesis and Chemistry Branch, the Pharmaceutical Resources Branch, and the Toxicology and Pharmacy Branch. The Grants and Contracts Operations Branch provides administrative oversight of all DTP extramural grantees and contractors.

Effective October 1995, the DTP was reorganized as part of a general NCI reorganization. It became part of the extramural Division of Cancer Diagnosis and Treatment. The three laboratories on the main campus joined the intramural Division of Basic Sciences, while the Frederick laboratories remained part of the DTP, which also includes all of the current extramural branches. It is unclear at this time how the laboratories that are transferring to the Basic Sciences Division will continue to operate in relation to the DTP.

b. Current Operational Focus

The DTP intramural and extramural contract laboratories are not exclusively involved with AIDS research. Because a significant proportion of the effort is directed against cancer targets, a "clean" delineation of the AIDS versus cancer endeavor is not easily made. NCI identifies approximately 52 percent of the total DTP budget as devoted to AIDS. Nonetheless, the functional operation of the AIDS drug discovery process can be described as a separate entity.

The central focus of the program is a mechanistically nonselective anti-HIV-1 cell-based screen that is designed to assess the potential of test compounds or natural products to inhibit the replication and spread of HIV in a human T-lymphoid cell line. The assay has been operational since 1987-88; a total of 71,247 synthetic compounds had been screened as of March 31, 1995. Compounds and natural products tested in the assay are actively acquired from a large variety of sources through the use of specific contracts. In addition, compounds are submitted to the screen from various private sources such as pharmaceutical concerns. Data from the assay are continually reviewed by an oversight body, the NCI Decision Network, which selects test substances for possible further evaluation. This includes purification and identification in the case of natural products, as well as biological and molecular mechanism of action studies for all substances exhibiting sufficient antiviral activity.

The Decision Network guides the continued evaluation of interesting compounds through a series of defined stages (see Appendix E). After proof of antiviral activity is established, these steps involve large-scale synthesis, synthesis and testing of derivatives, and preliminary toxicologic and pharmacologic analyses, activities that are performed by the various intramural laboratories and extramural branches of the DTP. The process is highly interactive and appropriate expertise is brought to bear as required. The Network has adequate resources to move interesting compounds (or their derivatives) through formal toxicology and pharmacology

studies sufficient to support an investigational new drug (IND) filing. As of March 31, 1995, 1,248 compounds had been determined to have at least a low level of antiviral activity (less than 100 micromolar), of which 36 were designated "high priority." Eighteen compounds with potential for development had been presented to the Decision Network. A compound of sufficient interest may eventually lead to Phase I clinical studies which are performed by the NCI intramural clinical trials program.

c. Basic and Targeted Research within the DTP

In addition to the functions described above that support the evaluation of active compounds identified by the antiviral screen, a number of the intramural and extramural laboratories of the DTP are involved in basic and targeted research aimed at several HIV-1 molecular therapeutic targets, primarily viral enzymes. Subjects studied include structural analysis of protease and RT to understand the physical basis of antiviral resistance, the biochemistry and enzymology of integrase, the genetics of virus resistance to nonnucleoside RT inhibitors, and the structure and function of the viral nucleocapsid.

Assessment

The logistical scope of the DTP effort is significant and essentially replicates the typical range of efforts found in the pharmaceutical industry. There is an interactive process, guided by the Decision Network, by which anti-HIV-1 compounds are studied and evaluated. However, the heavy dependence of the NCI drug discovery program on a single nonselective antiviral screen is problematic. Since the screen is not aimed at specific viral molecular targets, the entire discovery effort is driven by agents that are active in this assay, irrespective of the mechanistic target that is inhibited. Of the many thousands of defined compounds and natural products that have been screened, the few that have been advanced to further study represent a restricted number of antiviral mechanisms. Many compounds that have the same viral target as agents already well-studied in the clinic, particularly nonnucleoside RT inhibitors, have been identified and pursued to varying degrees. Several are putative inhibitors of the viral nucleocapsid protein. Several compounds were introduced into the DTP development process at later stages following their initial identification as antiviral agents elsewhere. As a result, the productivity of the program over the last 8 years has been poor and the overall program is rather diffuse.

Much of the basic research that has contributed to elucidating the mode of action of these compounds has been of good quality, as has the research required to establish the mechanism-based assays needed for these studies. Unfortunately, these assays have been used as secondary screens. Overall, the NCI research effort has not been used in a way that enhances the ability of the program to discover and study truly novel inhibitors of the virus.

In addition, drug discovery research for the treatment of AIDS-associated malignancies appears to have been insufficient.

Recommendations

1. **DTP should no longer focus primarily on the nonselective antiviral screen.**

2. **DTP management structure should be reviewed, given its apparent inability to overcome the poor productivity of the AIDS drug discovery effort.**

3. **DTP should use its core resources to support NIH-wide antiretroviral discovery efforts by providing compounds and natural products for various screening endeavors as well as medicinal chemistry, pharmacologic, and toxicologic support, as needed. Ongoing assessment of the DTP AIDS drug discovery program should include its ability to support the overall NIH drug discovery effort.**

4. **DTP resources should also be used to support the anti-OI discovery efforts of other ICDs.**

5. **An external scientific advisory board should be constituted to provide guidance regarding appropriate DTP support for NIH drug discovery programs. It is not cost-effective to reproduce the considerable DTP infrastructure in other ICDs.**

6. **The operational logistics of the DTP require review and restructuring. A substantial decrease in the size and funding of the DTP's current HIV drug discovery effort may be appropriate.**

7. **The DTP's efforts in cancer therapeutics discovery should include an appropriate proportion of its expenditures that is realistically HIV/AIDS-related.**

8. **Research on developmental therapeutics for HIV-associated malignancies needs support.**

F. Opportunistic Infections Subpanel

Background

The overwhelming majority of NIH-sponsored efforts toward the discovery of new therapies for the treatment of AIDS-associated OIs is funded and administered through NIAID. For FY 1992, the total expenditure for the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs was $104.5 million. While minor research efforts in this area were supported by other ICDs (e.g., NINDS, at $661,000), it is clear that the vast majority of both drug discovery and basic research aspects is supported by NIAID. While no attempt was made to separate basic research from drug discovery (nor is it possible to do so on a fiscal basis, as there is a single strategic plan code for basic, applied, and

clinical OI research), the Subpanel attempted to focus on that research most clearly identified with drug discovery and left evaluation of basic research issues to the joint OI Subpanel.

As early as 1991, it was recognized in the report "The Obstacles to Drug Development for HIV-Related Opportunistic Infections" (Seventh Report from the Committee on Government Operations, 102nd Congress, December 1991) that the "opportunistic infection research effort has lacked a systematic plan which sets goals and timeframes, assigns priorities and identifies resource needs and these sources and opportunistic infections received inadequate attention within the NIAID research program due to the high priority of research on anti-retroviral drugs." This report was the impetus for the changes that resulted in the current OI program at NIAID. Responsibilities for this program are divided between DAIDS and the Division of Microbiology and Infectious Diseases. Similarly, support for OI research comes from both the AIDS and non-AIDS budgets, although the relative proportions obtained from each are unclear.

During FY 1994, NIAID supported 47 RPGs on OIs and 18 in the NCDDG-OIs. In addition, 9 contracts were funded for *in vitro* and *in vivo* evaluation, and an unknown number of contracts to aid in the resynthesis, formulation, toxicology, and pharmacology of potential anti-OI drugs. The dynamics of RPG funding from FY 1990-94 is shown in Appendix F. The table illustrates the shift in priorities relative to perceived therapeutic needs. Other than issuing Program Announcements (PAs) or targeted initiatives, NIAID has no influence on the relative proportion of RPGs devoted to the various opportunistic pathogens. The Institute has attempted to focus the scientific community on underinvestigated OI pathogens by shifting the focus of the NCDDG-OIs and various support contracts. Each NCDDG-OI consists of several projects and core groups that interact and concentrate on a particular organism or organisms. Each time this initiative has been reissued, it has specified the target pathogens and number of groups that will be funded for each.

During FY 1994, the following NCDDG-OIs were funded: *M. tuberculosis* (three), *M. avium* complex (two), *Candida* (two), *Cryptococcus* (two), *Cryptosporidium* (two), *Toxoplasma* (three), *Pneumocystis* (two), and CMV (three). This balance among OI pathogens is in contrast to the RPGs, where 17 of the 47 grants were funded for research on *Candida* or *Pneumocystis*. The shift in priorities has been more striking in the changes in funding for OI animal model and drug screening contracts: the number of contracts for *Pneumocystis* decreased, while contracts for *M. tuberculosis* increased. However, it is unclear how decisions are made about which organisms will be targeted or what proportion of the total research effort will be committed to OI research. Total support for research on opportunistic pathogens at NIAID includes substantial funds from the non-AIDS budget; however, the total amount of funding is unknown and could not be ascertained from the data made available to the Panel.

In addition to contracts for animal models and screening, NIAID can channel funds into high-priority areas with the use of contracts for the limited resynthesis,

formulation, toxicology, and pharmacology of new agents against OIs. However, it is not clear what impact these latter contracts had on past drug development efforts or the total funds that were committed to them.

Assessment

Determining the accomplishments and impact of the RPGs assigned a drug discovery code was very difficult, as the quantity or quality of publications associated with this support could not be readily ascertained. However, it is clear from the literature that, in general, the increased funding of R01s devoted to opportunistic organisms has enhanced the understanding of the basic biology of these organisms, including the determination of new potential drug targets.

A number of agents developed under the NCDDG-OI program, including atovaquone, macrolides, and pyrimethamine, have been studied in large clinical trials, and new therapies for *Cytomegalovirus*, *Pneumocystis*, and *Cryptosporidium* are in the late stages of preclinical development. This program has elucidated several new drug targets, has developed new *in vitro* assays, and has contributed to an increased understanding of the immunology, microbiology, and biochemistry of OI pathogens. This program has been critical in attracting many highly competent investigators to the field of OI research.

According to program and budget information provided by NIAID, a number of achievements have been accomplished through the OI contracts despite the early contracts, which appear to have been ill-planned and poorly supervised. For example, it is impossible to compare data from the screening of agents for *Pneumocystis* by one group with the screening efforts of two other groups, and it is not clear why three separate contracts were necessary. The Subpanel was encouraged by the current focus and priorities of more recent contracts, although it is too early to evaluate the effectiveness of those devoted to screening drugs for *M. tuberculosis*. The OI contracts for drug testing can provide a valuable service to the biomedical research community if they provide a unique service and are accessible and user-friendly.

The immediate future directions outlined by NIAID include an initiative for increased funding for OI research via the Small Business Innovative Research (SBIR) and the Small Business Technology Transfer (SBTT) programs. There also will be an increased focus on infectious causes of diarrhea and wasting syndrome. The NCDDG-OI program goals will include a greater focus on *Mycobacteria*, *Cryptosporidium*, and *Microsporidia*, with an emphasis on identifying new drug targets and improving *in vitro* assays for drug screening. Increased drug company involvement is another goal; it was not clear how many of the current NCDDGs have commercial involvement, although this was a requirement of the original NCDDG program.

Overall, the current management and focus of NIAID's OI drug discovery programs are appropriate. It is encouraging that NIAID support for OI research has steadily

increased since FY 1990, as a funding base to study many of these OIs does not exist in the pharmaceutical industry, and funds from other sources are very limited. Recently, NIAID has successfully focused research funds, through the NCDDG-OI program and contracts, on the opportunistic pathogens of importance in AIDS that are not considered "primary targets" by major pharmaceutical firms. The single exception appears to be the high level of funding for *Candida*, which is also the focus of considerable pharmaceutical industry interest and support.

Recommendations

1. **Continue support for the NCDDG-OI program at the present level.**

2. **NIAID should continue to monitor private sector's development of new therapies, especially for *M. avium* complex, with the goal of redirecting funds at the appropriate time. (Even though it may be anticipated that some pharmaceutical industry support of mycobacterial research will be forthcoming, the present medical need justifies short-term support by NIH.)**

3. **Emphasize support for research directed to *Microsporidia*, *Cryptosporidium*, JC virus, and other pathogens that have less attractive market potential. In general, when projecting future needs, the NIH should consider where pharmaceutical industry efforts are being placed, so that Federal funds can be used to target understudied pathogens.**

4. **Redirect funds currently devoted to drug discovery research in *Candida* to address mechanisms of antifungal resistance and to the development of agents that work via novel mechanisms.**

5. **Consider the establishment of an external advisory group to provide assistance in selecting organisms to be studied by the NCDDG system. The selection process should consider several factors, including the number of RPGs devoted to each organism and its relative importance in the clinical management of AIDS patients, as well as the commitment of pharmaceutical companies to research on the organism.**

6. **Encourage NIAID to periodically assess the overall value of individual contracts with respect to productivity, reliability, and user accessibility.**

Appendix A

Acknowledgments

The Drug Discovery Area Review Panel would like to thank the people listed below who, through interviews, presentations, conversations, and the submission of written materials, provided information important for our work. Affiliations are those at that time of contact.

John P. Bader, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Michael R. Boyd, M.D., Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Robert Buckheit, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

James C. Cassatt, Ph.D.
National Institute of General
Medical Sciences
National Institutes of Health
Bethesda, Maryland

Stephen P. Creekmore, M.D., Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

David R. Davies, Ph.D.
National Institute of Diabetes
and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Carl W. Dieffenbach, Ph.D.
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

John S. Driscoll, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

John Erickson, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Stephen H. Hughes, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Judith Karp, M.D.
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Barbara E. Laughon, Ph.D.
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Hiroaki Mitsuya, M.D., Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Yves G. Pommier, M.D., Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Jerry Rice, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Nava Sarver, Ph.D.
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Edward A. Sausville, M.D., Ph.D.
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Sharilyn K. Stanley, M.D.
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Sherman F. Stinson, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Jeffrey G. Supko, Ph.D.
National Cancer Institute
National Institutes of Health
Frederick Cancer Research
and Development Center
Frederick, Maryland

Robert Yarchoan, M.D.
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Appendix B

Drug Discovery Area Review Panel

Meeting Schedule

April 20, 1995	Full panel meeting
June 28, 1995	Full panel meeting
July 11, 1995	Joint Animal Models Subpanel with Etiology and Pathogenesis Area Review Panel meeting
August 17, 1995	NCI Drug Discovery Program Subpanel meeting
September 21, 1995	Full panel meeting
November 29-30, 1995	Full panel meeting

Joint OI Subpanel with Etiology and Pathogenesis Area Review Panel meetings

October 18, 1995

December 11, 1995

January 19, 1996

Appendix C

Subpanel Structure and Membership

HIV/Immunology—Basic*
- John Coffin (lead)
- Alan Frankel
- James Hogle
- Judy Lieberman

HIV/Immunology—Drug Targeted*
- Manuel Navia (lead)
- Brenda Lein
- Richard Lynn
- John Secrist

Opportunistic Infections—Basic** and Drug Targeted
- Richard Tidwell (lead)
- William Current
- James Hogle

Molecular Studies
- James Hogle (lead)
- Alan Frankel
- Manuel Navia
- John Coffin

Animal Models
- Joseph M. McCune (lead)
- William Current
- Emilio Emini

NIAID Drug Discovery Program (NCDDG-HIV/SPIRAT/ Reference Reagent)
- Judy Lieberman (lead)
- Alan Frankel
- Brenda Lein
- Mike McCune
- John Secrist

NCI Drug Discovery Program (Developmental Therapeutics Program)
- Emilio Emini
- Richard Lynn
- John Secrist
- Richard Tidwell

* These two Panels were subsequently merged.

** A joint subpanel with Etiology and Pathogenesis Panel was created to review basic research.

Appendix D

Budget Commitments by ICD for Drug Discovery, FY 1994*
(dollars in thousands)

Institute	Extramural	Intramural	Total	Percent†
NIDR	$448 (HIV) 954 (OI)‡	$586	$1,034 954	8.65 7.99
NIDDK	—	463	463	4.44
NIAID	41,025 (HIV) 76,613 (OI)‡	8,026 5,433	49,051 82,046	9.59 16.04
NIGMS	15,686	—	15,686	65.80
NIEHS	3,989	401	4,390	78.36
NIAMS	—	598	598	44.59
NIMH	2,934	—	2,934	3.55
NCRR	2,555 (HIV) 7,279 (OI)‡	— —	2,555 7,279	4.26 12.15
NCHGR	—	637	637	100.00

* FY 1994 budget figures from the FY 1996 Strategic Plan

† Percent of the ICD's total

‡ Within the Therapeutics section of the Strategic Plan (section III), there is a separate code (3.1) for "discover and develop HIV treatments" that is distinct from the conduct of clinical trials of antiretroviral therapies. Code 3.4, "prevent and treat opportunistic infections," and analogous codes for other complications of HIV disease, covers drug discovery and clinical trials, so the allotted amount to drug discovery alone cannot be determined from overall NIH budget figures.

Appendix E.1

National Cancer Institute (NCI)
Drug Discovery Program

Budget Allocation, FY 1995
(dollars in millions)

Intramural

NCI Laboratory	Amount	%AIDS*
Biological Chemistry	$2.69	23
Molecular Pharmacology	2.95	25
Medicinal Chemistry	2.57	44
Drug Discovery	2.40	85
Pharmacologic Chemistry	0.96	35
Extramural Overhead†	4.58	46

* The percentages reflect the overall proportion of the laboratory's activities. The Laboratory Branch Chief assigned the fraction of individual projects that are considered AIDS-related.

† This includes a number of activities (in the Office of the Associate Director, Toxicology & Pharmacology, Drug Synthesis & Chemistry, Pharmacology Resources, Natural Products, Grants & Contracts, Biological Testing, Information Technology, and Antiviral Evaluation) that are seen by NCI as intramural program resources.

Appendix E.2

NCI Drug Discovery Program

Budget Allocation, FY 1995
(dollars in millions)

Extramural

Activity (FCRDC Contracts)	Amount	%AIDS
Screening/Computer Support	$7.8	60
Natural Products	3.36	77
Cell Line Testing	1.15	35
RT Modeling	0.49	100
Shared Service (renovation)	1.41	80

Activity (non-FCRDC contracts)	Amount	%AIDS
Biologic Testing	$4.16	36
Drug Synthesis/Chemistry	3.23	44
Grants/Contracts	0.51	50
Information Technology	1.42	68
Natural Products	1.48	97*
Pharmacology Research	5.23	37
Toxicology and Pharmacology	6.82	57
Antiviral Evaluation (mutants/combo)	1.03	100

* All extracts are tested for anti-HIV activity and are also tested for anti-cancer activity.

Appendix E.3

NCI Drug Discovery Program

Costs for DTP AIDS Drug Screen*
(dollars in millions)

Activity	Amount	%AIDS
Pure Compound (acquisition, catalog)	$2.38	43
Computer Support	1.42	68
Natural Products		
non-FCRDC Acquisition	1.48	97
Extraction Repository	3.36	77
Screening†	4.96	100

* These represent total costs for all components of the program, regardless of location or funding mechanism.

† Includes the following: HIV *in vitro* screen, determination of antiviral drug mechanism, SORI RT, drug preparation, computer support, AIDS lymphoma.

Appendix E.4

NCI Drug Discovery Program

Decision Network Process: Stages

I	→	**IIA**	→	**III**	→	**IND**
acquisition screening		proof of activity optimize schedule bulk synthesis Preliminary tox & Pharmacology		pharmacology toxicology (IND- directed) formulation		phase I protocol INDA filing

Overall management is provided by the AIDS Operating Committee.

Appendix F

National Cooperative Drug Discovery Group

Opportunistic Infections (NCDDG-OI)

OI Drug Discovery: Total NIAID RPGs per Year*					
Organism	**FY 1990**	**FY 1991**	**FY 1992**	**FY 1993**	**FY 1994**
Pneumocystis	5	6	8	7	7
Candida	3	5	4	8	10
Cryptococcus	1	1	1	1	2
M. avium	3	3	3	5	6
Cryptosporidium	3	6	7	6	5
Microsporidia	0	0	1	1	2
Toxoplasma	2	3	4	4	6
M. tuberculosis	0	0	3	4	5
CMV	3	4	4	4	4
Total	20	28	35	40	47

* Provided by NIH/NIAID/DAIDS.

Appendix G

Drug Discovery Area Review Panel Members

Emilio A. Emini, Ph.D.
Chair
Executive Director, Department of Antiviral Research
Merck Research Laboratories

John M. Coffin, Ph.D.
American Cancer Society
Research Professor, Department of Molecular Biology and Microbiology
Tufts University School of Medicine

Bill Current, Ph.D.
Senior Research Scientist
Eli Lilly and Company

Alan D. Frankel, Ph.D.
Assistant Investigator
Department of Biochemistry and Biophysics
University of California at San Francisco

James M. Hogle, Ph.D.
Edward S. Harkness Professor
Harvard University

Brenda Lein
Director, Information and Advocacy
Project Inform

Judy Lieberman, M.D., Ph.D.
Assistant Professor, Medicine
Harvard University

Richard Lynn, M.D.
Director
Pfizer Pharmaceutical

Joseph M. McCune, M.D., Ph.D.
Associate Investigator
Gladstone Institute of Virology and Immunology

Richard Mulligan, Ph.D.
Professor, Molecular Biology
Fomatix

Manuel Navia, Ph.D.
Vice President and Senior Scientist
Vertex Pharmaceuticals

John Secrist, Ph.D.
Executive Vice President
Southern Research Institute

Richard R. Tidwell, Ph.D.
Professor, Pathology
University of North Carolina

Appendix H

Biographies of Panel Members

Emilio A. Emini, Ph.D., Panel chair, is the Executive Director of the Department of Antiviral Research at the Merck Research Laboratories. Dr. Emini received his Ph.D. in Virology from the Cornell University Graduate School of Medical Sciences in 1980. His research has focused on immuno biological studies of various viral systems and on the discovery and evaluation of antiviral chemotherapeutic agents. His interests have included alphaviruses, poliovirus, several human herpesviruses, hepatitis A and B viruses, and the human immunodeficiency virus (HIV). In 1993, he organized Merck's Department of Antiviral Research to consolidate Merck's overall antiviral discovery and development efforts. Dr. Emini's recent research interests have involved understanding the genetics of HIV resistance to the viral reverse transcriptase and protease inhibitors. He also participated in the discovery and clinical evaluation of several HIV chemotherapeutic agents. Dr. Emini has co-authored more than 120 scientific research and review publications. He has served on various NIH panels for review of HIV-related grant/contract applications and programs.

John M. Coffin, Ph.D., is American Cancer Society Research Professor of Molecular Biology at Tufts University School of Medicine in Boston, MA. Dr. Coffin's scientific career has been centered on developing an understanding of the association of retroviruses with their hosts. As a student with Howard Temin, he performed some of the initial studies defining subviral structures and their presence in cells as markers of infection. As a postdoctoral fellow in the laboratory of Charles Weissmann, he developed methodology to show the nuclear synthesis of retrovirus RNA by RNA pol II and performed some of the initial studies on genetic structure of the retrovirus genome. In subsequent work, he has analyzed many facets of retrovirus biology, including genome structure and genetics, mechanisms of replication, coevolution of viruses and hosts, and pathogenic mechanisms. Although most of his laboratory work has been with simple retroviruses of chicken and mice, he has taken an active role in the HIV problem and has authored a number of critical reviews on aspects of HIV biology. Dr. Coffin is an Editor of the *Journal of Virology* and holds offices in several professional associations. He has served with a number of Government review and oversight committees relevant to the AIDS problem. He has contributed more than 120 articles to the scientific literature, largely on the mechanisms of transformation by and replication of retroviruses.

William L. Current, Ph.D., is a Senior Research Scientist, Infectious Diseases Research, Lilly Research Laboratories, Indianapolis, IN; Alumni Professor of Pathology, Indiana University School of Medicine; and Alumni Professor of Pathobiology, Purdue University School of Veterinary Medicine. Dr. Current received his M.S. in Biology from Eastern Washington State University in 1974 and a

Ph.D. in Life Sciences from The University of Nebraska Lincoln in 1977. He joined the faculty of Auburn University in 1977 and was promoted to Alumni Professor in 1983. He joined the Animal Health Research group at Lilly Research Laboratories in 1984 and has been a member of the Infectious Diseases Research group since 1989. Awards received by Dr. Current include the 1982 Alabama Agricultural Experiment Station Director's Research Award for outstanding research, the 1986 Henry Baldwin Medal presented by the American Society of Parasitologists as the highest scientific honor and recognition the society can bestow, and the Senior Research Recognition Award (July 1993) for unique contributions to the success of Lilly Research Laboratories. His areas of expertise include protozoan and fungal biology. Dr. Current presently coordinates the activities of a multidisciplinary team involved in antifungal drug discovery research. At the time of this writing (2l5196), his publications include 106 refereed papers, invited papers and book chapters, and 65 abstracts of papers presented at meetings. He has also presented 88 invited lectures and symposium papers.

Alan D. Frankel, Ph.D., is Associate Professor of Biochemistry and Biophysics, University of California, San Francisco. Dr. Frankel received his Ph.D. in Biochemistry from Johns Hopkins University in 1983. Following postdoctoral training at Johns Hopkins School of Medicine, he was appointed a Fellow of the Whitehead Institute for Biomedical Research at MIT in 1989. He joined the faculty at the University of California in 1992 and held a joint appointment at the Gladstone Institute of Virology and Immunology until 1995. Dr. Frankel currently holds appointments in the Departments of Biochemistry and Biophysics and Cellular and Molecular Pharmacology. He has authored or co-authored more than 50 scientific publications. His areas of expertise include RNA-protein interactions, RNA structure, and regulation of HIV gene expression.

James M. Hogle, Ph.D., is the Edward S. Harkness Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, and Chair of the Committee on Higher Degrees in Biophysics, which administers the interdepartmental Ph.D. warding Program in Biophysics at Harvard University and Harvard Medical School. He has held the position of Professor at Harvard Medical School since July 1991 and was appointed Chair of the Committee on Higher Degrees in Biophysics in July 1992. Dr. Hogle received his B.S. in Biochemistry from the University of Minnesota at Minneapolis in 1972 and his Ph.D. in Biochemistry from the University of Wisconsin at Madison in 1978. Dr. Hogle obtained his postdoctoral training at Harvard University from 1978-1981 and subsequently joined the Department of Biochemistry as a Research Associate from 1981-1982. From 1982-1985, Dr. Hogle joined the Department of Molecular Biology at The Research Institute of Scripps Clinic as an Assistant Member, was an Associate Member from 1985-1986, and a Member from 1987-1991. In 1985, Dr. Hogle received the AAAS Newcomb-Cleveland Prize. In 1991, he was awarded the Wallace P. Rowe Award for Excellence in Virology. He has authored or co-authored more than 50 scientific publications. Dr. Hogle serves on the editorial boards of *Journal of Virology*, *Virus Genes*, and *Protein Science*. Dr. Hogle's research focuses on the structure and function of viruses and viral

proteins, using a combination of x-ray crystallographic and molecular biological approaches. His current research programs involve the study of several viruses including poliovirus, herpes virus (HSV and CMV) and the hepatitis virus.

Brenda Lein is the Director of the Information and Advocacy Departments and the Director of Project Immune Restoration at Project Inform, one of the most influential AIDS treatment information and advocacy organizations in the United States. Ms. Lein directs and oversees the production of HIV/AIDS treatment information, which has been distributed throughout the years to hundreds of thousands of people living with HIV/AIDS and their caregivers and providers. Ms. Lein also directs advocacy efforts at Project Inform as well as an advocacy program, Project Immune Restoration, focused on furthering the development of immune-based therapies for HIV-disease and focusing research attention on the problems of late-stage HIV-disease through a component of the project, Immune Restoration Think Tank: The Dobson Project. The Think Tank is an internationally acclaimed project providing a model for community interaction with the research establishment.

Judy Lieberman, M.D., Ph.D., is Senior Investigator at the Center for Blood Research, Harvard Medical School, and consultant in Hematology at Children's Hospital, Boston. She received her Ph.D. in physics at Rockefeller University and an M.D. in the Joint Harvard-MIT Program in Health, Science and Technology. She was trained in Internal Medicine and Hematology-Oncology at New England Medical Center and is board certified in Internal Medicine and Hematology. She trained in Immunology at the Center for Cancer Research at MIT. Her laboratory studies the cytotoxic T cell response to viral disease and the development of immunotherapy to treat HIV infection. She is the director of the Boston SPIRAT Program on Immune Based Therapy for HIV Infection. She has been conducting clinical trials of cellular immunotherapy with HIV-specific cytotoxic T lymphocytes. She is a member of the ACTG Working Group on HIV-specific Immune Modulation Therapeutics and of the Steering Committee of Project Inform's Immune Restoration Think Tank. She is the author of more than 30 original research publications.

Richard Lynn, Ph.D., is Director of Pharmaceutical Systems in the US Pharmaceuticals Group of Pfizer Inc. Dr. Lynn received his Ph.D. in 1989 from Harvard University, where he studied the mechanism of DNA topoisomerases. He serves on the Scientific Advisory Boards of the American Foundation for AIDS Research and the Community Research Initiative on AIDS in New York City. He is a member of the Treatment Action Group in New York City. Dr. Lynn's area of expertise includes drug discovery and development, disease pathogenesis, and research and treatment advocacy.

Joseph M. McCune, M.D., Ph.D., is an Associate Investigator of the Gladstone Institute of Virology and Immunology/University of California San Francisco (UCSF), the Associate Director of the General Clinical Research Center at San Francisco General Hospital/UCSF, and Associate Professor in the Department of

Medicine at UCSF. Dr. McCune received his Ph.D. from Rockefeller University in 1981 and his M.D. from Cornell University Medical College in 1982. He completed an internship and residency in Internal Medicine at UCSF and is board certified in Internal Medicine. He did fellowship training in Infectious Diseases at UCSF and postdoctoral training in the Department of Pathology at Stanford. His research focuses on the definition of pathogenic mechanisms of viral diseases, particularly HIV-1 disease.

Manual A. Navia, Ph.D., is Vice-President and Senior Scientist at Vertex Pharmaceuticals Incorporated in Cambridge, MA. His expertise is in x-ray crystallography and in the application of structural biology to the design, synthesis, and development of novel therapeutic agents. Dr. Navia was trained as a physicist and received his Ph.D. in Biophysics from the University of Chicago in 1974. He completed postdoctoral training in structural biology at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1980 and joined the Merck Research Laboratories in Rahway, NJ, where he established the first industrial macromolecular crystallography laboratory in the US. That effort led to a first success for structure-based drug design, the topical carbonic anhydrase inhibitor dorzolamide, recently approved by the FDA, as well as the first three-dimensional structure of an AIDS target protein, the HIV protease. At Vertex, Dr. Navia's interests have focused on drug targets for immunosuppression (calcineurin), inflammation (IL-lB converting enzyme), and antivirals (hepatitis C and HIV proteases). The HIV protease effort has led to a potent series of subnanomolar inhibitors of the enzyme, currently in clinical development, whose design specifically addressed issues of bioavailability, resistance and ease of synthesis as well as *in vitro* potency. Dr. Navia is coinventor of the cross-linked enzyme crystal (CLEC) catalyst technology, for which he received an R&D 100 Award this year. CLECs may ultimately contribute to the development of environmentally benign commercial-scale chemistry by allowing the power of enzyme catalysis to be used under the harsh conditions characteristic of manufacturing processes.

Richard R. Tidwell, Ph.D., is Director of the Division of Cellular Biology and Biological Chemistry and Professor of Pathology and Medicinal Chemistry at the University of North Carolina at Chapel Hill. He is a consultant to numerous pharmaceutical companies and serves as the Interim President of CaroTech, Inc., Durham, NC. Dr. Tidwell received his Ph.D. in Medicinal Chemistry in 1974 from the University of Tennessee Center for Health Services, Memphis, TN. He has co-authored more than 70 manuscripts in peer-reviewed journals and 5 book chapters. He has been issued 8 patents and has filed an additional 13 patent applications. His current work is directed toward the design, synthesis, and preclinical testing of new agents for the treatment of AIDS-associated opportunistic infections. He is the Principal Investigator of a National Cooperative Drug Development Group (NCDDG) grant to develop new drugs to treat opportunistic infections. This group includes projects at Duke University, Georgia State University, and Auburn University as well as the University of North Carolina at Chapel Hill. One of the compounds developed in his laboratories is due to begin clinical trials this spring for the treatment of *P.*

carinii pneumonia. Several drugs discovered by his NCDDG are in preclinical development for treatment of *C. parvum*, *C. neoformans*, *C. Albicans*, and *M. tuberculosis* infections.