

Strategies for the Identification of New Agents for the Treatment of AIDS: A National Program to Facilitate the Discovery and Preclinical Development of New Drug Candidates for Clinical Evaluation

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The National Institutes of Health (NIH), the major biomedical research component of the United States Public Health Service (US PHS), has launched a comprehensive set of new programs to confront the burgeoning worldwide epidemic of acquired immune deficiency syndrome (AIDS). Strategies encompassed in these efforts not only include an increased emphasis upon specialized intramural AIDS-related basic and clinical research projects at the NIH, but also include AIDS-targeted efforts of an extensive cross-section of the extramural scientific community.

The extramural programs are supported through NIH grants, cooperative agreements, and contracts. Grant-supported activities focus predominantly upon the development of a critical foundation of scientific knowledge through basic research. AIDS-related activities supported under cooperative agreements give additional emphasis to applied research and development, specifically toward the expeditious application of new scientific discoveries to new treatment strategies. The AIDS National Cooperative Drug Discovery Group (NCDDG) Program, developed jointly by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI), provides an excellent example of how the cooperative agreement mechanism provides support for extramural investigator-initiated, basic and applied, interdisciplinary, multicenter

programs aimed specifically at development of new treatments for AIDS.

Major contract-supported programs encompassed within the NIH strategies for AIDS are intended to provide comprehensive centralized resources for AIDS treatment research. These resources give focus to synergistic, cooperative efforts in AIDS treatment research among the NIH, other government agencies, academia, industry, and other potential collaborators worldwide. Key NIH extramural initiatives in this regard include: the implementation of complementary national programs to facilitate the discovery and prompt preclinical development of promising new candidate agents for treatment of AIDS and to facilitate the clinical evaluation and development of new potential agents and applications. The NIAID is focusing predominantly upon the clinical program, as exemplified by the implementation of the national AIDS treatment/evaluation units (ATEUs), a clinical evaluations network involving major medical centers throughout the United States. The NCI is primarily responsible for the preclinical program and, as described herein, has implemented a contract-based drug development program of a national / international scope, for the support of the worldwide effort to expeditiously discover and develop the most promising candidate agents for clinical evaluation against AIDS.

For the past several years the NCI has played an active role in supporting certain specialized aspects of AIDS drug development. However, the implementation

by the NCI of a more comprehensive program for support of a full preclinical drug development program for AIDS, including a national AIDS drug screening resource, was initiated after the recommendation of the Board of Scientific Counselors of the NCI Division of Cancer Treatment (DCT). The Board formally approved the NCI AIDS drug development program concept in February 1987.¹ The NCI's charge to implement a national AIDS preclinical drug development program was based on the urgent need for such a resource and the Institute's extensive experience and pre-existing program for preclinical development of anticancer agents.

A NATIONAL PROGRAM TO FACILITATE THE DISCOVERY AND PRECLINICAL DEVELOPMENT OF NEW DRUG CANDIDATES FOR CLINICAL EVALUATION AGAINST AIDS

Background: The Drug Development Program of the National Cancer Institute

The NCI's drug development program is a unique entity within the federal government. In both organization and function, it is similar to a large multinational drug corporation, although it is not profit-driven and lacks a marketing component. The rationale for the creation of such a federal program over 30 years ago was a national commitment to enhance the discovery and rapid development of new agents for the treatment of cancer, a disease area where private-sector pharmaceutical industries were, and continue to be, relatively reluctant to engage their greatest efforts. Anticancer drug discovery and development has been generally perceived by industry as a high-risk, exceedingly expensive venture, with relatively limited profit potential compared to other, more accessible pharmaceutical areas. Clearly, therefore, an important function of the NCI program in achieving its goal of expediting the entry of effective new anticancer agents into the population at large has been its role in assuming a major portion of the costs and "risks" involved in the early phases of anticancer drug discovery and development. Ultimately, for any effective new drug or treatment developed either partly or completely by the NCI, the pharmaceutical industry always assumes a critical role in commercialization, marketing, and distribution of the new products to the target populations.

The federal program is in an ideal position to serve as a bridge between academia and industry to bring the best ideas from all sectors to fruition as quickly as possible. The NCI's drug development program has indeed evolved with a rich tradition of highly productive, cooperative efforts among government, academia, and industry on both a national and an international scale. A review of the NCI preclinical drug development program status up to 1982 revealed that half of the current

commercially available anticancer agents discovered since 1955 were initially discovered by the NCI screens and that the NCI has played an important role in the preclinical and/or clinical development of essentially all of the drugs receiving New Drug Application (NDA) approval from the U.S. Food and Drug Administration (FDA) for entry into the marketplace.²

It is important to note that a very high percentage of substances acquired by the NCI program for initial testing and/or consideration for potential development come from non-NCI sources. Such materials are obtained under the protection of formal confidentiality documentation to ensure the original suppliers' patent positions. On the other hand, in those less common instances where the drug originates from within the NCI itself (e.g., from an intramural laboratory) or from an outside investigator independent of industry, the NCI seeks to facilitate the negotiation and execution of licensure arrangements with industry, again to ensure the ultimate delivery of a useful new drug product to the population if and when appropriate.

Potential Role and Contribution of a National AIDS Drug Development Program

It is important to consider these precedents in the face of the current AIDS crisis. Regardless of whether the future responsibility for operation of a federal program to facilitate AIDS drug development continues to reside with the NCI, there is clearly ample experience from the NCI anticancer drug development program to illustrate vividly the potential impact of such a program on a major public health problem. A federal program providing centralized support for new drug development can indeed provide a critical interface among the best of academia, private industry, and government to enhance the attack on a problem of the potential magnitude of AIDS.

Current industry perspectives regarding AIDS drug development appear to be substantially different than those for anticancer drug development. One of the greatest differences appears to be the perception of a high profit potential for AIDS drugs, making the financial "riskiness" of AIDS drug discovery and development less an obstacle. Clearly there is considerable interest within industry to engage very substantially in AIDS-related drug research and development. To that extent, therefore, the federal program does not appear to be essential to help provide incentive for involvement. For confronting the AIDS epidemic, the federal program should nevertheless make a major contribution by enhancing the pace and efficiency of progress. An effective government program can expedite the process of drug discovery and development from the earliest stages of screening through the point of delivery of the finished pharmaceutical

products to the clinical trials specialists. The recent development of dideoxycytidine (DDC), the antiviral activity of which was discovered in an NCI intramural laboratory,³ exemplifies how the NCI preclinical drug development program can accelerate the progress of a new drug candidate. From the point of entry of DDC into the drug development program described herein, the total time for completion of all the steps of preclinical development (see below) to the point of readiness and FDA approval for clinical testing was an unprecedented 12 months. The NCI program also played a substantial supportive role with industry in expediting the development of azidothymidine (AZT), which was the first drug approved and marketed for the treatment of AIDS.

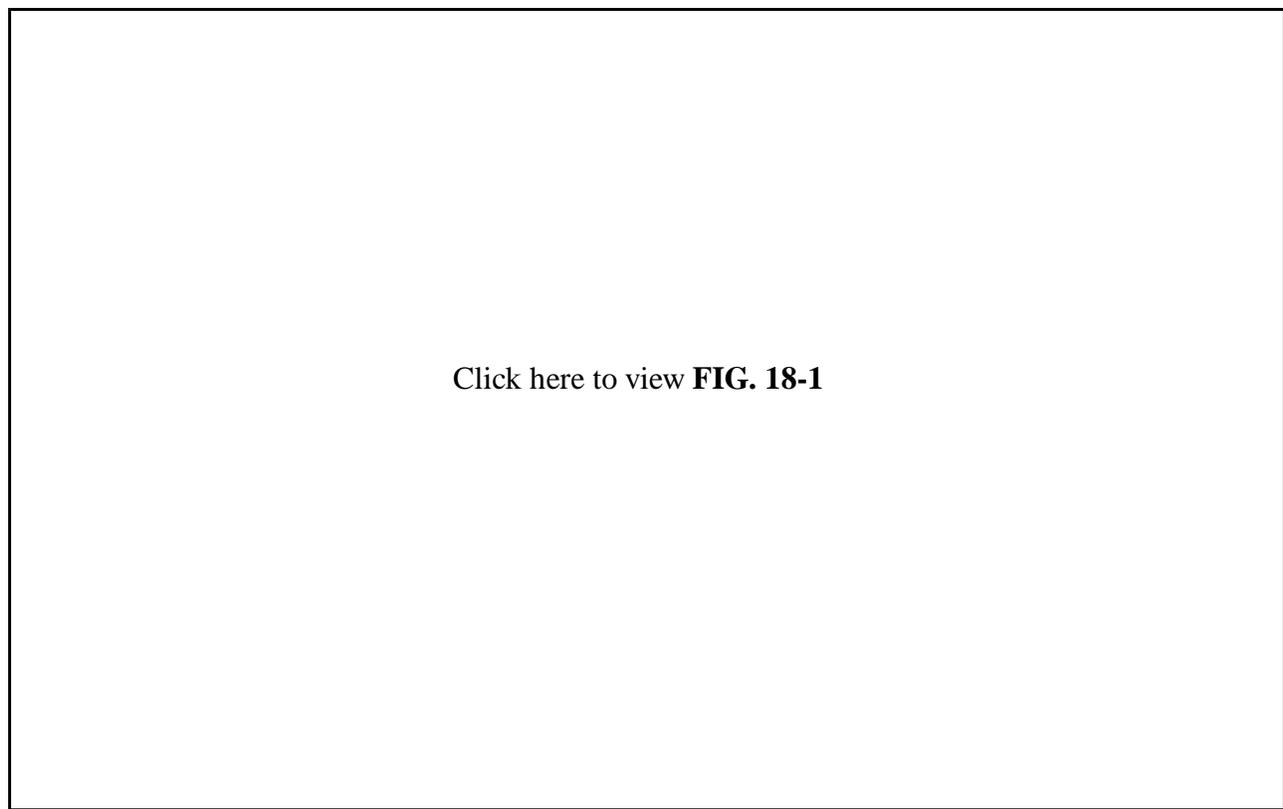
**Organization of Contract-Supported AIDS
Preclinical Drug Research and Development
Responsibilities Within the National
Cancer Institute**

To facilitate the most rapid deployment, AIDS program requirements were integrated with the existing NCI extramural contract-based anticancer drug development program, the general organization of which is depicted in Figure 18-1. The NCI preclinical drug development program is a part of the Developmental Therapeutics Program (DTP), located within the Division of Cancer Treatment (DCT). Although it will not be discussed

further herein, the DTP organization also encompasses an extramural research component supported by grants and cooperative agreements, as well as an intramural research component with laboratories located in Bethesda, Maryland, and at the Frederick Cancer Research Facility in Frederick, Maryland.

Key extramural program managers within DTP presently have responsibility for organizing and operating both the anticancer and the AIDS-antiviral drug development areas; additional specialized staff are assigned as necessary to meet the more detailed requirements of each area. AIDS program operations described herein are accomplished primarily through a portfolio of specific AIDS-designated contracts. Decision making and/or prioritization responsibilities are performed jointly for AIDS and anticancer drug development by committees strategically placed within the operational/management framework shown schematically in Figure 18.2.

The remainder of this chapter details further the organization, functions, contact points, committee functions, and other specific issues of relevance to the contract-based AIDS preclinical drug discovery and development components of the DTP. The discussion does not encompass non-NCI drug development programs; nor does it cover other areas of related NCI research, such as the intramural AIDS research



Click here to view **FIG. 18-2**

components described elsewhere (see Chapters 2 and 5). Other NCI AIDS-related contract-based programs, such as vaccine development, also are reviewed in Chapter 6. The purpose of the present discussion is to describe, and to indicate both the availability and the current status of, NCI resources potentially applicable to AIDS drug research and development, and to invite the input and utilization of this program by responsible members of the academic, private industry, and government sectors.

NATIONAL CANCER INSTITUTE AIDS PRECLINICAL DRUG RESEARCH AND DEVELOPMENT PROGRAM: DRUG DISCOVERY PHASE

Acquisition of Materials for Evaluation

The NCI for many years has operated a worldwide acquisitions program for identifying and obtaining promising substances (more than 10,000 new materials per year); including both synthetic and natural products, for evaluation for potential anticancer activity (Fig. 18-3). Both the Chemical Repository and the Natural Products Repository of the NCI, which contain a broad sampling of previous years' acquisitions, and the nonproprietary portions of their structure/activity databases, are available to support the search for new leads with promising anti-HIV activity. On-going NCI natural products collection projects, currently focusing upon new or relatively unexplored areas (e.g., marine biology, novel plant sources, microbial fermentations including bacteria, cyanobacteria, and fungi) for discovery of active constituents with antitumor / antiviral and other biologic activities, will provide further materials for anti-HIV testing.

To complement the existing NCI repositories and acquisitions programs, an additional AIDS-designated acquisitions program has been implemented to enhance the input of substances specifically for anti-HIV testing. This initiative also includes the development of a separate AIDS-designated chemical/biologic database.

Analogous to the acquisitions component of the anticancer drug program, materials for testing are acquired both through active solicitations and through voluntary submissions from a wide variety of sources including the NIH intramural programs, NIH extramural programs (grantees, contractors, NCDDGs), other government agencies, private research institutes / foundations., individual investigators, universities, pharmaceutical / chemical industries, and international collaborations (see Fig. 18-3). Initial reports of the evaluation of discreet compounds thus acquired are sent to suppliers as soon as the screening data are available.

Suppliers' commercial or other proprietary (e.g., patent) interests are protected, whenever necessary, through written confidentiality agreements, which are preferably formalized prior to acquisition and testing. Testing data and other information produced by the NCI program may be used by the original suppliers or their assignees in support of their publications or patent applications. A copy of the confidentiality agreement used currently for suppliers of compounds to be evaluated is provided in Appendix A. Potential suppliers are encouraged to contact the NCI Developmental Therapeutics Program for further details concerning submission of compounds and the securing of confidentiality documentation.

Click here to view **FIG. 18-3**

commonly used antiviral assays.^{5,6} Such tests are based upon the ability of an "active" substance to prevent virus-induced cytopathic effects in appropriate target cells in culture. A test for anti-HIV activity therefore typically utilizes HIV-infected human host cells; an active test shows an enhancement of survival of the virus-infected host cells at drug concentrations that are relatively nontoxic to the uninfected host cells.^{3,4}

Unfortunately, the availability of anti-HIV test systems to the research community at large has been exceedingly limited, owing to the low capacities of the few laboratories performing such tests, the difficulties of scale-up, and the reluctance of many investigators to become directly involved with the active AIDS virus. Moreover, there has been considerable variation in the specific test protocols used by various laboratories, substantially compromising meaningful detailed comparisons of compounds among laboratories. For these reasons, a high-capacity national AIDS-antiviral screening resource is essential to serve a variety of drug discovery research needs. The need is further exemplified in the following.

Rational versus Empirical Approaches to Drug Discovery

All so-called rational approaches (e.g., molecular design) for new drug discovery ultimately require the availability of appropriate biologic screening models against which to test the chemical products of the medicinal chemists' ideas. Moreover, in the empirical approach to new drug discovery, the biologic screening models per se are the primary tools for new drug discovery.

The process of empirical screening of large, chemically diverse sets of organic compounds, recently criticized by some as inefficient⁷ yet also encouraged by others⁸ as essential for AIDS drug research, is nonetheless the most successful drug discovery approach used for many areas of pharmaceuticals. This is nowhere better exemplified than in the area of anticancer drugs where a majority of the clinically useful agents have been initially discovered by the process of empirical screening.²

For the natural products area, empirical screening is the primary avenue to the discovery of new leads. Furthermore, the critical process of bioassay-directed isolation and structure identification of the active pure constituents from a crude natural product extract frequently requires extensive screening of the partially purified fractions. Many of the most important clinically used drugs, across all pharmaceutical classes, have their origins as natural products discovered predominantly through the empirical process.

Biologic Testing

Need for a Centralized Resource

One of the most critical factors determining the potential value of a national program as described in this chapter is the ability to provide investigators throughout the country—indeed, worldwide—with an adequate central standardized resource for rapid initial screening of substances for anti-HIV activities and/or other relevant biologic properties. Based upon the experience of the cancer drug program, it was projected that an initial testing capacity of at least 10,000 substances per year is required to examine an adequate fraction of the total potential new submissions for antiviral activity. Moreover, substantial testing capacity is also required to systematically reexamine for anti-HIV activity the existing NCI synthetic and natural products repositories containing over 200,000 materials, many of which were initially acquired on the basis of known or suspected "biologic activities," including antiviral, of potential interest.

In vitro anti-HIV tests recently used with success for initial identification of promising new agents such as AZT and DDC^{3,4} are conceptually analogous to other

Once an initial new lead is identified empirically, regardless of whether it is of synthetic or natural origin, the rational approach may then be applied by the medicinal chemist to modify the structure to improve the lead compound's characteristics (e.g., stability, solubility, biologic potency or selectivity) as a potential pharmaceutical agent. This process of "lead optimization" obviously also depends upon the use of biologic screens to monitor the progress of optimization. Thus, not infrequently the rational drug design approach occurs much later, only after an initial new active lead structure is discovered by empirical screening and the molecular/biochemical basis for its activity in the screen is elucidated. The designer chemist then conceives of ways to improve the lead structure or to develop entirely new molecules to address the new molecular/biochemical targets thus discovered.

The explosion in the knowledge of the molecular biology of the AIDS virus and its effects upon its cellular targets certainly make the prospects for success of rational drug design all the more appealing. However, the record of success for purely ab initio rational design of effective antivirals is, as yet, no greater than the slim record for anticancer agents. For the present, the rational and the empirical approaches to drug discovery in both the anticancer and the antiviral areas are most prudently viewed and utilized as complementary and potentially synergistic.

Testing Strategy

Presently, the emphasis for biologic testing is primarily toward the identification of anti-HIV active leads. Other types of screens to detect other kinds of agents potentially useful against AIDS (e.g.,

immunomodulatory agents; anti-infectives) may later be incorporated into the program as the available technology and resources allow.

Figure 18-4 illustrates the antiviral screening strategy currently being implemented by the DTP. Although not yet in place, anti-HIV related screening at the biochemical/ molecular level will be a part of the integrated AIDS drug discovery resource. Like other retroviral infections, HIV infection of cells involves a series of critical steps including the binding of virus to cellular receptors, internalization of the virus, transcription of the viral RNA into DNA by means of viral enzyme reverse transcriptase, integration of the viral DNA transcript into host chromosomal DNA, and subsequent transcription of viral DNA resulting in synthesis and release of new infective virus particles. Efforts at rational drug design focusing upon these targets are underway in many laboratories; however, a generally available biochemical screening resource specifically addressing such targets has not been available.

The biochemical/molecular screens should be potentially useful not only to support specific target-directed, rational drug design projects, but also to enrich the input of bioactive materials to the other screens. For example, it is anticipated that the biochemical/molecular screening resource will be utilized for empirical screening of widely diverse synthetic molecular structures (e.g., from the existing repositories). Such a resource may not only help preselect for novel drug candidates, but also may yield useful new probes for basic research on HIV and potential molecular targets therein. Moreover, the complementary use of the biochemical prescreens resource, with the cell-culture-based screens used to identify active reads from crude natural products, also may facilitate the identification and

Click here to view **FIG. 18-4**

isolation of the most biologically diverse new natural product drug candidates.

In order to address a diversity of molecular targets with the biochemical/molecular screen, a battery of screens will be operated simultaneously and new screens will be added as technology and resources permit and/or as other screens are deleted. On an annual basis it is anticipated that multiple screening models, each addressing unique molecular targets, will be utilized and that each will have a testing capacity of approximately 10,000 compounds. It is anticipated that critical input for the selection and review of potential targets for screening will come from the extramural scientific community by way of NCI advisory groups, such as the DCT Board of Scientific Counselors and Ad Hoc Expert committees, and through national workshops or other suitable forums. Implementation of the biochemical screens project is expected to begin during 1988.

Currently, there do not appear to be any appropriate in vivo animal model systems that could have practical application as a primary drug screen. However, as depicted in Figure 18-4, any currently available in vivo models will be considered for follow-up testing and secondary evaluations of new leads whenever possible. The development of new in vivo models, particularly short-term models employing HIV-infected human host cells, is a current research priority within OTP. Suitable short-term animal models, if adequately validated, would be particularly useful for preclinical experimental therapeutics (e.g., dose route/schedule dependency studies) and further prioritization of promising agents identified by the primary in vitro screens.

Presently, the NCI program for initial selection of drug candidates for consideration for preclinical development and possible clinical testing relies principally upon a cell-culture-based assay system (see Fig. 18-4). As described further below, the highly automated, high capacity-assay system currently being deployed for the national AIDS- antiviral drug screening program has evolved directly from technology developed initially by DTP staff and contractor staff (Program Resources, Inc.) for NCI's new cell-culture-based anticancer drug screens at the Frederick Cancer Research Facility.

Development and Implementation of a High-Capacity, Cell-Culture-Based Antiviral Screen

For the past 2 years, DTP has been intensively involved in the development of an entirely new anticancer drug screening program based upon the use of human tumor cell line panels in complementary in vitro and in vivo testing models.⁹⁻¹³ The technical goal has

been the implementation of a program for the annual in vitro evaluation of at least 10,000 substances, each tested over a multi-log range of concentrations against each of 100 or more different kinds of human tumor cell lines. Therefore, to accomplish this goal it has been necessary to develop new technology amenable to an anticipated operational level of over 10 million cultures per year. The successful implementation of this program is based upon the development of high-flux microculture tetrazolium assay (MTA) technology for the precise, highly reproducible quantitative measurement of cell growth in culture.¹⁴⁻¹⁸

The MTA technology, although originally developed for the NCI antitumor screen, appears to have many other potential applications in other kinds of assays or drug screens in which the end point involves either an inhibition or an enhancement of cell growth in culture. In addition to the adaptation to use as an antiviral screen as described below, other applications of the MTA technology currently being explored by DTP scientists include new screens for radiomodulators, differentiating agents, and modifiers of drug resistance.

The conceptual basis for the antiviral application of the MTA assay technology is straightforward. Appropriate host cells susceptible to the cytopathic effects of HIV in vitro are grown in microtiter plate wells in the presence or absence of virus and in the presence or absence of the test substance of interest (Fig. 18-5). Antiviral activity is indicated by an enhanced growth/survival of the virus-infected cells, measured quantitatively by a colorimetric procedure as described below, in the presence of the drug. The virus-free cells used as controls in the assays provide a measure of the direct growth inhibitory effect of the drug on the host cells.

A new MTA reagent (XTT), currently being used to determine the cell growth endpoint in this assay^{15,16,18} was developed by DTP staff and contractor colleagues. The basis for its use in the antiviral assay as well as its potentially broader usage in a variety of other cell culture assay systems is depicted in Figure 18-6. The colorless XTT tetrazolium salt is metabolically reduced in the presence of viable cells and an electron coupling reagent (e.g., phenazinemethosulfate [PMS]) to a highly colored formazan. The special feature of the XTT formazan, which makes it attractive for application to the antiviral assay, is its solubility in the culture medium, which allows direct spectrophotometric assay of optical density in the culture wells. Indeed; the entire assay procedure after addition of the XTT reagent is carried out in sealed culture wells, thereby potentially enhancing the safety of the assay as well as simplifying the problems of disposal of the assay plates and contents. All steps of the

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antiviral assay are carried out under BL3 containment facilities.

This is the general framework from which the particular assay protocol currently in use has been developed. The specific parameters, such as choice of host cell line, viral strain(s) to be used, viral multiplicity, drug exposure times, and numerous other variables, have been the subject of considerable discussion, debate, and experimentation. Indeed, shortly after the DCT Board of Scientific Counselors approval of the DTP plan to proceed with the implementation of an antiviral screen, a workshop was organized and held in Bethesda, Maryland on April 8-9, 1987, entitled "Issues for Implementation of a National Anti-HIV Preclinical Drug Evaluation Program; Critical Parameters for an in Vitro Human Host-Cell Based Primary Screen." Participants in the workshop included a broad representation of experts from groups actively involved in virology and antiviral research throughout the country. Both the feasibility and the specific assay protocol issues were discussed in great detail. A verbatim transcript of the workshop proceedings is available.¹⁹ Participants at the workshop were in general agreement that the screen proposed by DTP was feasible.

Based upon recommendations from this workshop, a variety of potential host cell lines for the assay, as well as assay protocols, have been under consideration and evaluation. The cell lines include human lymphoblastoid lines such as MT-2, ATH8, CEM, C3-44, LDV-7 and Sup-T1, as well as others such as

U937 and HeLa/T4.¹⁹ The ATH8 line, used by NCI intramural scientists for preclinical studies of agents such as suramin, AZT, and DDC,^{3,7} was viewed by workshop participants as useful for follow-up or secondary testing of materials emanating from the primary screen.²²

Among the individual cell lines evaluated for the primary screen, the MT-2 line originally developed in Japan²⁰ initially appeared to best meet many of the optimal criteria. However, the simultaneous use of several different host cell lines is feasible with the automated microculture assay technology. A detailed description of the assay protocols evaluated to date, and the basis for the particular selection of "standardized" protocols, and the validation thereof for current use in the primary screen, will be provided in a separate publication. A detailed, periodic review of the primary assay, its further development, and the development of related secondary assays will be the task of an extramural ad hoc review committee for the AIDS screen project.

Currently, screening with the new assay is ongoing at both the FCRF and at a contractor laboratory (Southern Research Institute, Birmingham, Alabama). Screening capacity as of fall 1987 is approximately 120 samples per week, which will be further expanded to approximately 250 samples per week in the near future. During 1988 the goal is full implementation of the primary screen to a total capacity of approximately 500 samples per week (24,000/yr).

Appendix B shows a DTP supplier report exemplifying the current format of the screening data provided to the original supplier of the test compound. Presently, each material is evaluated over a wide range of concentrations (8 log₁₀ dilutions), in duplicate, for both the control and the virus-infected cells. Sample curves of typical assay responses, including an example of an inactive substance, and two examples of substances with differing patterns of anti-HIV activity, are routinely provided as a part of the report (see Appendix B).

Potential AIDS Antiviral Applications of New in Vivo Models Under Development by NCI

It is of interest to consider other potential applications of new NCI antitumor screening models to antiviral assays. For example, agents identified in the new NCI in vitro cancer screen as having antitumor activity in particular cell lines of interest are further evaluated against these same cell lines using novel in vivo models specifically developed for this program. One such model is the microencapsulated tumor assay (META).²¹ In this model the desired cell line (e.g., any line of interest from the in vitro screen) is encapsulated within small (~1 mm) nutrient- and drug-permeable

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spheres implanted within the peritoneal cavities of athymic mice. The mice are treated (IV, SC, PO, or as desired) with the test substances, and after the appropriate interval, the microcapsules are re-covered, lysed, and cell viability determined (e.g., by cell count and/or by metabolic assay such as XTT).

An in vivo antiviral application of the META appears obvious: to grow the micro-encapsulated host cells of interest in athymic mice and evaluate the drug effects on host cell survival. As in the in vitro antiviral assay, a positive antiviral effect of the test drug is indicated by an enhancement of the growth/survival of the virus-infected human host cells contained in the microcapsules. At its February 1987 meeting, the DCT Board of Scientific Counselors approved a DTP plan to explore application of the META to antiviral testing.¹ Feasibility evaluations of this approach to in vivo anti-HIV screening have been encouraging.²²

NATIONAL CANCER INSTITUTE AIDS PRECLINICAL DRUG RESEARCH AND DEVELOPMENT PROGRAM: DRUG DEVELOPMENT PHASE

Overview

Of the major functions depicted in Figure 18-1, those subsequent to acquisition and biologic testing comprise the preclinical development phase. Most of the activities encompassed therein are generally required for most classes of drugs whether for treatment of AIDS, cancer, or other diseases. These activities include bulk chemical synthesis and drug production, toxicology and pharmacology, clinical formulation production, and quality control. It should be emphasized that, when appropriate and if the necessary resources are available,

the preclinical drug development program can be utilized not only for primary anti-HIV agents, but also for rapid development of other high-priority candidate agents (e.g., agents for treatment of opportunistic infections; agents for stimulation of the immune system) of potential value in therapy of AIDS.

The preclinical development phase is subdivided into two stages, A and B.

Stage A Preclinical Development

Stage A (Table 18-1) focuses upon feasibility evaluations relevant to consideration for further development and the elucidation of additional biologic information to further assess merit and relative priority as a drug candidate. Abbreviated toxicologic and pharmacokinetic evaluations are intended to guide the follow-up evaluations of the drug candidates in any relevant in vivo disease models available, as well as, where necessary, to provide a basis for selection/prioritization of potential candidates for further development based on in vitro preclinical screening data alone.

Stage B Preclinical Development

Stage B (Table 18-2) represents the final phase of preclinical development and is generally undertaken only for agents for which there is a clear commitment to clinical testing. The major tasks include the production of bulk drug properly formulated for clinical usage, the detailed evaluation of toxicology and pharmacokinetics, and the performance of additional preclinical studies as needed to guide the optimal design of clinical trials protocols.

Table 18-1**Activities Encompassed in Stage A Preclinical Development**

1. Develop and optimize method for isolation and/or synthesis; evaluate scale-up feasibility and costs
 2. Optimize leads through congener/prodrug synthesis when appropriate
 3. Develop method for production of acceptable pharmaceutical formulation
 4. Develop qualitative and quantitative analytical methods
 5. Prepare radiolabeled drug if feasible
 6. Determine maximally tolerated dose (MTD) in one or more animal species; measure relevant body compartmental concentrations of drug at MTD
 7. Measure oral bioavailability
 8. Test for in vivo activity in appropriate model(s) if available
-

Table 18-2**Activities Encompassed in Stage B Preclinical Development**

1. Produce and/or purchase necessary amounts of bulk chemical
 2. Prepare suitably formulated drug
 3. Monitor purity of bulk chemical and formulated drug
 4. Perform route- and schedule-dependency studies in in vivo model if feasible
 5. Perform detailed pharmacokinetic analyses in at least one species
 6. Perform full toxicologic evaluation in rodents and dogs
 7. Develop sufficient quantity of formulated drug for clinical distribution; monitor quality control
-

Stage B also encompasses many activities addressing the complex regulatory requirements that are encountered increasingly as a drug progresses through the late steps of preclinical development and into the clinical arena. Bulk production of synthetic or natural products must be accomplished in facilities meeting rigidly defined regulatory requirements. Likewise, drug formulations and purities must meet established standards and be monitored extensively. Highly defined quality control requirements must be addressed, and detailed drug inventory and distribution protocols, and records thereof, must be managed. particularly in the area of toxicologic evaluation, the last major preclinical development step, the regulatory requirements are complex. Indeed, DTP staff often work very closely with the FDA to finalize the toxicology database providing the

critical support for filing of the investigational new drug application (INDA) for a new agent.

Approval of the INDA by the FDA marks the beginning of the clinical development phase. Although the primary role of the preclinical program is thus completed, certain difficulties encountered in the early clinical trials may require re-involvement of the preclinical program in additional stage B activities. This most commonly results from unexpected problems with formulations, or stabilities thereof, and unpredicted toxicities. Often, then, the preclinical program and clinical program staff can work effectively together to address and successfully resolve such problems when they arise with an otherwise promising new drug.

KEY DTP/DCT COMMITTEE FUNCTIONS FOR NCI PRECLINICAL DRUG RESEARCH AND DEVELOPMENT PROGRAM**Discovery Phase*****Acquisitions/Input Committee***

The Acquisitions/Input Committee (AIC) is composed predominantly of senior DTP staff from the acquisitions and biologic testing areas. The focus of the AIC is Decision Point (DP) I-A as depicted in Figure 18-2. This committee regularly reviews the current acquisitions inventory and selects and prioritizes the available agents for initial screening. Relative priorities are determined principally upon criteria of chemical or biologic uniqueness or novelty of the agent, or any other relevant known property (Table 18-3). However, if sufficient screening capacity is available, the policy of the program is to screen essentially all new acquisitions. The AIC also is responsible for identifying potential "bypass" agents for which there is some reasonable rationale or prior information to recommend immediate entry to a more advanced stage of development. Such "bypass" recommendations go initially to the DTP Operating Committee, then to the DCT Decision Network Committee for further consideration (see below). The AIC chairpersons or their designates serve as the initial contact point for potential entry of new agents to the NCI preclinical drug development program.

Biologic Evaluation Committee

The Biologic Evaluation Committee (BEC), composed predominantly of senior DTP staff, addresses decision point I-A (see Figure 18-2). In so doing, the Committee regularly reviews all screening data emanating from the in vitro screens, and selects and prioritizes "active" agents for presentation to the DCT Decision Network Committee (see below). Recommended

Table 18-3

Responsibilities of DTP Acquisitions/Input Committee: Decision Point (I-A)

1. Recommend and prioritize materials for biologic testing.
2. Recommend potential "bypass" candidates.

Criteria for Recommendations

1. Available testing capacity
 2. Uniqueness of structure or source
 3. Known or predicted biologic activity of interest
 4. Previous performance in screens (e.g., as crude or partially purified product)
 5. Relevant other properties (e.g., opportunistic anti-infective; immunostimulatory)
-

Table 18-4

Responsibilities of DTP Biologic Evaluation Committee: Decision Point (I-B)

1. Recommend and prioritize active drug candidates for presentation to Decision Network Committee (DNC)
2. Recommend additional testing as appropriate

Criteria for Recommendations

1. Appropriate in vitro antitumor and/or antiviral activity and/or other relevant bioactivity
 2. Relative potency or other potentially favorable characteristics
-

priorities are likewise based pre- dominantly upon biologic and structural novelty, as well as other potentially favorable pharmacologic characteristics (Table 18-4). At DP II-A, in vivo preclinical studies mayor may not have yet been undertaken and are not considered obligatory at this point. On an annual basis it is anticipated that the BEC will bring to the Decision Network Committee a maximum of 100 to 200 of the highest priority new leads for further consideration and selection and for prioritization of its subsets for stage A development.

Development Phase

Decision Network Committee

The Decision Network Committee (DNC) functions at three critical decision points, DP II-A, II-B, and III, within the preclinical development phase (see Fig. 18-2). The regular DNC membership includes the

Table 18-5

Responsibilities of DCT Decision Network Committee: Decision Point (II-A)

-
1. Recommend and prioritize new candidates for stage A development
 - 2 Recommend other supplementary studies as appropriate

Criteria for Recommendations:

1. Appropriate antitumor and/or antiviral activity and/or other relevant bioactivity
 2. Uniqueness of structure and/or biologic properties
 3. Availability of resources for further preclinical development
 4. Consideration of potential options for current and/or
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DCT director, the DCT associate directors, the chairpersons of the AIC, BEC, DCT operating committee, and selected other senior DCT, NCI, and NIAID staff. Additional ad hoc members with specialized expertise may be appointed by the DNC chairman whenever appropriate for specific DNC meetings. At OP II-A, the DNC is responsible for selecting and prioritizing new drug candidates for stage A development (see Fig. 18-2). Generally, in accord with current available resources, a maximum of only 10 to 20 agents will be selected annually for stage A. As indicated in Table 18-5, the major criteria considered are similar to those for earlier stages- However, at this point there are additional considerations of potential options for current and/or future industrial participation in development.

It is the policy of the program to encourage maximum industrial participation as soon as possible in the development of a promising new agent. This maintains maximum flexibility and responsiveness of the program to facilitate the development of the most promising agents at any stage, as well as to accommodate the development of other potential agents that may be relative "orphans" (i.e., have no patent positions) with respect to industrial or other interests in development. The resources of the program are finite and the expenses for development escalate rapidly as an agent proceeds to the later stages. Direct contract costs for preclinical development of an agent through stages A and B may be generally expected to average a million or more dollars.

At decision point II-B (Table 18-6; see Fig. 18-2), a positive recommendation by the DNC for stage B development generally is based upon the view that the available biologic information on the agent is of sufficient interest and merit to justify eventual clinical testing. The decision and the priority assigned therewith must also

take into account the limits of the available resources for stage B development; currently the program can accommodate four to six new drugs per year through stage B. Decision point III is confronted by the DNC at the completion of stage B development and prior to filing of an INDA. Chief concerns of the DNC at this point are to ensure that the appropriate regulatory, safety, and other issues relevant to the prudent design and execution of the clinical trials have been adequately addressed. Approval of a drug by the DNC at decision point III is followed by a period of intensive interaction between NIH preclinical and clinical program staff for preparation of the INDA. Subsequent approval of the drug by the FDA for clinical testing provides the final impetus for entry

into the NIH extramural clinical trials network and/or the NIH intramural clinical programs.

Operating Committee

The Operating Committee (OC) does not have primary responsibilities at any of the specific decision points discussed above. Nonetheless it plays a very important role (Table 18-7) in expediting and monitoring the flow of compounds through the various stages of development encompassed within the DTP. The OC is comprised of senior DTP staff predominantly representing the development area. The committee is responsible for organizing the DNC meeting agenda, as well as for ensuring implementation of its recommendations. DNC agenda candidates are provided to the chairperson of the OC from the AIC (re: "bypass" candidates) and the BEC (re: actives identified from the screens). The OC chairperson also serves as the contact point for inquiries for consideration of assistance in specific, limited aspects of development.

Table 18-6

*Responsibilities of DCT Decision Network Committee:
Decision Point (II-B)*

1. Recommend and prioritize new candidates for stage B development
2. Recommend other supplementary studies as appropriate

Criteria for Recommendations

1. Major technical, time, and cost considerations resolved
2. Peak in vivo drug concentrations in plasma and/or other appropriate fluids or tissues (e.g., in cerebrospinal fluid for AIDS.antiviral agents) at MTD in at least one animal species are equal to or greater than those known to give positive in vitro antitumor and/or antiviral activity
3. Other potentially favorable characteristics (e.g., activity in in vivo model; oral bioavailability)
4. Consideration of potential options for current and/or

Table 18-7

*Responsibilities of DCT Decision Network Committee:
Decision Point (III)*

1. Recommend and prioritize drug candidates for INDA filing and clinical evaluation
2. Recommend other supplementary studies as appropriate

Criteria for Recommendations

1. Safe starting dose for humans predicted from animal toxicology studies
 2. Normal tissue toxicity for humans estimated from animal toxicology studies
 3. Drug pharmacokinetic studies in animals allow optimal design of clinical studies in humans
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SUMMARY AND PERSPECTIVE

There has been an urgent need for an adequate national program to which scientists from the broadest possible spectrum of the entire research community can submit materials for rapid evaluation for anti-HIV activity. The need has been similarly urgent for a national program to support the expeditious preclinical development of the most promising new drug candidates through any or all the stages of preclinical development as required. The resource described herein is intended to help provide a focus for the best talents and resources from government, academia, and industry to work effectively in concert toward the rapid discovery and development of new anti-HIV drug candidates. This resource will complement and substantially enrich the expanded AIDS NCDDGs (multi-disciplinary, multi-institutional) and other drug discovery efforts based on rational design and/or screening, located throughout the country-indeed, worldwide. These synergistic approaches to new anti-AIDS drug discovery might also prove to have important ramifications for additional disease areas such as cancer, arthritis, multiple sclerosis, and others for which slow-growing viruses with long incubation times are implicated.

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