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New Antitumor Drugs in Development

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The National Cancer Institute: Cancer Drug Discovery and Development Program

Michael R. Grever, Saul A. Schepartz, and Bruce A. Chabner

The discovery and development of novel therapeutic products for the treatment of malignancy is vitally important to those physicians responsible for the management of cancer patients. A description of the ongoing efforts at the National Cancer Institute (NCI) is intended to provide insight into those complex processes necessary to accomplish this mission. An update on the NCI's revised cancer screen is accompanied by a brief summary of those new agents scheduled to be entered into clinical investigation in the near future. The tremendous potential advantages and challenges associated with the use of a molecular approach to cancer drug design are discussed. Despite the differences of opinion that may exist regarding the optimal strategies for accomplishing the mission, there is no disagreement regarding the importance of the effort to find effective new therapies for cancer patients.

ALTHOUGH THE DISCOVERY of effective anticancer agents has occurred in academic centers and industry, the National Cancer Institute (NCI) has played a pivotal role in cancer drug discovery and development.[1-3] In 1955, the Cancer Chemotherapy National Service Center (CCNSC) at the NCI was established.[1] Since the creation of this national resource, the NCI has been involved with either the discovery or developmental tasks that were essential for the approval of the majority of commercially available anticancer agents.

The primary responsibility of the NCI's preclinical drug evaluation program was intended to focus on the treatment of malignancy. However, the public health emergency that emerged over the past decade from the human immunodeficiency virus (HIV) necessitated the involvement of the NCI in the discovery and development of effective therapeutic products to treat patients with acquired immunodeficiency syndrome (AIDS). Although substantial changes in the organizational structure occurred, many of the preclinical functions (ie, pharmacology, toxicology, analytical chemistry, formulation research, etc.) are essentially identical for both programs. Thus, resources already in existence for cancer drug discovery and development were rapidly mobilized in response to the critical public health issues associated with HIV-induced illness. The National Institute of Allergy and Infectious Diseases (NIAID) also maintains a preclinical drug evaluation program that works closely with the NCI to address this major crisis.

The NCI will remain committed to the arduous tasks of drug discovery and development because a meaningful extension of high-quality life for patients with either cancer or AIDS hinges on continued success in these areas. The propensity for malignancies to develop in patients receiving effective treatment for AIDS underscores the necessity for the NCI to be integrally involved in the search for novel therapeutic agents for both fatal diseases. The Developmental Therapeutics Program (DTP) of the Division of Cancer Treatment (DCT) at the NCI is responsible for those preclinical activities necessary for both cancer and AIDS drug discovery and development. It is important to emphasize that promising drugs may be submitted to the program for consideration at virtually any stage in development in order to maximally use the preclinical and clinical resources of the NCI. This willingness to cooperate with industry is reflected in the growing number of Investigational New Drug Applications (INDs) being filed in recent years, many of these representing cooperative drug development efforts with industry. The purpose of this article is to describe the current structure and functional operation of this important preclinical program.

OVERVIEW OF NCI CANCER DRUG DISCOVERY AND DEVELOPMENTAL EFFORTS

The actual preclinical responsibilities and tasks of the DTP are accomplished through the

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use of intramural research efforts and extramural resources involving diverse mechanisms (eg, contracts, grants, cooperative agreements). There are five intramural laboratories and nine extramural branches within the DTP that bring agents from the point of discovery to clinical trial (Table 1). Although many of the research functions are conducted within a specific laboratory or branch, the majority of the projects require an interdisciplinary collaboration between these well-defined administrative units. The basic preclinical drug discovery and developmental tasks are summarized in Table 2.

Over the past 2 years, an emphasis has been placed on the use of agent-specific working groups to usher each agent over the many preclinical hurdles in the drug evaluation "pipeline." This general approach to project management directed at a specific therapeutic product has been successfully used by the pharmaceutical industry. In the past at the NCI, specific agents were handed on to individual administrative units as each defined task was completed. This change in product management will expedite the complex processes encountered with drug development.

Although various approaches could be used to describe the NCI's drug discovery and developmental efforts, the schematic diagram depicted in Fig 1 outlines the current functional components of the DTP. The procurement of defined chemical entities and crude natural products for testing in either the NCI's cancer screen or the antiviral screen is coordinated through two extramural branches (ie, Drug Synthesis and Chemistry Branch and the Natural Products Branch). Vigorous programs of acquisition are supported to search for novel chemical structures or natural products to be tested in the in vitro screens. Substantial effort has been made to seek submissions from academic institutions and industrial sources. The advent of the in vitro screens has made the requirement for large quantities of material for the initial submission less important. In the past, the cancer screen used in vivo models for the initial antitumor evaluation and thus required submission of gram quantities of material. In contrast, the current screen can provide an initial evaluation using an amount in the range of 25 to 50 mg. This microacquisition approach has enabled individual chemists working with limited resources to contribute novel chemical structures for evaluation and has altered the profile of the suppliers to the program as shown in Fig 2. Whereas past acquisition of agents for evaluation was somewhat limited to those suppliers with resources for making large quantities of new chemicals, the current approach should optimize the chemical diversity of compounds submitted to the program.

Table 1. Developmental Therapeutics Program of the National Cancer Institute Administrative Units

Intramural Laboratories
Biological chemistry
Molecular pharmacology
Medicinal chemistry
Drug discovery research and development
Pharmaceutical chemistry
Extramural Branches
Drug synthesis and chemistry
Biological testing
Natural products
Antiviral evaluation
Pharmacology
Toxicology
Pharmaceutical resources
Information technology
Grants and contracts operations

Table 2. National Cancer Institute Preclinical Program

Drug Discovery: Functions	Drug Development: Functions
Acquisition	In vivo testing
Defined chemical entities	Evaluate therapeutic index
Crude natural products	Optimize dose/route/schedule
Chemical modification:	
Lead optimization	Scale-up bulk drug production
Retest modified structures	Formulation research and production
Examine structure-activity relationship	Pharmacological studies
	Toxicological evaluation
	File investigational new drug application (IND)*

*This task performed by CTEP, DCT, and NCI.

Acquisition

The chemical acquisition program is aided by an extramural contractor with an annual target to procure approximately 10,000 new chemical structures that have not been previously exam-

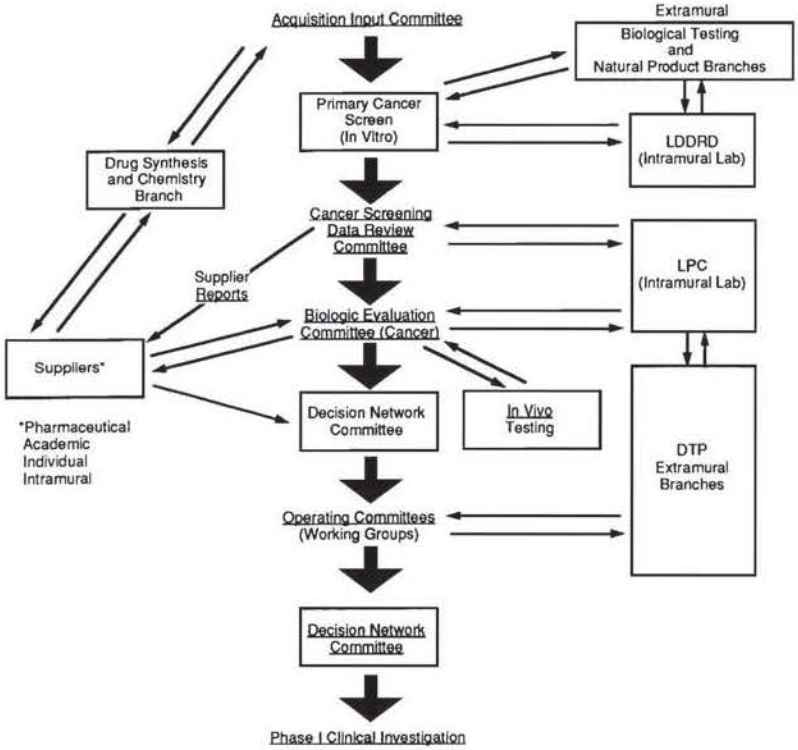

Fig 1. Preclinical cancer drug discovery and development at the NCI. This schematic representation of the major components of the preclinical program outlines the overall flow that agents traverse at the NCI during the processes involved with drug discovery and development. Suppliers may enter agents into this system at any stage in their development in order to use the preclinical and clinical resources of the NCI.

ined by the NCI. A major stipulation for submission of an agent is disclosure of the chemical structure to permit the NCI staff to verify that the compound has not been previously submitted by another supplier. After testing, the NCI will provide a full report of the results from the in vitro assay(s) for anticancer and/or anti-HIV activity. In general, suppliers are encouraged to permit compound testing in both NCI screens (ie, the anticancer screen and the anti-HIV screen).[4,5] This testing is performed at no cost to the supplier, and the results are maintained in strict confidence.

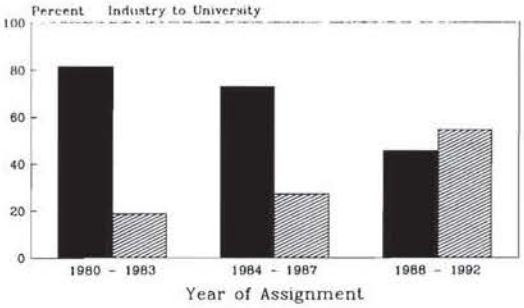

Fig 2. Agents acquired for testing by the NCI: Industry versus university. Over the past decade, there has been a change in the relative contribution of various suppliers of chemical agents for testing in the NCI cancer screen. The previous cancer drug screens used in vivo testing procedures that required the submission of gram quantities of prospective agents for initial testing. Since the NCI's development of the current in vitro screening procedures permits an initial analysis of antitumor activity to be made with much smaller amounts of material, the diversity of chemicals acquired for testing can now be increased by extending the opportunity for compound submission to many suppliers with limited resources for large-scale production. ■, industry; and ▨, university.

The NCI has recognized that natural products represent a tremendous potential resource for cancer drug discovery. Many of the currently used anticancer agents are natural products or are derived from leads discovered from natural sources.[6] The complex chemical structures that are found within nature far exceed the imagination and synthetic capabilities of medicinal chemists. The chemical entities that are discovered to have potential medicinal value may serve either as a drug candidate or as a critically important lead for structural modification. Thus, careful assessment of the chemical repository existing within nature provides substantial opportunity to secure novel drug candidates.

Collection contractors for the NCI have made a concerted effort to use native expertise to

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