Division of Extramural Activities

Report of the National Cancer Institute Developmental Therapeutics Program Review Group Report

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EXECUTIVE SUMMARY

The formation of the Developmental Therapeutics Program (DTP) by the National Cancer Institute (NCI) 43 years ago was a crucial step in initiating the search for drugs useful in the treatment of cancer. This occurred at a time when there were essentially no major programs whose focus was on drug development in the area of cancer therapeutics. The program has been held in high esteem throughout the world and has made major contributions to the discovery and development of cancer chemotherapeutic agents. In fact, many of the drugs used in the clinic today came through this program.

In the ensuing years, interest in cancer therapeutics has burgeoned with academic laboratories, cancer centers, and pharmaceutical and biotechnology companies actively participating in the search for new cancer drugs. One incentive for this activity relates to the explosion of knowledge in cancer biology and the availability of new molecular targets for drug development. At the same time, it has become abundantly clear that cancer represents a number of different diseases and that the workings of each cancer cell are complex and devious. To date, a reliable and effective formula for searching for, synthesizing, and screening new drugs remains elusive. In 1997, the Director of NCI formed the Developmental Therapeutics Review Group and charged it with the task of defining the future of NCI with respect to the discovery and development of new chemical and biological therapies for the treatment

of cancer.

Over the course of a year, the Review Group worked to develop a series of recommendations that it believes will enhance the ability to discover new and useful antitumor drugs during the next decade. The goal is to foster the discovery of drugs which are not simply antiproliferative agents, but rather have unique and novel mechanisms of action. To attain this goal, the Review Group adopted four recommendations that will result in far-reaching and major changes in the activities of the DTP.

Allocation of Funds and Roles of the Extramural and Intramural Programs

The Review Group strongly recommends that the in-house portion of the DTP budget be limited to approximately 15 percent of the total budget. An important role of DTP should be to assume a leadership position in informatics to facilitate the development of cancer therapeutics. It should assume responsibility for coordinating and disseminating information through an expansion of its current operations. Resources such as the natural product repositories, select chemical libraries, engineered cell lines, hybridization assay technology, standardized reagents for cancer immunotherapy, and information databases useful in the determination of protein structures, should be made available by DTP to qualified investigators. At the present time there is an insufficient flow of new information to cancer investigators working in the area of drug development. DTP should play a leadership role in facilitating such information flow. Extramural funding should be used to support cooperative groups such as the National Cooperative Drug Discovery Groups, National Natural Products Discovery Groups, contracts, and Centers of Excellence. Such centers should be sited in those areas of the country where there is a population of academic scientists who have the relevant expertise and the ability to collaborate with colleagues in government laboratories, and in the biotechnology and pharmaceutical industries. The goal is to assure that nationwide the most talented and best-trained scientists are working on cancer therapeutics.

Monitoring and Oversight of the DTP Research Portfolio

The Review Committee was enthusiastic about adopting a plan that would enhance dramatically the ability of DTP to make decisions concerning its resource allocations through the development of a mechanism to continuously monitor DTP activities. A major goal of this plan would be to create a discovery and development process for any drug target or drug candidate by bringing together and coordinating distinct proposals from different laboratories or institutions. This ability becomes particularly important when considering the multidisciplinary nature of drug development and the necessity of collaborations and coordination if progress is to be made in this area. An example of a glaring lack of strength at DTP, as well as in many academic laboratories interested in drug development, is in medicinal chemistry, an area that is crucial to modern drug discovery and development. By coordinating different proposals in different areas of research, for example in medicinal chemistry and

mechanisms of action, progress in drug development would be enhanced.

The Review Group believes that NCI must have a flexible and rapid response mechanism in place to deal with changing research objectives and resource requirements that arise on a month-to-month basis. This could be accomplished by creating a committee of scientists (5 to 8) chosen from among the leadership of DTP, academia, and industry. This committee would be charged with the mandate to evaluate and fund or invest contract resources in projects that are submitted to DTP through the extramural program or proposed by in-house DTP personnel. The budget for this committee should be no less than $50 million that should come from the existing DTP budget. The Review Group felt that a lower budget would not give the committee a reasonable chance of demonstrating success.

The proposed committee would prioritize the distribution of resources available to DTP and be responsible for the discovery of novel therapeutics and novel drug discovery technologies as well as the development of candidate therapeutics. This committee would meet on a regular basis, at least four times a year, and would be empowered to issue Requests for Applications (RFAs), create Task-Order Agreements, or conclude contracts. The committee would further be empowered to recommend use of additional consultants to advise its membership on the quality of the scientific proposals it receives. However, the committee would retain the right to dispense funding to any proposals that it deemed useful whenever such proposals came to the attention of the committee. This approach would involve a "rolling approval" process for submitted proposals rather than the current system of joint review of all proposals at a single meeting.

The proposed committee would also have the authority to match scientists from different institutions that might possess complementary technologies and to encourage these individuals to work together by offering them seed money to conduct joint investigations. The committee would also be responsible for the composition of DTP and could dictate that the DTP scientific staff be changed over time to include, for example, more pharmacologists, chemists, or drug metabolism personnel, so as to open up any bottle necks in the drug development pipeline that may occur. Last, the committee would be empowered to recommend tenure and promotions to DTP staff based on their contributions to drug discovery and development projects, irrespective of a scientist's publication record. In many ways, the committee would function as an independent entity within NCI and would be responsible for its decisions solely to the NCI Director. In turn, the Director would be responsible for appointing the members of the committee and for evaluating the productivity of DTP under this new format.

The Decision Network Committee

There was agreement among the Review Group that the NCI Decision Network Committee, responsible for prioritizing drugs for clinical development, was not functioning properly. The membership of this committee should be expanded to include representatives of academia, including cancer centers, as well as NCI staff. A

majority of the Review Committee believed that there should be a single Decision Network Committee with broad representation, including outstanding scientists in the area of biologics. Depending on the drugs being introduced at each meeting, scientists with expertise in specific areas should be invited to participate in the discussions. With a single broad-based Decision Network Committee, all drugs, including biologics, should be reviewed and compared in a fair manner. In opposition, however, the Review Group's Subcommittee on Biologics believed strongly that biologics should be analyzed for feasibility and prioritized by its own Biological Resources Branch (BRB) advisory board, and not by the Decision Network Committee.

Special Role of the Developmental Therapeutics Program Related to Drug Screening

The Review Group recommended four activities related to drug screening in which the DTP role is appropriate and relevant: 1) a focused screening program for active compounds using assays for which it has developed expertise and capacity; 2) providing public access to its repository of compounds, research tools, and information databases; 3) working with the government, academic, and industrial communities to develop, evaluate, and deploy new assays in both the internal and external scientific communities; and 4) fostering a more collaborative approach to screening by serving as a matchmaker between chemists and biologists for the analysis of novel agents.

The Review Group recognizes that some of the assays will be conducted by DTP in-house but most will be conducted extramurally at sites nationwide where relevant expertise exists. In this context, NCI should serve as a facilitator of external scientific study in these areas. To achieve these goals, the Review Group recommends that NCI establish an ongoing review mechanism (relying on internal and external expertise) to continuously evaluate the status of screening assays and advise the NCI Director on the best use of resources in this area.

Major Recommendations of the Review Group Subcommittees

The Review Group was divided into five subcommittees, each of which addressed a specific topic in detail. The groups were: the Subcommittee on Small Molecule Diversity and Screening Technology; the Subcommittee on Structural Inventory of Potential Drug Targets; the Subcommittee on Animal Models; the Subcommittee on Pharmacology and Toxicology, and Formulation; and the Subcommittee on Biologics. The full report is organized around the deliberations of the subcommittees; each chapter contains a series of recommendations that are programmatic in nature and will result in changes in existing programs. The entire Review Group discussed all of the recommendations. Detailed recommendations appear in the full report; major recommendations are as follows.

- NCI should support a chemical diversity program with the explicit goal of finding small molecules that can manipulate the function of all proteins or processes relevant to cancer.

- NCI should undertake a major new interdisciplinary initiative to acquire structural information on cellular targets that are potentially relevant to cancer. This would include establishment of an instrumentation and education resource dedicated to making X-ray crystallography broadly accessible to members of the cancer research community, in addition to vigorous participation in efforts to determine the structure of all proteins encoded in the human genome-alone and in complex with interacting cellular partners-that may be involved in the malignant process.
- NCI should reconfigure its program for screening compounds for anti-tumor activity to ensure responsiveness to changes in science and technology. The current 60-cell-line screen should be reduced to 3 cell lines focused on the identification of lead compounds based on inhibition of cell proliferation. The COMPARE program has been very valuable for identifying drug targets and should be maintained for selected compounds. However, NCI should establish a network of extramural sites that have expertise in the development of new assays to assess the effects of compounds on the biochemical, cell biological, and tissue physiological parameters that govern cancer cell pathogenesis and pathophysiology.
- NCI should establish Centers of Excellence in a variety of scientific areas, for example, pharmacology/toxicology core facilities with the technology in place to do state-of-the-art drug metabolism, pharmacokinetics, and drug absorption studies and simulations. NCI should develop methods to allow more accurate a priori determination of the potential for metabolism and/or toxicity.
- NCI should expand the scope of the Biologic Resources Branch by augmenting the categories of biological reagents that are currently being produced, and developing capabilities for production of recombinant vectors and novel production technologies.

Throughout the Review Group's deliberations there was a continual emphasis on the need for the DTP to be flexible, agile, and responsive to the needs of rapidly changing science and technology. New basic knowledge and technologies must be integrated into the process of discovering and developing anticancer drugs. It is only in this way that the DTP will be able to meet the challenges of drug development in the next decade.

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INTRODUCTION

The development of new drugs for the treatment of cancer is a difficult task, yet the need for anticancer drugs has never been greater. Approximately 8 million Americans alive today have a history of cancer. This year about 1.2 million new cases will be diagnosed. Over half a million Americans will die of cancer this year, more than 1,500 people a day. This number will tend to increase as our population ages. In the United States, cancer is the second leading cause of death-responsible for one out of every

four deaths-exceeded only by heart disease. The financial costs of cancer are staggering at over $107 billion a year.

While prevention is the ideal route to cancer control, there will always be cases of cancer which cannot be prevented and for which aggressive intervention is needed. Drugs that can prevent the initiation of cancer, slow its growth, or stop it altogether, are sorely needed.

In 1955, Congress recognized the need for public investment in the discovery and development of anti-neoplastic agents. The Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) was established to support programs necessary for the development of new therapies for cancer. It currently supports programs necessary for:

- the preclinical development of novel therapeutic modalities for cancer (including chemotherapeutic agents, antibodies, and vaccines)
- acquisition, synthesis, and definition of activity in in vitro and in vivo models of cancer and HIV disease; and
- advancement of active agents in preclinical models toward clinical trials by establishing workable pharmaceutical formulation and definition of clinical pharmacology and toxicology.

During the past 43 years, NCI has been involved in the discovery and development of many of the anti-neoplastic agents currently in use. Over that period of time, the program has become an international resource: It has been the largest such public investment in the world and one that is without parallel in any other therapeutic area. However, full realization of the complexities of the malignant cell and rapid advances in cancer biology and chemistry plus the growth of a large and active biotechnology and pharmaceutical industry have renewed the debate about the suitable role of government in the drug development process. Is NCI investing in the right areas of innovation? Are its drug screening and acquisition programs state-of-the-art and appropriate?

CHARGE TO THE DEVELOPMENTAL THERAPEUTICS REVIEW GROUP

In 1997, the Director of NCI formed the Developmental Therapeutics Review Group (hereafter referred to as the Review Group, or the Group) to consider the role of NCI in drug development activities. Specifically, the Director asked the Review Group to:

- Evaluate how NCI conducts and facilitates drug discovery and the development processes that turn molecules into drugs suitable for human testing;
- Review comprehensively NCI's major tool for screening and characterizing anti-cancer activity (the 60-cell-line panel);
- Assess NCI's process for compound acquisition;

- Evaluate natural products discovery;
- Examine the various mechanisms for investigator-initiated discovery such as the National Cooperative Drug Discovery Groups and the National Natural Product Drug Discovery Groups.
- Review the contract activities by which lead improvement, bulk synthesis, toxicology, and pharmacology are accomplished.
- Examine the production facilities in Frederick, Maryland, including the fermentation plant and the monoclonal antibody and recombinant protein facility.
- Assess the role and outcomes of the Decision Network; and
- Evaluate how well NCI's development capabilities serve the needs of intramural scientists who are trying to bring new therapies to the clinic.

More generally, the Review Group was asked to review the status of NCI's drug development activities in a contemporary and futuristic context. Given the level of private activity in the development of new anticancer drugs how can NCI assist in the translation of biological and chemical discovery into agents with potential therapeutic importance? What should be NCI's involvement in screening? And is it appropriate to continue searching for natural products as anti-neoplastic agents?

To organize its review, the Group formed subcommittees in the following areas: 1) small molecule diversity and screening technology; 2) structural inventory of potential drug targets; 3) animal models; 4) pharmacology, toxicology, and formulation; and 5) biologics (see Appendix A for membership and meeting dates). This report is organized around those themes.

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SMALL MOLECULE DIVERSITY AND SCREENING TECHNOLOGY

INTRODUCTION

Recent scientific progress in understanding signaling pathways and cell cycle regulation has provided a wealth of potential new targets for anti-cancer drugs. Targeting the signaling pathways involved in cancer cell growth may make it possible to treat cancer with far fewer side effects than are caused by conventional cytotoxic therapies. But in order to exploit these pathways fully, researchers must be able to find small molecules that can manipulate protein function and protein-protein interactions.

The traditional source of anticancer agents, as well as other drugs, has been natural products obtained from living organisms and identified through biological assays. To date, natural products have proven to be the most effective small molecules in terms of their ability to alter the function of proteins relevant to cancer. The DTP plays a special role in the collection of natural products both because of its extensive experience in organizing collection efforts and its long history of ensuring the

intellectual property rights of the country from which a product originates. By continuing the discovery of new anticancer natural products and by applying the insights derived from a study of these natural products to the design and construction of libraries of synthetic molecules, it should be possible to develop new anti-cancer agents.

A general method for synthesizing small-molecule ligands that modulate protein functions would be extremely valuable both in cancer research and cancer drug design. Promoting the development of these molecules and exploiting their properties should be high priorities for NCI. With a focused effort, NCI should be able to facilitate the development of methods that will make the discovery of such ligands routine and to apply these methods to the discovery of ligands that modulate processes relevant to cancer.

It is important to note, however, that improved screening methods are needed to identify lead compounds. Each source will require its own effective means of screening. In addition, because new sources of compounds will yield large numbers of new chemical entities, new miniaturization and automation techniques will be needed to perform large numbers of assays in a short period. NCI can play a vital role in the development of high throughput "smart" assays, compatible with the new techniques for small molecule production and capable of detecting molecules that can regulate the newly discovered pathways critical to the etiology and maintenance of cancerous states.

In its deliberations, the Review Group assessed optimal strategies for incorporating advances in molecular diversity and screening into NCI programs.

MOLECULAR DIVERSITY

The Use of Small Molecules in Studying and Treating Cancer

Chemotherapy is an essential component in the treatment of cancer today. But current drugs are both toxic and ineffective against many common cancers. More effective drugs could be developed through two different approaches. One would be to develop improved cytotoxic agents that lack major toxicities of existing agents but continue to kill cancer cells by related mechanisms. An example would be an anti-mitotic agent that lacks the neurotoxicity of Taxol and the vinca alkaloids. The second approach, perhaps more difficult, but ultimately more effective, would be to develop agents that directly target the causes of cancer, such as the uncontrolled activation (mitogenic) or malfunctioning inactivation (checkpoint) pathways that initiate the disease. Both approaches require small molecules that specifically inhibit (or activate) novel target proteins.

Small molecules that specifically target new proteins can also serve as tools for basic cancer biology research. To understand a protein's function in vivo, we must be able

to either inhibit it or activate it, preferably both, and preferably at controlled times. Until now, the most successful approach has been to mutate the gene encoding the protein of interest. But it is increasingly clear that cell-permeable, small molecules that bind to the target protein can complement, and possibly even replace, genetics.

Like mutations, small molecule ligands can either inactivate the protein (examples include staurosporine binding to protein kinase C, or trapoxin binding to the chromatin remodeling enzyme histone deacetylase) or activate it. Activation can result from an allosteric change (e.g., small molecule ligands binding to nuclear hormone receptors), the formation of a new binding site leading to the gain of a new function (e.g., when cyclosporin A binds to cyclophilin, a binding site for calcineurin is formed), or a ligand-induced change in protein localization (e.g., the use of FK1012 to co-localize fusion proteins). Two different routes will likely obtain ligands for all of these functions: biosynthesis or chemical synthesis.

MOLECULAR DIVERSITY FROM BIOSYNTHETIC PATHWAYS

The traditional source of anticancer agents has been natural products that were obtained from the producing organism, animal or plant, and identified through biological assays. NCI has traditionally played a strong role in this type of research, and there are still persuasive arguments for continuing these efforts either directly or through collaborations. Because biological diversity generates chemical diversity, these efforts should be broadly based.

Now is our last best chance to preserve at least a portion of the earth's biological diversity. The biological diversity that can be directly accessed is diminishing, and the habitats with the greatest diversity, such as tropical rain forests and coral reefs, are diminishing the most rapidly. Along with vanishing habitats, traditional knowledge about the uses of those habitats is also disappearing. In addition, the rate of species extinction is likely greater than is generally appreciated. This is because the disappearance of one species, such as a tropical plant, also leads to the extinction of mutualistic species such as insects and specialized microorganisms such as viruses and endophytic fungi. Forces that include increased development, population pressure, and, possibly, global climate change is likely to accelerate the rate of species extinction.

Ironically, the impediments to collecting have increased along with the urgency of doing so. Individual investigators face enormous difficulties in ensuring the intellectual property rights of all participating parties. NCI, however, through a tradition of pioneering mutually acceptable arrangements and its long experience in collecting, can facilitate the collection process.

Advances in our ability to understand and control biosynthetic pathways in the laboratory have opened exciting new prospects for chemical diversity from

biosynthesis. Entire biosynthetic operons have been moved from one producing organism to another, and the modular nature of many biosynthetic pathways has been analyzed in detail. We can already modify the final products of biosynthesis by manipulating genetic information. For example, we can produce a novel variant of erythromycin by disabling some biosynthetic steps and providing an "unnatural" starting material. Plans to construct combinatorial biosynthetic pathways that exploit the modular nature of known pathways are well advanced and could potentially lead to large libraries of biosynthetic products ("unnatural natural products").

Another exciting prospect for using the genetic information of biosynthetic pathways to provide molecular diversity is direct cloning of soil DNA. Several groups have investigated the DNA content of soil and concluded that traditional culturing methods capture roughly 0.1 percent of the available genetic pool. While some groups have focused on alternative culturing methods, others have begun to directly extract soil DNA, chop it into fragments likely to catch entire biosynthetic pathways, and introduce these new genes into more readily cultured organisms. The prospect of large clone banks representing the "metagenome" available from soil microorganisms is a potential outcome.

MOLECULAR DIVERSITY THROUGH CHEMICAL SYNTHESIS

It seems likely that synthetic molecules that mimic natural products are most likely to target proteins successfully and that attempts to design small molecules that target proteins will be most successful if the lessons of natural product chemistry are applied. This is because known natural products epitomize the properties that define optimal ligands: high affinity, selective binding to proteins, and promotion or disruption of specific protein-protein interactions.

Today, modern asymmetric synthesis can be used to synthesize virtually any naturally occurring substance, albeit in multi-step processes which often require years of focused effort to develop. In the future, large libraries of natural product-like compounds with rigid frameworks and diverse substituent groups will likely be synthesized. This will be accomplished by applying the new synthetic techniques in the context of new methods to combine synthetic building blocks combinatorially (see below).

A general method for synthesizing small-molecule ligands that modulate protein functions would be extremely valuable both in cancer research and in cancer drug design. We believe that it is now possible to develop a method to make the discovery of such ligands routine and apply that method to the discovery of cell-permeable small molecules that manipulate protein functions relevant to cancer.

LEARNING FROM NATURAL PRODUCTS

It should be possible to apply the lessons of natural product chemistry to the development of new anti-cancer agents. This could be done by employing the insights derived from a study of natural products known to bind to proteins to the design and construction of libraries of synthetic molecules. Although we do not fully understand the principles that govern the interaction between small molecules and proteins, several observations can be made that should be used to guide library design. It is an important priority to continue to try to more fully understand the processes and mechanisms and to explore additional principles that govern interactions between small molecules and proteins.

A major proportion of the known biologically active natural products is relatively large structures with a high degree of stereochemical complexity. A common theme among the molecules is a spatially well defined presentation of functionality, usually over large distances. Many natural products are therefore relatively rigid structures (e.g., Taxol, which interacts with and binds to microtubules, has a very rigid structure). Natural products bearing large, acyclic arrays, such as the polyketides, also have relatively rigid structures due to minimizing syn-pentane interactions and allylic strain. It is easy to rationalize the idea that rigid molecules should be better at binding to proteins; more rigid molecules will have fewer degrees of freedom, so the loss of entropy upon binding to a large molecule such as a protein will be reduced. It has also been learned from nature that, to bind large and often shallow protein surfaces, large chemical structures will be required.

Charge is often used sparingly in natural products (e.g., for alkaloid molecules such as aspidospermine, often one or two nitrogen atoms provide most of the charge in the form of an ammonium ion at physiological pH). If a natural product does possess a large number of charged functionalities, it is often balanced with a large proportion of hydrophobicity. Such is the case for amphotericin B, which displays polyhydroxylated and polyeneyl surfaces. This balancing of charge with hydrophobicity may be important for cell permeability, and it may be particularly important for targeting small hydrophobic pockets on protein surfaces

The known examples of natural product-protein interactions provide some insight into the requirement of size, as well as functionality, for the design of libraries that will interact with diverse protein binding surfaces. Most, if not all of the libraries that have been constructed have been relatively small, focused structures. In the future, it will be important to construct libraries of unprecedented size and complexity, using the power of modern asymmetric synthesis. Natural-product-like libraries will be far more likely to contain protein ligands than the libraries built to date.

The Use of Synthetic Chemical Libraries to Mimic the Evolution of Natural Products

Organic synthesis has allowed us to access complex molecular structures on demand. Until recently, these molecules were assembled in a "one reaction per vessel" process,

followed by further optimization of the structure. The new approach of synthesizing collections, or libraries, of compounds simultaneously has revolutionized our ability to construct large numbers of related molecules rapidly.

There are currently two methods for the construction of small molecule libraries. The first is parallel synthesis, a miniaturized version of the traditional "one reaction per vessel" method using a multi-vessel apparatus and robotics. Most libraries in the pharmaceutical industry have been constructed with this technique and have been limited in size and diversity. The library members are typically heavily biased to be similar to a well-known "pharmacophore." These libraries often yield large quantities (over 100 mg) of small heterocyclic molecules devoid of stereochemistry.

The second method has similarities, in principle, to methods seen in nature. The synthesis of polyketides such as rapamycin and FK506 involves an iterative sequence that includes sequential Claisen condensations, ketone reductions, dehydrations, and enone reductions. The enzyme modules that perform these functions appear to have been shuffled throughout evolution by genetic recombination. Over time, this shuffling can be viewed as having produced a library of related molecules. The molecules that confer a growth advantage on their host organism are favored, and the organisms that express them tend to form the basis for the next round of gene shuffling. The "split-pool" synthesis method, which involves simply the mechanical intervention of pooling and then splitting flasks during key coupling reactions of multi-step syntheses, does not generate diversity by gene shuffling. It does, however, subject diverse monomers to iterative chemical reactions in an order defined by the user. Split-pool synthesis allows for the convenient synthesis of large libraries of compounds (>one million) in a small number of chemical steps.

The split-pool method is promising, but it is not yet capable of generating compounds of complex natural-product-like structures. It typically yields only minute quantities for use in the early stage of biological analysis, thus making it necessary to develop miniaturized screening methods. (After finding an interesting compound, however, large quantities of the compound are generally available via re-synthesis on the solid phase.)

Although the total syntheses of complex natural products such as rapamycin, Taxol, and calicheamicin have been accomplished, there remains a significant gap between the synthetic strategies that have been used in these projects and the current state of the art in library synthesis, especially split-pool synthesis. However, some strides toward the synthesis of such libraries have been made, and through these efforts, it has become apparent that the library synthesis strategies will have to diverge from those traditionally used to synthesize natural products. Solid phase reactions will play a key role during the coupling steps (where pooling and splitting of reaction flasks occurs), yet traditional solution phase reactions will be required to efficiently prepare the key building blocks of such syntheses. Linkers will be required that are compatible with modern reaction processes, yet that will allow the controlled release of synthetic molecules into miniaturized assay systems. Finally, improved public domain encoding

strategies will be required.

ASSAYING THE NEW MOLECULES

The Need for Nanoscale, High-Throughput Assays

Conventional screening in the pharmaceutical industry is generally performed using automated systems that conduct analyses in a 96-well plate format. Small molecules are added in the form of stock solutions, which are made using relatively large amounts of compound stored in vials. This approach has been very useful for screening natural product libraries and synthetic libraries of limited complexity. It is expensive, however, and the high costs (in both money and space) for consumables and robotics tend to preclude its application in academic laboratories. Also, the method is neither rapid nor sensitive enough to screen the million-member libraries that will be constructed using solid phase split-pool synthesis.

Screening Methods Based on Small-Molecule-Dependent Genetic Selections and on the Use of Other Engineered Cell Lines

As previously mentioned, targeting signaling pathways involved in cancer cell growth might make it possible to treat cancer with far fewer side effects than conventional cytotoxic therapies. Finding drugs that block specific protein-protein interactions is a particularly important goal. Signaling pathways function by virtue of a series of such interactions, and disrupting them would be a powerful new approach to cancer therapy. Improved screening methods are needed to identify lead compounds.

Traditionally, the main approach to finding inhibitors of a specific protein, or of a specific protein-protein interaction, has been to purify or express the relevant proteins, and then screen for small molecule inhibitors using pure proteins *in vitro*. This proven approach has generated many useful drugs. However, pure protein assays have the disadvantage that they do not require the small molecule to manifest its effect in the environment of the living cell, with all of its defense systems and alternative targets.

In contrast, cell-based assays do require the small molecule to act in an environment that is relatively similar to the environment that will be experienced by the small molecule during its experimental or therapeutic use. These assays are thus more likely to generate useful drugs. In the past, however, cell-based assays have tended to be restricted to specific phenotypic effects inherent to a given cell line. There is an increasing interest in the pharmaceutical industry in the genetic engineering of cells to allow the assaying of specific protein function in live cells. But no successful, general methods for screening for compounds that either bind to a specific protein inside a cell, or disrupt a specific protein-protein interaction have yet been found.

It is easy to list the features one would desire from such assays: the target proteins should be introduced into the cell as cDNAs; the assays should be general for any

protein or protein interaction; and the assays should be robust and suited to high throughput screening. For synthetic libraries, the assays should be performed in tiny volumes to allow screening of our large split-pool synthesized libraries.

A more subtle, desirable feature is for the assay to take the form of a genetic selection, so that cells where the small molecule has its specific effect can be detected by some optical means or by a growth advantage. This would allow the small molecule to select out a single cDNA-the cDNA for the protein with which it interacts-from a library. This feature would facilitate identification of the protein targets of small molecules selected from cytotoxicity or cytology-based screens. In the future, it would also allow screens of libraries of compounds against libraries of cDNAs, which would lead to accumulation of large amounts of information about protein-ligand interactions, information that could be significant in cancer research.

USING MOLECULES TO ADVANCE OUR UNDERSTANDING OF CANCER BIOLOGY

Target Identification

When anti-cancer drug leads are discovered by their phenotypic effect on cells, for example in cytotoxicity or cytological assays, it is important to identify their targets. Target identification allows us to preview the likely utility of a new agent. For example, a small molecule that targeted DNA would engender little excitement, as we already have many such compounds. However, a small molecule that targeted topoisomerase would be more interesting, as this is a proven therapeutic target for which fewer drugs exist. By far the most exciting compounds would be those that target new proteins such as proteins involved in signal transduction pathways or proteins other than *a*/ß-tubulin that are involved in mitosis. Target identification also sets the stage for optimizing the affinity of the small-molecule-protein interaction and understanding how the small molecule works structurally and functionally.

Currently, methods for target identification are relatively slow and unreliable. An exception is the NCI multiple cell line screen, which, when employed in conjunction with the program COMPARE, is very useful as an empirical method for identifying molecules that are likely to target DNA or any protein that is the target of a known anti-cancer agent. It can also provide an indication that the effect of a small molecule may be novel. But for small molecules with novel activities, this screen cannot suggest a likely target. Researchers have tended to rely on methods in which the small molecule is used to purify its target from a cell extract, usually in an affinity chromatography format. This method is often effective.

Affinity chromatography suffers from some disadvantages, however. If the protein target is present at low abundance in the cell extract, it can be difficult to detect in the face of more abundant nonspecific binders. Furthermore, protein targets are identified only as gel bands. Identifying the cDNA that encodes the protein found in a particular gel band is much easier than it used to be, but microsequencing is still time-

consuming and expensive, and cloning from microsequence can be difficult if the protein is not already known.

A technique that leads directly from small molecule to cDNA would be preferable. Several techniques in the literature have this capacity in principle. For example, phage display allows the construction of bacteriophage that express a specific protein from a cDNA library on their outer surface. Phages that bind to a small molecule could be selected and amplified. Phage display is an attractive technology, and as it improves from work in other laboratories, it may be adopted for target identification. Currently phage display is limited because the protein of interest may not express well or fold properly on the phage surface, and efforts to express cDNA libraries on the surface of phage have failed. Successful application of the technique has therefore been mostly limited to small proteins and peptides.

Similar problems exist with other target identification systems that rely on protein expression in bacteria. Strategies for identifying small molecule targets directly from cDNA libraries may also be developed based on in vitro expression of cDNA pools in reticulocyte lysate, a technique that has been used successfully to identify kinase substrates, specific protease substrates, and proteins degraded during mitosis.

FUNCTIONAL GENOMICS AND HYBRIDIZATION ARRAY TECHNOLOGY

A more radical approach to target identification is now becoming available from progress made in the area of functional genomics, in particular hybridization array technology. Functional genomics deals with whole genome experiments. Using these new tools, we can study the influence of perturbations on a whole genome, not just an isolated portion. The NCI has invested heavily and wisely in genomics and related technology. The Review Group focused on mechanisms for promoting the growing interface between these technologies and small molecule diversity.

Hybridization arrays allow the measurement of the levels of a large panel of mRNAs in a cell. In yeast, the whole genome can now be used as the panel, and this may become possible in human cells over the next few years. For example, fingerprints of the expression levels of tens of thousands of mRNA species from cell and tissue samples will be routinely available. Panels of such mRNAs from normal cells, drug-resistant cells, and from tissues at different pathologic stages or with differing proliferative stages can be set up for probing and high throughput screening. Through hybridization arrays, we can determine how the levels of specific mRNAs respond to the addition of a small molecule whose target is unknown and compare this to its response to the effects of other small molecules and mutations.

Hybridization array technology is a rapidly developing field and two main strategies appear to be emerging: 1) chemical synthesis of relatively small DNA fragments that probe the entire genome; and 2) spotting technologies. Both have advantages and

disadvantages and it is too early to prescribe the best approach for any given problem.

This technology provides a kind of "digital fingerprint" of the phenotypic effect of a small molecule, and it is expected that small molecules with similar mechanisms of action will provide related fingerprints. For example, all inhibitors of a given signaling pathway should provide a related fingerprint, and all tubulin binders should provide a different fingerprint. This technology will greatly facilitate the process of determining whether the effect of a small molecule is similar to that of a previously known small molecule.

Similarly, the fingerprint of a small molecule that inhibits a certain signaling pathway will be similar to that of a mutation that disrupts the same pathway. By mapping small molecule effects onto mutations, it should be possible to directly identify candidate gene targets. Banks of mutations that systematically cover the genome are already available in yeast and will eventually become available for other organisms, including the mouse and humans.

RECOMMENDATIONS

2-1. NCI should support a chemical diversity program with the explicit goal of finding a small molecule that can manipulate function for all proteins relevant to cancer. This chemical diversity should come from: a) traditional natural products programs; b) chemical synthesis of molecular libraries with stereochemical complexity and conformational rigidity; and c) the small molecule products of genetically accessed and manipulated biosynthetic pathways. The products of chemical diversity programs should be made widely available.

2-2. NCI should maintain the current natural products collection program and expand it into new geographical areas and ecological niches. The current practice of using contractors, International Cooperative Biodiversity Groups, or National Cooperative Natural Product Drug Discovery Groups is appropriate. The Natural Products Repository should remain an open repository, available to other researchers. In addition, NCI should substantially increase efforts to capture natural product, biosynthetic, and synthetic chemical diversity. Using multi-investigator proposals for centers and/or cooperative grants in these efforts is appropriate.

2-3. NCI should make select chemical libraries available to qualified outside investigators for screening. Because format compatibility issues will be an increasing problem as larger libraries are screened against increasing numbers of targets, general formats should be established. Therefore, there must be an increase in funding for natural product, biosynthetic and synthetic chemical diversity by a factor of three-an increase to $30 to $40 million a year. The bulk of the funds should be directed to the extramural program.

2-4. NCI should develop a cell-based assay program with the explicit goal of engineering cell lines to assay cancer-relevant proteins in live cells. These cell lines and the information gathered using them should be widely

available.

a. NCI should foster the development of assays using specially engineered cell lines through funding of multi-investigator or cooperative agreements to assemble appropriate cell panels.

b. NCI must assume responsibility for coordinating and disseminating the information generated by the cell assays through an expansion of its current operations.

c. NCI should assure that engineered cell lines are available to qualified researchers.

2-5. NCI should fund the development and maintenance of cell-based assays and associated technologies at $10 million/year for 10 years with roughly 15 percent spent on internal information processing capabilities and 85 percent spent on external groups.

2-6. NCI should support the establishment of hybridization array technology (DNA chips) in a variety of formats. These formats should include relevant human tumor types (e.g., breast, prostate, lung, and colon) and cell lines to serve as high throughput systems for screening small molecule libraries. A special area of concern is the availability of this technology to qualified investigators.

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STRUCTURAL INVENTORY OF POTENTIAL DRUG TARGETS

INTRODUCTION

Anticancer drugs counter cellular proliferation and tumor growth by targeting the macromolecular components of the cell that function in these processes. Most of the anticancer drugs used in clinical practice today target the genome, either directly, through covalent modification (e.g., cyclophosphamide, cisplatin, mitomycin C) or indirectly, through interference with nucleotide metabolism (e.g., fluorouracil and its derivatives) or chromatin dynamics (e.g., Taxol, vinca alkaloids). Because these agents do not target the genomes of transformed cells with a high degree of selectivity, they tend to kill all rapidly dividing cells indiscriminately and exhibit high systemic toxicity at therapeutic dosages. The poor therapeutic index of such cytotoxic agents is thus inextricably linked with their mechanisms of action. For this reason, nonspecific targeting of the genome appears to hold little promise for the development of safer and more effective anticancer agents.

A convergence of advances on three research fronts has created the opportunity to

reinvent the process by which anticancer drugs are discovered:

- The elucidation at a molecular level of many fundamental processes underlying cellular function;
- The advent of methods for synthesizing and screening large collections of structurally defined small-molecule ligands; and
- The development of instrumentation and software that enables relatively routine determination of macromolecular structure at high resolution through X-ray crystallography and NMR spectroscopy.

The first of these advances provides previously unexplored macromolecular targets-invariably proteins-for the development of drugs that act by novel mechanisms, such as interruption of mitogenic signaling in transformed cells, inhibition of extravasation, and prevention of tumor vascularization. The second and third advances are capable of generating ligands that bind specifically to these protein targets. Such ligands are essential links in the chain connecting basic science to the cancer clinic. They provide a way to test proposed mechanisms of target action through cellular assays and to evaluate directly the therapeutic relevance of particular anticancer targets in animal models. Most importantly, ligands that modulate the function of validated anticancer targets represent lead structures for the development of new and powerful therapeutic agents.

How can structure be used to discover ligands that bind target proteins? From the mid- to late-1980s, it was thought that ligands might be designed entirely *de novo* through computer-based modeling, using high-resolution structures as negative-impression design templates. Despite the enormous promise of this so-called "rational drug design" approach, it has proven unfeasible. This is largely because the fundamental forces driving ligand-protein association in water remain poorly understood.

Structural analysis has nonetheless proved to be tremendously valuable when employed in a more empirical mode, particularly in the optimization of ligand affinity and selectivity. Structures of weak or nonspecific ligands bound to target proteins represent powerful hypothesis-generating tools that instruct subsequent rounds of synthetic optimization. Indeed, the following iterative cycle of lead optimization has come to be widely employed in the pharmaceutical and biotechnology industries:

The astonishing speed with which HIV protease inhibitors were developed is a clear testament to the value of this approach, and a number of the most promising anticancer drug candidates currently in clinical trials-including the mechanistically novel inhibitors of matrix metalloproteases-were developed via iterative structure-based drug discovery. In addition, many other ongoing preclinical development programs throughout the industry, aimed at inhibiting such diverse targets as cell cycle-dependent protein kinases (CDK2,4), the papillomavirus E2 protein, and

vasoendothelial growth factor (VEGF), are making extensive use of structural analysis.

Structural analysis of target proteins in the unliganded state or bound to other macromolecules can provide an impetus for the initiation of drug discovery programs. One recent discovery involves the interaction of the tumor suppressor protein p53 with a modulator protein, MDM2. Because MDM2 inactivates p53 by directly binding its transcriptional activation domain, and because MDM2 over expression is associated with a loss of p53 function in certain tumors, it is widely thought that an MDM2-binding small molecule that out-competes the p53 activation domain (p53-AD) would be a valuable therapeutic agent. However, experience has proven that protein-protein interactions are generally difficult to antagonize with small molecules because the binding interfaces typically comprise flat hydrophobic surfaces. Unexpectedly, however, the co-crystal structure of p53-AD bound to MDM2 revealed that the activation domain binds into a deep hydrophobic cleft on MDM2. This finding has greatly increased the prospect of small-molecule inhibition, and several companies have since launched efforts aimed at discovering small-molecule MDM2 inhibitors.

Thus there are numerous examples of how structural analysis can facilitate the process of ligand and drug discovery. One exciting direction for the future will entail the use of combinatorial chemistry to drive the initial discovery of ligands to target proteins and to optimize these ligands in close conjunction with high-resolution structural analysis.

The Review Group believes that NCI, operating through the DTP, should focus on removing the obstacles to the process of ligand discovery. In this way, NCI would contribute to the war against cancer by facilitating discoveries that would drive drug development efforts in universities and the biotechnology and pharmaceutical industries.

IMPEDIMENTS TO THE EFFECTIVE DEPLOYMENT OF STRUCTURAL ANALYSIS IN THE WAR AGAINST CANCER

Although structure-aided ligand discovery is an extremely promising strategy, several serious obstacles, discussed below, have prevented it from reaching its potential.

Limited Access to Specialized Instrumentation and Training Required for Structural Analysis

The current system of federal research support does not provide an adequate mechanism for investigators not already expert in structural analysis to gain access to the required equipment and training. The high cost of X-ray and NMR equipment and the specialized expertise required to run experiments on these instruments exclude

large numbers of scientists who are interested in pursuing structural studies.

Many of the most interesting structural problems will involve complex multicomponent systems, such as those involved in intracellular signaling, transcriptional activation, and protein trafficking. Multicomponent complexes are notoriously difficult to crystallize, and, frequently, usable diffraction data can be obtained only by using a synchrotron radiation source. But because there is insufficient synchrotron time for current users, a significant expansion of users is not practical without a corresponding increase in the availability of synchrotrons. Moreover, there is no mechanism in place for noncrystallographers to obtain training and assistance at these facilities.

Difficulties in Protein Expression

The difficulty involved in expression of proteins is one of the most serious practical factors limiting structural analysis today. There is a need for increased emphasis on the development of novel protein expression systems. For example, even though biosynthetic deuterium labeling of proteins has extended the range of NMR spectroscopy into the 30-50 kDa range, efficient expression systems using D2O are available only for *E. coli*. Even in normal media, many proteins fail to fold properly when over expressed or are toxic to the over expressing organism. The small volume of the outer-cell membrane to which these proteins are usually targeted seriously limits the over expression of membrane proteins.

Lack of Structural Representation

High-resolution structures of more than 3,000 unique proteins and protein domains are now available, and new structures are being deposited into public-domain databases at a rate of roughly two per day. However, these structures still comprise an almost minuscule fraction of the protein structures that are potentially relevant to cancer. Fewer than 1 percent of the proteins encoded in the human genome have been structurally characterized, and fewer yet of these "characterized" examples involve proteins that have all of their functional domains intact.

Need for Novel Approaches in Rational Ligand/Drug Design

Much of the burden on high-resolution structural analysis and synthetic chemistry would be relieved if computational modeling could be used to predict the absolute or even relative binding energies of ligand-macromolecule complexes. For this to become possible, fundamental advances are needed in our understanding of the attractive and repulsive forces that control binding interactions in water.

STRUCTURE-BASED APPROACHES AND THE DTP

At present, the capabilities for determination of more explicit high-resolution structures in the DTP consist of a small and skilled crystallography group at Frederick, Maryland. This group operates in a manner that is disconnected from other small-molecule drug discovery and development efforts. The lack of a close connection between synthesis, screening, and structure is a serious deficiency that renders inadequate and outdated the overall DTP effort in small-molecule anticancer drug discovery. The DTP does provide some support to academic laboratories involved in ligand-target interactions relevant to cancer through investigator-initiated research grants, and especially noteworthy contributions have been made in the area of cyclin-dependent kinases and their complexes with inhibitors. However, groundbreaking research in high-resolution structural analysis is not a readily identifiable strength of the extramural NCI program.

RECOMMENDATIONS

The Review Group recognizes that some of the following recommendations can and should be undertaken within the constraints of the current NCI budget for developmental therapeutics. Other recommendations are highly meritorious, but their scope extends both scientifically and financially beyond that of the current NCI developmental therapeutics program.

3-1. NCI should be part of a major new initiative to determine the structure of all proteins in the human genome and in complex with interacting cellular partners. In conjunction with this effort, NCI should establish and manage databases that will make the coordinate conditions of sample preparation freely available without delay. Furthermore, the expression constructs and even the over expressing organisms should be made available through commercial vendors. In the short-term, three efforts should be initiated:

a. New dedicated beam lines should be established at each of the five national synchotron radiation sources, and staff these with personnel whose primary responsibilities are training and assisting investigators with data collection.

b. A postdoctoral program should be established to encourage young scientists to train in high-resolution structural analysis of cancer-related drug targets. This fellowship would guarantee support for 5 years of postdoctoral study, followed by 2 years of support as an independent research scientist. Recipients of these fellowships who wish to pursue X-ray analysis would be automatically awarded high-priority access to the NCI-dedicated synchrotron facilities.

c. A program should be initiated aimed broadly at fostering the development of new and innovative protein expression technology. This should be interfaced with parallel initiatives to develop robotic technology for the refolding and crystallization of proteins.

3-2. NCI should encourage novel approaches to understanding the fundamental

forces that control ligand-receptor interactions in biologic systems, and employ this information in computational routines for ligand design and semi-empirical protein structure prediction.

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ANIMAL MODELS

INTRODUCTION

The Review Group responded to four specific questions regarding appropriate NCI activities in the development of preclinical models:

1. What animal models, if any, are useful in the selection of cancer drug development candidates?
2. How should the DTP proceed in the discovery, development, and prioritization of candidate anticancer drugs?
3. What is the role of the DTP and NCI in cancer drug discovery?
4. What assays, if any, should the DTP provide to the wider scientific community?

ANIMAL MODELS

The Review Group believes that there are few, if any, animal models currently available that are predictive of anticancer activity in man for compounds tested in these animal models. In particular, the experience using subcutaneous tumor cell line xenografts in nude mice has been discouraging. These xenograft assays have failed to predict tissue specific utility in man for compounds that were found to be active against specific tumor cell types in the xenograft assays. However, data has been accumulated which suggests that activity against a broad spectrum of xenografted cell lines in nude mice does correlate with some antiproliferative activity versus cancers in man. This latter observation was felt to most likely reflect the compound's pharmacokinetic properties of half-life and tissue distribution, i.e., compounds that were capable of distributing to the site of the xenograft in mice were likely to exhibit greater bioavailability in man as well. Therefore, it is reasonable to substitute the use of the "hollow fiber" assay developed by the DTP to serve as a simplified evaluation of the pharmacological activity of appropriate candidate anticancer agents in rodents.

Appropriate candidate compounds for example would be agents identified in the DTP's tumor cell line screen. Alternatively, other drugs that function primarily as antiproliferative agents could also be evaluated via the "hollow fiber" assay. The

"hollow fiber" assay consists of human tumor cell lines inoculated into 1mm. by 2 cm. polyvinylidene tubes that are subsequently implanted into the peritoneal cavities of mice. The mice are then treated with test compounds for several days and the effects of drug treatment on the proliferation and viability of the tumor cells in the "hollow fiber" tubes are assessed by standard techniques. This change over to "hollow fiber" assays should save time and money in the evaluation of novel compounds, and shorten the time needed to bring promising compounds forward to clinical trials.

The Subcommittee was uniformly supportive of the development of transgenic mouse models to be used as preclinical assays to determine the likelihood of success for novel agents being considered for clinical studies. In this regard the DTP review committee fully supports the recommendations of the "Mouse Models of Human Cancer Subgroup Committee" for the creation, testing, and distribution of novel transgenic mouse models of cancer. The major recommendations of that committee-including the funding of teams of investigators to create and evaluate transgenic mouse models that reproduce the histological, pathological and molecular features of common human cancers, and the subsequent distribution of these animal models to interested investigators around the world-are appropriate and desirable goals. Moreover, transgenic cell lines harboring human genes that participate in the regulation of cell transformation may also prove to be useful reagents that should be accumulated and distributed by the DTP to interested investigators. By contrast, the Review Group felt that the use of non-mammalian, lower eukaryotic species (e.g. Nematodes, Xenopus, and Drosophila) are not appropriate models for screening assays intended to identify cancer agents for man. These model systems can be extremely useful for the identification and characterization of biochemical pathways and molecular targets that may prove to be critical regulators of mammalian cell physiology. However, from a drug discovery standpoint, human proteins should always be used in screening assays to insure that subtle differences in protein structures between species do not confound the isolation and optimization studies of drugs intended for human use.

DISCOVERY, DEVELOPMENT, AND PRIORITIZATION OF CANDIDATE ANTICANCER DRUGS

The Review Group developed the following algorithm for the most practical pursuit of anticancer drugs:

1. Identification of novel potent and specific compounds in one of several primary biochemical, cell biological, or tissue physiological assays (e.g. kinase antagonist, antiproliferative agent, or angiogenesis inhibitor).
2. Characterization of the biological properties in an appropriate animal model, if such an assay exists (e.g., hollow fiber studies for antiproliferative agents identified in the DTP's cell-line screen). If no

appropriate assay exists then proceed directly to number 3.

3. Explication of the pharmacokinetic and/or pharmacodynamic properties of the test compound in rodents and dogs.
4. Assessment of the toxicological properties of the test compound in at least two species (e.g., rats and dogs).
5. Proceed with Phase I clinical trials utilizing the biological, pharmacological, and toxicological properties to determine the optimal dosing and schedule parameters for the initiation of human studies.

THE ROLE OF NCI IN CANCER DRUG DISCOVERY AND PROVISION OF ASSAYS

The Review Group agreed that the current drug-screening program at the DTP is too narrowly focused on antiproliferative agents with cell growth as the single guiding read-out of the DTP's cell-based, 60-cell-line screen. Screening assays based on biological properties such as cell growth, cell morphology, cell mobility, tissue invasion, and promotion of angiogenesis were fully supported as important and relevant parameters to measure in evaluating the anticancer potential of novel agents. However, these biologically based measurements only represent a limited set of cell transformation characteristics. A much wider set of biochemically and molecularly defined assays was uniformly supported as necessary to encompass our expanded understanding of the molecular pathophysiology of cancer.

As new sources of compounds and biologics become available, new paradigms for evaluation will be required. New assays must be created to assess the effects of compounds on the biochemical, cell biological, and tissue physiological parameters that govern cancer cell pathogenesis and pathophysiology.

In this regard there was also support for reducing the current 60-cell-line screen to three cell lines for the identification of lead compounds based on inhibition of cell proliferation. A subset of the interesting compounds identified in this three-cell line screen could then be analyzed in the entire 60-cell-line screen to gain insight into the compound's mechanism of action via the COMPARE program analyses. The Review Group also stressed that the 60-cell-line assay should be made available to investigators in academic institutions to permit characterization of additional novel agents via the COMPARE program.

RECOMMENDATIONS

A much wider role for DTP is urged to foster the development of novel technologies, facilitate the discovery and development of novel anticancer agents, and serve as a

repository of critical reagents and research tools for cancer research. In this context there are several specific recommendations.

4-1. The drug development algorithm outlined above should be adopted.

4-2. DTP's role in screening compounds should be reconfigured to ensure responsiveness to changes in science and technology. DTP should be more innovative and comprehensive in its screening methodologies: a) current DTP assays based on cell proliferation are too narrowly focused; b) new sources of compounds and biologicals should be sought for evaluation including combinatorial chemistry libraries; c) new assays should be created to assess the effects of compounds on the biochemical, cell biological, and tissue physiological parameters that govern cancer cell pathogenesis and pathophysiology; and d) these assays should be robust, inexpensive, and capable of analyzing samples from individual cancer patients so as to create a physiological "finger print" of individual patient's cancers. These goals can be met through the establishment of a network of extramural sites with expertise in these areas.

4-3. There are three areas in which NCI and DTP can have a major impact on cancer therapeutics development in addition to carrying out a reconfigured screening program: a) in providing public access to its repository of compounds, research tools, and information databases; b) in working with the academic and industrial communities to develop, evaluate, and deploy new assays in both the internal and external scientific communities; and c) in fostering a more collaborative approach to screening by serving as a matchmaker between chemists and biologists for the analysis of novel agents. NCI should serve as a facilitator of external scientific study in these areas.

4-4. NCI should establish an ongoing review mechanism (relying on internal and external expertise) to continuously evaluate the status of screening assays and pharmaceutical development programs at the NCI to assure their continuing value and appropriate application towards the identification and evaluation of novel cancer therapeutics.

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PHARMACOLOGY, TOXICOLOGY, AND FORMULATION

INTRODUCTION

The advent of genomics, combinatorial chemistry, and high-throughput screening for the identification of potential lead compounds will undoubtedly result in a marked expansion in the number of candidate drugs progressing from discovery to development. Moreover, the enormous progress in identifying the molecular bases for cancer has intensified efforts to identify more selective and efficacious anticancer

compounds.

This predicted increase in the number of candidate drugs has already begun to alter the preclinical models and methods used in many therapeutic areas. As drugs move from discovery to development, costs increase exponentially. Unfortunately, this has contributed to attrition in the drug discovery and development process, with less than 0.1 percent of preclinical compounds ever reaching human clinical trials. This high attrition rate results in a significant loss of time and money. Consequently, there is an urgent need to review and improve the drug discovery/development process to improve the early selection of appropriate compounds.

More than fifty years of research has shown that in vitro studies cannot readily be extrapolated to reliable in vivo activity. There are four primary reasons why preclinical compounds are rejected during the development process: 1) intrinsic toxicity of compounds; 2) extensive metabolism; 3) undesirable plasma half-life or protein binding; or 4) poor bioavailability or solubility. Almost 40 percent of all new in vivo candidate drugs (not just in cancer research) have been withdrawn because of serious pharmacokinetic problems. These properties are traditionally determined from efficacy and toxicity studies in animals, which are time-consuming and relatively expensive. Often, however, the contemporary models inadequately mimic the *in vivo* situation in humans. Recent advances in molecular, cell, and computational biology raise the hopes that methods can be developed that more faithfully reflect human drug pharmacokinetics, pharmacodynamics and toxicodynamics.

THE IMPACT OF THE NCI PROGRAM IN PHARMACOLOGY, TOXICOLOGY, AND FORMULATION

In the past the Developmental Therapeutics Program (DTP) and, more specifically the Pharmacology, Toxicology, and Formulation Program (PTF), has been viewed as a leader in promoting pharmacological analysis of new anticancer drugs and in the implementation of pharmacokinetically guided clinical trials. As such, industrial and academic scientists have viewed DTP as an invaluable resource for cancer drug discovery. First, the NCI/European Organization for Research and Therapy Against Cancer annual meeting is the established site where major new international anticancer agents from the international community are introduced. Second, the DTP remains a key participant in the drug discovery process internationally. And third, DTP interactions with the Food and Drug Administration are excellent and facilitative for all partners (government, academia and industry).

While some members of large pharmaceutical companies interviewed by the Review Group indicated the DTP does not have the same impact on their program as it did years ago, they believe it still has the international stature to influence the world community. Almost all agreed the DTP could and should have a role in assisting small

emerging biotechnology companies as well as companies from developing nations.

There will be increasing economic importance in identifying pharmacologically and toxicologically desirable agents quickly. Because the Food and Drug Administration regulations often guide the requirements for these studies, pharmacology and toxicology studies are essential first steps to clinical studies. Formulation will also be an important determinant for dosage and scheduling of new agents. Moreover, the current focus on agents that function to affect deranged signaling pathways that are causal in the malignant process are likely to produce drugs that are taken chronically rather than acutely. This will almost certainly mandate oral administration and appropriate "drug-relevant" properties. Many of the approaches that have been applied in the past are unlikely to facilitate the entry of the next generation of anticancer agents. It seems likely that anticancer drugs of the future will share some of the attributes expected of effective chemopreventive agents. Therefore, there is a serious need for innovative leadership in anticancer pharmacology, toxicology and formulation that have not been fulfilled by either academia or industry.

It is the view of the Review Group that NCI's PTF program should serve as the public entity that provides reliable and comprehensive information about the potential pharmacological and toxicological aspects of cancer therapeutics. There is, therefore, a strong need to maintain and improve the service component of DTP. It is essential, however, that DTP improve its intellectual environment and openness to innovation, if NCI is to retain any reasonable ability to foster cancer drug discovery.

Leadership in the implementation of computer-based structural analysis to predict a priori pharmacokinetics, toxicology, and formulation profiles should be a key goal of the PTF program, as should information dissemination. The Review Group does not believe the PTF program can function effectively, if all of its research activities are extramural; there is an essential need to have some national and international intellectual presence in the in-house program to maintain credibility. It is suggested that serious consideration be given to establishing a Center of Excellence, a National Pharmacology/Toxicology Core Facility, at Frederick, Maryland.

In its deliberations, the Review Group attempted to define the mission and structure of the PTF program within the DTP. The Review Group examined possible NCI activities in informatics, drug metabolism and evaluation, education and communication, and made recommendations about how NCI might improve the review process and intellectual environment for PTF activities.

INFORMATICS

In theory, parallel analyses of lead compounds can reduce the risk of lost time due to unexpected toxicity. This approach requires early evaluation of toxicity and use of computational strategies that permit iterative evaluation of toxicity profiles. NCI's

DTP has unique access to significant animal and human data on the toxicity of both cancer and noncancer therapeutics. Libraries of toxicity profiles could be created to allow potential toxic pharmacophores to be identified a priori. Although some commercial programs are currently available, they are primitive, not tailored to potential cancer chemotherapeutic agents, and often proprietary and not accessible to most cancer investigators.

NCI's PTF program should become the leader in managing informatics on pharmacokinetics and toxicities of potential anticancer compounds (i.e., pharmacoinformatics and toxicoinformatics) as it already has with the COMPARE program. Investigators from academic and biotechnology laboratories could then be provided with access to these informatics systems and learn how to "mine" such publicly available information.

DRUG METABOLISM AND EVALUATION

In drug development, early information on human metabolism of a new drug is critical in predicting potential clinical drug-drug interactions and in selecting the appropriate animal species. Unfortunately, considerable interspecies variability exists with respect to drug metabolism, making problematic predictions extrapolated from lower organisms to humans. Moreover, animal studies are both expensive and drug-intensive. Several technologies have converged to permit a better assessment of the fate of drugs in humans well before they enter clinical trials. For example, advances in *in vitro* enzyme systems used for drug metabolism studies can facilitate predictions of metabolic fate. Such integrated systems could prove extremely valuable for both academic and industrial investigators.

- Precision-cut human liver slices are useful to obtain the complete *in vitro* metabolic profile of a drug because this system retains the physiological conditions of enzymes and cofactors of both Phase I and II reactions. Isolated and cultured hepatocytes also are used as *in vitro* models for identifying metabolic pathways of drugs.
- The availability of cloned cDNA for each of the human cytochrome P450 isotypes provide both *in vitro* and cellular mechanisms for evaluation of drug metabolism. Various microorganisms have been shown to possess cytochrome P450 mono-oxygenase enzyme systems that mimic the mammalian microsomal mixed-function cytochrome P450-dependent oxidase system. These microbial systems may have application in conjunction with combinatorial libraries for rapid assessment of drug metabolism potential.
- The availability of transgenic techniques now permits the development of "humanized" mice that contain one or more human drug metabolizing systems.

The completion of the Human Genome Project and the attendant field of genomics are likely to radically alter future clinical trials. This has stimulated the exploding field of pharmacogenetics. The recognition that single nucleotide polymorphisms exist in many drug metabolizing enzymes, including cytochrome P450s, and that such polymorphisms can be extremely important for drug fate, fosters the belief that future anticancer drug clinical trials should include patient genotyping prior to drug administration to avoid untoward drug effects. Very little research is currently being done on this important topic in preclinical and clinical anticancer drug studies.

Major instrumentation advances have occurred that are directly useful for drug metabolism studies. Unfortunately, the instrumentation is expensive for academic laboratories or small biotechnology companies. These include but are not limited to LC-MS/MS (liquid chromatography-mass spectroscopy/mass spectroscopy). Such techniques permit multiple- component analysis for determination of drug and metabolite levels in biological fluids. These quantitative methods are now being used for drug discovery with candidate drugs from combinatorial libraries to accelerate the candidate selection process.

It is highly desirable to design *a priori* compounds that undergo either no metabolic inactivation (i.e., so-called "hard drugs") or predictable metabolic inactivation (i.e., "soft drugs"). NCI is well positioned to catalogue a large database on basic pharmacophores and drug metabolism.

Drugs often fail in clinical trials because of plasma t1/2 that are too short or too long. The quality of pharmacokinetic research in oncology has been criticized as inadequate and under appreciated; methods for calculation of plasma concentration-time curves were seriously deficient in a great majority of studies reviewed. This has likely hindered the progress of drug development in cancer. There has been some progress, however, in developing physiological models for the pharmacokinetics of toxic chemicals, including cytotoxic anticancer drugs, and these models may be applicable for future preclinical and clinical trials. It is also becoming increasingly apparent that chirality within small molecules can be responsible for unwanted toxicity. Analytical methods are becoming available to allow the rapid and simultaneous determination of plasma half-life in rodents and other preclinical models.

As mentioned above, new instrumentation now permits the parallel (multiplex) processing of several compounds in the same animal to determine quickly those compounds with desirable or undesirable absorption or pharmacokinetic profiles. There are emerging models developed from existing compounds that may allow for the prediction *a priori* of absorption and bioavailability using physicochemical properties and cell-based reductionist approaches. The two most important physiochemical factors that affect both the extent and rate of absorption are lipophilicity and solubility. Such issues are especially important if an orally active agent is targeted, which is highly desirable in a managed care environment. The ideal lipophilicity is not yet known although a vast majority of orally active compounds

have a mass of <515 daltons and a log P of 1-2. Experimental methods to estimate the level of intestinal permeability have been developed such as the Caco-2 intestinal epithelial cells grown in culture.

EDUCATION, COMMUNICATION, AND INNOVATION

The Review Group believes that the use of the PTF program by small emerging biopharmaceutical firms and academic laboratories could be expanded markedly without any major increase in cost and with improvement of the types of compounds being tested. In general, the Review Group thinks that there is insufficient flow of new information into the existing program. This is evidenced in the limited membership of the Decision Network, which should be made more widely available to the public and include members external to NCI. In addition, the DTP should engage in activities where the in-house and extramural communities discuss new approaches in pharmacology, toxicology and formulation. One way that this could occur is through highly publicized and accessible workshops.

These exchanges should focus on emerging technologies, such as the use of "humanized mice" with human drug metabolizing enzymes, parallel *in vivo* drug metabolism systems, microtiter-based metabolism systems for anticancer drugs, high throughput pharmacokinetic systems, and new drug delivery systems. The proceedings of these conferences and workshops should be widely available via the Internet.

Although the PTF program has a clearly defined service component that is appropriate and required, there is a serious need to broaden the intellectual support within the program to ensure ongoing innovation. The key attributes of this environment should be agility, the capability to accommodate "moving targets," and synergy among the discovery and service components. The PTF program needs to maintain some in-house capability to interface with the increasing number of compounds that will almost certainly result from contemporary combinatorial chemistry, high throughput assays, robotics, and combinatorial cell biology. The Review Group believes that new individuals with the proper credentials should be recruited into Centers of Excellence, one of which could be situated appropriately at Frederick. New investigators could be hired to develop and implement computer-based modeling systems to exploit NCI's large database, or to rapidly assess pharmacophores with optimal anticancer properties ("relevant drug-like" properties). Finally, the PTF Program should continue to facilitate and fortify the unique NCI Natural Products Program to ensure it will continue to be widely used.

RECOMMENDATIONS

5-1. **NCI should make available the latest technology that will allow drug metabolism, pharmacokinetic, and drug absorption simulations and**

establish two or more National Pharmacology/Toxicology Core Facilities to encourage wider use of these technologies. This will require an infusion of approximately $10 million. Murine model systems, such as the humanized mouse, that may afford more accurate predictions of human metabolic profiles should be encouraged.

5-2. **NCI should create a postdoctoral program that will encourage students to engage in new and innovative programs that facilitate the development of new anticancer drugs.** There is a desperate need to stimulate new student interest in the Pharmacology and Toxicology of anticancer drugs. Failure to do so will seriously decrease the movement of new drugs into clinical application.

5-3. **The DTP should establish periodic reviews (every three years) of its contractors, relying on the expertise of outside reviewers as well as its own staff.**

5-4. **The NCI Decision Network should be expanded and broadened to include representatives of academia and cancer centers.**

5-5. **The productive interactions between DTP and the Food and Drug Administration should be encouraged. The DTP should assist emerging biopharmaceutical companies in their interactions with the Food and Drug Administration.**

5-6. **NCI should develop computational methods that will facilitate the design of nonmetabolized drugs and drugs with a predictable metabolic profile.**

5-7. **NCI should assist in the large-scale purchase of gene chip technology integrated with existing genomic initiatives that will allow a priori**

determination of toxic and metabolic risk assessment for new drug candidates. Such information should also be integrated into future preclinical and clinical trials.

5-8. **The DTP should assume a leadership position in developing and promulgating informatics programs that can be used on UNIX and PC platforms to facilitate anticancer drug development.** These programs should be quickly placed in the public domain and will require at least a minimum three-fold increase in funding over current levels.

5-9. **To enhance the activities of the PTF Program, NCI should encourage the integration of related in-house basic research in medicinal chemistry, molecular pharmacology, molecular toxicology, "checkpoint" biology, and structural biology with the existing programs in drug discovery and cancer chemoprevention. Moreover, the DTP should foster and encourage an intellectual environment that will embrace and inform the in-house drug discovery program and the existing service programs.** To enhance innovation and the infusion of new ideas, the DTP should create the opportunity for in-house scientists to take sabbaticals and create an environment at Centers of Excellence at which scientists from around the world would want to spend a sabbatical year.

5-10. **The distribution of extramural to in-house expenditures in the DTP should be 85 percent to 15 percent to ensure that the strengths of the extramural community are fully realized.**

5-11. The DTP should incorporate the above **mentioned informatic data in the criteria used to select drugs to be screened early in the drug discovery process in order to be more selective**

and to use its resources more productively. Compounds eligible for screening should also involve unique structures and different targets as well as contain pharmacological and toxicological profiles that are promising for clinical use. In addition DTP should enforce single submission from homologous series from an individual source.

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DEVELOPMENT OF BIOLOGICS BY NCI

INTRODUCTION

The Developmental Therapeutics Program (DTP) Review Group was charged with the task of evaluating NCI's efforts in the development of new cancer therapeutics. To conduct this evaluation, the Biologics Subcommittee reviewed the Biological Resources Branch (BRB. The Review Group's findings and recommendations are presented below.

CHARACTERISTICS AND ACTIVITIES OF THE BIOLOGICAL RESOURCES BRANCH

The BRB currently functions as a contractor-operated, multi-use facility for the GMP production of biological products for early stage (i.e., Phases I and II) clinical trials. Roughly half of the BRB projects support NIH in-house programs, 30 to 40 percent of its projects are conducted extramurally, and 10 to 20 percent involve industry-government collaborations (predominantly involving the in-house research program).

The capabilities of the unit currently include mammalian cell fermentation; fermentation recovery of recombinant bacterial and natural products; development of analytical folding and purification procedures for peptides and proteins; aseptic processing and filling; and GMP documentation. The major clinical reagents currently being produced by the BRB are monoclonal antibodies, chimeric antibody-protein conjugates, and immunotoxins. The Branch is also producing a limited number of cytokines and other biologically active proteins and peptides for clinical use.

Over the past decade, three developments have paved the way for the development of many novel approaches that use biological materials as the therapeutic reagent and that have demonstrated tremendous promise in animal models:

1. the explosion of knowledge in molecular immunology;
2. the ability to genetically manipulate a wide range of cell types, viruses and bacterium with diverse biologic properties, thereby converting them from pathogens into therapeutics; and
3. the definition of molecular targets in cancer cells.

Biotechnology and pharmaceutical companies show significant interest in capitalizing on these developments. However, because there is much less expertise available in the development of biological therapeutics than there is for small molecule therapeutics, these companies look to NCI-supported academic programs to provide initial proof of principle in humans before tackling these projects on a larger scale.

The current activities of the BRB with regard to reagent production are occurring in important areas where need is expected to grow over the next five to ten years. In addition, there has been an explosive proliferation of therapeutic approaches using recombinant vectors (e.g., genetically modified tumor cells, recombinant antigen specific viral vaccines, recombinant antigen-specific bacterial vaccines, and gene therapy vectors). Thus the BRB should expand its capabilities to support the early stage translation of these novel, biologically based, therapeutic approaches.

Moreover, it is expected that as recombinant viral, bacterial, and nucleic acid vaccines-as well as other reasonable gene therapy approaches-are created, the BRB will need to develop capabilities for producing both replication-defective and replication-competent recombinant vectors.

One of the most important endeavors for the BRB should be the development of novel technologies for the general improvement of yield, efficiency, and quality of biologic products. Such an investment in areas of technology development would, in the long run, greatly enhance the Branch's ability to support reagent development for a much larger and broader set of specific reagents and products.

REVIEW OF BRB ACTIVITIES

The Review Group identified a number of issues that need to be addressed so that the BRB can effectively support the most promising ideas in developmental therapeutics in the biologics area. These involve prioritizing projects; coordinating study section applications; and enhancing access to the BRB.

Prioritization of Projects

The Review Group concluded that although the BRB staff members are highly competent and dedicated, some of the currently supported projects do not represent

the most promising biologic therapeutics being developed nationally. There are a number of reasons for this situation. First and foremost, the BRB has been supporting a disproportionately large number of in-house projects to the exclusion of extramural projects. This bias toward the in-house program is largely due to the historical connections between the in-house programs and the Decision Network, which is responsible for project prioritization. Second, most extramural programs are unaware of the BRB's capabilities and the ways in which it could assist in the development of promising new biological reagents. Third, the Decision Network members' expertise in the most important areas of biologically based therapeutics is limited.

A critical element of scientific merit review should be the consideration of the preclinical evidence for potency of a particular biologic reagent as a therapeutic. Evaluation of the impact value would include the potential of the proposed reagent to open new therapeutic inroads compared to the potential of reagents already under development. Proposals submitted to the BRB from in-house and extramural programs should be reviewed, ranked, and prioritized using a standard application procedure and proposal format. The proposal format should be shorter than a current R01 proposal, but should include specific aims, background, preliminary studies (including a preclinical summary outlining both scientific validity and safely/toxicity studies), and reagent requirements. Both in-house and extramural investigators should use the same application process, and all proposals should be placed in a single rank order. Current projects should also be formally re-evaluated in this review process. Those projects with low priority rankings should be phased out over a 6- to 12-month period.

Coordination of Study Section Applications

A critical component of the development of a biological therapeutic is the analysis of its *in vivo* effects in patients-the ability to monitor in vivo biology after administration of the reagent. One of the most difficult problems for extramural programs developing biologic therapeutics is that programs must coordinate 1) applications to the BRB for production of the reagent and 2) applications for review by study section to conduct early-stage clinical trials and perform biologic monitoring of patients receiving the reagent. To more effectively coordinate this process, applications submitted by groups that require funding for production of the reagent as well as for carrying out and monitoring the clinical trials should be submitted in tandem to the proposed BRB advisory committee as well as to the standing study section.

The study section application can be used as a scientific supplement to the BRB application so that the BRB advisory committee can assess the scientific merit of the proposal. The BRB advisory committee would perform an expedited review to determine the priority ranking of the project relative to the total pool of BRB proposals and to determine whether the BRB can produce enough reagents for the proposed initial clinical trials. This review will be sent to the study section and will be available during grant review. In addition, BRB staff members will be present during the study section review of the proposal to provide information to the reviewers regarding the BRB's interest in the proposal and its capability to produce the biologic

reagents.

It is recognized that this process may represent a form of "double jeopardy" for groups who do not have funding for clinical testing of the reagent. This is because the BRB advisory committee and the study section would review both of the proposals. However, the Review Group believes that this would be the only way to provide a standardized review in which in-house and extramural proposals could be fairly compared and prioritized based on merit.

Access to the BRB

Significant obstacles to extramural programs gaining access to the BRB include the absence of readily available information on BRB capabilities and the lack of guidelines for submitting proposals. Once the proposed BRB review process is in place, a brochure containing this information should be aggressively disseminated to extramural programs. The brochure should also be sent to all NIH grant holders and in-house investigators, and its availability should be promoted in several publications available to biotechnology companies.

One of the current functions of the BRB is to provide a repository of cell lines and reagents that can be distributed to in-house and extramural scientists. The Review Group recommends that this repository be expanded to include reagents for commonly utilized cancer immunotherapy models. The BRB should standardize these reagents in detail so that therapeutic efficacy studies can be compared between different laboratories. The BRB should also coordinate with the American Type Culture Collection (ATCC) so that it becomes the primary developmental resource for all cell lines. In this way, duplication of effort in the development and standardization of cell lines can be avoided. The contract to ATCC may have to be expanded to cover these additional developmental tasks.

INTELLECTUAL PROPERTY ISSUES

While it is appreciated that the intellectual property issues associated with biologic therapeutics are often extremely complex, the prioritization of projects by the BRB should be accomplished relatively independent of the perceived intellectual property status of the reagent or approach being taken. Nonetheless, because it would be wasteful for the BRB to be engaged in the production of biologic reagents that are being actively developed by a third party, it is critical that BRB applications include a description of current activities or lack of activities in the development of a particular biologic reagent by groups other than the applicant. Active development of a particular biologic product by a qualified group other than the applicant (either academic, biotechnology, or pharmaceutical) will affect the assessment of impact and the ultimate prioritization of the particular project proposal.

FUNDING OF PROPOSALS

It is expected that, initially, the BRB budget will cover most of the reagent production costs, with a relatively small portion of the cost burden being transferred to the investigator. However, because there are widely varying resource requirements for different types of biologic reagents, cost-benefit analyses must be a critical component of the review and prioritization process. In addition, the review process should be flexible, reflecting a cooperative and collaborative relationship between BRB staff and applicants in the development of reagents. Thus, academic applicants should be encouraged, but not required, to contribute some funding for cost sharing. Sharing the reagent development burden with the BRB will allow the BRB to allocate its resources to a larger number of projects. Companies should be required to cover BRB reagent development costs. The Review Group strongly believes that a small royalty should be returned to the BRB for successfully marketed products to which the BRB contributed in the early stage of development.

THE BRB BUDGET

It is anticipated that the expansion of BRB activities to support extramural programs as well as the development of facilities to produce novel recombinant vectors will require a budget increase of roughly 80 percent. A number of specific items requiring this increase are summarized below:

Increase Staff Salaries-Salaries of employees operating the biopharmaceutical production unit are, in general, significantly lower than salaries available for comparable industry positions. This discrepancy seriously threatens the integrity of the unit, because the highest quality trained staff members often seek higher paying positions.

Establish a Biopharmaceutical Team in the Production Facility-This team is needed to conduct formulation and stability studies, tasks that are anticipated to overwhelm the current protein biochemistry staff.

Establish Technology Development Teams-These teams would bring experience in molecular biology, a wider range of expression systems, and protein and DNA biochemistry. It would be the role of the Technology Development Teams to develop novel approaches to enhance efficiency, yield, and purity of reagents through the development of novel production systems. These teams would also provide advice regarding outsourcing and insourcing decisions.

Increase Materials and Supplies-It is expected that a significant increase in the use of

materials and supplies will accompany the expanded functions of the BRB.

Establish a Flexible Use Technology Suite-A one-time renovation budget will be needed to create facilities with greater flexibility for the production of biological materials-particularly replication competent recombinant vectors-in a modular clean room that supports laboratory format.

NATIONAL COOPERATIVE DRUG DISCOVERY GROUP (NCDDG) MECHANISM

The National Cooperative Drug Discovery Group (NCDDG) mechanism was established to fund team approaches that involve multiple investigators collaborating with a company that is focused on the development of a particular class of therapeutics. This mechanism was created to account for the fact that standard program project grants are not suited to this kind of integrated approach to therapeutics development. Program project grants are also poorly suited for funding early stage academic-corporate collaborations.

Because biotechnology and pharmaceutical companies look to academia for leadership in the development of biologic therapeutics, the Review Group recommends that the NCDDG mechanism be expanded specifically to support a larger number of programs in biologic therapeutics. The current NCDDG grants cover therapeutics development up to but not including clinical trials. However, a critical element of the early stage evaluation of a biologic therapeutic involves the analysis of the effects in humans. Thus, the Review Group recommends that NCDDG grants in the biologics area be extended to include early stage (Phase I) clinical trials with a focus on evaluation of in vivo biologic effect as an indicator of the potential efficacy of the biologic reagent.

NEED FOR CENTERS OF EXCELLENCE

The successful creation and development of a biologic therapeutic involves a continuum from basic laboratory science to clinical translation, including early stage clinical trial design and evaluation of biological effects in humans. The development of an infrastructure to foster and promote effective collaborations between basic scientists and clinical investigators requires support that is often not available through standard NIH funding mechanisms. Recognition of this problem in other areas represented the basis for the creation of SPORE grants, which support centers of research excellence that focus on cancers of specific histology (breast cancer, lung cancer, prostate cancer, gastrointestinal cancer). The Review Group believes that creation of a funding mechanism similar to the SPORE grants, but focused on a particular field of biologic therapeutics, rather then a disease entity (examples are toxin conjugated monoclonal antibody therapies, recombinant viral vaccines,

recombinant oncolytic viruses), be established to encourage the development of long-term collaborations among groups of basic and clinical scientists.

THE RAPID ACCESS TO INTERVENTION PROGRAM (RAID) PROGRAM

The Review Group is enthusiastic about NCI's institution of the RAID Program to support the rapid development of the most highly promising therapeutic approaches. There is some concern, however, about the grouping of biologic and small molecule therapeutics because of significantly different considerations required in the development and evaluation of each. Thus, it will be important that the RAID review committee contain enough experts in the areas of biologics to fairly handle these distinct applications.

Given that the primary recommendations of the Biologics Subcommittee regarding expanding and strengthening the BRB and improving access by the extramural community are very much concordant with the mission and mechanics of the RAID Program, the process of project submission to RAID and to BRB should be coordinated.

RECOMMENDATIONS

6-1. Increase the BRB budget by 80 percent in order to expand the scope of BRB activities on three levels.

a. Augment the categories of biological reagents that are currently being produced.

It is anticipated that as the BRB expands to support the extramural developmental therapeutics community, there will be a dramatic increase in high-quality proposals for the production of monoclonal antibodies, bioactive proteins, chimeric antibody-bioactive proteins, and peptide- based reagents. BRB staffing and facilities must be expanded in order to reasonably accommodate worthy proposals.

b. Develop capabilities for production of recombinant vectors.

Many of the GMP mammalian cell culture and fermentation facilities under development at the BRB can be modified to accommodate these expanded areas of development. In these efforts, the Branch should continue to coordinate with the National Gene Vector Laboratories so that duplication does not occur.

c. Develop novel production technologies.

The development of novel technologies for the general improvement of yield, efficiency, and quality of biologic products is ongoing in many biotechnology

and pharmaceutical companies. Therefore, BRB activities must include: 1) outsourcing of projects to contract facilities that can use their enhanced technologies to produce some reagents of higher quality and efficiency than can the BRB; and 2) insourcing of new technologies that would be critical to the BRB producing biologic reagents more efficiently.

6-2. Create a rapid, formal, merit-based review structure to enable the BRB to support the most promising new approaches in biologics, which includes the following activities:

a. enhancement of access to BRB by extramural community and prioritization of projects

It is recommended that the DN be eliminated from the project prioritization process. It should be replaced with a BRB advisory group or study section consisting of members from within the BRB and scientific leaders in various areas of biologics drawn from the extramural community. This BRB advisory committee would be responsible for ranking proposals based on scientific merit, scientific impact and feasibility of production. BRB applications should include a description of current activities or lack of activities in the development of a particular biologic reagent by groups other than the applicant. This application and review process should be coordinated with and possibly merged with the RAID application and review process.

b. use of the same application process for intramural and extramural investigators, with all proposals placed in a single rank order.

c. coordination of study section applications

To more effectively coordinate these applications, the following is recommended: applications submitted by groups that require funding for production of the reagent as well as for carrying out and monitoring the clinical trials should be submitted in tandem to the proposed BRB advisory committee as well as to the standing study section.

6-3. The BRB should provide supplemental funding for approved proposals through cost sharing and collection of a small proportion of royalties from marketed products in which the BRB was involved in developing.

6-4. Expand the BRB repository.

6-5. Form a BRB Oversight Committee.

A BRB Oversight Committee consisting of five to seven leaders in the field of biologic therapeutics should be formed to oversee the operations and directions of the BRB. This committee should meet annually with BRB leadership and the NCI director to assure that the BRB is adequately developing and utilizing its capabilities to support the most promising projects.

6-6. Expand the National Cooperative Drug Discovery Group (NCDDG)

mechanism for support of biological therapeutics development.

There should be a minimum of 5 NCDDGs in biologics. Biologics NCDDGs should allow funding for evaluation of responses in Phase I clinical trials.

6-7. Establish 5 to 8 Centers of Excellence in Biologics.

These should be funded at $1 million to $1.5 million annually and should provide in-house production staff, data management, sample collection and banking capabilities, as well as a place for the development of innovative early-stage projects, and training.

6-8. Expand support of biologics through the RAID Program with a commitment of $20 million - $30 million per year in addition to the proposed increase in funds to support expansion of the BRB facility itself.

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