ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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H&O What is the NExT Program?

JD The NExT (NCI Experimental Therapeutics) program is the result of the reorganization and expansion of the drug development effort at the National Cancer Institute (NCI), particularly the early drug development effort. The NCI has been developing new cancer therapies since its Developmental Therapeutics Program began in 1955; and approximately 70% of all cancer drugs approved by the US Food and Drug Administration (FDA) have in some way been worked on by the NCI. Approximately one-third of all drugs approved by the FDA were either discovered by the NCI, or fundamentally developed from the preclinical stage. Over the past 3 years, the NCI has unified its drug development pipeline, and in the past year, expanded its chemical biology activities, bringing high throughput screening and target discovery resources to academic investigators to complement the toxicology and preclinical pharmacology activities that have been ongoing for many years.

H&O What are the goals of the program and why was it created?

JD Approximately 35 years ago, the NCI had 50–100 chemists working on the discovery and development of new drugs. Over the course of the past 35 years, that activity waned dramatically to the point that in 2004, there were fewer than 12 chemists working on drug development at the NCI. Hence, it was clear from the perspective of the NCI's intramural program, as well as from the lack of chemistry expertise in the Division of Cancer Treatment and Diagnosis (DCTD), that more scientists were needed to assist the extramural community in the area of chemistry. In order to enhance the ability of academic investigators to bring agents to the clinic, we needed to have resources in the areas of chemistry, medicinal chemistry, and chemical biology. Consequently, we created an extramural consortium of university chemists interested in academic cancer drug discovery and have collaborated with them to provide a network of expertise that would allow investigators at institutions that do not have access to these resources to have their ideas tested.

H&O How do companies that are interested in NCI partnership apply to participate in this program?

JD Academic investigators, biotech firms, or larger pharmaceutical concerns looking for partnerships can apply at any stage of development. The investigator may have found a new gene that might be a suitable target, but that requires exploratory screen development. The investigator could have developed a target but does not have the resources for preclinical development for this target, or the researcher may have some original molecules that inhibit a target but a more effective formulation of the agent may be required. Also, investigators seeking pharmacodynamic assays or imaging techniques to determine if their drug is modulating its target, or those looking for other resources to support the discovery and development of their drug may apply for partnership with NCI. We, in turn, provide access to whatever resources the investigator may need if his or her application passes peer review.

Those who are interested must fill out an application outlining their hypothesis and provide information on their research strategy and a specific request of the kinds of resources they require to move their project forward. These proposals are not grants; the NCI does not provide money for this research. We provide the data that the investigator needs by providing access to the necessary infrastructure to advance his or her project.

The proposals are evaluated quarterly for scientific merit, feasibility, alignment with NCI mission, novelty, and clinical need. Depending on the stage of drug development, either an extramural Discovery Special Emphasis Panel (mostly chemists, some pharmacologists) or a Development Special Emphasis Panel (half academic, half industry scientists) prioritizes all proposals.

H&O How does the NCI prioritize research opportunities?

JD The Special Emphasis Panels assign priorities based on the criteria that have been outlined; scientific merit is most important. Subsequently, committees of NCI scientists evaluate the proposals in relation to what else is in the pipeline, whether one project will compete with others, the cost of the proposals, and whether the NCI can afford to do the project. Overall, the proposals are prioritized across the whole pipeline by a committee of NCI chemists, pharmacologists, and clinical scientists, but mostly are driven by extramural peer review.

In order to effectively transition a project from one stage to the next, we employ a Stage Gate evaluation process, which guides the progress of the project based on a set of guidelines and milestones. For each project, we assign milestones, divide projects into these milestones, and budget accordingly.

When the proposals are approved, they are approved for the work to get from the starting point to milestone 1. After the project meets the first milestone, it then gets presented again to NCI's internal and extramural committees to confirm that there is still sufficient interest in the project and that no industry factors have supplanted the need for the project, to evaluate cost, and to determine whether progress has been made or if the project is no longer feasible.

H&O How many projects are in the NCI's portfolio simultaneously?

JD This is a complicated question, as each proposal has varying requirements and costs. For example, small molecules are less expensive to develop and produce compared to producing a unique gene vector. It can be 2–3 times more expensive to develop a biologic product than something that is a small chemical entity. Therefore, we have to continuously balance the progress of the pipeline, the priority of each project, and the resources allocated to that project. Funding decisions are made by the NCI staff, but the outside panels not only make the initial priority recommendations, but also provide input into whether the prioritization is still consistent with their original recommendations.

H&O What are phase 0 clinical trials? Are there any challenges to implementing such trials?

JD A phase 0 trial is a first-in-human trial, involving a limited number of human subjects (about 10–12). It tests drugs at low, supposedly nontoxic doses for no more than 7 days. A phase 0 trial has no therapeutic or diagnostic intent and can be initiated with less extensive pre-clinical data than are needed for a phase I trial. The Developmental Therapeutics Section (DTS), which oversees our early phase therapeutics program, was created as part of a joint initiative between the NCI Center for Cancer Research and the DCTD to enhance the drug development effort. The major focus of the DTS is to design and conduct early phase trials, including phase 0 studies, of investigational drugs in order to assess them at the initial stage of the clinical development process.

The major challenge with phase 0 trials is the significant investment necessary for developing proof-of-mechanism pharmacodynamic assays. They are expensive, and not everyone has the resources to conduct these assays; they require medical oncologists, hematologists, radiologists, technicians to process samples, and laboratories to do the assays. This is not beyond the realm of what can be done at any of the NCI-designated comprehensive cancer centers, but it does require resources, some of which are not easy to obtain for smaller cancer centers.

Early phase trials are useful because by getting information that will help us understand early on whether or not we are hitting the target, we will be able to reduce the time spent on development and therefore reduce cost. The results of many phase 0 trials are being published now, and we are in discussions with a substantial number of companies that are very interested in conducting such trials with us. However, I think it will be many years before we know just how valuable these investigations are.

H&O What does the NCI hope to see in the future with such initiatives?

JD We hope to be able to support the burgeoning interest in therapeutics discovery within the academic community by providing resources that bridge the gap between the laboratory and the clinic. We hope to assist the process of taking the knowledge that is produced by the oncology community, in terms of novel genetic abnormalities or new targets, and applying this knowledge to the drug development process. There are many institutions that have hired individuals from industry, hoping to exploit these discoveries. The NCI hopes to be able to provide an infrastructure to facilitate those academic investigators. We are also very interested in helping small biotechnology companies that may have interesting projects but that lack the resources to bring their discoveries to the clinic.