

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The NCI Developmental Therapeutics Program

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H&O When and why was the Developmental Therapeutics Program begun?

JC Congress established the Cancer Chemotherapy National Service Center at the National Cancer Institute (NCI) in 1955, which evolved into the Developmental Therapeutics Program (DTP). The program was created to serve as a central source for drug discovery and for the testing of drug activity in the anticancer arena. Thus, the main function of the DTP is to facilitate the discovery and development of anticancer drugs.

H&O How much of the funds allotted to the DTP are for grants versus on-site research?

JC As for most National Institutes of Health (NIH) programs, about \$0.85 of every dollar of the DTP is reserved for the grant pool, which funds investigator-initiated research. The grant pool is a national innovation engine, and investigators with the best cutting-edge ideas are the ones who receive funding. Grants are awarded through the NIH peer-review process and the research is driven by the investigators, not directed by the NCI.

The other 15% of DTP's funds is reserved for highly focused contracts and internal laboratory programs on drug development. The DTP provides tools for cancer researchers (eg, samples of drugs, tumors cells, open databases of testing results for a wide range of molecular structures), and the resources needed to move candidate molecules closer to clinical testing. The desirability of further work is reconsidered as results are generated at each stage.

H&O What is the role of the DTP in the various steps needed to take a drug from the theoretical stage up to the point of the initiation of human studies?

JC One of the key steps needed for drug development is the ability to produce enough of the drug to conduct large-scale human testing. Frequently, an academic or nonprofit investigator is able to produce a few milligrams of a compound, but much larger amounts are needed for clinical trials. The DTP specializes in synthesizing large quantities of drugs. Another transition point in the development of a new drug is whether the agent will have activity in an intact in vivo system. The DTP has established many models for these pharmacology and drug efficacy studies. Substantial effort is sometimes required to create a suitable drug formulation. If the drug is given orally, it needs to be absorbed from the gastrointestinal tract to then circulate through the body. If the drug is given intravenously, it needs to be soluble in a substance that can be delivered through a vein. The DTP provides substantial expertise in formulation methods.

Finally, as an agent approaches human studies, it is important to demonstrate to regulatory authorities and institutional review boards that the dose and schedule that will be employed in the clinical study are reasonably safe and that toxicity is reversible. These studies are difficult, requiring specialized expertise in animal testing procedures and histopathology, and are the most expensive part of drug development for DTP and other organizations.

Like pharmaceutical companies, the DTP considers these various stages of drug development as a pipeline, and the DTP contains three separate pipelines. The internal pipeline is the Drug Development Group. Here, ideas from our own laboratories, from independent investigators wishing to partner with the DTP, and sometimes from pharmaceutical companies of various sizes wishing to partner with the DTP, are collected for possible development. The Rapid Access to Intervention Development (RAID) program is another pipeline and provides a structure for investigators who want to retain a lead role in the development of a compound but do not have the resources to do so on their own. Proposals for RAID projects are prioritized by an external peer review

panel. The DTP provides the drug supply and data from toxicology and other studies to the investigator so that all components necessary to begin the first human study are available. The most recently developed pipeline is a partnership with the intramural NCI laboratories, many of which are interested in moving new ideas into early human evaluation. We have a drug development committee run jointly by the Division of Cancer Treatment and Diagnosis, of which the DTP is part, and the intramural Center for Cancer Research. At any given time, there are molecules in each of these pipelines in various stages of the journey from laboratory to clinical testing.

H&O What roles do the NCI and pharmaceutical companies play?

JC Pharmaceutical companies did not previously emphasize anticancer drugs, but over the last 20 years, a major surge in research and investment by these firms has had a profound impact, including a number of successful drugs now available for patients. Commercial factors create a tendency to focus on highly prevalent cancers. The NCI may partner with a company that is evaluating a molecule for one cancer and collaborate with the firm to study it in less common diseases, such as cervical cancer or pediatric cancers. We try to focus our resources on areas that do not overlap with industry-based studies and to find the niches where our work can complement other ongoing research. The discovery of drugs from natural products is particularly suitable for federal involvement because of the many challenges in acquiring samples, production of adequate supplies, and a generally long period of development with uncertain return. Molecules that have no patent protection are another niche for federal programs.

H&O How does DTP contribute to the new NCI initiatives for early clinical studies?

JC Recently the DTP has been focusing more attention on starting the first human studies of a drug with a clearer understanding of that drug's mechanism of action, and having an assay available to determine whether the new molecule actually works by the mechanism by which it is thought to work. Ultimately, the DTP is interested in studies that can determine whether a drug's effect is in fact being achieved through its supposed mechanism of action, but there are many earlier questions to be addressed. Such studies take advantage of a new US Food and Drug Administration regulatory tool called an exploratory Investigational New Drug (IND) study. As the name of this tool implies, this approach is not full-scale drug development, but rather an exploratory study to answer a specific question.

H&O Where do these studies fit in terms of the phase I-IV clinical trial process?

Exploratory IND studies could be considered as phase 0. The drug dose is not pushed to the maximum tolerable amount and extreme toxicity is not expected to occur. At the same time, efficacy is also not expected. These studies are conducted solely to determine whether a drug does in humans what is expected, based on preclinical studies. Downstream outcome measures are not considered until subsequent phases.

H&O Have methods for this kind of study already been defined?

JC The framework is in place, but the limiting factor is usually assay methods. For example, if an investigator is studying a DNA repair enzyme, there may be adequate tests available for laboratory studies, such as isolated subcellular fractions from cells growing in culture. These initial assays need to be converted into assays that will work in vivo in animals and subsequently in human tumor specimens. More effort would need to be made toward developing an assay than has been traditionally done. Such an assay needs to be reliable, sensitive, and reproducible. If the earliest human studies are intended to determine whether a drug works as intended from preclinical studies, then the right tools need to be available at the time human studies begin.

H&O Are efforts to improve the development of assays underway?

JC Absolutely. Without the right assay, it is not possible to answer a focused question. Indeed, the elegant science and careful testing procedures for an assay must not distract us from the central importance of asking the pivotal questions. What information is needed to determine whether a candidate molecule continues forward or is sent back to the drawing board? What data must be generated so that they can be effectively synthesized into information for decision-making?

H&O What is the difference here between information and data?

JC It depends strongly on the question. For example, the pivotal question might be: Can I achieve an adequate concentration of the molecule in the body to drive its intended effect? A piece of data would be, for example, the concentration of a drug circulating in the body. Information would be gained by comparing those data with the concentration that is necessary in vitro to produce a particular mechanistic or antitumor effect. Thus, to answer this specific question, all that is needed is an assay

that measures the concentration of the drug circulating in the body. If the answer is acceptable, this first level of question would then lead to another set of questions to guide future studies.

In addition to information about concentration or drug exposure in the body as the molecule progresses, an investigator also needs information about the drug's effect. With a DNA repair inhibitor, for example, one would want to know whether the particular DNA repair process has been inhibited. If the specific process has been inhibited or modulated, the drug development program would be continued. If not, an investigator might return to the laboratory to search for a replacement for the agent that had been selected.

H&O What are the goals of this approach?

JC In some cases, the goal of this approach is to select a certain molecule from a range of molecules that are in the same class. No organization has unlimited resources to develop all the molecules in its pipeline and so selecting the most promising compound in advance would help expedite research. Also, when a completely novel mechanism of action has been defined in laboratory studies, this approach enables one to determine whether that mechanism works the same in humans. Many variables are introduced in human studies, and this approach focuses on the specific phenomenon in question.

H&O Would an example of this approach be determining whether a targeted therapy agent is achieving its intended effect by inhibiting the specified target?

JC By the late preclinical stage, several molecules of a certain kind may appear to be equivalent in terms of target effects, and this mechanism could be used to make the final selection for full-scale development based upon a phase 0 study comparing several analogs. As an example, if one is developing a new drug directed against the epidermal growth factor receptor (EGFR), the molecule that will be selected for development will be the one with the most specificity against the EGFR. In the first human studies, the investigator will be watching to see whether that specificity is maintained in humans to the same degree as it was in the preclinical setting.

There will always be some degree of uncertainty regarding whether the benefit seen with a given targeted agent is a direct result of inhibiting the specified target. Prior to full-scale clinical testing, there is no way to eliminate the possibility that the most specific anti-EGFR agent available will not be effective because inhibition of some other pathway is needed. Nonetheless, preclinical allocation of resources is driven by a view of the desired

effect of the molecule in a tumor, and phase 0 provides the option of extending that paradigm to the first evaluation step in patients.

H&O What are some of the most innovative ideas on which the DTP is focusing its resources?

JC Every day, new discoveries are made in terms of the downstream effects of sequencing the human genome and in terms of understanding the cancer genome. Comparisons between host and tumor cells provide clues about which targets might be most effective, and what molecule might inhibit those targets. The DTP is very interested in moving forward with these types of studies, and we have tried to make the RAID program as flexible as possible in order to best facilitate such work.

With the phase 0 studies, tools such as genomics and noninvasive imaging are being used to study mechanisms of action. At any stage of drug development, specific questions must be answered: Is the target novel? Is the effect quantitatively accurate? Is it possible to deliver the drug? Are there metabolic issues that interfere with the drug reaching the target? Once the drug reaches the target, does it act in the predicted way?

The DTP also specializes in the development of natural products. As mentioned earlier, the development of natural products involves an enormous amount of logistical work, and such projects can take years or decades to complete. It is difficult for commercial investors to know whether they will receive a return on their investment, but the DTP is not bound by the same constraints.

H&O What resources are available through the DTP Web site?

JC The DTP has large stores of data from tests of drugs against known targets, and these results are available on the Web site so that investigators can analyze the findings and generate new ideas. The site also contains descriptions of all of the programs within the DTP. Samples of drugs, tumor cells, and natural product extracts are made available for investigators to use in laboratory testing. Investigators can send requests for compounds and assistance through the Web site.

Online Resources and Suggested Reading

Developmental Therapeutics Program of the NCI and NIH.
<http://dtp.nci.nih.gov>.

Food and Drug Administration. Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies. January 2006. <http://www.fda.gov/cder/guidance/7086f1.pdf>

Zubrod CG, Schepartz SA, Carter SK. Historical background of the National Cancer Institute's drug development thrust. *Natl Cancer Inst Monogr.* 1977;45:7-11.