

*Congressional Update: Report from the Biomedical Imaging Program  
of the National Cancer Institute*

## **Imaging Drug Development<sup>1</sup>**

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Recent advances in our understanding of the genome and of cellular and subcellular biology at the molecular level have generated a different view of health and disease, as well as new approaches to therapy. These advances have created new demands on imaging as a tool for diagnosis and monitoring. Whereas diagnostic imaging was formerly used primarily to illuminate anatomy or structure at the organ and tissue levels, it is currently being asked to provide information about activity at the cellular and molecular levels. In addition, diagnostic imaging is now being asked to characterize molecular targets and processes with not only spatial but also quantitative accuracy.

Within the field of oncology, new insights into the genetic and molecular biological basis of cancer have led to a revolution in drug discovery and therapeutic approaches. The concept of "rational drug discovery" is displacing the former approach of empirical observation. For example, previously the end point for screening potential cancer drugs was usually antiproliferative activity. Today, however, the focus is the drug's effect on its molecular target. These molecular effects can be determined with *in vitro* testing and with tissue assays in animal models, but noninvasive *in vivo* tests are needed for use in humans. Imaging has the potential to fill this need.

Although substantial improvements in imaging technology are constantly being made and new imaging devices are on the horizon, imaging's greatest opportunity to play a pivotal role in the postgenomic era may be through the development and implementation of highly specific molecular imaging probes. However, this ability to elucidate an array of targets and generate specific therapies and probes creates a practical dilemma. In the past 20 years, the cost of drug development and clinical introduction has increased by over

800% and in 1997 was estimated at \$500 million. It is also estimated that for every 5,000 compounds screened, only one is successfully approved and introduced into the market. With this level of risk, commercial pharmaceutical companies must carefully evaluate the market potential, realizing that only candidates with broad application in both market share and sales volume are likely to represent a rational business decision. The need for effective therapies in limited markets is appreciated, however, and was the social force that prompted the Orphan Drug Act of 1983 (ODA). The ODA was intended to promote the development of drugs for diseases affecting fewer than 200,000 people or for which a developer would have no reasonable expectation of cost recovery in a larger population. The ODA has been considered effective, and among the designated compounds are a number directed at acquired immunodeficiency syndrome and cancer. It is estimated that almost 50% of drugs designated as orphan apply to populations of fewer than 25,000.

Many therapies designed to interact with specific molecular targets are likely to have limited market potential and attributes similar to those of other drugs that have received ODA designation. Imaging probes to elucidate and interrogate these targets may be even more vulnerable than their therapeutic counterparts. However, the development of clinical imaging probes that will enable a better understanding of cancer *in vivo* at the molecular level represents an extraordinary opportunity. The greatest challenge to realizing this opportunity, however, is the seemingly endless number of targets and possible probes. In recognition of this challenge, the National Cancer Institute (NCI) has recently introduced new programs to facilitate imaging drug development similar to programs previously implemented for therapeutic drugs.

From a practical standpoint, the challenge for imaging drug development can be divided into three elements: scientific feasibility, alignment, and rapid evaluation. Two associated programs are being implemented to address these elements.

The Development of Clinical Imaging Drugs and Enhancers (DCIDE) program of the Biomedical Imaging Program

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(BIP) (<http://cancer.gov/bip/dcide.htm>) is a competitive program to expedite and facilitate the development of promising imaging agents. It is intended to supply or enable missing steps in the preclinical development process so that promising discoveries can be translated to the research and clinical environments. The DCIDE program will focus on promising imaging agents that are not otherwise likely to receive an adequate and timely evaluation. DCIDE will facilitate development of and/or provide probes for preclinical *in vivo* imaging and clinical research, but it will not fund clinical research studies.

The DCIDE program is intended to address all three elements at the preclinical level. The rationale for this program is derived from the realization that a substantial number of promising diagnostic imaging agents are not available for use in clinical trials and are not likely to undergo preclinical development to the level sufficient for Investigational New Drug (IND) application. Many of these agents have the potential to enhance clinical medicine, either by providing a measure of response to chemopreventive interventions or therapy or by serving as surrogate end points to preventive measures or therapy. The program is designed to mitigate two fundamental barriers: (a) uncertain economic potential that prohibits access to necessary resources and (b) lack of knowledge of clinical and regulatory requirements. Removal of these barriers has become more critical as interdisciplinary boundaries have expanded to include technical researchers such as combinatorial chemists and bioengineers.

To optimize the return from resources devoted to the program, developed probes will be maintained in a Translational Probe Library. This library will facilitate accessibility of housed probes for clinical trials groups or investigators, as well as for preclinical researchers interested in *in vivo* imaging studies, including proof-of-principle animal model studies.

In keeping with its goals, the DCIDE program will provide any or all of the following assistance: (a) The program will provide performance or facilitation of steps in preclinical development that are necessary to convert a potential new agent into a diagnostic drug candidate suitable for early clinical testing (IND status) and that are generally not otherwise available to the investigators. These steps may include dosim-

etry, pharmacokinetics, imaging feasibility, and IND-directed toxicology. (b) The program will provide assistance with regulatory affairs, so that requirements of the Food and Drug Administration may be satisfied by any investigator who seeks IND status. (c) The program will provide access to probes for approved preclinical protocols (including animal models).

Opportunities for further clinical development, including Phase 1 and 2 clinical trials, are likely to be available for imaging agents that have completed preclinical evaluation and IND filing through the DCIDE program. In fact, a new program that provides resources to conduct Phase 1 and 2 trials of imaging drugs from various sources has recently been approved and will be implemented in fiscal year 2001.

This program, the second of the two new programs being implemented by the BIP, is the Early Clinical Trials for Imaging Agents program. These Safety and Preliminary Clinical Efficacy contracts will create an early clinical trials infrastructure poised to rapidly evaluate molecularly targeted imaging probes, ligands, radiopharmaceuticals, and contrast agents to assess anticancer agents on their molecular targets and determine clinically relevant correlates. The objectives of this program are (a) to rapidly conduct clinical trials necessary to assess the safety and imaging capabilities of promising imaging agents; (b) to characterize the molecular interactions of new molecular imaging agents with their targets through biopsies, assays, and other appropriate technologies and to correlate those effects with clinically relevant end points; and (c) to develop new scientific insights into molecular pathways and determinants of the relationship of the targeted imaging agents to therapeutic drug response.

Important advances in the technology of current imaging modalities and in clinical techniques are likely to improve resolution in anatomical imaging, but the greatest impact in oncology will probably be made by advances in functional and molecular imaging. In fact, the addition of functional data to enhanced anatomic data will improve overall accuracy by increasing specificity, but it will also enable study of metabolic changes independent of anatomic changes. Most of this functional data will be the byproduct of using molecular probes that enable quantitation of the correlation between imaging and a specific molecular process.