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

The NCI Biomedical Imaging Program:

Five-year Progress Report[1]

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The National Cancer Institute (NCI) established the Biomedical Imaging Program (BIP) in October 1996 with David Bragg, MD, as the first acting director. Daniel C. Sullivan, MD, became the first full-time director in September 1997. During the subsequent 5-year period, the number of full-time staff members has grown from two in 1996 to 21 in 2001. The total amount of grant money administered by the BIP has expanded from $47 million in fiscal year 1996 to $126 million in fiscal year 2001. The staff members and administered grants are divided among four branches: the Diagnostic Imaging Branch, the Molecular Imaging Branch, the Image-guided Therapy Branch, and the Imaging Technology Development Branch.

The overall activities of any institute within the National Institutes of Health can be thought of in terms of three general categories: application review, program development, and grants financial management. The BIP deals with the second of these categories, program development. The mission of the BIP is to promote and support outstanding basic, translational, and clinical research in the biomedical imaging sciences and technologies and to apply any new discoveries related to solving national health care needs, such as treatment for cancer. We seek to identify and exploit the most promising areas of science and technology that will lead, with the use of imaging, to better diagnostic and therapeutic interventions for cancer. We do this by several means:

1. Investigator-initiated research. BIP staff facilitates investigator-initiated research that has been identified as meritorious at the competitive peer-review process. When areas of particular importance are not being fully developed with the unaided investigator-initiated process, BIP staff conceptualizes and identifies special initiatives to target funds for specific purposes. Examples of these initiatives are the In Vivo Cellular and Molecular Imaging Centers (ICMICs) and the American College of Radiology Imaging Network (ACRIN).

2. Directed research and development. In some cases, there are substantial obstacles that impede research and development of important devices or agents. We have begun to develop programs in which BIP staff will direct clinical trials or initiate other developmental steps necessary for the evaluation of devices or agents that are identified as potentially important for research or clinical needs. For example, a request for proposals has recently been announced for sites to perform, under contract, clinical trials of imaging agents.

3. Industrial collaborations. The imaging device and pharmaceutical (imaging agent) industries are major sources of innovation and product development. Therefore, BIP collaborates with companies when, in our judgment, promising new products would otherwise not be developed or would not develop as quickly or as ade-

Acad Radiol 2002; 9:122–125

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quately. An example is a large clinical trial in which digital mammography is being compared with conventional screen-film mammography. This is referred to as the Digital Mammography Imaging Screening Trial, or DMIST. We are collaborating with four manufacturers of digital mammographic devices for this study.

4. Research resources. We try to provide the research community with a variety of research resources and tools that would otherwise not be available. Examples include the Small Animal Imaging Research Resources, the Lung Imaging Database Consortium, and the Washington University Isotope Resource.

5. Scientific forums. We convene members of the research community in large or small groups, as appropriate, to share scientific information and/or to provide recommendations about the best way to invest funds available to the BIP. A listing of most of these forums and reports from them, as well as information about all of our activities, are available on our Web site, *www.cancer.gov /bip.*

The following is a status report of specific programs.

ICMICs were designed to capitalize on the extraordinary opportunity for studying cancer noninvasively, and, in many cases, quantitatively, due to recent advances in molecular imaging modalities and molecular and cellular biology. The ICMICs are intended to bring together investigators with a variety of expertise in fields such as molecular biology, biomedical engineering, radiology, pharmacology, computer science, and chemistry, to facilitate interaction and develop methods that will provide information about what is happening at the molecular level in the intact organism. Two types of grants have been made available.

The planning grants (Pre-ICMICs or P20s) provide funding of 3 or 4 years' duration to allow the awardees enough time and money to formally plan and establish the organizational and operational structure necessary for new, multidisciplinary collaborative scientific efforts. Ten Pre-ICMIC grants were awarded during fiscal year 2000, and six additional Pre-ICMICs were awarded in fiscal year 2001. The 5-year specialized center grants (ICMICs or P50s) provide a formal framework in which scientific synergy can occur on a stable and continuing basis. In fiscal year 2000 we funded three ICMICs, and in fiscal year 2002 we will fund one or two more. ICMIC budgets are in the range of $2 million per year.

Small-animal models, particularly genetically engineered mice, have become essential discovery tools in cancer research. Small-animal imaging techniques can be used to obtain data about biochemical, genetic, or pharmacologic processes in vivo, and they can be used repetitively in the same animal without having to sacrifice the animal for analysis. The Small Animal Imaging Research Resources program provides *(a)* shared imaging research resources to be used by cancer investigators, *(b)* research related to small-animal imaging technology, and *(c)* training for investigators and technical staff in small-animal imaging. We funded five Small Animal Imaging Research Resources programs in fiscal year 1999 and five more in fiscal year 2001. Funding levels are approximately $1.5 million in the 1st year and $750,000 in subsequent years for each grant.

The Development of Clinical Imaging Drugs and Enhancers (DCIDE) program is intended to supply critical missing steps in the development and validation of imaging compounds, including contrast agents used for positron emission tomography (PET). The DCIDE program focuses on promising imaging agents, including many PET-labeled compounds that are otherwise not likely to receive an adequate and timely evaluation. DCIDE is a competitive program created to expedite and facilitate the development of promising imaging enhancers (contrast agents) or molecular probes from the laboratory to early clinical trials. The DCIDE program will facilitate some of the work necessary to bring contrast agents to the point of Food and Drug Administration Investigational New Drug application approval.

The DCIDE program is intended to supply or enable the establishment of missing steps that will allow promising discoveries to be translated to the research and clinical environments in the absence of development capacity, clinical connections, or industry interest. The DCIDE program is not intended to provide full-scale clinical development by itself, but it will facilitate the performance of clinical trials to establish proof of principle of a compelling hypothesis. Once this is accomplished for specific products, it is anticipated that clinical development will continue along established lines under the sponsorship of either private companies or the NCI. Through the DCIDE program, the developer of a promising imaging agent or probe will be given access to the development resources of the NCI to remove the most common barriers between laboratory discoveries and clinical trials. Two contrast agents are currently in development in the DCIDE program, and about $2 million is budgeted for this program per year.

ACRIN is an NCI-sponsored cooperative group that was established in January 1999 to perform multi-institu-

tional clinical trials in diagnostic imaging that relate to cancer. As a national clinical trial resource, ACRIN provides a stable infrastructure in which clinical trials can be conducted. If investigators have an idea for a large-scale clinical trial but do not have access to a sufficient number of clinical patients to adequately implement such a trial, ACRIN resources are competitively available. Base funding for ACRIN is approximately $5 million per year. In addition, a multimillion-dollar supplement has been awarded for the Digital Mammography Imaging Screening Trial. Active or approved trials include *(a)* the Role of Radiology in the Pretreatment Evaluation of Invasive Cervical Cancer, *(b)* Computerized Tomographic Colonography: Performance Evaluation in a Multicenter Setting, *(c)* Digital versus Screen-Film Mammography, *(d)* Contemporary Screening for the Detection of Lung Cancer Pre-Malignancy and Malignancy, *(e)* Chemoembolotherapy for Liver Metastases from Colon Cancer, *(f)* Comparison of [magnetic resonance] MR Image Segmentation Algorithms for Brain Tumors, *(g)* Image Processing Algorithm for Supraglottic Tumors, and *(h)* Radiofrequency Ablation for Bone Metastases.

The Lung Imaging Database Consortium is a cooperative group of institutions funded to develop the necessary consensus and standards for a database of computed tomographic (CT) images of the lung and to construct a database of spiral CT lung images. Image-processing algorithms are increasingly important as biomedical imaging becomes more electronic in terms of image acquisition and display. However, the development of optimal image-processing software has been hampered by the lack of standardized data sets on which to test new algorithms and display the results. Five institutions have been funded for 5 years, beginning in fiscal year 2001, to demonstrate that a group of experts can develop a process that will serve as a model for other groups to develop additional image database resources.

A request for proposals for sites to perform, under contract, phase 1 and 2 clinical trials of imaging agents was released in October 2001. The sites selected by peer review from the applicant pool will be funded beginning in September 2002 to perform phase 1 and 2 imaging trials (safety and preliminary clinical efficacy) of novel imaging agents.

Clinical ultrasonographic (US) procedures currently account for a substantial fraction of imaging studies in the United States, and US is a leading modality in terms of its clinical impact. At US, radiofrequency pulses stimulate a transducer probe to generate ultrasound waves. The echoes reflected from different biologic structures form images. However, access to raw, unprocessed echo data is not possible with commercially available US machines the way analogous signals are with MR or CT. This is a substantial impediment to research of new US techniques conducted by biomedical engineers. Manufacturers' reluctance to provide access to the echo data has been based on cost, proprietary issues, safety, and liability considerations. A US research interface is necessary as a research resource to overcome this barrier. A request for proposals was issued last year, and a $2 million award was given in September 2001 to a partnership of a US equipment manufacturer (Siemens) and multiple academic centers to develop and test a US research interface. It is expected to be available to the research community within 2 years.

The Exploratory/Developmental Grants program provides support for 2 years of funding at a level adequate for completion of initial feasibility testing and generation of preliminary experimental data. This program was initiated in 1997. These grants fund innovative and creative approaches in diagnostic imaging that lead to new avenues of research and provide investigators with the initial resources required to accomplish pilot testing of ideas. Since the inception of this ongoing program, over 240 applications have been received, and approximately 58 grants have been awarded for a total of $14.9 million. The funded grants cover a wide array of technology development, preliminary work on molecular imaging, and early feasibility clinical trials.

The Novel Imaging Technology Development program uses a two-phase mechanism (the R21/R33 mechanism) for technology development and is directed toward the development of imaging methods and enhancers and toward the limited evaluation or feasibility studies that use either preclinical or clinical models. The intent is to stimulate *(a)* the development of highly innovative imaging methods and enhancement methods, including high-risk and/or high-gain technologies that exploit our expanding knowledge of the molecular basis of cancer, and *(b)* the integration of these emerging and more traditional technologies to find more effective solutions for cancer. To date, about $1.5 million has been awarded through this initiative.

The request for applications (RFA) for the Image Agent Development initiative was issued for funding in fiscal year 1999. The initiative supports research projects that address the development and application of labeled therapeutic agents as compounds for imaging studies and/or the development and application of imaging agents

as metabolic markers of response to newly developed therapeutic agents. In response to this RFA, 33 applications were received, and eight awards have been given. The funded research focuses on a wide range of cancer therapies that use numerous imaging methods, including PET, single photon emission CT (SPECT), MR imaging, and MR spectroscopy.

The Image-guided Prostate Diagnosis or Therapy initiative was designed to encourage research on improved imaging methods for image-guided biopsy or therapy of prostate cancer. Specific goals included the development and application of one or more of the following interrelated components: *(a)* means for measuring local extent of disease by using anatomic, metabolic, or alternative novel imaging methods, *(b)* means for improving image-guided biopsy, staging, or identification of aggressive cancers by using metabolic or alternative novel imaging methods, and *(c)* means for navigation and control of image-guided therapy or measurement of early biologic effects of therapy. Sixty-four applications were received. Of these, 12 were funded by the NCI in fiscal year 2001, and another three were funded by the National Institute of Aging, which participated in the RFA. Five Small Business Innovative Research grants were also funded. NCI funding for this initiative equals $11.9 million over the 4-year life of these grants.

In 2001 a new National Institutes of Health institute was created, the National Institute of Biomedical Imaging and Bioengineering (NIBIB). It is anticipated that NIBIB will support general imaging research, and that the NCI BIP will continue to support imaging research related to cancer. We expect that the NCI commitment to the priority area of cancer imaging will continue at a high level for the next several years, at least.