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

NCI-funded Small Animal Imaging Programs[1]

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The use of small animal models as surrogates for humans in the study of normal and disease states has a long history. The models used have ranged from the simplest possible to those as complex as the investigator's imagination and skills allow. Growing opportunities to apply methods of molecular and cellular biology to the study and treatment of human disease have increased demand for the creation of animal models with more humanlike diseases. Cultures of cancer cells growing in vitro, or as tumors on the flank of a small animal, no longer suffice because treatment agents and techniques that enjoy even great success in such milieus too frequently prove to be utter failures in phase I testing in humans. These failures propel investigators to understand disease, and its progression and treatment, by better means than observations of less-faithful models, such as a growing cell line. They see more fruitful approaches in molecular and cellular manipulations of animals to model the whole disease process more faithfully.

Successful creations of live, whole animals that more faithfully model human diseases led to an obvious desire for a way to image disease progression in each animal, without resort to biopsy or sacrifice to answer every question. Most early animal imaging studies used instruments and techniques designed for human use, during hours when this equipment was not in clinical use. However, systems optimized for human use frequently yield suboptimal results for small animal studies. In addition, there are other problems associated with mixing animal and patient studies on clinical instruments.

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The growing need for dedicated small animal imaging systems was noticed by the Biomedical Imaging Program of the National Cancer Institute (NCI) and was included among other issues explored in series of workshops held to better define the needs for cancer imaging and areas in which special NCI initiatives might provide the most impetus for change and advancement. One subgroup addressing small animal imaging—the In vivo Molecular/Functional Imaging Subgroup (MIS), chaired by Elias Zerhouni, MD—recommended that the National Institutes of Health (NIH) and NCI should support dedicated small animal imaging facilities focusing on the study of genetically engineered tumor models (*http://cancer.gov/bip/ISWG3.htm*). They also recommended that the greater part of the efforts of the facilities be directed toward imaging, not the creation of new instruments. Workshop participants concluded that the facilities should provide imaging by more than one technique because they did not like the prospect of limiting the range of scientific questions open to investigation by having only one modality at hand.

With this workshop recommendation in mind, the Biomedical Imaging Program developed a concept for Small Animal Imaging Resource Project (SAIRP) grants, which the May 1998 NCI Board of Scientific Advisors approved enthusiastically. The concept was for the Biomedical Imaging Program to budget support for approximately four SAIRPs under the R24 mechanism, which specifies the development of research resource centers. Each grantee would be expected to provide access to at least two different imaging modalities and serve at least six funded cancer research projects by the end of the 2nd year of operation. The Biomedical Imaging Program translated the concept into a request for applications, set a receipt date of November 1998, and defined the objectives and scope as follows: (*a*) multiple imaging technologies for small animals, emphasizing, but not limited to those technologies that can provide biochemical, genetic or

pharmacological information in vivo; (*b*) technology research and development of innovative imaging methods appropriate for small animals, as well as refinement and development of technologies already established; (*c*) capabilities and personnel to assist in the development and/or production of necessary imaging probes for the imaging systems provided; and (*d*) capabilities and personnel to aid in small animal care, maintenance, and anesthesia, and provide expert consultation on optimal choices of animal models and imaging system use for the imaging experiments under consideration.

About 30 applications were received and reviewed by a panel of peer reviewers convened by the Division of Extramural Activities of the NCI. Of those scoring favorably, five were approved for funding by the Executive Committee of the NCI. Total funding for 5 years for the five projects is expected to cost $16.3 million. A telling comment made by a number of applicants for SAIRPs was that in the course of preparing their applications, they made contact with cancer researchers with whom they had not previously interacted, and that they expected future valuable collaborations with them, whether or not their SAIRP application was funded.

The five funded sites, their principal investigators, and titles of their projects are as follows: (*a*) the University of Michigan, Brian Ross, "Development of a Regional Tumor Imaging Resource"; (*b*) the University of Arizona, Robert Gillies, "Southwest Small Animal Imaging Resource"; (*c*) the University of Pennsylvania, Jerry Glickson, "Small Animal Multi-Modality Imaging Center (SAMMIC)"; (*d*) Washington University in St Louis, Joseph Ackerman, "Washington University Small Animal Imaging Resource"; and (*e*) Memorial Sloan Kettering Cancer Center in New York City, Jason Koutcher, "Animal NMR and Radionuclide Imaging."

Original funding occurred in the summer and fall of 1999, so the SAIRPs have been in operation for 18 months or so. Since there is a requirement that the equipment purchased with SAIRP funding be installed and operating at the end of the 2nd year of operation and be servicing at least six grants, these SAIRPs will be reviewed after their 2nd year to determine if they are in compliance.

Imaging modalities represented include magnetic resonance (MR) imaging and MR spectroscopy at 2.0, 4.7, 7.0, and 9.4 T, positron emission tomography, single photon emission computed tomography, x-ray computed tomography, optical coherence tomography, ultraviolet to near infrared optical imaging, flying spot scanning, and quantitative autoradiography. The base grants serviced include research to assess receptor levels, follow tumor progression and metabolism, study tumor infiltration, monitor the behavior of gene therapy agents, visualize mouse embryos with genetic variations, image metastatic lesions, and investigate the effects of biochemical manipulation on tumor sensitivity to therapeutic ionizing radiation. A number of these investigations incorporate more than one modality, and the images will be co-registered. A number of strains of transgenic mice are involved in protocols within the five SAIRPs.

SAIRP funding includes travel funds for an annual meeting of investigators. The first of these was held at Washington University in St Louis, Mo, in March 2000, and the second is planned for March 2001 in Tucson, Ariz. The meeting agenda will include reports on progress, a discussion of problems in common, and a tour of the local facility.

The enthusiasm of the research community for small animal imaging may be estimated by several measures. The good response to the SAIRP initiative was detailed above. The Society of Nuclear Medicine held an all-day animal imaging session at their 1998 meeting. An international meeting, HiRES 1999, addressed the topic of small animal imaging, in Amsterdam, the Netherlands, at the Free University. Small animal imaging methods were prominent among sessions exploring drug research problems at meetings of the Society for Nuclear Imaging in Drug Development, and Functional Imaging in Drug Discovery and Development held over the past 3 years. HiRES 2001 is now planned for September 2001, in Bethesda, Md. It will feature sessions on small animal imaging techniques and results, as well as sessions on animal handling techniques for imaging.

There are other NIH efforts in small animal imaging. The National Institute of Allergy and Infectious Diseases, with cosponsoring by the NCI's Biomedical Imaging Program, issued an announcement in February 1999 entitled "New Imaging Technologies for Autoimmune Diseases," which resulted in seven funded applications. The NCI issued a grant to one of them, the Massachusetts General Hospital for Ralph Weissleder's project entitled "High Efficiency Lymphocyte Labeling for in Vivo Tracking." The National Center for Research Resources (NCRR) held a workshop entitled "In Vivo Microscopy: Technologies and Applications" in March 1999 (see the proceedings at *http://www.ncrr.nih.gov/biotech/btpublic.htm*). The NCRR also funds a Biomedical Technology Resource Center grant to G. Allen Johnson, Duke University, entitled "Integrated Center for in Vivo Microscopy," under their P41 program. The Duke Resource features three fully integrated MR systems: one 30-cm-horizontal-bore magnet operating at 2.0 T (85 MHz), one 15-cm-bore magnet operating at 7.1 T (300 MHz), and one 8.9-cm-bore magnet operating at 9.4 T (400 MHz) (*http://www.ncrr.nih.gov/ncrrprog/btdir/bt-c.htm#Anchor4*). The NCI sponsored an initiative entitled "Shared Resources for Scientists Outside NCI Cancer Centers" (PAR-99-127), under which Thomas Lewellen at the University of Washington received a grant for an "UWMC Positron Emission Imaging Animal Facility." The NIH-wide Bioengineering Research Partnerships (current announcement PA-01-024) have encouraged efforts in a number of areas, among them small animal imaging. Of course, there are also investigator-initiated applications funded for development of small animal imaging instrumentation and methods. Among them are

grants to Simon Cherry at UCLA and Thomas Lewellen at the University of Washington.

The interest generated by the first round of SAIRPs, as well as the activity generated by the award of 20 Mouse Models of Human Cancer Consortium grants (RFA CA-98-013), motivated the Biomedical Imaging Program to re-issue the SAIRP Request for Applications. An additional total of approximately $20 million is authorized for this effort. Among the applications received in November 2000, five institutions are expected to receive awards in July 2001 for the second round of SAIRPs. The second announcement differed from the first most notably in its requirement for a training component, as a response to the point that there are just not enough people trained to participate in this research effort and that more well-trained individuals are needed.