FY 2005 High-End Instrumentation Grants

NCRR awards **High-End Instrumentation (HEI) Grants** to research institutions around the country; these one-time grants support the acquisition of instruments that cost more than $750,000, with a maximum of $2 million each. During FY 2005, NCRR will provide nearly $18 million for 11 HEI grants that will fund the purchase of new state-of-the-art equipment required to advance biomedical research.

- Arizona Sate University - In-Vivo Spectroscopy/Imaging System
- Cold Spring Harbor Laboratory - High-Performance Computing Cluster
- Kennedy Krieger Institute, Inc. - 7 Tesla Whole-Body MRI Scanner
- University of California, San Diego - Acquisition of an MALDI TOF-TOF Mass Spectrometer
- University of Cincinnati - Acquisition of a Hybrid Fourier Transform Mass Spectrometer
- University of Maryland, Baltimore - High-Field Animal Magnetic Resonance Imaging System
- University of North Carolina at Chapel Hill - Acquisition-Ultra-High Resolution Mass Spectrometer
- University of North Carolina at Chapel Hill - 9.4 Tesla Small Animal Magnetic Resonance Scanner
- University of Southern California - 3T MR Imaging/Spectrometer for Heart and Brain Research
- University of Virginia - 9.4 Tesla MR Scanner for Murine Imaging
- Washington University in St. Louis - The Purchase of a Combined PET CT Scanner

Arizona State University

In-Vivo Spectroscopy/Imaging System
Tempe, AZ

Principal Investigator
Ranu Jung
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Grant No. 1-S10-RR019945-01
Award: $1,309,550

Description (provided by applicant):

With recent genetic and molecular advances, small animal models of human disease have become increasingly important resources for the investigation of the underlying mechanisms of disease. Many traditional investigational approaches require sacrificing the animals for *ex vivo* tissue and molecular analysis. This prevents the researchers from observing *in vivo* the natural or perturbed evolution of the processes under study. Additionally, small animal models are becoming increasingly important test beds to investigate the ability of novel implantable miniaturized devices and biomaterials to repair, regenerate, or replace the living system. Imaging on the scale of small animals offers an opportunity to noninvasively repeat investigations of biological processes *in vivo* in the same animal and efficiently test treatments for disease. One approach for bioimaging is to use nuclear magnetic resonance. The ability to perform *in vivo* imaging and spectroscopy in small animals or large tissue samples is absent at Arizona State University. The gap's significance is increased due to a lack of such a capability in the entire Metropolitan Phoenix Valley area that is home to several excellent clinical and research medical facilities. The 120-mile distance to the closest facility is not conducive to conducting longitudinal chronic studies on large numbers of small animals to support the needs of research in the Phoenix Valley. We request support for a 7.0 Tesla, 30 cm clear bore system. This is a multipurpose research scanner for high resolution, fast-speed, Nuclear Magnetic Resonance 2-D and 3-D image reconstruction, and *in vivo* spectroscopy. Several investigators would significantly benefit from utilizing this system in their research. The applications would range from assessing effects of chemotherapy for tumors; to developing, testing, and implementing noninvasive, brain-imaging indicators of Alzheimer's

Disease (AD) in double transgenic mice containing AD genes; to assessment of central nervous system neuroplasticity after spinal cord injury or stroke.

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Cold Spring Harbor Laboratory

High-Performance Computing Cluster
Cold Spring Harbor, NY

Principal Investigator
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Grant No. 1-S10-RR019958-01
Award: $1,985,558

Description (provided by applicant):

The multidisciplinary research community at Cold Spring Harbor Laboratory is devoted to understanding the molecular and physiological bases of human cancer, neurological disorders, plant genetics, genomics, and bioinformatics. This broad-based research community has embarked on research areas that require significantly more computing power than is available at the laboratory. Technical innovations like microarrays and comparative techniques in bioinformatics have also greatly intensified data storage requirements. The foundation of this proposal is to improve and expand the computing infrastructure to support current and new research in these areas. The equipment requested will enable investigators to achieve results in ambitious projects and support further exploration in areas of biomedical research.

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Kennedy Krieger Institute

7 Tesla Whole-Body MRI Scanner
Baltimore, MD

Principal Investigator
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Grant No. 1-S10-RR019927-01
Award: $2,000,000

Description (provided by applicant):

Magnetic Resonance Imaging (MRI) at 7.0 Tesla is the new frontier to be explored in human research. However, no 7.0T human scanner is presently available for extramural research in Maryland. We propose to acquire a 7.0T wide-bore MRI instrument to upgrade the F.M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute to a state-of-the-art, very high field MRI facility. Investigators at the Kennedy Krieger Institute, the Johns Hopkins University, and the University of Maryland presently have 28 NIH-funded grants with several aims that can strongly benefit from the improved technical capabilities at the high field strength of 7.0T compared to the presently available equipment. These investigators presently use the 1.5T and 3.0T systems in the F.M. Kirby Research Center for brain and cardiac studies related to functional MRI, quantitative physiological MRI (e.g., absolute blood flow experiments), magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI), and diffusion tensor imaging (DTI). This proposed 7.0T instrument will provide the following benefits for the users: 1.) All studies will benefit from the increased signal-to-noise ratio (SNR) proportional to the field. Such an increase in SNR would allow either a reduction in scan time with the square of the field or an increase in spatial resolution (voxel size) linear with the field. This is important for all studies listed in this application. 2.) Several of the projects study functional MRI using the Blood Oxygenation Level Dependent (BOLD) effect, which increases—at least linearly—with the magnetic field. It has also been shown that BOLD data at high field reflect more of the microvasculature instead of large vessels. In addition, spin-echo BOLD effect may become better measurable, allowing its use for the study of frontal lobe and in the quantification of physiological parameters. 3.) The prolonged T1 at high field should allow improved sensitivity for arterial spin-labeling studies of absolute cerebral blood flow. 4.) Spectroscopy studies should benefit from the

increased chemical shift separation. Furthermore, coupled spins—such as those in glutamate, glutamine, and myoinositol—should become better distinguishable as they approach the weak-coupling limit. Heteronuclear spins and water-exchangeable protons will be more easily measurable at high fields, the latter leading to completely new imaging possibilities. This 7T whole-body upgrade is essential for continued high-quality state-of-the-art research at our institutions and for the national facilities provided by our research resource.

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University of California, San Diego

Acquisition of an MALDI TOF-TOF Mass Spectrometer
La Jolla, CA

Principal Investigator
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Grant No. 1-S10-RR019897-01
Award: $758,095

Description (provided by applicant):

The Mass Spectrometry Facility at the University of California, San Diego wishes to acquire a Matrix-assisted laser desorption ionization (MALDI) tandem time-of-flight (TOF-TOF) mass spectrometer. This mass spectrometer has novel patented tandem sources in which collision-induced dissociation occurs from the high-energy (1-2 keV) singly charged parent ions generated by MALDI. This technology is critical for determining the protein functional landscape, the next step after completion of the human genome project. The genome sequence revealed many fewer proteins than expected, suggesting that proteins have multiple states with differing functions. Protein function can be altered by participation in multiprotein complexes, post-translational modification state, and these modifications can result in different conformational states. The MALDI-TOF-TOF instrument will be available to everyone in the UCSD research community and will be used to approach all three of these questions. First, we will identify proteins in complexes in a robust and comprehensive way, even when the genome sequences of the organism from which the complex was isolated are not available. Second, we will identify the post-translational modifications on each of the proteins in the complex, beginning with glycosylation and phosphorylation. Third, we will identify the individual amino acids on surfaces of the proteins that interact in the complex and understand the conformational changes that accompany binding. Professors who are expected to be primary users of this new instrument include H. Zhou, J. Dixon, S. Taylor, R. Tsien, B. Tebo, and P. van der Geer, who are engaged in development of proteomics experiments to identify proteins in cellular complexes. Professor E. Komives pioneered the use of MALDI amide H/2H exchange for identification of protein interfaces and conformational changes that accompany protein-protein interactions. For this project, the MALDI-TOF-TOF will enable measurements of amide deuteration down to the single amino acid level.

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University of Cincinnati

Acquisition of a Hybrid Fourier Transform Mass Spectrometer
Cincinnati, OH

Principal Investigator
Patrick Limbach
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Grant No. 1-S10-RR019900-01
Award: $918,973

Description (provided by applicant):

This proposal supports the acquisition of an ion trap-Fourier transform ion cyclotron resonance hybrid mass spectrometer. This new instrumentation is intended for the identification and quantitation of proteins from protein complexes, whole proteomes, and single cells. This

instrument is arguably at the forefront of mass spectrometry instrumentation and represents a new platform for undertaking sophisticated proteomics-related studies. Proposed use of this instrumentation will support and enhance existing NIH-funded projects and provide avenues of research support that can lead to new funding for future projects for UC-affiliated investigators. Six NIH-supported users of this equipment will form the core research team. Their research interests, in some form or another, cover a wide spectrum of proteomics-related investigations. Examples include the effects of environmental agents such as estrogens, metals, and Polycyclic Aromatic Hydrocarbons (PAHs) on proteomes; examining the underlying biochemistry associated with microorganisms as they relate to biofilm production; proteomic examinations of post-translationally modified proteins involved in protein-protein interactions; and understanding the lamellar body proteome. All of the investigators participating in this instrument request have vigorous and well-funded research programs. The PI, who has been active in the field of mass spectrometry for nearly 15 years, will be responsible for the managerial oversight of the requested instrumentation. The equipment will be housed in the University of Cincinnati Mass Spectrometry Facility. This 3,500 square foot facility was renovated in 2001 and is equipped with the ancillary instrumentation required for proteomics. The instrumentation will be operated and maintained by two Ph.D.-level facility staff scientists, with one of these scientists having prior experience in both Fourier Transform Mass Spectrometry and proteomics being designated as the primary operator. These staff scientists are supported by B.S.-level staff technicians to ensure that the services are provided in a timely manner.

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University of Maryland, Baltimore

High-Field Animal Magnetic Resonance Imaging System
Baltimore, MD

Principal Investigator
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Grant No. 1-S10-RR019935-01
Award: $1,978,000

Description (provided by applicant):

The University of Maryland, Baltimore currently has 18 NIH-funded research projects that could greatly benefit from the availability of a shared high-field animal imaging magnetic resonance system. The projects cover a wide array of high-impact, cutting-edge, biomedical research, including topics such as brain development and disease processes through diffusion tensor imaging; understanding brain metabolism involved in white matter disease; understanding progression of breast and prostate cancer; and studying the efficacy of therapeutic agents, the pathogenic mechanisms of human herpesvirus, tumorigenesis, the progression of neurodegenerative events; and investigating the long- and short-term consequences of pharmacological treatment, the neuronal mechanisms of pain, cardiac dynamics, metabolic and development aspects of mental retardation, development of drug delivery agents for effective treatment of cancer, and many other such projects that are state-of-the-art and push the envelope of our scientific knowledge. The availability of a shared 7.0 Tesla animal magnetic resonance imaging system would allow investigators to probe into basic biological processes, understand the progression of disease, and follow the effects of novel pharmacological interventions through the use of multi-nuclear spectroscopy and imaging. The purchase of a 7.0T animal imaging system will be an important component to our existing shared resources on campus and will complement the high resolution Nuclear Magnetic Resonance (NMR) spectrometers that are used primarily for studying biological structures. This imaging resource will be located in specially designed space, in close proximity to the animal holding area and right next to two animal surgical suites. The Schools of Medicine, Pharmacy, and Dentistry; the Greenebaum Research Center; and the University of Maryland Biotechnology Institute join together in this shared instrument application. Institutional commitment for supporting the expenses and responsibilities for its operations will also be shared by the different schools and institutes of this campus. The number and quality of biomedical research projects performed at the University of Maryland Baltimore campus has reached a level that will guarantee a continued and pressing need to a high-field animal imaging system.

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University of North Carolina at Chapel Hill

Acquisition-Ultra-High Resolution Mass Spectrometer
Chapel Hill, NC

Principal Investigator
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Grant No. 1-S10-RR019889-01
Award: $1,000,000

Description (provided by applicant):

The University of North Carolina School of Medicine requests funding for the purchase of a Fourier Transform Ion Cyclotron Resonance (FTICR) mass spectrometer. This instrument is for the demand to study structural aspects of proteins, glycans, and metabolites related to various biomedical research projects throughout the institution. This includes the study of non-covalent complexes related to different cell cycle stages and enzymology; "top-down" proteomics for charaterizing and identifying post-translational modifications, such as phosphorylation and glycosylation (glyconomics); "bottom-up" proteomics for identifying interacting proteins to low abundant proteins; and structural identification of metabolites relevant to disease stages. Nine primary users, two of whom are collaborating on a project, and three secondary users require this instrument in their studies. The eight primary projects involve: 1.) structural analysis of the anaphase promoting complex (APC); 2.) phosphorylation and regulation of PTEN degradation; 3.) metabolic analyses of knockout mice lacking ligands for EGRF signaling; 4.) investigating the interaction of heparan sulfate and herpes simplex virus 1 glycoprotein D; 5.) novel modifications of SLBP; 6.) the identification of CFTR-interacting proteins and post-translational processing of epithelial Na+ channels and protein interactions involving the ENaC sytosolic domains; 7.) structure, function, and genetics of coagulation factors; and 8.) determining whether noncovalently bound water molecules trapped in a transition state analogue are complexes of cytidine deaminase and other enzymes.

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University of North Carolina at Chapel Hill

9.4 Tesla Small Animal Magnetic Resonance Scanner
Chapel Hill, NC

Principal Investigator
Weili Lin
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Grant No. 1-S10-RR019924-01
Award: $2,000,000

Description (provided by applicant):

The purpose of this application is to seek funding for purchasing a 9.4 Tesla dedicated small animal magnetic resonance imaging (MRI) scanner. Recently, extensive efforts have been devoted to the development of non-invasive imaging methods for offering insights into the biological systems, including computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), and optical imaging. Among these modalities, MR is definitively the method of choice for providing superb soft tissue contrast, allowing for the investigation of subtle structural abnormalities. In addition, since MR is completely non-invasive, repeated measurements are readily available without worrying about radiation effects, allowing animals to be studied longitudinally. This is likely to substantially reduce the sample size while achieving a sufficient power. Although small animal imaging can be conducted independent of the field strength, the available signal-to-noise ratio (SNR) is proportional to the field strength as well as the spatial resolution. For example, in order to obtain high-resolution small animal images with a sufficiently high SNR, the required data acquisition time is about 36 times longer at 1.5T when compared to that at 9.4T, practically impossible for *in vivo* small animal imaging. Therefore, in order to obtain high-quality and high-resolution small animal images, a 9.4T system is requested. Such a system is likely to have profound implications for a wide variety

of research projects and greatly enhance the research capability of the investigators at the University of North Carolina at Chapel Hill. The research projects listed in our application include cancer-related projects such as brain tumor and colorectal cancers, neurodegenerative, cardiovascular, cerebral vascular, and neurological diseases. All of these projects currently require sacrificing the animals and are unable to follow each animal longitudinally. Therefore, one of the immediate benefits of the 9.4T scanner is to offer insights into the biological system non-invasively, allowing longitudinal studies. In addition, through the utilization of MR spectroscopy as well as novel imaging methods, functional information is also readily available with the requested MR scanner. Therefore, there is no doubt that the requested 9.4T scanner will contribute substantially to the biological research at UNC-Chapel Hill. Finally, establishing a small animal imaging center is the highest priority at UNC-Chapel Hill. We have recently devised a CT and SPECT scanners for small animal imaging. The requested 9.4T MR scanner will definitively play a vital role and substantially strengthen our ability to establish a small animal-imaging center at UNC-Chapel Hill.

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University of Southern California, Los Angeles

3T MR Imaging/Spectrometer for Heart and Brain Research
Los Angeles, CA

Principal Investigator
Gerald Pohost
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Grant No. 1-S10-RR019942-01
Award: $2,000,000

Description (provided by applicant):

There is a critical need for a 3T whole body magnetic resonance (MR) imaging/spectrometry platform dedicated to research at the University of Southern California (USC). This was reinforced by the dean of the Keck School of Medicine at USC and the USC president who have stated their support for the construction of a state of the art magnetic resonance imaging center to be located on the Health Sciences Campus. The interdisciplinary nature of this platform, with the advantages and capabilities it brings to a wide range of studies, typifies the theme of unifying research in both cardiovascular and neurological sciences at USC in the coming decade. This proposal has support from investigators at the House Ear Institute, Huntington Memorial Hospital of Pasadena, Children's Hospital of Los Angeles, and both the University Park and Health Sciences campuses of USC. None of these institutions/locations has a dedicated research platform that has the capabilities that we are requesting, and all of these researchers are extremely enthusiastic about the experiments that this instrumentation will make possible. There is a substantial amount of technical expertise with MR imaging and spectroscopy at USC, with investigators from radiology, neurology, and biomedical engineering. In addition, experience with high field MR systems is present in cardiovascular medicine, and electrical engineering. This state-of-the-art system will provide ultra-high-speed imaging, superb spectral localization, and diffusion capabilities that are required by the cutting-edge research in both cardiovascular and neurological sciences; these capabilities are critical for a number of NIH-funded projects that are currently underway at this institution. Moreover, it will provide an ideal experimental platform for numerous grants that are currently under review.

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University of Virginia

9.4 Tesla MR Scanner for Murine Imaging
Charlottesville, VA

Principal Investigator
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Grant No. 1-S10-RR019911-01
Award: $1,980,000

Description (provided by applicant):

The University of Virginia Schools of Medicine and Engineering have established successful research programs in the development and application of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) for non-invasive serial studies of the molecular mechanisms underlying ischemic heart disease (IHD), atherosclerosis, and gastric cancer in transgenic and knockout mice. Experiments to date have utilized a 4.7 Tesla MRI/MRS system, which (by current standards) is outdated in terms of field strength and gradient performance. We propose to purchase a 9.4T MRI/MRS system with state-of-the-art magnet, gradients, and radio-frequency coils to enhance these lines of research. The new system is expected to provide higher signal-to-noise ratio (SNR), shorter echo times, and shorter repetition times, which would result in higher spatial, temporal, and spectral resolutions, as well as reduced scan times. These technical enhancements will be used to either improve upon existing studies or enable entirely new areas of investigation. For example: in the heart, the increase in temporal resolution would not only improve the evaluation of myocardial function at rest, but would also enable the evaluation of contractile reserve during dobutamine infusion. In addition, the new system will enable us to begin studying myocardial perfusion in mouse models of IHD, an important and understudied area. Specifically, the new system will enable first-pass, contrast-enhanced imaging with high spatial and temporal resolutions, and improved arterial spin labeling methods. The increase in SNR and spectral resolution should also enable localized *in vivo* 31P MRS studies of myocardial energetics. For atherosclerosis and gastric cancer, the improvement in SNR will be used to achieve high spatial resolution for vessel wall imaging of the mouse aorta and carotid arteries, and for imaging the wall of the stomach—all of which are severely SNR limited at 4.7T. The enhanced capabilities of the new system will be brought to fruition through an existing comprehensive technical, scientific, and administrative plan.

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Washington University in St. Louis

The Purchase of a Combined PET CT Scanner
St. Louis, MO

Principal Investigator
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Grant No. 1-S10-RR017206-01A1
Award: $2,000,000

Description (provided by applicant):

Washington University School of Medicine has a long history of invention, development, and application of positron emission tomography (PET). Currently, there is a large number of active, NIH-funded, research projects that use imaging, and specifically PET, as a primary tool in making important physiological measurements. We propose that the acquisition of a new scanner that has an extremely high-performing PET scanner, combined with an advanced computed tomography (CT) scanner, will greatly enhance the ongoing research program here at Washington University. We plan to purchase and install a scanner that combines a state-of-the-art, 16-slice CT scanner with a Lutetium Ortho Silicate (LSO)-based PET camera that uses narrow coincidence window and high-speed electronics to yield high-count rate capabilities. The Mallinckrodt Institute of Radiology will site the scanner on the 10th floor of the Barnes-Jewish Hospital as part of the new Center for Clinical Imaging Research. This new scanner will allow investigators to achieve the following goals: 1.) The new PET/CT scanner will allow acquisition of both physiologic data from PET scanning and anatomic image data from CT scanning in a single session. This will greatly enhance the ability to extract physiologic data from specific regions of tumors and other organ systems for oncology research. The PET/CT scanner will be used to develop and validate new PET tracer methods, such as the ability to predict and monitor tumor response from therapy. 2.) The new scanner will provide greatly enhanced ability to conduct high-count rate brain and cardiac PET scanning. This will allow investigations of function and metabolism with unparalleled accuracy and reliability. 3.) The location of the new scanner on the 10th floor of Barnes-Jewish Hospital and near to hospital intensive care units will allow investigators to conduct research PET and CT imaging studies on in-patients while they are being safely monitored by the patient's own nursing and medical staff. 4.) The CT component of the new PET/CT scanner will be used to expand the activities and enhance the quality of the NIH-funded CT research that currently depend completely on the existing clinical scanners. The significance

of this project will be that the acquisition and placement of a dedicated research PET/CT scanner with LSO crystals and high speed electronics will substantially enhance the ongoing NIH research portfolio at Washington University School of Medicine through a variety of mechanisms.

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