Integrated Biomedical Technology Research Resources for Proteomics and Glycomics

The National Center for Research Resources (NCRR) proposes to foster the development of improved technologies and methods for proteomics and glycomics research by sponsoring integrated biomedical technology research resources through the P41 mechanism. One way to confront the growing analytical challenges of the genome era is to pursue technology development primarily along integrated lines of inquiry rather than single technologies. This is particularly true in the field of proteomics. The focus of these integrated research resources will be to develop a range of innovative analytical tools and methods, and apply these tools to biologically significant problems. The resources will also provide broad access to these integrated technologies through collaboration, service, training, and dissemination activities.

Proposed integrated research resource centers should focus on the core technological and methodological problems of proteomics. Responses with special expertise in analytical glycobiology are encouraged, and this solicitation is open to unconventional or alternative approaches. Regardless of the specific experimental approaches taken in proteomics experiments, a common theme in this field is the need for synergy among three principal domains: 1) biological competencies, 2) analytical chemistry, and 3) computational tools. These domains should each inform the development of tools and methods in their counterpart areas. Accomplishing this goal in a climate of specialization demands a fundamentally collaborative approach.

It is anticipated that these integrated centers may be significantly larger and more complex than a more narrowly defined research resource. These centers may be expected to draw together the expertise of experienced investigators whose areas of specialization and established research focus will contribute to the overall goals of the project. Because of the need for integration of technologies at a fundamental level, it is considered critical that participating investigators be in a position to work closely together in an iterative manner.

Development of complex integrated approaches to proteomics problems will require a context within which development of methods can proceed. Investigators may wish to select a model system or define a biological research topic that will serve as a framework for the technological research and development activities of the resource. Investigators will be expected to clearly define the scope of their activities, and this definition should inform their choice of biological context, if any.

Integrated research resources in proteomics will eventually be expected to have a broad-based significant impact on a variety of biological problems, through both collaborative projects and those initiated within the resource. However, ultimately the most important deliverables will be state-of-the-art technology and methods for proteomics research.

Posttranslational modification is a point of concern in the development of strategies for proteomics. Because these modifications cannot be inferred directly from gene sequence, they generally can only be characterized directly. This raises issues about sequence coverage and stoichiometry of modifications that are not presented by proteomics problems focused on protein identification. In particular, the complexity and diversity of glycosylation events significantly complicates the linkage between genetic sequence and mature, active proteins. Because glycosylation is mediated by a wide range of factors, discovery-based analytical tools that can survey the complexities of glycosylation on a systemwide basis may have significant biological impact.

Besides obstacles presented by proteomics in general, glycobiology-focused proteomics (glycomics) requires the development of novel approaches and tools directed at the special challenges of glycobiology. Strategies for separation, profiling, quantitation, and detailed characterization of carbohydrate structures are central challenges. Bioinformatics tools are needed for data handling and reduction, correlation of carbohydrate and protein information, recognizing shifts in glycoprotein microheterogeneity, and model building. Synthesis, 3-D structural analysis, and a variety of other carbohydrate-specific analytical tools may prove necessary to varying degrees, depending on the global strategies adopted and thematic focus of a center.

Ultimately, laboratories engaged in glycomics will need the tools of mainstream proteomics as well as these additional specialized capabilities. Because of the breadth of challenges inherent in developing effective tools in both proteomics and glycomics, we encourage laboratories with special expertise in analytical glycobiology to address those technological problems that are inherent in and unique to glycomics.

The deadline for letters of intent is January 1, May 1, and September 1. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Complete information on this announcement is available at http://grants1.nih.gov/grants/guide/pa-files/PA-02-132.html.

Contact: Douglas M. Sheeley, Division of Biomedical Technology, NCRR, 6705 Rockledge Drive, MSC 7965, Bethesda, MD 20892-7965 USA, 301-435-0755, fax: 301-480-3659, e-mail: sheeleyd@ncrr.nih.gov. Reference: PA No. PA-02-132

Basic and Preclinical Research on Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) invites applications to help stimulate the amount and elevate the quality of basic, mechanistic, and preclinical research in all domains of complementary and alternative medicine (CAM) to provide a stronger foundation for ongoing and planned clinical studies. The NCCAM encourages the most rigorous CAM and conventional researchers to focus on the opportunities in CAM research, and to use the most current and emerging technologies to strengthen the biomedical research knowledge bases needed to elevate clinical practice. Chemists, physicists, psychologists, neuroscientists, endocrinologists, immunologists, geneticists, pharmacologists, and others in relevant fields of inquiry are encouraged to apply. The National Cancer Institute, the National Institute of General Medical Sciences, and the National Institute of Mental Health share programmatic interests in some areas of CAM research with the NCCAM.

To strengthen the biomedical research knowledge bases needed to inform CAM clinical practice, more basic, mechanistic, and preclinical research is needed across the broad spectrum of biomedical science underlying CAM practices. These practices may be grouped in five major domains—alternative medical systems, mind–body interventions, biologically based treatments, manipulative and body-based methods, and energy therapies—with some overlap across categories.

The individual systems and treatments within each category of CAM are numerous, so the following examples are presented to demonstrate the broad range of research contemplated by this initiative, and are not meant to be exclusive: 1) immunomodulatory mechanisms underlying CAM therapeutics, such as basic and animal model studies aimed at determining whether and what changes are induced in immune response pathways by CAM therapeutics, and whether any such changes might be relevant to resolving a disorder or preventing one; 2) neurophysiological, neuroendocrinological, and biochemical pathways in massage therapy, including studies utilizing animal models, and instrumentation-based approaches including imaging; 3) mechanistic studies of biologically based treatments, herbs, nutritional supplements, or natural products for enhancing cognitive function in brain disorders; 4) chemical and physical reactions during the dilution process and the principles of biophysics associated with homeopathy; 5) mechanisms underlying the biochemical and/or neurophysiological causes of spinal dysfunction, and investigations of the therapeutic pathways being impacted by manual therapies such as spinal manipulation and mobilization as performed in chiropractic or osteopathic practices; 6) studies on the rationales for the use of complex products from a single plant species and studies to evaluate the mechanisms of action and to help establish the biomedical bases for the belief in the therapeutic efficacy of using multiple plant species simultaneously; 7) basic biological mechanisms and processes underlying acupuncture; 8) identification and properties of bioenergies used in treatment modalities, especially new biophysical approaches involving instrumentation; 9) mechanisms of action of saw palmetto, PC-SPES, *Pygeum africanum*, and other complex botanicals on the male reproductive tract; and of black cohosh, red clover, and other complex botanicals on the female tract; focusing on the cellular, molecular, endocrinological, and metabolic changes induced *in vitro*, in animal models, and in human subjects treated with these botanicals; and 10) interactions between CAM and conventional therapeutic modalities, including but not limited to those of complex botanicals with pharmaceutical drugs.

Applications must use the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applications submitted in response to this PA will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Complete information on this PA is available online at http://grants.nih.gov/grants/guide/pa-files/PA-02-124.html.

Contact: Neal B. West, Program Officer, NCCAM, Two Democracy Plaza, Suite 401, 6707 Democracy Boulevard, Bethesda, MD 20892-5475 USA, 301-402-5867, fax: 301-480-3621, e-mail: westn@mail.nih.gov; Wendy B. Smith, Program Director, Office of Cancer Complementary and Alternative Medicine, NCI, 6130 Executive Boulevard, EPN, Suite 102, MSC 7302, Bethesda, MD 20892-7302 USA, 301-435-7980, fax: 301-480-0075, e-mail: smithwe@mail.nih.gov; Michael E. Rogers, Director, Pharmacology, Physiology, and Biological Chemistry Division, NIGMS, Room 2As.49c, Natcher Building, Bethesda, MD 20892-6200 USA, 301-594-3827, fax: 301-480-2802, e-mail: RogersM@nigms.nih.gov; or Linda Brady, Division of Neuroscience and Basic Behavioral

Science, NIMH, 6001 Executive Boulevard, Room 7185, Bethesda, MD 20892 USA, 301-443-5288, fax: 301-402-4740, e-mail: lb@helix.nih.gov. Reference: PA No. PA-02-124

Research on Ethical Issues in Human Studies

NIH invites research grant applications to investigate ethical issues in research using human subjects. The *Code of Federal Regulations* (45 CFR, Part 46) provides a regulatory framework that all NIH-supported researchers must follow. However, recent developments in biomedical and behavioral research—including the rapid growth of new interventions and technologies (e.g., stem cells, genetics research), increasing involvement of foreign populations in clinical research, and concerns about financial conflicts of interest among researchers—challenge investigators' abilities to interpret and apply the regulations. Other situations (e.g., research with vulnerable populations, the use of data banks or archives, research on stigmatizing diseases or conditions) may present difficulties for identifying strategies, procedures, and/or techniques that will enhance and ensure the ethical involvement of human participants in research.

The purpose of this PA is to support empirical research addressing the ethical challenges of involving human participants in research in order to inform and optimize protections for human participation in research. Examples of the types of topics that would be appropriate for applications submitted under this announcement include, but are not limited to, the following:

Minimizing Risks in Human Research

1) Assess how features of the research and research setting affect evaluations of risks versus potential benefits of different types of research for investigators, institutional review board (IRB) members, and potential participants, groups, and communities. Examples of features of the research or research setting may include characteristics of the participants (e.g., age, health status and stage of disease, ethnic/cultural background, cognitive capacity, social status, gender, incarceration), aspects of the condition/disease (e.g., prevalence, severity, chronicity, degree of disability), and the nation or culture in which the study will take place.

2) Identify potential social, psychological, and/or economic harms (e.g., stigma, discrimination, personal distress, loss of insurance coverage, loss of employment) that may be associated with recruitment, participation, or self-determined or study-determined withdrawal from research. Evaluate strategies or procedures for minimizing these harms in regard to individuals', groups', communities', and populations' willingness to participate in different types of research.

3) Assess the conditions and assumptions under which IRB evaluation of risk versus potential benefits is similar to or different from the evaluation of risks versus potential benefits by individuals, groups, communities, and populations.

4) Assess the impact of obtaining a certificate of confidentiality on perceptions of IRB members and/or participants in terms of evaluation of risks, understanding of the research, and/or understanding of the rights to privacy.

5) Identify and evaluate strategies for protecting and minimizing disclosure of private information when identifiable data are collected via the Internet, preserved for secondary analysis (e.g., in a tissue or gene bank, data archive, warehouse), and/or collected about third parties in research (e.g., network studies).

Issues in Informed Consent

1) Determine how features of the informed consent process affect participants' comprehension and/or willingness to participate in research. Examples of these features include a) variations in the style of presentation (e.g., oral, written, graphic, video); b) readability, complexity, and/or format of the consent document; c) characteristics of the participants (e.g., language preference, age, health status, education, cultural/ethnic background, personal motivations, cognitive capacity); and d) contextual features or circumstances in which informed consent takes place (e.g., characteristics of the research staff, location such as research hospital versus private office versus home, presence/involvement of family members, presence/involvement of patient advocates).

2) Evaluate different methods and identify best-practice strategies for consulting with communities in the United States and/or other countries regarding comprehension, willingness to participate, and/or willingness to continue with research at the individual, group, community, and/or population level.

3) Assess how recontacting participants to obtain informed consent for additional uses of their data affects participant comprehension, willingness to participate, and sense of coercion.

4) Identify and evaluate strategies, procedures, and/or techniques for improving comprehension of research by individuals, groups, communities, and/or populations at the time of initial consent, during, and/or after completion of the study. Also, determine how these strategies may differ depending on age, health status, ethnic/cultural background, cognitive capacity, social status, and/or gender of the target audience.

5) Assess how participants' willingness to participate versus sense of coercion, may be affected by use of different types of incentives, remuneration, and/or provision of medical care; different features of the research setting (e.g., personal physician as recruiter and/or researcher, private funding versus federal funding); and characteristics of the participants (e.g., health status, age, ethnic/cultural background, education, gender).

6) Assess the impact of communicating or not communicating individual test results, study progress, and/or study results on participants' willingness to continue with the protocol and/or participate in research again.

Oversight of Research and Research Data

1) Identify and evaluate strategies to improve the oversight of human participants protection by IRBs, data and safety monitoring boards (DSMB), conflict of interest (COI) committees, etc. Examples may include a) develop and evaluate best-practice outcome measures for decision making about the acceptability of research protocols; b) assess the consistency of protocol review decisions within DSMBs, IRBs, or COI committees; c) assess the impact of conflicts of interest among members of oversight committees on decision making about the acceptability of research protocols, interpretations of adverse events, and/or perceptions of "independence of review" by the research community; and d) assess the impact of disclosing varying degrees of financial conflicts of interest involving the principal investigator, members of oversight committees, sponsor, institution, etc. on research participant willingness to participate and/or continue with research, and/or participant understanding of the research.

2) Compare and evaluate different methods and strategies for identifying, reporting, and handling adverse events based on the perspectives of individual participants, institutions, DSMBs, and/or IRBs.

This PA will use the NIH R01 award mechanism and Just in Time concepts. It will also use the modular as well as the nonmodular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for nonmodular research grant applications.

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Complete information on this PA is available at http://grants1.nih.gov/grants/guide/pa-files/PA-02-103.html. To assist in identifying which NIH institute/office most closely matches your research topic, the following website provides additional information about institute- and office-specific research interests that will be supported by this PA: http://grants.nih.gov/grants/funding/ethics_contacts.htm.

Contact: Della M. Hann, Office of Extramural Research, NIH, Building 1, Room 152, Bethesda, MD 20892 USA, 301-402-2725, fax: 301-402-3469, e-mail: hannd@od.nih.gov. Reference: PA No. PA-02-103