Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases Research

The National Institute of Allergy and Infectious Diseases (NIAID) invites applications for funds to develop Regional Centers of Excellence (RCEs) in areas related to biodefense and emerging infectious diseases research. The overall goal of the RCE program is to develop and maintain strong infrastructure and multifaceted research and development activities that will provide the scientific information and translational research capacity to make the next generation of therapeutics, vaccines, and diagnostics against the CDC Category A–C Agents (http://www.bt.cdc.gov/agent/agentlist.asp#catagoryadiseases), with particular emphasis on Category A.

To accomplish this goal, the RCEs will be provided with support to 1) develop and conduct programs of investigator-directed research; 2) train researchers and other personnel for biodefense research activities; 3) develop and maintain comprehensive core facilities to support the research and training activities of the RCE; 4) develop translational research capacity for testing and validating vaccine, therapeutic, and diagnostic concepts for biodefense and emerging infectious diseases; 5) maintain and make available core facilities and other support to approved investigators from academia, biotech companies, the pharmaceutical industry, and other appropriate entities in the region for the purpose of performing basic research and for testing and evaluating vaccines, therapeutics, and diagnostics for CDC Category A–C Agents; and 6) be ready and available to provide facilities and scientific support to first-line responders in the event of a national biodefense emergency.

This RFA invites research institutions and groups of investigators to form consortia and develop applications for programs to address the fundamental research and development questions that will provide the information needed to counter the threat of bioterrorism. Diverse research and development approaches are encouraged, as long as they include the following essential features: a biodefense research focus on CDC Category A–C Agents, particularly Category A, that incorporates a translational component with the long-term goal of developing testable products.

A group of center member researchers with expertise in biodefense and emerging infectious diseases research is required to lead the research thrust that underlies all the other activities of the RCE. In addition, the RCE should designate specific platforms and technologies that will serve as the basis for the center's development programs. Platforms are cross-cutting technologies or experimental approaches that integrate the research and development activities. Examples of platforms include genomics, proteomics, animal models, and preclinical development, but others are welcome.

As identified by the recently convened NIAID Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research, there is a critical need for the establishment of highly developed research and development infrastructure with strong translational research capacity to implement the Biodefense Research Agenda of the NIAID (for more information, visit http://www.niaid.nih.gov/dmid/bioterrorism/).

The following are examples of research within the scope of the RCE program (for a more detailed list of NIAID biodefense research priorities, applicants are encouraged to consult the strategic plan): 1) basic biology of Category A–C Agents, with particular emphasis on Category A; 2) mechanisms of pathogenesis of Category A–C Agents; 3) application of genomic and proteomic strategies to Category A–C Agents; 4) basic aspects of the innate and adaptive immune responses to Category A–C Agents; 5) rapid, sensitive, and specific approaches for detection and identification of Category A–C Agents; 6) target identification for diagnostics, therapeutics, and vaccines, including assay development; 7) development of new animal models for pathogenesis studies, for therapeutics and vaccine evaluation, and for rapid diagnostic studies; and 8) testing through Phase I clinical trials of drugs, diagnostics, and vaccines.

For fiscal year 2003 the NIAID intends to commit approximately $40 million to fund up to 4 RCEs in response to this RFA. An applicant may request a project period of up to five years. To achieve nationwide distribution of the RCEs, the NIAID has divided the United States into 10 regions. It is the long-range goal of this program, contingent upon the availability of funds, to establish at least one RCE within each region.

Prospective applicants are asked to submit a letter of intent by 15 November 2002, with final applications due 15 January 2003. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001), available online at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. In addition, applicants must consult and use "Instructions for Applications for Multi-Project Awards" (http://www.niaid.nih.gov/ncn/grants/multibron.htm) with the additional instructions specific to this RFA noted in the online version available at http://grants1.nih.gov/grants/guide/rfa-files/RFA-AI-02-031.html.

Contact: Rona Hirschberg, Division of Microbiology and Infectious Diseases, NIAID, 6700B Rockledge Drive, Room 3129, MSC 7630, Bethesda, MD 20892-7630 USA, 301-496-1884, fax: 301-480-4528, e-mail: rhirschberg@niaid.nih.gov. Reference: RFA No. AI-02-031

Genetic Architecture, Biological Variation, and Complex Phenotypes

This PA updates PA-98-078, "Genetic Architecture of Complex Phenotypes." The purpose of this PA is to solicit applications for new studies on genetic variation and the architecture of complex phenotypes. It restates the interest of several components of the NIH in studies of the underlying causes and architecture of complex phenotypes, including human diseases. It is motivated by the amount and complexity of biological data that are being generated and by the understanding that complex phenotypes involve many genetic components that evolve in a variety of environments.

Complex phenotypes are those that exhibit familial clustering, which may mean that there is some genetic component, but that do not occur in Mendelian proportions in pedigrees. Complex phenotypes may be continuous in distribution (e.g., height or blood pressure), or they may be dichotomous (e.g., affected and not affected). The complexity arises from the fact that one cannot accurately predict the expression of the phenotype from knowledge of the individual effects of individual factors considered alone, no matter how well understood each separate component may be.

The past few decades of biological research using largely a reductionist approach have yielded vast amounts of data. In addition, genome sequencing projects, as well as structural and functional genomics initiatives, are producing data far more rapidly than scientists can analyze them and understand their implications to biology and to health. As overwhelming as the current data are, they are only the beginning. Protein structures, DNA sequences, and gene expression patterns vary among individuals, among species, among populations within a species, and across environments. It will soon be possible to utilize information on thousands of variable genetic sites to investigate the relationships among genotypes, phenotypes, and environments.

The term *genetic architecture* refers to the full range of genetic effects on a trait; however, when studying variation on such a large scale, it is especially important to consider the context or environments in which genetic variation arises, is selected, and is maintained. Genetic architecture is less a fixed property of the phenotype than a characteristic of a phenotype in a particular population. Genetic architecture is a moving target that changes according to gene and genotype frequencies, distributions of environmental factors, and such biological properties as age and sex.

Studies of variation or genetic architecture may employ a variety of conceptual approaches. A researcher may consider the combinatorial effects of many variable sites, whether the scale is within a gene or across a genome. Comparative genomics, where the goal is to identify patterns of variation among genomes, is also a productive way of identifying attributes of variation, such as which genomic regions are rapidly evolving. Another approach is to study variation related to biological levels of organization, such as DNA sequence, protein structure, metabolic pathways, cell dynamics, individual phenotype, and population characteristics. The following are typical of research areas targeted by this initiative:

Biological variation: Studies of genetic architecture have historically focused on associations of genotype and phenotype (e.g., between DNA markers and a disease). However, an organism is a unique consequence of both genes and environment and is created by complex interactions of multiple events and forces. How genes are expressed depends on their cellular, developmental, physiological, and environmental context. This initiative encourages research on biological variation and interactions such as 1) variation in basic biological systems, including sequences, structures, and pathways that direct metabolism and development; 2) variation in these systems within individuals, among individuals, among populations, and among species with the goal of learning how these complex systems interact and evolve; 3) determination of the extent to which genetic architecture is shared across populations and among species; 4) effects of admixture, population history, recombination, mutation, population structure, selection, and drift on the organization of variation; 5) collection and analysis of both new and existing data; 6) tools and models for identifying and measuring important contextual features; and 7) measuring the impact of context on biological data.

Evolution of genome properties: An emerging area of research focuses on how properties of genomes arise in evolutionary history. Such research has important consequences for understanding genome organization and for interpreting data on genetic and phenotypic variation. Such research could include the evolution of haplotypes, selection for genetic interactions, and the evolution of recombination and methylation patterns.

Extensions to other organisms: Many organisms have been studied for their value in agriculture or ecology. Thus, there is considerable information about the population structure, natural history, and genetics of these systems. It will be valuable to take advantage of this wealth of information to study variation in the natural settings in which it evolved.

Bioinformatics: The study of biological variation depends heavily on rich data sets; researchers need the ability to access many kinds of information (e.g., DNA sequence, protein structure, development, natural history, and phenotype) in organisms from different habitats, from different populations, and from different species. This initiative supports development of tools to help researchers use data from many databases to address research questions.

Improved dynamic modeling and statistical methods: Mathematical approaches to studying biological variation have changed little in several decades. There is a need to develop new dynamic models to illuminate how systems interact and evolve. Just as important, it is critical to study the nature of biological and mathematical assumptions of models and statistics. Tools for analyzing and interpreting data on the architecture of complex phenotypes should be developed in the context of real biological information. Areas of particular interest for this initiative include 1) implications and appropriate uses of different sampling strategies; 2) analytical tools to discover patterns of genotypic variation and their roles in conferring phenotype; 3) incorporation of data from new technologies; 4) development of robust methods that are compatible with real data (missing or incomplete data, typing errors, experimental errors); and 5) development of mathematical models based on empirical information, which includes such biological realities as epistasis, recombination, mutation, protein structure, cell biology, metabolic pathways, development, population history, and evolution.

Applications submitted in response to this PA will be accepted at the standard application deadlines, available at http://grants.nih.gov/grants/dates.htm. Complete information on this PA is available at http://grants1.nih.gov/grants/guide/pa-files/PA-02-110.html. Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001), available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format.

Contact: Irene Anne Eckstrand, Division of Genetics and Developmental Biology, NIGMS, 45 Center Drive, MSC 6200, Bethesda, MD 20892-6200 USA, 301-594-0943, fax: 301-480-2228, e-mail: Irene_Eckstrand@nih.gov; Lisa Brooks, NHGRI, 31 Center Drive, 31/B2B07, Bethesda, MD 20892-2033 USA, 301-435-5544, fax: 301-480-2770, e-mail: lisa_brooks@nih.gov; Winifred Rossi, Genetic Epidemiology and Translational Research, NIA, 7201 Wisconsin Avenue, Suite 3E327, Bethesda, MD 20892-9205 USA, 301-496-3836, fax: 301-402-1784, e-mail: wr33a@nih.gov; Lisa Neuhold, Division of Basic Research, NIAAA, 6000 Executive Boulevard, Suite 402, Bethesda, MD 20892-7003 USA, 301-594-6228, fax: 301-594-0673, e-mail: lneuhold@willco.niaaa.nih.gov; Steven Moldin, Genetics Research Branch, Division of Neuroscience & Basic Behavioral Science, NIMH, 6001 Executive Boulevard, Room 7189, MSC 9643, Bethesda, MD 20892-9643 USA, 301-443-2037, fax: 301-443-9890, e-mail: smoldin@mail.nih.gov; Robert Karp, Division of Digestive Diseases and Nutrition, NIDDK, 6707 Democracy Boulevard, Room 671, MSC 5450, Bethesda, MD 20892-5450 USA, 301-451-8875, fax: 301-480-8300, e-mail: karpr@extra.niddk.nih.gov; Jonathan Pollock, Genetics and Molecular Neurobiology Research Branch, NIDA, 6001 Executive Boulevard, Room 4274, Bethesda, MD 20892 USA, 301-435-1309, fax: 301-594-6043, e-mail: jp183r@nih.gov; Jose Velazquez, Division of Extramural Research and Training, NIEHS, 111 Alexander Drive, Research Triangle Park, NC 27709 USA, 919-541-4998, fax: 919-316-4606, e-mail: velazqu1@niehs.nih.gov; or Katrina Gwinn-Hardy, NINDS, 6100 Executive Boulevard, Room 2142, MSC 9525, Bethesda, MD 20892 USA, 301-496-5745, fax: 301-402-1501, e-mail: gwinnk@ninds.nih.gov. Reference: PA No. PA-02-110

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