■ GENOMIC CENTERS FOR INFECTIOUS DISEASES (U19): RFA-AI-13-009

Components of Participating Organizations

National Institute of Allergy and Infectious Diseases

Application Receipt Date(s): June 24, 2013

The purpose of this initiative is to establish Genomic Centers for Infectious Diseases as a collaborative program that will utilize a combination of next generation sequencing and related genomic technologies, bioinformatics capabilities and computational analyses to understand infectious diseases, with a focus on the pathogen and its interaction with the host. The knowledge generated, including research data, analytical software tools, computational models, experimental protocols, and reagents, is expected to be widely disseminated to the scientific community through publicly accessible databases and reagent repositories.

The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) supports research related to the basic understanding, treatment and ultimately prevention of infectious, immunologic and allergic diseases that threaten millions of human lives. The NIAID Division of Microbiology and Infectious Diseases (DMID) supports a comprehensive extramural research portfolio focused on the prevention and control of diseases caused by virtually all infectious agents. This includes basic research, such as studies of microbial biology and physiology; applied research, including the development of medical diagnostics, therapeutics and vaccines; and clinical trials to evaluate experimental drugs and vaccines.

NIAID/DMID has made a significant investment in genomic-related activities that provide to the scientific community comprehensive resources for genome sequencing, transcriptomics, proteomics and bioinformatics, as well as rapid availability of data and reagents for basic and applied research in support of the Institute's mission. NIAID-supported genomic research programs include the:

- Genomic Sequencing Centers for Infectious Diseases – provide rapid and cost-efficient production of high-quality genome sequences of human pathogens and related organisms, invertebrate vectors of infectious diseases, human and microbial genotyping and metagenomics analysis.
- Bioinformatics Resource Centers – collect, integrate and provide open access to research data of microbial organisms and vectors of infectious diseases in a user-friendly format, develop and share open source software tools, and provide bioinformatics services and training to the scientific community.
- Clinical Proteomics Centers for Infectious Diseases and Biodefense – identify candidate pathogen and host biomarkers important for infectious diseases.
- Systems Biology Centers for Infectious Diseases – identify and analyze molecular interaction networks of microbial pathogens and their host cells through a combination of computational and experimental high-throughput technologies.
- Structural Genomics Centers for Infectious Diseases – focus on experimentally characterizing the three-dimensional atomic structure of proteins of pathogenic organisms.

Over the last decade, NIAID has supported the sequencing of many genomes of pathogenic and related microorganisms, including those that are the cause of emerging infectious diseases, such as influenza, drug resistant tuberculosis, dengue fever, and potential agents of bioterrorism. During this time, the DNA sequences of the genomes of almost 5,000 microorganisms and invertebrate vectors of disease and an additional 15,000 viruses have been sequenced. Coupled with other biochemical and microbiological information, this sequence data is facilitating the identification of novel and specific targets for improving both forensic strain identification and molecular genotyping, development of sequence-based detection technologies and diagnostics, and the development of therapeutic targets for new drugs and vaccines. In addition, comparative genomics (comparing the sequences of different strains, species and clinical isolates) has become vitally important, providing critical data that enable identification of genetic polymorphisms that correlate with phenotypes such as drug resistance, morbidity and infectivity.

This wealth of sequence information, as well as the availability of the human genome, provides a valuable resource for the research community. Specifically, the functional genomic analysis of DNA sequences from microbial pathogens is enhancing the understanding of a pathogen's biology and its ability to cause disease. Human genome sequence analysis is enhancing the understanding of the host immune response and an individual's genetic susceptibility to microbial pathogens. These efforts may provide insights regarding how an individual may respond to drugs, treatments and vaccines.

Currently, NIAID supports contracts with the J. Craig Venter Institute, University of Maryland and the Broad Institute, which comprise the NIAID Genome Sequencing Centers.

Research Objectives and Scope

This Program will be established to build upon and expand the sequence data, resources and technologies that have been generated through the current NIAID Genomic Sequencing Centers for Infectious Diseases and other programs. Through this FOA, two to three Genomic Centers for Infectious Diseases (hereinafter also referred to as "Program") will be established to support a diverse set of genome sequencing activities using next generation sequencing and related genomic technologies. In addition, this new effort will encourage a shift towards high-throughput genomic sequencing approaches to infectious diseases research that focuses on the pathogen and its interaction with the host. This focus will provide insights into the biology of microbes, their role in pathogenesis, and their interactions with the host, including the microbiome. To that end, the Program will use and develop or improve innovative applications of sequencing such as RNA sequencing and metagenomics, and provide rapid and cost-efficient production of high-quality genome sequences of microorganisms and invertebrate vectors of infectious diseases, host and microbiome.

Moreover, the Program shall provide comparative genomics analyses to examine genetic variation in populations and communities of human pathogens and also across the human genome to identify genetic associations with observable phenotypes in the pathogen and in the human host. Ultimately, it is anticipated that the Program will provide methods and protocols developed for next generation sequencing and genomic technologies and bioinformatics analyses that are applicable to studying infectious diseases and can be used by the broad infectious diseases community.

Genomes that will be sequenced include those from microorganisms from NIAID's List of Emerging and Re-emerging Infectious Diseases (http://www.niaid.nih.gov/topics/emerging/Pages/list.aspx), which includes NIAID Category A-C Priority

Pathogens, clinical isolates, closely related species and strains, and invertebrate vectors of diseases. Emphasis will be placed on sequencing multiple strains and isolates of specific microbial species, populations and communities rather than on sequencing individual microorganisms.

For purposes of this initiative, genome sequencing activities include high throughput sequencing, comparative genomic sequencing, single nucleotide polymorphism identification, genotyping, and gene expression. High throughput sequencing is defined as the capability to: a) produce high quality sequencing data in a highly efficient manner with continuous increase in efficiency and decrease in costs; b) generate a diverse variety of genome sequence products; c) develop and implement new technologies, bioinformatics resources, data analysis, and laboratory management systems; and d) maintain an automated production pipeline with at least a throughput of one terabyte (TB) successful sequence reads per year. Comparative genomics and genotyping are defined as using high throughput platforms to examine the whole genome or exomes for genetic variation.

NIAID recognizes that large-scale pre-publication DNA sequence and other genomic data and information are a unique research resource for the scientific community and that rapid and unrestricted sharing of genomic data sets are essential for advancing research on infectious diseases. Therefore, it is expected that pre-publication genome sequence data sets generated by the Centers will be made freely and publicly available through publicly accessible international databases, such as Genbank, as rapidly as possible. NIAID strongly endorses the rapid release and public dissemination of experimental data, metadata, new analysis tools, novel reagents and other resources generated under the Program to enable the broad scientific community to utilize the available resources and pursue new research hypotheses. The Centers funded under this FOA are expected to follow the guidelines and timelines described in the NIAID Data and Reagents Sharing and Release Guidelines (http://www.niaid.nih.gov/LabsAndResources/resources/dmid/gsc/Pages/data.aspx).

Overall Structure

Each Center shall have a multi-disciplinary research and technology team with expertise in genomics, bioinformatics and data management and analysis, statistics, microbiology, epidemiology, and infectious diseases that includes the following:

- Program Director(s)/Principal Investigator(s) (PDs/PIs) who will serve as the Center Director to oversee, manage and coordinate the research and ensure that the individual projects and cores are synergized to advance the goals of the Center. The PD(s)/PI(s) must have experience in managing a high throughput, large scale genomic sequencing center for infectious diseases.
- Four thematic Research Projects, focused on viruses, bacteria, fungi, and parasites and vectors, respectively. A Project Leader with relevant expertise is expected to be named for each thematic area.
- Three required cores, including a Technology Core; a Data Management, Analysis and Resources Dissemination Core; and an Administrative Core.
- Other Scientific Cores (optional).

NOTE: This FOA will not support applications that focus exclusively on genomic technology development in the absence of use of the technology to sequence and characterize human pathogens and their interaction with the host. Applications of this type are unresponsive and will not be reviewed.

Each application should describe the central theme of the proposed Center and propose four Research Projects that are centered around the themes of viruses, bacteria, fungi, and parasites and vectors (i.e., there should be one project on viruses, one on bacteria, one on fungi and one on parasites and vectors). Each Research Project must utilize a combination of next generation, state-of-the-art genomics sequencing technologies and bioinformatics analyses to understand infectious diseases with a focus on human pathogens and their interaction with the host. Applicants should explain how the proposed Research Projects are synergistic and fit under the Center's overarching central theme.

Applicants must provide milestones and timelines for each research project.

Note: Costs associated with prospective human sample collection will not be covered by the grant.

Technology Core. Each Center must include three or more high-throughput genomic technologies organized into a Technology Core to provide shared resources to the Research Projects. Next-generation large scale high throughput sequencing, transcriptomics, metagenomics and related microbiome technologies must be included as three of the technologies in the core.

Data Management, Analysis, and Resources Dissemination Core. It is expected that a vast amount of data and other types of resources will be generated by the application of genomics and other related technologies on a large number of samples. The ability to perform sample tracking, laboratory data management, data storage, data access, data transfer, data analysis and integration and management of data and information from a variety of genomics technologies is essential for the efficient and successful performance of the Center. Sample tracking may include managing and reviewing IRB documentation and clinical and meta data associated with clinical samples. In addition, the core must have the capability to provide state of the art bioinformatic and computational infrastructure that is necessary for large scale, high throughput genomic sequencing and data analysis on data generated in the Center or independently, including implementation of new, improved and enhanced bioinformatic and computational platforms.

A primary objective for the Program is to maximize the public benefit of the data produced under the Centers through the rapid release and public dissemination of genomic and related data, metadata, new analysis tools, strains, novel reagents (e.g., expression vectors, expression arrays, libraries), among other resources generated under the Program. To achieve the objective of producing and broadly sharing the resources generated by Program, the Centers funded under this FOA are expected to follow the guidelinesdescribed in the NIAID Data Sharing and Release Guidelines (http://www.niaid.nih.gov/LabsAndResources/resources/dmid/gsc/Pages/data.aspx), and other NIH and NIAID sharing policies (see http://ott.od.nih.gov/policy/research_tool.html and http://sharing.nih.gov/).The Center should also assure that data is rapidly released according to approved criteria, that licensing and sharing practices ensure the availability of data and research resources for future use by the scientific community, and that research collaboration or sponsorship agreements are consistent with meeting the goals and the requirements of the Program. The Data Sharing and Release Plan, once approved, will also become a Term and Condition of award.

Applications submitted in response to this FOA should provide details of the data integration, management and tracking activities of the Program and include a Plan for public dissemination of generated resources to the scientific community.

Administrative Core. Each Center must include an Administrative Core, headed by the PD/PI, which is responsible for managing, coordinating, and supervising all Center activities. The Core should include the following:

Milestones and Timelines

Applicants must provide milestones and timelines in a section of the Administrative Core entitled "Milestones and Timelines" that should address all Core activities.

Management Plan

The Administrative Core should provide a Management Plan that describes the organization of the proposed program and its management structure. The Management Plan should include a Staffing Plan that describes the structure and roles of scientific and administrative staff; the committed level of effort; the training and experience of proposed staff; and the functions to be performed.

Training Program Plan

A Training Program will begin in the first year of the award and is expected to instruct and increase the number of infectious disease researchers that can use the approaches, methodologies and resources (datasets, analysis tools, etc.) generated under the Center.

Examples of appropriate training programs include workshops to promote the use of technologies and analysis tools developed by the Center, and short-term training appointments of undergraduate, graduate, post-doctoral candidates and junior faculty with expertise in microbiology and infectious diseases.

Supplemental Research Projects Plan (subject to availability of supplemental funds)

NIAID is interested in supporting Supplemental Research Projects during the period of grant award. Supplemental Research Projects will focus on one of the four thematic areas and will take advantage of genomic sequencing technologies and new and innovative opportunities to study infectious agents and their interaction with the host. To that end, the Administrative Core should include a Supplemental Research Project Plan that describes procedures to be used by the Centers for identifying and selecting Supplemental Research Projects to be recommended to NIAID Program Staff. Applicants should not submit descriptions of Supplemental Research Projects in their application.

Annual Programmatic Meetings. Each year a one-two day meeting will be held and each awarded Center will assume responsibility for the meetings' organization at least once over the award period. These meetings are anticipated to be held at a location at/near Bethesda, MD or at another NIAID-approved site. Each awardee should budget for travel to the yearly meeting. Costs for organizing the annual meeting should not be included in the budget. Funds for hosting a meeting will be provided via an administrative supplement. Each Center should ensure that support for meeting attendance by the PD/PI, the Project Leaders and Cores leaders, and other key personnel is included in the budget.

Steering Committee. A Steering Committee will be established by the NIAID in collaboration with the awardees to review the progress in meeting the goals of all Centers funded under the Program and will make recommendations for the continuation or re-direction of all projects and activities of the funded Centers on an ongoing basis and in consultation with the NIAID staff. In addition, the Steering Committee will make recommendations about Supplemental Research Projects (see Supplemental Research Projects). The Steering Committee is expected to consist of investigators who are not current collaborators of the funded programs. Names of Steering Committee members should not be proposed as part of the application since Steering Committee members will be independent, non-affiliated experts and will be selected in collaboration with NIAID.

Optional Components

Other Scientific Cores

These cores should provide scientific services or resources that are justified and not duplicative of other services or facilities available in the required cores.

Note: Applications lacking any of the required projects, cores or Data Sharing and Release Plan will be deemed not responsive and will not be reviewed.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are eligible to apply.

Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete the following registrations as described in the PHS 398 Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the PHS 398 Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-13-009.html.

■ OBESITY POLICY EVALUATION RESEARCH (R01): PA-13-110

Components of Participating Organizations

National Institute of Diabetes and Digestive and Kidney Diseases
National Cancer Institute
National Heart, Lung, and Blood Institute
National Institute on Aging
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Office of Behavioral and Social Science Research

Application Receipt/Submission Date(s): Multiple dates, see announcement.

Obesity is a major contributor to many serious health conditions that increase morbidity and mortality and reduce quality of life. The prevalence of obesity in children and adults in the United States has dramatically increased in the past four decades. Nationally there is an imperative to take action at local, state and federal levels, especially related to obesity in children. While helping people achieve and maintain a healthy weight is a critical public health goal, relatively little is known about the effectiveness of large scale policies and programs that could help achieve this goal at the population level, or any differential effects on sub-populations. As noted in the 2010 Institute Of Medicine (IOM) report, Bridging the Evidence Gap in Obesity Prevention: A Framework to Inform Decision Making (http://www.iom.edu/Reports/2010/Bridging-the-Evidence-Gap-in-Obesity-Prevention-A-Framework-to-Inform-Decision-Making.aspx), rigorous scientific evaluation of these policies and programs can help build an evidence base to better inform policy public health approaches to prevent excess weight gain and/or improve weight management.

For the Purposes of This FOA

Policy is broadly defined to include both formal public policies at local, state and federal levels of government, and organizational level policies, such as those implemented by large organizations, worksites or school districts. Examples include, but are not limited to, the development of supermarkets in underserved areas, calorie labeling requirements, taxes on foods and/or beverages, after-school and summer programs, modification of the built (or human-made) environments to encourage walking or cycling for transportation or leisure.

Program is defined as a set of activities initiated by governmental or other organizational bodies to enhance obesity prevention and control. Examples might include programs implemented worksites, healthcare organizations, after-school or summer programs, or communities that can be expected to improve obesity related behaviors such as energy intake and activity level. This FOA is not intended to support the initiation and delivery of new programs; rather, it is intended to support evaluation of the effectiveness of programs and/or policies that are being or will be implemented regardless of NIH grant funding.

The obesity program or policy to be evaluated should reasonably be expected to affect behaviors relevant to obesity such as energy intake, sedentary behavior, or physical activity in the target population. Further, research proposed in response to this FOA should demonstrate that measures collected and evaluated will allow for meaningful and scientifically valid conclusions to be made about the effects of the policy or program on the target behaviors and/or weight.

Examples of appropriate studies include, but are not limited to, the following:

- Introduction of food or beverage taxes/subsidies/price changes/other incentives;
- Infrastructure initiatives such as retailers offering healthier food options in underserved areas;
- Changes to workplace food and/or physical activity environment;
- Polices expected to influence available options and purchasing, such as calorie labeling in restaurants, menu or food product reformulation, and supermarket layout or pricing strategies;
- Significant changes in policy or practice in large healthcare organizations that are expected to improve weight outcomes; such as changes in reimbursement, incentives, or wide scale implementation of prevention or treatment services;
- Modifications to the built environment to encourage active transportation or leisure physical activity, such as the implementation of bike lanes in urban areas, multi-use trails, subsidies for public transit, upgrades of sidewalks, or improved access to parks and recreation facilities.

Note: The focus of this FOA is on research in humans, not animals.

Primary outcomes under study should be assessed using objective measures, or in the case of dietary intake, by using standardized and comprehensive 24-hour recall methods. Examples of acceptable primary outcomes include objective measures of behavior change (purchasing behavior, use of resources intended for physical activity, energy intake with a focus on lowered calories or lower calorie substitutions, activity changes such as reduced sedentary behavior or increased physical activity) and/or weight related variables (e.g. BMI, body composition). Other self-reported measures of dietary intake and physical activity can be included but should not be the primary outcome measure/s.

Where possible and relevant, grant applications should include secondary outcomes that evaluate potential unintended consequences of a policy or program, degree of implementation, and an assessment of barriers and facilitators associated with implementation. This includes measures that will help identify why the policy or program succeeds or does not succeed.

This FOA encourages innovative scientific partnerships between researchers and public or private partners (e.g., community based organizations, local governments, school districts, employers). Where possible, applicants should provide letters of support from those who hold ownership or management of the program and/or policy that indicate their full cooperation with the research team. This should include support for access to the data required for the evaluation. Where appropriate, agreements must also be in place that allow for unrestricted publication of findings regardless of study outcomes. Research applications that include comparison group/s must include letters of support/agreement for access to the comparison group.

Institute Specific Interests

NIDDK: The National Institute of Diabetes and Digestive and Kidney Diseases is particularly interested in the evaluation of large scale weight related programs or policy that are targeted to obesity and/or diabetes prevention.

NHLBI: The National Heart, Lung, and Blood Institute is especially interested in research on programs and policies that target cardiovascular disease risk factors such as obesity, diabetes, and adverse health behaviors (physical inactivity, poor dietary behaviors, sleep disorders).

NICHD: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development is interested in applications that propose to evaluate the impact of weight related policies or programs on children, families, pregnant women, or children with disabilities.

NCI: The National Cancer Institute is particularly interested in the evaluation of programs or policies that may affect dietary or physical activity behavior and/or weight, and studies incorporating economic research.

NIA: The National Institute on Aging is especially interested in research on programs and policies affecting sedentary behavior and physical activity among older adults, including programs and policies based on research in behavioral economics.

Applicants are strongly encouraged to contact the Scientific/Research Contact(s) listed in this FOA to discuss their planned research prior to submission to this announcement.

Given the possibility for changes in policy or program implementation that are beyond the control of the grantee, grant awards may be terminated early if these changes limit the possibility to collect meaningful outcome data.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

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All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

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Complete details at: http://grants.nih.gov/grants/guide/pa-files/PA-13-110.html.

■ MECHANISTIC INSIGHTS FROM BIRTH COHORTS (R01): PAR-13-109

Components of Participating Organizations

National Institute of Diabetes and Digestive and Kidney Diseases

National Heart, Lung, and Blood Institute
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Application Receipt/Submission Date(s): Multiple dates, see announcement.

Emerging epidemiological evidence has shown that prenatal exposures such as placental function, maternal over- or under-nutrition, maternal physical activity behaviors, and maternal sleep disorders may be associated with an increased risk of chronic diseases in the offspring, either as a child or adult. Little is known about the mechanisms by which such prenatal exposures lead to diabetes or obesity, renal, pulmonary, or cardiovascular or hematologic disease, neurodevelopmental disorders, or reproductive health (i.e. fertility). A number of studies over the past ten years in sheep, rodents, and non-human primates have provided evidence that alterations in nutritional, metabolic, immune and hormonal milieu in utero can have profound long-term effects on offspring. Although there is increasing evidence for the roles of inflammatory pathways and epigenetic modifications, the mechanisms by which these effects are transmitted from mother to offspring have not been fully elucidated. Given the evidence pointing towards the role that alterations in the intrauterine environment have in the future pathophysiology of the offspring, it is necessary to better understand: 1) The factors in utero that mediate these effects; 2) The critical periods in prenatal exposure/development that have untoward effects; and 3) The measurements/biomarkers along the developmental path that can predict disease in the offspring. Ultimately, a better mechanistic understanding of how prenatal exposures contribute to the etiology of chronic diseases and health conditions later in life will allow for the development of effective interventions during pregnancy or early life that may have a profound impact on disease prevention and the future health of the offspring.

Scope and Areas of Research Interest

Proposed studies must take advantage of existing (or accruing) birth cohorts, with well-characterized pregnancies, such that targeted mechanistic questions regarding the developmental origins of diabetes or obesity, renal, pulmonary, or cardiovascular or hematologic disease, neurodevelopmental disorders, or reproductive health (i.e. fertility) can be addressed. Applications that address diseases that are not within the mission of the participating Institutes and Centers (ICs) are not appropriate to this announcement. A description of the existing cohort(s) to be used must be included in the application. Cohorts that are ongoing, but have not completed enrollment, could also be used. This announcement would not fund the originally-planned cohort but could, for example, fund ancillary data collection while the cohort is accruing. The establishment of new cohorts is not appropriate for this announcement; nor will the funding of infrastructure for follow-up visits of an existing cohort be allowed. This announcement seeks existing mother/child cohorts that have a rich depth of phenotypic information, including clinical data and bio-specimens starting in early pregnancy. Data on pre-pregnancy measures in the mother (and, if available, in the father) would also be desirable.

Applications should focus on potential mechanisms that mediate the developmental origins of human disease. Measures should come from analysis of stored or readily collectable samples from mother or offspring (such as cord blood, placenta, tissue, blood, serum, saliva, or urine). Applicants are encouraged to include specific measures, collected at defined times along the prenatal to postnatal life continuum, that will provide insight into the potential mechanistic links between maternal metabolism and fetal exposures during pregnancy and subsequent disease in the offspring. In addition to using existing and new samples for mechanistic studies, there should be a measure of disease, or disease risk, in the offspring.

Applications submitted to this FOA should target diabetes or obesity, renal, pulmonary, or cardiovascular or hematologic disease, neurodevelopmental disorders, or reproductive health (i.e. fertility). Research areas may include, but are not limited to, the following topics.

- Prenatal exposures that alter the epigenetic profile and predispose to disease susceptibility.
- Factors that alter the maternal or offspring microbiome.
- Specific gene-environment interactions influenced by prenatal exposure.
- Prenatal exposure to maternal disease, condition, or medication.
- Presence of significant inflammation in utero and how it might be quantitatively related to altered function of specific cell types in the offspring.

Potential applicants are strongly encouraged to contact the relevant Scientific/Research Contact listed in Section VII. Agency Contacts to discuss specific topics.

It is anticipated that there will be an investigators' meeting in the Bethesda, MD area shortly after awards are made so that investigators can share study plans and discuss whether there are common measures that should be conducted in all funded studies. Thereafter, there will be an annual investigators' meeting to share plans, findings and issues of common interest. Each applicant should include funds for attending these meetings in his/her budget.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian-serving institutions; Asian American Native American Pacific Islander- serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

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A team approach representing investigators that have access to the clinical samples and knowledge of the birth cohorts, with investigators having expertise in genomic, epigenomic, metabolomic and/or other in depth mechanistic analysis is encouraged. Given the potential breadth and depth of the data that will be accrued in the proposed studies, evidence of personnel that are qualified to perform the appropriate statistical and bioinformatic analysis should also be provided.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

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- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Complete details at: http://grants.nih.gov/grants/guide/pa-files/PAR-13-109.html.

■ SAFETY AND EFFECTIVENESS OF TRIPLE ANTIRETROVIRAL DRUG STRATEGIES FOR PREVENTION OF MOTHER TO CHILD HIV TRANSMISSION (R01): RFA-HD-14-027

Components of Participating Organizations

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Application Receipt Date(s): August 30, 2013

This funding opportunity announcement (FOA) issued by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH) invites applications to evaluate the safety and effectiveness of implementation of triple antiretroviral drug strategies for prevention of mother to child HIV transmission in resource-constrained settings - either an approach in which antiretroviral drugs stop after breastfeeding cessation in women who don't require therapy for their own health (termed by the World Health Organization "Option B") or a strategy in which life-long antiretroviral therapy is started in all pregnant women regardless of immune or clinical status (sometimes referred to as "Option B+").

Guidelines for prevention of mother-to-child HIV transmission (PMTCT) in resource-constrained settings are rapidly changing due to: increasing availability and decreasing cost of antiretroviral (ARV) drugs in such settings; new evidence to support ARV treatment of infected individuals with high CD4 cell count to reduce sexual transmission to uninfected partners; increasing country experience with use of triple ARV regimens in pregnant women; and ambitious goals for elimination of pediatric HIV infection by 2015 (WHO/UNICEF Global Plan Towards the Elimination of new HIV Infections Among Children by 2015 and Keeping Their Mothers Alive). The World Health Organization (WHO) currently recommends that all pregnant women with CD4+ lymphocyte counts <350 cells/μL or advanced HIV disease (WHO Stage 3 or 4 disease) should have immediate initiation of ARV therapy (ART); approximately 50–60% of HIV-infected pregnant women are in this category. The 2010 WHO guidelines recommended that women with higher CD4 counts receive either zidovudine after 14 weeks gestation with additional peripartum drugs and if breastfeeeding, infant nevirapine prophylaxis through cessation of breastfeeding (termed by WHO as "Option A") or a triple ARV drug regimen after 14 weeks gestation through cessation of breastfeeding (termed by WHO as "Option B").

In an April 2012 program update, WHO emphasized the potential programmatic and health benefits of the triple ARV drug regimen approach ("Option B") for all pregnant women; this recommendation will significantly increase the number of pregnant women receiving combination ARV drugs during pregnancy and breastfeeding. WHO also suggests that administration to pregnant women of a simplified, one daily, single pill, fixed-dose combination ARV regimen (tenofovir/lamivudine/efavirenz) that is the same as that recommended for treatment of non-pregnant individuals will result in greater efficiency and improve program implementation at the country level. Additionally, many countries are considering switching to a strategy of starting all pregnant women on ART for life regardless of CD4 count ("Option B+"), which in addition to increasing the number of women receiving ARV drugs during pregnancy will also result in subsequent pregnancies being conceived while the women are receiving ARV drugs. While the Option B/B+ strategies offer many benefits, there remain many important unanswered questions regarding wide-scale implementation of such programs and an urgent need for careful monitoring and evaluation, particularly of effectiveness and safety of these approaches.

With expansion of ARV drug use in pregnancy, more fetuses will be exposed to multiple drugs, often from conception through delivery. The new WHO program update recommends use of tenofovir/lamivudine/efavirenz in pregnancy because it is a simple, fixed dose combination one pill once daily regimen and is used in non-pregnant adults. However, data on the safety of tenofovir and efavirenz in pregnancy for the fetus are limited. Efavirenz has been associated with severe central nervous system birth defects in primates including neural tube defects, although the risk in humans is unclear. Because the underlying

incidence of neural tube defects in the general population is low (0.1–0.3%), a large number of exposures are needed to definitively rule out potential teratogenicity of first trimester efavirenz exposure. Data on overall birth defects with tenofovir exposure are reassuring but renal and bone toxicity are seen with tenofovir used for therapy, some data suggest potential negative effects of in utero exposure to maternal TDF on infant growth, and primate data suggest a potential effect on fetal bone development. The short-term and long-term effects of in utero exposure to ARVs in the fetus/infant/child have not been evaluated in resource-constrained settings; additionally, the underlying background incidence of birth defects in these settings has not been well defined. The high incidence of malnutrition, including folate deficiency, and other comorbidities in pregnant women, could serve to increase the risk of birth defects with ARV use. Widespread use of efavirenz in women of childbearing age, as now recommended by WHO, in resource-constrained settings may lead to increased rates of birth defects that will be difficult to detect without systematic study, particularly as the background rate of birth defects has not been defined in these settings.

Additionally, data from Europe and more recent data from Africa suggest that combination ART use in pregnancy, particularly use at conception and throughout pregnancy, may increase the risk of preterm birth, low birth weight, and stillbirth, leading to additional morbidity and mortality. Systematic study of outcomes with appropriate control groups to establish the background rates of abnormalities such as birth defects, preterm birth, and developmental and growth abnormalities is required to delineate the benefits and risks of perinatal ARV exposures and to identify the most appropriate ARV regimens in pregnancy.

There are very limited data related to acceptability of initiation of ART, particularly life-long ART with Option B+, when administered for the purpose of prevention of transmission to partners and infants in women who would otherwise not be taking ARV drugs for treatment. A number of studies from both resource-rich and constrained settings suggest particular problems with adherence to ART in women during the postpartum period and possibly also during pregnancy. Recent studies from Africa also suggest that pregnant women starting ART may have a higher risk of loss-to-follow-up than non-pregnant individuals starting ART. It is critical to obtain data to assess to what extent women are adherent to ART through the period of risk for MTCT and whether they continue to be adherent after the risk for MTCT has ceased (i.e., cessation of breastfeeding).

Integration of HIV care and treatment into maternal-child health programs, especially in rural areas, is difficult. In addition, retention of women in care after delivery is challenging with high loss to follow up rates thus far. Innovative mechanisms must be developed to facilitate starting women on ARV drugs during pregnancy and then maintaining them on treatment as they transition from pregnancy care to HIV care to minimize interruptions in therapy or suboptimal adherence which can lead to development of resistant virus and loss of treatment options. These strategies may need to include task shifting, or training of nurses or mid-level providers in initiation and monitoring of ARV regimens with remote physician consultation. Service delivery must be designed to maximize retention in care and adherence to drug regimens and to ensure a reliable supply chain of ARV and avoid stock-outs.

Studies to evaluate effectiveness of PMTCT interventions in resource-constrained settings on the ground have generally focused on short-term efficacy, evaluating infant infection status at age 6 weeks. However, breastfeeding may continue for 12 months or longer, and data on the long-term efficacy of ARV interventions in terms of infant HIV-free survival after the period of breastfeeding has ceased is critical to understand the overall efficacy and safety of interventions.

It is hypothesized that Option B/B+ offers significant benefits of ARV for maternal health in women with high CD4 count and for prevention of sexual transmission. Data to document these benefits will be critical to determine the true effectiveness and cost-efficacy of these interventions. Cost-efficacy studies are needed to be able to provide governments with data to determine what PMTCT program is optimal for their setting. Finally, the impact of the B/B+ ART interventions on the ability of country programs to serve all adults in need of ART needs to be evaluated, and whether the country is able to meet the needs of individuals who meet standard criteria for ART initiation with implementation of B/B+ ART for PMTCT programs.

Applicants should propose novel methods for evaluating safety and effectiveness of implementing the strategy of use of triple ARV regimens for PMTCT (Option B/B+) in pregnant women in resource-constrained settings. Areas of interest include, but are not limited to:

- Systems for surveillance of adverse pregnancy outcomes including preterm birth, stillbirth, and congenital anomalies among women receiving ARV with appropriate unexposed control groups; of particular interest are cohorts of women who conceive while receiving ART that is then continued throughout pregnancy.
- Studies to evaluate the acceptability of and adherence to triple ARV regimens given to HIV-infected women for PMTCT, particularly in women not yet candidates for ART for their own health.
- Optimal service organization and models to deliver ART and monitor its efficacy in maternal/child health and primary care settings.
- Models to maximize retention in care and adherence to antiretrovirals during pregnancy, breastfeeding, and beyond.
- Systems for surveillance for HIV resistance among women initiating on long-term ARV and among infants who become infected despite maternal ART.
- Studies to evaluate the effectiveness of Option B/B+ on MTCT rates, both early, 6 week and importantly overall rates at the end of breastfeeding, and on HIV-free survival.
- Studies to evaluate the hypothesized effectiveness and benefit of Option B/B+ on maternal health and prevention of sexual transmission among discordant partners.
- Studies to evaluate the costs and cost-benefit of Option B/B+.
- Studies to evaluate the impact of Option B/B+ on the ability of the country program to serve all adults in need of treatment.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School

Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Late Submission of Grant Applications states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) – All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (formerly CCR) – Applicants must complete and maintain an active registration, which requires renewal at least annually. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
- NATO Commercial and Government Entity (NCAGE) Code – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

All PD(s)/PI(s) must have an eRA Commons account and should work with their organizational officials to either create a new account or to affiliate an existing account with the applicant organization's eRA Commons account. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

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Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-14-027.html.

■ IMPROVEMENT OF ANIMAL MODELS FOR STEM CELL-BASED REGENERATIVE MEDICINE (R24): PAR-13-113

Also see: Improvement of Animal Models for Stem Cell-Based Regenerative Medicine (R01): PAR-13-114
Details at: http://grants.nih.gov/grants/guide/pa-files/PAR-13-114.html.
Also see: Improvement of Animal Models for Stem Cell-Based Regenerative Medicine (R21): PAR-13-115
Details at: http://grants.nih.gov/grants/guide/pa-files/PAR-13-115.html.

Components of Participating Organizations

Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs

Application Receipt/Submission Date(s): Multiple dates, see announcement.

This FOA encourages Resource-Related Research Project Grant (R24) applications from institutions and organizations proposing research aimed at characterizing animal stem cells and improving existing and creating new animal models for human disease conditions. The Division of Comparative Medicine (DCM) in ORIP convened an NIH workshop in 2012 that addressed the current status of animal stem cell biology and made recommendations concerning improvements in technologies and applications of animal stem cells to regenerative medicine. The results of this workshop provide the basis for this FOA. The intent of this initiative is to facilitate the use of stem cell-based therapies for regenerative medicine. The initiative focuses on the following areas: 1) comparative analysis of animal and human stem cells to provide information for selection of the most predictive and informative model systems; 2) development of new technologies for stem cell characterization and transplantation; and 3) improvement of animal disease models for stem cell-based therapeutic applications.

Regenerative Medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to damage or congenital defects. Regenerative medicine has the potential to solve the problem of the shortage of organs available for donation. It also holds the promise of repairing or replacing damaged tissues and organs in the body by stimulating organs previously considered irreparable to heal themselves. The recent discovery of the reprogramming of adult cells to a pluripotent state provides opportunities to address a major problem

of regenerative medicine, immune rejection of transplanted tissue. The ability to generate differentiated cells and tissues using cells from specific patients will facilitate individualized medicine and eventually will lead to specialized therapies. The field is moving toward translation to clinical practice and is becoming increasingly dependent on animal models and information regarding the potential therapeutic efficacy of new technologies. Generating the correct type and quantity of the specific cell types required for replacement therapy is a significant challenge, as are the problems associated with introducing these cells into the proper environment in vivo and overcoming immune reactions. Finding solutions to these problems will require extensive testing in experimental animal models.

Major advances have been made in the past several years in deriving pluripotent cells, such as embryonic stem cells (ESCs) and induced pluripotent cells (iPSCs) from both humans and animals. In parallel, other investigations have isolated and characterized multipotent "somatic" or "adult" stem cells from various tissues, including Mesenchymal Stem Cells (MSCs) and Germinal Stem Cells (GSCs). The discovery of mouse ESCs in 1981 revolutionized the field of developmental biology and provided new capability for genome manipulation and investigations of gene function. Isolation of human ESCs created new possibilities for the field of regenerative medicine. ES-like cells have been derived from a number of animal species, including rats, fish, cows, pigs and non-human primates. Many characteristics of animal ES-like cells, including surface markers, growth factor requirements, ability to differentiate and others can be quite different from human ESCs.

The field of stem cell research experienced a dramatic new direction with the isolation of iPSCs, derived by reprogramming human or mouse somatic cells to a pluripotent state. Several studies on various animal systems suggest that the basic pluripotency network appears to be conserved among different species, allowing derivation of iPSCs from a variety of animals.

MSCs, a type of somatic stem cell, were originally identified as a subpopulation of bone marrow cells with osteogenic potential. The properties of MSCs have been examined extensively over the past decade. Studies using animal models have shown promising results following MSC therapy for induced injury in the musculoskeletal, cardiovascular, digestive and nervous systems. In addition, many clinical trials have demonstrated the efficacy of MSC infusion for treating various human diseases. Given the wide range of tissue sources, the recognition of subpopulations with specific properties, and the frequent production of genomic alterations upon expansion in cell culture, extensive characterization of MSCs and development of improved techniques are required. Most importantly, there is relatively limited understanding of the normal biological functions of MSCs and the mechanisms by which they participate in tissue repair.

GSCs are another type of somatic stem cells of great interest for regenerative medicine. They are an essential component of reproductive biology. Genetic manipulation of GSCs provides a powerful tool for producing transgenic animals, for elucidating mechanisms underlying germ cell development and differentiation and for understanding the interactions between stem cells and their niche. Further development of the methods for unlimited production of GSCs (for producing either sperm or eggs) will impact the ability to investigate the molecular basis of germ cell differentiation and for treatment of infertility by transplantation. Numerous reports using animal and human GSCs have shown generation of pluripotent cells during in vitro cultivation, which potentially can solve a number of issues. However, it remains difficult to isolate, derive and maintain stable cultures of these cells from humans and model animal species. Furthermore, the mechanisms that determine the reprogramming of GSCs into pluripotent stem cells are not well understood and efficient methods for directed reprogramming of these still have to be developed.

Along with rodents, several other animal species are being developed as models for various studies in the field of regenerative medicine. Understanding the properties and capabilities of stem cells derived from animals such as rabbits, pigs, sheep, goats and monkeys will increase the potential for the use of the most appropriate systems for modeling particular human disease conditions or for other medical applications. Non-rodent species (often referred to as "large animal models") provide important advantages for transplantation studies, including large size, similarity to human physiology and pathology and longer life span, thus facilitating translation to studies in humans. The use of animal stem cells as a model for human cells in procedures related to regenerative medicine requires in-depth understanding of common regulatory pathways as well as species-specific properties and their impact on potential therapeutic applications.

Animal experiments have historically made a significant contribution to understanding human disease. However, animal studies need to be improved in order to better predict the efficacy of treatment strategies in clinical trials. Several possible causes of the disparity between the results of animal studies and clinical trials have been identified, including failure to acknowledge the limitations of animal models, inadequate animal data and conclusions from them, less than optimal disease models and overestimation of treatment efficacy due to the preferred publishing of positive results. These problems should be addressed in the design and execution of preclinical, animal-based studies involving stem-cell based therapies.

Research activities that are being sought to achieve the objectives of the program:

Projects supported by ORIP/DPCPSI under this FOA are intended to improve existing and create new animal models for regenerative medicine. Efficient use of animal models is facilitated by development of specific resources for characterizing, archiving and distributing animals as well as research tools, reagents and stem cell lines of utility to research on a variety of animal species. Development of an animal-based resource often requires preliminary work that is research-based. This resource-related research is often not hypothesis driven and cannot be addressed appropriately by NIH R01 or R21 grant applications. Accordingly, ORIP/DPCPSI supports R24 grants which have the following features:

- The grants support applied studies to characterize and develop new animal based resources or to improve existing resources.
- The grants support research projects that contribute to the knowledge of a model system, making the system more useful and accessible to the research community.
- In all cases, the potential results of investigations must be applicable to the interests of two or more of the NIH Institutes and Centers (ICs). Furthermore, investigations of a disease that predominantly relates to the interests of one NIH IC and peripherally relates to the interests of other NIH ICs are not appropriate for this FOA. Preference will be given to investigations that examine general principles involved in developing the most informative animal models for regenerative medicine, rather than focusing on a specific disease. However, investigations involving specific diseases can be used as proof of principle. An example of

an inappropriate request is one exclusively involving an animal model of cancer. The ultimate objective of these efforts should be to provide essential preclinical knowledge that can help inform future clinical investigations.

- The particular emphasis of a specific R24 grant can vary in regard to the balance of research- versus resource-related activities, depending on the state of the art at the time. A R24 grant can be predominantly research based, if the research will plausibly lead to development of a resource, or can be predominantly aimed at final development or enhancement of a resource if most of the necessary research has already been accomplished.
- The R24 grant application must demonstrate a need for the resource (or resource to be developed) by the biomedical research community.
- Cost recovery is not required.

The following are examples of research topics of particular interest to ORIP. Other innovative projects are also encouraged:

- Characterization and enhancement of animal stem cells as model systems for human stem cells. Innovative approaches to understand the biology of stem cells from species widely used in regenerative medicine. Rat stem cells are of particular interest, taking into account current advances in isolation and characterization of stem cells from rats, the progress of the rat genome project and current advances in the ability to manipulate rat genes.
- Development and characterization of stable, well characterized pluripotent stem cell lines from large animal species, such as rabbits, dogs, pigs, sheep and monkeys. Development of stem cell lines from this type of animal model should be justified as having direct relevance to potential uses in the field of regenerative medicine. Creation of biomarkers, standard protocols, species-specific reagents, proteomics, transcriptomics and genetic tools to assist the use of these cells is also of interest.
- Comparative analysis of animal and human stem cells to define criteria that will assist in choosing the most appropriate animal species and stem cell type for a particular application.
- Redirection of existing or creation of new national centralized facilities with robust capacity to purify, characterize and store stem cells from large animal species for regenerative medicine applications, to maintain databases and make biomaterials available to the wide biomedical community as well as to develop and produce isogenic lines.
- Development of new techniques for: Guiding and verification of the accuracy of cell injection, tracking cell migration, evaluating off-target effects, and monitoring long-term integration and the phenotype and function of transplanted stem cells and their derivatives.
- Development of new approaches to: Understand and target the cell fate determining niche to improve extrinsic effects on stem cell function; increase cell survival and proper integration into the host environment; establish correct regulatory connections after cell-grafting experiments.
- Investigations of the therapeutic benefits of human and animal MSCs in animal models and mechanisms of their biological action. Improvement of methods for testing the efficacy and potency of MSCs in animals and for controlling the MSC secretome post-transplantation. Development of definitive markers for the multipotent state of the cells. Investigations of the cause of the high sensitivity of MSCs to the microenvironment. Standardization of culture conditions for scale up of production.
- Investigations of animal GSCs as models for understanding embryogenesis and organogenesis, stem-cell niche interactions and fate decisions. The focus should be on facilitating the application of GSCs for regenerative medicine, for example, exploring potential for generating pluripotent cells and for deriving genetically modified animal models, including the use of haploid cells for this purpose. Preference will be given to applications working with large animal models, such as rabbits, dogs, pigs, sheep and monkeys.
- Investigations to improve existing humanized animal models and create new ones. Preference will be given to studies involving species other than rodents. Of particular interest are advances in the reproducible and cost-effective generation of humanized chimeras, which is currently technically challenging. Development of humanized animals for in vivo generation of complex human tissues and organs using stem cells.
- Development of high throughput genetic and therapeutic screens to study stem cell biology and homeostasis in appropriate animal species, such as Drosophila and zebrafish.
- Improvement and distribution of the reagents, protocols, stem cell lines, vectors, genetically altered animal strains and disease models, suitable for such screening.
- Improvement of animal disease models for regenerative medicine, which will better emulate physiological, cellular and molecular manifestations seen in humans. Development of methods to increase the predictability of stem cell based treatments in regard to effectiveness, major complications, safety and off target effects. Demonstration of the functionality of specific stem cells or their derivatives and the effectiveness of achieving specific results in improved animal disease models.
- Investigations of mammalian stem cell reprograming and somatic cell transdifferentiation. Further development of approaches and protocols for manipulating cell fate using efficient and safe methods, including removable vectors and vector systems with temporal expression of transcription factors, RNA or small molecules. Investigations regarding how these modifications can be used to control the expansion and differentiation of resident progenitor cells for direct reprogramming in vivo.
- Development of animal models for effective and sustained gene therapy using ex-vivo engineered stem cells and their derivatives as well as endogenous stem cell populations to correct gene defects. Preference will be given to applications that provide general approaches for a broad array of uses. Applications should not be focused on therapy for specific diseases. However, a specific disease can be used as a proof of principal, if also applicable to other disease conditions. Improvement and investigations of the safety of newer technologies such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), allowing targeted approaches for the elimination of disease-causing mutations, as tested in animal models.
- Development of solutions to problems of stem cell therapy that have already been identified, such as: Heterogeneity of cell populations, genetic instability, high mutation rate during in vitro manipulations, epigenetic memory of differentiated iPSCs and immune responses induced after stem cell transplantation. Of particular interest is the development of functional assays and high-throughput techniques that will predict the potential immunogenicity of transplants and the tumorigenicity or metastatic potential of stem cell lines.

- Development of new methods or animal models to evaluate the safety of stem cell transplantation in animals, including studies of adsorption, distribution, metabolism, excretion and toxicity of stem cell-based therapeutic products. These models should take into account properties of the specific stem cell populations and should mimic the intended use of the cells in humans.
- Development of public databases that will contain information on: Reproducible experimental conditions; Cell lines and related biomaterials; Results of testing animal and human stem cells in animal models, and; Cross-species and unique phenotypes that will assist future biomedical scientists and medical practitioners in the selection of the most relevant pre-clinical model.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are not allowed.

Applicant organizations must complete the following registrations as described in the PHS 398 Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the PHS 398 Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

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Complete details at: http://grants.nih.gov/grants/guide/pa-files/PAR-13-113.html.

■ SPECIALIZED COOPERATIVE CENTERS PROGRAM IN REPRODUCTION AND INFERTILITY RESEARCH (U54): RFA-HD-14-017

Components of Participating Organizations

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Application Receipt Date(s): July 25, 2013

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), through the Fertility and Infertility Branch (FIB), provides funding for a limited number of research centers in the reproductive sciences. These centers provide an arena for multidisciplinary interactions among basic and clinical scientists interested in establishing high quality translational research programs in the reproductive sciences. The centers also serve as national resources for the training and career development of young scientists electing to pursue careers conducting research in high priority areas of reproduction and infertility. Accordingly, the purpose of this FOA is to announce the competition of the Specialized Cooperative Centers Program in Reproduction and Infertility Research (SCCPIR). Applications are sought from investigators willing to participate with the NICHD under a cooperative agreement in a multicenter cooperative research program. Center investigators will be expected to work with NICHD staff in facilitating research collaborations and interactions within and among centers. Such a cooperative program will form a national network that facilitates and accelerates bidirectional knowledge transfer between the laboratory and clinic with the ultimate goal of improving human reproductive health through enhanced communication, innovation and research excellence.

Families, family values, and family planning form the cultural essence and cohesiveness of our existence as human societies. One of the most basic of human rights - the right to procreate - is frustrated or denied by the occurrence of infertility in couples desiring children. It has been estimated that infertility affects between 37 and 70 million married couples around the world.

In studies described over 50 years ago, it was stated that up to 10 percent of U.S. married couples were sterile, with the remaining 90 percent having varying degrees of fertility. More recent and technically rigorous U.S. survey studies have conservatively identified that there are approximately 2.0 million infertile couples, which is about nine percent of the domestic married couple population base with wives aged 15–44. According to the 2010 National Survey of Family Growth, 6.0 percent of married women were infertile (12 months or longer without birth control and without a pregnancy). This represents a significant decline from the prevalence of 8.4 percent reported in 1982. On the other hand, about 11% of married women had an impaired ability to have children (impaired fecundity) in 2010 compared to 8.5% of married women in 1982. This latter trend likely is indicative of the delay in childbearing found in the contemporary couple population base in which significant age-related increases in infertility and subfecundity have been reported.

Physician office visits reflecting current societal life-style requirements for infertility services have markedly increased in the U.S. over four fold between 1968 and 2010 (>2,000,000 visits annually). Indeed, it is estimated that 12 percent of American women aged 15–44 have received infertility services at some point during their lifetime. Interestingly, this represents only half the number of women who actually need infertility services. Of the infertile couples seeking treatment for infertility, it has been estimated that up to one half will be unsuccessful in achieving their desired outcome. In concert with the increased medical assistance sought, U.S. infertility service costs have risen to exceed several billion dollars annually.

In couples, at least 25–40 percent of infertility is attributable to male factor infertility for which the pathophysiology is either not understood at all or, at best, poorly understood. The prognosis for male infertility treatment outcomes is extremely poor at present. Indeed, whereas 80 percent of infertile women can be successfully treated, male infertility can be treated in only 10–20 percent of such men. Even though artificial reproductive technologies such as intracytoplasmic sperm injection can, in most cases, circumvent male infertility, the process is expensive, both from a monetary and psychological standpoint for the couple. Furthermore, while ICSI and other assisted reproductive technologies have enabled otherwise infertile men to father children, these technologies may bypass genetic or epigenetic causes of infertility that may also be linked to other health problems that will negatively impact the life of the unborn child (and possibly later generations).

Reproductive tract disorders affecting fertility are associated with significant morbidity and a degree of mortality in some specific instances that cannot be ignored. Accompanying the human costs of morbidities of reproductive tract disorders are the attendant substantial costs to the U.S. health care system involving the diagnosis, treatment, and follow-up services provided to the patients, as well as the added costs to the patient and the U.S. economy of lost employment and family service hours. In reproductive-aged couples, the obstructive sequelae of male accessory gland infections account for eight to 12 percent of male partner diagnostic costs for fertility impairment. In reproductive-aged females, it has been estimated that the general incidence of endometriosis is five to 15 percent, but can be as high as 50% in women with pelvic pain or infertility. While the causative role of endometriosis in infertility remains poorly understood and its optimal diagnosis and treatment remain a goal not an accomplishment of contemporary medicine, the morbid impact of the associated pelvic pain has significant human cost as well as national economic costs. Indeed, the health care burden of endometriosis has been estimated to be an astounding 22 billion dollars per year! Similarly, the role of dysfunctional uterine bleeding, either in the presence or the absence of uterine leiomyomata (fibroids), is not well understood despite its common occurrence and decades of research. It is a significant factor in noncompliant contraceptive use or discontinuance and, therefore, in the unintended pregnancy problem.

Uterine leiomyomata occur in 20-30% percent of all reproductive-aged women. Uterine fibroids are the single most common diagnosis in gynecological hospital admissions, may be the only abnormality observed in an infertile couple, and represent the most common medical indication for an unintended and often unwanted hysterectomy that prematurely ends a female's reproductive options. Fibroids disproportionately affect African Americans with some studies indicating a three-fold higher prevalence in this racial group than in the Caucasian population, exacting a profound health care burden on a population of women that often times lack good health care coverage or any coverage at all. Annual cost expenditures for this condition have recently been estimated to be between 6 and 34 billion dollars.

Polycystic ovary syndrome (PCOS) is a major cause of female infertility, as well as of other reproductive system and other tissue and organ system morbidities. Identified more than 60 years ago, the etiology of PCOS still remains misunderstood. This insidious disease is currently the most common endocrine disorder of reproductive-aged women, affecting between five and 10 percent of women aged 15–44 or more than four million women in the U.S. Most, if not all, women with PCOS present with hyperandrogenemia, irregular menstrual cycles and polycystic ovaries. Often these conditions are accompanied by obesity and insulin resistance. Indeed, the risk of type 2 diabetes mellitus among PCOS patients is five- to 10-fold higher than in the normal population, and the prevalence of the Metabolic Syndrome is nearly two-fold higher in PCOS women than in the general population. Considering the high prevalence of diabetes in PCOS women, a very recent study estimated that the total annualized cost of evaluating and providing care to PCOS women is $4.6 billion dollars. However, the costs associated with endometriosis, PCOS and fibroids do not take into account that these women generally experience a lower quality of life due to the obesity, hirsutism, acne, and pain associated with these disorders.

Also poorly understood is the pathogenesis of premature ovarian insufficiency (POI) that affects one in 100 women by age 40. Interestingly, 16 percent of women carrying the fragile X premutation present with POI. The mechanism(s) underlying premutation-based ovarian insufficiency is not known, but once known could provide critical insights into the basic biological processes regulating ovarian follicular growth, differentiation and atresia. The scientific 'dogma' that oocytes progressively decline in number until exhausted as women age and cannot be renewed has been called recently into question. Furthermore, dietary interventions may delay ovarian aging and improve oocyte (and sperm) quality as aging advances.

With the hopes that earlier diagnosis of these devastating infertility disorders will result in earlier intervention and amelioration of the condition, attention is now turning to the adolescent. Here, research efforts are needed to better define hormonal changes during normal progression of sexual maturation, particularly at the time of menarche. In this regard, initial menstrual cycles are often irregular and are anovulatory, making it difficult to diagnose conditions such as PCOS. Likewise, endometriosis had been thought to occur rarely in adolescence, but it is being diagnosed more frequently in this population thanks to a greater awareness by the medical community. Efforts to refine diagnostic criteria for children

and adolescents so that effective interventional strategies can be employed are likely to pay enormous dividends in decreasing the incidence of disease and infertility in adulthood.

Data now firmly support the contribution of genetics and epigenetics in male and female infertility. In males, there is considerable evidence from animal studies that mutation of over 100 separate genes results in infertility. More limited studies in humans show that a number of inherited diseases are associated with abnormal sperm morphology and function. These data suggest that a significant number of men with infertility may have one or more mutations that predispose to their condition. However, it is currently not possible to determine which men have genetic infertility. Similarly, it is estimated that 15–20 percent of human pregnancies are chromosomally abnormal as a result of division errors during oocyte meiosis or early embryonic cleavage. Such errors not only are the leading cause of birth defects, but may be the single most important factor contributing to human infertility. Finally, evidence is mounting to show that altered epigenetic modification of gene expression through histone modifications, changes in DNA methylation or RNA stability changes may underpin diseases such as endometriosis.

It is becoming increasingly apparent that male infertility can be considered a marker for the general health of the individual, i.e., infertility is correlated with higher rates of cardiovascular disease, diabetes, and certain types of cancers. Furthermore, contrary to previous thinking, the sperm contributes more than its DNA to the oocyte as the epigenome has been shown to play a critical role in the developing embryo. Alterations in the establishment and/or maintenance of the various epigenetic marks have been shown to affect the fertility status of males. Of particular importance is the demonstration that environmental factors such as toxicants and diet promote multi- and transgenerational inheritance of adult-onset disease. Epigenetic alterations are generated in the male gamete and then stably passed to subsequent generations, where the result can be e.g., insulin sensitivity and infertility.

An area of emerging public health interest is the preservation of fertility in individuals undergoing treatments for diseases such as cancer. Currently, there are more than 9 million cancer survivors in the U.S. of whom approximately 5% are under the age of 35. The chemical or radiological consequences of these treatments oftentimes target vital reproductive organs such as the gonads, depleting the gamete stem cell pool and causing permanent infertility. For example, more than 1 in 5000 men of reproductive age who are childhood cancer survivors suffers from infertility or sub-fertility. However, in the future the ability to cryopreserve a testicular biopsy prior to treatment, followed by expansion of the spermatogonial stem cells and transplantation back into the testis may afford the opportunity to generate normal offspring without contaminating malignant cells and epigenetic and/or genetic errors. Providing options for preserving fertility in men, women and children is not only an important reproductive health issue, but a quality of life issue as well.

Another high priority topic for reproductive health is preconception care. This area has its roots in the Barker Hypothesis which states that adult diseases have their origins prior to birth. To this point, most experimentation has examined possible adverse birth outcomes (e.g., low birth weight, intrauterine growth restriction, preeclampsia, pre-term birth, birth defects) and adult disease incidence as a result of perturbing the maternal-fetal environment. However, it is now clear from animal models that these adverse outcomes can occur during the embryonic period and even prior to implantation or conception itself (and can even be due to the paternal contribution). Thus, increased efforts are needed to define important developmental periods in which perturbations to normal physiological systems can result in poor pregnancy outcomes and to determine if these periods coincide with periods for important epigenetic modification of the genome.

Finally, the need for the availability of contraceptive options acceptable to diverse populations remains globally unmet. Among the 600 million women of reproductive age in today's world, as many as 228 million women are at risk of unintended pregnancy. Up to 64 percent of all worldwide pregnancies and approximately one-third of pregnancies in the U.S. are unintended (mistimed or never wanted). About 40-50 million abortions occur worldwide each year, with minimal estimates of at least 100,000 abortion-related deaths annually. In the U.S., more than three million unintended/unwanted pregnancies occur annually, with half resulting in abortion as an outcome. In half of the abortions occurring in the U.S. each year, a contraceptive method being used failed to prevent pregnancy. Clearly, new innovative strategies are needed for pregnancy prevention. As such, discovery of novel contraceptive targets remains a high priority research area for the institute.

The Fertility and Infertility Branch recognizes that the interactive needs of basic and clinical research necessary to address the above and related problems may be so complex that they cannot be solved by individual investigators working alone. Therefore, it is the intention of the FIB, contingent upon the availability of funds, to continue and maintain organized, multi-component reproduction and infertility research programs of high quality that focus on topics of high priority and significance that are critically important to the mission of the FIB, and that address important reproductive health concerns of the American public.

A major objective of the SCCPIR is to support specialized translational reproductive research programs of high quality, and to facilitate and accelerate bidirectional transfer of knowledge between the laboratory and clinic. This process of translating research between the laboratory and clinic is a continuum that encompasses all aspects of knowledge transfer from non-human animal models to humans. For example, application of information from rodent species to non-human primates is considered part of the translational continuum. However, the ultimate goal of supporting translational research through the SCCPIR is to improve human reproductive health.

This FOA is specifically designed to stimulate the reproductive sciences research community to organize and maintain research-based centers of outstanding quality that, serving as national research resources, form a cooperative network with NICHD that fosters communication, innovation and high quality reproduction and infertility research. Such networking as afforded by the cooperative nature of this Centers Program will ensure that the reproductive research community remains in the forefront of the development and utilization of new technologies that can be used to diagnose, treat and ameliorate reproductive diseases and disorders, as well as to identify novel leads for fertility regulation.

The SCCPIR is composed of research-based center grants designed to support interactive groups of research projects and supporting core service facilities. The research activities included in these center grants must comprise, by definition, a multidisciplinary approach to biomedical problems addressing the specific research topic areas announced in this FOA (see below). These centers may have more than one theme, focus or emphasis, but all of the research projects involved must be responsive to one or more of the specific research areas of reproduction supported by the FIB. Furthermore, the objectives of this Program require that one of the research projects be entirely or predominantly clinical and that all basic science projects be linked to the clinical project (s) of the center.

Topics that are considered to be responsive to the research mission areas of the FIB include but are not limited to those bulleted below. Additionally, these topics identify areas where research at the basic/clinical interface is deemed essential to the potential development of new leads or approaches to fertility regulation, as well as of diagnostic tools and procedures for the detection, treatment and effective management of reproductive disorders that impact on reproductive competence.

- Reproductive Developmental Biology: origins and differentiation of germ cells including gametic stem cells; the endocrine, paracrine and physiologic mechanisms involved in gametogenesis, including germ cell-somatic cell interactions, germ cell proliferation and apoptosis, blood-testis barrier formation and remodeling and germ cell transplantation; fertilization, including sperm motility and capacitation, zona pellucida binding and mechanisms to block polyspermy; pre-implantation embryonic development including zygotic gene activation, mechanisms regulating embryonic stem cell self-renewal and differentiation and maintenance of stem cell pluripotency including the importance of oocyte reprogramming factors; use of genetically modified stem cells to treat animal models of reproductive disorders impacting fertility.
- Reproductive Tract Biology and Physiology: folliculogenesis, including studies addressing intraovarian control of follicle selection and atresia by growth factors, cytokines and their respective binding proteins and receptor antagonists; luteogenesis and luteolysis, including intraovarian mechanisms that control luteal life span; implantation, including cell-to-cell interactions and embryo-uterine communication; the role of angiogenesis in ovarian and endometrial function; correlation of segmental gene expression with structure and function of the oviduct and epididymis.
- Reproductive Endocrinology and Neuroendocrinology: fundamental mechanisms of hormone synthesis, secretion, regulation and action in the context of reproduction; developmental control of GnRH neuronal migration and targeting; intraneuronal mechanisms and glia-neuron interactions controlling pulsatile GnRH secretion; intrapituitary mechanisms governing gonadotropin secretion; identification of elements and factors controlling gene transcription including ensembles of co-activators and co-repressors, and identification of signaling molecules and pathways mediating hormone action; interaction of the immune and neuroendocrine systems in controlling fertility; mechanisms by which nutritional modification alters the hypothalamo-pituitary-gonadal endocrine axis.
- Reproductive Genetics and Epigenetics: genetics of sex determination including clarification of the functional interactions between the known sex determination genes; genes, pathways; epigenetic mechanisms that are important in reproduction, including those involved in genomic imprinting,, changes in DNA methylation, post-translational modifications of histones, and small non-coding RNAs during gametogenesis and embryogenesis; and elucidation of the genes, genetic and epigenetic mechanisms responsible for normal and skewed X chromosome inactivation.
- Reproductive Medicine: etiology, pathophysiology, prevention and treatment of male or female infertility, with particular emphasis on defining those conditions that are either genetically based or may have a significant epigenetic component; relation of endometriosis and uterine leiomyomas to infertility, research leading to improved outcomes across the spectrum of assisted reproductive technologies, as well as development of new approaches for assisted reproduction and preserving fertility; use of genomics and proteomics to develop novel diagnostics for reproductive diseases and disorders particularly in adolescents; role of parental health on gamete quality and function.

Because this list is not meant to be all-inclusive, prospective applicants preparing either a new or renewal center grant application are encouraged to discuss program relevance issues with the Scientific/Research Contact indicated in Section VII. Agency Contacts. However, applicants should note that the research scope of this FOA does not include studies in the area of reproductive oncology, reproductive toxicology or reproductive epidemiology, or studies dealing with post-implantation pregnancy and parturition. These topic areas are outside the scope of research supported by the FIB and, therefore, will be deemed non-responsive to this FOA. Further, applications proposing research activities focused exclusively on basic research, or applications or components thereof proposing epidemiological or large-scale clinical trial research, will not be considered responsive to this FOA.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander- serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete the following registrations as described in the PHS 398 Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the PHS 398 Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-14-017.html.

■ NINDS STROKE TRIALS NETWORK - NATIONAL CLINICAL COORDINATING CENTER (U01): RFA-NS-13-012

Components of Participating Organizations

National Institute of Neurological Disorders and Stroke

Application Receipt Date(s): June 04, 2013

The purpose of this funding opportunity announcement (FOA) is to invite applications to participate as a National Clinical Coordinating Center (NCC) for the NINDS Stroke Trials Network. The network will develop and conduct high-quality, multi-site phase 1, 2 and phase 3 clinical trials focused on key interventions in stroke prevention, treatment, and recovery. The network will consider the breadth of cerebrovascular disease beginning with patients identified with acute stroke through stroke rehabilitation and secondary stroke prevention for pediatric and adult patients.

The network will provide a robust, standardized, and accessible infrastructure to facilitate rapid development and implementation of NINDS-funded stroke trials. It will include multiple regional coordinating stroke centers (RCC) and their affiliated stroke centers with a proven track record of enrolling stroke patients into clinical studies, one NCC, and one National Data Management Center (DMC). The network is designed to increase the efficiency of stroke clinical trials by facilitating patient recruitment and retention, supporting novel methodologies and streamlined approaches to accelerate the development of promising stroke therapies, and enabling comparison between approaches.

Stroke is a disabling, often fatal and expensive disorder that is a major public health burden. Globally it is the second leading cause of death, but in North America stroke has fallen to the fourth most common cause of mortality as the result of ongoing successes in prevention and acute care. Vascular disease of the brain can manifest not only as overt stroke but also as silent infarction and diffuse white matter disease with cognitive and functional decline. Stroke is a syndrome, with two broad types (ischemic and hemorrhagic) and with multiple possible underlying causes. Although stroke impacts all age groups (including children and especially neonates), the incidence is strongly linked to aging. Stroke will become increasingly prominent in the next 30 years with the projected rise in the proportion of elderly in the US, and it will impose an even more significant toll on individuals, families, and society.

NIH-funded basic, translational and clinical research offers the promise to reduce the burden of stroke.

The Stroke Progress Review Group and NINDS stroke planning efforts identified a need for stroke trial network infrastructure to effectively pursue a number of scientific opportunities and to accelerate translation (see http://www.ninds.nih.gov/find_people/ninds/OSPP/Stroke-Research-Priorities-Meeting-2012.htm). The unbiased evaluation of newly-developed and existing interventions-drugs, devices and systems of care-in randomized, controlled clinical trials are necessary to establish efficacy of interventions for improving important clinical outcomes. Phase 1, 2 trials explore safety, target engagement, proof of biological concept, and dose response to inform phase 3 efficacy trials. Phase 3 efficacy trials are designed to demonstrate clinical benefit that patients consider meaningful. Comparative effectiveness trials examine how to best apply established efficacious treatments.

Investigators in the NINDS Stroke Trials Network will forge collaborations to engage in the planning, development and execution of innovative trials designed to best answer the highest priority scientific questions for advancing stroke treatment. The success of the network's phase 1, 2 activities will be enhanced by strong relationships with preclinical experts in the basic science of cerebrovascular disorders. The investigators will be expected to judge the feasibility of the network's performance of trials designed outside the network as well as to develop original grant applications for submission to NINDS peer review.

Biomarkers, especially neuroimaging markers of vascular pathology, brain ischemia, or recovery after injury, have been developed for stroke research. Biomarker-validation studies that are immediately preparatory to trials will also be considered by the Stroke Network. The potential applications of biomarkers are to guide early neuroprotective and reperfusion interventions, to monitor neuroplasticity in stroke recovery, and to expedite therapy development. Some biomarkers have been validated in multicenter studies, but their full potential to impact research awaits standardization and adoption across a clinical trials network.

Clinical trials require a network of experienced clinical researchers, data management, clinical trial personnel, as well as infrastructure for data capture and storage, and the recruitment and retention of participating patients. Clinical trials are time consuming and expensive, often requiring as much as 10 years or more to complete. These constraints can drain the resources of funding agencies, investigators, industry, clinical resources, and patients and may discourage innovative strategies and collaborations with industry and international stroke trial consortia intent on achieving common goals.

In the traditional model, a consortium of clinical sites is created for each new multi-center trial. This leads to redundancy because infrastructure resources are duplicated. Also, time is lost when common start-up activities are repeated for each trial. Multiple, uncoordinated contract negotiations and Institutional Review Board (IRB) approvals often cause further delays and create challenges

for industry partnerships. This is especially critical given industry's perception that new stroke therapies are too difficult and risky to pursue. Therefore, highly meritorious, peer reviewed clinical trials developed under Collaborative Research and Development Agreements (CRADA) between NINDS and industry partners may also be performed by the network.

Another limitation of the traditional research model is that it is difficult to access and combine data across trials to enable meta-analysis and the development of new research questions. A major opportunity for the network is to coordinate and integrate data across the spectrum of NINDS funded stroke trial research. This and the use of Stroke Common Data elements (CDE's) will ensure synchronized and uniform collection of clinical, neuroimaging and biological data, and it will potentially lead to innovative new methods such as the integration of patient reported outcomes or electronic health record data in large, "pragmatic", clinical trials. Comparison of results across studies and for metadata analysis would increase the value of collected data, and thus the contribution of study participants.

Lastly, without an ongoing trial network, there may be loss of expertise and real-world clinical knowledge as stand-alone trials finish. The lack of consistent activity at a site may lead experienced research coordinators to move to other fields after a trial is completed. The NINDS Stroke Trials Network will enable the integration of lessons learned from previous or ongoing trials to ensure successful, impactful clinical research. Involvement in most NINDS-funded stroke trials will allow the development of an experienced clinical stroke trial workforce and enhance stroke research training.

Stroke care requires contributions from a variety of health professionals across multiple disciplines. Lack of integration of these multiple components into an effective stroke research infrastructure limits the ability of NIH-funded research to advance the care of stroke victims. The stroke trials network will be expected to integrate the various stroke-related disciplines and develop and execute interdisciplinary research applications that answer questions with high public health impact. The interdisciplinary nature of the NINDS Stroke Trials Network will also serve to build research capabilities that match the scientific opportunities across the spectrum of stroke research.

The network aims to harness multidisciplinary stroke expertise to collaboratively and efficiently conduct exploratory NINDS-sponsored phase 1 and 2 clinical trials for stroke interventions with the goal to quickly move potential treatments into larger, confirmatory phase 3 trials. In addition, the network may perform biomarker validation studies that are immediately preparatory to clinical trial(s). Collaboration with the NETT or international consortia will facilitate the execution of the larger, phase 3 definitive trials. Together with the larger U.S. and international stroke research community, stroke patients, and stroke-related nonprofit associations, the investigators at the RCC's will work to design and execute the most clinically impactful stroke research.

Study execution and performance will be monitored by the NINDS and the National Clinical Coordinating and Data Management Centers to ensure that all eligible stroke patients are considered for NINDS-funded trials.

Once the network has been established, the NINDS expects that it will be the primary and first-line infrastructure involved in implementing all multi-site stroke trials submitted to the NINDS.

Network Organization. The NINDS Stroke Trials Network will include: one NCC, one DMC and up to 25 RCC's that have the capacity of coordinating activities in a large number of Stroke Centers across the United States. This FOA solicits applications for funding of infrastructure for the NCC. The additional project-specific funds to support the implementation of protocols conducted in the network will be from separate awards. Projects may come from academic investigators, from small business or industry through a CRADA or from the NINDS through a specific funding opportunity announcement. Collaborative projects developed by investigators in the network will be strongly encouraged. These funds will be distributed to the RCC via the NCC on a per-patient basis, according to protocol budgets approved by the network Steering Committee (SC) and via master trial agreements with the RCC's. The NCC must be willing to follow this funding arrangement for each trial protocol conducted in the Network.

It is advantageous if the NINDS Stroke Trials Network consider working with a central IRB which will be implemented by the CCC similar to the NeuroNEXT (NINDS Network for Excellence in Neuroscience Clinical Trials) model (see as an example NeuroNEXT.org for the IRB reliance agreements and master trial agreements used in NeuroNEXT). The actual templates to be used in the stroke network may be different from the ones used in NeuroNext. The CCC will have to coordinate a central IRB of record and manage all required IRB communication and documentation including but not limited to tracking approval, maintaining regulatory documents, communicating with the local IRBs, and handling adverse event reporting and notifications.

For large, simple, acute stroke trials the NCC or DMC of the NINDS Stroke Trials Network may collaborate with the NINDS Neurological Emergencies Treatment Trial (NETT) network to coordinate trial activities. The network should also be able to conduct trials in adult populations, pediatric populations, or both, and it should have a rapid stroke system to treat and enroll patients within the first couple hours of a stroke. The NIH Clinical Center may also function as an additional clinical site.

Responsibilities of the National Clinical Coordinating Center include, but are not limited to:

- Overseeing from conception to analysis/publication the implementation of at least 6–8, multi-center clinical trials.
- Monitoring human subjects' protection and adequate gender and minority representation among subjects enrolled at network clinical sites.
- Coordinating all network SC activities including, but not limited to, organizing teleconferences at least twice monthly and in-person meetings at least three times each year, maintaining documentation such as meeting minutes of SC activities, and coordinating the network SC working groups. SC working groups will be established on an as-needed basis to develop and oversee the implementation of specific protocols and to provide in-depth evaluation and recommendations on such issues as publications/presentations, quality control, conflict of interest, per-patient budgets, and others.
- Participating in the SC and serving on network SC working groups.
- Coordinating and documenting all communication and reporting between the NCC, RCC's, central IRB of record, and local IRBs, which includes but is not limited to maintaining documentation of IRB initial approvals, amendment approvals, and adverse event and other reports. Working with the DMC and the project PD/PI in providing study data to the NINDS-appointed Data and Safety Monitoring Board (DSMB).
- Establishing standard master trial agreements with the RCC's. Develop and implement a plan to reduce the start-up time of each network project through the use of these standard master trial agreements and distribute the approved per-patient cost according to these agreements.

- Coordinating study drug management, including but not limited to drug and placebo acquisition, delivery plan for bulk drug, secondary packaging/labeling/distribution/storage, blindedness testing, coordinating stability testing and accommodating expiration timelines, and drug accountability.
- Working with the Project PD/PI and IND sponsor (investigator or industry partner) on obtaining FDA regulatory approval for the trial (IND/IDE or exemption), on reporting, documenting and coordinating follow-up correspondence, and on registering with clinicaltrials.gov.
- Working closely with the DMC in a collaborative and interactive manner. The NCC and DMC, once selected for potential funding, will jointly submit to the NINDS their Standard Operating Procedures (SOPs), revised from the version originally submitted as part of the application, based on a plan that is collaboratively developed. They will also submit a scope of work document that details the division of tasks and responsibilities within the budget they had proposed. It is essential that the tasks required in planning and executing a complex, multi-centered trial be clearly defined, and that the responsibilities of the collaborators (including NCC and DMC) be delineated. It is therefore required that the joint DMC and NCC SOPs and scope of work document show excellent and seamless communication and coordination and reflect an in-depth understanding of the overall operational conduct of a complex, multi-center trial.
- Providing collaborative leadership to the clinical sites, including to potential ad-hoc sites.

During the Conceptual Phase of each potential new network project, the CCC is responsible for:

- Collaborating with RCC PD/PI's within the network to develop original stroke clinical trial or biomarker validation grant applications for submission to the NINDS for peer review.
- Providing information necessary to the potential investigators as they apply for NINDS funding (e.g., review protocol synopsis and schedule of activities, create project work scope and timeline, ensure the feasibility of the proposed projects by analyzing the numbers of potentially eligible participants at the proposed sites and by including patient representatives in the conceptual process).
- If needed, the NCC will support project PD/PI's in the IND/IDE submission.
- During the Planning Phase of approved network projects, the NCC is responsible for:
- Working with project lead team of investigators to finalize the protocol and consent form.
- Collaborating with the DMC to create case report forms (CRFs).
- Participating in the selection of additional sites as needed.
- Developing a written, detailed patient recruitment plan, with attention to adequate minority recruitment.
- Monitoring the IRB approval process and promoting rapid approval through a well-developed and complete documentation at the initial submission, and through rapid and comprehensive responses to any IRB comments or concerns.
- Collecting regulatory documents (1572 forms, curricula vitae, Good Clinical Practice [GCP] certifications, etc.).
- Finalizing details of per-patient payments to sites within approved budgets, developing site payment schedule, and finalizing subcontracts with sites per master trial agreements.
- Finalizing study drug packaging and labeling.
- Holding investigator meetings and ensuring initial study personnel training for GCP and protocol adherence.
- Working with the DMC as they establish a trial database.

During the Implementation Phase, the NCC is responsible for:

- Overseeing the enrollment of eligible subjects.
- Tracking enrollment and retention and developing outreach interventions as needed.
- Distributing study drug to centers.
- Working with sites to ensure appropriate protocol implementation and adherence to protocol and GCP.
- Answering queries from the centers regarding protocol, drug dose adjustments, adverse events, premature withdrawals, etc.
- Conducting site visits, as needed.
- Supporting the DMC in their monitoring and data quality assurance procedures. Coordinating activities with the NETT or other International consortia and sites as warranted in the enrollment of subjects into the clinical trial.

During the Analysis and Publication Phase, the NCC is responsible for:

- Assisting the DMC and network centers in resolving final queries, finalizing reporting to the FDA and IRBs.
- Coordinating the communication of the trial results to the investigators, patients and public.
- Working with the DMC and network investigators in the publication of the primary and, if applicable, secondary manuscripts.

National Data Management Center. The DMC will support protocol data management, data quality control (including data monitoring), and undertake interim monitoring, analyses and reporting for the Clinical Coordinating Center, NINDS, and Data and Safety Monitoring Boards (DSMBs). The DMC will also initiate and coordinate activities to promote standardization of data elements using the NINDS Stroke Common Data Elements and support sharing of de-identified data. The funding announcement describing the responsibilities of the network DMC will be released subsequent to this FOA.

Regional Coordinating Stroke Centers. The RCC's selected for funding in the network will have both clinical science excellence and specialized expertise in stroke management, a strong background in stroke research, and a proven ability to recruit stroke patients that include patients from various racial and ethnic groups. Each RCC will include stroke specialists from neurology, pediatric neurology, emergency medicine, neurosurgery, neuroimaging, interventional radiology, neurointensive care, neurorehabilitation, and other medicine specialists and emergency medical services. The RCCs will propose, develop, and conduct protocols, recruit patients, and disseminate research findings. Each RCC will be expected to take part in multiple concurrent protocols. All individual RCCs will be required to participate in a cooperative and interactive manner with one another and with the NCC.

A typical RCC in the network is envisioned as a regional academic medical center or tertiary care facility capable of providing research support for its collaborative stroke centers. RCCs may choose to include geographically or organizationally linked partners or satellite stroke centers, such as other academic centers and/or private and community hospitals and clinics. Such satellite stroke centers could be venues for additional patient enrollment or might provide access to patient populations not traditionally

cared for at the RCC. The RCC will be responsible for providing scientific leadership and regular communication to satellite centers regarding protocols and study progress and for providing administrative and budget support for protocol initiation. In addition, preclinical stroke activities at the RCC's will contribute to the development of compelling phase 1 and 2 research applications and also enhance training opportunities. All centers will be strongly encouraged to increase the value of clinical research data through an aggressive data sharing.

The NINDS will be responsible for organizing and providing overall support for the network. The NINDS Office of Clinical Research staff and the NINDS Office of Grants Management will be responsible for the overall management of the network. In addition to regular grant stewardship, an NINDS Project Scientist will be involved substantially with the awardees as a NINDS partner, consistent with the Cooperative Agreement mechanism. The NINDS will appoint the Data and Safety Monitoring Board (DSMB) and the Scientific Advisory Board (SAB). The SAB is an external group of experts who will review the network program and provide individual feedback to the network investigators and the NINDS.

Network Committees

1. An Operations Committee for the network will consist of the PD/PI of the NCC (who will serve as chair), a co-PD/PI, if designated, the PD/PI of the DMC, the NINDS Project Scientist, NINDS Program Official, and selected PD/PI's or their designees from the RCC's. The Operations Committee will oversee all the network's activities and monitor performance. It is anticipated the Operations committee will meet by telephone conference calls on a weekly basis.
2. A Steering Committee (SC) will consist of the PDs/PIs of the NCC and DMC, the NINDS Project Scientist, and the PD/PI or their designees from each of the RCC's. The Steering Committee will be the main governing body of the network's scientific operation and conduct.

- All major decisions will be determined by majority vote of the SC;
- It is anticipated that the SC will meet two times per month by telephone conference call (potentially more frequently during the start-up phase of the network) and at least twice per year by in-person meetings;
- SC working groups will be established by the SC to perform specific functions, such as:

○ Developing network stroke trial proposals for grant submission;
○ Developing protocol concepts;
○ Finalizing protocols for funded studies;
○ Reviewing the feasibility of trial applications submitted to NINDS from both inside and outside the network;
○ Facilitating the execution of newly-funded or on-going NINDS-funded stroke trials;
○ Producing and submitting publications;
○ Developing per-patient budgets;
○ Assuring quality control;
○ Monitoring conflicts of interest;
○ Developing data sharing policies.

- Awardees will be required to accept and implement approved by the SC.
- Independent of the governance above, the NINDS Director retains responsibility for all NINDS funded research. The Director's authority overrides all SC decisions made by the network.

Network Projects. Over the next 5-year project period, the network will initiate approximately 4–5 NINDS-funded exploratory phase 1 and2 stroke clinical trials and 2–4 phase 3 trials. The exact number of protocols supported will depend on the nature and extent of the investigations proposed and the availability of funds. Projects proposed to and conducted through the network may come from the collaboration of investigators within the network, from investigators outside of the network, or from a CRADA between the NINDS and an Industry partner. The network may also be used to conduct NINDS-funded projects that were initiated before the network was established. Informed by the results of ongoing research and the stroke planning effort it is anticipated that a number of projects will be solicited by NINDS to be performed in the network. Projects may also be submitted using the standard NINDS clinical trial funding announcements (e.g., PAR-10-199: NINDS Exploratory Clinical Trials (R01) or PAR-11-173: NINDS PHASE III Investigator-Initiated Multi-Site Clinical Trials (U01)). Future funding announcements by the NINDS for the solicitation for network trials may also be developed.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are not allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Only one NCC application per institution (normally identified by having a unique DUNS number or NIH IPF number) is allowed.

Investigators at the NCC institution are strongly encouraged to also apply for a RCC award (RFA-NS-13-011). However, it is preferred that the NCC and a RCC at the same institution be led by separate PD/PI's to ensure that the NCC activities as well as the local RCC activities receive full attention.

Awards for a NCC and a DMC will not be made to the same PD/PI to ensure that data analyses and data acquisition are performed independently.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-NS-13-012.html.

■ REGIONAL AND INTERNATIONAL DIFFERENCES IN HEALTH AND LONGEVITY AT OLDER AGES (R03): PA-13-123

Also see: Regional and International Differences in Health and Longevity at Older Ages (R21): (PA-13-124)
Details at: http://grants.nih.gov/grants/guide/pa-files/PA-13-124.html.
Also see: Regional and International Differences in Health and Longevity at Older Ages (R01): (PA-13-125)
Details at: http://grants.nih.gov/grants/guide/pa-files/PA-13-125.html.

Components of Participating Organizations

National Institute on Aging

Application Receipt/Submission Date(s): Multiple dates, see announcement.

This Funding Opportunity Announcement (FOA) encourages Small Grant (R03) applications from institutions/organizations proposing to advance knowledge on the reasons behind the divergent trends that have been observed in health and longevity at older ages, both across industrialized nations and across geographical areas in the United States. This FOA is intended to capitalize on provocative findings in the literature which have been insufficiently understood and addressed. This FOA is also intended to capitalize on NIA's investment in the development of cross-nationally comparable datasets that can be harnessed to study these research questions; these include the Health and Retirement Study (HRS), the English Longitudinal Study on Ageing (ELSA), the Survey of Health, Ageing and Retirement in Europe (SHARE), and the Human Mortality Data Base. Applications proposing secondary analysis, calibration of measures across studies, development of innovative survey measures, and linkages to administrative sources are encouraged. Applications are not restricted to projects using the NIA-supported datasets above and may propose research using any relevant data.

The NIH R03 grant mechanism supports discrete, well-defined projects that realistically can be completed in two years and that require limited levels of funding. Examples of the types of projects that can be supported with the R03 mechanism include, but are not limited to: pilot or feasibility studies, secondary analysis of existing data, small, self-contained research projects, calibration of measures across studies, linkages to administrative data sources, and development of research methodology. Because the research plan is restricted to 6 pages, an R03 grant application will not have the same level of detail or extensive discussion found in an R01 application. Accordingly, reviewers should evaluate the conceptual framework and general approach to the problem, placing less emphasis on methodological details and certain indicators traditionally used in evaluating the scientific merit of R01 applications including supportive preliminary data. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or from investigator-generated data. Preliminary data are not required, particularly in applications proposing pilot or feasibility studies.

Life expectancy at birth in the United States has improved dramatically over the past century. Also, throughout the second half of the century, advances in medicine—particularly in the treatment of heart disease and stroke—along with healthier lifestyles, better access to health care, and better overall health before age 65 combined to produce impressive improvements in life expectancy above age 65. Yet U.S. life expectancy (at birth and at older ages) – especially for women – has lagged behind other wealthy nations since 1980. And evidence from cross-national research indicates that older Americans get sicker sooner compared to older Europeans. Within the United States, similar disparities in health and longevity are observed across geographical areas.

The recent availability of longitudinal data expressly designed to be cross-nationally comparable has begun to prompt research inquiry into the underlying dynamics of, and reasons for, these differences in health and longevity at older ages. For example, research using the Health and Retirement Study (HRS), English Longitudinal Study of Ageing (ELSA) and the National Health and Nutrition Study (NHANES), indicates that older white non-Hispanic U.S. adults aged 55–64 are less healthy than their English counterparts for a range of diseases including diabetes, hypertension, heart disease, myocardial infarction, stroke,

lung disease, and cancer (Banks et al., 2006). This analysis also controlled for education and a standard set of comparably-measured behavioral risk factors (smoking, overweight, obesity, and alcohol drinking), which explained little of these health differences. In addition, analysis of biomeasures from ELSA and NHANES showed that the differences between the U.S. and England and across SES groups within each country are not due to biases in self-reported disease or screening rates, because biological markers of disease (although they have not been calibrated against one another) exhibit exactly the same patterns. Finally, the results showed that these differences are not solely driven by the bottom of the SES distribution, and that for many diseases, the top of the SES distribution (which in the U.S. has near universal health insurance coverage) is less healthy in the United States as well. Surprisingly, English lower SES individuals have better health than high SES U.S. individuals. This is a provocative finding, that U.S. residents in late middle-age are much less healthy than their English counterparts and that these differences exist at all points of the SES distribution. Possible explanations include survival advantages among U.S. adults with chronic illness, behavioral differences in risk factors not (or imperfectly) measured in these studies, psychosocial factors, the obesity epidemic (which is more advanced in the U.S.), differences in health care systems, social policy contexts other than medical care (e.g., social retirement benefits, unemployment compensation, sick pay, housing policies, transportation options, social integration, etc.), how health influences wealth (e.g., in the U.S., major health events lead to wealth depletion), measurement differences across studies, quality and comparability of biospecimen assays, etc.

A subsequent analysis using data from the HRS, ELSA, and the Survey of Health, Ageing and Retirement in Europe (SHARE) found similar results (Avendano, 2009). American adults ages 50-74 of all wealth levels reported worse health than did European adults at comparable wealth levels. Indeed, on many measures England was shown to have worse health than other European countries. Similar to the paper discussed above, this analysis excluded U.S. minorities, indicating that the worse health of Americans compared with Europeans cannot be attributed to racial disparities within the United States. And, similar to the U.S.-U.K. results, this analysis also found that the disparities were only partially explained by differences in a standard set of behavioral factors. Finally, while poor Americans were at particularly worse health compared with their English or other European counterparts in this analysis, even well-off Americans reported health comparable to substantially poorer Europeans – suggesting that access to and quality of health care is unlikely to be the full explanation.

Cross-national analyses provide insight into potential causal explanations for observed differences in health and longevity because institutional factors vary (e.g., universal health care in England at all ages vs. universal health care after age 65 in the U.S.). However, comparative analyses can also be done within the U.S. where there is also variation. Extensive research has focused on health disparities within the U.S. and many investigations have documented the consistent gap in measures of mortality and functional health by race, income, social class, education, community characteristics, insurance coverage, health care access and utilization, quality of care, etc. Less has been done exploiting the internal variations by geography in the U.S. Using data from the U.S. Bureau of the Census and the National Center for Health Statistics, researchers have divided the U.S. into eight subgroups based on a number of sociodemographic and geographical variables (such as location of county of residence, race and income), which they termed the "eight Americas" (Murray, 2006). They found disparities in mortality across the "eight Americas" that are enormous by international standards and that cannot be explained by race, income or basic health-care access and utilization alone. A related analysis looked at trends in U.S. county mortality and cross-county mortality disparities from 1961–1999, including the contributions of specific diseases to county level mortality trends (Ezzati, 2008). This study found that there was a steady increase in mortality inequality across the U.S. counties between 1983 and 1999, resulting from stagnation or increase in mortality among the worst-off segment of the population, and that female mortality increased in a large number of counties, primarily because of chronic diseases related to smoking, overweight and obesity, and high blood pressure. Other examples of U.S. geographic disparities in health include scholarship on the "stroke belt". While no consensus has been reached to explain geographic differences in stroke mortality, recent research suggests that both early life exposures and adult residence independently contribute to stroke mortality risk (Glymour, 2009).

A recent National Academy of Sciences panel determined, based on available evidence, that past smoking rates are a major reason for shorter lifespans in the U.S. compared to other high-income countries, and that obesity rates in the U.S. also appear to be a significant factor. The summary report from the National Research Council, which also identified research gaps, is entitled "Explaining Divergent Levels of Longevity in High Income Countries" (NRC, 2011) and is available at http://www.nap.edu/catalog.php?record_id=13089. A volume of background scientific papers is entitled "International Differences in Mortality at Older Ages: Dimensions and Sources" (NRC, 2011) and is available at http://www.nap.edu/catalog.php?record_id=12945.

Applications are encouraged that pursue possible explanations for the divergent trends that have been observed in health and longevity at older ages, both across industrialized/high life expectancy nations and across the U.S. by geographic area. Research projects are not restricted to using NIA-supported datasets and may propose research using any relevant data. Applicants are encouraged to consult the aforementioned National Research Council consensus report entitled "Explaining Divergent Levels of Longevity in High Income Countries" and a companion volume of scientific papers written or invited by the NRC consensus report committee, entitled "International Differences in Mortality at Older Ages: Dimensions and Sources" (see References below). These reports discuss potential explanations for the observed divergent trends that have been observed in longevity and health at older ages across high-income countries; discuss internal heterogeneity in the U.S.; present the available cross-national harmonized data useful for analysis; and raise many interesting and provocative hypotheses for future research. Following a previous Funding Opportunity Announcement (RFA-AG-11-004), the National Institute on Aging funded seven research projects exploring the extent and determinants of international and U.S. regional differences in health and longevity at older ages. These projects are described at this website: http://www.nia.nih.gov/research/announcements/2012/12/updates-selected-rfas .

Applications submitted to this Funding Opportunity Announcement should advance beyond the NAS reports and existing projects to assess determinants of trends and of international and interregional differences, quantify the contributions of particular determinants, point the way to likely policy or systemic changes that can improve population health measurably in the United States, and make existing studies more suitable for comparative analyses of health status and longevity in middle aged adults. Projects appropriate for this R03 mechanism include pilot or feasibility studies, secondary analysis of existing data, small, self-contained research projects, calibration of measures across studies, linkages to administrative data sources, and development of

research methodology. Examples of approaches and topics include but are not limited to:

- The prevalence of a condition is a function of its incidence, duration, and survival. These three parts have not been adequately differentiated in the comparative analysis of major chronic conditions. Do Americans have a higher prevalence of major conditions because they have a higher incidence of a condition, are more likely to have it diagnosed earlier or at all, or experience better survival from it?
- The cross-national studies discussed above found that differences were not explained by behavioral risk factors. Applicants are encouraged to conduct investigations of the adequacy and comparability of the behavioral risk factors measured in these studies and consider whether a fuller set of risk factors and would offer additional explanatory power. Also, these studies do not include data on past differences in risk factors, or may not adequately measure cumulative exposure over the life course. Behavioral risk factors of interest include: physical activity, exercise, diet, eating patterns, tobacco/smoking, alcohol, drug use and abuse, obesity, sleep duration, sleep quality, time use, etc. Environmental exposures and risk factors are also of interest. Studies that quantify the contribution of risk factors and conditions to observed differences (as, for example, Preston and Stokes, 2011, did for obesity) are encouraged.
- Smoking behavior has been hypothesized to account for a significant portion of the mortality differential among countries. Recent methodological research estimating the number of deaths attributable to smoking has shown that the ranking of the U.S. in international comparisons of longevity is heavily affected by the smoking history of American men and women (Preston, 2009). When the mortality profiles of a set of industrialized countries were adjusted by removing the effect of smoking, the relative position of both U.S. women and men significantly improved. Related analysis suggests that because of reductions in smoking that have already occurred or can be reliably projected, U.S. mortality is likely to decline much faster than is commonly anticipated (Wang and Preston, 2009). Applicants are encouraged to study the effect of smoking and cohort smoking histories as a potential explanation for the U.S.'s international standing in health and longevity.
- Psychosocial factors such as social support, social integration, stress, well-being, etc. have not adequately been studied as potential explanations for observed health and longevity differences. Applicants are encouraged to develop better measures of psychosocial factors for incorporation into the abovementioned NIA-funded cross-national surveys of the older population, and investigate their potential explanatory power.
- Available cross-national comparative data do not include much information on early life factors. Applicants are encouraged to gather retrospective data (both recall data and information from administrative records including vital statistics) from older cohorts in ongoing studies.
- Social policy contexts differ between the U.S. and Europe and it has been hypothesized that contextual factors may have causal effects in producing the observed health disadvantages in the U.S. Studies of the effect of contextual factors including retirement benefits, unemployment compensation, sick pay, working conditions, housing policies, transportation options, social integration etc. are encouraged.
- Despite its huge policy implications, the role of health and long-term care systems in international variations in disease prevalence and mortality is only beginning to be understood. The cross-national, longitudinal studies of older people referenced in this FOA, which have frequent follow-up via biomarkers and linked data on medical records, should be further exploited to shed light on differences in the way medical systems interface with patients, and how such differences may have survival and disability implications. Applicants are also encouraged to take advantage of available natural experiments in medical care as they occur internationally.
- Applicants are encouraged to calibrate the biomeasure assays (e.g., assays of CRP, cholesterol, etc.) and self-reported physical performance measures across datasets used for comparative analyses.

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Ezzati, M., Friedman, A.B., Kulkarni, S.C., and Murray, C.J.L. (2008) The Reversal of Fortunes: Trends in County Mortality and Cross-County Mortality Disparities in the United States. PLoS Med 5(/4): e66:557–68.

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National Research Council. International Differences in Mortality at Older Ages: Dimensions and Sources. Washington, DC: The National Academies Press, 2011. Authors:

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Wang, H and Preston, SH. (2009) Forecasting United States Mortality Using Cohort Smoking Histories. PNAS 106(2): 393–398.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically

Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Complete details at: http://grants.nih.gov/grants/guide/pa-files/PA-13-123.html.

■ ALZHEIMER'S DISEASE RESEARCH CENTERS (P50): RFA-AG-13-019

Components of Participating Organizations

National Institute on Aging

Application Receipt Date(s): June 11, 2013

Alzheimer's disease (AD) is estimated to affect millions of older people in the United States. Although it is occasionally identified in patients in their forties and fifties, it is most frequently associated with advancing age. AD is the most frequent cause of institutionalization for long-term care. It destroys the active, productive life of its victims and devastates their families financially and emotionally. It has been estimated that the United States spends well over 100 billion dollars/year for the direct and indirect costs of care for people with AD. The risk of AD increases greatly with age, and projections suggest that the numbers of people with AD will increase with the aging of the population unless effective interventions are found.

In the United States, the Executive and Legislative Branches of the Federal Government have both expressed concern about the enormity of the problem posed by AD, and in 2011, Congress passed the National Alzheimer's Project Act (NAPA). Congressional concern has focused on funding for research on the causes, diagnosis, treatment, and prevention of the disease, as well as on disparities and on the cost and coordination of care. In 1984, Congress directed the National Institutes of Health (NIH), and in particular the National Institute on Aging (NIA), to foster further research related to AD. The NIA Alzheimer's Disease Centers (ADCs) program is authorized by the Public Health Service Act, Section 445, and currently includes fifteen Alzheimer's Disease Research Centers (ADRCs) and twelve Alzheimer's Disease Core Centers (ADCCs).

The ADC program is moving into a new era, preparing to capitalize on the extraordinary opportunities presented by leveraging the strengths of the network of centers to provide large numbers of samples and standardized clinical data collection from well-characterized participants as well as a large pool of potential participants for future AD-related research. At the same time, strong emphasis is placed on the unique contributions and new directions of each individual center. Additionally, renewed emphasis is placed on possibilities for utilizing the resources within and across the ADCs to advance and augment the fields of drug discovery and drug development for novel therapeutics for AD.

The principal aim of the ADRCs should be to enhance the performance of innovative research on AD and related topics, including research that may lead to potential disease-modifying therapy or behavioral or other symptom treatments. Centers are requested to concentrate their attention on better defining normal aging and the transition from normal aging to mild cognitive impairment (MCI) to the earliest stages of dementia, whether AD itself or other related dementias associated with aging. Clinical

and pathological information about the earliest cognitive changes is now beginning to make it possible to develop strategies to prevent the disease from developing or slow its progression. Attention should also be paid to mixed dementias and overlapping neurodegenerative syndromes that often occur with AD, such as vascular dementia, Lewy Body disease, Frontotemporal degeneration and Parkinson's dementia, in order to better differentiate among them and to recognize commonalities. In addition, co-occurring conditions in other organ systems that may contribute to clinical dementia could be studied.

Centers are expected to provide an environment and core resources which will enhance cutting-edge research by bringing together biomedical, behavioral, and clinical investigators to study the etiology, pathogenesis, diagnosis, treatment, and prevention of AD, and to improve health care delivery. Centers should also foster the development of new lines of research and provide a rich training environment for fellows and junior faculty to acquire research skills and experience in interdisciplinary AD research. The Centers provide investigators and research groups with well-characterized patients and control subjects, family information, and brain tissue and biological specimens. Centers should incorporate contemporary biochemical/molecular techniques and pursue research, when feasible, in genomics, epigenomics, proteomics and metabolomics. Centers are encouraged to develop in accordance with local talents, interests, and resources, but should also be responsive to national needs related to AD.

The ADCs provide a mechanism for fostering and coordinating the interdisciplinary cooperation of a group of established investigators conducting programs of research on AD and related dementing disorders of older people. The central focus may be translational research, clinical – pathological research, basic research or a combination. Applicants are strongly encouraged to include efforts to address the needs of, and research on, ethnically and racially diverse people as well as other underserved populations.

As part of a network, centers should be poised to participate in cooperative efforts on a massive scale within a relatively short time frame. Applicants must agree to collect a standard clinical data set (the Uniform Data Set, or UDS) that is common to all Centers and will be transmitted to the National Alzheimer's Coordinating Center (NACC). To support the unique research needs of the center, most centers collect additional data to supplement those required by the UDS. Centers should demonstrate a readiness to provide biological samples and data, with proper consent from well characterized populations, to enable participation in large scale collaborative national or international research projects.

Centers should work together with other AD research groups in collaborative research activities and cooperate with other Federal, State, and Local agency-supported AD programs (such as the Alzheimer's Disease Cooperative Study (ADCS) and the Alzheimer's Disease Neuroimaging Initiative (ADNI)), as well as the Alzheimer's Association in furthering mutual goals. Centers should also, whenever possible, cooperate with other NIA Centers such as Pepper, Shock, and RCMAR Centers, and Udall Centers sponsored by the National Institute of Neurological Disorders and Stroke (NINDS).

The use of NIH resources, such as those available from the chemical genomics center (http://www.ncats.nih.gov/research/reengineering/ncgc/ncgc.html /) or the Biomedical Informatics Research Network (BIRN, http://www.nbirn.net/) is also encouraged. In addition, AD Centers should consider, where there are research questions in common that are consistent with the scientific goals of the center, collaboration with Centers for Drug Discovery or Clinical and Translational Science Award recipients (see http://www.ncats.nih.gov/research/cts/ctsa/ctsa.html).

Alzheimer's Centers are required to include the following five cores:

- Administrative
- Clinical
- Data management and statistical
- Neuropathology
- Outreach, Recruitment and Education

Other cores can be proposed if they contribute to the overall mission of the Center, are scientifically justified, support projects affiliated with the Center, and fit within the budget guidelines

ADRC applications will include, in addition, two or three research projects with a duration of up to five years (equivalent to small R01 grants) at least one of which should depend on Clinical or Neuropathology Core resources at the home Center or another Center. The number of research projects funded and their duration will depend upon scientific quality. Funding for one to three smaller one year pilot grants should also be requested. Centers should show plans of career progression for junior investigators including leadership of projects and cores within the center and successful pursuit of independent funding.

The Center Grant may incorporate ancillary activities such as longitudinal studies and limited patient care necessary to support the primary research effort. The spectrum of activities should comprise a multi-disciplinary approach to the problem of AD and other neurodegenerative diseases, including distinguishing early stages from normal aging, investigating mixed dementias, as well as studying unique aspects and subtypes of these very complex and heterogeneous disease processes

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Eligible institutions should support an ongoing base of high-quality AD research or research in other neurodegenerative diseases, or in aging of the nervous system. To be eligible, an institution must support:

- at least five Program Director(s)/Principal Investigator(s) with any PHS agency (or comparable peer-reviewed federal, state, or foundation) funded research grants related to AD, neurodegenerative diseases or aging of the nervous system and each with at least two years of support remaining at the time of application; or
- one or more program project grants (P01s) related to AD, neurodegenerative diseases or aging of the nervous system and with at least two years of support remaining at the time of application.

The work that you propose in the ADC should be different from the ongoing supported research. NIA will review overlap of existing support through P01s or other award mechanisms and adjust support of the center appropriately prior to any award. Your institution can have only one active Alzheimer's Center receiving NIA support.

Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the SAM.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) and component Project Leads that are not yet registered in eRA Commons must work with their institutional officials to register. Also, institutional officials at the applicant organization should ensure that the eRA Commons account for the contact PD/PI is affiliated with their organization.

eRA Commons accounts are necessary to use ASSIST to prepare and submit applications.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

The PD/PI should be a scientific leader experienced in the field of AD and/or other neurodegenerative disease research and must be able to coordinate, integrate, and provide guidance in the establishment of programs in AD research and allied areas. A significant time commitment (2.4 person months) must be made by the PD/PI.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Only one application per institution (normally identified by having a unique DUNS number or NIH IPF number) is allowed.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-13-019.html.

■ SMALL BUSINESS INNOVATION RESEARCH ON RARE MUSCULOSKELETAL, RHEUMATIC AND SKIN DISEASES (SBIR) (R43): RFA-AR-14-005

Components of Participating Organizations

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Application Receipt Date(s): August 01, 2013

The purpose of this funding opportunity announcement (FOA) is to advance translational research for rare musculoskeletal, rheumatic or skin diseases by supporting preclinical projects conducted by small business concerns (SBCs) to develop biomarkers and/or therapies. The 2010 Institute of Medicine Report "Rare Diseases and Orphan Products: Accelerating Research and Development" (http://www.iom.edu/Reports/2010/Rare-Diseases-and-Orphan-Products-Accelerating-Research-and-Development.aspx) called for active involvement and collaboration by the public and private sectors, and emphasized the role of NIH in integrating various stake holders into a comprehensive strategy for supporting all phases of rare diseases research. NIAMS supports research on rare diseases and orphan drugs through various grant mechanisms including research project grants, center awards and training/career development awards. SBCs play an important role in disease research by developing innovative technologies and increasing the commercial application of Federally-supported research results. However, it can be more challenging for SBCs to achieve profitability in rare diseases research and development due to inherent scientific risks and market limitations caused by the small number of individuals affected by each disease. With this FOA, NIAMS intends to support and enhance research and development conducted by SBCs that may lead to important biomarkers and/or treatments for rare musculoskeletal, rheumatic or skin diseases.

Specific Areas of Research Interest. There are many rare diseases and conditions (with a prevalence of fewer than 200,000 affected individuals in the United States) within the NIAMS mission, including chondrodysplasias, cutis laxa, epidermolysis bullosa, familial Mediterranean fever, genetic rickets, inflammatory myopathies, muscular dystrophies, nemaline myopathies, osteogenesis imperfecta, pachyonychia congenita, pediatric rheumatic diseases, pemphigus, pseudoxanthoma elasticum, scleroderma, and vasculititis, as well as conditions such as chronic wounds unique to a rare disease(s), etc. The NIH Office of Rare Diseases Research provides a listing of many other rare diseases (http://rarediseases.info.nih.gov/RareDiseaseList.aspx?PageID=1), but only those within the NIAMS mission should be the focus of research projects supported by this FOA. The NIAMS Long-Range Plan (http://www.niams.nih.gov/About_Us/Mission_and_Purpose/long_range.asp) provides a more complete description of NIAMS research interests. If the proposed project focuses

on FDA-designated orphan products for a disease/condition in the NIAMS mission with a prevalence of more than 200,000 persons (i.e., not a rare disease), the application can also be considered responsive to this FOA, but the applicant must provide documentation of Orphan Product Designation from the FDA no later than September 30, 2013 (http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm). Applications primarily focused on one or more rare diseases are not required to provide documentation of Orphan Product Designation. However, all applications should include a paragraph with the heading "Justification for Rare Disease or Orphan Product Designation" within the six-page limit of the Research Strategy section in the PHS 398 Research Plan. More information on this requirement can be found in Section IV. 2. Content and Form of Application Submission. One of the considerations in funding applications in response to this FOA will be the potential of the project to decrease the burden of disease on patients or families affected by that disease/condition. Because the intent of this FOA is mainly to overcome the inherent scientific risks and market limitations caused by the small number of individuals affected by a rare disease, approaches that are also likely to find applications in the large markets associated with common diseases may receive a lower funding priority.

Research topics that would be responsive to this FOA include but are not limited to:

- Development of therapies such as drugs, biologics, devices, cells, genes or behavioral interventions
- Development of innovative strategies for the delivery of existing or new drugs
- Biomarker studies focusing on changes in disease-associated biochemistry, imaging, physiology or other measures that would facilitate screening, diagnosis or outcome measures
- Development of outcomes measures and methodologies that are tailored for rare diseases and would enhance future observational studies and clinical trials
- Development of FDA-designated orphan products

This FOA is designed to stimulate translational research on rare diseases and is therefore limited to Phase I SBIR awards. Applications for this FOA may include human subjects' research; however, clinical trials are excluded. Applicants could propose to analyze samples from affected subjects and controls, conduct subject interviews or other procedures of clinical research; however, applications that propose to conduct intervention studies will not be considered responsive to the FOA and will not be reviewed.

Applicants are strongly encouraged to develop partnerships with the appropriate patient advocacy groups and/or foundations. These groups are a valuable source of scientific and medical expertise that can help guide product development and provide access to research subjects for future clinical testing.

NIH supports several "innovation platforms" that can facilitate and accelerate therapy development including the NIH Molecular Libraries Program (http://mli.nih.gov/mli/), Bridging Interventional Development Gaps (BrIDGs, http://www.ncats.nih.gov/research/reengineering/bridgs/bridgs.html), the Therapeutics for Rare and Neglected Diseases program (TRND, https://rarediseases.info.nih.gov/TRND/), and the Rare Diseases Clinical Research Network (RDCRN, http://rarediseasesnetwork.epi.usf.edu/). Small business concerns should consider utilizing these resources to enhance their efforts in developing and testing biomarkers and treatments for rare diseases. This FOA encourages applications for studies that will better position the applicants to leverage these innovation platforms.

Beyond the work proposed for this early stage of translation, applications should briefly describe the plan for following through on the results of the Phase I SBIR award to develop the biomarker, therapy, or other proposed methodologies and approaches to the point of readiness for clinical studies or clinical trials. This plan should be included in the Research Strategy section of the PHS 398 Research Plan in a separate paragraph with the heading "Therapy/Biomarker Development Plan". This plan may include the future utilization of the NIH-supported research resources described above, or other established public or private resources or partnerships that will increase the likelihood of successful clinical testing of the biomarkers or therapies.

Only United States small business concerns (SBCs) are eligible to submit applications for this opportunity. A small business concern is one that, at the time of award of Phase I and Phase II, meets *all* of the following criteria:

1. Is organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. Is in the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there must be less than 50 percent participation by foreign business entities in the joint venture;
3. (i) SBIR and STTR. Be a concern which is more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), or any combination of these; OR
   (ii) SBIR-only. Be a concern which is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these. No single venture capital operating company, hedge fund, or private equity firm may own more than 50% of the concern; OR
   (iii) SBIR and STTR. Be a joint venture in which each entity to the joint venture must meet the requirements set forth in paragraph 3 (i) or 3 (ii) of this section. A joint venture that includes one or more concerns that meet the requirements of paragraph (ii) of this section must comply with § 121.705(b) concerning registration and proposal requirements.
4. Has, including its affiliates, not more than 500 employees.

If the concern is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these falls under 3 (ii) or 3 (iii) above, see Section IV. Application and Submission Information for additional instructions regarding required application certification.

If an Employee Stock Ownership Plan owns all or part of the concern, each stock trustee and plan member is considered an owner.

If a trust owns all or part of the concern, each trustee and trust beneficiary is considered an owner.

Definitions:

- Hedge fund has the meaning given that term in section 13(h)(2) of the Bank Holding Company Act of 1956 (12 U.S. C. 1851(h)(2)). The hedge fund must have a place of business

located in the United States and be created or organized in the United States, or under the law of the United States or of any State.

- Portfolio company means any company that is owned in whole or part by a venture capital operating company, hedge fund, or private equity firm.
- Private equity firm has the meaning given the term "private equity fund" in section 13(h)(2) of the Bank Holding Company Act of 1956 (12 U.S.C. 1851(h)(2)). The private equity firm must have a place of business located in the United States and be created or organized in the United States, or under the law of the United States or of any State.
- Venture capital operating company means an entity described in § 121.103(b)(5)(i), (v), or (vi). The venture capital operating company must have a place of business located in the United States and be created or organized in the United States, or under the law of the United States or of any State.

SBCs must also meet the other regulatory requirements found in 13 C.F.R. Part 121. Business concerns, other than investment companies licensed, or state development companies qualifying under the Small Business Investment Act of 1958, 15 U.S.C. 661, et seq., are affiliates of one another when either directly or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both. Business concerns include, but are not limited to, any individual (sole proprietorship) partnership, corporation, joint venture, association, or cooperative. The SF424 (R&R) SBIR/STTR Application Guide should be referenced for detailed eligibility information.

Small business concerns that are more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these are NOT eligible to apply to the STTR program.

Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. Organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, may be allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) SBIR/STTR Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration(formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- SBA Company Registry – *New requirement*. See Section IV. Application and Submission Information, "SF424(R&R) Other Project Information Component" for instructions on how to register and how to attach proof of registration to your application package. Applicants must have a DUNS number to complete this registration. SBA Company registration is NOT required before SAM, Grants.gov or eRA Commons registration.
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Under the SBIR program, for both Phase I and Phase II, the primary employment of the PD/PI must be with the small business concern at the time of award and during the conduct of the proposed project. For projects with multiple PDs/PIs, at least one must meet the primary employment requirement. Occasionally, deviations from this requirement may occur.

The SF424 (R&R) SBIR/STTR Application Guide should be referenced for specific details on eligibility requirements. For institutions/organizations proposing multiple PDs/PIs, see Multiple Principal Investigators section of the SF424 (R&R) SBIR/STTR Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept similar grant applications with essentially the same research focus from the same applicant organization. This includes derivative or multiple applications that propose to develop a single product, process, or service that, with non-substantive modifications, can be applied to a variety of purposes. Applicants may not simultaneously submit identical/essentially identical applications under both this funding opportunity and any other HHS funding opportunity, including the SBIR and STTR Parent announcements.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Contractual/Consortium Arrangements. In Phase I, normally, a minimum of two-thirds or 67% of the research or analytical effort must be carried out by the small business concern. The total amount of all consultant and contractual arrangements to third parties for portions of the scientific and technical effort generally may not exceed 33% of the total amount requested (direct, F&A/indirect, and fee).

A small business concern may subcontract a portion of its SBIR or STTR award to a Federal laboratory within the limits above. A Federal laboratory, as defined in 15 U.S.C. § 3703, means any laboratory, any federally funded research and development center, or any center established under 15 U.S.C. §§ 3705 & 3707 that is owned, leased, or otherwise used by a Federal agency and funded by the Federal Government, whether operated by the Government or by a contractor.

The basis for determining the percentage of work to be performed by each of the cooperative parties in Phase I or Phase II will be the total of the requested costs attributable to each party, unless otherwise described and justified in "Consortium/ Contractual Arrangements" of the PHS 398 Research Plan component of SF424 (R&R) application forms.

Additional details are contained in the SF424 (R&R) SBIR/ STTR Application Guide.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-AR-14-005.html.

■ SHORT-TERM MENTORED CAREER ENHANCEMENT AWARDS IN THE BASIC BEHAVIORAL AND SOCIAL SCIENCES: CROSS-TRAINING AT THE INTERSECTION OF ANIMAL MODELS AND HUMAN INVESTIGATION (K18): RFA-DA-14-002

Components of Participating Organizations

National Institute on Drug Abuse
John E. Fogarty International Center
National Center for Advancing Translational Sciences
National Center for Complementary and Alternative Medicine
National Cancer Institute
National Eye Institute
National Human Genome Research Institute
National Heart, Lung, and Blood Institute
National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Biomedical Imaging and Bioengineering
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institute on Deafness and Other Communication Disorders
National Institute of Dental and Craniofacial Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of General Medical Sciences
National Institute of Mental Health
National Institute on Minority Health and Health Disparities
National Institute of Neurological Disorders and Stroke
National Institute of Nursing Research
National Library of Medicine
Office of AIDS Research
Office of Behavioral and Social Science Research
Office of Dietary Supplements
Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs
Office of Research on Women's Health

Application Receipt Date(s): December 11, 2013

The overall goal of the NIH Research Career Development program is to help ensure that a diverse pool of highly trained scientists is available in appropriate scientific disciplines to address the Nation's biomedical, behavioral, and clinical research needs. More information about Career programs may be found at the NIH Extramural Training Mechanisms website.

This funding opportunity announcement (FOA), issued by the NIH Basic Behavioral & Social Science Opportunity Network (OppNet), invites applications for short-term mentored career enhancement (K18) awards in basic behavioral and social sciences research (b-BSSR). This funding mechanism will support development of research capability in b-BSSR, with specific emphasis on cross-training and establishing collaborations between researchers with expertise in animal models of basic behavioral and social processes and those studying similar or related processes in human subjects. Basic research using any non-human species or with human subjects in laboratory- or field-based settings is appropriate for this FOA. Eligible candidates for this K18 will be either: (a) scientists conducting b-BSSR in animal models who seek training in the study of similar or related behavioral or social processes in humans; or (b) investigators conducting b-BSSR in human subjects who seek training in the study of similar or related processes in animal models. Candidates may be at any rank or level of research/academic development beyond three years of postdoctoral experience.

About OppNet. OppNet is a trans-NIH initiative that funds activities to 1) build the collective body of knowledge about the nature of behavior and social systems, and 2) deepen our understanding of basic mechanisms of behavioral and social processes. All 24 NIH Institutes and Centers that fund research and four Program Offices within the NIH Office of the Director (ICOs) co-fund and co-manage OppNet. All OppNet initiatives invite investigators to propose innovative research that will advance basic social and behavioral sciences and produce knowledge and/or tools of potential relevance to multiple domains of health- and life course-related research. Applicants should understand that the NIH Institute or Center (IC) that made this FOA available to the public is not necessarily the NIH IC that ultimately will manage a funded OppNet project. For more information about OppNet and all its funding opportunities, visit http://oppnet.nih.gov.

OppNet uses the NIH definition of b-BSSR (http://obssr.od.nih.gov/about_obssr/BSSR_CC/BSSR_definition/definition.aspx) to determine application responsiveness. Consequently, OppNet strongly encourages prospective investigators to consult this definition, in addition to OppNet's answers to frequently asked questions (FAQs) about b-BSSR (http://oppnet.nih.gov/about-faqs.asp), and FAQs regarding this specific FOA (http://oppnet.nih.gov/pdf/FAQsRFA-DA-14-002.pdf). Prospective applicants are encouraged to reach out to the NIH Scientific/Research Contacts listed under Section VII. Agency Contacts for additional guidance about this FOA.

Background. The use of animal models to understand and predict human behavior and the environmental or social factors affecting behavior, provides several distinct advantages over human subjects approaches. These include tighter control of experimental subjects and their environments, the use of invasive techniques to study otherwise inaccessible tissues and test mechanistic hypotheses, and shorter life-spans that allow for longitudinal and intergenerational studies, among others. While these approaches have provided valuable information, failures of "translatability" or "generalizability" are many. Challenges to translation from animal findings to the human condition may be due to species differences, the use of artificial versus naturalistic environments, lack of cross-validation of behavioral/social phenomena between human and non-human organisms, non-equivalence of metrics and measurement systems, and the difficulty of modeling complex human processes (e.g., decision-making, self-regulation, empathy, transmission of behaviors among individuals, social adversity, population dynamics, and vocal communication). Additional complexity arises because behavioral and social processes occur in dynamic environments that are influenced by physical, social

and developmental contexts – factors not often taken into account in studies using animal models.

Scientific experts who participated in a 2010 meeting, OppNet: Expanding Opportunities in Basic Behavioral and Social Science Research (http://oppnet.nih.gov/news-events.asp) and an OppNet workshop, Improving Animal Models of Behavioral and Social Processes in July, 2012 (http://oppnet.nih.gov/news-07232012.asp) identified the need for increased collaboration between researchers working with animal models and those working with human subjects, in order to improve the back-and-forth translation of b-BSSR findings between animal studies and the human condition. This FOA begins to address this need using a career enhancement strategy. Its goal, to develop a cadre of researchers who will be better equipped to work across species, will help address the challenges of modeling complex human social and behavioral processes in non-human organisms.

Purpose. The opportunities afforded by this FOA are as follows:

- Expose animal model researchers to the unique theoretical, conceptual, methodological and practical issues involved in studying behavior and psychological or social processes with human subjects in laboratory or field-based settings.
- Likewise, expose investigators studying behavior and psychological or social processes with human subjects to the difficult challenges of modeling these phenomena in non-human species.
- Foster the interaction of a mentor-mentee relationship, by supporting a shared research project appropriate to the interests of both individuals. Such a shared project will require discussions and problem solving about diverse environments, measurement systems, species limitations, experimental design and statistical analyses.

It is anticipated that this interaction – on multiple levels including mentoring, discussion, shared research participation, and an academic enrichment plan (if appropriate) – will improve both the development of animal models for human processes and the design of human subject research that draws from, and is amenable to, modeling in experimental animals. It is also expected that cross-training will facilitate future collaborative endeavors between researchers working with human subjects and those employing animal models to study similar behavioral and social processes, thus improving forward-and-back translation between these two approaches.

For the purposes of this FOA, individuals conducting research in animal models may mentor investigators studying similar basic behavioral or social processes in human subjects; conversely, investigators conducting research on basic behavioral or social processes in humans may mentor animal model researchers. This FOA is not intended as a substitute for research project support. It is expected that either the candidate or the mentor has sufficient research funding to support the proposed shared research project, in excess of the allowable costs of this award. It is not a requirement that the candidate or the proposed mentor receive his/her primary research funding from the NIH. Candidates for K18 support may be at any rank or level of research/academic development beyond three years of postdoctoral experience.

Applicants must propose a mentored career enhancement program that includes a collaborative research project that will meet the goal of this FOA. Candidates are expected to devote 3–6 person-months of full time professional effort to a career enhancement program that will be from three months to one year in duration. The career enhancement activities are to be conducted in a host department or institution different from that of the applicant's current primary appointment. An academic enrichment plan of coursework, seminars, journal clubs, etc. may also be included, if appropriate. The host program is expected to demonstrate the availability of appropriate resources to provide research experiences that will meet the goals of this FOA and the applicant's career enhancement plan. In most cases, the candidate and the proposed mentor will not have any previous research collaborations, but candidates may propose such arrangements with justification as to why this program will facilitate the FOA goal in a manner that could not be accomplished through a research grant mechanism or current collaborative efforts.

The relevant administrators (e.g., department chairs, deans) of the candidate's home institution must provide a clear and unambiguous statement of assurance that during the active period of the K18 award the candidate will be released from all administrative, teaching and/or clinical duties that infringe on his/her commitment to the award, and that he/she will be able to devote 3-6 person-months of full time professional effort to the research career enhancement program in b-BSSR. The home institutional representatives should also indicate what, if any, duties or commitments the candidate will continue to maintain, including grant-related responsibilities. In addition, the mentor(s) and host institution should provide documentation of any requisite commitments to the candidate during the career enhancement program.

Any topical area that fits the definition of b-BSSR, as defined by NIH (http://obssr.od.nih.gov/about_obssr/BSSR_CC/BSSR_definition/definition.aspx), is appropriate for support through this FOA. According to this definition, these topics include, but are not limited to the following:

(A). Research on basic behavioral and social processes.

Research on behavioral and social processes involves the study of human or animal functioning at the level of the individual, small group, institution, organization, community, or population; the study of the interactions within and between these levels of aggregation; and the study of how environmental factors affect behavioral and social functioning.

(B). Research on interactions among biological, behavioral and social processes.

This topic includes the identification of interacting biological and behavioral or social variables, including studies to determine how these different processes affect each other (i.e., bi-directional, multilevel relationships).

(C). Research on methodology and measurement in the behavioral and social sciences.

This category encompasses the development of new approaches for research design, data collection, measurement, and data analysis. Of particular interest is the development of measures that are comparable across human and animal populations.

In addition, OppNet has identified topics that may be particularly amenable to this type of career enhancement activity, examples of which are listed below. Note, however, that while a need has been identified for collaborations between animal modelers and human subject researchers on these topics, this is not an all-inclusive listing of appropriate topics for the FOA.

- Vocal learning and communication
- Non-vocal modalities of communication
- Improved technologies and validated measures of behavioral or social processes
- Behavioral phenotyping
- The transmission of behaviors across generations and among peers
- Mechanisms underlying individual differences in basic behavioral or social processes
- Emotions (including social emotions) and emotion regulation
- Prolonged emotional states (e.g., distress, loss)
- Component processes underlying more complex behaviors, such as decision-making, self-regulation, cooperation, and competition
- Ecologically valid measures and models of psychosocial stress across species and environments
- Critical periods of development, including periods during which social adversity shapes adult function
- Affiliative behaviors such as friendship, attachment, pair-bonding, and empathy
- The formation and dynamics of social hierarchies

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are not allowed. http://grants.nih.gov/grants/policy/nihgps_2010/nihgps_ch16.htm#_Toc271265275

Applicant organizations must complete the following registrations as described in the SF424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- Grants.gov
- eRA Commons

All Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any candidate with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director/Principal Investigator (PD/PI) is invited to work with his/her mentor(s) and organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support. Multiple PDs/PIs are not allowed.

By the time of award, the individual must be a citizen or a non-citizen national of the United States or have been lawfully admitted for permanent residence (i.e., possess a currently valid Permanent Resident Card USCIS Form I–551, or other legal verification of such status).

This award is intended for researchers early in their careers through established investigators holding a research or health professional doctorate who are at any rank or level of research/academic development beyond three years of postdoctoral experience. Applicants should have established records of b-BSSR experience using animal models and be seeking an intense, mentored career development experience which will substantially improve their understanding of similar phenomena in humans and their ability to design animal studies that will be more "translatable" to humans. Alternatively, applicants should have established records of b-BSSR experience in humans and be seeking an intense, mentored career development experience which will substantially improve their understanding of similar phenomena in animals and their ability to design human studies that draw on, or inform, animal research.

Candidates (i.e., applicants) must identify one or more mentors willing to sponsor the short term research career enhancement experience. If the candidate works in humans, the mentor(s) should have expertise in researching a similar behavioral or social process in non-human organisms. Alternatively, if the candidate works in animals, the mentor(s) should have expertise in researching a similar behavioral or social process in humans. It is expected that the proposed career enhancement plan will represent a novel extension of the research of the candidate. In most cases, the candidate and the proposed host laboratory/research program will not have any previous research collaborations, but candidates may propose such arrangements with justification as to why this program will facilitate the goals of this FOA in a manner that could not be achieved solely through a research grant mechanism or current collaborative arrangement.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Level of Effort. At the time of award, the candidate must have a "full-time" appointment at the academic institution that is the applicant institution. Candidates who have VA appointments may not consider part of the VA effort toward satisfying the "full time" requirement at the applicant institution. Candidates with VA appointments should contact the staff person in the relevant Institute or Center prior to preparing an application to discuss their eligibility. Under certain circumstances, an awardee may submit a written request to the awarding component requesting a reduction in minimum required percent effort, which will be considered on a case-by-case basis. Details on this policy are provided in NOT-OD-09-036.

Mentor(s). Before submitting the application, the candidate must identify a mentor or mentoring team who will supervise the proposed career development and research experience. The mentor(s) should be active investigator(s) in the area of the proposed research and be committed both to the career development of the candidate and to the direct supervision of the candidate's research. The mentor(s) must document the availability of sufficient research support and facilities for high-quality research. The mentor, or a member of the mentoring team, should have a successful track record of mentoring. Candidates are encouraged to identify more than one mentor, i.e., a mentoring team, if this is deemed advantageous for providing expert advice in all aspects of the research career development program. In such cases, one individual must be identified as the principal mentor who will coordinate the candidate's research. The candidate must work with the mentor(s) in preparing the application.

The mentor(s) should describe the career development plan for the candidate (coordinated with the candidate's research strategy). The description of the career development plan should include items such as classes, seminars, and opportunities for interaction with other groups and scientists. Training in career skills, e.g., grant-writing and making effective presentations, is strongly encouraged. The research environment and the availability and quality of needed research facilities and research resources (e.g., equipment, laboratory space, computer time, available research support, etc.) must also be described.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-14-002.html.

■ DEVELOPMENT AND TRANSLATION OF MEDICAL TECHNOLOGIES TO REDUCE HEALTH DISPARITIES (SBIR) (R43/R44): RFA-EB-13-002

Components of Participating Organizations

National Institute of Biomedical Imaging and Bioengineering
National Institute on Minority Health and Health Disparities

Application Receipt Date(s): May 23, 2013, September 23, 2013; AIDS Date: September 7, 2013, January 7, 2014

The purpose of this funding opportunity is to reduce health disparities through the development and translation of appropriate medical technologies. The NIH defines health disparities as differences in the incidence, prevalence, morbidity, mortality, and burden of diseases and other adverse health outcomes that exist among specific population groups. These population groups include racial and ethnic minorities (African Americans, American Indians, Alaska Natives, Asian Americans, Hispanic Americans, Native Hawaiians, and other U.S. Pacific Islanders, subpopulations of all of these racial/ethnic groups), socioeconomically disadvantaged individuals, and medically underserved populations including individuals residing in rural and urban areas. Appropriate medical technologies must have the following basic characteristics: effective, affordable, culturally acceptable, and easily accessible to those who need them. Responsive grant applications must involve a formal collaboration with a healthcare provider or other healthcare organization serving one or more health disparity populations during Phase I and Phase II. This announcement supports applications to develop medical devices, imaging systems, and other technologies that adequately address the healthcare needs of health disparity populations. It is expected that responsive grant applications will result in advances in medical technologies that will be invaluable in reducing health disparities within and across the priority areas of cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity, as well as lung, liver, and kidney diseases, psoriasis, scleroderma, and other diseases, illnesses, and conditions of public health importance.

Medical and scientific advances have introduced new opportunities for the continued improvement of health for all Americans. However, in spite of notable improvements gained as a result of the technological advancement, there continues to be an alarming disproportionate burden of illness among minority and other health disparity populations. Overcoming persistent disparities in healthcare access and health outcomes remains a foremost challenge. To meet this challenge, the NIH is committed to supporting a wide range of research, aimed at the development of innovative diagnostics, treatments, and preventative strategies to reduce, and eventually eliminate, health disparities.

The primary objective of this funding opportunity is to support the translation of medical technologies, new or existing, that can have a significant impact on healthcare access and health outcomes for health disparity populations. Small business concerns (SBCs) are invited to submit grant applications proposing to develop and deliver appropriate technologies to health disparity populations. Responsive grant applications must involve a formal collaboration with a healthcare provider or other healthcare organization serving one or more health disparity populations during Phase I and Phase II. A requisite component of the research plan is a description of the healthcare requirements and needs of the population and the existing barriers to adequate healthcare delivery. Several of these barriers have been identified and are described below. Applications submitted to this funding opportunity must address one or more of these barriers in developing technologies that will impact health disparities:

- Physical Barriers—factors such as proximity to healthcare facilities and transportation may limit access to healthcare
- Knowledge Barriers—health literacy and language barriers can inhibit healthcare delivery, as well as a lack of patient information for the healthcare provider
- Infrastructure Barriers—rural hospitals and community health centers may not have the same resources and expertise of large hospitals, and may not be able to afford advanced medical technologies
- Economic Barriers—lack of insurance coverage or financial resources may also contribute to disparities in healthcare access
- Cultural Barriers—religious beliefs and social customs often deter certain populations from seeking healthcare

Appropriate technologies may be new and innovative, or they may be existing technologies that have been redesigned based on the needs of a specific health disparity population. Appropriate technologies have been defined as effective, affordable, culturally

acceptable, and deliverable to those who need them. To be effective, a technology must provide an improvement over the current quality of care for a health disparity population by overcoming one or more of the barriers. The technology must also be low-cost, so as to be affordable to the local hospital, community health center, primary care physician, or individual patient in need. For a medical technology to be adopted by a health disparity population, the technology development must be amenable to the population's cultural beliefs and social customs. Acceptance of the technology by the population is critical to the successful delivery of quality healthcare. To be physically delivered to those in need, a technology must be developed within the specifications of the operating environment of the end-user. The technology must be able to function given the existing resources and expertise within health disparity populations. Keeping in mind the barriers that contribute to health disparities, a non-inclusive list of appropriate medical technologies that might achieve the objectives of this initiative may be found below:

- Telehealth technologies for remote diagnosis and monitoring
- Sensors for point-of-care diagnosis
- Devices for in-home monitoring
- Mobile, portable diagnostic and therapeutic systems
- Devices which integrate diagnosis and treatment
- Diagnostics or treatments that do not require special training
- Devices that can operate in low-resource environments
- Non-invasive technologies for diagnosis and treatment
- Integrated, automated system to assess or monitor a specific condition
- Some examples include, but are not limited to
- Inexpensive diabetic test strip and/or blood sugar monitoring. With the growing obesity epidemic and the growing incidence and prevalence of type 2 diabetes, health disparity communities struggle with diabetes and its many sequelae (#1 cause of blindness, dialysis, and amputations).
- Use of currently available basic technology (e.g. phone lines, televisions with remote controls, cellphones, weight scales, diabetic glucometers, thermometers) within underserved settings to promote self-management and patient education, increase patient-clinician communication and surveillance of chronic disease conditions.
- Telemedicine to improve access to specialty care which would normally not be accessible because of high cost and transportation. This would also link up academic tertiary-oriented health centers with community-based primary care homes.
- Improved early detection (via saliva testing, breath testing, blood testing) of diseases where there are significant health disparities.
- Low-cost portable imaging for prevention and early detection of conditions where there are significant health disparities (e.g. breast cancer screening and portable retinal imaging).

Only United States small business concerns (SBCs) are eligible to submit applications for this opportunity. A small business concern is one that, at the time of award of Phase I and Phase II, meets all of the following criteria:

1. Is organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. Is in the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there must be less than 50 percent participation by foreign business entities in the joint venture;
3. (i) SBIR and STTR. Be a concern which is more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), or any combination of these; OR
   (ii) SBIR-only. Be a concern which is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these. No single venture capital operating company, hedge fund, or private equity firm may own more than 50% of the concern; OR
   (iii) SBIR and STTR. Be a joint venture in which each entity to the joint venture must meet the requirements set forth in paragraph 3 (i) or 3 (ii) of this section. A joint venture that includes one or more concerns that meet the requirements of paragraph (ii) of this section must comply with § 121.705(b) concerning registration and proposal requirements.
4. Has, including its affiliates, not more than 500 employees.

If the concern is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these falls under 3 (ii) or 3 (iii) above, see Section IV. Application and Submission Information for additional instructions regarding required application certification.

If an Employee Stock Ownership Plan owns all or part of the concern, each stock trustee and plan member is considered an owner.

If a trust owns all or part of the concern, each trustee and trust beneficiary is considered an owner.

Definitions:

- Hedge fund has the meaning given that term in section 13(h)(2) of the Bank Holding Company Act of 1956 (12 U.S. C. 1851(h)(2)). The hedge fund must have a place of business located in the United States and be created or organized in the United States, or under the law of the United States or of any State.
- Portfolio company means any company that is owned in whole or part by a venture capital operating company, hedge fund, or private equity firm.
- Private equity firm has the meaning given the term "private equity fund" in section 13(h)(2) of the Bank Holding Company Act of 1956 (12 U.S.C. 1851(h)(2)). The private equity firm must have a place of business located in the United States and be created or organized in the United States, or under the law of the United States or of any State.
- Venture capital operating company means an entity described in § 121.103(b)(5)(i), (v), or (vi). The venture capital operating company must have a place of business located in the United States and be created or organized in the United States, or under the law of the United States or of any State.

SBCs must also meet the other regulatory requirements found in 13 C.F.R. Part 121. Business concerns, other than investment companies licensed, or state development companies qualifying under the Small Business Investment Act of 1958, 15 U.S.C. 661, et seq., are affiliates of one another when either directly

or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both. Business concerns include, but are not limited to, any individual (sole proprietorship) partnership, corporation, joint venture, association, or cooperative. The SF424 (R&R) SBIR/STTR Application Guide should be referenced for detailed eligibility information.

Small business concerns that are more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these are NOT eligible to apply to the STTR program.

Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, may be allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) SBIR/STTR Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- System for Award Management (SAM) – must maintain an active entity registration (formerly CCR registration), to be renewed at least annually. Use the Sam.gov "Manage Entity" function to manage your entity registrations. See the Grants Registration User Guide at SAM.gov for additional information.
- SBA Company Registry – *New requirement.* See Section IV. Application and Submission Information, "SF424(R&R) Other Project Information Component" for instructions on how to register and how to attach proof of registration to your application package. Applicants must have a DUNS number to complete this registration. SBA Company registration is NOT required before SAM, Grants.gov or eRA Commons registration.
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD(s)/PI(s)) must also work with their institutional officials to register with the eRA Commons or ensure their existing eRA Commons account is affiliated with the eRA Commons account of the applicant organization.

All registrations must be completed by the application due date. Applicant organizations are strongly encouraged to start the registration process at least 6 weeks prior to the application due date.

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

Under the SBIR program, for both Phase I and Phase II, the primary employment of the PD/PI must be with the small business concern at the time of award and during the conduct of the proposed project. For projects with multiple PDs/PIs, at least one must meet the primary employment requirement. Occasionally, deviations from this requirement may occur.

The SF424 (R&R) SBIR/STTR Application Guide should be referenced for specific details on eligibility requirements. For institutions/organizations proposing multiple PDs/PIs, see Multiple Principal Investigators section of the SF424 (R&R) SBIR/STTR Application Guide.

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept similar grant applications with essentially the same research focus from the same applicant organization. This includes derivative or multiple applications that propose to develop a single product, process, or service that, with non-substantive modifications, can be applied to a variety of purposes. Applicants may not simultaneously submit identical/essentially identical applications under both this funding opportunity and any other HHS funding opportunity, including the SBIR and STTR Parent announcements.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

A Phase I awardee may submit a Phase II application either before or after expiration of the Phase I budget period, unless the awardee elects to submit a Phase I and Phase II application concurrently under the Fast-Track procedure. To maintain eligibility to seek Phase II support, a Phase I awardee should submit a Phase II application within the first six due dates following the expiration of the Phase I budget period.

Partnership with Health Care Provider. To be eligible for funding, applications must involve a formal collaboration with a healthcare provider or other healthcare organization serving one or more health disparity populations during Phase I and Phase II. Applications that do not include this collaboration are ineligible to this FOA and will not undergo peer review.

Contractual/Consortium Arrangements. In Phase I, normally, a minimum of two-thirds or 67% of the research or analytical effort must be carried out by the small business concern. The total amount of all consultant and contractual arrangements to third parties for portions of the scientific and technical effort generally may not exceed 33% of the total amount requested (direct, F&A/indirect, and fee).

In Phase II, normally, a minimum of one-half or 50% of the research or analytical effort must be carried out by the small business concern. The total amount of consultant and contractual arrangements to third parties for portions of the scientific and technical effort generally may not exceed 50% of the total Phase II amount requested (direct, F&A/indirect, and fee).

A small business concern may subcontract a portion of its SBIR or STTR award to a Federal laboratory within the limits above. A Federal laboratory, as defined in 15 U.S.C. § 3703, means any laboratory, any federally funded research and development center, or any center established under 15 U.S.C. §§ 3705 & 3707 that is owned, leased, or otherwise used by a Federal agency and funded by the Federal Government, whether operated by the Government or by a contractor.

The basis for determining the percentage of work to be performed by each of the cooperative parties in Phase I or Phase II will be the total of the requested costs attributable to each party,

unless otherwise described and justified in "Consortium/Contractual Arrangements" of the PHS 398 Research Plan component of SF424 (R&R) application forms.

Additional details are contained in the SF424 (R&R) SBIR/STTR Application Guide.

Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-EB-13-002.html.

■ GENOMES TO NATURAL PRODUCTS (U01): RFA-GM-14-002

Components of Participating Organizations

National Institute of General Medical Sciences

Application Receipt Date(s): July 17, 2013

This Funding Opportunity Announcement (FOA) seeks to speed the rate of discovery of natural products through development of genome and synthetic biology based platforms thus overcoming present technical and knowledge barriers in natural products discovery and in the ability to translate the genetic code (biosynthetic genes) into a chemical read-out (natural products).

This FOA solicits applications from multidisciplinary research teams with well-integrated genomics, synthetic biology, and bioinformatics expertise, to develop innovative, high-throughput, and broadly applicable genome-based methods for natural products discovery that overcome technical barriers and fill knowledge gaps for translation of genetic information into chemical information.

The research proposed should:

- be applicable regardless of whether the natural product source(s) is cultivable, or the biosynthetic pathways are expressed in the native producer;
- be applicable to a large variety of organisms and/or biosynthetic operons and with the production of natural products in model organisms being sufficient for high-throughput chemical characterization;
- include uncharacterized natural products producers and/or biosynthetic operons and should not necessarily focus on natural products of proven medical relevance; and
- advance studies of the regulation and function of biosynthetic enzymes, and is expected to contribute to the identification of novel enzymatic function and chemical entities.

Studies conducted under this FOA will advance our current understanding of biosynthetic pathways, regulatory networks, and chemical scaffolds encoded in natural product producers' genomes. It is also anticipated that new tools, model production organisms and chemical methods for high-throughput and broadly applicable natural products production and characterization will be developed. Tools and technologies developed under this FOA should be an integral part of a novel approach that allows for the rapid determination of the potential of an organism as a natural products producer.

Optimized through evolutionary genetic processes for their biological activity, natural products serve as defensive and signaling molecules, and impart defining chemical features that help make organisms biologically distinct. Approximately 75% of antibacterial and anticancer drugs are natural products or inspired by natural products. Despite their impact, the discovery process for natural products has conceptually and technically not changed over the past three decades. This "grind and find" method entails identification of natural products through biological or phenotypic screening of partially purified mixtures of compounds obtained from cultivable organisms. Thus, this method is limited to organisms that can be cultured and whose biosynthetic operons are sufficiently expressed under culture conditions to provide assayable amounts of active material. These intrinsic limitations have led to a significant reduction in the rate of new discoveries. Recent studies of known natural products' producers suggest that less than 1% of bacteria and fungi can be cultivated and of these, only a small fraction of their natural product operons are active under culture conditions. This suggests that the current approach to discovery of natural products has barely tapped into the potential pool of encoded products.

The last decade has witnessed rapid technical advances and cost-reduction in DNA sequencing, DNA synthesis, and DNA cloning, enabling the sequencing of a wealth of genomes and metagenomic DNA. These technical advances and abundance of sequencing data have opened opportunities for an entirely new approach to natural products discovery that overcomes current limitations. Now it is realistic to use the genomic information to infer the structure of natural products and to leverage advances in synthetic biology to engineer model microorganisms for the production of natural products. This initiative seeks to rapidly expand the pool of natural products by addressing technical and knowledge barriers to the development of genome-based natural products discovery approaches that can take advantage of advances in synthetic biology and the wealth of genomic and metagenomic data being generated across the world.

Specific Areas of Research Interest. For this FOA, specific topics of interest include, but are not limited to, those listed below:

- molecular biology and bioinformatics toolboxes for design and high-throughput assembly of biosynthetic operons
- development of model organisms for natural products production
- identification and characterization of transcriptional and translational regulators
- development of a robust set of expression production tools
- expression of silent biosynthetic pathways and biosynthetic pathways from uncultivable organisms in model organisms
- functional characterization of uncharacterized and functionally unpredictable biosynthetic enzymes
- high-throughput analytical methods for structural characterization of natural products
- bioinformatics tools for analysis of genomics and functional data, and for natural products structural prediction

Topics excluded under this FOA are:

- approaches applicable to only one organism, biosynthetic pathway and/or natural product
- approaches not amenable to high-throughput methods
- approaches focused primarily on the production of analogs of natural products
- optimization of model or native organisms for large-scale production of natural products
- chemical synthesis of natural products
- isolation of natural products from native producers
- assay development for screening of natural products libraries
- characterization of biosynthetic enzymes of established or easily predictable function

This FOA seeks to achieve its scientific goals by promoting highly interactive partnerships that strongly integrate synthetic biology and the natural products expertise necessary to overcome challenges in natural products discovery. Research teams should include specific expertise to reach their goals including but not limited to:

- bioinformatics expertise for designing, testing and modeling synthetic biological systems
- experimental expertise for designing and testing synthetic biological systems
- bioinformatics and biosynthetic natural products expertise for genomic analyses and comparison, and for functional annotation
- biosynthetic natural products expertise
- chemical natural products expertise
- expertise on regulation of expression of natural products' biosynthetic pathways

Special Requirements. The Genomes to Natural Products Network and Governance

The cross-disciplinary research teams funded through this FOA in collaboration with interested and leading experts from academic, government, and industry will form the *"Genome to Natural Products" Network* (GNPN). The Network will be governed by a Steering Committee, which will provide overall leadership for the Network. Specifically, the GNPN will:

- identify common goals and barriers to progress for natural products discovery
- establish a common website format and establish data reporting requirements for all funded projects so as to best foster exchange of information and resources among the GNPN members and with the outside community
- raise awareness of the individual projects' achievements to the greater scientific community
- promote relationships with new partners that enhance the research projects and benefit the field as a whole
- organize an annual GNPN meeting, as well as ad hoc workshops, and sessions at conferences relevant to natural products discovery

In out years, this FOA will support collaborative research projects and other joint GNPN activities among members of the GNPN with funds to be included in all budget requests. No description or plans for these projects are to be included in the Research Strategy Section (see Section IV.2.).

Membership of the GNPN. The GNPN will be composed of full members from the multidisciplinary project teams funded through this FOA and by affiliate members accepted for membership by the Steering Committee and approved by NIGMS.

Affiliate members. Affiliate members may be self-nominated or nominated by full members or by the NIH Project Coordinator. Their request for membership will be reviewed by the Steering Committee for benefit to the GNPN, and recommended to the NIH Program Official for approval. Affiliate members may be researchers from the non-profit and profit sectors. The GNPN Steering Committee may set a cap on the number of profit affiliate members. Affiliate membership of early career investigators is highly encouraged but should not constitute the majority of the non-profit affiliates.

Scientists selected as an affiliate members are expected to:

- perform state-of the art-science in research fields pertinent to this FOA, with high priority for those possessing expertise not present among full members
- demonstrate interest, willingness and availability to participate fully in the GNPN
- show evidence of successful and significant cross-disciplinary collaboration

The *GNPN Steering Committee* will be the main governing body of the GNPN and will participate in setting directions, policies, and operating procedures. GNPN Steering Committee membership will include one voting member representing and appointed by each project awarded through this FOA, the NIGMS Project Coordinator who will serve as a voting member, and one non-voting member representing the affiliate members from the non-profit and profit sectors. The non-voting member will be nominated by the steering committee and must be approved by NIGMS.

The Steering Committee Chair will be one of the voting members funded through this FOA, and nominated by the voting members of the committee. The chair must be approved by NIGMS. The chair may serve a renewable term of 2 1/2 years.

The GNPN Steering Committee will:

- meet via (video)conference at least bimonthly
- set yearly project goals and milestones for the GNPN as a whole
- work with project teams to develop common operating procedures, policies, and reporting guidelines
- set standards for a common format for the projects funded by this FOA's websites
- set standards for data management and deposition
- establish ethical practices to address bioethical implications in a social context
- establish rules for resource and data sharing within the GNPN
- establish procedures for formulation of GNPN collaborative projects, their review, and the recommendation of these projects to NIGMS
- establish guidelines for handling intellectual property issues in accordance to NIH guidelines
- organize and run an annual scientific meeting of the GNPN
- meet at least annually with the External Scientific Advisory Committee and NIGMS staff to discuss progress of the Network to discuss progress on goals and milestones
- communicate the minutes of their meetings to NIGMS within 10 days of the close of the meeting
- communicate with the scientific community through reports, publications, meeting presentations, etc. on scientific and technological achievements of the GNPN

The *GNPN External Scientific Advisory Committee* (ESAC) will consist of three senior scientists appointed by the GNPN Steering Committee and approved by NIGMS, who will meet at the annual GNPN Scientific Meeting, and assess the progress of the GNPN in meeting its goals and milestones. They will advise the GNPN on proposed goals, milestones, and distribution of resources for the next year. The ESAC will provide its findings as a report to the GNPN Steering Committee, and to NIGMS. The ESAC's findings will advise the GNPN on how best to leverage resources and knowledge as a group, to achieve the greatest

impact on and accelerate contributions to the field of natural products discovery. The NIGMS Project Coordinator will attend the meeting of the ESAC but s/he will not be a member of the ESAC.

Members of the ESAC should not be named in the application or contacted prior to the award.

Evaluations and Milestones. The NIGMS Director retains the right to call a meeting of scientific advisors at any time to provide advice on the scientific progress of the projects funded through this FOA and of the GNPN. The group of advisors may opt to attend a GNPN Steering Committee meeting.

It is expected that milestones will be adjusted and reported annually at the time of the non-competing continuation, both to incorporate the project's scientific accomplishments and progress in the field in general, as well as to reflect the recommendations of the ESAC and of any NIGMS advisor groups. Progress against milestones needs to be specifically addressed in the non-competing continuation.

Renewal. Only one renewal will be allowed for each award, limiting the total length of support under this program to a maximum of ten years.

Eligible institutions and organizations include: public or state controlled institutions of higher education; private institutions of higher education; Hispanic-serving institutions; Historically Black Colleges and Universities; Tribally Controlled Colleges and Universities; Alaska native- and native Hawaiian- serving institutions; Asian American Native American Pacific Islander-serving institutions; nonprofit organizations with 501(c)(3) IRS status (other than institutions of higher education); nonprofit organizations without 501(c)(3) IRS status (other than institutions of higher education); small businesses; for-profit organizations (other than small businesses); state governments; county governments; city or township governments; special district governments; Indian/Native American tribal governments (federally recognized); Indian/Native American tribal governments (other than federally recognized); eligible agencies of the Federal Government; U.S. territories or possessions; Independent School Districts; public housing authorities/Indian housing authorities; Native American tribal organizations (other than federally recognized tribal governments); faith-based or community-based organizations, and regional organizations. Non-domestic (non-U.S.) entities (foreign institutions) are not eligible to apply. Non-domestic (non-U.S.) components of U.S. organizations are not eligible to apply. Foreign components, as defined in the *NIH Grants Policy Statement*, are allowed.

Applicant organizations must complete the following registrations as described in the SF424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

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- Grants.gov
- eRA Commons

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For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

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Complete details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-14-002.html.

■ INVESTIGATOR INITIATED MULTI-SITE CLINICAL TRIALS (COLLABORATIVE R01): PAR-13-128

Components of Participating Organizations

National Heart, Lung, and Blood Institute

Application Receipt/Submission Date(s): Multiple dates, see announcement.

Research Objectives

- The purpose of this program announcement is to provide a vehicle for investigator-initiated applications to conduct multi-site (Phase II or Phase III) clinical trials of public health and clinical importance.
- The FOA is appropriate for clinical trials that randomize individuals or groups and tests an intervention that is either clinical or behavioral.
- The rationale for the clinical trial must be clear. The proposed research must address a scientifically important question, must have the potential to augment the existing knowledge base with valuable information, and must have public health or clinical applicability. Research topics should be based on the NHLBI™s national program plan areas of heart, lung, and blood diseases, and sleep disorders. Clinical trials submitted for this FOA should be aligned with the objectives of the NHLBI strategic plan (http://www.nhlbi.nih.gov/about/strategicplan/index.htm).

- All research projects should be designed to maximize efficient use of pre-existing resources for example, through funded Clinical & Translational Science Award (CTSAs) Centers, operational Data Coordinating Centers (DCCs) or other research operations resources where it is possible to leverage existing data infrastructure (e.g., electronic health records)
- This FOA is not intended to support single-center clinical trials or multicenter observational studies that are not testing an intervention.

Multi-site clinical trials

- Multi-site clinical trials are trials that recruit study subjects from two or more geographically distinct enrollment sites or centers where the protocol will be implemented.
- Multi-site clinical trials may utilize a design anywhere along the continuum between explanatory and pragmatic. For this FOA, pragmatic trials are considered those that test an intervention under the usual clinical conditions in which it will be applied, while explanatory trials do so under ideal circumstances. The design should be appropriate for the study question.

Examples of appropriate trials may include but are not limited to those listed below:

- Pragmatic large scale clinical trials are increasingly important to enhance generalizability and efficiency, mitigate the costs of conducting trials, and to determine the effects of the intervention in usual or real-world circumstances (i.e., settings in which usual clinical care is delivered to a wide variety of patients). These trials maintain critical aspects of rigorous clinical trial design such as randomization, while streamlining other aspects – such as data collection – to answer the scientific questions in a cost and time efficient manner. Comparative effectiveness research trials could be well-suited to a pragmatic trial design.
- Explanatory clinical trials can be key to determining the efficacy of an intervention (such as phases II studies); however, all projects should be designed to maximize efficiencies and generalizability to real-world settings as much as possible.
- Multi-site randomized clinical trials may also be vital to complete studies in rare disease populations, in which the trial can only expect to be completed through involvement of multiple centers.

Multi-site Clinical Trial Application(s) Submission

- All multi-site randomized controlled trials with direct costs of $500,000 or more (excluding consortium F&A costs) in any year must include plans to submit at least two applications, one of which is for the support of a CCC and the other which is for support of a DCC.
- Multiple collaborative (R01) applications submitted as part of a Phase II or Phase lll clinical trial are considered as a cluster for the purposes of peer review and funding.
- When multiple applications are submitted as part of a cluster, then all the requirements for applications of $500,000 or more apply. Thus the direct costs of the combined budgets are the unique trigger for applying the $500,000 policy requirements (http://www.nhlbi.nih.gov/funding/policies/500kweb.htm).
- Separate applications for Core functions such as monitoring patient-reported outcomes, conducting economic analyses, conducting biomarker analyses, or a radiological imaging center may be submitted, but are not required. Separate applications for cores should only be submitted if it is scientifically and administratively more efficient and reasonable to have a separate grant award for the core function rather than to use a subcontract or fee-for-service agreement under the CCC or the DCC. Justification for separate core applications must be provided.
- Each application in the cluster must be prepared in response to this Funding Opportunity Announcement and be submitted electronically through Grants.gov (http://www.grants.gov/) using the SF424 Research and Related (R&R) forms and the SF424 (R&R) Application Guide.
- If the proposed direct costs are less than $500,000 per year (excluding consortium F&A costs) – in all years – a single application may be submitted, but all trial functions (i.e., clinical coordination and data management and analysis) must be achievable and justified within the auspices of the same grant.

Institute Staff Involvement

- All grants awarded under this FOA may be converted to a cooperative agreement (U01). NHLBI routinely considers the desirability of substantial continued staff involvement in a supportive mode. NHLBI staff will closely monitor progress at all stages, including review of the Data Monitoring Plan (www.nhlbi.nih.gov/funding/policies/dsmpolicy.htm), review of the study protocol, review and monitoring of accrual (http://www.nhlbi.nih.gov/funding/policies/accrual_guidelines.htm), monitoring of safety, participation on the steering committee and related meetings, and oversight of a data and safety monitoring board.
- The Terms and Conditions for an award for a clinical trial will include recruitment milestones expected to be met by the study as a whole at specific time periods, accrual goals for women and minorities (as appropriate), any requirements regarding minimum effort of specific key personnel, and any other identified requirements for completion of the approved research.
- As with any award, continuation, even during the period recommended for support, is conditional upon satisfactory progress. If, at any time, recruitment falls significantly below the projected milestones for recruitment, the NHLBI will consider ending support and negotiating a phase-out of the award. The NHLBI retains, as an option, periodic external peer review of progress.

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- Of an application with a changed grant activity code.

This FOA will utilize the NIH Research Project Grant (R01) award mechanism. An award may be converted by NHLBI to a cooperative agreement (U01).

Renewal applications that have been converted to cooperative agreements (U01s) will be accepted at the receipt dates of this and subsequent reissuances as R01s.

Each application (renewal or resubmission) that is a part of a cluster may provide a separate introduction and response to reviewer's critiques pertinent to that application.

Complete details at: http://grants.nih.gov/grants/guide/pa-files/PAR-13-128.html.