■ ANCILLARY STUDIES IN CLINICAL TRIALS (R01): RFA-HL-12-012

Components of Participating Organizations

National Heart, Lung, and Blood Institute

Application Receipt Date(s): May 27, 2011; September 27, 2011; January 27, 2012

Clinical trials and large observational cohorts represent a substantial research investment, and are unique sources of well-characterized patient populations. They are not, however, usually structured to permit a detailed investigation of underlying mechanisms of the disease and its progression. For example, identifying surrogate markers is crucial for predicting which patients are at high risk and for designing treatments that can be tailored and targeted to patients with specific characteristics. Such investigations often are best conducted as ancillary studies, and thus require supplementary funding. The FOA program described in this initiative has provided a flexible, cost-effective, and administratively efficient mechanism to facilitate the use of existing large patient cohorts for the study of disease processes and outcomes, genetics and proteomics, therapeutic response, quality of life, behavioral and lifestyle issues, treatment adherence, and health economics. Overall, a relatively modest investment in time-sensitive ancillary studies can result in significant scientific gains in translational and clinical research without incurring the substantial cost of recruiting a new cohort, and can lead to improved diagnostic and prognostic assessments and patient care. Experience has shown us that the standard NIH grant procedures generally take too long to initiate ancillary studies quickly enough to utilize existing large cohorts to full advantage.

The purpose of this FOA is to solicit research grant applications to conduct time-sensitive ancillary studies related to heart, lung, and blood diseases and sleep disorders in conjunction with ongoing NIH- or non-NIH-supported clinical trials. The ancillary study can address any research question related to the mission of NHLBI for which the parent study (which can also be an observational study or registry that can provide a sufficient cohort of well-characterized patients) can provide participants, infrastructure, and data. All ancillary study applications must demonstrate the time-sensitive nature of their application and must explicitly address why an expedited review is essential to its feasibility.

Clinical trials represent a substantial research investment but usually are not structured to permit a detailed investigation of underlying disease mechanisms or of behavioral or economic consequences of the disease. The same is true of some observational studies and registries. Standard grant mechanisms often do not permit the initiation of ancillary studies in a timely fashion to take advantage of these unique and well-characterized cohorts. This FOA provides a flexible mechanism to capitalize on the existing investment in these clinical studies by using their patient cohorts, data, and biological materials to address new research aims. Information gained from such ancillary studies will permit better correlation of clinical course and outcome and may lead to improved prognostic assessments and patient care.

Each ancillary study application submitted under this FOA will propose to study a new research question in the areas of heart, lung, blood, and sleep disorders. The research will be conducted in the venue of a "parent study" that will provide patients and/or patient materials and infrastructure that will facilitate the research and make it more efficient than initiating the same research de novo. The parent study will most often be a Phase II-III clinical trial, since these studies often have large, well-characterized cohorts and frequently lack the resources to study ancillary questions in a timely fashion. However, observational studies and registries that share these characteristics may also qualify as parent studies under this FOA.

Parent studies must be funded independently and will not receive support under this FOA. The objectives of the parent study (unlike those of the ancillary study) need not be related to the NHLBI's mission, so long as the parent study provides an appropriate venue for the proposed ancillary study. Parent studies need not be funded by the NHLBI; they may be funded by other Institutes or government agencies or by private sponsors. However, the objective(s) of the ancillary study must fall within the mission of the NHLBI. Information about clinical trials currently supported by a variety of public and private entities can be obtained from http://www.clinicaltrials.gov/.

Ancillary studies supported under this program might involve the entire cohort participating in a parent study or selected subsets of the participants, depending on the scientific questions posed and the sample size required to answer them. They may even draw patients from two or more parent studies if they have obtained the support of these studies and if their research plan is feasible. In general, this FOA will not support the recruitment of patients who are not already enrolled in the parent study or studies; however, recruitment of a small number of normal controls is acceptable provided that the cost is minimal (e.g., no more than one budget module). A Monitoring Plan for the ancillary study as appropriate should be described in the Research Strategy/Human Subjects section.

The Principal Investigator of the proposed ancillary study must provide documentation of permission from the parent study to use its patient cohorts, data, and biological materials and that there is adequate time remaining in the parent study to complete the ancillary research project as scientifically and technically appropriate. Ancillary studies must not interfere with the parent study or unduly burden participants. All approved procedures and policies of the parent study must be followed.

This program encourages basic scientists and clinical investigators from academia and industry to work together. In addition, this FOA encourages junior investigators to take a leading role in clinical research with the support and collaboration of senior investigators. In general, the Principal Investigator of the ancillary study should not be a principal investigator of the parent study. However, partnerships in which a senior investigator from the parent study mentors a junior PI in the conduct of the ancillary study are appropriate.

This program will use a modified application process, accelerated peer review, and modular funding. This accelerated approach is expected to decrease the time from application to funding to approximately 20 weeks.

Ancillary studies must focus on areas that will not already be studied in the parent trial, such as:

- Basic physiologic, cellular, and genetic mechanisms
- The basis for therapeutic benefits from interventions
- Biomarkers
- Quality of life and psychosocial factors
- Economic implications of the disease and its treatment
- Statistical methods for the study design or the analysis of data

The following are examples of research that might be proposed under this program. These are only examples and are not meant to be inclusive. Applicants may also propose other ancillary studies consistent with the goals of this program.

- Cardiovascular: Mechanisms underlying cardiovascular diseases, cardiovascular disease risk factors, and sequelae of cardiovascular diseases, including hypertension, heart failure, sudden death, and sleep disordered breathing; studies of cardiac energetics before and after control of metabolic abnormalities; imaging studies to elucidate disease progression or to clarify the mechanism of action of interventions; identification and validation of biomarkers of cardiovascular diseases.
- Pulmonary: Pathophysiological and inflammatory mechanisms of lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acute respiratory distress syndrome (ARDS), pulmonary hypertension, interstitial pulmonary fibrosis, and bronchopulmonary dysplasia (BPD); role of genetic factors in the clinical heterogeneity of lung diseases; host response to lung injury; airway injury and repair; airway/tissue and vascular remodeling; regulation of vessel tone; mechanisms underlying the maintenance and severity of asthma; surrogate markers of lung diseases including rejection and infection in transplant patients.
- Hematological: Mechanistic studies and biomarker research on non-malignant hematologic disorders including hemoglobinopathies and disorders of thrombosis and hemostasis. Examples include mechanisms of action of therapeutic agents in sickle cell disease, identification of biomarkers of sickle cell crisis and other organ damage, and biomarkers to predict clinical events in disorders of thrombosis and hemostasis. Mechanistic studies and biomarker research on the outcomes and complications associated with cellular therapies and the transfusion of blood products. Examples include identifying the immune mechanism of cellular therapies, biomarkers to predict graft vs. host disease and immune and other effects of transfusion.
- Behavioral: Behavioral and psychosocial aspects of disease progression; lifestyle factors and their assessment or relationship to biomarkers; gene-environment interactions; adherence to treatment; quality of life indices; relationships with sleep; delivery of health services; and health economic factors.
- Sleep: Sleep-disordered breathing (sleep apnea) phenotypes and the impact of lifestyles characterized by insufficient sleep on cardiovascular, lung and blood diseases and risk factors; markers of human sleep apnea and sleep duration, quality, genotypes, and sleep timing that can be used to stratify apnea severity, and predict the cardiovascular, lung, and blood disease risk; variations in sleep timing and duration (including racial and ethnic differences) associated with disease risk; and the validation of efficient strategies to define normal and abnormal phenotypes through questionnaires or simple non-invasive testing.

Renewals are not allowed and the proposed studies for this FOA must be able to be completed in four 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; Alaskan native- and native Hawaiian- 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; regional organizations; non-domestic (non-U.S.) entities (foreign organizations); non-domestic (non-U.S.) entities (foreign organizations) are eligible to apply.

Foreign (non-U.S.) components of U.S. organizations are allowed.

Applicant organizations must complete the following registrations as described in the SF 424 (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.

- Central Contractor Registration (CCR) – must maintain an active registration, to be renewed at least annually
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD/PIs) 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 four (4) 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 PD/PI 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 SF 424 (R&R) Application Guide.

This program does not require cost sharing as defined in the current *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 in response to this FOA that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application. NIH will not accept any application that is essentially the same as one already reviewed. Resubmission applications may be submitted, according to the NIH Policy on Resubmission Applications from the SF 424 (R&R) Application Guide.

Complete details available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-12-012.html.

■ INCREASING OPPORTUNITIES IN ADVANCED HEART FAILURE AND PALLIATIVE CARE RESEARCH (R01): RFA-NR-11-006

Components of Participating Organizations

National Institute of Nursing Research

Application Receipt Date(s): May 02, 2011

Advanced Heart Failure (HF) is a life threatening condition that affects nearly 5 million people in the U.S. Not only does

it represent a major adverse pathologic consequence of the effect on the heart of diseases originating in many discrete organ systems (e.g. cardiac, pulmonary, renal, endocrine), it also may occur as a negative sequela of pharmacologic exposures such as adriamycin, herceptin, and other drugs used in common multidrug regimens for the treatment of high prevalence cancers among both children and adults. In addition to the multiple etiologies, HF may also progress along various trajectories and may involve years of chronicity before becoming refractory to treatment. Advanced heart failure may therefore play a unique role in enhancing our understanding of the inter-relationships between palliative and end-of-life (EOL) care due to its position as a transition point between palliative care and pre-emptive end-of-life care.

Despite the improving outcomes in HF, one of every eight deaths in the U.S. is due to HF. HF is characterized by symptom burden, diminished QOL, and high costs to the health care system. Although the 2006 Comprehensive Heart Failure Practice Guideline advocates for palliative care, symptom management, referral to hospice and end of life support for advanced HF patients and their caregivers, to-date, little empirical evidence is available to guide palliative care, including hospice, for these patients. Good clinical care can prevent or alleviate suffering for many patients at the end of life by assessing symptoms and providing psychological and social support to the patients and their families. End-of-life care has been identified by the Institute of Medicine as one of the priority areas to improve the quality of health care. This IOM report identified specific gaps related to end-of-life care, such as pain control in advanced cancer and care for patients with advanced organ failure, a topic germane to advanced HF that still needs to be examined robustly. High-quality evidence on palliative or end-of-life care is limited for this condition, and most of the evidence is derived from the literature focusing on patients with cancer. Therefore, this knowledge resulting from this Initiative, and based at least in significant part on a population of non-cancer patients, will fill a specific deficit in what we know to-date. Some important topics in end-of-life care, such as interpersonal and social interventions, remain especially difficult to study and it is expected that this Initiative will stimulate work in this area. Further, to improve palliative care at the end of life is important for patients, caregivers, and clinicians/providers. This Initiative, by laying the groundwork for developing palliative and EOL care interventions among advanced heart failure patients and their caregivers will go far in stimulating this body of work.

Little is known about the burden of illness associated with advanced HF and the complex palliative care needs brought about by the varying trajectories and the many causes of this adverse health condition. Understanding the complex medical and psychosocial care needs of the population suffering from Advanced HF, and the impact on caregivers and family members, requires the conduct of palliative and end of life care research that could ameliorate the negative health outcomes, enhance Health Related Quality of Life (HRQOL), QOL in general, and manage disease related symptoms that could affect these variables negatively.

The purpose of this research initiative is to explore the complex needs of advanced HF patients; study the medical, physical and psychosocial relationships between disease status, symptoms, psychological issues, functional conditions, spiritual concerns and QOL; and develop and test appropriate palliative and EOL care interventions for those with advanced HF and their caregivers. This concept is consistent with the NINR Strategic Plan areas of Quality of Life, Symptom Management, Palliative Care and End of Life.

Specific research areas of interest for this FOA include, but are not limited to, the following:

- Examine similarities and differences in palliative and EOL care needs among those suffering from HF due to organ system dysfunction or pharmacologic exposures.
- Explore unique needs by ethno cultural background, age or medically underserved group status.
- Examine and develop algorithms for the introduction of progressively intense palliative care interventions and the appropriate timing of such interventions.
- Assess varying needs by developmental stage or life course perspective.
- Develop and assess components of palliative care interventions for varying severities and trajectories of HF.
- Assess the impact of inter- disciplinary teams on outcomes among advanced HF patients and their families.
- Examine EOL care needs among HF patients and care-givers.
- Study physical and psychosocial relationships between various trajectories and severities of advanced heart failure.
- Assess whether and how the EOL care experiences of older advanced HF patients and their caregivers can inform the development of new approaches to Advanced care planning (ACP).
- Evaluate and implement appropriate palliative care interdisciplinary interventions for populations with advanced heart failure and caregivers.
- Assess barriers to care and examine similarities or differences in barriers by disease etiology and by ethno cultural diversity or medically underserved status.
- Examine the impact of interventions on symptom management with attention to symptom onset, duration, severity, and overall burden.

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; Alaskan native- and native Hawaiian- 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 organizations) are not eligible to apply. Foreign (non-U.S.) components of U.S. Organizations are not allowed.

Applicant organizations must complete the following registrations as described in the SF 424 (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.

- Central Contractor Registration (CCR) – must maintain an active registration, to be renewed at least annually
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD/PIs) 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 four (4) 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 Project Director/Principal Investigator (PD/PI) 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 SF 424 (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 in response to this FOA that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to a funding opportunity, it is to be prepared as a NEW application. That is, the application for the funding opportunity must not include an "Introduction" describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

Complete details available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-NR-11-006.html.

■ GENOMIC RESEARCH IN AAT-DEFICIENCY AND SARCOIDOSIS STUDY (GRADS) COOPERATIVE RESEARCH PROJECT GRANT: CLINICAL CENTERS (U01): RFA-HL-12-013

Also note: Genomic Research in AAT-Deficiency and Sarcoidosis study (GRADS) Cooperative Research Project Grant: Genomics and Informatics Center (GIC) (U01): RFA-HL-12-014

Details at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-12-014.html

Components of Participating Organizations

National Heart, Lung, and Blood Institute

Application Receipt Date(s): May 17, 2011

The purpose of this funding opportunity announcement (FOA), issued by NHLBI, NIH, is to invite applications to participate in the NHLBI Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS) study as Clinical Centers. This initiative will 1) study patients with AAT or sarcoidosis using state of the art genomics and microbiomics analyses to identify molecular abnormalities and their relationship to patients clinical characteristics and 2) conduct hypothesis-based clinical studies at each Clinical Center to elucidate pathogenetic mechanisms or identify predictors of disease development/progression. GRADS will assemble a multidisciplinary team of investigators to conduct state-of-art genomics, microbiomics and phenotypic studies of two serious and understudied conditions that affect the lungs: alpha-1 antitrypsin deficiency (AAT) and sarcoidosis. GRADS will include multiple Clinical Centers and one GIC. This FOA solicits applications for Clinical Centers and runs in parallel with a separate FOA that solicits applications for the GIC (RFA-HL-12-014). The GRADS Clinical Centers will enroll and clinically and immuno- phenotype AAT and sarcoidosis subjects and appropriate controls. Clinical Centers will also collect and process biospecimens for biomarker, genomic, and microbiomic analyses. Up to 8 Clinical Centers will be funded, each led by Investigator(s) with expertise in AAT, sarcoidosis, pulmonary medicine, immunology, cell biology, or genomics. A Steering Committee of all the Principal Investigators involved with the project will be organized by the GIC (see RFA-HL-12-014) to develop the necessary protocols and monitor study operations. This is a one-time solicitation to support GRADS for a three-year project period.

AAT and sarcoidosis affect young adults in their 20–40s. Pulmonary involvement is the leading cause of morbidity and mortality for both diseases. Complex interactions between genetic and environmental exposures (involving dysregulated immune responses) probably contribute to the development of both conditions. AAT is an autosomal recessive genetic condition with an estimated prevalence of 1 case per 3000 to 5000 persons in the United States. AAT is associated with an increased but variable risk of developing chronic obstructive pulmonary disease (COPD). Overall, the sole presence of homozygous status is not sufficient to explain the clinical phenotypes found in AAT patients. Development of COPD in severe AAT is associated with a history of asthma, pneumonia, childhood respiratory illnesses, or chronic bronchitis. In addition, gender may have a role in the development of COPD in people with AAT. Sarcoidosis is a systemic disease characterized by the formation of granulomatous lesions especially in the lungs, liver, skin, and lymph nodes. Estimates of the numbers of Americans afflicted with this disease range from 13,000 to 134,000. In the U.S. between 2,600 and 27,000 new cases are diagnosed each year. Sarcoidosis has no known etiology, but a genetic predisposition to the disease is indicated by familial clustering, increased concordance in monozygotic twins, and variations in susceptibility and disease presentation among different ethnic groups. Immune dysregulation and sex hormones may play a role in disease development. For both AAT and sarcoidosis, the pathogenetic mechanisms (besides the role of the genetic mutation for AAT) are not well understood, gene modifiers remain unknown, and neither disease can be effectively managed with existing therapies, including replacement therapy in AAT. Because of these characteristics, improved understanding of the molecular abnormalities in these conditions and their relationship with the diverse clinical presentations is essential for developing better methods for detecting, diagnosing, and managing these diseases.

Integrated genomic and phenotypic approaches represent a feasible and promising strategy to better understand the pathogenetic mechanisms of complex diseases. This research approach is expected to generate new scientific hypotheses that will promote development of new targeted diagnostic and therapeutic applications in ATT and sarcoidosis.

This initiative will define the molecular, cellular, and clinical characteristics of 1) representative AAT deficient adults and 2) recently diagnosed sarcoidosis patients, both with varying degrees of lung involvement. The data obtained will provide

a basis for better disease definition, patient sub-type classifications, and the development of new diagnostics or therapies. Data analyses for the two different diseases will, in general, be performed independently. The two diseases are combined in this program to take advantage of efficiencies from sharing of infrastructure, resources, analytical capabilities, and clinical expertise. It is anticipated that each of up to eight Clinical Centers will recruit approximately 60-80 subjects. One or both diseases and appropriate controls will be represented in the recruited cohort. Applicants are strongly encouraged to gain access to existing cohorts of sarcoidosis and AAT patients in which careful clinical phenotyping and genetic linkage and association studies have already been performed. Utilizing such well characterized populations should facilitate the development of the GRADS program. Clinical Center applicants may propose to enroll balanced or unbalanced cohorts of each population (AAT and sarcoidosis). NHLBI will consider the availability of subjects by condition when making funding decisions to ensure a balance between the two diseases in the program.

GRADS will support study-wide research programs in AAT and sarcoidosis as well as multiple Clinical Center-specific research studies. According to study-wide protocols, each GRADS Clinical Center will enroll, clinically phenotype (including HRCT), and immunophenotype approximately 60–80 AAT and/or sarcoidosis subjects and appropriate controls. Clinical Centers will also collect, process, and ship biospecimens to the GIC for analyses. In addition to these collaborative genomics studies, the Clinical Centers will perform center-specific, hypothesis-based research projects to elucidate pathogenetic mechanisms or identify predictors of disease development/progression in AAT or sarcoidosis.

A Steering Committee comprised of all the Principal Investigators involved with the project will be organized by the GIC to develop study-wide protocols and monitor study operations. The final study-wide protocols (one for AAT and one for sarcoidosis) will be based on proposals submitted by the successful GIC and Clinical Center applicants. In general, GIC applicants are asked to propose in their applications those aspects of the protocol that will be performed primarily by the GIC (overall study design and management, biospecimen analyses, data processing and analysis, dissemination of results) and Clinical Center applicants are asked to propose those aspects of the protocol that will be performed primarily at the Clinical Centers (subject identification and recruitment, clinical and immune-phenotyping, and biospecimen collection and handling). The study-wide protocols will be finalized by the GRADS Steering Committee in the early stages of the program. Funds to support study-wide protocol activities at the Clinical Centers will be part of the GIC grant award and will be distributed to the Clinical Centers on a per subject basis and according to the final approved protocol budgets developed by the Steering Committee. All Clinical Centers must be willing to accept funding for the study-wide protocols according to this arrangement.

Clinical Center applicants are asked to propose those portions of a study-wide protocol that deal with background information about the diseases, subject selection and enrollment, characterization and phenotyping, and biospecimen collection and handling. Clinical Center applicants may describe phenotypical (clinical and immunological) characterization protocols for AAT or sarcoidosis or both diseases, depending on their expertise and access to patients. Clinical Center applications must also include a distinct proposal for a Clinical Center-specific research study that seeks to identify mechanisms of pathogenesis or predictors of AAT or sarcoidosis disease development/progression. Applicants should use the following content guidelines in preparing their applications:

- Introduction/background: description of the importance of the study-wide protocol and of the clinic-specific study in the context of the current understanding of the disease (AAT, sarcoidosis, or both).
- Inclusion/exclusion criteria for enrollment in the study-wide protocols and the Clinical Center-specific study (these may or may not differ between the studies). Plans for identifying and enrolling the proposed number of subjects. Characteristics of the anticipated subject population(s).
- Proposed methods for clinical phenotyping, including immunophenotyping and microbiome methods as appropriate. Rationale for choosing these phenotypes for the interrogation of the molecular biospecimen data in the integrative analyses to be performed by the GIC.
- Description of biospecimen collection and sample in vitro manipulation/processing for the study-wide protocols and for the clinical-specific study (if applicable). Samples to be analyzed by the GIC will be prepared by the Clinical Centers. Applicants should propose and justify the collection of specific biospecimens (e.g. blood and bronchoalveolar lavage (BAL) for AAT subjects, and blood, skin or lung tissue and bronchoalveolar lavage (BAL) for sarcoidosis subjects). Microbiome and transcriptome analysis of mRNAs and miRNAs are anticipated, and these will be performed by the GIC (see RFA-HL-12-014). Preparation of samples for GIC measurements of mRNA and miRNA transcripts for phenotyping may include biospecimen immune-stimulation to allow assessment of evoked phenotypes.
- Description of and justification for the Clinical Center specific study: hypothesis, research objectives (i.e. to elucidate pathogenetic mechanisms or identify predictors of disease development/progression in AAT or sarcoidosis), methods, and statistical analysis. Applicants are encouraged to identify possible synergy and leveraging between the Clinical Center-specific and study-wide studies.

Study-wide research program objectives may include but are not limited to the research questions listed below:

- What is the transcriptional profile, as assessed by mRNA and miRNA expression analysis, in lung, blood cells, and plasma of AAT subjects at steady state? Can these data be correlated with the clinical characteristics of the subjects in reference to appropriate control subjects?
- What is the transcriptional profile, as assessed by mRNA and miRNA expression analysis, in lung, other affected pathological tissues, blood cells and plasma in sarcoidosis patients? Can these be correlated with the clinical characteristics of the subjects in reference to appropriate control subjects?
- What are the dynamic molecular patterns of biomarkers and mRNA and miRNA expression in peripheral blood mononuclear cells and plasma before and after stimulation with specific TLR agonists in AAT patients, sarcoidosis patients, and appropriate control subjects? Can these be correlated with the clinical characteristics of the subjects?
- Are there differencies in RNA and miRNA expression in sarcoidosis patients at different stages; aggressive or mild disease; diffuse or localized disease?
- What viral and/or bacterial phyla are present in lung or extra pulmonary tissues in AAT and sarcoidosis patients? Does the microbiome correlate with clinical characteristics of the subjects?

In addition to the study-wide protocols, Clinical Centers will each propose and conduct a research study aimed at identifying mechanisms of pathogenesis or predictors of disease development/progression. These Clinical Center-specific studies

may address AAT or sarcoidosis or both diseases, depending on the availability of expertise and research subjects at the Clinical Center. Clinical Center applicants are strongly encouraged to utilize in their Clinical Center-specific studies subjects, data, and biospecimens available through the study-wide protocols whenever possible to minimize the costs and burden to subjects.

Clinical Center specific research program objectives may include but are not limited to the research questions listed below.

- What molecular and clinical characteristics predict the progression of lung disease in AAT subjects?
- Do COPD exacerbations with or without antibiotic treatment induce changes in the microbiome of induced sputum in subjects with AAT?
- What clinical and biochemical measures are associated with the presence of fibrosing lung disease in sarcoidosis patients?
- Are there rare, nonsynonymous genetic variants in exomes encoding immunity-related proteins in genomic or granuloma DNA from subjects with sarcoidosis?
- Is there a diagnostic marker or panel of markers that can be used to predict early development of lung disease in AAT subjects?
- Can the pathogenesis of sarcoidosis or AAT be understood using models derived from human induced pluripotent stem (iPS) cells?

GRADS will be supported and governed by Cooperative Agreements of up to eight Clinical Centers and one GIC with NHLBI.

- Both GIC and Clinical Center investigators will contribute to the development and implementation of the study-wide protocols; the conduct of the research; the analysis, interpretation, and publication of the results; and the dissemination of study findings. Each Clinical Center will be required to participate in a cooperative and interactive manner with all other Clinical Centers and the GIC in all aspects of the research.
- The GRADS Clinical Centers will provide expertise regarding the two diseases and methods of clinical phenotyping. The Clinical Centers will each enroll, clinically phenotype (including HRCT), and immunophenotype approximately 60–80 AAT and/or sarcoidosis subjects and appropriate controls, using common protocols in a study-wide effort. Clinical Centers will also collect, process, and ship biospecimens to the GIC for analyses. In addition, Clinical Centers will receive funding to support core activities and carry out a center-specific protocol aimed at elucidating pathogenetic mechanisms or identifying predictors of AAT or sarcoidosis disease development/progression.
- The Principal Investigator(s) and other investigators of the Clinical Centers will provide expertise in AAT, sarcoidosis, immunology, microbiology, and cellular and molecular pathobiology. At a minimum, each clinical center must contribute expertise in clinical aspects of at least one of the diseases and in at least one scientific discipline relevant to pathogenesis and subject phenotyping. The multiple principal investigators (PI) option (see http://grants.nih.gov/grants/multi_pi/index.htm) may be used.
- Clinical Centers may include satellite recruitment and protocol implementation sites (that is, additional recruitment sites at a different location than the Clinical Centers).
- The GIC will lead the development of study-wide protocols, oversee conduct of the overall study, serve as a repository for study data and biospecimens, perform or subcontract the analysis of biospecimens, coordinate the activities of the Steering Committee and OSMB, provide quality assurance, and carry out the primary analyses of study data. The GIC will provide expertise in study design; transcriptome, viro-, and phylo-chip analyses; systems biology; and statistical analysis of data sets with high dimensionality. The GIC will prepare a study dataset in an accessible format for sharing and distribution. The GIC will be responsible for distributing protocol funds to the Clinical Centers for the implementation of study-wide protocols on a capitation basis.
- The NHLBI will be responsible for directing and providing overall support for GRADS. The NHLBI Program Office and Office of Grants Management will be responsible for the overall management of GRADS. In addition to regular grant stewardship, the NHLBI Project Officer(s) will be involved substantially with the awardees as a NHLBI partner, consistent with the Cooperative Agreement mechanism. The NHLBI will appoint the Observational Study Monitoring Board (OSMB) and the Steering Committee Chair.
- A Steering Committee (SC) composed of the Principal Investigators of the Clinical Centers, the PI of the GIC, the NHLBI Program Officer(s), and the Study Chair will be the main governing body of GRADS. The NHLBI will appoint the Study Chair, who may be independent of the Clinical Centers and the GIC, to preside over SC meetings and serve as a SC representative. All major scientific decisions, including use of study data and biospecimens, will be determined by majority vote of the SC. Each Clinical Center, the GIC, and the NHLBI will have one vote; the Study Chair will have one vote in case of a tie vote among the other SC members. It is anticipated that the SC will meet one time every month by telephone conference call and three times by in-person meetings in the first year, with an initial in-person meeting two months after award. In subsequent years, the SC will meet one time every month by telephone conference call and two times by in-person meetings. The SC will have primary responsibility for prioritizing proposed topics for investigations, developing the protocols for the studies of each disease, conducting and monitoring the studies, reporting study results in a timely manner, and working with the NHLBI to disseminate the findings. The SC has final responsibility for proposing protocols, protocol budgets, and protocol revisions. Subcommittees of the SC may be established to perform specific functions such as Publications and Presentations, Quality Control/Assurance, and Ancillary Studies. The SC will monitor disclosures of financial interests and potential conflicts of interest among investigators and clinic coordinators according to NHLBI conflict of interest policy (see http://www.nhlbi.nih.gov/funding/policies/coi-res.htm), but such monitoring will not preclude the investigators' responsibility to make financial disclosures to their respective institutions.
- An independent Observational Study Monitoring Board (OSMB), established by the NHLBI in accordance with NIH policies and with input from the SC, will monitor patient safety and review study progress and performance. The OSMB will consist of a chair, clinicians with expertise in AAT and sarcoidosis, and scientists with expertise in clinical research, -omics, bioethics, and biostatistics. An NHLBI scientist, other than the NHLBI's GRADS Project Officer(s), will serve as the Executive Secretary to the OSMB. The OSMB will meet semi-annually by telephone conference call or in-person meetings in the Bethesda area, MD. The OSMB will review serious adverse event reports on an ongoing basis, according to NHLBI policies. Following each meeting, the OSMB will submit recommendations to NHLBI regarding the continuation of the study. The NHLBI will prepare a summary of the OSMB recommendations that Principal Investigators can provide to their Institutional Review Boards.

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; Alaskan native- and native Hawaiian- 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; regional organizations, and non-domestic (non-U.S.) entities (foreign organizations). Foreign (non-U.S.) components of U.S. organizations are allowed.

Applicant organizations must complete the following registrations as described in the PHS398 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.

- Central Contractor Registration (CCR) – must maintain an active registration, to be renewed at least annually
- eRA Commons

All Program Directors/Principal Investigators (PD/PIs) 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 four (4) 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 Project Director/Principal Investigator (PD/PI) 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 PHS398 Application Guide.

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

Complete details available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-12-013.html.

■ ANCILLARY STUDIES TO THE NIDDK INTESTINAL STEM CELL CONSORTIUM (R01): PAR-11-107

Components of Participating Organizations

National Institute of Diabetes and Digestive and Kidney Diseases

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

This Funding Opportunity Announcement (FOA) issued by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH) invites investigator-initiated research project applications (R01) for ancillary studies to a major ongoing study, the Intestinal Stem Cell Consortium, supported by the NIDDK. Research projects must be designed to capitalize on the already established ISCC infrastructure and ongoing research to enhance the scientific output of the ISCC. The ancillary study proposed must be clearly within the scientific mission of the NIDDK and focused on topics or diseases of interest to the Institute. The scientific areas funded by the NIDDK may be found at http://www2.niddk.nih.gov/Research/. The study must also conform to the ISCC Ancillary Studies Guidelines posted on the ISCC web site at http://iscc.coh.org or available through the program staff contact listed in this announcement.

The ISCC represents a substantial financial commitment from the NIDDK to establish a scientifically integrated approach to the study of intestinal stem cells. This consortium offers unique opportunities to conduct additional investigations to fully exploit the research potential of the parent studies. These studies may also provide the opportunity to learn more about stem cells, diseases and conditions outside the original scope of the ISCC but within the interest and mission of the NIDDK.

It is recognized that there is considerable potential for obtaining new knowledge beyond the core activities of the ISCC parent studies by means of ancillary studies. This knowledge may include identification of mechanisms that control stem cell differentiation and division, common means of identification of stem cell populations in other digestive system organs, understanding of the stem cell niche and its alteration in diseases and conditions that affect the intestine, understanding of changes to stem cells or involvement of stem cells in development of diseases and conditions affecting the intestine, in vivo means of assessing stem cell activity, and in vivo means of manipulating stem cells in situ or through transplantation, and other subject areas of relevance to the NIDDK.

It is expected that the proposed ancillary studies will make outstanding use of already developed techniques, reagents, expertise and resources that are a part of the ISCC. For this reason, the studies must be proposed as collaborations developed with ISCC parent study PIs according to the ISCC guidelines posted at the ISCC web site at http://iscc.coh.org. Studies that include substantial collaboration outside of the ISCC are encouraged.

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; Alaskan native- and native Hawaiian-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; regional organizations, and non-domestic (non-U.S.) entities (foreign organizations). Foreign (non-U.S.) components of U.S. organizations are allowed.

Applicant organizations must complete the following registrations as described in the SF 424 (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.

- Central Contractor Registration (CCR) – must maintain an active registration, to be renewed at least annually
- Grants.gov
- eRA Commons

All Program Directors/Principal Investigators (PD/PIs) 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 four (4) 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 Project Director/Principal Investigator (PD/PI) 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 SF 424 (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 in response to this FOA that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application. NIH will not accept any application that is essentially the same as one already reviewed. Resubmission applications may be submitted, according to the NIH Policy on Resubmission Applications from the SF 424 (R&R) Application Guide.

Complete details available at: http://grants.nih.gov/grants/guide/pa-files/PAR-11-107.html.