



Alliance *for* Lupus Research

PREVENT. TREAT. CURE.

FUNCTIONAL GENOMICS AND MOLECULAR PATHWAYS IN SYSTEMIC LUPUS ERYTHEMATOSUS APPLICATION

PROGRAM GUIDELINES

Effective – November 24, 2009

APPLICATION DUE DATE – February 26, 2010

Applications will be administered by:

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Mission

*The mission of the Alliance for Lupus Research is to prevent,
treat and cure lupus through medical research.*

ALLIANCE FOR LUPUS RESEARCH: PROGRAM GUIDELINES

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FUNCTIONAL GENOMICS AND MOLECULAR PATHWAYS IN SLE

Alliance for Lupus Research

GENERAL DESCRIPTION

Background:

Lupus is a complex immunological disorder characterized by interferon production, a loss of tolerance to self-antigens, persistent production of autoantibodies, complement activation, inflammation and tissue damage. There is significant variability in the severity of symptoms, and the disease tends to be relapsing and remitting in nature. Affected systems may include the skin, blood, heart, lungs, kidneys, joints and nervous system. Lupus can also be associated with pregnancy complications, including fetal loss.

The disorder can appear at any age but is most commonly diagnosed in patients between the ages of 20 and 45. Lupus is approximately 9 times more common in females than males and while it can affect people of all racial, ethnic and socioeconomic groups, lupus is especially prevalent in African Americans and people of Latino and Asian descent.

Patients with lupus may exhibit significant malfunction of both B cells and T cells. Potential abnormalities include dysregulation and expression of cytokines, abnormal development of B cell and T cell subsets, and the abnormal function of important signaling cascades. Lupus patients may also demonstrate alterations of macrophage and neutrophil function and vascular abnormalities.

The causes of lupus are obscure but the disorder is highly heritable and replicated linkages have been reported at several genomic sites. The disorder almost certainly involves a complex interaction between genes and the environment.

In 2008, advances in technology have made feasible genome-wide association (GWA) studies searching for genetic variants associated with the disease. To facilitate the search for these genetic variants, ALR funded the establishment of the Systemic Lupus Erythematosus Genetics Consortium (SLEGEN). The consortium, which currently consists of laboratories in the United States and Europe, has organized DNA samples, resources and expertise to hasten the discovery of relevant genomic regions. In 2008 SLEGEN reported the results of an SLE case-control GWA study and a large replication experiment, comprising a total of 6,728 women of European ancestry, complementing other GWA studies in lupus. More recently, additional genes and loci that are associated with lupus have been revealed, with subphenotyping based on clinical manifestations or serologic profiles aiding analysis.

The Alliance for Lupus Research:

Founded by Robert Wood Johnson, IV and headquartered in New York City, the Alliance for Lupus Research (ALR) is the nation's largest and most prominent voluntary health agency dedicated to supporting investigators studying systemic lupus erythematosus.

The primary mission of ALR is to help people with lupus lead fulfilling and rewarding lives by funding peer-reviewed research into the cause, cure, treatment and prevention of lupus and its secondary complications. In addition to funding lupus research, ALR develops and disseminates educational material about lupus and works to educate legislators about the importance of government funding for lupus research. ALR advocates on behalf of lupus funding at the NIH, Department of Defense and other federal agencies. ALR's interests are broad and it supports projects ranging from investigations into the genetic basis of lupus, to the underlying pathogenic mechanisms, to research searching for lupus biomarkers, to programs developing novel therapies.

Research Objectives:

In view of the clear role of genetic factors in lupus susceptibility, a body of research has developed focused on identifying genes and gene variants that contribute to disease susceptibility or modulate tissue response to immune system activation. Research using animal models has succeeded in identifying several putative lupus-associated genes and gene variants. Recent collaborative studies of lupus patients and appropriately matched controls using the genome wide association approach have identified or confirmed gene variants with strong statistical association with SLE. In addition, sequencing of genes of interest has identified rare mutations that are associated with human lupus and provide clues to disease etiology. While extremely important, the discovery of these genes/variants is only a first step in understanding the underlying molecular mechanisms of lupus. Less well understood are the molecular pathways leading from these genes to inflammation and the other clinical manifestations of the disease. A variety of emerging fields such as functional genomics, proteomics, epigenetics and others hold the promise of providing important answers pertinent to the etiology of lupus.

Program Goals:

Applications submitted should focus on two principal areas: (1) functional validation to determine which candidate genes/variants identified in *human lupus* have an authentic role in the disease and (2) detailed elucidation of the molecular pathways modulated by these candidate genes/variants identified in *human lupus*.

Functional Validation:

The most desirable functional validation would be demonstration of a gene/variant effect on a human phenotype relevant to lupus. However, some functional validation studies may not be feasible or ethical in humans, necessitating the use of *in vivo* animal models or *in vitro* strategies. A gene/variant could manifest itself phenotypically at the level of a molecular pathway, cell, circuit or organism, leading to phenotypic differences in protein function, cell motility, cell morphology or a variety of other parameters. ALR encourages validation studies at any of these levels to identify phenotypic differences relevant to lupus and further elucidate the molecular pathways that converge to elicit the clinical manifestations of disease.

There are public resources available to facilitate functional validation of genes/variants involved in lupus. ALR encourages investigators to take advantage of all of these resources. **All proposals submitted in response to this Request for Applications (RFA) must be based on information on genetic variants in the public domain.**

Molecular Pathways:

Understanding of the intracellular pathways that govern the response of a cell to external stimuli has increased dramatically in the past decade largely as a result of efforts to understand how cancer and diseases of the immune system develop, since many of the pertinent genes code for proteins that participate in these signaling cascades. It is a remarkable development of twentieth century science that all eukaryotic cells from all species and from all organs and physiological systems within a species share a common set of signaling elements. The signals ultimately control the metabolism, transcriptional status, or the motility of the cells. ALR encourages molecular studies of these pathways, informed by the discovery of candidate genes, which hold the promise of shedding light on lupus.

Responsive applications will propose research to elucidate the functional implications of the genetic variants identified in human lupus studies. Lupus-associated genes studied in animal models that are not among those also identified in human studies are not appropriate topics for this grant mechanism. Examples of responsive applications include but are not limited to:

1. Human Studies: Functional validation studies could use human DNA samples from phenotypically well-characterized individuals to correlate a gene variant with a particular phenotype. Such human studies are particularly encouraged.
2. Genetic Models: Established genetic models as well as emerging genetic models can be used to look at *in vivo* gene/variant function. Strategies could include exploitation of available genetic knockout/mutants or development of knockouts corresponding to identified disease-associated genes with unknown function, knock in of human gene variants, conditional reduction or over expression of wild type and variant alleles, or studies investigating gender differences with respect to gene/variant function. Functional validation approaches that could lead to the development of *in vivo* models or could facilitate future screening for therapeutic agents are of great interest.
3. RNA interference: RNAi depletion of candidate genes in cells, tissues or whole organisms can be used to identify phenotypes. These phenotypes could range from the cellular (*i.e.*, changes in morphology or function of specific cells) to the organismal (*i.e.*, changes in physiological responses to particular drugs).
4. Imaging strategies: Imaging of cell trafficking *in vivo* might be useful in characterizing the impact of lupus-associated gene variants on immune responses or inflammation.
5. Systems-level approaches: Bioinformatic resources (*i.e.*, interactome, gene expression, proteomic, metabolomic, and anatomical databases) can be mined to generate testable hypotheses concerning the function of candidate genes and groups of genes. Studies could test to see if sets of candidate disease genes are co-expressed in a particular cell type, or function together in a signal transduction cascade. Studies could use proteomic approaches to generate maps of the physical interactions between genes or unexpected relationships between candidates.
6. Cellular or circuit-level approaches: Studies might compare gene/variant functional consequences at the cellular and circuit levels, especially with respect to a drug challenge. Functional responses to physiological changes due to hormones, cytokines and chemokines, are relevant.

7. Epigenetics: Functional validations of epigenetic mechanisms of gene regulation in the context of lupus, including potential maternal and paternal imprinting or X chromosome inactivation, are of interest.
8. Comparison of wild type and gene variant functions: The molecular alteration associated with a gene variant frequently does not reveal whether the function of a particular gene is increased, decreased, or leads to unexpected functional consequences. Approaches using *in vivo* transgenes, *in vitro* biochemical assays, or other validation methods that can address these issues will help to identify the most promising molecular targets for therapeutic interventions.

Eligibility Criteria:

Individuals with doctoral degrees (MD, PhD, DO or equivalent) who have achieved the academic rank of assistant professor (or the equivalent rank outside the United States) or higher are eligible to apply. Applications are open to investigators working at established research institutions (both for profit and not-for profit) as well as investigators at state health agencies, the FDA, VA and at intramural divisions of NIH. The ALR does not impose geographic restrictions on its applicants. Investigators working anywhere in the world are eligible to apply. Please note that applicants from outside the United States must conduct their research at institutions that have provisions for the protection of human subjects substantially similar to those imposed by U.S. Institutional Review Boards. The ALR is willing to appropriately support research in industry or collaborations between academia and industry; however, the ALR does not support clinical trials.

APPLICATION INSTRUCTIONS

Application Information:

Each application should contain the following information (please log into Altum proposalCENTRAL for a detailed description of all forms to be completed):

1. Abstract: A technical abstract of the research plan that includes the application's long term objectives and specific aims. Investigators should highlight the relevance of the work to lupus. The abstract should not exceed 3000 characters.
2. Biosketch: A standard NIH Biosketch for all key personnel working on the project. This should include a description of other financial support available to the applicant for his/her research endeavors. This should also include a description of currently active support and all projects and proposals pending review and/or awarded whether or not financially and/or scientifically related to this application.
3. Proposal Narrative (applies to Research Grants and Pilot Grants): A research plan not to exceed ten pages single-spaced (excluding citations). The plan should: highlight the significance and novelty of the work; describe the relevance of the project to the cause, cure, treatment or prevention of lupus and/or its secondary complications; highlight the relevance of the project to the goals of this Request for Proposals; provide background information and brief plans for experiments that can be accomplished within two years. The publicly available data that support the selection of the particular lupus-associated

gene or genes of interest should be clearly described and cited in the background section of the application. This requirement applies to both research and pilot grants.

4. Assurances: A copy of all materials used to obtain the informed consent of project participants and appropriate institutional assurances regarding human subjects and animals.
5. Budget: A detailed budget for the project prepared in U.S. dollars.
6. Budget Justification: A detailed justification for the budgetary requests.
7. Facilities & Equipment: A short description of the facilities and equipment available to support the project.

Resubmission Information:

- A resubmission is considered an application un-funded in one of the previous two application cycles. An applicant who is unsuccessful in a competition may resubmit a similar revised application three times (the original, plus two resubmissions).
- If major changes are made to the application or if this is an entirely different/new project, the application should not be submitted as a resubmission. Reviewers for applications checked as resubmissions will be provided with the critiques from the previous application cycle.
- If you include changes to your original proposal, highlight the changes. Explain how the application has been strengthened or modified (additions, deletions, revisions).
- If the changes are so extensive as to include most of the proposed Proposal Narrative, explain this exception here.

REVIEW PROCESS

Rating of Applications:

Applications will be evaluated based on relevance to the program goals of the ALR, relevance to this RFA, originality, and feasibility. Feasibility will be evaluated based on the ability to accomplish the work proposed within a two year time frame.

Review/Notification:

Proposals will be reviewed during the spring of 2010 and applicants will be notified of the status of their proposals during June 2010. Funding will commence on or about **August 1, 2010**.

ALR Peer Review:

By applying, you are acknowledging your understanding that critiques will not be available. All applications are subject to peer review. ALR will utilize an aggressive triage process to limit the number of proposals that will receive a detailed examination by the full review committee.

Factors utilized during this triage process include the reviewers' initial assessment of the quality of the research plan, the relevance of the project to the goals of ALR and whether the experience of the applicant provides a good chance of success for the project. Results from that peer review will be forwarded to the ALR Scientific Advisory Board (SAB). The SAB will consider the recommendations from the Study Section, as well as review the existing ALR portfolio to determine which applications would complement existing grants or address an unfilled area of research. The SAB will submit their recommendations to the ALR Board of Directors. This Board will consider all the previous recommendations and will also provide a lay perspective.

The ALR Board of Directors will make all final funding decisions. Decisions of the Board of Directors are final and may not be appealed. Applicants who are not comfortable with this prescreening procedure should not apply. **Electronic submission is mandatory through the Altum proposalCENTRAL website.**

TERMS OF AWARD

Award Period:

1. **Research Grant:** Grants will be awarded for a two year time frame. Funding decisions will be made by the SAB and the ALR Board of Directors.
2. **Pilot Grant:** Grants will be awarded for a one year time frame. Funding decisions will be made by the SAB and the ALR Board of Directors.

Amount of Award:

1. **Research Grant:** This grant mechanism provides up to \$350,000 USD for two years (\$175,000 per year for two years of support) and is not renewable. Research grants must provide evidence of preliminary data. Requests for funds less than the maximum amount are encouraged and should be justified by the work proposed. The ALR limits indirect costs to 8 percent of direct costs excluding equipment and are included in the indicated total allowed budget.
2. **Pilot Grant:** For pilot research projects that are not supported by preliminary data at the time of application, support for up to \$75,000 USD is provided for one year and is not renewable. Requests for funds less than the maximum amount are encouraged and should be justified by the work proposed. Principal Investigator salaries are not supported for Pilot Grants. Salary requests may be made for technical assistance, graduate students and postdoctoral fellows. The ALR limits indirect costs to 8 percent of direct costs excluding equipment and are included in the indicated total allowed budget.

Equipment:

Title to all equipment purchased with ALR funds shall vest in the sponsoring institution provided that, for the duration of the research grant and for a period not to exceed sixty days from the termination date of the grant, the ALR may, at its option, direct the sponsoring Institution to transfer title to a new sponsoring institution. Please note that equipment purchases in the second year of the grant are rarely approved.

Laboratory Visits:

As a condition of support, the Principal Investigator agrees that a representative of the ALR may visit the laboratory or other venue where the grant is being funded upon reasonable prior notification.

Dissemination of Information:

To disseminate information about the ALR research program to our volunteers, supporters, and the public, grantees are expected to occasionally give brief presentations of their research to professional audiences or the general public. All applicants are required to provide a summary of their research project in non-technical language. The summary should be brief and should explain the relevance of the project to lupus in such a way that lay advocates involved in the

review process can evaluate the potential contribution of the project to the mission of the ALR.

Sharing of Research Resources:

Consistent with the policies on intellectual property outlined in the ALR Policy Statement on Research Grants, the ALR strongly encourages the sharing of biomaterials, reagents and data in a timely fashion. Sharing of research resources and timely dissemination of data has been proven to be an essential element in expediting progress in biomedical research. It is expected that de-identified large datasets (such as microarray or GWA data) generated with support of the ALR will be made available to other investigators once published.

Publications:

It is expected that the results of research supported by the ALR shall be published as rapidly as possible in the open literature, consistent with high standards of scientific excellence and rigor. The responsibility for publication lies exclusively with the Principal Investigator (and his/her collaborators) and the result of any work supported by the ALR may be published without prior review of the ALR. Any publication arising in whole or in part from a research grant funded by the ALR shall acknowledge funding support by the ALR. As soon as a manuscript is accepted for publication (whether during the term of the grant or after it has expired) a copy of the publication along with the name of the journal and expected date of publication should be forwarded to the ALR. As soon as reprints are available, two copies of the reprint should be forwarded to the attention of the Coordinator of Research Administration in the ALR office.

Internal Revenue Service Information:

Personnel compensated in whole or in part with funds from the ALR are not considered employees of the ALR. Institutions shall be responsible for issuing the appropriate IRS tax filings for all individuals receiving compensation from Grantor's funds hereunder, and shall be responsible for withholding and paying all required federal and state payroll taxes with regard to such compensation.

Scientific Conduct and IRB Approval:

The ALR does not assume responsibility for the conduct of the investigation or the acts of the investigator since both are under the direction and control of the grantee institution and subject to the institution's medical and scientific policies. Grantee institutions must safeguard the rights and welfare of individuals who participate as subjects in research activities by reviewing proposed activities through an Institutional Review Board (IRB) as specified by the National Institutes of Health (NIH) Office for Protection from Research Risks (OPRR). In addition, institutions must adhere to current US Department of Health and Human Services guidelines regarding financial conflict of interest, recombinant DNA, biohazards, research misconduct, and vertebrate animals. Investigators working outside of the United States must work at Institutions that follow procedures for the protections of human subjects that are substantially similar to the procedures followed by a U.S, IRB.

Principal Investigator Assurance:

All research grants funded by the ALR are subject to the terms and conditions outlined in this document and the funding letter. Deviations from the policies outlined in this document are valid only if made in writing and signed by an official of the ALR. Research performed under

ALR grants is the sole responsibility of the Principal Investigator of that grant and the Sponsoring Institution. The Principal Investigator and Sponsoring Institution are both responsible for insuring that all research activities are conducted in a safe, responsible, and ethical manner.

Intellectual Property and Patent Policy:

The ALR’s policy on intellectual property and patent ownership will be shared upon request.

Cancellation:

Any grant may be terminated or cancelled by the ALR upon written notice to the Principal Investigator and responsible Administrative Official at the Sponsoring Institution if in the sole discretion of the ALR: (i) the Principal Investigator is unable to carry out the research for any reason, (ii) the Principal Investigator or any member of his/her research team is found by an institutional investigation to have committed scientific misconduct or fraud, (iii) the Principal Investigator has failed to comply with any of the terms and conditions of this award, (iv) the ALR concludes that the Principal Investigator has received overlap funding for the award or that the funds are not being used for the purposes originally outlined in the research protocol, or (v) the IRB approval for the grant has been rescinded.

SUBMISSION INSTRUCTIONS AND DEADLINES

Submission Instructions:

Applications are to be submitted electronically through Altum proposalCENTRAL. Altum proposalCENTRAL can be accessed directly at <https://proposalcentral.altum.com>. Instructions and application forms should be downloaded from the Altum proposalCENTRAL website and the completed proposal submitted electronically.

In addition to this electronic submission, applicants are required to submit the original grant application to:

Alliance for Lupus Research
Attention: Research Administration Department
28 West 44th Street
New York, New York 10036
Phone: 212-218-2840

The original application carries the signatures of both the applicant and the applicant's institution. These documents represent the official application.

Please complete the following steps to print the online application:

Step 1: Before you print the application, click the red ‘**Validate**’ button from any page of the online application. ‘Validate’ checks for missing required entries on all pages of the application, and any missing attachments.

Step 2: After successfully passing the validate check you are ready to print the signature pages. This is done by clicking on the ‘Print Signature Pages’ section of the application. This information will serve as the title page for the paper copy of your application.

Step 3: Print all completed templates required for the grant application. This will include all system required templates (e.g., Biosketch, Other Support, etc.), as well as those required templates that are program/applicant specific. **It is important that you print and include all templates required.** You may print your completed templates either from the files on your computer, or you may click on the ‘Show’ link for each attachment in the ‘Proposal Narrative and Other Attachments’ page of your online application (#8 in the gray navigation menu). The templates will open in a separate window – if using Windows, use the ‘Print’ button to print the templates.

Step 4: Assemble the application packet in the following order:

1. Title Page (from proposalCENTRAL)
2. Abstract – technical only not to exceed 3,000 characters
3. Proposal Narrative – not to exceed ten pages
4. Resubmission Statement (if applicable)
5. Budget Summary
6. Budget Justification
7. Biosketch
8. Facilities and Resources
9. Key Personnel
10. Other Support
11. Consultant/Co-Investigator Letters (optional)
12. Appendix Materials (optional)

Additional notes:

- Cover letters are not required.
- Attachments and completed templates must be in PDF format prior to uploading to the Altum proposalCENTRAL site.
- Only the original copy should be mailed to the ALR and it must be complete and legible.

Deadlines:

The deadline for the electronic submission is **February 26, 2010**. The electronic application must be received by the close of business (5:00 PM Eastern time) on the deadline date. **Do not submit your application electronically before obtaining the required institutional signatures.**

The signed original (including all appendices) must be postmarked by February 26, 2010 and received in the ALR office within seven business (7) days after the electronic submission deadline.

November 24, 2009	Request for Application launch
February 26, 2010	Grant Due to the ALR
March- May 2010	Grant Review and Approval Meetings

July 2010	Notification to applicants
August 2010	Grant Activation Date

Late or Incomplete Packages:

An application will not be reviewed if: (1) it arrives after the deadline, (2) is incomplete, (3) the principal investigator is ineligible; (4) it exceeds the page limit, or (5) uses a printer font smaller than standard type size (Arial 12 pt.). An application will be considered incomplete if it fails to follow the instructions or if the material presented is insufficient to permit an adequate review without the solicitation of a substantial amount of additional information. The principal investigator bears the responsibility for submission of a complete application by the designated deadline date.

Change of Application Status:

Any change in application status after submission including a withdrawal of application, a change of address, etc. should be communicated to the ALR’s research department via e-mail immediately at grant.administration@lupusresearch.org.

CONTACT INFORMATION

ALR contact information:

Questions concerning the paper submission or administration of the grant application should be directed to the ALR Research Administration Department at (212) 218-2840.

Altum proposalCENTRAL contact information:

For help with the electronic grant application process, please contact the help desk of Altum proposalCENTRAL by email at pcsupport@altum.com. You may also contract them by phone at 1-800-875-2562, extension 227.