DESCRIPTION OF GRANT MECHANISM

The Alliance for Lupus Research (ALR) is an independent, voluntary health agency with the goal of supporting research leading to the prevention, treatment and cure of systemic lupus erythematosus (lupus or SLE). The ALR has partnered with Pfizer’s Centers for Therapeutic Innovation (CTI), a research unit that collaborates with leading academic medical centers, foundations, and the NIH to speed the translation of novel targets into potential therapeutics. The specific goal of the ALR-CTI collaboration is to facilitate and accelerate development of new therapies for lupus patients. Through our joint funding for lupus research, we have designated grant funds for studies of high scientific merit and translational potential focused on the role of interferon-beta (IFN-β) in the pathogenesis and/or maintenance of systemic lupus erythematosus (SLE).

Program Goals: With this request for applications (RFA), the ALR-CTI collaboration endeavors to support research that: (1) investigates the expression and function of IFN-β and/or related gene products in blood and tissue samples from SLE patients and other interferonopathies including rare autoimmune diseases; and/or (2) informs development of therapeutic approaches that target IFN-β by identifying novel ways to stratify patients; and/or (3) characterizes the regulation and unique functional properties of IFN-β. The program is self-limited, involving a one-time request for proposals. It is anticipated that up to three research grants will be funded.

Amount of Award: Funding for the ALR-CTI Challenge Grant Program award will be up to $150,000 USD per year, for a maximum of two years (i.e., each total award ≤ $300,000 USD). The second year of project funding is dependent upon successful completion of Year 1 milestones, as well as agreement from the ALR-CTI joint steering committee.

Background: Evidence supporting an important role for the type I IFNs (IFN-I) in the pathogenesis of SLE and other systemic autoimmune diseases has developed over several decades, beginning with demonstrations of elevated levels of circulating IFN-I in patients with lupus and gaining new momentum with the recognition of an IFN-I gene signature in studies of peripheral blood and tissue from patients. Many of the common genetic variants associated with SLE encode proteins associated with molecular pathways involved in induction of or response to IFN-I, and several monogenic disorders associated with autoimmunity or inflammation that are also associated with elevated levels of IFN-I. In lupus patients, presence of an IFN-I signature is associated with the presence of RNA-associated protein-targeted autoantibodies (e.g., anti-Ro, anti-Sm), and in vitro studies and investigations in murine models support a contribution of
RNA-activated Toll-like receptors (e.g., TLR7) to induction of IFN-I. Recent studies of cytoplasmic nucleic acid receptors demonstrate induction of IFN-I through pathways that involve activation of interferon regulatory factor 3. Plasmacytoid dendritic cells are highly active producers of IFN-I, although many cell types are capable of IFN-I production, particularly in the setting of virus infection. In view of data from both murine and human systems, IFN-I is considered a rational therapeutic target for patients with SLE, with drug development efforts taking several approaches.

The type I IFNs are encoded on human chromosome 9p and comprise a family of cytokines, all of which bind to the IFN-I cell surface receptor, IFNAR. IFN-α comprises 13 subtypes encoded by distinct genes, and their protein products represent the majority of the IFN-I detected in lupus sera. However, analysis of gene transcripts preferentially regulated by IFN-α in comparison to those preferentially induced by other IFN-I’s suggests potential roles for IFN-β or IFN-ω as inducers of the IFN-I signature in lupus patients. Additional data demonstrate presence of IFN-I in lupus sera that is inhibited by antibodies specific for IFN-β or IFN-ω. Recent reports from extensive bioinformatics analyses of gene expression signatures present in lupus peripheral blood suggest that in addition to IFN-α, which generates a relatively stable pattern of IFN-I regulated gene transcripts over time, other gene clusters may reflect induction by IFN-β or IFN-γ and present a more variable pattern in longitudinal samples. Studies in a related autoimmune disease, dermatomyositis, have supported a contribution of IFN-β, as well as IFN-α, to the IFN-I signature. As the extent of inhibition of the IFN-I gene signature in peripheral blood of lupus patients treated with monoclonal antibodies specific for IFN-α has been incomplete, it is possible that other IFN-I family members, including IFN-β or IFN-ω, may be contributing to IFN-I pathway activation in patients with lupus.

There is considerable overlap in the mechanisms of IFN-I induction and regulation, and in the genes induced by each of the members of the IFN-I family. However, there are also data indicating that IFN-α or IFN-β may be preferentially induced depending on the molecular pathways engaged (and that the various IFN-I subtypes have distinct affinities or interactions with IFNAR). Furthermore, different tissues and/or cell types express different IFN-I’s, raising the possibility that while downstream gene expression profiles are often largely similar in response to the various IFN-I’s, blockade of IFN-β might have different therapeutic consequences on the pathobiology of SLE than would blockade of the multiple IFN-α subtypes. Determining the contribution of the different IFN-I’s to the inflammatory milieu in affected tissues in SLE would thus better inform the development of IFN-directed therapies in SLE.

The goal of this ALR-CTI RFA is to support research that will provide new knowledge regarding the role of IFN-β in immune regulation, with a particular focus on its role in the pathogenesis of SLE and other interferonopathies, as well as its regulation and function in the context of a particular disease.

**Collaborative Approach:** ALR and CTI support a collaborative research environment. Investigators may use this grant as an opportunity to draw on the collective Interferon insight of these two organizations.
Eligibility Criteria: Individuals with doctoral degrees (MD, PhD, DO or equivalent) are eligible to apply. Scientific independence, as evidenced by direction of a research program, a publication record, or other experience that establishes scientific leadership is necessary to apply. Investigators from any institution worldwide are invited to apply.

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 and uploaded):

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. Proposal Narrative: A research plan (up to 7 pages) highlighting the significance and novelty of the work; describe the relevance of the project to the stated aims of the ALR-CTI Challenge Grant Program and the overall goals of the ALR regarding gaining knowledge that will elucidate the cause, cure treatment or prevention of lupus and/or its secondary complications; provide background information and rationale, approach and anticipated results for experiments that can be accomplished within two years.
3. Milestones: A list of milestones (the expected status of the project at various points in time). These milestones will be used to evaluate progress and to facilitate communication between the principal investigators and the ALR-CTI Joint Steering Committee. The list of milestones should reflect the specific aims of the proposal. The list of milestones is part of the proposal narrative but not included in the 7-page limit. See Instructions for Proposal Narrative in the electronic templates section (proposal section 11).
4. Budget Period Detail and Summary: A budget for the project prepared in U.S. dollars. This information should be entered directly into the electronic application. The budget should be for a maximum of two years and should not exceed $300,000 total (up to $150,000 per year).
5. Budget Summary and Justification: A detailed justification for the budgetary requests. This information should be entered directly into the electronic application. The information in this section should be divided into two sections. The first section should include the following line items: personnel, consultant costs; equipment and supplies (both office and medical of laboratory). The second section should include all other line items including but not limited to: travel, patient care, other expenses, consortium and contractual costs. Each section should not exceed 2000 characters. Any additional information should be included as an appendix to the application.
6. Facilities & Equipment: A short description of the facilities and equipment available to support the project.
7. 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 award whether or not financially and/or scientifically related to this application. Applicants must include accurate and complete information regarding all other sources of grant support from the main PI (current and pending), including title, abstract, annual and total amount of the grant, inclusive funding period, and
percent effort of the applicant. It is not necessary to include this information for all Key Personnel.

8. **Assurances:** Appropriate institutional assurances regarding human subjects and animals, as applicable.

9. **Consultant/Co-Investigator/Collaborator Letters:** Optional, only submit if relevant to the application.

10. **Consent Forms:** If relevant, copies or drafts of all informed consent forms to be distributed to participants for signature in this study (or their legal guardians).

11. **Appendix Materials:** Optional, see instructions for appendix material allowed.

**Restriction on Number of Applications:** Only one application will be accepted per principal investigator in a grant cycle.

**REVIEW PROCESS**

**Rating of Applications:** Applications will be evaluated by the ALR-CTI Joint Steering Committee based on the following criteria:

- Relevance to the aims of the ALR-CTI Challenge Grant Program and the overall goals of the ALR: prevention, treatment, or cure of lupus
- Feasibility will be evaluated based on the ability to accomplish the work proposed within a two year time frame and the likelihood that the work will:
  - characterize key IFNβ-driven steps in the pathogenesis of the disease
  - further characterize Interferon signatures in patients
  - facilitate the clinical evaluation of innovative approaches to the prevention and/or treatment of lupus and its complications
  - adhere to high standards of appropriate research design, originality, and scientific rigor

**TERMS OF AWARD**

Funding for this collaboration is being administered by the ALR and is contingent upon finalizing a collaborative research agreement between your institution and Pfizer’s Centers for Therapeutic Innovation. For successful applications, funding will commence following finalization of this collaborative research agreement between your institution and Pfizer.

**SUBMISSION INSTRUCTIONS AND DEADLINES**

**Applications:** The electronic application must have the signatures of both the applicant and the representative of the applicant's institution. These documents represent the official application. It must be submitted electronically through the ALR-CTI section of the Altum proposalCENTRAL website by 5PM EST on April 1, 2016. Altum proposalCENTRAL can be accessed directly at https://proposalcentral.altum.com. Instructions and application forms are available on the proposalCENTRAL website.
**Deadline:** The deadline for submission of applications for the ALR-CTI Challenge Grant Program is April 1, 2016. The electronic application must be received by the close of business (5:00 PM EST) on the deadline date.

**CONTACT INFORMATION**

**ALR Contact Information:** Questions concerning the application submission process, or the administration of grant applications, should be directed to the ALR Research Administration Department at (212) 218-2840 or research.admin@lupusresearch.org.

**Altum proposalCENTRAL Contact Information:** For help with the electronic grant application process, please contact the help desk of ProposalCENTRAL by email at pcsupport@altum.com or by phone at 1-800-875-2562, extension 227.