Request for Applications
2025 Mechanistic Clinical Award
$500,000 over 2 years or $1,000,000 over 3 years

CONTENTS

BACKGROUND

The Lupus Research Alliance (LRA) is the largest private funder of lupus research worldwide. The organization aims to transform lupus treatment while advancing towards a cure by funding cutting-edge, innovative, and translationally relevant research.

At present, therapy for lupus is mostly empiric and involves largely non-specific anti-inflammatory and immunosuppressive agents. While these treatments are frequently beneficial, many patients do not respond adequately or suffer significant side effects. Importantly, even patients with low disease activity accrue organ damage over time. Thus, new conceptual and therapeutic approaches are urgently needed.

A major hurdle to developing successful therapeutic strategies in lupus is disease heterogeneity. Lupus is known for high variability in symptoms and manifestations and in disease severity, progression, and response to therapy. This heterogeneity is reflected at the molecular and cellular level, especially in the phenotype of patients' immune systems. Many clinical trials for new targeted therapies in lupus fail to meet their endpoints, as positive data may be clouded by disparate responses among individual patients. A deeper mechanistic understanding of interventions and their interactions with human biology, and more nimble clinical testing of novel approaches, could enable the expansion of the therapeutic armamentarium and improve the quality of life for lupus patients.

Within the challenge of heterogeneity lies an opportunity to replace a “one-size-fits-all" approach to drug development with a precision medicine strategy. The increased accessibility and advancement of sequencing and other technologies opens the door to personalized therapies that target the unique biological drivers (genetic, epigenetic, cellular, metabolic, etc.) of an individual’s disease.

To advance a precision medicine framework for therapeutic development in lupus, the LRA has developed the Mechanistic Clinical Award (MCA), which offers two types of grant awards: 1) Mechanistic Studies using patient biospecimens and 2) Small Mechanistic Clinical Trials. The MCA will leverage LRA capabilities across the research continuum, including its research grants program, resources (Lupus Nexus), and Lupus Clinical Investigators Network (LuCIN).

- **Lupus Nexus (LNx)** is the LRA’s lupus registry, biorepository, and knowledge portal. It will include a rich source of highly curated, longitudinal, clinical and patient-reported data from 3,500 patients and linked biospecimens, which will allow investigators to address emerging questions in lupus research. Biospecimens include whole blood and blood derivatives, urine, saliva, and stool (see Appendix I). Applicants to the Mechanistic Studies using patient biospecimens grant mechanism are strongly encouraged to consider the LNx samples as part of their research plan. For more information on LNx resources, please contact lupusnexus@lupusresearch.org.
- **Lupus Clinical Investigators Network (LuCIN)** is a network of 50+ premier lupus academic medical research centers across North America comprised of 200+ providers with expertise in lupus care and clinical trials. Founded and sponsored by the LRA, with oversight by its fully owned affiliate, Lupus Therapeutics, LuCIN brings together experts to evaluate the safety and effectiveness of potential new treatments for lupus. As the clinical research arm of LRA, Lupus Therapeutics partners with biopharmaceutical companies, clinical investigators, and community organizations to improve and accelerate the clinical research process. All mechanistic clinical trials proposed through this Request for Applications (RFA) must be conducted within LuCIN.

PROGRAM OBJECTIVES AND SCOPE

The award will fund two types of grant mechanistic studies pursuing either studies on patient biospecimens or small mechanistic clinical trials with the goal of testing novel biomarkers, therapeutic or lifestyle approaches, or mechanistic hypotheses for proof-of-principle and evaluation of the approach. Clinical trials funded through this mechanism should pursue hypothesis-driven approaches and those not readily undertaken by conventional, industry-sponsored drug development trials.

Proposals should align with the LRA’s strategic objectives to:

- Improve understanding of patient heterogeneity and disease pathogenesis as a basis for individual therapeutic choices.
- Expand the repertoire of therapies and lifestyle interventions to enable rational, precision combination therapies

- Increase the number of molecular stratification, prognostic/diagnostic tools, and biomarkers

RESEARCH EMPHASIS AREAS

Proposals may encompass the research areas listed below. Studies may reflect, but are not limited to, the sub-bulleted examples.

- **Improving understanding of disease heterogeneity as a basis for individualized therapeutic choices or a translationally relevant mechanistic understanding of disease pathogenesis**
  - Dissecting the molecular or cellular response to therapy within specific genetic ancestry subgroups
  - Stratification of patient subgroups by their molecular profile, assessing resulting pathway activation and downstream phenotypic outcomes in response to therapy
- **Mechanistic underpinnings of lifestyle interventions**
  - Assessing biological measures following a behavioral or physical intervention
- **Mechanistic investigations in pursuit of drug repurposing/expanded indications**
  - Molecular and immunologic analysis of the downstream effects of a therapy which may have expanded indication benefits
  - Pursuit of organ- or symptom-specific biological effects of therapy
- **Proof-of-concept studies for assessing novel biomarkers or diagnostics**
  - Pilot study of a specific biomarker or panel
  - Assessment of a novel imaging method or agent to measure a phenotypic outcome
- **Expanding mechanistic understanding of approved or novel therapies**
  - Exploration of a novel mechanism of action for an existing therapy that could enhance its clinical application
  - Ancillary studies validating the mechanism of action of a novel therapy

FUNDING MECHANISMS

The following two types of grants will be supported through this RFA:

1. **Mechanistic studies using patient biospecimens** from individuals diagnosed with lupus will be supported for up to $500,000 over two years. These studies should aim to better understand disease progression and pathogenesis; investigate treatment selection, response, or mechanism of action; or identify or evaluate biomarkers.
   - Preference will be given to studies leveraging biospecimens and data from the Lupus Nexus (LNx). Please refer to the Appendix for further information.
   - Given that the number of samples available through LNx may be limited at the time of RFA release, the use of external sample sources (outside of LNx)—such as those collected as part of an ongoing third party-sponsored trial or with independent institutional efforts—will be considered. Applicants must provide a rationale justifying why their resource is better suited to the proposed study and the feasibility of gaining timely access to samples and/or data.

- Biospecimen source must be specified when providing the Intent to Submit (see Application Process and Instructions below) and must be available prior to the start of the study.

2. **Small mechanistic clinical trials** will be supported for up to $1,000,000 for up to three years. Mechanistic clinical trials funded through this mechanism should not exceed 20 participants and two to three study sites. The primary outcome of a funded clinical trial must be mechanistic and may test both therapeutic and lifestyle interventions or investigate a potential therapeutic target or biomarker. Applicants must demonstrate project feasibility, including administrative and regulatory approvals, access to the drug or intervention and letters of support from third-party participants.
    - **Trials must be conducted within LuCIN, utilizing LuCIN centers**. Investigators who are outside the LuCIN network need to have a collaboration within the network in order to apply. *For further information on connecting with LuCIN centers, please consult the LuCIN Center Directory and contact Kari Fischer, Ph.D. (kfischer@lupusresearch.org) prior to October 15, 2024.*
        - IND (or waiver) and IRB approval, as appropriate, at the first study site; and submission of the full clinical protocol will be required prior to the initial grant payment **and** within six months of the date of the grant award letter. Failure to do so may result in termination of the award.
    - Applicants must demonstrate the feasibility of gaining timely access to the **study intervention** (e.g., an MTA) so as to complete their grant within three years.
    - Studies pursuing a new indication of a drug still under patent must include a letter of support from the biopharmaceutical company.
    - The LRA is dedicated to patient centricity in research, preference will be given to applications that have a patient engagement strategy, involving patients and advocates in the study design process.

For project proposals outside of the described scope (number of participants or sites), please contact Kari Fischer, Ph.D. (kfischer@lupusresearch.org) to discuss the responsiveness of your application to the program.

ELIGIBILITY

Applicants must have a doctoral degree (MD, PhD, DO, or equivalent); hold a faculty or equivalent position; and lead an independent research team at an academic, nonprofit, or government research institution. US federal government research laboratories are not eligible for this award. There are no citizenship requirements for investigators applying to this program.

Special Considerations regarding for-profit Collaborators
The LRA recognizes the need for for-profit partnerships and collaborations to enable certain studies. Partnerships and cost sharing agreements between academic applicants and for-profit organizations are allowed and encouraged. Please contact Kari Fischer, Ph.D. (kfischer@lupusresearch.org) to consult on this issue.

Applicants who previously received LRA funding must be in good standing with all required reports and previously agreed to Terms and Conditions of the LRA-funded project(s) at the time of application submission.

The same research project may not be submitted for consideration to multiple LRA grant mechanisms in the same year. Such submissions will be triaged without review.

Projects with significant overlap with currently active LRA-funded grants will not be considered and may be administratively withdrawn. Applicants are advised to review the LRA research portfolio to determine if overlap exists and may consult with Kari Fischer, Ph.D. (kfischer@lupusresearch.org) if necessary.

APPLICATION PROCESS AND INSTRUCTIONS

Applicants intending to submit an application in response to this RFA must submit a non-binding Letter of Intent (LOI) through ProposalCentral by 11:59pm US ET on the stated deadline. This brief intention to submit will be used for the purpose of convening an appropriate review panel.

KEY DATES

RFA Release:	September 25, 2024
Intention to Submit (LOI) Due:	November 13, 2024
Full Applications Due:	January 3, 2025
Application Decision:	April 2025
Expected Start Date:	July 2025

SUMMARY OF REQUIREMENTS

If the following required information is not available at the time of application, it must be supplied prior to receiving this award:

Mechanistic Study Using Patient Biospecimens
- Biospecimen Source Pre-Identified

Small Mechanistic Clinical Trial
- LuCIN Investigator or LuCIN Partner Letter of Collaboration
- IRB (or waiver)
- IND (or waiver)
- MTA (if applicable)
- Biopharmaceutical Company Letter of Support (if applicable)

Applications must be submitted electronically, via ProposalCentral, **by 11:59pm US ET on the stated deadline**. Applications will not be accepted via any other means.

The following information is required to submit a complete application. Numbers correspond to the application sections found on the left side navigation bar of the ProposalCentral website

1. **Title Page:** Enter the title of the proposed project. Indicate whether:
   - The application is in the Mechanistic Study Using Patient Biospecimens or Small Mechanistic Clinical Trial category.
   - The applicant is currently funded by the LRA.

2. **Download Templates & Instructions:** The Request for Applications, Research Plan Instructions, Research Plan Templates, and Milestones Templates can be downloaded from Proposal Central and are provided as an Appendix to this RFA.

3. **Enable Other Users to Access this Proposal:** Enter the information for any other users who will need to work on the application.

4. **Applicant/PI:** The applicant's information is pre-loaded with the contact information from their ProposalCentral profile. Click the Edit Professional Profile button if any changes need to be made. Upload a standard NIH Biosketch. Applicants who are not based in the United States may submit a copy of their curriculum vitae, which must be limited to five pages in length.

5. **Institution & Contacts:** The lead institution will be pre-loaded with the applicant's institution. Enter the requested information for the Signing Official and Financial Officer.

6. **Key Personnel:** Enter the requested information for all key personnel and upload a standard NIH Biosketch for each co-investigator. For co-investigators who are not based in the United States, a copy of their curriculum vitae, which must be limited to five pages in length, may be submitted.

7. **Facilities & Resources:** Specify the facilities to be used for the proposed research for each category. List the most important equipment items already available for the project.

8. **Lay & Scientific Abstracts:** Provide both lay and scientific abstracts, limited to 3,000 characters each, for the proposed project. The lay abstract should be suitable for public distribution. Provide an impact statement, limited to 1,000 characters, explaining the potential of the proposed project to translate to the clinic and how the proposed research will impact people with lupus.

9. **Budget Period Details:** Enter the budget period for each year of the grant and complete the required information for each budget period. Please keep the following in mind:
    - MCA grants will be supported for up to US$500,000 for up to two years or US$1,000,000 for up to three years.
    - Please provide a budget breakdown by year.
    - Funds may be used for any appropriate research costs.
    - The LRA follows the NIH salary limitation guidelines for principal investigators and postdoctoral fellows.
    - Indirect costs may not exceed 10% of the total amount budgeted and must be included within the $500,000 or $1,000,000 budget cap.
    - Funds cannot be used to pay for major pieces of laboratory equipment.
    - Funds cannot be used to pay for tuition or education expenses.
    - Funds cannot be used to pay for study drug if the drug is in development or under patent.
    - Up to $2,000 per year should be budgeted to pay for travel expenses related to attending Forum for Discovery, LRA's annual scientific conference.
    - The budget is not scored, but it will be carefully assessed and the LRA may request alterations as necessary.

10. **Budget Summary & Justification:** Provide a detailed budget justification, limited to 5,000 characters.

11. **Other Support:** List all pending and current support (institutional, federal, commercial, etc.) for the applicant's research endeavors. Indicate specific aims, funding amounts, percent effort, funding period, and whether there is scientific overlap with the proposed research. If overlap exists, a statement regarding intended dispositions of funds in the event of dual granting is required.

12. **Organizational Assurances:** Answer all organizational assurance questions and provide their status, if applicable.

13. **Research Plan & Other Attachments:** Upload the Research Plan, Milestones, Letters of Collaboration (if applicable), and Appendix Materials. For Small Mechanistic Clinical Trials include the requested documentation of study approvals and feasibility. **Please note that when a template is provided, it must be used.**

    - **Letters of Collaboration:** Signed letters from each co-investigator, collaborator or consultant stating their role in the project and confirming their agreement to participate in the project must be provided. These letters should include a detailed explanation of the programmatic, fiscal, and administrative arrangements made between the applicant institution and collaborating organizations and individuals. The letters should be combined into one PDF document. For Small Mechanistic Clinical Trial applications, <u>if the applicant is not a LuCIN investigator</u>, a letter of collaboration from a LuCIN investigator must be included.

- Small Mechanistic Clinical Trial applications must also upload as appendix materials the following information or a document summarizing the status of the listed study approvals and feasibility information**:**
  - **IRB Approval:** If acquired by the time of submission, the applicant must provide documentation of IRB approval (or waiver) at the first study site. If not available, the applicant must provide a copy of their IRB application (or draft) and projected timeline of approval.
  - **Regulatory Approval:** If acquired by the time of submission, the applicant must provide documentation of regulatory approval (e.g., Investigational New Drug application, or equivalent) or waiver. If not available, the applicant must provide the projected timeline of approvals, including any additional institutional approvals that are required first (e.g., an institutional IND committee).
  - **Study Drug or Intervention Feasibility:**
    - When applicable, studies must include a fully executed Material Transfer Agreement (redacted if necessary).
    - Studies pursuing an expanded indication of a drug still under patent must include a letter of support from the biopharmaceutical company.
- **Milestones:** Using the template provided on ProposalCentral, indicate during which months of the grant term each milestone is proposed to be completed by filling the corresponding cells with a light color. Upload as a PDF document.
- **Appendix Materials:** Identify each file with the name of the applicant. Up to five publications, manuscripts accepted for publication, abstracts, patents, or other printed materials directly relevant to this project may be uploaded. Do not include manuscripts that have only been submitted for publication.

14. **PI Data Sheet:** Please verify the applicant's gender, race, and ethnicity. This information will not be used in any way during the selection process.

15. **Validate:** Click the "Validate" button to check for any missing required information or attachments.

16. **Sign:** Click the "Sign" button to electronically sign the application. By signing, the applicant certifies that the information contained in the application is true, complete, and accurate to the best of their knowledge and agrees to facilitate the availability of data and materials by executing a Data Sharing Plan based on the Final NIH Policy for Data Management and Sharing should the proposed project be funded by the LRA. The institution's signing official must also sign.

17. **Submit:** After successfully passing the validate check, click the "Submit" button. An e-mail will be sent confirming submission.

Restrictions

Only one application will be accepted per applicant in a grant cycle (applications on distinct projects can be submitted to other grant mechanisms).

REVIEW CRITERIA

The most important review criteria are project significance, feasibility, innovation, and approach. Applications that are not aligned with the outlined objectives of this funding mechanism, as well as the goals and the mission of the LRA, will not be peer-reviewed.

Review Process

All eligible grant applications will be peer-reviewed by a panel of external reviewers, the results from which will be considered by the LRA Scientific Advisory Board (SAB) in the context of the LRA grant portfolio and LRA's strategic research priorities. The SAB will make funding recommendations to the LRA Board of Directors, which will, in turn, consider all previous recommendations and provide a lay perspective including patients' concerns and expectations, as well as deliberations on the business aspects of funding the recommended grants. The LRA Board of Directors will make all final funding decisions.

Review Feedback

A summary statement containing the reviewers' critiques will be provided within three months of the funding decision notification date. The LRA does not provide scores or application rankings to applicants.

AWARD TERMS AND CONDITIONS

The MCA provides up to US$500,000 over two years for mechanistic studies using patient biospecimens and up to US$1,000,000 for up to three years for small mechanistic clinical trials. Once an execution payment is made, distribution of periodic scheduled payments will be contingent upon timely and satisfactory completion of progress reports, financial reports and successful completion of project milestones, as determined by the Scientific Program Officer with input from external experts where necessary. Indirect costs must not exceed 10% of the total budget and must be included within the total annual budget.

Grant recipients must attend and present at Forum for Discovery, the LRA annual scientific conference, each year. Travel funds (up to $2,000 per year) provided by the grant must be used to pay for travel expenses related to attending Forum for Discovery meetings.

The LRA is committed to the publication and dissemination of data/information and materials developed using the organization's resources. LRA staff will work with the awardees to enable this key LRA principle while ensuring intellectual property and commercialization potential.

INQUIRIES

Scientific:
Kari Fischer, PhD
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ProposalCentral:
For assistance with the electronic grant application process, please contact ProposalCentral at pcsupport@altum.com or 800-875-2562, extension 227.

APPENDIX I

Lupus Nexus Information:

- Lupus Landmark Study Flyer & Sample Information

Application Materials:

- Research Plan Instructions

The following documents are included to provide examples of the information expected. Please download the templates from ProposalCentral.

- Research Plan Sample Templates:
  - Biospecimens Research Plan Sample Template
  - Clinical Trials Research Plan Sample Template

- Milestones Sample Templates:
  - Biospecimens Milestone Timeline Sample Template
  - Clinical Trials Milestone Timeline Sample Template