PROGRAM DESCRIPTION

Global Lyme Alliance encourages proposals for the 2018-19 Research Grant Award Program that explore regulation of Lyme disease and other tick-borne disease pathogenesis, with an emphasis on the role of an individual’s microbiome as well as genetic and epigenetic factors that might inform a “personalized medicine” approach to treatment. Proposals in other topical areas related to Lyme and other tick-borne diseases also will be accepted. Small-scale grants for proof-of-concept studies lasting one year, can be requested for between $50,000 and $100,000. Full-scale grants may request larger amounts, up to $175,000 per year to be spent over the course of a two to three-year period of funding. Clearly defined milestones will be required for both one and multi-year proposals.

KEY DATES

August 1, 2018: Applications are due by midnight EST
August 15: Review assignments to GLA Scientific Advisory Board (SAB) members
October 15: Discussion of scientific merit by SAB
January 28, 2019: Award decisions announced

BACKGROUND

Lyme disease, first identified in Connecticut in the 1970s, now afflicts at least 329,000 people in the United States annually. Caused by a bacterium spread by tick bites, Lyme disease is treatable by antibiotics in most people with early diagnosis. However, the diagnostic test for Lyme disease is highly inaccurate and is one reason for delays in treatment. About 10-20% of those treated for Lyme disease continue to suffer persisting and debilitating illness that derails normal life. Additionally, ticks can transmit other bacterial and viral pathogens that can have severe sequelae, and in some cases are fatal.

Global Lyme Alliance was formed by the merger of Lyme Research Alliance and Tick-borne Disease Alliance, with the common goals of increasing awareness of tick-borne illness and supporting evidence-based, peer-reviewed scientific research on Lyme and tick-borne diseases. Our objective is to further the understanding of such illnesses and to ultimately lead to more effective diagnostics and treatment. To date, GLA has funded over $10 million in basic science research carried out in academic institutions, and among other discoveries, has led to findings of antibiotic-tolerant persister bacteria, immune cell dysfunction, and chronic inflammation in patients experiencing persisting symptoms.

ELIGIBILITY

Applications are accepted from investigators at academic, not-for-profit institutions in the United States and abroad. Researchers who hold a Ph.D., M.D., or equivalent degree are encouraged to apply.
REVIEW PROCESS

All applications are due by midnight EST on August 1, 2018 and must be submitted online via the GrantMaker portal available on the GLA website (GLA.org).

Proposals will be reviewed by members of GLA’s SAB using the following criteria: Significance, Innovation, Investigator, Approach, and Milestones. There must be a reasonable expectation of achieving the objectives of the proposal over the course of the funding period. Investigators submitting multi-year proposals will be required to meet mutually agreed-upon milestones to ensure receipt of subsequent years’ funding. All candidates will receive notification of the outcome of their application by GLA staff and written critiques of the application will be provided.

FIVE CRITERIA
Below are descriptions of the five criteria on which the scientific merit of proposals will be evaluated:

1. **Significance.** Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

   **In addition, for applications involving clinical trials:** Are the scientific rationale and need for a clinical trial to test the proposed hypothesis or intervention well supported by preliminary data, clinical and/or preclinical studies, or information in the literature or knowledge of biological mechanisms? For trials focusing on clinical or public health endpoints, is this clinical trial necessary for testing the safety, efficacy or effectiveness of an intervention that could lead to a change in clinical practice, community behaviors or health care policy? For trials focusing on mechanistic, behavioral, physiological, biochemical, or other biomedical endpoints, is this trial needed to advance scientific understanding?

2. **Investigator(s).** Are the Project Director (PD)/Principal Investigator (PI), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi- PD/PI, do the investigators have complementary and integrated expertise; are their leadership approaches, governance and organizational structure appropriate for the project?

   **In addition, for applications involving clinical trials:** Regarding the proposed leadership for the project, do the PD/PI(s) and key personnel have the expertise, experience, and ability to organize, manage and implement the proposed clinical trial and meet milestones and timelines? Do they have appropriate expertise in study coordination, data management and statistics? For a multicenter trial, is the organizational structure appropriate and does the application identify a core of potential center investigators and staffing for a coordinating center?

3. **Innovation.** Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation,
or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

**In addition, for applications involving clinical trials:** Does the design/research plan include innovative elements, as appropriate, that enhance its sensitivity, potential for information or potential to advance scientific knowledge or clinical practice?

4. **Approach.** Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility, and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (exclusion) of children, justified in terms of the scientific goals and research strategy proposed?

**In addition, for applications involving clinical trials:** Does the application adequately address the following, if applicable?

**Study Design.** Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/ premise of the study based on previously well-designed preclinical and/or clinical research? Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results? Is the trial appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?

Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate? Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate? Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria been addressed? Are differences addressed, if applicable, in the intervention effect due to sex/gender and race/ethnicity? Are the plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection or distribution guidelines appropriate? Is there a plan to obtain required study agent(s)? Does the application propose to use existing available resources, as applicable?
Data Management and Statistical Analysis. Are planned analyses and statistical approach appropriate for the proposed study design and methods used to assign participants and deliver interventions? Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

Study Timeline. Is the study timeline described in detail, considering start-up activities, the anticipated rate of enrollment of study participants, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate? Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

Protections for Human Subjects. For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46 (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html), the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials. For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials.

Inclusion of Women, Minorities, and Children. When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals based on sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed.

5. **Milestones.** A milestone is a finding or set of findings that signal the achievement of a specific aim in the research plan. Applicants must propose one or more milestones for each specific aim. For each milestone, provide sufficient details on methods, assumptions, experimental designs, data analysis plan (if the results are quantitatively measured), and specify the quantitative criteria for measuring success and related rationale. Quantitative criteria should be robust and consistent with the state-of-the-art in the field. Most of the time, the quantitative criteria for success in the milestones will also be used for making go/no-go decisions and this should be specified. Specify the timeline for each milestone; there should be at least one milestone each year. Timely publication of research findings in peer-reviewed scientific journals, with appropriate funding attribution to GLA, is a required milestone. A reasonable timeline for anticipated submission of manuscripts should be included in this section.
ADDITIONAL REVIEW CONSIDERATIONS

Vertebrate Animals. The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals.

Biohazards. Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resource Sharing Plans. Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genomic Data Sharing Plan.

Authentication of Key Biological and/or Chemical Resources. For projects involving key biological and/or chemical resources, reviewers will briefly comment on the plans proposed for identifying and ensuring the validity of those resources.

REGULATIONS ON DISBURSEMENT OF FUNDS

Proposals may request between $50,000 and $100,000 USD for smaller scale one-year proposals and up to $175,000 per year, for two to three years, for larger scale multi-year proposals. GLA will fund 10% indirect costs as part of the total budget request. For example, a $100,000 total budget request would dedicate $90,000 and $10,000 to cover direct and indirect costs, respectively.

Permissible direct costs include:
- Personnel expenses of the Principal Investigator and non-administrative staff including salary, wage, or stipend with fringe benefits
- Supplies and materials as itemized in the budget
- Annual travel expenses of no more than $1500 for one researcher, for attendance at a nationally-recognized scientific/medical conference

Permissible indirect (also referred to as institutional) costs:
- May not exceed 10% of direct costs.

Impermissible Costs:
- Membership dues, books, journals, and tuition.

The funds awarded shall be used solely for the purposes specified in the application submitted to GLA and executed by the Principal Investigator, collaborating staff and institution in compliance with the budget appended to the application.
APPLICATION INSTRUCTIONS

A. General Requirements
   i. **Overarching Relevance**: Proposed basic/translational and preclinical research in Lyme and other tick-borne diseases, which is intended to develop a greater understanding of pathogenesis, and lead to innovative diagnostic and therapeutic treatment approaches.
   
   ii. **Required Format**: Applications must be in English, with single-spaced text using Arial 11 or 12 pt font, and half-inch margins. Page limitations must be observed for each section as described below. The overall page limit is six pages for a one-year proposal or 12 pages for a multi-year proposal.
   
   iii. **Good Standing**: Applications will only be accepted from research investigators who are currently in good standing with GLA. An applicant will automatically be in good standing unless he or she has failed to provide acceptable progress reports and accurate accounting on previous GLA-funded grants.

B. Abstracts
   This section should contain the following:
   
   i. **A lay-language abstract**: briefly describe your proposed project in ≤ 200 words using non-technical language and avoiding the use of acronyms (*i.e.*, at a level that a ninth-grader would understand).
   
   ii. **A technical abstract**: briefly describe your proposed project in ≤ 200 words using language commonly found in peer-reviewed publications and NIH grant proposals.

C. Biographical Sketch
   This section should contain the biographical sketches of the PD/PI and all key personnel, essentially anyone referenced in the budget. Do not exceed five pages per biographical sketch. A biosketch modeled on the NIH format is preferred.

D. Other Research Support
   Other support is defined as any specific funds or resources, whether governmental, non-governmental, industrial, or institutional, available to the PD/PI (and other key personnel named in the application) in direct support of their research endeavors. This should include active support and pending support.

   Information regarding active or pending sources of support available to the PD/PI (and other key personnel named in the application), whether related to this application or not, is an important part of the review and award process and must be included.

E. **Project Description**
   Limited to **six pages for a one-year and 12 pages for a multi-year proposal**, excluding face page and abstracts, supporting materials (*e.g.*, references, figures, and tables), and appendices (*e.g.*, pdf versions of recent publications most relevant to proposal [limited to two published studies] and letters of collaboration). **Any application in which the project description exceeds this limit may be rejected from consideration for an award.**

   The project description should be presented in the following sequence and contain the listed content:
i. **Face Page and Abstracts**: Includes Project Title, Applicant’s Name, Position, Institutional Affiliation, Names of other collaborators, Duration of Proposed Research, and Lay and Scientific Abstracts (1 page)

ii. **Specific Aims** (1 page)

iii. **Significance and Innovation** (1 page)

iv. **Approach**: Includes a) Previous Work/Preliminary Data, b) scientific rationale and technical details (e.g., related to experimental design and controls, methodologies, instrumentation, assays/assay development), and c) anticipated results/pitfalls/alternatives (3 pages for a 1-year proposal or 9 pages for a multi-year proposal).

ii. **Milestones** (1 page)

iii. **Supporting Materials**: Includes references, figures, and tables.

iv. **Appendices**: Includes letters of collaboration and/or pdf versions of publications immediately relevant to proposal. Clinical research protocols, if part of the application, should be submitted as Appendix material. Include Institutional Review Board or Ethical Committee approval/compliance number or indicate pending and an anticipated approval date.

*Items iii-v indicate suggested, not required, page limits although the content of ii-v cannot exceed 6 pages for a one-year or 12 pages for a multi-year proposal.*

F. **Supporting Materials**
The list of references, figures, and tables should be submitted, but do not count against the page limit in Section E of the Project Description. Illustrations should be of a number, size, and black & white or color (for the sake of legibility) that is reasonably appropriate to the scope of the project.

G. **Appendices**
If the proposal includes collaborations and participation with researchers at non-home institutions, a letter from collaborators is needed to show that they are willing and able to commit to participation in the study.

H. **Laboratory Animals Statement**
For projects which involve laboratory animals, the Institutional Animal Care and Use Committee (IACUC) Approval Date and Animal Welfare Assurance number must be provided. Non-US applicants should submit approval documentation from the equivalent of their host institute’s Animal Ethics Committee.

I. **Biohazards Statement**
An institutional statement and assurances regarding potential biohazards and safeguards must be included. This may not be applicable to applicants from countries outside the US.

*Note: The Department of Environmental Health and Safety (or equivalent office) at most institutes and universities can provide the applicant with a letter stating that the laboratory and/or the applicant is following applicable laws. This is the document that should be submitted.*

J. **Authentication of key biological and chemical reagents**
If applicable to the proposed project, briefly describe methods to ensure the identity and validity of key biological and/or chemical resources to be used (maximum one page). Key biological and/or chemical reagents can be described as: 1) reagents or samples that may differ between laboratories or over time; 2) may have qualities and/or qualifications that could influence the research data; and
3) are integral to the proposed research. These include, but are not limited to, cell lines, specialty chemicals, antibodies, patient samples, and other biologics. Commonly used standard laboratory reagents, such as buffers, commercial growth media, and other reagents that are not expected to vary need not be included.

K. Relevant Publications
A set of the applicant's publication reprints which are relevant to the proposed project may be included as PDF documents. Limit: applicants will be limited to two (2) publication reprints. Applications with more than two (2) publications appended will not be accepted.

L. Budget
Please provide a detailed budget and budget justification, especially for multi-year proposals, fully outlining specific needs for professional and technical staff and itemized supplies by category. The definition of permissible and impermissible charges is mentioned above in section on Regulations on Disbursement of Funds. This document is to be uploaded into GrantMaker as a "Supporting Document". Note that budgets are sometimes reduced below the amount requested based on availability of funds and the scientific and programmatic merit of proposals received in a particular funding cycle.

M. Signatures
The signature page is provided at the end of this document and is the last step before submitting the application. Applicants should print the signature page. The signatures of the applicant (PD/PI) and an appropriate institutional representative, such as the Institute’s Grants Officer, are required. Once signed, the document should be scanned, converted to a PDF and submitted along with the grant application.

N. Complete submission package checklist
Please assemble the following sections (excluding appended publications and budget) into one PDF document, and upload into GrantMaker.
   i. Face Page and Abstracts
   ii. Biographical sketch(es)
   iii. Other Research Support
   iv. Project Description
   v. Supporting Materials
   vi. Appendices
   vii. Laboratory animals statement and IACUC approval date
   viii. Biohazards Statement
   ix. Authentication of Key Biological/Chemical Reagents
   x. Publications directly relevant to proposal, attached as PDFs
   xi. Budget and Justification
   xii. Signature Page

FOR SCIENTIFIC AND ADMINISTRATIVE INQUIRIES CONTACT

Mayla Hsu, Ph.D., Director, Research and Science, GLA
203.989.3456 or mayla.hsu@GLA.org
2018 GLA RESEARCH GRANT APPLICATION
SIGNATURES PAGE

This page acknowledges that the investigator named below is applying for a research grant from Global Lyme Alliance and agrees to comply with the conditions stated in the program guidelines supplied by GLA.

_______________________________________________________
Printed name, Principal Investigator

_______________________________________________________
Signature, Principal Investigator

_______________________________________________________
Date

_______________________________________________________
Printed name, Institutional Signing Authority

_______________________________________________________
Title, Institutional Signing Authority and Name of Institute

_______________________________________________________
Date