Acute Rheumatic Fever Biomarker Project

The Challenge

Acute rheumatic fever initiates a slow but progressive process of heart valve damage termed rheumatic heart disease. While the incidence of acute rheumatic fever declined sharply in high income countries throughout the second half of the 20th century, rheumatic heart disease remains a significant cause of cardiovascular morbidity and mortality in in low- and middle-income countries. There is currently no sensitive and specific diagnostic test for acute rheumatic fever. Instead, a constellation of clinical and laboratory findings is used to make the diagnosis. Initially proposed in 1944, the Jones criteria have been used since to guide the diagnosis of acute rheumatic fever. These criteria have been revised in 1992 and again in 2015, but they remain imperfect.

Comparison of the number of individuals living with rheumatic heart disease to the incidence of acute rheumatic fever suggests that acute rheumatic fever is frequently undiagnosed. Better accuracy in the diagnosis of acute rheumatic fever would lead to greater and more appropriate antibiotic therapy for prevention of recurrent rheumatic fever, which is a major determinant of prognosis. Beyond the direct patient benefit, greater diagnostic certainty could reduce inappropriate antibiotic use. Additionally, a definitive diagnostic test for ARF would facilitate surveillance, accurate assessments of disease burden, better informed policy-making, and group A streptococcal vaccine development efforts.

One key barrier to the development of a diagnostic test for acute rheumatic fever is our incomplete understanding of the disease pathogenesis. While group A strep infection is well substantiated as the initiating event, the contributions of bacterial factors and host responses, which ultimately determine whether a given patient develops acute rheumatic fever, are still poorly understood. The role of pathogen and host genetic determinants remains an area of ongoing investigation, as does the immune response, both humoral and cellular, in disease development. The quest for a sensitive and specific diagnostic test for acute rheumatic fever will therefore almost certainly begin with new insights into the molecular pathogenesis of the disease.

The Goal

The challenge for the applicants is to identify a biomarker(s) for acute rheumatic fever that can serve as a basis for a test or panel of tests to accurately distinguish patients with acute rheumatic fever from individuals who do not have acute rheumatic fever.

What we are looking for

This call seeks to fund a collaborative, interdisciplinary, and scientifically rigorous network to discover a biomarker or biomarkers that can ultimately serve as the basis for a sensitive and specific diagnostic test that can accurately diagnose acute rheumatic fever in a clinical setting. It

is important that the test be able to discriminate patients with ARF from those without ARF, even in cases of recent group A strep infection. Immune response characterization, pathogen

characteristics and host factors including genetics may be included in the scientific proposal. Imaging techniques may also be incorporated in the biomarker discovery effort. Use of human samples from ARF endemic areas is anticipated and mandatory.

Key to any biomarker discovery study is the avoidance of false positive discoveries. Studies that utilize hundreds or thousands of potential biomarkers for the differentiation of a small group of patients with a specific diagnosis run a high risk of false positive discoveries (e.g., finding "significant" differences when there are no underlying biological differences). Statistical techniques to control the rates of such false positives are available and should be applied.

Successful applicants will design an innovative research program that takes advantage of the interdisciplinary collaboration of the network members. Recognizing that innovation often arises at the intersection of different fields, we welcome the recruitment of investigators with diverse expertise who may bring new approaches to bear on this topic. It is not a requirement that all members of a proposed network have a track record of scientific accomplishment in group A strep or rheumatic heart disease. In the assessment of the application, a track record of previous collaborative successes, either with prospective network members or with other investigators, will be considered a strength. For clarity, however, given the interdisciplinary character of the project, it is not necessary for members of the network to have collaborated with each other prior to the proposed network program.

To achieve the greatest global impact, an ARF diagnostic must ultimately be capable of cost-efficient large-scale manufacturing, distribution to, and implementation in low-income settings. However, such considerations lie beyond the scope of this initial discovery phase project.

Proposals should specifically address the following core elements, but investigators are welcome to propose creative strategies and designs to accomplish the core goals of this call. In addition, it is expected that study design will be refined after award through a collaborative forum involving the foundation and its scientific advisors.

Winning proposals should:

- Clearly indicate the sample sizes for each experiment and justify those sample sizes with appropriate power calculations.
- Provide a strong scientific rationale for their scientific approach to biomarker discovery whether it is candidate based, unbiased, or contains elements of both.
- Assure the integrity of the collected samples for the investigatory methods that will be employed.

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- Include expertise (at a minimum) in bacteriology, immunology, biomarker discovery, and epidemiology.
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- Clearly delineate the role of the multiple investigators.
- Describe how their scientific approach and anticipated findings will advance our understanding of the molecular pathogenesis of acute rheumatic fever.
- Provide a detailed scientific plan outlining the approach and its rationale. Although some aspects of the scientific approach will be exploratory and unbiased, a well-developed rationale for the specific proposed approach shall be part of the application.
- Demonstrate expertise in managing and analyzing large data sets.
- Contain a plan for prioritizing results and downstream follow-up studies including strategies for discovery validation.
- Demonstrate the added synergistic value of collaboration and interdisciplinary approach.
- Address the following:
    - Relevant approvals from local authorities/institutions/Government on the research methodology, sharing of data and transfer of material (if applicable) among collaborators
    - Data analysis and adherence to relevant local laws/ policies pertaining to data sharing, hosting and data protection
    - Secure handling of personally identifiable information data and research results
    - Institutional Review Boards or equivalent human study regulation strategy
    - Protocols and capacity for sample collection and storage.

We will not consider funding for:

- Proposals that do not include an investigator from a rheumatic heart disease endemic country (N Engl J Med 2017; 377:713-722).
- Proposals aimed primarily at the creation of a biobank. While use of human samples for this study is a necessity, proposals must go beyond the simple collection of human samples.
- Proposals that do not demonstrate a capacity to perform the research proposed; investigators should describe capacity for human sample collection, processing and storage, transport if necessary, and characterization, including data analysis, follow-up strategies, and test validation. The use of well-phenotyped pre-existing sample collections is permitted.
- Network programs that are based exclusively or predominantly on high-throughput screening, or other techniques best pursued in a commercial/industrial context.

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Mechanism of Funding

- One application will be selected for funding in the first year of this RFA.
- The funding mechanism will be similar to that of the traditional Leducq Network
- One network coordinator will be responsible for directing the research team.
- The funding amount is 8M USD over a five-year funding period.
- Reporting requirements Leducq networks include:
    - A biannual call with the Chief Scientific Officer to update the foundation on progress
    - A year one written and in-person progress report
    - A written and in-person mid-term review
    - A year four written progress report
    - A final written progress report due at the end of the funding period

Application Process

- Letters of intent are due January 21, 2022
- Selected applicants will be asked to submit a full application due end of May 2022
- Notification of funding decisions will be made in July 2022

Questions about the letter of intent, or about Leducq Foundation, should be directed to the Leducq Foundation office at contact@flcq.org.

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