



# *Lyme Disease Association, Inc.*

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March 13, 2019

Dr. Michael Lauer, M.D.  
Director Office of Extramural Research  
NIH Deputy Director for Extramural Research  
BG 1 RM 144  
1 Center Drive  
Bethesda, MD 20814

Dear Dr. Lauer:

The national, volunteer-run Lyme Disease Association, Inc. (LDA) is submitting this letter in response to RFI notice NOT-OD-19-077. We also have included comments on the online form of the RFI notice; this letter provides the same comments with some in an expanded form, as well as some background on the LDA.

## **Background of the LDA**

The Lyme Disease Association, Inc. (LDA) is a 501(c)(3) non-profit organization. Its mission is promoting awareness of and controlling the spread of Lyme and other tick-borne diseases (TBD) and their complications through education and other means; raising and distributing funds for Lyme and tick-borne diseases (TBD) research, education and other related Lyme and TBD issues; assisting underprivileged patients in connection with Lyme and other TBD.

On average, 97% of funds raised go directly to programs. LDA is a GuideStar Exchange Gold participant, signifying a high level of transparency and has been an approved national charity in the Combined Federal Campaign for 13 years. LDA [heads an umbrella organization, LDAnet](#), of 45 associated organizations nationwide that work together on national issues.

Last fall, the Lyme Disease Association held its 19th annual CME approved scientific conference, ***Lyme & Tick-Borne Diseases: Turning the Corner Through Research*** in Providence, RI. This educational conference was held jointly by Columbia University and was designed for medical & health professionals & researchers but was also open for registration to the general public. LDA's 20<sup>th</sup> annual conference will be in Philadelphia in September, 2019. LDA also provides scholarships to conference for individuals such as medical students and post-docs.

LDA has awarded 115 research grants since 1992, resulting in 50 peer-reviewed publications. LDA strives to fund the most relevant and cutting edge research aimed at investigating the prevention and treatment of tick-borne diseases, choosing projects led by top scientists able to publish in peer review to move the field forward. To help increase awareness and education throughout the country, LDA has provided 138 educational grants, in 22 states and 2 countries, for publications, meetings/symposia, School nurse materials, medical conferences and other purposes. LDA has a program to provide funds for children with economic difficulties who do not have/receive insurance coverage for Lyme disease treatment and has awarded \$345,000 to date.

LDA also has provided major input to state and federal legislation over more than 20 years for both

authorizations and appropriations, and LDA President Pat Smith has been testified before many different state legislative bodies and twice testified before Congress and has been a member of the first HHS Tick-Borne Disease Working Group IN DC.

## **Comments and Suggestions on the TBD Strategic Plan – Research Priorities and Other Critical Considerations**

In addition to science topics and research priorities described below, we have included some comments on organizational entities and operational/process issues important to advancing TBD research and development. As you know, a plan should be more of a pathway, rather than just a listing of research topics and required technological resources. Including information describing goals from the perspectives of engagement of organizational entities and integration into operations, processes and programs, makes the plan a more effective and efficient tool within the agency and also is more informative for the community.

### **Research gaps and/or barriers not identified in the framework**

1.) Research on diagnosis and detection and treatment needs to include late stage and chronic disease, as well as early disease. Specific discussion needs to be included in the Strategic Plan describing the strategies for developing the tools to effectively diagnose and treat late stage and chronic disease. Priority should be given to Lyme disease which has a high public health burden in the United States, has a significant patient population who are not diagnosed until late stage when treatment is more difficult, and has a significant percentage of patients who relapse and go on to develop chronic symptoms.

A goal also should be developing diagnostics with appropriate sensitivity and specificity for the detection of subclinical or low-level infection for use in disease eradication. Similar goals should be established for other TBD based on what is known regarding the sensitivity and specificity of existing diagnostic tests for those diseases and patient treatment outcomes.

Research priorities also should include developing effective treatments at all stages of Lyme disease or another TBD, and include specifics, such as determining optimal combinations of new candidate or older drugs and exploring novel combinations. Although a cure may be defined to include sustained remission, a goal of treatment should be eradication of the pathogen, in which case resurgence is not possible. As much research is pathogen specific, establishment of research priorities should weigh disease burden.

Within DMID, TBDs or select diseases and/or pathogens should be considered for inclusion in organizational entities and, as appropriate, be presented to the advisory council or leadership of the organizational entity, such as the Partnerships for Countermeasures Against select Pathogens and Centers for Excellence for Translational Research. Inclusion of Lyme disease and other TBD should be significantly based on disease burden in the U.S.

TBDs may already be integrated into programs, initiatives, and related Centers and Partnerships, but development of the TBD Strategic Plan provides a platform for assessments and evaluations.

2.) Give a high priority to systematic, thorough and comprehensive studies of the molecular and functional mechanisms that *Borrelia burgdorferi* employs to evade and subvert the immune system of the human host. It is overdue that an exhaustive study and evaluation be conducted of survival mechanisms involving immune suppression and evasion of TBD, in particular for *Borrelia burgdorferi* (*Bb*). The immunological and molecular adaptations that the Lyme disease spirochete uses for suppression and evasion of the host immune system are complex, yet eloquent in their evolutionary design to escape immune clearance by the host. This Request for Information (RFI) notes factors in tick saliva, but, as well known, that is only the tip of the iceberg. Plans for addressing the range of well-documented mechanisms need to be explained.

A prime example of the type of workshop that should be held for *Borrelia burgdorferi* and, as appropriate, other TBD pathogens is a workshop NIAID held on September 19 – 20, 2017, *Molecular Mechanisms and Immune Consequences of Pathogen Reservoirs: Battling Unseen Enemies*. The workshop included multidisciplinary participants to consider shared and unique characteristics of pathogens that shield themselves from detection by the host immune system in order to understand host immune mechanisms that maintain privilege and modulated inflammatory responses. *Kinks in the Armor – Bypassing the Immune Barriers of the Skin*, jointly hosted by DAIT and DMID in 2016 – addresses the one immune evasion specifically mechanism addressed in the RFI framework.

It is critical that the multiple defense mechanisms of *Bb* be evaluated and recognized by the premier research agency in the world. Understanding these mechanisms and their significance underpins the ability to develop effective diagnostics and treatments. Numerous peer-reviewed articles have been published on specific mechanisms and scientists have put together extensive bibliographies. Excellent studies were conducted nearly 20 years ago and longer on *Bb* and immune cells, such as independent-T-Cells, B-cell activations and humoral responses.

### **Resources required or lacking that may be critical to advancing TBD research priorities**

1.) NIH should evaluate existing government and private biorepositories for TBD and assess whether specimens and samples meet the current and anticipated needs of researchers and are readily available to researchers and whether there are barriers to researcher access, such as cost, handling, storage requirements, or other factors such as requirements for researchers to share rights relating to publications, patents, commercialization or other rights that may otherwise belong to a researcher or his/her institution. An evaluation also should be made of the availability of and access to required animal and animal strains of whatever nature, including cost, care, maintenance, facilities, etc.

2.) Community-based physicians, advocates and patients are potentially valuable resources and should be utilized in Strategic Planning, Research Portfolio Design, Programs, Special Initiatives, Grant Proposals and Peer Review.

It is noted that this RFI solicits input from clinical practice and advocacy communities and the general public. An up-front solicitation for comments on the TBD strategic plan is not sufficient. TBD, most notably Lyme disease, patients have suffered and treating physicians have been constrained by a lack of formal consideration of the experiences and perspectives of those groups, and the rate of progress of the science on TBD could have been accelerated by recognizing the importance of the perspectives and experiences of patients and community-based physicians.

While much of the literature on Community-based Participation Research (CBPR) addresses behavioral change of individuals, groups, and communities, the value of CBPR has been extended to other types of research, and a much broader systematic evaluation for incorporation of CBP into NIH activities relating to TBD needs to be undertaken.

NIH should establish a Community-Based Participation (CBP) initiative for TBD, to include identification of community-based resources, such as patient registries. NIAID should partner with the Office of Extramural Research, Office of Intramural Research and the Center for Scientific Review to evaluate how community-based perspectives can add significant value to and be incorporated into the broad range of TBD activities. If there is no significant value added, then it is not worth doing, but certainly some mindsets will need to be changed to be capable of envisioning the value.

In addition to the establishment of a CBP in TBD Initiative, community-based physicians, and, as may be appropriate, advocates and/or patients should be a resource, even as temporary members or guest speakers,

at NIAID Council meetings and meetings of the subcommittees. DMID and DAIT should evaluate activities and organizational entities for inclusion of community based physicians and other individuals, particularly for workshops and planning initiatives.

Community-based physicians should provide input to the development of TBD research portfolios in NIAID or other NIH components. RFAs for TBD research should consider requiring applicants to partner with community-based physicians. Grant review panels for RFAs, RO1s, and other types of applications should include community-based physicians as permanent or temporary members on standing committees or temporary review committees. The use of patients/advocates, as appropriate, should be considered as temporary members of a standing committee or as members of a temporary, special committee.

### **Emerging scientific advances or techniques in basic, diagnostic, prevention, or therapeutic research that may accelerate NIH research priorities detailed in the framework**

1.) NIH and NIAID researchers' access, manage, analyze, integrate and make available huge amounts of biomedical data, which are generated by intramural and extramural sponsored- researchers, as well as other researchers in the biomedical research ecosystem. In addition to the huge amounts of data generated from basic biological research, biomedical "Big Data" also encompasses clinical data from hospitals, patient electronic medical records, data from imaging modalities, and electronic medical devices, as well as other sources. Anywhere along the spectrum from basic research to translational to clinical research, to clinical practice big datasets may be generated. Increasingly, agency and academic researchers may use clinical datasets as an emerging resource to inform their upstream research.

NIH and NIAID are driving force in the Omics revolution -- genomics, epigenetics, transcriptomics, proteomics, metabolomics, and microbiomics – and researchers are generating and analyzing huge amounts of data on infectious disease pathogens.

In January 2017, Dr. Maria Giovanni provided to the NIAID Council a comprehensive overview of the various programs that fall under the purview of the DMID Office of Genomics and Advanced Technologies. She noted that NIAID/DMID has made a significant investment in genomics, functional genomics, structural genomics, systems biology, proteomics and bioinformatics resources, which provide the research community with data sets, technologies, and computational tools to study infectious diseases. She described how NIAID has been at the forefront, assisting scientists with all aspects of big data, including data access, data management, training, data analysis, workspaces, and computational tools to develop the next generation of modeling, statistical methods, and machine learning algorithms that can be applied to infectious diseases research; providing new strategies for developing diagnostics and therapeutic interventions; and identifying predictive markers of disease and health.

NIAID also reported that the NIAID Bioinformatics Resource Center would make publicly available relevant clinical data or other metadata that are essential for the biological interpretation of genome sequence data and other omics and experimental data sets.

We do not know the penetration of data on TBDs, including Lyme disease, into these and other infectious disease data-driven initiatives, projects, and centers of NIH, NIAID, or their data-sharing partners, but it is critical that TBDs be systematically considered at all appropriate junctures. NIAID funded centers and projects should consider TBD pathogens as appropriate, such as the Bioinformatics Resource Centers for Infectious Diseases, Genomics Centers for Infectious Diseases, the Office of Genomics and Advanced Technologies, the Infectious Biology for Infectious Diseases Program, as well as other NIAID-funded large-scale centers and projects.

## Other Comments

1.) DMID and DAIT activities in support of development of TBD vaccines should be described in a vaccine section of the Plan. The minutes for the NIAID Council meeting held on September 17, 2018, described an Initiative, unanimously approved during the meeting, “Targeted Prevention for Tick-Borne Diseases” to support the development of prevention approaches for TBD such as identification and testing of antigens for human vaccines against tick-borne pathogens or modification/improvement of candidate vaccines. The need to include multiple, relevant tick-borne pathogens under the initiative was stressed. Planned efforts need to be elaborated in the Strategic Plan and the goal of transparency explicitly expressed. In deference to patient, advocate and community physicians experiences with the withdrawn LYMERix vaccine, the description should include special initiatives, ensuring both safety and efficacy of vaccines intended to prevent a TBD or combinations of TBDs, including, at a minimum, a description of enhanced oversight to provide assurances to the TBD community that scientific concerns relating to vaccine safety have been fully addressed and that effectiveness is at a high level.

Also, the description needs to include the strategy for communicating all important and relevant information to the TBD community, including patients, advocates and community-based physicians. In fact, the NIAID Council Minutes for the Sept. 17, 2018 minutes did state that the DMID “Subcommittee also noted that, given the history of the human vaccine for Lyme disease, which is no longer available, it is critical that the scientific community communicate appropriately and effectively with the public regarding prevention approaches for tick-borne diseases.” The concept of “Critical” needs to be remembered and conveyed in the Strategic Plan.

2.) The Strategic Plan should describe how the total NIH research portfolio on TBD will be strengthened by expanding TBD studies to other NIH Centers and Institutes and by considering TBD in Trans-NIH Initiatives.

Many Institutes have expertise and primary responsibility/jurisdiction for areas of science and medicine that are critically important to TBD. NINDS and NIAMS may expedite TBD research on neurologic Lyme, joints, tissues, and the skin and related aspects of the immune system. NIBIB is cross-cutting and may spur progress on imaging of TBD throughout the human anatomy. NICHD may offer valuable leadership in addressing concerns of children with TBD, particularly Lyme disease, for which disease approximately 37% of patients are under the age of 18. NHLBI and NEI could provide expertise for specific tissue and functional areas. NIMH involvement could lead to more effective interventions and outcomes for patients. NIGMS’ foci on diagnosis/treatment/prevention, the whole human organism, and diseases affecting multiple organs could offer significant insight for TBD research, as well as fostering development of the next generation of TBD scientists and the development and access to research resources.

Overall needed funding for TBD research also may be strengthened by broadening the portfolio to other Institutes and Centers.

Trans-NIH Initiatives should actively consider inclusion of TBD. An example of such a previous trans-NIH initiative was 2017 workshop on *Chronic Inflammation Biomarkers in Disease Development and Prevention*. Having other NIH Institutes and Centers share the TBD research portfolio would strengthen consideration of TBDs in NIH led, cross-cutting initiatives.

3.) It would be beneficial to the TBD community and the general public and serve to expedite progress on TBD within NIH to include within the Strategic Plan a vision for seminars, workshops and other public meetings. All desirable public meetings and workshops cannot be known at the beginning of a 5-year plan, but the need for some core meetings may be known.

The Strategic Plan should provide both the intent to and the strategy for holding seminars, workshops and other scientific or public meetings to help inform the agency, researchers and the community on critical issues

for advancing the basic and translational science on TBD to develop the tools to effectively prevent, diagnose, treat and cure those diseases. At least some workshops, seminars, scientific meetings, or public meetings could be identified in the strategic plan to jump start the path forward.

A few examples of workshops/meetings that may be worthwhile to include in a strategic plan are:

*Molecular Mechanisms and Immune Consequences of Borrelia burgdorferi and other TBD Pathogens and Assessments of the Relative Importance/Effectiveness of the Various Mechanisms;*

*The use of biosignature and biomarker profiles in diagnosis and treatment of TBD.*

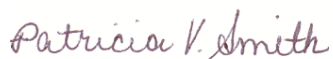
*Perplexing Issues and barriers to designing and recruiting for clinical trials for Lyme disease, other TBD, and co-infections, including the effective use of patient registries and other community-based resources for subject identification and recruitment.*

*The use of patient registries and de-identified patient databases as a resource for researchers in study design and implementation.*

*The potential for the use of small business grant mechanisms to foster development of diagnostics, treatments, or prevention of TBD.*

Thank you for the opportunity to submit comments in response to your RFI. The TBD Strategic Plan is of enormous interest to everyone in the tick-borne disease community.

Sincerely,



Patricia V. Smith  
President

/s/

Timothy S. Lynagh  
Board Member and Policy Advisor