

# Tick-Borne Disease Research Program

## Strategic Plan

### INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,<sup>1</sup> the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Tick-Borne Disease Research Program (TBDRP). The TBDRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the TBDRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The TBDRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

### TBDRP BACKGROUND AND OVERVIEW

The TBDRP was established in fiscal year 2016 (FY16), when the efforts of Lyme disease advocates led to a Congressional appropriation of \$5 million (M). The intent of the TBDRP is to support innovative and impactful research that addresses fundamental issues and knowledge gaps in tick-borne diseases. In a letter from the House Lyme Disease Caucus to the Chairman of the Congressional Subcommittee on Defense requesting this appropriation, it was noted that "Lyme and other tick-borne diseases are a significant threat to military forces and their dependents, not only at domestic bases and training facilities, but worldwide."<sup>2</sup> The TBDRP was urged to "recognize that tick populations and the diseases they carry are not static, but are emerging and growing threats in many regions, such as the Southeastern and Midwestern U.S.," and that many of these newly discovered TBDs are "becoming more prevalent and deadly." The need for funding "for research on TBDs, including to develop more sensitive and accurate diagnostic tests for Lyme and to increase understanding of the full range of Lyme disease processes, as well as the numerous mechanisms that may allow organisms to persist post-treatment," was detailed. The TBDRP now offers a voice to the often unheard individuals living with Lyme disease or other tick-borne illnesses via representation on our peer review and programmatic panels, along with scientists, clinicians and other reviewers. Through the work of the TBDRP Programmatic Panel, the program has developed the following vision and mission to address Congressional intent.

**VISION:** To prevent the occurrence, better diagnose and resolve or minimize the impact of Lyme disease and other tick-borne illnesses, with emphasis on burden of disease

**MISSION:** To understand the pathogenesis of Lyme disease and other tick-borne illnesses and to deliver innovative solutions to prevent, diagnose, and treat their manifestations for the benefit of U.S. Service members and the American public





**FUNDING HISTORY**

The TBDRP has received Congressional appropriations of \$5M annually since FY16, for a total of \$15M in funding for the period FY16–FY18. A total of 13 projects have been funded by the TBDRP.<sup>3</sup>

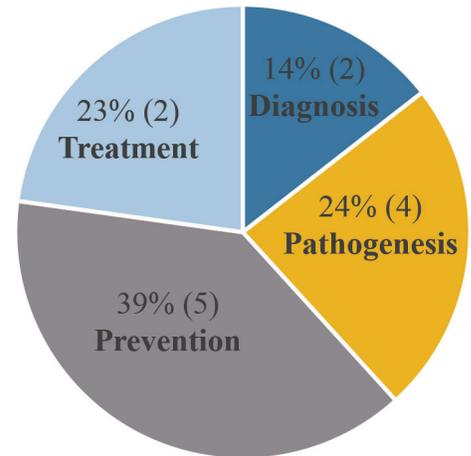
**RESEARCH PORTFOLIO AND RESEARCH ACCOMPLISHMENTS**

As shown in the figure on the right, the TBDRP established four focus areas to address research gaps in tick-borne diseases: Diagnosis, Pathogenesis, Prevention, and Treatment. Prevention and Pathogenesis are the two focus areas receiving the greatest investment, together comprising 63% of the TBDRP portfolio to date.

In FY16, the TBDRP spent 44% of its annual research budget on projects focused on treatment, 31% on pathogenesis, 16% on prevention, and 9% on diagnosis. Key studies initiated in FY16 focused on innovative treatment approaches for persistent Lyme disease and rickettsial infections, host-pathogen interactions in ehrlichiosis, development of a human Lyme disease vaccine, heritable immunization of white-footed mice to interrupt the natural cycle of tick-borne disease, and development of a genomic biomarker assay for direct detection of Lyme disease and other tick-borne infections.

In FY17, the TBDRP spent 32% of its annual research budget on projects focused on pathogenesis, 48% on prevention, and 20% on diagnosis. FY17 funded awards included studies of mechanisms involved in host protective immunity to the Lyme disease pathogen and mechanisms of the persistence of spirochetes; a live attenuated multivalent vaccine against a number of tick-borne pathogens; an OspA-specific human monoclonal antibody as a pre-exposure prophylactic for Lyme disease; and metabolic biomarkers of Lyme disease in urine and transmission of the alpha gal allergen. Research funded in FY17 will begin no later than 30 September 2018.

**FY16–FY17 TBDRP Portfolio by Focus Area\***



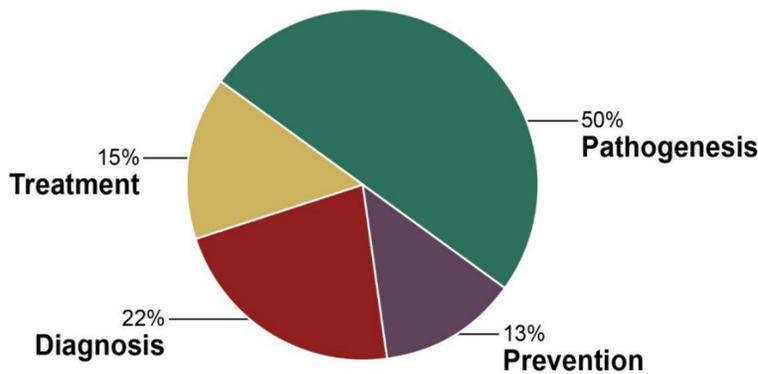
\*Percentages of total investment (number of awards)

**RESEARCH AND FUNDING ENVIRONMENT**

**STATE OF THE SCIENCE**

The figure below depicts the total federal intramural and extramural investment in studies of the diagnosis, pathogenesis, prevention, and treatment of tick-borne diseases during the period FY11–FY17. The majority of the funded studies have been focused on disease pathogenesis. Data generated using NIH RePORTER indicate that, during the period FY11–FY17, ~40% of total federal intramural and extramural funding for tick-borne diseases has been focused specifically on Lyme disease (see figure containing bar graph on page 3). Despite these funding efforts, there are still numerous challenges and gaps in knowledge associated with research in the diagnosis, pathogenesis, prevention, and treatment of Lyme disease, as well as all other tick-borne diseases.

**Total Federal Intramural and Extramural Funding for Tick-Borne Disease Studies by Focus Area (FY11–FY17)\***



\* Data generated using NIH RePORTER (<https://projectreporter.nih.gov/reporter.cfm>).



Diagnosis of tick-borne illnesses and determining appropriate treatment and therapy remain a challenge. The current standard in Lyme disease diagnosis, for example, is a two-tier testing procedure that starts with an enzyme-linked immunosorbent assay (ELISA) and could involve a subsequent Western blot. Other options include polymerase chain reaction (PCR), antigen detection tests, and culture. All of these methods have limitations in sensitivity and run the risk of false negative results due to many factors, including failure to develop an antibody response if tested too early. Developing more sensitive and accurate diagnostic tests and discovering diagnostic biomarkers would remove barriers that prevent patients from getting treatment.

Continued efforts in research are needed to better understand tick-borne disease pathogenesis, including host-pathogen interactions and the human immune response to these pathogens. Without understanding the biology, clinical problems cannot be adequately addressed. Understanding the pathology underlying tick-borne diseases and persistent symptoms will aid in diagnosing patients with persistent Lyme disease and differentiating between patients presenting with Lyme disease and those presenting with other diseases with similar symptoms. In addition to improved diagnosis, understanding pathogen evasion of the immune system could lead to identification of more effective therapeutics, which has the potential to provide the basic knowledge needed to develop effective vaccines.

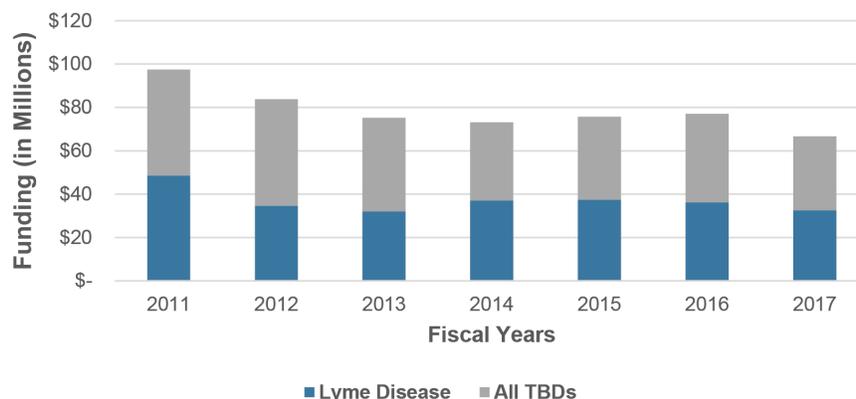
Prevention is the first line of defense in minimizing the public health burden of tick-borne diseases. Prevention starts with personal protection measures and having access to easy-to-use, affordable methods of prevention. Currently, there are no licensed human vaccines for tick-borne diseases on the market. Prevention also relies on tick-targeted control interventions that individuals are actually willing and able to implement. Developing more acceptable and proven methods of prevention that are safe for humans and the environment would be ideal.

Currently, the most optimistic treatments for Lyme disease are combination therapy regimens using antibiotics. There are two current, divergent standards of care for Lyme disease. The Infectious Diseases Society of America advises resolving infection with a short course of antibiotics, but suggests that infection does not persist in the body post-treatment. The International Lyme and Associated Diseases Society advocates for individualized treatment based on symptom severity, presence of co-infections, patient response to treatment, and other factors. Treatment recommendations vary depending on whether the infection is caught at an early stage or at a late stage with persistent symptoms. Investigating new and optimized therapeutic options for tick-borne diseases in animal models can be used, first to elucidate the mechanisms underlying how the drugs work, and second to better guide treatment protocols for acute and persistent illnesses.

## RESEARCH FUNDING LANDSCAPE

To maximize the TBDRP’s ability to fill research gaps and leverage the findings of others, it is important for the program to understand the focus and successes of other major funders of tick-borne disease-related research. The program’s approach to coordinate with other major funding agencies is facilitated by incorporating individuals from those federal organizations into the TBDRP Programmatic Panel. These representatives can provide data to supplement what is publicly available via sources (such as Federal RePORTER) and can provide more information about the efforts being funded by their agencies and how to work synergistically, while avoiding duplication of effort. During the period FY11–FY17, the total intramural and extramural investment in tick-borne disease studies by federal agencies equaled approximately \$549 million. Of the total investment, NIAID funded 78%; the Centers for Disease Control and Prevention (CDC) funded 12%; and the remaining 10% was funded by other NIH departments. The figure below depicts the total and annual federal intramural and extramural funding for research on all tick-borne diseases during FY11–FY17.

**Total Federal Intramural and Extramural Funding for Tick-Borne Disease Research (FY11–FY17)\***



\* Data generated using NIH RePORTER <https://projectreporter.nih.gov/reporter.cfm>.



## OTHER MAJOR RESEARCH INITIATIVES

There are a number of research and funding programs aligned with the vision and mission of the TBDRP. In addition to the primary federal funders noted previously, the National Science Foundation, Biomedical Advanced Research and Development Authority (Department of Health and Human Services), and the Deployed Warfighter Protection Research Program (part of the Department of Defense [DoD]) provide a nominal amount of funding in the area of tick-borne disease research.

In addition, numerous private funding initiatives are spearheaded by advocacy groups that provide a voice to individuals living with Lyme disease or other tick-borne illnesses who may otherwise be unheard. These initiatives include, but are not limited to, the Lyme Disease Association, Global Lyme Alliance, Bay Area Lyme Foundation, LymeDisease.org, Lyme Innovation, Steven & Alexandra Cohen Foundation, National Research Fund for Tick-Borne Diseases, Inc., Focus on Lyme, and Stand4Lyme Foundation.

Information on tick-borne disease surveillance and/or management from many established organizations is used to help inform TBDRP strategy. Such groups within the DoD include the Global Emerging Infections Surveillance section of the Armed Forces Health Surveillance Branch, as well as the Armed Forces Pest Management Board. Additionally, surveillance and/or management efforts are underway by the U.S. Department of Agriculture, U.S. Geological Survey, National Park Service, Environmental Protection Agency, and the CDC, including their regional Centers of Excellence.

As a result of efforts by these various federal and private programs and others, several valuable resources are aligned with the TBDRP vision and mission and are available to investigators. The DoD has developed VectorMap, which provides disease maps, mapped collection data, and distribution models for disease vectors, including ticks, while the CDC maintains a passive arbovirus surveillance system known as ArboNet. Tick-borne disease biorepositories include the CDC/NIH Lyme Serum Repository, the Lyme Disease Research Foundation Repository at the Johns Hopkins Lyme Disease Clinical Research Center, the Columbia Specimen Resource Repository at the Columbia University Lyme and Tick-Borne Diseases Research Center, and the National Lyme Disease Biobank established by the Bay Area Lyme Foundation. In addition, MyLymeData has established an extensive, big data-driven Lyme disease patient registry. The transformational research at these centers and the data available via these resources further shape the environment in which the TBDRP operates.

## STRATEGIC DIRECTION

Lyme and other tick-borne diseases are both a significant burden on the health and welfare of the American public and a particular threat to military Service members and their families at military installations and training facilities. Because there is no clear understanding of the full range of these disease processes, including the implications of simultaneous co-infections, the diagnosis and treatment of civilians and military personnel are further complicated.

The strategic priorities of the TBDRP remain focused on supporting new ideas and discovery, as well as established research to advance the development of improved methods of prevention, direct detection, and treatment to reduce the public health burden of tick-borne diseases. As the underlying pathogenesis of tick-borne diseases (including the cause of persistent symptoms in Lyme disease) continues to be elucidated, the TBDRP aims to support researchers in building on their findings to pursue further optimization and preclinical development, as well as eventual validation and translation of these advancements.

These TBDRP priorities are based on the current state of the science, as well as the current research funding landscape and Congressional intent, as described above. Taking into consideration the TBDRP appropriation amount and the mission of other aligned research programs, this approach is not intended to address all the needs of the community.

## STRATEGIC GOALS

The TBDRP's strategic goals are aimed toward addressing the gaps in the diagnosis, pathogenesis, prevention, and treatment of the numerous tick-borne diseases that increasingly impact civilian and military populations. The TBDRP seeks to invest in and make progress toward the following goals/priorities; however, investigators are encouraged to propose their own best ideas. The program does not define what types of knowledge or technology products will be funded and is open to any aspect of the current needs defined by the state of the science at any particular time. Near-term and medium- to long-term strategic goals are detailed below.

## NEAR-TERM

The TBDRP will address its FY18 focus areas (diagnosis, pathogenesis, prevention, and treatment) via the following near-term strategic goals.

Support research toward improving detection and diagnosis of tick-borne diseases, including the following:

- Development and validation of accurate diagnostics for Lyme disease and co-infections and/or other tick-borne diseases



- Discovery and validation of biomarkers to identify tick-borne diseases or their products in humans
- Identification of diagnostic biomarkers for Lyme disease that distinguish between active infection and previous exposure and/or monitor response to treatment

Support research toward better understanding the pathogenesis of tick-borne diseases at the cellular and molecular level, including the following:

- Investigation into immunological mechanisms of immune protection for Lyme disease or other tick-borne diseases
- Investigation of the complex biology of Lyme borrelia in the host (beyond in vitro studies), including its survival, evasion of the host immune system, and subversion of the effectiveness of antibiotics
- Identification of biomarkers that aid in exploring underlying mechanisms of persistent symptoms associated with Lyme disease

Support research toward more effective and widely acceptable measures for the prevention of tick-borne diseases, including the following:

- Identification, validation, and/or improvement of tick-targeted prevention and control interventions
- Investigation of human vaccines for tick-borne diseases

Support research toward effective tick-borne disease treatments, including the following:

- Investigation of antibiotic combinations and/or therapeutic options for treating acute and persistent illness

## **MEDIUM- TO LONG-TERM**

Moving beyond the near term, the TBDRP will continue to build its funding efforts to address the focus areas detailed above (diagnosis, pathogenesis, prevention, and treatment). Supporting strategic goals and specific focus areas will evolve on an annual basis. For example, as a medium- to long-term priority, the TBDRP will consider additional emphasis on supporting more translational studies in disease transmission and surveillance to enhance the area of tick-borne disease prevention.

Potential long-term supporting goals will be added to or possibly replace some of the near-term strategic goals should advances in the research of tick-borne disease pathogenesis make them more viable and impactful to the program and the community. However, the scope and scientific nature of medium- to long-term goals will depend on the funding available in the future and the progress made in the field as a whole.

## **INVESTMENT STRATEGY**

The TBDRP's annual investment strategy outlines the program's approach to soliciting the type of research that will facilitate accomplishment of its near-term strategic goals, while ensuring synergy of program investments with other funding agencies. The program aims to invest in basic, translational, or clinical studies through a number of mechanisms that promote idea development across the entire career-development pipeline. This investment strategy will be re-evaluated and updated as necessary during the annual TBDRP Vision Setting meeting, taking into account the state of the science and available appropriations at future points in time.

## **NEAR-TERM**

To achieve the vision of the TBDRP, the near-term investment strategy includes both idea- and career development-focused award mechanisms, which align with the near-term strategic goals. Current and archived funding opportunities can be accessed via the CDMRP website.<sup>4</sup>

The TBDRP Career Development Award is being offered for the first time in FY18 and is designed to support early-career investigators under the mentorship of an experienced tick-borne disease researcher. The TBDRP Idea Award, which has been offered since the program's inception, is intended to support studies based on conceptually innovative, new ideas in tick-borne disease research. The studies should not be incremental in nature, however, and preliminary data are not required. The TBDRP Investigator-Initiated Research Award, also offered since the program's inception, is designed to support studies that are based on established ideas in tick-borne disease research and have clear short- and long-term impacts. These studies can be any phase from basic through translational research, and preliminary or published data to support feasibility are required.



## **MEDIUM- TO LONG-TERM**

In the medium to long term, the TBDRP intends to continue funding basic research covering a wide range of tick-borne diseases with a broad set of unanswered research questions via idea-focused award mechanisms. Scientific priorities will be assessed annually during the Vision Setting meeting and may change over time. Depending on the progression of the field and availability of funds, the TBDRP may move toward funding more translational or clinical research via appropriately more complex and tailored award mechanisms. The program also may consider promoting expansion awards to build on the progress made through efforts already initially funded by the TBDRP, or it may consider promoting more collaborative award mechanisms if the need arises.

## **MEASURING PROGRESS**

### **NEAR-TERM OUTCOMES**

The TBDRP will measure its near-term success by assessing the receipt, funding, and management of high-quality applications that contribute toward meeting the program's focus areas and strategic goals. In the near term, the TBDRP will monitor the responses to award mechanisms and the number of funded applications for each of its overarching program priorities.

Award progress, including near-term publications and other outcomes, will be tracked on a quarterly reporting basis and will vary based on the stage of the funded research project. This progress will be provided to the TBDRP Programmatic Panel as a tool to aid in their development of the annual program investment strategy. As the TBDRP evolves, the program will encourage more research in focus areas that are understudied.

### **MEDIUM- TO LONG-TERM OUTCOMES**

Medium- to long-term success will be evaluated based on how research funded by the TBDRP advances the strategic goals or contributes to progress in the field of tick-borne disease research and patient care. Contributions to progress in the field include measurable long-term outcomes aligned with each strategic goal, such as publications, patents, clinical trials, commercialization, and changes in standard of care.

The TBDRP will work with the major federal funders of tick-borne disease-related research, as well as other major research initiatives, to monitor the overall tick-borne disease research funding landscape. Together, the overall research and funding environment, as well as the TBDRP's research portfolio and research accomplishments, will drive the program's strategy moving forward at both the annual near-term investment strategy level and the long-term strategy levels.

## **REFERENCES**

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process, a Report of the National Academies of Sciences, Engineering, and Medicine*. 2016. The National Academies Press, Washington, DC. (<http://nationalacademies.org/hmd/reports/2016/cdmrp.aspx>).
2. [https://www.lymediseaseassociation.org/images/NewDirectory/Government/2015\\_LymeDefenseAppropsSigned15.pdf](https://www.lymediseaseassociation.org/images/NewDirectory/Government/2015_LymeDefenseAppropsSigned15.pdf)
3. FY18 awards will not be recommended for funding until early 2019.
4. <http://cdmrp.army.mil/>