Current Efforts in Lyme Disease Research, 2019 Update

Original Report 2015
Current Efforts in Lyme Disease Research

Table of Contents

Introduction ............................................................................................................................... 2
History of NIAID’s Lyme Disease Research Program ............................................................. 3
Ongoing Research.................................................................................................................... 3
  Fundamental Studies of Pathogen Biology ............................................................................. 4
  Studies on Persistence ........................................................................................................... 5
  Studies on Human Immunity to Infection ............................................................................. 5
  Studies on the Vector ........................................................................................................... 6
  Studies on Lyme Disease Diagnostic Testing ....................................................................... 6
  Studies on Lyme Vaccines ..................................................................................................... 7
  Clinical Studies ................................................................................................................... 7
Recent NIAID Lyme Disease Scientific Advances ................................................................. 8
NIH Collaborations with Other Federal Agencies and External Organizations ................. 13
Funding Opportunities and Research Resources ................................................................. 13
Future Plans/Directions ........................................................................................................ 13
Current Efforts in Lyme Disease Research

Introduction

Ticks can transmit a variety of disease-causing pathogens, including bacteria, viruses and parasites. Lyme disease, the most prevalent of the tick-transmitted infections in the United States, is named after a town in Connecticut where a group of arthritis cases in children appeared in the early 1970s. By the mid-1970s, the symptoms of the disease were being described, and the pathogen that causes Lyme disease was identified in the early 1980s by scientists from NIAID and Stoney Brook University. The bacterium, transmitted by deer ticks, is now named *Borrelia burgdorferi* after Willy Burgdorfer, an NIAID scientist who co-discovered the pathogen with other scientists.

Reported cases of Lyme disease, like most tickborne diseases, have been increasing in the United States. In 2017, 42,743 confirmed and probable cases were reported to the U.S. Centers for Disease Control and Prevention (CDC), up from 36,429 the previous year. Those cases do not represent the true incidence of Lyme disease, as CDC estimates the number to be closer to 300,000 annually.

The initial symptoms of Lyme disease can vary, though they often include a circular or oval “bullseye” rash called erythema migrans, which spreads from the bite site over several days. Other common symptoms include fever, headache, stiff neck, body aches, and fatigue. Untreated, the infection can spread and lead to facial or Bell’s palsy (weakness of the muscles on one or both sides of the face), meningitis, and/or heart involvement. Additionally, some individuals may develop Lyme arthritis, usually in the large joints such as the knees.

The diagnosis of Lyme disease is based on signs and symptoms of the infection, history of exposure to infected black-legged ticks, and laboratory tests. Serologic tests may take several weeks after infection to become positive, highlighting the need for new diagnostic tests that can detect the earliest stages of infection. Moreover, the current two-tier standard test is open to subjective interpretation. New, rapid, unequivocal, point-of-care diagnostics would improve diagnosis and patient care.

In most individuals, Lyme disease is effectively treated with oral antibiotics. Even with treatment, approximately 10-20 percent of patients report a range of continuing symptoms, collectively called Post-Treatment Lyme Disease Syndrome (PTLDS). The reasons for these symptoms are unknown, though causes such as autoimmune disease, persistent infection, other illnesses, or chronic inflammatory processes triggered by non-living bacterial components have all been considered.

Even in the absence of known tick exposure or laboratory-confirmed *B. burgdorferi* infection, some individuals report extended, often debilitating symptoms attributed to Lyme disease. This “chronic Lyme disease” syndrome has been dismissed by many clinicians and scientists, while others defend the diagnosis. Regardless of the cause, the suffering is real, and additional research is necessary to elucidate what causes these symptoms, including investigations of *B. burgdorferi* and any role the bacteria may play in long-term disability.
History of NIAID’s Lyme Disease Research Program

Since the seminal discovery of *B. burgdorferi* in 1981, NIAID has supported an extensive and diverse research portfolio that encompasses basic and clinical research studies on Lyme disease. These studies are conducted by extramural and intramural investigators, including intramural scientists at NIAID’s Rocky Mountain Laboratories in Hamilton, Montana and at NIAID laboratories in Bethesda, Maryland.

The Institute has remained at the forefront of Lyme disease research in addressing fundamental questions essential for progress in the field. NIAID’s many contributions include:

- Helping to sequence the entire genome of *B. burgdorferi* and improving the molecular tools available for studying the organism and the host response to infection. Without these early tools, research on the basic biology and disease-causing properties of *B. burgdorferi* would have lagged far behind that of other bacteria.

- Sequencing the genome of the tick that transmits *B. burgdorferi*, in the northeastern, mid-Atlantic, and north-central United States: the blacklegged or deer tick, *Ixodes scapularis*. This sequence has been important in understanding the genetic basis of tick biology and tick/*Borrelia* interactions. Genomic data and bioinformatics tools for researchers are available in VectorBase.

- Supporting researchers to sequence the genome of the white-footed mouse, *Peromyscus leucopus*, the primary wild animal reservoir for *B. burgdorferi*.

- Supporting basic research on disease transmission, including research on ticks and their role in the disease cycle, tick biology and behavior, and tick/pathogen and tick/host interactions.

- Supporting fundamental research on the human immune response to *B. burgdorferi*, identifying bacterial factors involved in that response, and studying disease pathogenesis. The identification of potential biomarkers of *B. burgdorferi* has informed current diagnostic tests and continues to be explored for development of improved tests.

- Addressing questions concerning the efficacy of long-term antibiotic therapy for the treatment of late or “chronic Lyme disease” through the support of three placebo-controlled clinical trials. The peer-reviewed, published results of these studies demonstrate that prolonged antibiotic therapy does not have a sustained benefit and that risks to the patient outweigh the benefits.

- Investigating the control of Lyme disease and other tick-borne pathogens by better understanding vector interactions with the pathogen and vertebrate host. Tick control approaches may involve the use of repellents and the treatment of wildlife and pets.

Ongoing Research

The overarching goals of the NIAID Lyme disease research program are to develop better
methods of diagnosing, treating, and preventing this disease in humans. To accomplish these objectives, the NIAID Lyme disease research portfolio includes a broad range of activities focusing on the pathogen, the vector, and the vertebrate hosts. Guided by the NIH Strategic Plan for Tickborne Disease Research, this research is conducted by extramural and intramural investigators and spans basic science through human clinical research studies. Many projects are investigator-initiated efforts, but several are the result of targeted grant and small business initiatives. NIAID has these initiatives to actively “grow” the Lyme disease research portfolio to address high-priority areas such as persistence of infection after antibiotic treatment and the development of diagnostics for both early and late-stage disease.

NIAID uses all of these approaches to maintain a dynamic and multifaceted Lyme disease research portfolio that addresses key basic, translational, and clinical research questions. The NIAID Lyme disease research portfolio includes systematic studies on microbial physiology; molecular, genetic, and cellular mechanisms of pathogenesis; mechanisms of protective immunity; vector biology and ecology; vector/pathogen and vector/vertebrate host interactions and influence on disease transmission; effect of co-infections with other tick-borne diseases; efficacy of different modes of antibiotic therapy; and development of more sensitive and reliable diagnostic tests for both early-and late-stage Lyme disease.

Additional information on NIAID-funded Lyme disease research and tick-borne disease research is available on the NIAID Lyme disease website. Detailed information about NIH funding for Lyme disease research is available on the NIH Categorical Spending page, accessible from the NIH Research Portfolio Online Reporting Tools (RePORT) website. Here project lists are available that show funding amounts for each project and the NIH Institute or Center that has provided the support. These lists can be downloaded for further analysis. All funded extramural NIAID research projects are competitively awarded based on the NIH dual-level peer review process. The first level of peer review is conducted by a panel of scientific experts, and the second level of review by the NIAID Advisory Council before support is initiated. Research in the intramural program undergoes a rigorous retrospective peer review process every four years by a Board of Scientific Counselors (BSC). The results of this review are used to determine future resource allocations. This process ensures that only highly meritorious science is supported.

The following summary highlights current major areas of research in NIAID’s extramural and intramural Lyme disease research portfolio:

**Fundamental Studies of Pathogen Biology**

NIAID supports multiple studies on the underlying biology of *B. burgdorferi*. This research helps scientists better understand how the pathogen infects the host, multiplies, survives, and ultimately causes human disease. An improved understanding of pathogen biology can lead to the identification of new targets for future diagnostics, therapeutics, and vaccines.

Examples of this research include:

- A comprehensive analysis of *B. burgdorferi* surface proteins and their cellular counterparts that could help scientists understand how the bacteria interact with human
cells and tissues and survive within people and may lead to new targets for vaccines.

- Research on the proteins and cellular structures used by \textit{B. burgdorferi} and related bacteria to travel through the body and affect multiple body sites.

- Studies aimed at understanding the surface composition of \textit{B. burgdorferi} at the biochemical and molecular levels, which may lead to novel ways of disrupting the interaction of the bacteria with the host or to novel vaccine/diagnostic targets for future testing.

- Investigations into how \textit{B. burgdorferi} obtains critical nutrients within its human host, and on how critical survival genes are regulated within the bacteria.

- Research on the underlying genetics and proteins that enable the bacteria to adapt to the very different internal environment of ticks and humans, and to switch between them.

**Studies on Persistence**

NIAID also supports basic research projects to address key questions regarding why symptoms persist in some individuals, even after completion of treatment. Some examples of current research in this area include:

- Studies on drug--tolerant \textit{B. burgdorferi} persister cells and the underlying mechanisms that may control their formation in response to antibiotic treatment.

- Investigations into how the bacteria respond to antibiotic stress.

- Research on how \textit{B. burgdorferi} may trigger persistent symptoms in the absence of living bacteria, such as autoimmune or chronic inflammatory responses to bacterial components.

- Investigations of persistent infections using xenodiagnosis, a strategy that uses the tick vector to detect the presence of \textit{B. burgdorferi} in patients when living bacteria are not otherwise detectable by traditional methods.

- Studies on the mechanisms behind Lyme arthritis, a common manifestation of untreated Lyme disease.

**Studies on Human Immunity to Infection**

The immune system attacks different pathogens through different mechanisms, and those pathogens in turn have evolved ways to partially evade those defenses. NIAID supports several investigators working to better understand both human immunity to \textit{B. burgdorferi} and the molecular strategies used by the bacteria to avoid these immune responses. These studies will provide insight into multiple areas of Lyme disease research including persistence of symptoms and potential new tools for combating or preventing disease. Some examples include:
• Research on bacterial factors that enable *B. burgdorferi* to evade multiple components of the immune system, such as antibody responses and critical elements of the early, innate immune response.

• Mechanisms of antigenic variation on the bacterial surface.

• Studies on how *B. burgdorferi* is cleared from the skin after infection.

**Studies on the Vector**
NIAID supports basic research on Ixodes scapularis and other ticks that transmit Lyme disease and other bacterial and arboviral infections. Ongoing efforts include:

• Research on tick feeding including identifying recent blood meals, which will shed light on the animal reservoirs responsible for maintaining *B. burgdorferi* in nature.

• Studies on the factors in tick saliva that affect transmission. These factors include proteins that block blood clotting, the pain response to a tick bite, acquired tick-resistance or other factors that may enhance the bacteria’s chance of infecting humans.

• Studies on the tick host-finding system and the development of ticks with reduced ability to transmit *Borrelia*, which could be used to interrupt the natural cycle of disease and its transmission to humans.

• Research on vector immunobiology in order to better understand how *Ixodes* ticks recognize and subdue invading pathogens such as *Borrelia burgdorferi*, including how the tick gut microbiome determines the response to these pathogens.

**Studies on Lyme Disease Diagnostic Testing**
NIAID has long highlighted the need for improved Lyme disease diagnostics. Currently, no point-of-care diagnostic test is available for Lyme disease that can substitute for laboratory-based testing. A point-of-care diagnostic that accurately detect sLyme disease early in infection would enable physicians to make more informed treatment decisions when a patient in a Lyme-endemic area presents with symptoms consistent with Lyme disease. NIAID efforts towards developing improved diagnostics include:

• Developing and testing a new cytokine-based immunoassay for Lyme diagnosis which, if successful, could allow for earlier and more rapid diagnosis of Lyme disease.

• Metabolic biomarkers and biosignatures for improved diagnostics are being identified and characterized. These studies may contribute to new methods for detecting Lyme disease, including diagnosis of early-stage of disease, accurate staging of disease, or indications of successful treatment. For example, researchers are exploring ways detecting small molecule metabolites in urine of early Lyme disease patients, which would be very helpful in the clinic since urine is an easily obtainable sample.
• New, rapid point-of-care Lyme diagnostic tests using lateral flow technologies.

• Research on multiplex qPCR assays to simultaneously detect Lyme disease and coinfections such as babesiosis.

**Studies on Lyme Vaccines**

The first Lyme disease vaccine, LYMErix, was approved for use in humans in 1998, but was voluntarily withdrawn by the manufacturer in 2001 due to low public demand. NIAID currently supports research to develop and evaluate new vaccine candidates for Lyme disease. In this regard, NIAID recently issued a Funding Opportunity Announcement focused on Tick-borne disease prevention ([RFA-AI-19-037](#)). Current research efforts include:

• Identifying *B. burgdorferi* antigens that could be used in next-generation Lyme disease vaccines.

• Studying the potential of a “chimerotope” vaccine, modeled after a recently approved canine vaccine for use in the veterinary field.

• Pursuing novel vaccine formulations and targets, including proteins in tick saliva that are critical for the transmission of *B. burgdorferi* to humans. Such proteins may hold potential as antigens for “anti-tick” vaccines.

• Research on reservoir vaccines to reduce Lyme disease in humans. These oral “bait” vaccines are designed to prevent mice from becoming infected, thereby interrupting the transmission cycle. Some groups are field testing their products with support from the Centers for Disease Control and Prevention (CDC) as well.

**Clinical Studies**

NIAID intramural scientists on the Bethesda, Maryland, campus conduct research to advance scientific knowledge of Lyme disease and translate these advances into clinical practice. Patients with Lyme disease are studied at the NIH Clinical Center with the goals of ameliorating disease and improving prognosis, as well as increasing the understanding of the laboratory diagnosis, clinical manifestations, and human immune responses associated with *B. burgdorferi* infection.

More than 500 volunteers are currently enrolled in ongoing studies focused on:

• Evaluation, treatment, and follow-up of Lyme disease patients to assess clinical course and outcomes and define immune responses to infection.

• Identification of biomarkers of infection and development of new diagnostic tools.

• Investigation of potential causes of PTLDS.

• Exploration of potential persistence of infection after completion of antibiotic therapy for Lyme disease.

Information about these and other studies can be found on [ClinicalTrials.gov](#), a registry and results database of publicly and privately supported clinical studies. For information on NIAID-conducted studies, refer to the study title or ClinicalTrials.gov identifier provided in the table.
below:

<table>
<thead>
<tr>
<th>Study Title</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenodiagnosis After Antibiotic Treatment for Lyme Disease</td>
<td>NCT02446626</td>
</tr>
<tr>
<td>Evaluation, Treatment, and Follow-up of Patients with Lyme Disease</td>
<td>NCT00028080</td>
</tr>
<tr>
<td>A Comprehensive Clinical, Microbiological and Immunological Assessment of Patients With Suspected Post Treatment Lyme Disease Syndrome and Selected Control Population</td>
<td>NCT00001539</td>
</tr>
</tbody>
</table>

**Recent NIAID Lyme Disease Scientific Advances**

NIAID intramural scientists at the Rocky Mountain Laboratories utilize molecular approaches in conjunction with animal models to analyze *B. burgdorferi*. Of particular interest is how *B. burgdorferi* adapts to the distinct environments it encounters in the tick vector and mammalian host. These basic research studies provide critical knowledge about key components of the Lyme disease bacterium that are important for tick-borne transmission and infection of mammals, including humans.

Some recently published findings of NIAID intramural researchers are summarized below.

- **What kind of quality of life can Lyme disease patients expect long term?**
  
  *Long-term follow up of Lyme patients* enrolled in an NIH-sponsored natural history study showed that health scores increased to greater than or equal to the national average by the end of follow-up, regardless of Lyme disease stage and severity at diagnosis.

- **Can one become immune to *B. burgdorferi*?**
  
  Many different strains of the Lyme bacterium, *B. burgdorferi*, are stably maintained in the wild, even within the same local population of infected wild animals and ticks. Once infected, people and animals are immune to re-infection by the same strain, but can become re-infected with a different *B. burgdorferi* strain. It was originally thought that factors in the immune host’s blood neutralized *B. burgdorferi* after the strain was transmitted to and circulating in the host. It is now known that protection of the host against infection occurs in the tick *before the bacteria leave the tick to enter the host*. When a tick ingests blood from a host immune to the same strain of *B. burgdorferi* that is living in its gut, *B. burgdorferi* is neutralized within the tick, loosing infectivity, even before it is transmitted. Conversely, if a host is immune to one strain of *B. burgdorferi* but the tick harbors another, the blood meal enhances the infectivity of the strain within...
the tick, allowing for a heightened ability of the bacteria to re-infect the host. These findings are pertinent to a broad spectrum of basic and applied research endeavors in the Lyme disease field, including vaccine development, evolution and population genomics, ecology and vector biology.

- **How does *B. burgdorferi* change as it moves between mammal and tick?**

  Transmission of *B. burgdorferi* between the tick vector and a mammalian host requires the bacterium to sense and adapt to these distinct environments. *B. burgdorferi* survival in these diverse conditions requires adaptation, a hallmark of which is a change in the composition of its outer surface. Researchers assessed whether the predominant **surface proteins** made by *B. burgdorferi* at different stages of the infectious cycle were interchangeable and found that while some could substitute for each other, others could not. The data confirm that the surface protein OspA both protects spirochetes within ticks from mammalian antibody and serves an additional role during tick colonization. Researchers also showed an enzyme, FtsH, that ensures membrane proteins are properly formed and biologically active, **is critical to *B. burgdorferi* survival.** This work provides insight into *B. burgdorferi* viability and could lead to the identification of novel therapeutic targets. These and other studies are providing insight into how *B. burgdorferi* regulates its adaptive response during transition from mammalian host to tick vector.

- **How can we facilitate laboratory investigations of *B. burgdorferi?***

  Many components of the Lyme disease bacterium are unique and of unknown significance to pathogenesis. While molecular genetics provides a powerful means of investigating novel and potentially important elements of bacterial pathogens, the tools currently available for such studies in *B. burgdorferi* are somewhat limited. Targeted mutagenesis and **complementation** are important tools for studying genes of unknown function in the Lyme disease spirochete *B. burgdorferi*. Recently, a powerful new tool has been adapted to the study of spirochetes, allowing **visualization of living cells.** Prior to this work, the molecular techniques available to identify virulence determinants and key cellular factors were more rudimentary in spirochetes compared to those available for other pathogens. With this work, researchers have developed vital new tools for molecular genetic investigations in *B. burgdorferi.*

NIAID also supports extramural scientists who are investigating multiple aspects of Lyme disease. This includes basic, translational, and clinical studies. Some of the most recent extramurally-supported research is described here, highlighting the diversity of studies funded.

- **Why do different *Borrelia* strains behave differently?**

  The Lyme disease bacteria spread to targeted tissues within both tick and mammalian hosts, but strain-specific differences in their distribution within the host and ability to cause disease have been observed. Researchers identified molecules on the surface of the Lyme bacteria that are involved in attaching to different tissue structures within mammalian and tick hosts. They discovered that **variations in those proteins** can help
direct where the bacteria go following infection. These studies may help explain different, strain-specific clinical manifestations of Lyme disease. NIAID-funded research continues to explore the spirochetal factors that allow for the persistence, maintenance, and dissemination of the pathogen in the tick vector. Researchers have also been investigating the role of proteins, such as P66 and its integrin-binding function, in the transmigration and dissemination of B. burgdorferi.

• **How prevalent is Borrelia miyamotoi?**

*Borrelia miyamotoi*, a bacterium that causes relapsing fever, is transmitted by the same ticks as Lyme disease and occurs in all Lyme-endemic areas of the United States. Investigators conducted epidemiologic studies in the Northeastern United States and found that *B. miyamotoi* infection may be common in southern New England and that some *B. miyamotoi*-infected individuals falsely test positive for Lyme disease.

• **Can biomarkers lead to a better diagnostic test for early Lyme disease?**

Lyme disease can be difficult to diagnose early in infection because current laboratory tests look for antibodies that take time to rise to detectable levels. In response to a specific NIAID solicitation for better early-stage Lyme diagnostics, researchers looked for biomarkers, which are non-antibody molecules that arise in response to infection, to see if a subset could be identified that was specific for Lyme disease. The study identified a group of biomarkers that can differentiate between Lyme disease and several other diseases with high sensitivity, and that could accurately indicate Lyme disease in many blood samples that had tested negative through the currently accepted two-stage antibody test.

• **Which B. burgdorferi genes are switched on, and when?**

An understanding of the genetic control of the Lyme bacteria life cycle is important for developing new diagnostics, treatments, and prevention measures. Scientists recently conducted a comprehensive study to determine which *B. burgdorferi* proteins are produced in tick nymphs and larvae, as well as in bacteria that had been adapted to mammalian hosts. The results showed clear differences in which *B. burgdorferi* genes are switched on in response to different developmental stages and environmental clues, providing the first detailed molecular blueprint of the carefully regulated Lyme bacteria life cycle. These studies provide the framework for further research on the genes critical for *B. burgdorferi* survival and pathogenesis.

• **Why do symptoms persist in some people after antibiotic treatment?**

Lyme disease is generally responsive to antibiotic therapy. However, in some patients, musculoskeletal symptoms may continue for months after treatment. Although ongoing infection is considered an unlikely explanation for persistent symptoms or disease, it cannot definitively be excluded. This is because *B. burgdorferi* is difficult to detect by culture, except in early infection when the telltale erythema migrans rash is present. NIAID-supported researchers used a mouse model to suggest that inflammatory,
immunogenic antigens, but not infectious bacteria, can persist near cartilage after treatment and might contribute to persistent symptoms.

In collaboration with NIAID intramural scientists, extramural researchers have discovered that elevated C-Reactive protein responses are associated with antibiotic-refractory Lyme arthritis and PTLDS, indicating that inflammatory mechanisms may be different from those in active infection.

Researchers also are continuing to search for persistence of infection after completion of antibiotic therapy for Lyme disease. NIAID scientists, in collaboration with researchers from Tufts University and New York Medical College, are investigating xenodiagnosis using live, disease-free, laboratory-bred ticks to see if Lyme disease bacteria can be detected in people after completing antibiotic therapy. Researchers are also studying whether persistence is more common in people who continue to experience symptoms, such as fatigue and joint pain. An initial study showed that xenodiagnosis was safe and well-tolerated. The results of the study were published in 2014. A phase 2 xenodiagnosis study is now open (see ClinicalTrials.gov, identifier NCT02446626).

It is possible that minimizing the time the bacterium interacts with the host can diminish the likelihood of developing post-treatment symptoms. Researchers are, therefore, exploring existing antibiotics that can effectively eradicate the pathogen at the early, acute stage of infection. Vancomycin has emerged as potentially more effective in killing the bacteria and clearing infection both in vitro and in mice, compared to doxycycline and ceftriaxone, which are the current standards of care for Lyme disease.

• **How important is antigenic variation in Lyme disease?**
  Recent studies on a *B. burgdorferi* surface protein, VlsE, highlight its importance in maintaining the Lyme bacteria life cycle in nature. These studies also describe the significant role played by antigenic variation, or changes in VlsE, in maintaining infections in mammalian hosts. Other studies have explored the antigenic structure of the protein OspC (Outer Surface Protein C) and the role that it plays in immune responses during infection and upon vaccination.

• **Does high cholesterol place you at increased risk of Lyme disease?**
  Since *B. burgdorferi* utilize cholesterol from their host to help construct their own membranes, researchers assessed whether individuals with lipid disorders, such as high cholesterol, might be at increased risk of Lyme disease. Using two different mouse models, the investigators determined that genetic conditions leading to elevated serum cholesterol may be a risk factor for increased severity of disease. Dietary cholesterol did not appear to lead to increased risk of Lyme disease. Since high cholesterol can stem from multiple genetic factors, additional work will be needed to identify the mechanism(s) behind the results.
• How do the Lyme bacteria cause arthritis?
A research group studying the factors leading to and sustaining Lyme arthritis identified a genetic locus in mice linked to type I interferon that is associated with *B. burgdorferi*-induced arthritis. The same group also recently began characterizing the role of microRNAs, which are small molecules that help to regulate which genes are switched on and off, in regulating Lyme arthritis. Other important research in this area is focused on the various systemic autoimmune joint diseases that may follow Lyme disease to determine the best course of treatment for these patients.

Recently, NIAID-funded researchers have identified that the overexpression of certain markers of immune response in the joints of postinfectious Lyme arthritis patients may prevent appropriate tissue repair and maintenance long after completion of antibiotic treatment and clearance of active infection. In addition, researchers at Yale University have shown that peptidoglycan (PGB\textsuperscript{B}), an important part of the cell envelope of *B. burgdorferi*, plays an important role in the development and persistence of Lyme arthritis. This research indicates that as the bacteria grows, it sheds fragments of PGB\textsuperscript{B} in the environment, which contributes to inflammatory responses in Lyme arthritis. As this antigen may persist in joints, it may contribute to synovitis even after resolution of infection following antibiotic treatment.

• How does coinfection with other tick-borne infections impact pathogenesis?
*Babesia microti* is a parasite transmitted by the same tick species that transmits *Borrelia burgdorferi*, and people can become infected with the two pathogens at the same time. Recently, researchers used a mouse model of the two infections that closely mimics human disease to investigate how each pathogen influences the other. They showed that infection with the *B. microti* parasite enhanced the severity of Lyme disease-like symptoms in the mice, while *B. burgdorferi* appeared to limit the growth and effects of the parasite.

• Is there a possibility of a single, multi-protein point-of-care diagnostic for Lyme disease?
There are no rapid, point-of-care diagnostics currently available for Lyme disease. The current standard two-tiered (STT) diagnostic approach for Lyme disease consists of an enzyme immunoassay (EIA) followed by an immunoblot, if results from the EIA are positive or equivocal. This approach has its shortcomings such as low sensitivity in early disease, high costs and turn-around time, inter and intra-lab variability as well as difficulties interpreting the results of the immunoblot. NIAID-funded researchers have recently compared the performance of a new microfluidic multiplexed assay (mChip-Ld) to the current STT, using human serum samples from patients of early Lyme disease as well as Lyme arthritis and PTLDS (Post Treatment Lyme Disease Syndrome). The mChip-Ld [43] demonstrated better sensitivity than the STT without sacrificing specificity. These results indicate the potential of mChip-Ld as a single, rapid, multiplexed point-of-care diagnostic that can detect different stages of disease, including early, acute Lyme disease.
NIH Collaborations with Other Federal Agencies and External Organizations

NIH participates in the Department of Health and Human Services (HHS) Tick Borne Disease Partners along with representatives from the Office of the Secretary of HHS, CDC, and the U.S. Food and Drug Administration (FDA) to facilitate coordination and planning among participating agencies. The group convenes twice a year to review the state of the science in Lyme disease research and has conducted public webinars over the past few years to brief the scientific and patient communities on topics of interest, including the state of diagnostics, the persistence of infection in animal model systems, emerging ticks and tick-borne pathogens, as well as vaccine research and development efforts.

NIAID actively participates in the HHS Tick Borne Diseases Working Group, which was established by Congress in 2016 as part of the 21st Century Cures Act to help ensure interagency coordination.

NIH is partnering with the CDC, FDA, university researchers, and industry to develop improved diagnostics using the CDC Lyme disease serum repository for new and existing assay validation. The repository contains serum from Lyme disease patients and other disease etiologies that can be used as positive and negative controls. NIH provided support for the development of the repository.

Funding Opportunities and Research Resources

NIAID maintains funding opportunities websites to inform the research community about current grant opportunities and contract solicitations. In addition, NIAID has a comprehensive set of product development services and research tools and technologies to facilitate development and evaluation of vaccines, diagnostics, and therapeutics: Resources for Researchers.

These services make critical data, expertise, standardized research materials, and state-of-the-art technologies available to eligible investigators worldwide at no charge. The purpose of these resources is to lower the financial risk to product developers by providing limited, but critical, information to fill specific gaps in the product development pipeline. Currently, NIAID is utilizing its preclinical resources to develop an improved methodology for culturing *B. burgdorferi*, which grows slowly and is very difficult to culture, particularly from patient samples. By developing better ways to grow the bacteria, NIAID hopes to enable faster and more efficient laboratory research on the pathogen.

Future Plans/Directions

NIAID’s Lyme disease research portfolio will continue to encompass basic, translational, and clinical research studies, as well as studies on the tick vector and tick/pathogen interactions. Specifically, efforts will continue to be focused on the study of basic biology and pathogenesis of *B. burgdorferi*, which will help provide insight into Lyme disease. Research areas will include persistence of infection after antibiotic treatment using a variety of animal models, clinical studies, and improvement of Lyme disease diagnostics.