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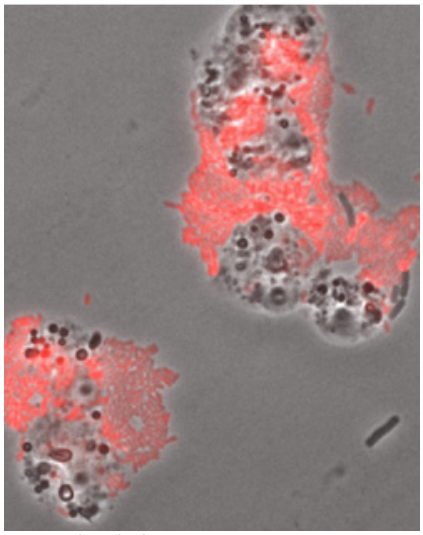
NEWS FROM THE SHERRILYN AND KEN FISHER CENTER FOR ENVIRONMENTAL INFECTIOUS DISEASES

Dedicated to the clinical research of environmental pathogens which improves the diagnosis and treatment of these infections.



Legionella (in red) infecting amoeba

WHAT'S INSIDE

Pneumonia Bug Remodels in a Surprising Home

Bacteria Transmitted Through Inhalation of Contaminated Water Mist

In July 1976 while the nation was celebrating its bicentennial of independence in Philadelphia, the American Legion held its annual convention with over 2000 attendees. Soon after the convention's conclusion, several attendees began to complain of pneumonia symptoms. Within the week, a local epidemic was apparent with 182 people, mostly Legionnaires, hospitalized. Twenty-nine deaths were documented from the then unknown respiratory infection called Legionnaires disease. To determine the outbreak cause, the CDC (Center for Disease Control and Prevention) mounted an unprecedented investigation, leading to the discovery six months later of a new bacterium, *Legionella pneumophila*, found in the cooling tower of the convention hotel air conditioning system.

Legionella pneumophila is naturally found in freshwater but also exists in up to one-third of potable drinking water distribution systems. Exposure to this pathogen occurs through inhalation of contaminated water mists, most commonly generated by air conditioners, humidifiers, hot tubs, spas, sprinklers and decorative fountains. Infection can manifest in two ways; life-threatening pneumonia or a flu-like illness called Pontiac fever. Healthy individuals are typically resistant to infection. Susceptible individuals include people with weakened immune systems, older ages > 65 years, smokers and those suffering from chronic respiratory conditions.

Legionella pneumophila is a leading cause of community-acquired pneumonia with 7,500 cases reported annually and 27 outbreaks of disease from 2000 to 2014 in the U.S. Because individuals infected with Legionella pneumophila typically present with flu-like symptoms, there are no unique features that distinguish it from other types of pneumonia. As it is challenging to grow in the clinical laboratory, *Legionella pneumonia* is often under-diagnosed. Other methods to detect Legionella exist but do not identify all Legionella types and species. Experts estimate that the reported cases in the U.S. are grossly underestimated with predictions closer to 20,000 per year in the United States. While there are highly effective antibiotics to treat *Legionella pneumophila*, antibiotics typically chosen to treat respiratory infections such as penicillins do not affect this organism, as it lacks the cell wall components found in bacteria such as streptococci or E. coli. *Legionella pneumonia* is among the most virulent of pathogens that cause community-acquired pneumonia. Up to 30% of cases are lethal, demonstrating an urgent need for more effective strategies to prevent and treat disease.

Although many bacteria inhabit water environments, *Legionella pneumophila* has proven difficult to eradicate from potable drinking water systems. Its enhanced survival appears partly due to an ability to survive both in biofilms and high temperatures. A crucial additional technique appears to be its preferred living habitat with a one-celled animal, the amoeba. Early studies with *Legionella pneumophila* demonstrated that this bacterium prefers to replicate within amoeba that also inhabit freshwater environments and water systems. Growth of *Legionella pneumophila* within amoeba protects them from chemicals disinfectants used to decontaminate drinking water. These properties of the bacterium likely allow it to persist in drinking water reservoirs, thereby increasing human exposure to this pathogen.

Within the lung, *Legionella pneumophila* replicate within a specialized form of white blood cell, called macrophages, that are the first line of defense against such invading pathogens. Macrophages share many common features with amoeba; both

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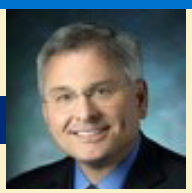
MESSAGE FROM THE DIRECTOR



After years of stagnant federal research funding levels, investment in tick-borne disease research has gotten a significant boost this year. The National Institutes of Health (NIH) has annually spent about $23 million on Lyme disease within a $56 million tick-borne disease research portfolio. As the most common vector-borne disease in the United States with an estimated 300,000 annual Lyme disease cases, this level of funding has been insufficient to make significant progress in fostering advancements understanding the mechanisms of disease, new vaccines and improved diagnostic tests. Private philanthropy has stepped in with foundations providing more than $60 million over the past decade to spur advances.

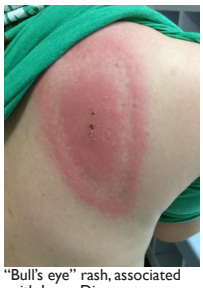
Recognition by federal funding sources lends urgency and helps stimulate bringing new investigators to the field. An additional $6 million devoted to Lyme disease in 2020, represents a 26% boost in research funding by the NIH, and the Centers for Disease Control (CDC) Lyme disease budget will grow by 12% to $12 million. Both represent significant advances in funding that likely developed from several efforts including advocacy by patient groups and professional societies.

Advocacy helped shape the 2016 21st Century Cures Act that included a Congressionally-mandated formation of a Tick-borne Disease Working Group (TDWG), including academic and government scientists as well as patient advocates. The first report from this group was issued this past winter. Recommendations included pushing for the development of next-generation Lyme disease tests and development of an effective Lyme disease vaccine. The second two-year cycle of the TDWG is just underway and this recomposed panel is charged with examing current federal efforts and issuing recommendations to the Secretary of Health and Human Services.

Now nearly forty years since the discovery of the bacterium Borrelia burgdorferi as the cause of Lyme disease, the push toward advancing the field is very welcome. Breakthroughs may happen. However, it is better to count on incremental improvements, which are how modern medicine mostly changes.

Paul G. Auwaerter, MD, MBA
Director, Fisher Center for Enviornmental Infectious Diseases

Lyme Disease Clinical Research



"Bull's eye" rash, associated with Lyme Disease

Lyme disease is a bacterial infection transmitted by tick bites. The infection may cause symptoms such as fatigue, muscle aches, joint aches, joint swelling, and rash. If untreated, the symptoms may progress to include arthritis or neurologic disease. Current FDA-approved blood tests for Lyme disease rely on testing for antibodies that develop in response to the infection. As with any human immune response to infection, the generation of antibodies may take 2-4 weeks to form. After a tick bite, these tests for Lyme disease may be negative in the early weeks of infection leading to a delay in both diagnosis and treatment if the characteristic "bull's eye" rash is not present. Also, antibodies cannot be used to monitor treatment effectiveness as these molecules may persist for decades after antibiotic therapy.

The Fisher Center is collaborating with MicroB-plex, Inc. of Atlanta, Georgia in the evaluation of a novel cell-based blood test for early Lyme disease that may signify the presence of the infecting Borrelia burgdorferi bacteria before traditional antibody-based assays. This testing approach may also track with response to antibiotics thereby confirming clearance of infection. If successful, the test may lead to breakthroughs in the diagnosis and management of Lyme disease.

People with early Lyme disease (symptoms less than seven days) with a rash consistent with erythema migrans may join the study. To learn more about our Lyme research, call (443) 287-4840 or visit our website at **EarlyLymeStudy.org**

Image source: Auwaerter, M.D.

DAVIS RECEIVES CATALYST AWARD

Congratulations to **Meghan Davis, DVM, PhD** recipient of a 2019 Johns Hopkins Catalyst Award for promising early-career faculty members. Her selection was based on accomplishments to date, creativity and originality, and academic impact. In addition to this $75,000 grant, Dr. Davis will participate in mentoring sessions and networking events. In 2014, Dr. Davis and Elizabeth Matsui, MD received a Fisher Center Discovery Program (FCDP) grant for their research on environmental pathogen exposures and asthma exacerbation. Pilot data from the FCDP grant led to large NIH grants for both Davis and Matsui. As faculty in the Bloomberg School of Public Health, Dr. Davis continues her environmental research into the interface of bacteria and hosts to reduce disease in humans and animals.

Pneumonia Bug Remodels in a Surprising Home

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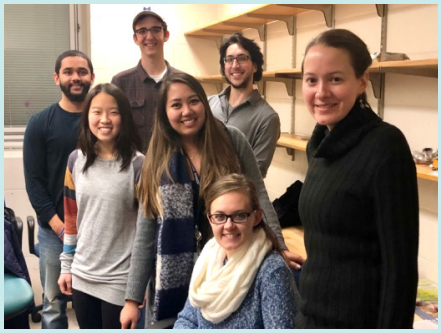
hunt down and kill bacteria. The strategies acquired by *Legionella pneumophila* to avoid predation by amoeba in the environment allow the bacterium to evade killing by macrophages in the lung. Importantly, early studies by Lucy Tompkins and colleagues at Stanford University demonstrated that *Legionella pneumophila* grown within amoeba are more infectious within human macrophages. While the mechanisms by which this interaction enhances *Legionella pneumophila* virulence remains unknown, the presence of amoeba in contaminated drinking water appears to be responsible for outbreaks of Legionellosis. This knowledge suggests a critical role for this bacteria-amoeba interaction in determining the incidence and severity of the infection.



Back row (L to R): Pavan Patel, Justin Greene, Jarrett Venezia Middle Row: Bessie Liu, Jasmine Ramirez Raneses Front Row: Alysha Ellison, Kim Davis

In 2018, **Kimberly Davis, PhD**, of the Johns Hopkins University Bloomberg School of Public Health and **Tamara O'Connor, PhD** of the Johns Hopkins University School of Medicine were awarded a Fisher Center Discovery Program grant to study the role of amoeba in enhancing the ability of *L. pneumophila* to cause human disease. Their experiments produced highly significant findings demonstrating that Legionella adapt during growth within amoeba that subsequently lessens the ability of human macrophages to find and to ingest them. This leaves infected people less able to fight infection with their immune system, especially if already impaired by smoking or pre-existing conditions. Davis and O'Connor's current research is focused on determining the specific bacterial features that are responsible for these properties and exploiting these changes to develop new strategies for water remediation and disease prevention.

Left to right: Saumya Bndypadhyay, Bhavyaa Tyagii, Jahangir Hossain, Rhishita Chourashi, Soma Ghosh, Tamara O'Connor

Laboratory research exploring how environmental factors impact infectious disease in humans can be difficult to fund through traditional agencies. The mission of the Fisher Center is to provide initial funding for innovative, high-risk avenues of research which allow scientists to develop research programs that address critical questions at the intersection of environmental biology and human infectious disease research. "We are extremely grateful to the Fisher Center Discovery Program for enabling and supporting this research, which is essential to understanding a key phase in the transition of an environmental pathogen to humans" both Davis and O'Connor replied. Their exciting findings will play a central role in guiding the development of more effective water treatment procedures and clinical practices to prevent and treat disease.

Image Source: Jason Park and Tamara O'Connor

FUNDING OUR FUTURE

Thank you to those who contributed so generously to support environmental infectious disease research and education in the past six months. Such gifts help facilitate innovative research, especially targeted to early-career investigators. In particular, we would like to acknowledge

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JULIE ROTHMAN AND SCOTT SHERMAN
EUGENE SCARPULLA

*IF YOU ARE INTERESTED IN SUPPORTING OUR WORK, PLEASE CONTACT DONNA BOLIN AT **410-550-9893** OR DBOLIN1@JHMI.EDU*

+ RECENT PRESENTATIONS

Are Showerheads Causing Chronic Lung Infections? **Paul G. Auwaerter, MD, MBA**. Medscape Infectious Diseases. https://www.medscape.com/viewarticle/905813. December 17, 2018

Baloxavir's Place in the Treatment of Flu. **Paul G. Auwaerter, MD, MBA**. Medscape Infectious Diseases. https://www.medscape.com/viewarticle/908076. February 01, 2019

'Zombie Deer Disease' Spreading; Watch What You Eat. **Paul G. Auwaerter, MD, MBA**. Medscape Infectious Diseases. https://www.medscape.com/viewarticle/909958. March 19, 2019

Severe Malaria: Only One Drug Option Remains. **Paul G. Auwaerter, MD, MBA**. Medscape Infectious Diseases. https://www.medscape.com/viewarticle/912145. May 6, 2019

+ RECENT PUBLICATIONS

Identifying Potential Provider and Environmental Contamination on a Clinical Biocontainment Unit Using Aerosolized Pathogen Simulants. Drewry DG 3rd, **Sauer LM**, Shaw-Saliba K, Therkorn J, Rainwater-Lovett K, Pilholski T, **Garibaldi BT.** Health Secur. 2018 Mar/Apr;16(2):83-91. doi: 10.1089/hs.2017.0064. Epub 2018 Mar 14. PMID: 29624490

Impact of air-handling system exhaust failure on dissemination pattern of simulant pathogen particles in a clinical biocontainment unit. Therkorn J, Drewry Iii D, Pilholski T, Shaw-Saliba K, Bova G, Maragakis LL, **Garibaldi B, Sauer L**. Indoor Air. 2018 Sep 7. doi: 10.1111/ina.12506. [Epub ahead of print] PMID: 30192402

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The Impact of High-Level Isolation Units Beyond High-Consequence Pathogen Preparedness. Andonian J, Galusha KE, Maragakis LL, **Garibaldi BT.** Health Secur. 2019 Jan/Feb;17(1):69-73. doi: 10.1089/hs.2018.0104. PMID: 30779609

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IL-1 receptor antagonist therapy mitigates placental dysfunction and perinatal injury following Zika virus infection. Lei J, **Vermillion MS**, Jia B, Xie H, Xie L, McLane MW, Sheffield JS, Pekosz A, Brown A, **Klein SL**, Burd I. JCI Insight. 2019 Feb 28;4(7). pii: 122678. doi: 10.1172/jci.insight.122678. eCollection 2019 Apr 4. PMID: 30944243

Effects of child and maternal Histo Blood Group Antigen status on symptomatic and asymptomatic enteric infections in early childhood. Colston JM, Francois R, Pisanic N, Yori PP, McCormick BJJ, Olortegui MP, Gazi MA, Svensen E, Ahmed MMM, Mduma E, Liu J, Houpt ER, Klapheke R, Schwarz JW, Atmar RL, Black RE, **Kosek MN**. J Infect Dis. 2019 Feb 15. pii: jiz072. doi: 10.1093/infdis/jiz072. [Epub ahead of print] PMID: 30768135

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