Fisher
Focus

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News from the Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases

From Bench to Bedside: How Fisher Center Funding is Helping Scientific Discovery to Directly Improve Patient Care

Background Histoplasmosis is one of the most common fungal infections acquired from the environment in the U.S. When soil is disturbed, existing microscopic spores are released and may be inhaled. Most people develop self-limiting infections consistent with other causes of pneumonia. However, *Histoplasma* organisms establish latent infections that can reactivate later in life. Persons with weakened immune systems, such as those with HIV, organ transplants, and the elderly can develop active disease that can disseminate throughout the body and may be fatal.

A significant difficulty in securing a diagnosis of histoplasmosis rests on low and slow recovery of the fungus from traditional cultures and relatively poor performance of other tests, including antibody and antigen presence. Existing tests for histoplasmosis miss many active infections so there is clear need for better diagnostics that could reduce delays in treatment, lead to better heath for patients and have the potential to save on costs.

Fisher Center Discovery Program (FCDP) In 2015 the program awarded **Dr. Kieren Marr** a grant to evaluate an existing prototype diagnostic test Dr. Marr's team had developed, an interferon-gamma release assay that "probes" the immune system for prior infection with *Histoplasma capsulatum*.

> "This test provides great opportunity to change patients' lives."
> Kieren Marr

With partial support provided by FCDP, a research team at Johns Hopkins University (JHU) and Vanderbilt University in Nashville, Tennessee evaluated performance as an aid to detect latent infection in geographic areas of variable endemicity. Studies performed to date suggest the HistoSPOT demonstrates a better than 90% rate in detecting both latent infection and active disease.

Business Development Translating research findings into a viable commercial test requires both scientific and business expertise. Additional support to transfer technology into clinical microbiology at JHU has been provided by the Johns Hopkins Accelerated Translational Incubator Pilot (ATIP). Additional resources within JHU, including the Carey Business School's *Discovery 2 Market* program, helped examine commercial opportunities and develop a business model.

Dr. Marr has been involved with translational research for over 20 years. In 2004 her team generated the data supporting FDA submission of another diagnostic assay that is currently in commercial use for aspergillosis, another fungal infection. Based on this experience, she has developed an interest in applying business principles to medicine, leading to the development of a new JHU spin off company called *MycoMed Technologies*. This is something not taught in medical school or training, but as Dr. Marr explains the motivation, "I find nothing more satisfying than translating research discoveries into products for patients."

As Dr. Marr has gained expertise both in the research lab and in business development, JHU and national organizations have sought her for leadership positions. Appointed by the JHU Department of Medicine as Vice Chair for Innovation and

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Inside

Mission Statement

The Sherrilyn and Ken Fisher Center for Environmental Infectious Diseases is dedicated to the clinical research of environmental pathogens which improves the diagnosis and treatment of these infections.

A word from our Director
Paul Auwaerter, M.D., M.B.A.

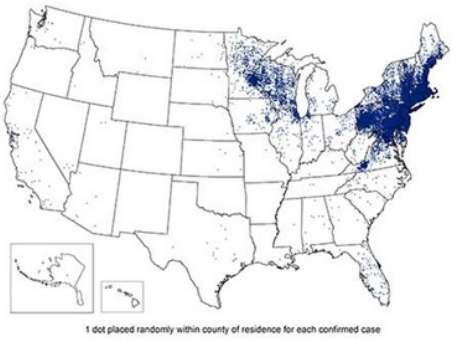
Clinical Director, Division of Infectious Diseases

Lyme Disease: The Need for Improved Testing

When I was an infectious disease fellow in the early 1990's, my knowledge about Lyme disease was limited. During our first year, all of our training occurred while seeing hospitalized patients at Johns Hopkins with problems such as pneumonia, sepsis, wound infections and fever of unknown origin. As almost all people who suffer from Lyme disease remain at home when dealing with fever, rash, neurological problems or arthritis, there was little opportunity to learn directly from a patient. I cannot remember ever discussing what tests were used to diagnose Lyme disease.

During those years, I only remember seeing one patient with Lyme disease, a young man who lived on the Eastern Shore of Maryland who had a very low pulse due to heart block conduction problems. The astute cardiologist asked our infectious diseases team to consider whether Lyme disease was the cause of his problems as an estimated one percent of people with Lyme disease experience cardiac inflammation causing heart block. This was indeed the case with a positive Lyme serology test documenting antibodies against this bacteria. Antibiotics quickly reversed the block within a matter of days, and this young man returned to vigor and avoided receiving a pacemaker.

US Reported Cases of Lyme Disease 2015



Now more than 25 years ago, I remember the key message about this patient from my infectious diseases attending, Dr. John Bartlett regarded by many as one of the keenest in his field. When asked where people might be exposed to the black-legged deer ticks that transmit the Lyme disease bacteria *Borreliella burgdorferi* (the newly updated name, previously *Borrelia*), he said: "we never consider it in anyone living south of the Potomac River."

The reason--cases at the time were not seen in the more southern states. Lyme disease occurred only in parts of New England, the Mid-Atlantic, and upper Midwest. Fast forward to the current day, a quick glance of the latest map of reported cases to the Centers for Disease Control shows decided geographic southern spread into Virginia, western spread throughout Pennsylvania, and northern spread to previously unaffected areas of New England and expansion to new areas in the Midwest such as Michigan.

This ever-expanding range means that gardeners and those enjoying outdoor activities need to be more concerned in these emerging regions and practice tick avoidance habits. In areas where clinicians never had to consider Lyme disease when evaluating

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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:

Thomas Owsley PNC Foundation Leslie and Barbara Isaacs

The Fisher Center extends a heartfelt thank you to those who donated in memory of Anne Marie Manzo

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Lyme Disease Testing

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patients, they may now need to step up tick-borne disease education and also understand how currently available testing for Lyme disease does or does not fit into their clinical practice. During discussions with physicians in Indiana, Ohio and southern Virginia, the key problem is that the standard antibody tests do not become positive until several weeks after acquiring the infection and that in areas where Lyme disease is not yet present, positive values may not reflect authentic infection but false positive values.

The need to develop improved diagnostics for Lyme disease is a leading focus of many researchers in the field, but it is especially acute in the states bordering high incidence areas. Tests that may document active infection just days after acquiring by an infected tick bite will go a long way in assisting when people do not have the characteristic bull's-eye rash of Lyme disease and also reassure if negative, that this infection is not of concern.

The Fisher Center is working with researchers in other academic centers and industry to evaluate a new generation of tests for Lyme disease. With an estimated 3.4 million tests for Lyme disease done annually in one 2014 report, but only 300,000 actual cases occurring per year in the United States, this mismatch means that a better test will lead to fewer missed cases and fewer misdiagnoses in patients who do not have the infection. A better test will also lead to less repeated testing, as the annual costs to the U.S. health system for this infection alone is $492 million but likely now even higher.

Image source: CDC

Fisher Center Discovery Program 2018 Awards

On December 15, 2017 the Fisher Center Advisory Board reviewed a record 19 grant applications for the 2018 Fisher Center Discovery Program (FCDP). The FCDP fosters innovative research and supports early career investigators by funding pilot studies, with the resulting data and research outcomes used to write grants for additional support.

The following three grants were awarded for 2018. Congratulations to the research teams on their successful grant applications.

Anthony K. L. Leung, PhD

Understanding how virus virulence is regulated by the ADP-ribosylhydrolase activity of the macrodomain—a potential drug target Chikungunya virus (CHIKV) is a disease transmitted to humans by mosquitoes, including species that spread dengue and Zika viruses. People infected with CHIKU develop fever and joint pain, which may be severe and debilitating. There have been over 1.7 million people infected in the Americas since 2013. Currently there is no vaccine or specific antiviral therapy for CHIKV.

This project will focus on understanding the role of a viral protein critical for CHIKV replication and virulence, which may be a potential antiviral drug target. In addition, understanding host antiviral mechanisms in general may help develop a rational approach for broad-spectrum antiviral therapeutics.

In 2016 Dr. Leung collaborated with Diane Griffin, MD, PhD on a FCDP project concerning the neurovirulence of CHIKV. The current project seeks to build on this earlier research and will provide much-needed resources to generate data that will be used to seek long-term funding from other sources, such as NIH.

Kimberly M. Davis, PhD

The role of amoebae in enhancing the virulence of environmental human pathogens Legionnaire's disease is caused by a bacterium, *Legionella pneumophila*, found naturally in fresh water lakes and streams, in addition to human created water systems such as indoor plumbing. Inhalation of contaminated water droplets from these sources may cause a severe, life-threatening pneumonia in humans that is fatal in 30% of cases. Symptoms include cough, shortness of breath, fever, muscle aches, and headache. About 6000 cases were reported in 2015, but the disease is likely underdiagnosed.

Legionella is treatable with antibiotics, but with the emergence of antibiotic resistant strains, there is a dire need to develop more effective methods for treating and preventing disease.

While in the water environment, Legionella bacteria replicate inside single celled, free-living amoebae, which protects Legionella from being killed during water disinfection procedures. Very little is known about Legionella during the amoebae stage in their lifecycle. Once inhaled by a human, the bacteria replicate in macrophages (specialized white blood cells), resulting in a respiratory infection, Legionnaire's disease. This research will provide critical information about Legionella when it transitions from water environment reservoirs to humans and understand if amoeba environments enhance virulence factors for causing human infection.

Brian Garibaldi, MD and Lauren Sauer, MS

Environmental transmission and traceability of aerosolized bio-simulants in a clinical biocontainment unit The Johns Hopkins Biocontainment Unit (BCU) is a state of the art facility designed to care for patients with highly infectious diseases, such as Ebola and drug-resistant TB. The JH BCU is one of ten regional centers with the capacity to handle highly infectious cases in a safe and controlled environment.

This project will use a cough simulator spreading simulated DNA particles to mimic healthcare worker exposure to a sick patient in the BCU. This will lead to a better understanding of risks associated with aerosolized pathogen transmission. The research will examine contamination levels in the patient room, surrounding areas and assumed clean spaces such as hallways. This will evaluate the capability of the BCU to reduce risk of disease transmission to health care workers and the general public, aid in the development of BCU protocols that reduce the risk of exposure for patients and staff, and may provide insight into the design, building and maintenance of BCUs. The cross-disciplinary team includes applied physics lab researchers.

Funding Our Future

Thanks to all of you that believe in the mission of environmental infectious disease research. As always, we are extremely grateful to those who have contributed. To donate, please consider the following options and designate the **Fisher Center for Environmental Infectious Diseases**

Online: To make a gift or pledge online, please complete our secure online giving form, https://secure.jhu.edu/form/infdis
Phone: To speak to someone directly about making a gift, please call 410-550-9893.
Mail: The Fisher Center, 725 N. Wolfe St., Suite 211, Baltimore, MD 21205

Bench to Bedside *continued from page 1*

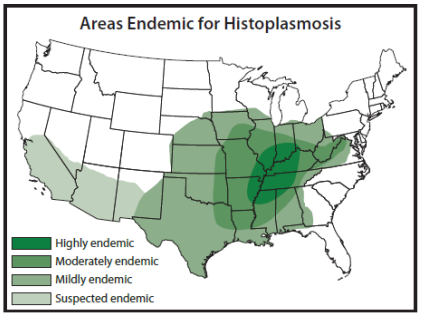
Commercialization, Dr. Marr is leading additional efforts to translate discoveries into marketable products that add value to the lives of patients. Dr. Marr was also recently elected as President-Elect of the prestigious *American Society for Clinical Investigation*, an honor society of physician-scientists who translate findings in the laboratory to the advancement of clinical practice. To further enhance her business development skills, Dr. Marr is currently completing an Executive MBA at the Massachusetts Institute of Technology (MIT).

Improving Patient Care Dr. Marr stresses that her motivation for success is based on "improving patient care, financial responsibility, and doing right for our patients, the institution, and society as a whole. Knowledge is not just for knowledge's sake but knowledge to diagnose a disease, develop new treatments and establish sustainable cures."

Optimizing University Intellectual Property JHU is actively uniting medical research and business with the creation of Johns Hopkins Technology Ventures (JHTV). JHTV assists researchers with technology transfer (patents and licensing), business development (collaboration with industry partners) and administrative support (finance, human resources).

To help small companies grow from JHU discoveries, JHTV has developed the FastForward Accelerator, housed on the East Baltimore campus. FastForward coordinates resources to efficiently move JHU developed technologies from startup to marketplace. More information on JHTV and the FastForward Accelerator may be found at https://ventures.jhu.edu/.

Image source: CDC



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Recent Presentations

Add Legionella to Your Differential Diagnosis for Pneumonia. **Paul G. Auwaerter, MD, MBA.** Medscape Infectious Diseases. https://www.medscape.com/viewarticle/884018. August 14, 2017.

Wound Care 101. Presentations Eliot Godofsky, MD, FIDSA and Anjum Owaisi, MD. Moderators: John B. Lynch, MD, MPH, University of Washington and **Paul Auwaerter, MD, MBA, FIDSA**, Johns Hopkins University School of Medicine. ID Week (Infectious Diseases Society of America) in San Diego, California. October 5, 2017

CMV Disease in the Non-immunosuppressed ICU Patient: New Study Offers Clues. **Paul G. Auwaerter, MD, MBA.** Medscape Infectious Diseases. https://www.medscape.com/viewarticle/886359. October 6, 2017

Not so Common? Late Neuroborreliosis in a Referred Population. Takaaki Kobayashi, **Yvonne Higgins**, Paul Lantos, **Michael Melia, Paul Auwaerter**. Poster Session: ID Week (Infectious Diseases Society of America) in San Diego, California. October 7, 2017

California Contagion: How to Control Severe Hepatitis A. **Paul G. Auwaerter, MD, MBA.** Medscape Infectious Diseases. https://www.medscape.com/viewarticle/889737. December 14, 2017

Congratulations

Longtime friend of the Fisher Center, **Katherine Feldman, DVM, MPH**, Chief of the Center for Zoonotic and Vector-borne Diseases for the Maryland Department of Health and organizer of the annual Mid-Atlantic Tick Summit, has accepted a new opportunity. Dr. Feldman will work on health and public health issues at MITRE, a non-profit company that operates federally funded research and development centers. We sincerely offer our best wishes to Dr. Feldman in her new role.

Two researchers with connections to the Fisher Center have assumed leadership roles in the infectious diseases community. At the recent annual meeting of the Infectious Diseases Society of America (IDSA), held October 4-8 in San Diego, Fisher Center Director, **Paul G. Auwaerter, MD, FIDSA,** assumed the role of President. Fisher Center Discovery Program grant recipient, **Cynthia L. Sears, MD, FIDSA**, was installed as President-Elect.