Translating Success

Three centers launched to battle infectious pathogens

By ELIZABETH COONEY
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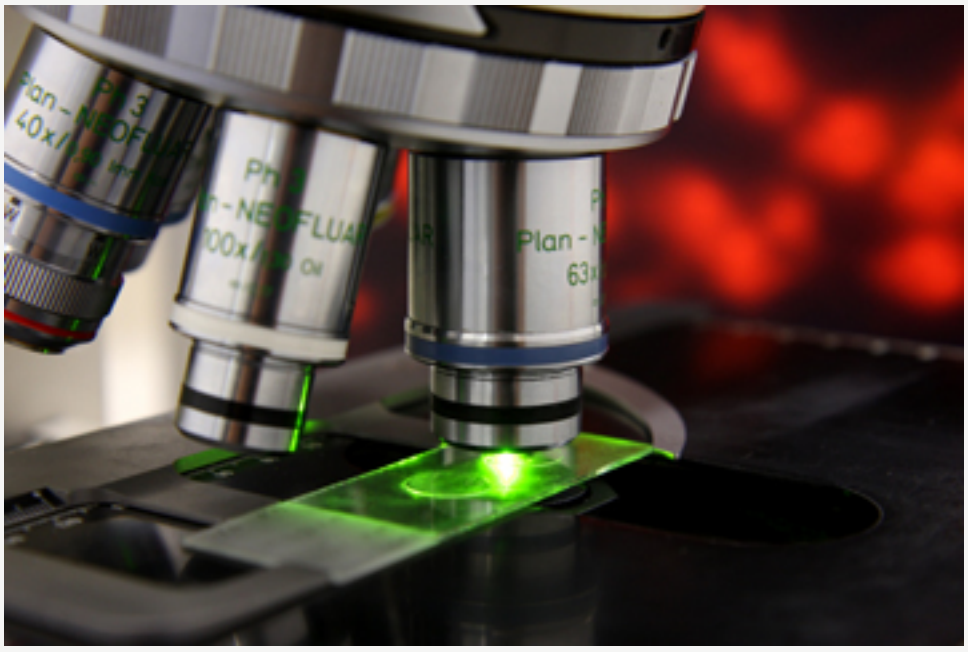
In order to better combat infectious disease, Harvard Medical School is creating three Centers of Excellence for Translational Research: one in tuberculosis, one in bacteriology and one in virology.

Three five-year grants totaling up to $15 million per year from the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health, will allow HMS researchers to move discoveries about TB and emerging infections closer to applications in diagnosis, treatment and prevention.



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Improving diagnosis, fighting drug resistance

The TB center will focus on improving diagnostics, especially in children, and on combatting drug resistance. **Megan Murray**, HMS professor of global health and social medicine, will lead the center.

Megan Murray

Megan Murray

"The TB epidemic is still fueled by the fact that people are diagnosed relatively late in the course of their disease and a lot of transmission happens before diagnosis," said Murray, who is also HMS associate professor of medicine at Brigham and Women's Hospital and director of research at **Partners in Health**. "There's no single therapy for TB, so there's a big need to know which drugs people are resistant to."

The TB center will build on **previous work** that used whole-genome

sequencing to identify genetic mutations associated with drug resistance. Using bioinformatics and evolutionary techniques, they will study some 1,500 TB strains collected from an ongoing clinical research study in Peru to characterize resistance mechanisms. The scientists will correlate what they find with a measure called quantitative drug resistance, or the specific amount of a drug to which a strain becomes resistant.

Another project in the center, to be led by **Eric Rubin**, professor of immunology and infectious disease at the Harvard School of Public Health, will apply functional genomics to the mutations found by sequencing to see if the mutations confer drug resistance.

The TB center will work with an industry partner, **Akonni Biosystems**, to develop a diagnostic tool to be used in the field. Led by Chief Scientific Officer **Darrell Chandler** and Director of Engineering **Christopher Cooney**, the molecular diagnostics company will optimize a microarray for TB to test mutations associated with drug resistance.

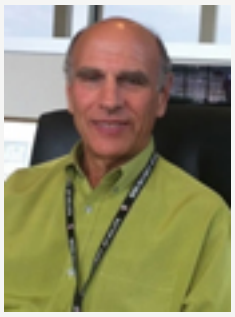
The TB center's fourth of four projects may be its most ambitious, Murray said. Inspired in part by techniques used to interpret archeological DNA in Neanderthal samples, the scientists hope to capture fragments of TB's genetic material from children. The standard TB test looks at sputum, but children can rarely cough up a useful sample. What if clinicians could examine bits of DNA in blood or urine and do other diagnostic tests as well?

“In the Neanderthal project, the challenge has been to take very degraded mammalian DNA mixed with bacterial DNA,” she said. “In our case, we’ve got the other problem: We try to pull microbial DNA mixed with human DNA in urine. Can we sequence that?”

Searching for new defenses

The two new centers in bacteriology and virology will build on the success of the **New England Regional Center for Excellence**, a regional research hub established at HMS after anthrax attacks in 2001 heightened national concerns about biological threats. **Dennis Kasper**, the HMS William Ellery Channing Professor of Medicine at Brigham and Women’s Hospital and professor of microbiology and immunobiology at HMS, is the principal investigator on the NERCE grant.

HMS researchers will continue to focus on pathogens and diseases for which no vaccines or therapies exist—and microbes that resist current drugs. These include the bacterium *Francisella tularensis*, considered a potential agent of bioterrorism, as well as dengue fever, a significant disease in much of the world, which is now creeping into Florida.



Dennis Kasper

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“In NERCE, there was a lot of basic research on biodefense pathogens and later on emerging infectious disease pathogens,” added Kasper. “These new centers are now here to take those discoveries to the next step: translation.” Kasper will head the bacteriology CETR, a program that will focus on tackling the cell

envelope that surrounds bacteria in such microbes as *burkholderia, brucella, Vibrio cholerae* and methicillin-resistant *Staphylococcus aureus*.

The virology CETR will be led by **Sean Whelan**, professor of microbiology and immunobiology and associate head of the Harvard Program in Virology. “This really is an opportunity to make a significant impact in understanding the entry mechanisms of emerging viral pathogens,” Whelan said. “We’re going to learn new biology and understand how some small molecules block viral entry.”

Viral entry is a target of our natural antibody response to viral infection, a step in the viral replication cycle that has not been well exploited by synthetic inhibitors.

Sean Whelan

Sean Whelan

One virology project involves small molecules that inhibit dengue virus replication and another concerns small molecules that block the Ebola virus from getting into cells. A third effort will search for cellular molecules that many viruses use to reach and enter cells. A fourth project will explore how viruses move from one cellular compartment to another before infecting cells with their genes.

New science for emerging threats

“We are looking at a very broad spectrum of emerging viruses that are threats to

human health and potential biodefense agents, asking what molecules and cellular factors are needed to get into cells," Whelan said. "We're hoping that we will identify both pathogen-specific host factors as well as those that are shared among different viruses."

In a similar vein, scientists in the bacteriology CETR hope to find common weaknesses to exploit.

"A lot of antibiotic research addresses enzymes or proteins that are involved in the synthesis of the cell wall of bacteria. There are key proteins that are very similar between different bacteria that could potentially serve as targets," Kasper said. "Vaccines tend to be organism-specific, but we're developing platforms that can be applied to any organism for which you want to develop a vaccine."

"For many years it was sufficient for people to talk about their basic research as perhaps leading to a drug or to a vaccine someday," said Gerald Beltz, administrative director for the two centers in the Department of Microbiology and Immunobiology. "Now it has to be much more direct, and I think these centers are part of that."

HMS investigators within the bacteriology CETR are **John Mekalanos**, the Adele Lehman Professor of Microbiology and Molecular Genetics and head of the department of microbiology and immunobiology; **Suzanne Walker** and **Stephen Lory**, both professors of microbiology and immunobiology;

Thomas Bernhardt and **David Rudner**, associate professors of microbiology and immunobiology; and **Daniel Kahne**, professor of biological chemistry and molecular pharmacology.

Virology CETR investigators at HMS include **James Cunningham**, associate professor of medicine (microbiology and immunobiology) at Brigham and Women's Hospital; **Stephen Harrison**, the Giovanni Armenise-Harvard Professor of Basic Biomedical Science; **Tomas Kirchhausen**, professor of cell biology; **Priscilla Yang**, associate professor of microbiology and immunobiology; and **Nathanael Gray**, professor of biological chemistry and molecular pharmacology.

Other researchers involved in the TB center include **Max Salfinger**, lab director of mycobacteriology and pharmacokinetics at National Jewish Health in Denver, who will lead quantitative genomics project. In the later years of the TB grant, scientists will work with **Ann Goldfeld**, HMS professor of medicine at Boston Children's Hospital, who heads a clinical research site in Cambodia. **Louise Ivers**, HMS associate professor of Global Health and Social Medicine and associate professor of medicine at Brigham and Women's Hospital, will lead similar clinical research in children in Haiti.

James Sacchettini, professor of biochemistry and biophysics and of chemistry at Texas A&M University, and **Thomas Ioerger**, associate professor of computer science at Texas A&M, will lead gene sequencing.

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