Rutgers Lab Sheds Valuable Light on How TB Survives in the BODY

Few more dreaded diseases reside in the global health repertory than tuberculosis. TB, which is spread person-to-person through the air, is responsible for an estimated 10 million infections and 1.6 million deaths annually. Equally sobering is the fact that 25 percent of the world's population—nearly two billion people—is infected with the causative germ *Myobacterium tuberculosis*. Fortunately, most people who are infected develop the latent form of the infection: they have no symptoms, don't feel sick, and cannot spread TB infection to others. Most will hold the infection in check for the rest of their lives, but between 5 and 10 percent will progress to active TB disease at some point, according to the Centers for Disease Control and Prevention (CDC). People with TB disease battle chronic cough, fever, fatigue, weight loss, and, ultimately, the risk of death if the infection is not treated effectively.

"We study the switches that determine how the bacterium that causes tuberculosis has the unique ability to evade being killed by our immune system and is able to persist for long periods of time in its host as a latent infection," says Nancy Woychik, PhD, professor of biochemistry and molecular biology.

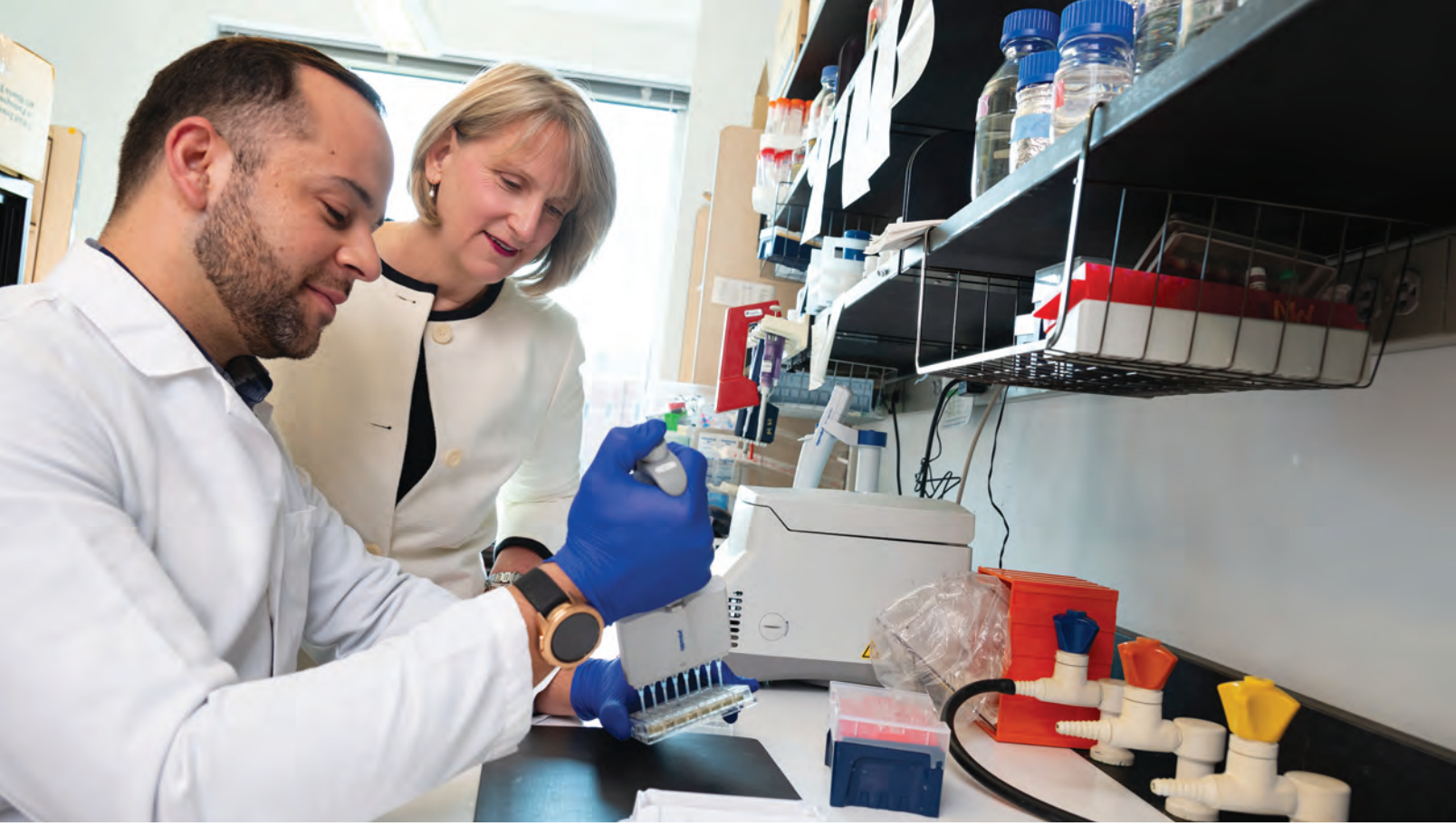
This delicate intersection of latent and active TB is where Nancy Woychik, PhD, professor of biochemistry and molecular biology at Rutgers Robert Wood Johnson Medical School, has targeted much of her research. As a recent study published in *Nature Communications* makes clear, her laboratory is breaking important new ground in understanding the complex series of cellular events that determine how *M. tuberculosis* responds to stresses produced by the human immune system that can tip the balance between latent and active TB.

"We study the switches that determine how the bacterium that causes tuberculosis has the unique ability to evade being killed by our immune system and is able to persist for long periods of time in its host as a latent infection," Dr. Woychik explains. "And latent infections can be reactivated, especially in immune-compromised individuals, to the highly contagious, active form of TB that accelerates spread of the disease." Underscoring the urgency of her research is the fact the number of deaths each year from *M. tuberculosis* has surpassed those from AIDS, making it the world's leading infectious cause of death.

Most susceptible to active TB are individuals whose immune systems have been weakened through viruses such as HIV, which causes AIDS, leaving them unable to fight the TB bacteria. Indeed, an individual with HIV is 25 times more likely to acquire TB than someone with a normal immune system, according to the World Health Organization (WHO). And about half of those who develop TB will do so within the first two years of infection.

In their study, Dr. Woychik and lead author

BY RANDY YOUNG ■ PHOTOS BY JOHN EMERSON



Valdir Barth, a PhD candidate in her lab, drilled down to the molecular and signaling levels to understand how cells react when faced with formidable stresses like immune system attacks. Working closely with Robert Husson, MD, senior physician in pediatrics, Boston Children's Hospital, and professor of pediatrics at Harvard Medical School, they learned that a single gene that may be activated during latent TB infection—known as mazF-mt9—is implicated in driving the pathogen into a dormancy-like state.

Through their research, they further discovered that this gene mediates the shift of *M. tuberculosis* to a nonreplicating state in a rather unexpected way: by controlling the levels of a very important molecule known as tRNA, which signals the bacteria to synthesize only specific proteins that may be beneficial to their survival during latent TB infection. Put another way, through its ability to lower the level of a specific tRNA, mazF-mt9 regulates protein production by a form of reprogramming that is thought to enable cells to exist in a dormant state. This finding in turn led the Rutgers researchers to a "new bacterial strategy" designed to remodel the physiology of the pathogen.

"By learning what this gene actually does, we uncovered a novel approach that *M. tuberculosis* cells may use to establish a latent state and enable this pathogen to hide from normal immune-clearing pathways," explains Barth, who will graduate in 2020 from Robert Wood Johnson Medical School's Graduate Program in Microbiology and Molecular Genetics. "This also has the effect of slowing its growth so that antibiotics are not able to easily kill it."

"We believe that molecular approaches like ours, aimed at understanding latent tuberculosis, hold great promise," says Nancy Woychik, PhD, professor of biochemistry and molecular biology (above), with PhD candidate Valdir Barth. "They could help health authorities respond more effectively on a global scale to a disease that continues to devastate developing countries."

But why focus on understanding the inactive, latent form of infection? The answer largely lies in the prolonged treatment required for inactive TB: six to nine months of an antibiotic drug. As Barth points out, "In many cases, the treatment may not be necessary because the vast majority of people with latent TB will keep the disease under control during their lifetimes."

Focused on how the *M. tuberculosis* stays alive rather than on how to eradicate it, Dr. Woychik and her lab are edging closer to two critical outcomes. One is discovering latency-inducing or -disrupting signals that could serve as predictive biomarkers for reactivation risk. The other is unearthing pathways that could lead to a new class of therapeutic targets for more effectively treating latent TB. "We believe that molecular approaches like ours, aimed at understanding latent tuberculosis, hold great promise," emphasizes Dr. Woychik. "They could help health authorities respond more effectively on a global scale to a disease that continues to devastate developing countries." M