In India: A search for more effective tuberculosis drugs

February 1 2009

Rajesh Gokhale has created a compound in his lab in India that stops tuberculosis in its tracks. In a test tube, the molecule hits four of the bacterium's crucial metabolic pathways at the same time, weakening and ultimately destroying the pathogen.

The problem is that Gokhale's compound will not work in humans. Not willing to set aside seven years of work, he has been knocking on the doors of pharmaceutical companies to see if he can get any takers to help design a less toxic version. Gokhale is pushing himself because he knows if he can design a single drug that is safe and effective, it might one day replace the costly cocktail of drugs that people with tuberculosis must currently take to cure their disease.

While a drug based on Gokhale's ideas is still years away from human testing, it offers a measure of hope that researchers may one day have more modern pharmaceutical "weapons" that can slow down the tuberculosis (TB) pathogen's relentless assault. According to the World Health Organization, TB remains one of the world's top-ten leading causes of death, killing nearly two million people each year. In Gokhale's native India, it kills roughly 1,000 people each day.

"Right now, tuberculosis patients take a cocktail of four drugs, and each inhibits a single enzyme," said Gokhale, a Howard Hughes Medical Institute international research scholar based at the National Institute of Immunology in New Delhi, India. Gokhale's group shows how they designed the molecule that targets multiple enzymes in Mycobacterium

tuberculosis in the January 25, 2009, issue of *Nature Chemical Biology*. "Targeting several enzymes at the same time is a much more efficient approach. Theoretically, patients wouldn't have to take several drugs, they could just take one."

The multi-drug regimen is a major problem for several reasons. It requires TB patients to manage taking four drugs exactly as prescribed over six to nine months. If patients don't take the full course of the medicines, the TB bacteria may develop resistance to the drugs and become even more difficult to treat. To reduce that risk, many countries require that patients go to a clinic so a healthcare professional can watch them take the medication and ensure they are complying with their drug-treatment regimen. This is both expensive and time consuming. Gokhale said that a single drug that targets multiple pathways could save time and money by eliminating the need to take so many drugs over such a long period of time.

To create their new compound, Gokhale and his colleagues exploited an evolutionary quirk in the way Mycobacterium tuberculosis builds the lipid layer that coats its surface. Unlike other organisms, M. tuberculosis displays a suite of complex lipids on its outer membrane. Some scientists have suggested that these long lipid molecules contribute to the bacteria's ability to maintain long-term infections by confusing the host's immune system.

"The complex lipids displayed by Mycobacterium tuberculosis are a big factor in its pathogenicity and virulence," Gokhale said. "But what was not known is how they were made by the organism."

For the past seven years, Gokhale and his colleagues have studied the intricate metabolic pathways that Mycobacterium tuberculosis employs to build complex lipids. He has come to regard the TB bacteria as a "chemical factory" where complex machines, in the form of enzymes,

work together to link simple building blocks—called fatty acids—into long chains. In 2004, Gokhale and his colleagues found a new class of enzymes that are critical for an early phase of the lipid-building process. Called fatty acyl-AMP ligases (FAALs), these enzymes tweak fatty acids so that a second class of enzymes can string them together like bulbs on a strand of Christmas lights.

In their most recent study, Gokhale and his colleagues show that particular molecules that inhibit FAALs also inhibit other, similarly-shaped enzymes involved in the assembly line that is lipid use and degradation. These enzymes are required during the life cycle of the TB bacterium in the humans. "A major challenge has been to develop drugs that could target different stages disease," Gokhale said. "Since this single molecule could potentially grind the assembly line to a halt at different stages of infection, this approach provides tremendous opportunity to develop unique antituberculosis drugs."

Gokhale has collaborated with a colleague at a colleague at the Centre for Cellular and Molecular Biology in Hyderabad, Rajan Sankaranarayanan, to examine the three-dimensional structure of the molecule. This will give his group the opportunity to modify the molecule or develop a new one that is less toxic and better targets the TB bacteria. Gokhale said that the drug industry is finally waking up to the idea that a single drug can work on multiple metabolic pathways, rather than making a molecule that acts in a very specific way on a single target.

"The 'one disease-one drug-one target' paradigm that has dominated thinking in the pharmaceutical industry for the past few decades is now being increasingly challenged by the discovery of compounds that bind to more than one target," Gokhale said. "That's the direction we're heading in trying to develop a single chemical entity that could simultaneously target a family of enzymes in TB."

Source: Howard Hughes Medical Institute