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# Mycolic Acids of Mycobacterium tuberculosis: An Achilles Heel or a Neutralizing Weapon

The Rockefeller University

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INFECTIOUS DISEASE CENTENNIAL LECTURE

# Mycolic Acids of *Mycobacterium tuberculosis*: An Achilles Heel or a Neutralizing Weapon?

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| **DATE:** | **Friday, January 19, 2001** | **PLACE:** | **Caspary Auditorium**<br>**The Rockefeller University**<br>**East 66th Street and York Avenue**<br>**New York City** |
| **TIME:** | **3:15 p.m. Tea**<br>**3:45 p.m. Lecture** | | |

*Mycobacterium tuberculosis*, the tubercule bacillus, was originally described by Robert Koch and, characterized by its unusual staining properties, proven to be the causative agent of tuberculosis (TB). These acid-fast staining properties have been found to result from the unique lipid surface that is predominantly long-chain fatty acids called mycolic acids. These mycolic acids are common to the entire genus of *Mycobacterium*, thus providing a unique signature for the species. The TB-specific drugs isoniazid and ethionamide have been shown to target the synthesis of these mycolic acids. Using a combination of genetic, biochemical and X-ray crystallographic analyses, the target, InhA, has been identified and characterized. Specific inhibition of InhA induces the lysis of mycobacterial cells, thus defining a key Achilles heel for the mycobacterial species that has led to novel drug development.

Both *M. tuberculosis* and *M. leprae*, the causative agent of leprosy, have been shown to decorate their mycolic acids with unique cyclopropyl groups. Mutations that affect cyclopropanations of mycolic acids have been shown to render *M. tuberculosis* unable both to cord and to cause a persistent infection in mice. The cyclopropanated lipids appear to represent a unique virulence factor that protects pathogenic mycobacteria against an effective immune response. Thus, mycolic acids represent a unique two-edged sword for *M. tuberculosis* pathogenesis.

William R. Jacobs Jr., Ph.D., began studying *M. tuberculosis* while a postdoctoral fellow with Barry Bloom, Ph.D., at Albert Einstein College of Medicine, where he sought to develop BCG as a recombinant vector for eliciting immune responses against cloned foreign antigens. Drs. Jacob and Bloom were the first to introduce foreign DNA into slow-growing mycobacteria using a novel recombinant DNA vector called a shuttle plasmid. This system further allowed Dr. Jacobs to achieve the first transformation of BCG and *M. tuberculosis*. Drs. Jacobs and Bloom went on to develop the first recombinant BCG vaccines and demonstrated that they could elicit protective immune responses to a variety of cloned foreign antigens. Dr. Jacobs has used phage systems to develop a variety of tools for genetically manipulating mycobacteria including transposon delivery phages, luciferase reporter phages and specialized transducing phages.

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