Mycobacterium tuberculosis is the leading cause of death due to infectious disease. By investigating the mechanisms that enable this bacterium to cause tuberculosis and evade current antibiotics, the Rock lab aims to lay the foundation for new therapeutic strategies to improve control of this epidemic.

Despite the discovery of antibiotics, tuberculosis (TB) remains an enduring global public health threat. New drugs, drug regimens, and innovative approaches to limit drug resistance are desperately needed—and to facilitate their development, the Rock lab seeks to provide a more complete understanding of the genetic and biochemical basis of Mycobacterium tuberculosis (Mtb) pathogenesis.

Genetic studies of this bacterium have thus far been hampered by the difficulties associated with conventional genetic tools. To fill this methodological gap, Rock and colleagues developed a CRISPR interference (CRISPRi) gene knockdown method for Mtb. This transformative tool is enabling the systematic interrogation of gene function in Mtb using high-throughput approaches to previously intractable problems in the field. The Rock lab uses this and other methods to study the mechanisms that enable chronic infection, antibiotic tolerance and resistance, and large-scale genetic and chemical interactions.

TB is a chronic, progressive disease. In most cases, the host immune system is capable of restraining but not eliminating Mtb, leading to lifelong infection. The mechanisms that enable the pathogen to persist in the face of a robust adaptive immune response, sometimes for decades, are poorly understood. The Rock lab is using new approaches to define the genetic basis for persistent Mtb infection.

Mtb infection can be treated with antibiotics. However, effective TB treatment requires a combination of four drugs taken for a minimum of six months. This lengthy treatment, thought to be necessitated by the presence of antibiotic-tolerant bacilli that arise during infection, is one of the most important roadblocks to effective TB control. Moreover, antibiotic tolerance can ultimately facilitate the evolution of antibiotic resistance, thereby fueling the growing problem of drug-resistant TB. The Rock lab is currently investigating the molecular mechanisms of antibiotic tolerance, as well as the mechanisms by which the bacterium can ultimately evolve antibiotic resistance.

Finally, the lab is interested in using genome-scale genetic and chemical interaction mapping to improve Mtb chemotherapy. The current four-drug combination to treat TB was developed in the 1960s. Rock seeks to better understand how anti-TB drugs (and combinations) work with the long-term goal of identifying ways to improve therapies by reducing treatment time and limiting the emergence of drug resistance.