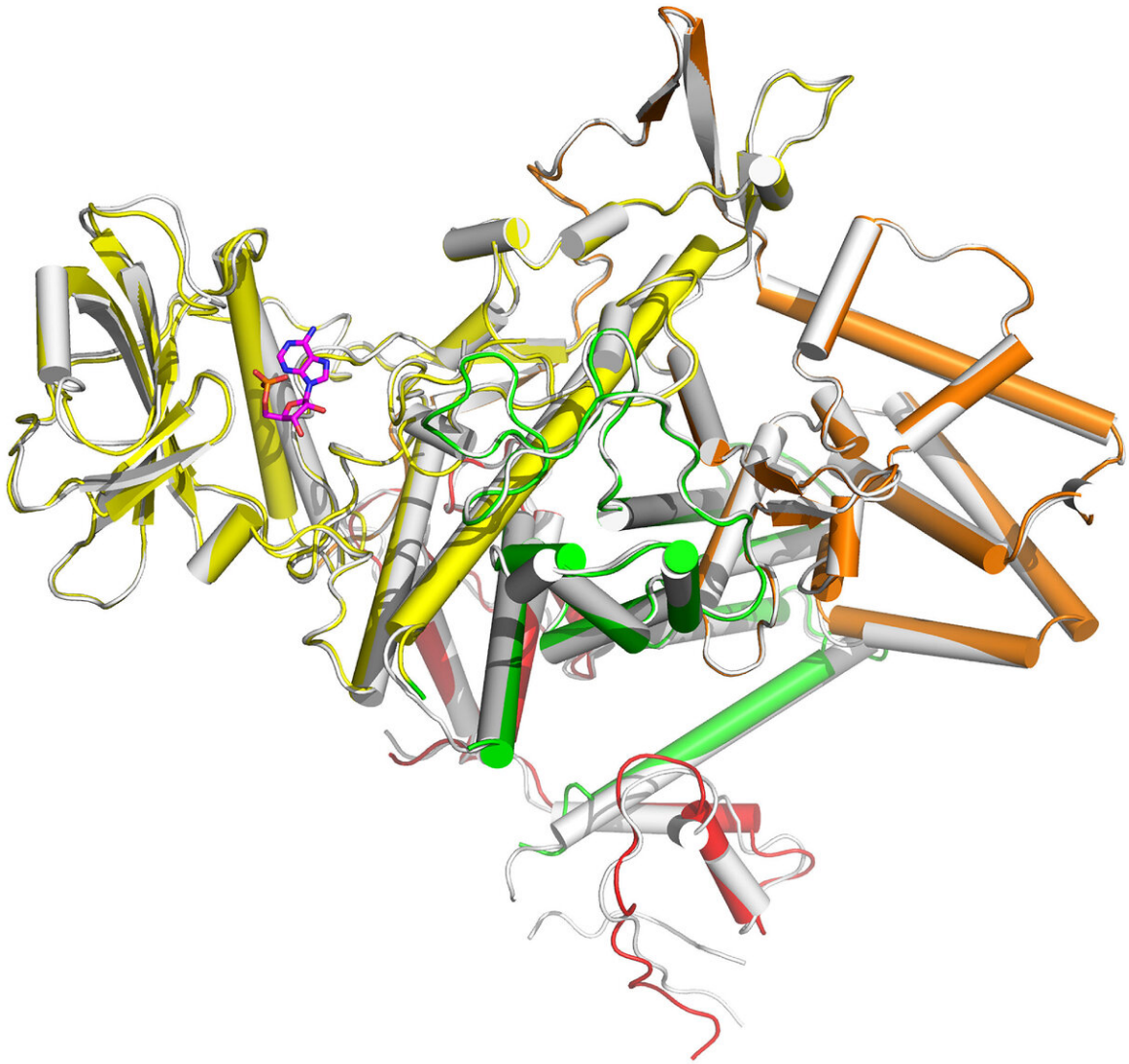
Discovery provides path to pathogen-targeted antibiotics

August 16 2019, by Steve Tally



A protein discovered in Legionella pneumophila shows how the bacterium

infects cells in the body, and may provide a path for new antibiotics that only affect virulent bacteria. Credit: Purdue University image/Luo

"Take with food" is a common warning for people using antibiotics, but a discovery announced this week in the scientific journal *Nature* may create a path to more targeted drugs.

This advice for taking antibiotics is needed because current drugs kill any type of bacteria, including the helpful bacteria in our intestines that help us digest our food. When we take current antibiotics, it can cause digestive distress, and even worse outcomes.

Although we may think of bacteria as disease-causing microorganisms, there are about as many bacteria in your body as human cells. And nearly all are helpful—they are nearly as essential for human survival as air, food, and water. Which is why a more selective antibiotic would be important.

Zhao-Qing Luo, professor of biology at Purdue University, and his team have found the mechanism by which the bacterium that causes Legionnaires' disease begins its invasion into host cells. This discovery by itself provides a path for treatment of the relatively rare disease, which affects fewer than 20,000 people per year in the United States.

But the implications of the discovery go well beyond Legionnaires'.

Luo and his colleagues found that bacteria inject approximately 300 proteins into the host cell, which allows the bacteria to survive and replicate once inside the host.

Studies from the Luo lab had previously shown that a single enzyme

produced by bacteria can override cell defenses speeding infections. The new discovery finds that that enzyme is regulated by a single enzyme through a unique mechanism.

"This provides a new target for drug therapy to fight virulent bacteria," Luo said. "One common problem for current antibiotics is that they kill indiscriminately because they attack the central functionality of the bacterial cells. This will disrupt the microbiome."

Instead, Luo said that a drug that attacked just this infection mechanism would not affect the good bacteria that live in our bodies.

Luo said the injected protein molecule uses the cellular molecule ATP in a way that is unique in how it cleaves the energy molecule, which might provide an attractive mechanism for a drug target.

"Now that we've identified this protein that's required for infection, we can screen for compounds that interfere with its action and investigate those to see if they might be suitable as new drugs," he said.

More information: Ninghai Gan et al. Regulation of phosphoribosyl ubiquitination by a calmodulin-dependent glutamylase, *Nature* (2019). DOI: 10.1038/s41586-019-1439-1

Provided by Purdue University