'Naked Darth Vader' approach could tame antibiotic resistant superbugs

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Rather than trying to kill bacteria outright with drugs, Université de Montréal researchers have discovered a way to disarm bacteria that may allow the body's own defense mechanisms to destroy them.

"To understand this strategy one could imagine harmful bacteria being like Darth Vader, and the anti-virulence drug would take away his armor and lightsaber," explained Dr. Christian Baron, the study's lead author and Professor at the Department of Biochemistry. "A naked Darth Vader would be an easy target and similarly, pathogenic bacteria without their virulence factors would be rendered harmless and eliminated by our immune system." Virulence factors are what make certain bacteria harmful to our bodies and different from most bacteria that live on our body or inside the intestinal system, which are harmless or even useful for us. Baron's research group will publish an article outlining the details of their findings in *Chemistry & Biology*.

Infectious diseases caused by pathogenic bacteria were a major scourge of mankind, but thanks to the introduction of antibiotics beginning in the middle of the 20th century, most bacterial infections were largely controlled. It was a widely held belief that biomedical research had largely won the battle against these diseases. However, as antibiotics kill by targeting the essential cell functions of most (not always all) bacteria, this leads to survival of the most adaptable. "Bacteria have the capacity to develop resistance to antibiotics and they transfer this capacity to their offspring and to other bacteria. As a consequence, resistance began to emerge among the bacteria soon after the introduction of antibiotics,"

Baron said. In their worst forms, "superbugs" have emerged, those resistant to all but a few or even to all antibiotics."

Baron's team has discovered small molecules that target proteins in a biological system (a type IV secretion system) that is required for many bacteria to be harmful. "As if we were pulling on a loose thread in Darth Vader's cape, we have found a way to unravel the molecular details of the binding of these molecules to a target protein known as VirB8, a key part of the virulence mechanism of human and animal pathogenic *Brucella* species of bacteria," Baron explained. This strategy has many advantages since resistance to such treatments would likely be slow or might not even occur. Virulent bacteria could be rendered as harmless as those that live in our gut.

The concept of anti-virulence drugs still has to be proven in the clinic, but in the new battles that will arise in our war on bacteria, such drugs could prove formidable new weapons.

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