New drug class offers potential new treatment for lethal bacteria

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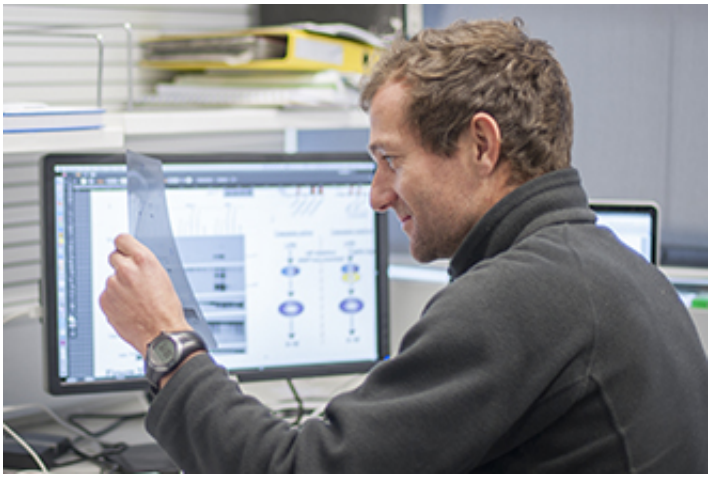

Dr James Vince and colleagues have revealed a potential new treatment for certain bacterial infections.

A new class of drugs has shown promise for treating the bacteria that cause legionnaires' disease, a potentially fatal lung infection.

The discovery that 'BH3-mimetic' drugs obliterate cells infected with Legionella bacteria could lead to new treatments for a variety of bacterial infections, even those that are resistant to antibiotics.

A research team including Dr James Vince of the Walter and Eliza Hall Institute, and Dr Thomas Naderer and PhD student Ms Mary Spier from the Monash University Biomedicine Discovery Institute, showed for the

first time that a protein called BCL-XL is an Achilles' heel of Legionella-infected cells. Turning off BCL-XL with BH3-mimetic drugs killed the infected cells, allowing the infection to be cleared from the body. The research is published in the March edition of *Nature Microbiology*.

People become infected with Legionella bacteria by inhaling contaminated water droplets, often from cooling towers or spas, or contaminated soil such as potting mix. The bacteria hide within human cells called macrophages, escaping the body's own immune defenses and being shielded from many types of antibiotics. People with a weakened immune system, including the elderly, are at particular risk of the serious lung Legionella infection called legionairres' disease.

Dr Vince said that soon after infecting a macrophage, Legionella bacteria alter the composition of proteins within their host cell to prevent the host from detecting the infection. "We were particularly interested that this drained the macrophage of a protein called MCL-1, that helps to keep cells alive," he said. "The bacteria inadvertently leave BCL-XL as the only survival protein keeping the cell alive - a single point of failure at the molecular level.

"We exploited this vulnerability by treating Legionella-infected cells with BH3-mimetic drugs that switch off BCL-XL. These agents could specifically kill the infected macrophages, leaving uninfected macrophages untouched - exactly what you would want to happen if you were treating an infected person," Dr Vince said.

BH3-mimetics drugs were initially developed to treat cancer, by switching off 'survival' proteins such as BCL-XL and MCL-1 that make cancer cells immortal.

"We were really excited to discover that BH3-mimetics can be used to

treat serious Legionella lung infections, killing the infected cells and allowing the bacteria to be cleared from the body," Dr Vince said. "Walter and Eliza Hall Institute scientists have spent three decades deciphering how 'survival proteins' including BCL-XL keep cells alive, and how this can be exploited to treat cancer. This is the first time BH3-mimetics have been used to successfully treat bacterial infections."

With the emergence of antibiotic-resistant strains of bacteria now posing a serious global health risk, new treatments for bacterial infections are urgently needed.

"In the future we are hopeful that BH3-mimetics may be a valuable new line of treatment for Legionella and other bacteria that similarly hide out within cells," Dr Vince said.

More information: Mary Speir et al. Eliminating Legionella by inhibiting BCL-XL to induce macrophage apoptosis, *Nature Microbiology* (2016). DOI: 10.1038/nmicrobiol.2015.34

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