# A 'warhead' molecule to hunt down deadly bacteria

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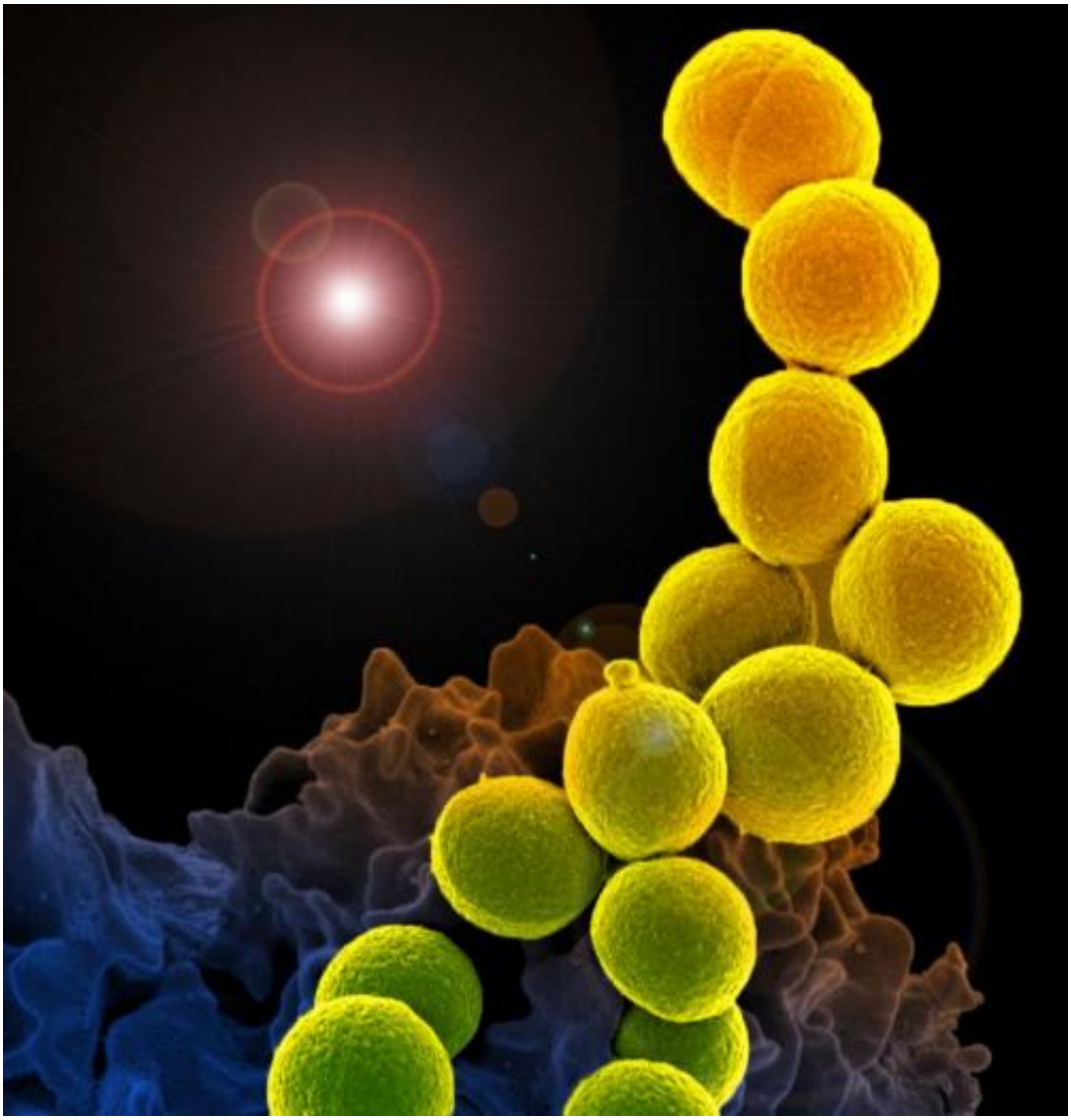

In this electron micrograph, a white blood cell eats an antibiotic resistant bacteria called methicillin-resistant *Staphylococcus aureus*, or MRSA. Credit: National Institute of Allergy and Infectious Diseases

Targeting deadly, drug-resistant bacteria poses a serious challenge to researchers looking for antibiotics that can kill pathogens without causing collateral damage in human cells. A team of Boston College chemists details a new approach using a "warhead" molecule to attack bacteria—and spare healthy human cells—by targeting a pair of lipids found on the surface of deadly germs, according to a report today in the journal *Nature Communications*.

The new strategy required the researchers to develop a novel type of "warhead molecule" capable of selectively targeting bacteria, overcoming biological conditions that interfere with bonding to pathogens and avoiding healthy human cells, said Boston College Associate Professor of Chemistry Jianmin Gao, the lead author of the report.

The BC team found answers to those challenges in the covalent chemistry of lipids, Gao said.

"In contrast to other efforts focused on the charge-to-charge attraction between molecules, we are using a completely different mechanism to target bacterial cells," said Gao. "Our method exploits the covalent chemistry of lipids - where the lipids react with synthetic molecules to form new chemical structures based on the formation of new covalent bonds."

Pathogenic bacteria that are resistant to conventional antibiotics pose increasingly serious threats to public health. Researchers in medicinal chemistry, particularly those who seek to develop new antibiotics, are constantly looking for new ways to identify and differentiate bacterial pathogens from host cells within the human body.

Gao said bacterial cells are known to display a different set of lipids in their membranes. Prior research has focused on the use of positively charged peptides to target negatively charged lipids on the surface of bacterial cells. The approach has seen limited success as the charge-charge attraction between the attacking molecules and bacteria is prone to weakening by the presence of salt and other molecules, said Gao.

The researchers developed a novel, unnatural amino acid that serves as a suitable molecular warhead to target bacterial pathogens. Gao and his group sent the warhead molecule after bacterial lipids known as amine-presenting lipids—specifically phosphatidylethanolamine (PE) and lysyl phosphatidylglycerol (Lys-PG) - which can be selectively derivatized to form iminoboronates, a covalent bond forming process that allows the selective recognition and labeling of bacterial cells.

In addition, because amine-presenting lipids are scarce on the surface of mammalian cells, they are able to seek out and label bacterial cells with a high degree of selectivity, Gao said. Furthermore, iminoboronate formation can be reversed under physiologic conditions, giving the new method a high degree of control and allowing the warhead molecules to self-correct if unintended targets are reached.

Gao said a large number of bacterial species present PE and Lys-PG on their surfaces, making the covalent labeling strategy applicable to many applications in the diagnosis of bacterial infections and the delivery of antibiotic therapies.

"For the short term, we hope this work will inspire other people to consider using covalent chemistry for interrogating biological systems," Gao said. "Going into the future, we are excited to explore the potential of our chemistry for imaging bacterial infections. We are also working hard to apply our current findings to facilitate the targeted delivery of potent antibiotics to bacterial cells only."

Provided by Boston College