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Priya Raman

Scientists Map Three Weak Points in Antibiotic-Resistant Bacteria

NTU and Imperial College researchers find three weaknesses in drug-resistant bacteria: energy production, virus defenses and the toxin-loading machinery of a bacterial speargun.

In brief

01 A new compound blocking the energy enzyme cytochrome bcc oxidase cut *M. abscessus* levels 100-fold in four days when combined with clofazimine, and is non-toxic to human cells.

02 Phage treatment of smooth *M. abscessus* strains produced rough variants lacking glycopeptidolipids, suggesting phage cocktails should target both forms to limit resistance.

03 Cryo-electron microscopy revealed how *P. aeruginosa* assembles its Type VI Secretion System, loading toxin 'cocktails' into Hcp protein rings before firing them into target cells.



Researchers at Nanyang Technological University (NTU), working with partners in Singapore and London, have exposed three distinct vulnerabilities in bacteria that resist antibiotics — their energy production, their defenses against viruses, and the microscopic weapons they use to attack rival cells.

The stakes are high. Antimicrobial resistance is one of the world's top public health threats, often called a silent pandemic, and resistant bacteria already cause millions of deaths each year. According to World Health Organization estimates, the death toll could reach 10 million annually by 2050 if the trend continues unchecked.

The new findings, published across three studies in *Nature Communications*, the *Proceedings of the National Academy of Sciences* and *Nature Microbiology*, suggest paths toward treatments that either kill resistant bacteria outright or disarm them.

Shutting down the power supply

The first study focuses on *Mycobacterium abscessus*, a bacterium that causes severe lung disease in people with cystic fibrosis and is naturally resistant to many common antibiotics. Like all opportunistic pathogens, it is especially dangerous to patients with weakened immune systems.

A team led by Professor Gerhard Grüber of NTU's School of Biological Sciences developed a compound that starves the bacterium of energy. The compound blocks a key enzyme — cytochrome bcc oxidase — in the bacterium's electron transport chain, the series of proteins cells use to produce ATP, the molecule that powers essentially all metabolic processes.

Using cryo-electron microscopy, a technique that freezes samples to reveal molecular structures in fine detail, the researchers identified a pocket on the cytochrome b subunit of the enzyme. This pocket binds the substrate and drives the enzyme's activity. The team then designed a compound that fits into the pocket like a key, switching the enzyme off.

Because the enzyme's structure is unique to *M. abscessus*, the compound leaves human cells unharmed. Combined with clofazimine, an existing antibiotic for mycobacterial infections, it reduced the bacterial population 100-fold within four days in laboratory experiments.

"As the currency of life, ATP delivers the energy for essential processes in *M. abscessus*, including its defense mechanisms against antibiotics," says Grüber, the study's corresponding author. "Silencing the electron transport chain that produces ATP is thus a potential treatment for difficult-to-treat *M. abscessus* infections that also disables the bacterium."

A patent has been filed, and the researchers are working with the U.S.-based pharmaceutical company Hsiri Therapeutics to license the compound.

When viruses make bacteria tougher

A second avenue is phage therapy, which uses viruses called bacteriophages. These viruses infect bacteria, hijack their replication machinery and multiply until the bacteria burst open.

But *M. abscessus* can push back, as researchers from NTU's Lee Kong Chian School of Medicine and the Agency for Science, Technology and Research (A*STAR) discovered. The bacterium comes in two variants: a smooth form, coated with lipids called glycopeptidolipids, and a rough form that lacks them. The rough variant causes more severe disease and is harder to treat.

When the scientists treated smooth strains with phages that target them, rough variants emerged. These carried mutations in genes responsible for building and transporting glycopeptidolipids to the bacterial surface. The researchers hypothesize that losing these surface lipids prevents phages from binding and attacking. Other bacteria became phage-resistant while staying smooth, acquiring mutations in different surface-related genes instead.

"These findings reveal an important challenge in developing phage-based therapies," explains Professor Pablo Bifani of LKCMedicine, the study's corresponding author. "Although phages can effectively eliminate bacteria, they may also inadvertently make infections more difficult to treat, as seen in the 'rough' form."

He adds that a cocktail of phages targeting both smooth and rough variants could reduce the likelihood of resistance developing during treatment.

A microscopic speargun, decoded

The third study concerns *Pseudomonas aeruginosa*, a highly drug-resistant pathogen that causes chronic infections in immunocompromised, hospitalized and critically ill patients. Its signature weapon is the Type VI Secretion System (T6SS), which works like a speargun, injecting toxins into rival bacteria and host cells to clear the way for colonization.

Researchers at NTU and Imperial College London, using biochemical analysis and cryo-electron microscopy, worked out how this weapon loads its ammunition. A protein called Hcp first captures a toxin. Five more Hcp proteins then wrap around it to form a ring resembling a flying saucer, with the toxin at its center; larger toxins may require two rings. The loaded rings stack into a tube, and when the system contracts, it propels that tube outward like a harpoon into the target cell.

Because the tube can carry different toxins at once, a single shot can deliver a cocktail of harmful compounds.

"This bacterium does not just fire a single toxin," says co-corresponding author Professor Alain Filloux, research director of the Biofilms & Health Cluster at NTU's Singapore Center for Environmental Life Sciences Engineering. "It loads a cocktail of toxins into a microscopic speargun and fires them in one strike, allowing it to attack different targets, including beneficial bacteria that normally live in the body, as well as the host's own defense cells."

Blocking this loading step, he suggests, could disarm the bacterium and make it less able to cause disease. The researchers also note that harmless bacteria could be engineered to carry a T6SS loaded with toxins against invading pathogens, including resistant gut bacteria.

"What is exciting about this work is that we can now see, at near-atomic detail, how a bacterial toxin is physically captured and enclosed inside the building blocks of the T6SS," says Associate Professor Tiago Dias da Costa of Imperial College London, who co-led the study. "High-resolution 3D images obtained from cryo-electron microscopy reveal that toxin loading is not a passive process, but a highly organized assembly pathway in which the secretion tube forms around its cargo."

Early promise, open questions

All three studies remain at an early stage, and the findings come largely from laboratory experiments rather than clinical trials. The anti-*M. abscessus* compound's effectiveness has so far been demonstrated in combination with clofazimine in preclinical settings, and the proposed phage cocktails and T6SS-blocking strategies are still concepts that require validation. Still, by mapping how resistant bacteria generate energy, evade viruses and load their weapons, researchers have identified concrete molecular targets — and new ways to stay one step ahead.

<https://scibeat.com/articles/scientists-map-three-weak-points-in-antibiotic-resistant-bacteria-5fa093da>