

New tool uncovers 'elegant' mechanism responsible for antibiotic tolerance in golden staph

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Credit: AI-generated image ([disclaimer](#))

Researchers have uncovered an elegant system that contributes to antibiotic tolerance in the "superbug" *Staphylococcus aureus*, identifying and characterizing a mechanism for drug tolerance and providing new lines for antibiotic defense.

An international team of researchers, including those from UNSW's School of Biotechnology & Biomolecular Sciences, have applied a promising new tool—CLASH—to capture hundreds of undiscovered mechanisms of gene regulation in a strain of multi-drug resistant *Staphylococcus aureus* (MRSA).

The 500 mechanisms uncovered by the new tool were based on the mRNA of *S. aureus*. Normally serving merely as instructions for making proteins, these newly revealed mRNAs were controlling other genes in *S. aureus* through direct interactions—regulating the bacteria's very own genetic information and antibiotic tolerance.

Among those RNAs found was a mechanism that thickens the bacteria's cell wall—a change commonly seen in clinical strains of MRSA that are tolerant to last-line antibiotics—potentially identifying new targets for antibiotic treatment. Their work has been published in *Nature Communications*.

"Before our study, only three other mRNAs had been shown to regulate bacterial RNA," says co-author Associate Professor Jai Tree. "It's relatively rare. But looking at our CLASH data was the real surprise. We found that in *Staphylococcus aureus*, there was evidence for 543 regulatory mRNA interactions."

"This is a shift from our current understanding of gene regulation in bacteria."

This system of adaptation in *S. aureus* has remained undetected due to a lack of tools for broadly capturing RNA interactions. In other disease-causing bacteria, related techniques rely on the presence of particular proteins, proteins that don't seem to function in *S. aureus*.

If mRNA can be compared to copied pages from a recipe book, the

regulatory mRNAs in *S. aureus* have eschewed the chef and begun dictating the pace and production of their own meals.

"When a gene (DNA) is transcribed into RNA, a little bit of extra sequence is transcribed from either side—like the aglets of a shoelace—these are termed the 'untranslated regions' or UTRs," says A/Prof Tree. "It's these UTRs of mRNAs in *S. aureus* that are performing a regulatory role.

"And where a typical UTR is 40 to 50 bases long, we found that around one-third of the UTRs in *S. aureus* are 100 bases long—which is long. This likely adds an entirely new layer of gene regulation."

The particular strain of *S. aureus* used in this study was taken from a patient with MRSA septicemia who was treated for 42 days with our "last-line of defense" and most effective antibiotic: [vancomycin](#). Since *S. aureus* do not acquire vancomycin tolerance extraneously from other *S. aureus* but evolve it through a series of mutations, the researchers analyzed this strain using CLASH to understand how they were becoming vancomycin tolerant.

"One of the mRNA UTRs we discovered was a regulatory RNA that promotes an enzyme involved in cell wall thickening. It's this thickening that is consistent with vancomycin-tolerant *S. aureus*," says A/Prof Tree.

"We found evidence of over 500 mRNA-mRNA interactions occurring in *S. aureus*—information uncovered by CLASH that allows us to ascribe functions to many regulatory RNAs in *S. aureus*—often for the first time.

"The 'superbug,' multi-drug resistant *Staphylococcus aureus*, is a major problem in both health care and community settings," says A/Prof. Tree. "Treatment options for MRSA septicemia—infections that enter the

blood—are limited to last-line antibiotics, and the treatment of choice is vancomycin.

"Vancomycin is an antibiotic that blocks assembly of a new cell wall in *S. aureus*. If the bacterium can't make a new cell wall during division, it explodes. Those *S. aureus* tolerant to vancomycin have thicker cell walls, likely limiting antibiotic at the site of cell wall synthesis."

By revealing one of the mechanisms of vancomycin tolerance in *S. aureus*, the once hidden line of defense is made visible for our offensive, 're-sensitizing' resistant *S. aureus* to vancomycin again.

"There has been renewed interest in using 'antisense RNA' that can be delivered into the bacterial cell, penetrating the cell wall and binding RNAs within the cell. In this way, we might be able to co-administer an antisense RNA with vancomycin—the antisense RNA would make MRSA sensitive and the vancomycin would kill the cell," says A/Prof Tree.

While the functions of some mRNAs in *S. aureus* have been ascribed, there remains a lot of work to do—especially given the varied mechanisms behind vancomycin-tolerance *S. aureus*.

"The next steps are to understand if [the regulatory RNA we've already isolated] is required for a [broad spectrum](#) of other, clinical strains of vancomycin-tolerant *S. aureus*. These are genetically heterogenous isolates and one of the difficulties has been the multitude of methods of becoming vancomycin tolerant.

"So we would like to understand if targeting the regulatory RNA would be a useful approach for many different vancomycin tolerant strains. Although we don't know exactly what all the mRNAs are doing, our next step is to identify the really important ones."

More information: Daniel G. Mediati et al, RNase III-CLASH of multi-drug resistant *Staphylococcus aureus* reveals a regulatory mRNA 3'UTR required for intermediate vancomycin resistance, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-31177-8](https://doi.org/10.1038/s41467-022-31177-8)

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