Oxford and OSCAR team report new modular antimicrobial platform: ‘Smart’ mini-SimCells targets drug-resistant bacteria

Antimicrobial resistance (AMR) has been described by the World Health Organization as a global health emergency that threatens to reverse nearly a century of medical progress. According to WHO estimates, bacterial AMR was directly responsible for 1.27 million deaths in 2019 and contributed to nearly 5 million deaths globally[i,ii]. The economic burden is also staggering: the World Bank estimates that AMR could result in an annual GDP loss of US$3.4 trillion and push 24 million more people into extreme poverty by 2030[iii]. Yet, the pipeline of new treatments remains alarmingly insufficient [iv].

In this context, research teams led by Professor Wei Huang at the University of Oxford and OSCAR have engineered a programmable, chromosome-free, nonreplicating bacterial particle, known as SimCell and mini-SimCell, which selectively recognises and kills antimicrobial-resistant pathogens while preserving beneficial microbes. Published in *PNAS*, this work introduces a dual-mechanism platform based on SimCells and mini-SimCells -a potential shift from broad-spectrum antibiotics to precision antimicrobials.

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Reprogrammed SimCells for antimicrobial therapy

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Engineering safe, non-replicating bioparticles

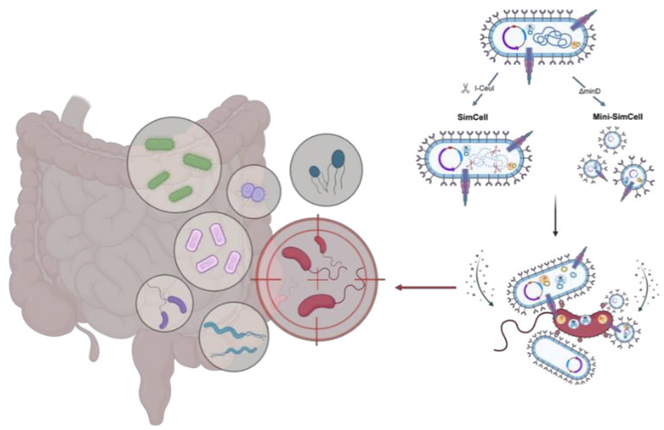

Fig. 1 SimCells are engineered and genome-free bacterial cells, providing a powerful tool for targeted elimination of specific pathogens without disrupting the broader microbial community in microbiome.

SimCells are engineered bacterial cells around 1-2 μm in size, while mini-SimCells are smaller particles of roughly 100–400 nm. They do not carry chromosomes, and therefore cannot grow or divide, yet retain designed cellular machinery for refined functions. In this work, researchers equipped SimCells and mini-SimCells with two distinct antimicrobial mechanisms, both activated only when the particle binds tightly to its target.

Demonstrated efficacy in laboratory tests

In single-dose experiments, dual-mechanism mini-SimCells eliminated 94.4% of the target bacteria within 24 hours and 99.3% within 48 hours. In mixed microbial communities, four serial doses achieved a selective 10^3-fold reduction of the targeted bacterial population while sparing non-target bacteria, highlighting the specificity of the approach.

Antimicrobial activity against a multidrug-resistant clinical strain

The team then applied the platform to a clinically important multidrug-resistant pathogen, *Escherichia coli* ST131. *Escherichia coli* ST131 is a globally disseminated high-risk pandemic lineage causing urinary tract infections and bloodstream infections, characterized by widespread resistance to fluoroquinolones and extended spectrum cephalosporins[v]. By replacing the targeting module with the nanobody Nb39, which recognises a native OmpA antigen on ST131, the researchers achieved more than 97% elimination of this strain at both 24 and 48 hours. Notably, this effect was observed even though the strain remained resistant to comparator broad-spectrum β-lactam antibiotics in the study's assays.

Modular "plug-and-play" design

The significance of this work lies not only in its antimicrobial activity but also in its "modularised"and "plug-and-play" design logic. Rather than relying solely on conventional antibiotics, the SimCell platform is modular and reprogrammable: the targeting nanobody, killing machinery, and enzymatic payload can each be reconfigured or redesigned. This architecture could enable rapid retargeting against newly emerging resistant strains and support a redirection towards pathogen-specific, microbiome-sparing precision antimicrobials.

The full paper is available to read online at
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