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BIOFILMS

Bubbly for bacteria

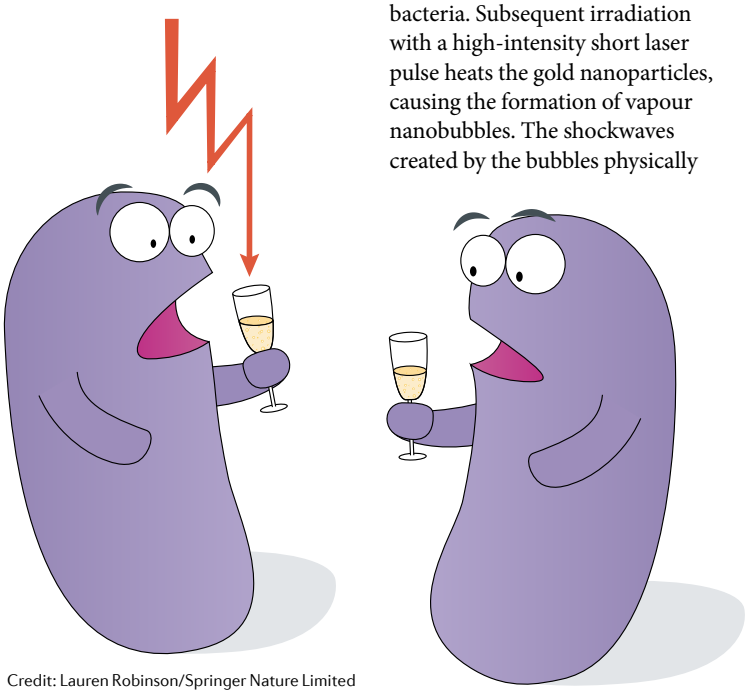
> In this era of rising antimicrobial resistance, our findings show that there is much to be gained, even with existing drugs, by improving their diffusion in biofilms

The decreased sensitivity of pathogenic bacteria to antibiotics is, in part, caused by the formation of biofilms. These biofilms prevent the diffusion of drugs and thus hinder the ability of antibiotics to kill the bacteria, leading to antibiotic resistance. Now, writing in *Nature Communications*, Kevin Braeckmans and colleagues report the disruption of biofilms by laser-induced vapour nanobubbles around plasmonic nanoparticles and the increased efficacy of antibiotic treatment as a result of disturbing the structural integrity of the biofilm.

Many bacterial strains, such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*, that can cause severe acute and chronic infections can grow as biofilms, which are dense aggregates of microorganisms, protecting the bacteria from being killed by antibiotics. "Well-known examples are infected chronic wounds or dental root canals," explains Braeckmans. "Bacteria organized in biofilms are typically more difficult to eradicate than free-floating single cells owing to a number of specific defence mechanisms, including the diffusion barrier to antimicrobial agents."

Inhibition and disruption of biofilm formation have been suggested as treatment strategies to address bacterial resistance to antibiotic treatment. However, most biochemical and physical methods to inhibit formation or disrupt biofilms, such as photothermal or ultrasound therapy, lack specificity and may induce tissue damage.

Braeckmans and colleagues exploit the possibility to locally induce vapour nanobubbles around gold nanoparticles using laser pulses. Suspensions of gold nanoparticles can penetrate biofilms of gram-negative and gram-positive bacteria. Subsequent irradiation with a high-intensity short laser pulse heats the gold nanoparticles, causing the formation of vapour nanobubbles. The shockwaves created by the bubbles physically interfere with the structural integrity of the biofilm by increasing the space between individual bacterial cells.



Credit: Lauren Robinson/Springer Nature Limited

The researchers then treated the biofilms with the antibiotic drug tobramycin for 24 hours and evaluated bacterial cell death. "We achieved an increase in eradication of one to three orders of magnitude of gram-positive and gram-negative biofilms, if the biofilms were pretreated with laser-induced vapour nanobubbles," says Braeckmans.

Moreover, vapour nanobubble formation in biofilms can be repeatedly induced, which further increases the efficiency of antibiotic treatment. For example, ten exposures to vapour nanobubbles of a *Pseudomonas aeruginosa* film leads to a 3,000-fold increase in killing efficiency compared with tobramycin treatment alone.

"In this era of rising antimicrobial resistance, our findings show that there is much to be gained, even with existing drugs, by improving their diffusion in biofilms," comments Braeckmans.

The researchers further demonstrate that laser-treatment does not cause the dispersal of bacteria into the supernatant and that, in contrast to photothermal therapy, the heat within the gold nanoparticles is converted into mechanical energy and, therefore, does not harm the surrounding tissue.

Braeckmans and colleagues intend to explore relevant in vivo models for their approach, although this will require the development of suitable laser devices. They are also investigating the use of gold nanorods and other types of plasmonic nanomaterials that can absorb near-infrared wavelengths, to be able to deeply penetrate tissues.

Christine-Maria Horejs

ORIGINAL ARTICLE Teirlinck, E. et al. Laser-induced vapour nanobubbles improve drug diffusion and efficiency in bacterial biofilms. *Nat. Commun.* **9**, 4518 (2018)