Microrobotics

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Living microrobots target cancer

Bacteria-based living microrobots may enable targeted delivery of cancer therapeutic agents deep into tumours by exploiting the inherent onboard sensing and self-propulsion of bacteria. In addition, intrinsic or genetically engineered therapeutic functions can be implemented in bacteria — for example, to stimulate an immune response or express therapeutic molecules. However, the innate propulsion of bacteria alone may not be sufficient to ensure targeted delivery, and thus, strategies are needed to bring bacteria efficiently to their intended destinations. Now, writing in *Science Robotics*, Simone Schuerle and colleagues developed a biohybrid system made of magnetically responsive bacteria and liposomes that act together as controllable living microrobots for targeted drug delivery. Importantly, the researchers have established a magnetic torque-driven control scheme that increases the transport of the microrobots across the endothelial barrier.

Magnetic fields can be used to manipulate bacteria-based microrobots by directing or overriding their self-propulsion. Magnetic responsiveness can result from functionalizing bacteria with magnetic nanoparticles or naturally produced iron oxide nanocrystals, as with magnetotactic bacteria, such as *Magnetospirillum magneticum*. However, current approaches, such as steering bacteria with directing magnetic fields or pulling them with magnetic field gradients, have considerable drawbacks, including the need to inject the bacteria near the tumour site. Magnetic field gradients, in particular, are poorly scalable and are limited to superficial targets.

Schuerle and colleagues established a hybrid control strategy using rotating magnetic fields (RMFs), which can be generated at clinically relevant scales, to drive magnetotactic bacteria with torques, followed by innate propulsion and autonomous taxis-based navigation. The team developed a model system of vascular endothelium and a three-dimensional spheroid tumour model to study and optimize the parameters of the RMFs in vitro for effective actuation. Notably, the magnetic torque-driven control approach makes the bacteria tumble along blood vessel walls, increasing their probability of passing through the gaps between endothelial cells and entering the tumour tissue. Once in the tumour, the bacteria migrate on their own into hypoxic regions of the tumour.

The researchers then tested the behaviour of the bacteria-based microrobots in mice. "Using this hybrid control strategy, we can significantly increase the number of intravenously-injected bacteria reaching and colonizing the tumour site," explains Schuerle. "Ultimately, we aim to use this approach to reduce the microrobots dose that needs to be injected to reach therapeutic efficacy."

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The RMFs can also be applied at a human scale with lower frequency and field magnitudes than magnetic resonance imaging. "We are now working on new electromagnets that can apply RMFs in a focused region in deep targets, and that can incorporate inductive detection to get feedback from the bacteria to monitor responses and ensure safety," says Schuerle. The researchers are also exploring clinically studied bacteria, such as *Salmonella* or *Escherichia*, which can be genetically engineered to include kill switches and to produce therapeutic molecules.

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