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Microswimmers for guided drug delivery

Medicines should act as quickly as possible and ideally only at the site of disease. However, this may be difficult when the medicines are taken up via the digestive tract or the blood system. Researchers at the Max Planck Institute for Intelligent Systems in Stuttgart have now developed a biohybrid microrobot consisting of red blood cells and bacteria that can be loaded with active ingredients and guided through the body to deliver drugs to specific regions.

Dr. Yunus Alapan and Oncay Yasa have developed a microrobot that can be loaded with medicines and directed to the site of disease before it is destroyed.
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Patients can be prescribed oral, injected or infused medications. However, this means that the drugs reach the intended body region more or less by chance. They may also affect areas of the body which they should not. Potentially, this could reduce or prevent the effect of the drug completely, and may also have serious adverse effects.

Researchers in the Department of Physical Intelligence at the Max Planck Institute for Intelligent Systems in Stuttgart have developed a microrobot that is able to transport and deliver medicine 'cargo' to specific regions in the body.

"This microrobot combines one of the most efficient naturally occurring swimmers - a bacterial cell - with one of the most powerful load carriers of the human body - red blood cells (erythrocytes, RBC)," says Yunus Alapan, an engineer who developed the microrobot together with molecular biologist Oncay Yasa. "The bacteria act as propellers, the red blood cells, which are specialised for carrying and transporting molecular cargos such as oxygen, encapsulate the cargo and transport it through the blood stream. We control and guide the bacteria-propelled microswimmers through the body using a magnetic field and destroy them as soon as they have reached their target and released the drug cargo."

An erythrocyte, which carries the cargo, is combined with a bacterium, which serves as a propeller

(a) Erythrocyte (RBC) and bacterium loaded with drug (DOX) and magnetic particles (SPIONs) are stably linked via avidin, biotin and antibodies. (b) Electron microscope image of the microrobot, (c) targeted movement of a loaded microswimmer
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The scientists have already been able to show that their idea works in practice and that the microswimmers can stably transport their cargo to specific targets. RBCs are particularly suitable as drug carriers; they are abundant and lose their nucleus and organelles during maturation, which makes their entire inner volume available for the encapsulation of drugs. The lack of organelles makes them deformable, so that they can squeeze through the narrowest capillaries and gaps, even through gaps that are smaller than their own diameter. The researchers used natural RBCs – commercially available mouse blood cells – for their tests as they have the ambitious goal of being able to use their invention for the personalised therapy of patients involving the patients' own blood at some stage in the future.

The researchers used bioengineered flagella-bearing E. coli MG 1655 bacteria as propellers, which they constructed in cooperation with researchers from the Max Planck Institute for Terrestrial Microbiology in Marburg. The bacterial "motor", which we have copied from nature, is attached to the RBC via a biotin-avidin-biotin binding complex which functions as a kind of snap hook, holding the two parts of the microswimmer together. On the side of the bacterium, the avidin protein binds to biotin, which is a natural avidin substrate. Biotin is expressed by the bacterial plasmid and protrudes from the bacterial membrane. On the other side of the construct, a specific antibody (Anti-TER-119) enables the avidin protein to attach to the blood cell. The resulting microswimmer is very flexible. As mentioned above, this flexibility is provided by the RBCs, which are deformable and can squeeze through narrow body gaps that are twice as small as the microrobot."

Guided by magnetic particles, destroyed with infrared light

The microswimmer can be loaded with active ingredients for the treatment of diseases. In one test, the microswimmers were produced by loading the RBCs with anticancer doxorubicin (DOX) molecules, which are usually administered intravenously. The RBCs were also loaded with iron oxide nanoparticles, known as SPIONS (superparamagnetic iron oxide nanoparticles), which enable the microswimmers to be guided via an external magnetic field.

Once the microswimmer has reached its target - in this case a cancer cell - the acidic environment attacks the RBC membrane, making it permeable and the drug is released. The drug release rate depends on the pH: the lower the pH, the more active ingredient is released. "We are delivering the drugs right to the door of the tumour," says Alapan. "The microswimmer has then fulfilled its task and will be destroyed."

In order to be able to destroy the microswimmer after it has fulfilled its mission, the scientists not only load the RBCs with the active ingredient and iron particles, but also with special molecules that are able to absorb infrared light. That's how the microswimmer can be destroyed from the outside. "Irradiation with infrared light has a hyperthermial effect on the RBC, resulting in the destruction of the RBC as well as the bacterial propeller. This is an excellent way to switch off the system quickly and easily," says Alapan. "We need to be able to do so as uncontrolled bacterial growth, and thus an excessive reaction of the body's immune system, needs to be prevented." However, the researchers hope to be able to exploit the fact that bacteria are able to trigger an immune response in the future. "This feature could be utilised in a form of immunotherapy and could possibly be used in conjunction with different forms of treatment."

Potential for a variety of non-invasive medical applications

The microswimmer can be guided with a magnet.

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Cargo-loaded RBCs were prepared using hypotonic treatment, which leads to the swelling of the cells and the formation of pores in the RBC membrane. This results in the inward diffusion of DOX molecules and SPIONs. The RBCs were subsequently transferred into an isotonic solution to close the pores again. Pore size is not a limiting factor. Alapan explains why: "All currently available drug molecules are so small that they should definitely pass through the pores."

The DOX- and SPION-loaded microswimmers can be controlled by applying a magnetic field. "The bacterium propels the cargo-loaded RBC forward with its flagella," says Alapan. "However, the bacterium does not move about randomly; an externally applied magnetic field causes the iron particles, with which the blood cell is loaded, make the microswimmer move in a particular direction. We are thus able to guide the microswimmer to the regions in the body where we want the drugs to be delivered."

The researchers used a microscope to guide the microswimmers under a magnetic field and now plan to carry out cell culture experiments and subsequently also preclinical tests involving experimental animals: "We would like to start with this next year," says Alapan. "The potential for many non-invasive medical applications is definitely huge." In the future, the researchers also want to test the applicability of the system to other organs, for example the gut or the stomach.

Article

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