Light-driven micro-swimmers for responsive drug delivery

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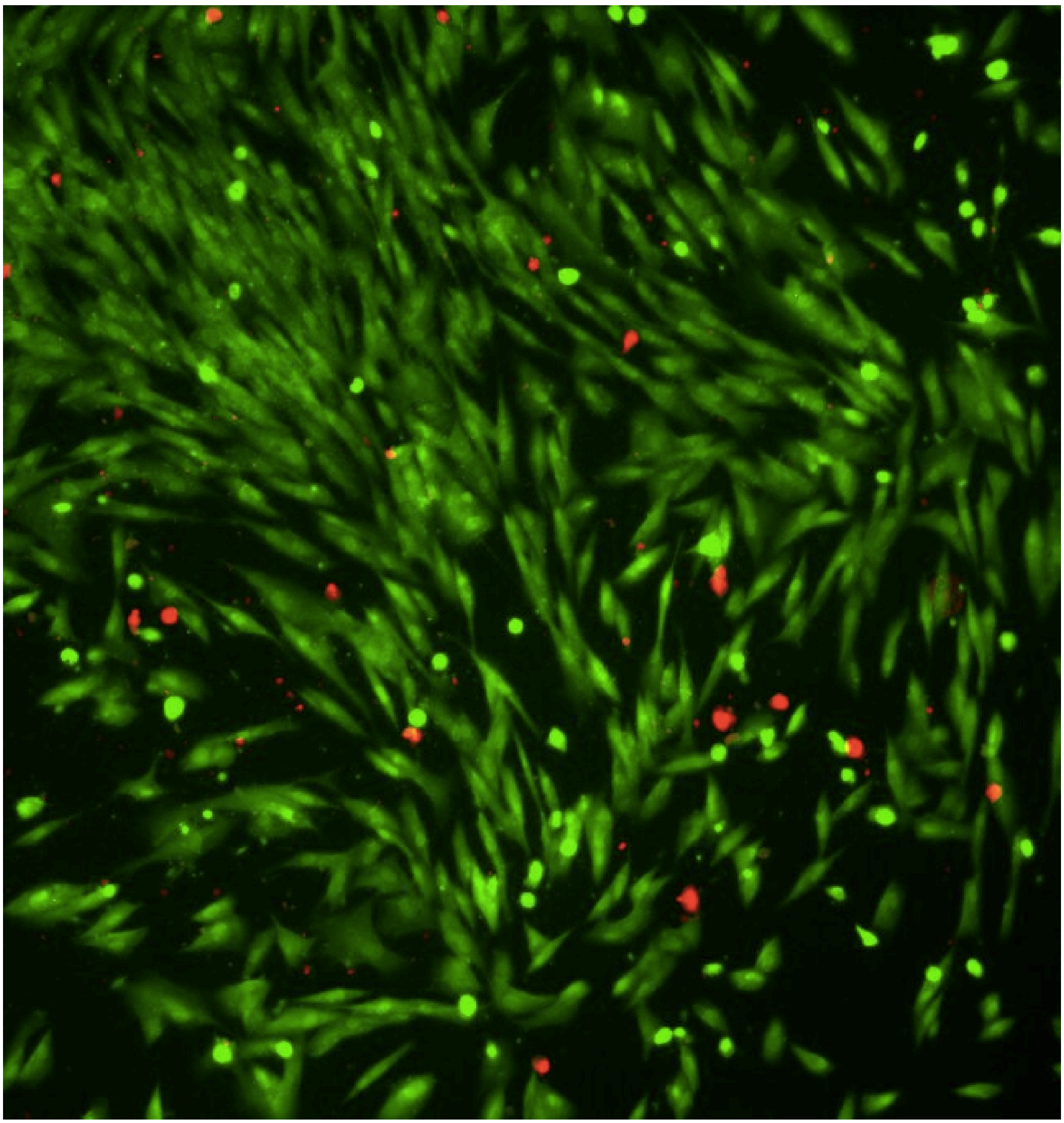

The biocompatible microswimmers and biological cells. Credit: Sridhar et al.

In recent years, scientists have introduced a wide variety of robots of all shapes and sizes. Among these are microswimmers, carefully engineered microstructures that can move in water and other liquids.

Microswimmers could have numerous interesting applications, for instance allowing doctors to deliver drugs to targeted regions inside the human body, or scientists to introduce specific substances in water-based environments. While some of these robotic systems achieved remarkable results, most of them were found to be unable to efficiently move inside the human body.

Researchers at the Max Planck Institute for Intelligent Systems (MPI-IS) have recently developed new light-driven microswimmers that could be more suited for navigating within biological systems, including body fluids. These microswimmers, introduced in a paper published in *Science Robotics*, are simple microparticles based on the two-dimensional (2D) carbon nitride poly(heptazine imide) or PHI .

"Our study came about due to the need for having a biocompatible organic material that can be used as light-driven microswimmers," Varun Sridhar, one of the researchers who carried out the study, told TechXplore. "Our objective was to build a biocompatible organic microswimmer that can swim in a biological medium containing salts and could thus deliver drugs on demand in an intelligent manner."

Sridhar previously conducted other studies exploring the potential of light-driven microswimmers (i.e., microswimmers that respond to visible light). In collaboration with Filip Podjaski, a researcher at the Max Planck Institute for Solid State Research, he started trying to validate and improve their propulsion mechanism, by using different materials to create them and then testing their performance.

Initially, the team at MPI-IS studied titanium dioxide and Cobalt monoxide, but then they tried using organic light conversion materials. They discovered that the latter were particularly promising and efficient, and started exploring the challenges impeding the performance of microswimmers in general, most of which are associated with the presence of ions hindering propulsion.

"Since the carbon nitride materials I worked on showed enhanced properties in the presence of ions, such as energy conversion catalysis being required for propulsion, ion pumping, and property changes going in hand with intrinsic charging assisted by ions, we decided to study them to overcome some limitations in the field, and it worked out super nicely," Podjaski told TechXplore. "We then added different carbon nitride systems to the study, which have less pronounced interactions with ions, to better disentangle what is going here (i.e., what properties are given by pure porosity, with our microswimmer particles being effectively sponge structures) and what comes on top from intrinsic 'ionic interactions' (material interactions with salt ions, such as Na^+ or K^+, which are found in all biological fluids)."

The new, light-driven microswimmers developed by Sridhar, Podjaski and their colleagues are made of an organic-based material known as Carbon Nitride, which has photocatalytic properties. This means that when light is shone on the material, it is absorbed and produces electric charges that are used to drive chemical reactions.

"The charges react with the bio fluids and this reaction combined with the electric field around the particle makes the microswimmers swim," Sridhar explained. "The carbon nitride PHI can also store charges when light shines on it, behaving like a solar battery, which can also be used to enhance their drug delivery properties."

PHI, the material used by the researchers, can absorb light energy in a similar way to solar cells. This energy is then used to propel each particle, allowing it to move in fluids. Essentially, the propulsion of the particles relies on catalytic reactions occurring on their surface.

"The process called 'photocatalysis' is being studied and used to convert solar energy directly into chemical energy," Podjaski said. "Carbon nitrides are very efficient photocatalysts, so they are also good light driven 'swimmers." In addition, their synthesis is very simple and cheap, as it is based on abundant organic precursors, such as urea (e.g., from urine.), making them very promising and widely accessible materials."

To propel the particles, the researchers relied on a driving force (i.e., light enabling photocatalysis) and symmetry breaking, which pushes them in a specific direction. They thus used a torch light that illuminates one half of a sphere, leaving the other dark, producing a gradient of reactions on both sides. Finally, as the swimmers were designed to be introduced in liquids, the team ensured that the propulsion force was stronger than the 'slowing down' of a surrounding environment.

"Salt ions in water are a big problem, since they break down the propulsion force field around the particle," Podjaski said. "We found that it is sufficient to enable an ion flow through the particle to overcome this strong 'slow down' in principle. And apparently, the intrinsic ionic interactions of our special carbon nitride PHI enhances this ion tolerance, as the flow through the particle is 'accelerated.'"

In initial experiments, the researchers demonstrated the efficient movement of the microswimmers in liquids with low to medium , such as those inside biological organisms, as well as highly salted waters, such as those of the dead sea. These findings suggest that the swimmers could eventually be used to deliver drugs inside the human body and in other biological systems.

"The microswimmers are also sensitive to environmental conditions inside the body and can be triggered by light or pH changes to release drugs," Sridhar said. "The light triggered release is also sensitive to oxygen deficient environments, such as those found around cancer cells. Thus, the microswimmers can release drugs more efficiently near cancer cells, eventually killing them efficiently."

In the future, the researchers plan to test the microswimmers they created in real biological environments, such as in cell cultures, body fluids or sea water. To create microswimmers that could move in these environments, researchers previously had to introduce toxic additives to fuel the propulsion. The ability to naturally move around in sea water and bodily fluids could thus make these microswimmers truly revolutionary.

"While we only tested them outside of living organisms so far, our carbon nitride particles are biocompatible and do not appear to create immune responses," Podjaski said. "Moreover, they retain all their properties when illuminated by visible light and do not degrade. This was not engineered, it was apparently a natural outcome from taking an organic based material that is very stable by itself (i.e., does not allow for spontaneous chemical interactions with cells body components)."

While many studies investigated carbon nitrites in the past, Sridhar, Podjaski and their colleagues are among the first to demonstrate their potential as microswimmers operating within living systems. In addition, the particles they used have a sponge-like structure, containing many pores and voids, which means that they could easily be soaked in drugs with large amounts. Remarkably, the team found that the chemotherapy drug Doxorubicin remains strongly bound to the particles, yet it could easily be released in targeted locations, simply by changing the pH or shining a light on the particles. This could also apply to other drugs.

"For our inherently porous particles without any special encapsulation, this does not happen at all by itself," Podjaski said. "The cancer drug Doxorubicin stays bound for over a month. For the delivery of drugs that target a single spot and work at a desired time, this is fundamental, and a very novel observation."

Microswimmers for drug delivery introduced in the past relied on 'artificial capsules," which were meant to be filled with drugs and delivered to specific locations in the body. Creating these capsules, however, could be both complex and expensive. In contrast, the particles used by the researchers are cheap, organic, and spongy by design, binding directly to drugs or other substances. This means that they could be easier to implement on a large-scale. Remarkably, they can also be loaded with more drugs (i.e., 185% of their own mass) than other materials used in the past.

"These mechanisms were already used before and they are useful, but only partially, since really aidic conditions are only found in the stomach and light is also required for propulsion, so the drug then is released all the way, which is not super controlled," Podjaski said. "The really amazing thing we found and anticipated is that our microswimmers can intrinsically sense or diagnose oxygen poor environments (a scenario that cancer cells naturally create, called hypoxicity) – and then boost the release of the loaded drug under illumination."

The microswimmers created by this team of researchers are 'theanostic," meaning that they could simultaneously have both diagnostic and therapeutic functions. Their operation mechanism mimics that of neurons, which sense their environment and convey messages to other parts of the body.

"All of the properties we demonstrated are possible using one material, without modifying it, tailoring its source functions to make it biocompatible, without adding artificial capsules for drugs and without sensing parts that look on pH or oxygen content," Podjaski added. "Engineering this on a micrometer scale (1/1000 of a mm, 1/100 of a hair) would technically be impossible currently, as it is both expensive and complicated. I think the true beauty of our work is that with our microswimmers this happens naturally, using a very cheap material that is easy to prepare."

Ultimately, this recent study could inspire the development of more affordable microrobots that can navigate in biological environments. The swimmers could be particularly valuable to deliver drugs or intervene in specific parts of the body that can be reached by light, such as the skin, transparent tissues, or inside the eye. Combinations of these novel, porous and organic materials with traditionally inorganic microrobots could also enable new functions.

"When made infrared(IR)-active (we are working on that), near skin applications would work," Sridhar said. "Transparent tissue, like the eyes, would work, and drug delivery in the stomach would be easy. They could also be interesting for all kind of cancer or biomedical laboratory research using petri dishes, where one studies the action of drugs on cells. "In these instances, ionic tolerance is a must, since all cells require such an environment to survive and operate."

In addition to delivering drugs inside the human body, the microswimmers could also help to introduce specific substances in lakes or in the ocean. For instance, the swimmers could be deployed in endangered natural environments to heal specific animal species or exterminate harmful organisms.

"Now that we have a blue-print of how to get light-driven microswimmers to move in real biological conditions, we would like to expand on it and make light-driven microswimmers that can swim under red light. That way they can penetrate deeper inside the skin and tissues and power the microswimmers," Sridhar said.

To make their microswimmers easier to introduce in the human body and other biological environments, the researchers now plan to make them active to infrared light. This would allow them to tailor the particles' adhesion and release properties using infrared light. Alternatively, they could explore the potential of tuning them using magnetic forces, by creating hybrid structures using metals.

"The charging, sensing and responsive properties of our microswimmers also open up entirely new applications for 'smart microrobots,'" Podjaski said. "Our next studies will also explore these, as they might enable very easy 'neuromorphic actions," that are planned to be used for next-generation computation, but are not at all advanced for real world scenarios, especially in the context of biology. This will be in the far future, but we are currently laying the foundations for with our research, by studying novel application concepts and other materials that could do this."

More information: Varun Sridhar et al, Light-driven carbon nitride microswimmers with propulsion in biological and ionic media and responsive on-demand drug delivery, *Science Robotics* (2022). DOI: 10.1126/scirobotics.abm1421