Sculpted 3-D particles could aid diagnostics, tissue engineering

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News Office

MIT engineers have used ultraviolet light to sculpt three-dimensional microparticles that could have many applications in medical diagnostics and tissue engineering. For example, the particles could be designed to act as probes to detect certain molecules, such as DNA, or to release drugs or nutrients.

The new technique offers unprecedented control over the size, shape and texture of the particles. It also allows researchers to design particles with specific chemical properties, such as porosity (a measure of the void space in a material that can affect how fast different molecules can diffuse through the particles).

"With this method, you can rationally design particles and precisely place chemical properties," said Patrick Doyle, associate professor of chemical engineering. Doyle is one of the authors of a paper on the work that appeared in the Dec. 3 issue of the journal Angewandte Chemie, published by the German Chemical Society.

The research team started with a method that Doyle and his students reported in a 2006 issue of Nature Materials to create two-dimensional particles. Called continuous flow lithography, this approach allows shapes to be imprinted onto flowing streams of liquid polymers. Wherever pulses of ultraviolet light strike the flowing stream of small monomeric building blocks, a reaction is set off that forms a solid polymeric particle. They have now modified that method to add three-dimensionality.

This process can create particles very rapidly: Speeds range from 1,000 to 10,000 particles per second, depending on the size and shape of the particles. The particles range in size from about a millionth of a meter to a millimeter.

The team's new process works by shining ultraviolet light through two transparency masks, which define and focus the light before it reaches the flowing monomers. The first mask, which controls the size and shape of the particles, is part of the technique reported last year by Doyle and his students. The second mask, which is based on MIT professor Edwin Thomas' work in multibeam lithography, adds three-dimensional texture and other physical traits, such as porosity.

The collaboration sprung from a conversation between Ji-Hyun Jang, a postdoctoral associate in Thomas' lab, and Dhananjay Dendukuri, a recent Ph.D. recipient in Doyle's lab, who are also authors on the paper.

"It's very easy to integrate the (second) phase mask into the microfluidic apparatus," said Thomas, Morris Cohen Professor of Materials Science and Engineering and head of the Department of Materials Science and Engineering. "Professor Doyle was controlling the overall shape, and now what we're doing is controlling these inner labyrinth networks."

Adding inner texture is desirable because it increases the particles' surface-to-volume ratio, which means if the particle is loaded with probes, there are more potential binding sites for target molecules.

In a paper published in Science earlier this year, Doyle and MIT graduate student Daniel Pregibon showed that the particles can be used as probes to identify DNA and other molecules.

Other applications for the particles include tissue engineering. For example, they could form a scaffold that would both provide structural support for growing cells and release growth factors and other nutrients. The particles can be designed so diffusion occurs in a particular direction, allowing researchers to control the direction of nutrient flow.

Alan Hatton, the Ralph Landau Professor of Chemical Engineering Practice, is also an author on the paper.

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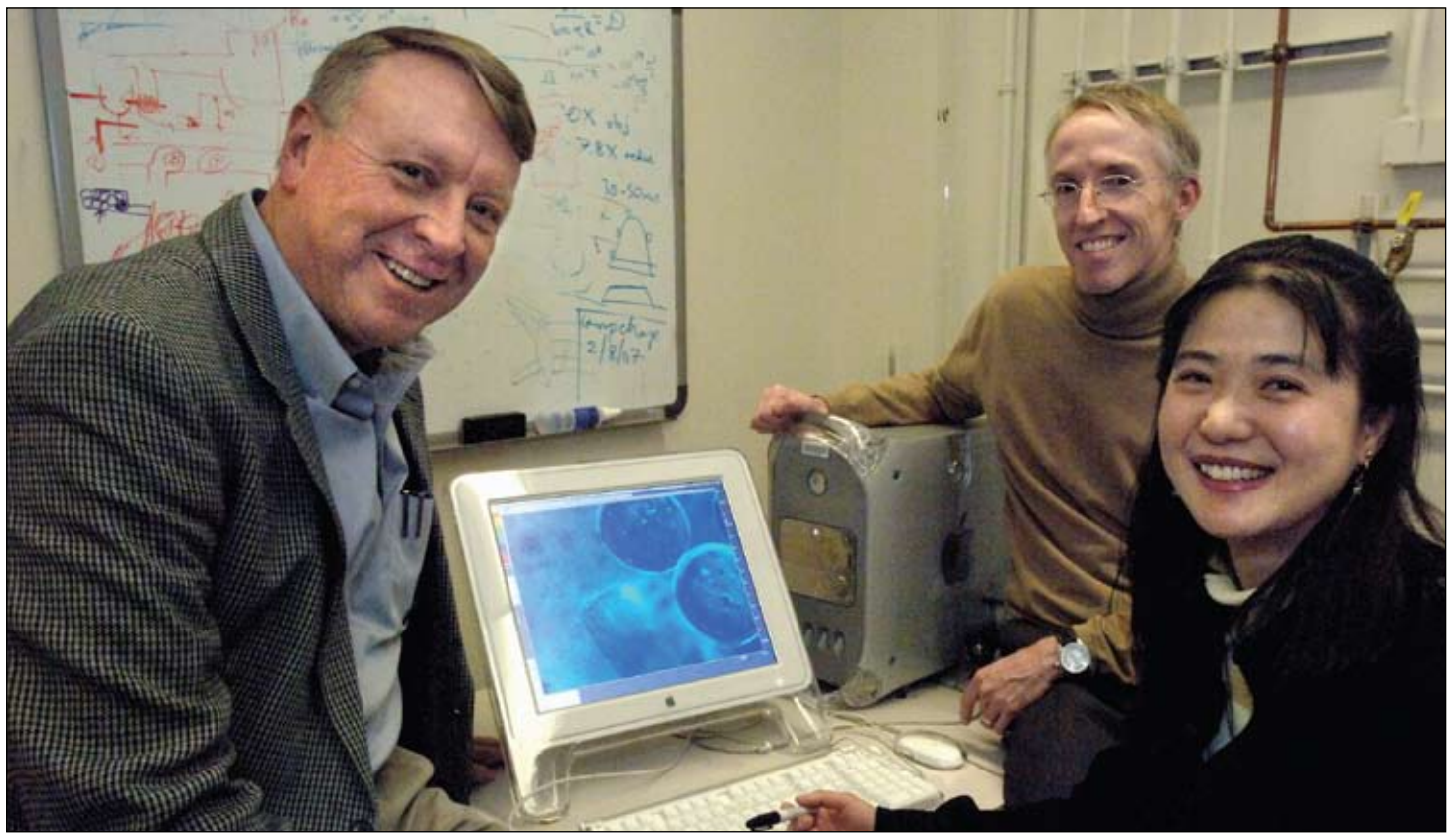

PHOTO / **DONNA COVENEY**

From left, Edwin Thomas, Morris Cohen Professor of Materials Science and Engineering, Patrick Doyle, associate professor of chemical engineering, and materials science postdoc Ji-Hyun Jang. The researchers have designed a technique to control the size, shape and texture of microparticles.

Remote-control nanoparticles deliver drugs directly into tumors

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MIT scientists have devised remotely controlled nanoparticles that, when pulsed with an electromagnetic field, release drugs to attack tumors. The innovation, reported in the Nov. 15 online issue of Advanced Materials, could lead to the improved diagnosis and targeted treatment of cancer.

In earlier work, the team, led by Sangeeta Bhatia, an associate professor in the Harvard-MIT Division of Health Sciences and Technology (HST) and in MIT's Department of Electrical Engineering and Computer Science, developed injectable multifunctional nanoparticles designed to flow through the bloodstream, home to tumors and clump together. Clumped particles help clinicians visualize tumors through magnetic resonance imaging.

With the ability to see the clumped particles, Geoff von Maltzahn, Bhatia's co-author in the current work, asked the next question: "Can we talk back to them?"

The answer, the team found, is yes. The system that makes it possible consists of tiny particles (billionths of a meter in size) that are superparamagnetic, a property that causes them to give off heat when they are exposed to a magnetic field. Active molecules, such as therapeutic drugs, are tethered to these particles.

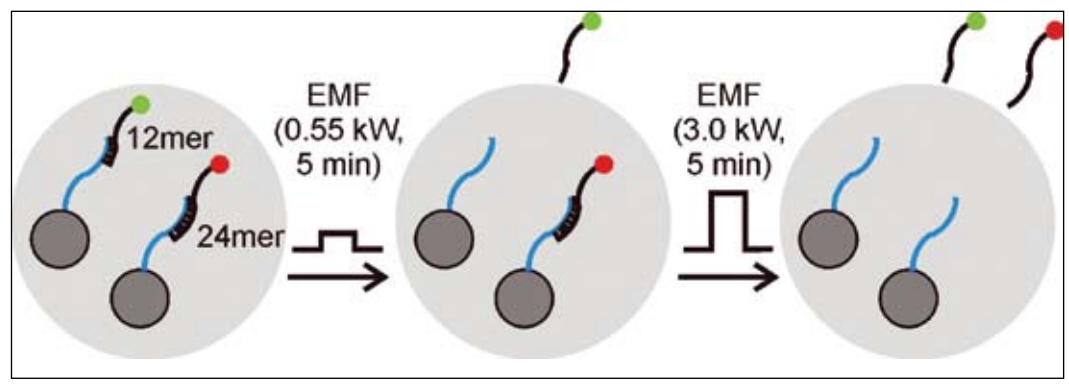

IMAGE COURTESY / **BHATIA/VON MALTZAHN, MIT; DERFUS, UCSD**

These dark gray nanoparticles carry different drug payloads (one red, one green). A remotely generated, five-minute pulse of a low-energy electromagnetic field releases the green drug. A five-minute pulse of a higher-energy electromagnetic field releases the red drug, which had been tethered using a DNA strand twice as long as the green tether, as measured in base pairs.

PHOTO / **DONNA COVENEY**

HST graduate student Geoffrey von Maltzahn and Professor Sangeeta Bhatia examine a medium containing iron oxide particles. Bhatia is leading a team using electric fields to remotely release drugs from nanoparticles inside the body.

Exposing the particles to a low-frequency electromagnetic field causes the particles to radiate heat that, in turn, melts the tethers and releases the drugs. The waves in this magnetic field have frequencies between 350 and 400 kilohertz—the same range as radio waves. These waves pass harmlessly through the body and heat only the nanoparticles. For comparison, microwaves, which will cook tissue, have frequencies measured in gigahertz, or about a million times more powerful.

The tethers in the system consist of strands of DNA, "a classical heat-sensitive material," said von Maltzahn, a graduate student in HST. Two strands of DNA link together through hydrogen bonds that break when heated. In the presence of the magnetic field, heat generated by the nanoparticles breaks these bonds, leaving one strand attached to the particle and allowing the other to float away with its cargo.

One advantage of a DNA tether is that its melting point is tunable. Longer strands and differently coded strands have bonds that require different amounts of heat to break. This heat-sensitive tunability makes it possible for a single particle to simultaneously carry many different types of cargo, each of which can be released at different times or in various combinations by applying different frequencies or durations of electromagnetic pulses.

To test the particles, the researchers implanted mice with a tumor-like gel saturated with nanoparticles. They placed the implanted mouse into the well of a cup-shaped electrical coil and activated the magnetic pulse. The results confirm that without the pulse, the tethers remain unbroken. With the pulse, the tethers break and release the drugs into the surrounding tissue.

The experiment is a proof of principle demonstrating a safe and effective means of tunable remote activation. However, work remains to be done before such therapies become viable in the clinic.

To heat the region, for example, a critical mass of injected particles must clump together inside the tumor. The team is still working to make intravenously injected particles clump effectively enough to achieve this critical mass.

"Our overall goal is to create multifunctional nanoparticles that home to a tumor, accumulate and provide customizable, remotely activated drug delivery right at the site of the disease," said Bhatia.

Co-authors on the paper are Austin M. Derfus, a graduate student at the University of California, San Diego; Todd Harris, an HST graduate student; Erkki Ruoslahti and Tasmia Duza of the Burnham Institute for Medical Research in La Jolla, Calif.; and Kenneth S. Vecchio of the University of San Diego.

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