Zeroing in on the best shape for cancer-fighting nanoparticles

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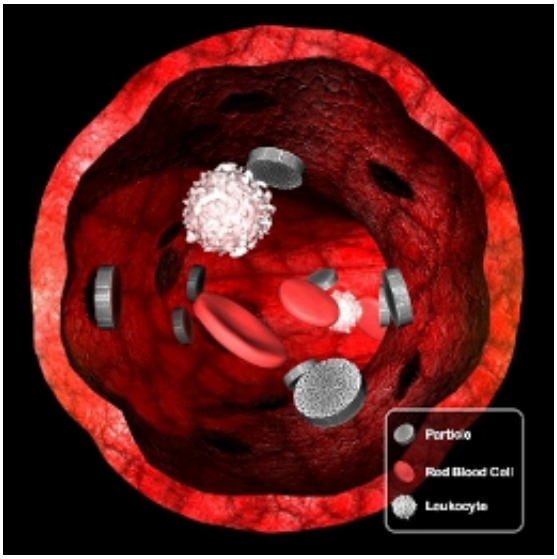

Cross section of a blood vessel showing discoidal particles adhering to the vessel walls (gray); red blood cells (red) and leukocytes (white).

(Phys.org) -- As the field of nanomedicine matures, an emerging point of contention has been what shape nanoparticles should be to deliver their drug or DNA payloads most effectively.

A pair of new papers by scientists at The Methodist Hospital Research Institute (TMHRI) and six other institutions suggests these microscopic workhorses ought to be disc-shaped, not spherical or rod-shaped, when targeting cancers at or near blood vessels.

"The vast majority -- maybe 99 percent -- of the work being done right now is using nanoparticles that are spherical," said TMHRI biomedical engineer Paolo Decuzzi, Ph.D., principal investigator for both projects. "But evidence is showing there may be better ways to get chemotherapy drugs to the site of a vascularizing cancer."

Despite their popularity, there are problems with sphere-shaped nanoparticles. They're small, and can't deliver a lot of drugs when they finally reach their targets. And they're also more likely to get pushed downstream by blood's powerful flow.

"The small surface exposed by spherical nanoparticles to the blood vessel walls – theoretically a single point -- in the tumor tissue cannot support stable, firm adhesion and they are easily washed away. And this hampers their effective accumulation within the diseased tissue," Decuzzi said. "So a number of laboratories have been asking, how can we maximize the accumulation of nanoparticles in the diseased tissues? Is there a better shape?"

In the August 2012 Biomaterials (Elsevier, now online), Decuzzi and coauthors show that at different, biologically relevant flow speeds, disc-shaped nanoparticles were less likely to get pushed off their targets than rod-shaped nanoparticles -- another shape previously proposed as an alternative to spheres. The ideal size was 1,000 by 400 nanometers (diameter by thickness). The experiments were conducted in vitro and confirmed by computational modeling.

Spherical nanoparticles are built around the drug payload in a free, three-dimensional fashion through self-assembly. The particle grows uniformly in all directions, forming a spherical -- or nearly spherical -- nanoparticle.

The Methodist nanomedicine group, led by TMHRI President and CEO

Mauro Ferrari, Ph.D., has developed a completely different technique. Disc-shaped nanoparticles are created with photolithographic technology, the same tools used to make the tiniest components in computers. Photolithography allows Ferrari, Decuzzi, and colleagues to specify the size, shape and surface properties of the nanoparticles with a great deal of accuracy. The nanoparticles are built with sponge-like holes through them, which is where the drugs are loaded.

"We can change the size, shape, and surface properties -- '3S' parameters -- of the particles independently," Decuzzi said. "It is a very powerful technique."

The nanoparticles are built with silicon, and biologically relevant molecules are later attached to the outside to improve binding to target cells and to delay destruction by the immune system. Silicon has an extremely low toxicity profile at the doses typically used in humans and animal models. Decuzzi said silicon nanoparticles are readily broken down and removed from the body within 24 to 48 hours.

The second paper published by Decuzzi and colleagues, in the Feb. 2012 *Journal of Controlled Release* (also Elsevier), used mouse models to show that 1,000 by 400 nm disc-shaped nanoparticles bind readily to and near melanoma cells, at 5 to 10 percent of the injected dose per gram organ -- concentrations that are competitive with or better than those previously reported for spheroid nanoparticles. The researchers also showed 1000 by 400 nm discs were least likely (than smaller or larger discs, or rods) to end up in the liver.

"These two papers are the culmination of eight years of work, looking at the properties of disc-, rod-, and spherical nanoparticles in computer simulations, in vitro, and then in vivo," Decuzzi said. "What has been most rewarding is that all the important things we predicted via mathematical models turned out to be true in real-life experiments. We

are getting close to answering crucial questions about what these nanoparticles need to look like."

Decuzzi says his group will continue working on the optimization of nanoparticles and, in particular, will be looking at what he calls the "4S" problem. After establishing the right size, shape, and surface chemistry, Decuzzi says he wants to see if the right amount of stiffness, or flexibility, can further enhance the in vivo performance of nanoparticles.

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