Nanoparticle pinpoints blood vessel plaques

February 6 2014

A team of researchers, led by scientists at Case Western Reserve University, has developed a multifunctional nanoparticle that enables magnetic resonance imaging (MRI) to pinpoint blood vessel plaques caused by atherosclerosis. The technology is a step toward creating a non-invasive method of identifying plaques vulnerable to rupture–the cause of heart attack and stroke—in time for treatment.

Currently, doctors can identify only blood vessels that are narrowing due to plaque accumulation. A doctor makes an incision and slips a catheter inside a blood vessel in the arm, groin or neck. The catheter emits a dye that enables X-rays to show the narrowing.

However, Case Western Reserve researchers report online today in the journal *Nano Letters* that a nanoparticle built from a rod-shaped virus commonly found on tobacco locates and illuminates plaque in arteries more effectively and with a tiny fraction of the dye.

More importantly, the work shows that the tailored nanoparticles home in on plaque biomarkers. That opens the possibility that particles can be programmed to identify vulnerable plaques from stable, something untargeted dyes alone cannot.

"From a chemist's point of view, it's still challenging to make nanoparticles that are not spherical, but non-spherical materials are advantageous for medical applications" said Nicole F. Steinmetz, assistant professor of biomedical engineering at Case Western Reserve. "Nature is way ahead of us. We're harvesting nature's methods to turn

them into something useful in medicine."

The rod-shaped nanoparticles are made from tobacco mosaic virus, tiny tubular organisms that infect plant cells but are benign outside the plant.

Steinmetz, a specialist in bioengineering plant viruses, teamed with Xin Yu, a professor of biomedical engineering, who specializes in developing MRI techniques to investigate cardiovascular diseases. They created a device that transports and concentrates imaging agents on plaques.

The research team includes: Michael A. Bruckman, a postdoctoral researcher, and Lauren N. Randolph, an undergraduate student, in the Steinmetz lab; Kai Jiang, a PhD student in Yu's lab; and Leonard G. Luyt, assistant professor, and Emily J. Simpson, a PhD candidate, both at department of chemistry at Western University, in London, Ontario.

Elongated nanoparticles have a higher probability of being pushed out of the central blood flow and targeting the vessel wall compared to spheres. Further the shape allows more stable attachment to the plaque, the researchers said.

The virus surface is modified to carry short chains of amino acids, called peptides, that make the virus stick where plaques are developing or already exist. Luyt and Simpson synthesized the peptides.

"The binding allows the particle to stay on the site longer, whereas the sheer force is more likely to wash away a sphere, due to its high curvature," said Yu, an appointee of the Case School of Engineering.

The virus surface was also modified to carry near-infrared dyes used for optical scanning, and gadolinium ions (which are linked with organic molecules, to reduce toxicity of the metal) used as an MRI contrasting agent. They used optical scans to verify the MRI results.

By loading the surface with gadolinium ions instead of injecting them and letting them flow freely in the blood stream, the nanoparticle increases the relaxivity—or contrast from healthy tissue—by more than four orders of magnitude.

"The agent injected in the blood stream has a relaxivity of 5, and our nanoparticles a relaxivity of 35,000," said Steinmetz who was appointed by the Case Western Reserve School of Medicine.

That's because the nanorod carries up to 2,000 molecules of the contrast agent, concentrating them at the plaque sites. Secondly, attaching the contrast agent to a nanoparticle scaffold reduces its molecular tumbling rates and leads to additional relaxivity benefit, the researchers explained.

While the view is better, they are able to use 400 times less of the contrast agent because it's delivered directly to plaques.

The tobacco virus-based nanoparticle, they said, offers another advantage: Most nanoparticles that have been developed to carry contrast agents are based on synthetic materials, some of which may stay in the body a while.

The tobacco virus is made of protein, which the body is well equipped to handle and flush from the system rapidly.

Steinmetz and Yu, members of the Case Center for Imaging Research, are now proposing to take the work a step further. They want to tailor the nanoparticles to show doctors whether the plaques are stable and require no treatment, or are vulnerable to rupture and require treatment. A rupture sets off the cascade of events that lead to heart attack and stroke.

To do this, they must first find different biomarkers of stable versus

vulnerable plaques and coat the nanoparticles with different peptides and contrast agents that enable the MRI to tell one from the other.

"Our understanding of vulnerable plaques is incomplete, but once we can diagnose vulnerable plaques from stable plaques, it will be a paradigm shift in diagnosis and prognosis," Yu said.

In addition to using the technology to find vulnerabilities, it may also useful for delivering medicines and monitoring treatment, the researchers say.

Provided by Case Western Reserve University