Small, Biodegradable Spheres May Have Big Impact On Tumor Treatments

University of Minnesota

Jafar Golzarian, M.D., has spent nearly 20 years redirecting traffic — not for vehicles, but for blood flow.

Golzarian works in University of Minnesota's Department of Radiology as an interventional radiologist, a specialist who uses imaging techniques like ultrasound and fluoroscopy to pinpoint and treat areas with precision, and without surgery. That includes procedures like opening blocked arteries with stents or angioplasty. But sometimes, doctors strategically block blood vessels to improve patients' health.

> *Arterial embolization — millions of tiny spheres injected into a blood vessel and clogging it — is an effective way to control bleeding in trauma patients while controlling some types of tumors by blocking the blood flow to tumor cells and letting them starve to death.*

Embolization is often used on benign tumors in the uterus, known as uterine fibroids. It's a non-invasive way to eliminate the tumor. But when Golzarian recommended this treatment to his uterine-fibroid patients, some of them refused — even though the technique has a proven track record. For nearly two decades, embolization has been used to treat uterine fibroids. (And it's been used on other tumors for nearly 50 years). When patients said no to the procedure, it often happened after they asked this question about the embolization microspheres: How long will they stay in my body? The answer: Forever. The particles are made of materials that can't be absorbed by the body. Golzarian would explain to patients that studies didn't show any serious side effects from the microspheres. Still, patients remained unconvinced. They didn't want to carry around millions of tiny beads for the rest of their lives.

"I understand the mentality of the patient," says Golzarian. "'If there's no need for the material to stay in my body, why can't you use something that's resorbable?'"

He's devoted the past five years to answering that question. His research led to the launch of a startup, EmboMedics Inc., based in Maple Grove, Minn., which hopes to earn FDA approval for a different type of microsphere — one made of natural materials that the human body can absorb within days and could improve treatment for tumors and also for cancer and other medical problems. These tiny spheres have the potential to make a big difference.

Building a Better Sphere

Most women have uterine fibroids — some estimates suggest as many as 75 percent of women do. And most women will never know it, because they don't have symptoms. For those who do experience symptoms, uterine fibroids can bring misery, including back pain and pelvic pain. About 10 to 20 percent of women who have fibroids require treatment. When they are treated with arterial embolization, the radiologist uses real-time X-ray imaging to guide a catheter (a thin tube about the size of a spaghetti strand) into position. The microspheres are loaded into a saline-filled syringe and injected through the catheter to a precise spot, where they clump together and block blood flow to the fibroid. Some studies show that after the procedure, nearly 90 percent of patients report significant or total relief from their symptoms.

After the microspheres create the blockage, it only takes a few hours for the fibroid to die. If they can eliminate fibroids so effectively, why not have microspheres that disappear after their work is done, instead of lingering? That's the challenge Golzarian began tackling in 2008. With internal funding, he set up a lab at the University of Minnesota and enlisted the help of polymer chemist Lihui Weng, Ph.D.

Their criteria included natural — not synthetic — materials that would be absorbed by the body and materials that could be manufactured with consistent quality and shape. That's no easy task when creating particles measured in microns (one millionth of a meter), and Golzarian knew he would need to make some of the microspheres as small as 100 microns. For comparison, the period at the end of this sentence is about 500 microns.

They also wanted materials that were easy to synthesize, without a hefty price tag. "We didn't want fancy expensive material, because that would be costly for the end user," says Golzarian.

After testing hundreds of substances, they found a combination that worked: chitosan, made from shells of shrimp and other crustaceans, and cellulose, the main component in plant cell walls. Cellulose is also on the ingredient list of many grocery items (it prevents clumping in prepackaged shredded cheese and makes low-fat ice cream seem creamier). When it's in the bloodstream, the chitosan-and-cellulose compound eventually breaks downs into carbon dioxide and water — things the body can easily dispose of.

With this material, the microspheres can be manufactured in various sizes (larger spheres work better for large arteries). That's not the only customizable aspect of the material. Using a chemical process, Golzarian and Weng were able to control the rate at which the body absorbs the microspheres, ranging from three days to 30 days.

Moving Beyond the Lab

The researchers knew they had developed a useful polymer. But was it patentable? To determine that, the University of Minnesota's Office of Technology Commercialization (OTC) conducted rigorous research on existing polymer patents — including hiring a patent attorney — in 2009.

"We spent more than the average amount of time trying to figure out whether this was patentable," says Karen Kaehler, technology strategy manager for life sciences at University of Minnesota's OTC. That effort paid off. Submitted in 2010, the 50-page patent, #8,617, 132, was issued in December 2013, with all of its 44 claims. That same month, a European patent (2485777) was issued. More patents are likely on the way — applications have been submitted in Australia, Canada, China, Hong Kong, and Korea.

In addition to patent assistance, the OTC helped with the search for a commercial partner to license the technology. "We talked with a lot of different companies," says Kaehler. "And we heard a lot of comments like, 'That sounds interesting. Let us know when you get it further along.'"

In this case, "further along" meant launching a startup to continue development of the embolization microspheres. Golzarian didn't want to lead a company, so the OTC vetted potential entrepreneurs in 2012. That search lead to Omid Souresrafil, who became cofounder and CEO of the startup, EmboMedics (the university owns 25 percent of the company). "I've worked with medical devices for more than 20 years, so I know a good idea when I see it," saysSouresrafil.

After a six-month process, the OTC licensed the technology to EmboMedics in April 2013. "They were always very helpful about getting things to the next level," says Golzarian, who is also EmboMedic's cofounder and chief medical officer. Souresrafil echoes that sentiment, noting the OTC played a vital role in obtaining the startup's most valuable asset: the patent. "[The OTC] also introduced us to people who could invest in the company," says Souresrafil. "They did a very good job."

Treating Liver Cancer

EmboMedics plans to call its product "resorbeads" — a nod to the shape (bead) and key attribute (resorbable). In March, the company began the application process for FDA approval. EmboMedics is also seeking regulatory approval for the microspheres in Europe and China. In addition to treating benign tumors, Golzarian and Souresrafil envision other uses. The microspheres could help stabilize patients with severe bleeding caused by trauma or ulcers — and after they served that purpose, the tiny beads would break down.

But the most dramatic way EmboMedics' microspheres could make a difference is by treating liver cancer. Liver cancer caused 745,000 deaths worldwide in 2012, making it second only to lung cancer. Arterial embolization is already being used to treat liver cancer. The microspheres act as tiny sponges loaded with cancer-fighting drugs. When the microspheres are injected, they deliver a one-two punch: They close off the arteries that feed to the liver's cancerous tumor and also gradually release the drugs.

Here's the problem with the current microspheres used for this treatment: Because they stay in the body, they continue to release the chemotherapy drugs even after they're taken care of the tumor. Also, the permanent particles may block the access to the tumors if the patient needs another treatment. That's not ideal, says Golzarian — and there is some data suggesting that the unnecessary drug release may provoke side effects. "It makes more sense that when tumor is dead, the spheres go away and don't release drugs anymore."

Golzarian would like to see EmboMedics' product used for this purpose, but that goal is still years away and would require clinical trials for FDA approval. In the meantime, he's hoping EmboMedics can change the conversation around arterial embolization, by making the absorbable material widely available.

When patients ask, "How long will these microspheres stay in my body," the doctors can finally give an answer they want to hear.

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