

Experimental mRNA Vaccine Hints at Potential Against Glioblastoma

Similar to COVID vaccines, this cancer vaccine uses mRNA. It boosts immune response against a type of brain tumor.

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By Carmen Phillips

Although immunotherapy is now a mainstay treatment for many cancers, it has yet to break through as a treatment for brain cancer, including the most common type, glioblastoma.

But recent results from several small [clinical trials](#) have hinted at the possibility of reversing this trend. Among them are findings from a very small trial testing a [cancer treatment vaccine](#) developed by researchers at the University of Florida.

Like two of the approved COVID vaccines and some other [experimental](#) cancer vaccines, this one uses genetic material called [mRNA](#) that is loaded into fat-coated [nanoparticles](#). But it also has a unique design aspect compared with these other vaccines: the nanoparticles have layers of fat inside, making it possible to layer each one with large numbers of mRNA.

In a study published May 1 in *Cell*, the researchers reported that the vaccine was effective in pet dogs with naturally occurring brain cancers, allowing them to live much longer than would typically be expected.

They also reported some initial findings [from a clinical trial involving four people with glioblastoma](#). Because it was the vaccine's first time being used in humans, the trial's primary goal was to ensure that the treatment was feasible and, secondarily, to look for evidence that it helps the [immune system](#) recognize and potentially attack tumors.

The trial largely succeeded on both fronts. The vaccine appeared to kick-start a robust [immune response](#) in all four participants, with rapid and dramatic changes in the levels and activity of immune system components needed to eliminate tumors.

Not unexpectedly, all four participants also had side effects from the treatment, explained the study's lead investigator, Elias Sayour, MD, PhD, a pediatric oncologist at the University of Florida and a member of the university's McKnight Brain Institute. But although some side effects were serious, in all cases they could be successfully managed, Dr. Sayour said.

Several immunotherapy experts stressed that there's still a long way to go before it's known whether the vaccine is in fact safe and, as importantly, can help people live longer.

Dr. Sayour agreed. Although these initial findings are encouraging, "we've only treated four patients with a few [vaccine] doses," he warned. "There are still a lot of unknowns to work through."

They hope to address many of these questions in additional small clinical trials of the vaccine already in the works, he said, including one in children with brain cancers.

Alerting the immune system that something dangerous is happening

One of the most lethal types of brain cancer, glioblastoma is largely resistant to nearly all treatments researchers have thrown at it, including targeted therapies and, more recently, immunotherapies.

While interest in mRNA vaccines has skyrocketed in the wake of the COVID pandemic, studies of mRNA cancer treatment vaccines have been underway for more than a decade. When it came to developing an mRNA vaccine to test against glioblastoma, Dr. Sayour and his team felt that the standard approach wasn't going to cut it.

"We felt like we needed [to try] new approaches that really shock the [immune] system," he said.

Although [the mRNA vaccines for COVID are remarkably effective](#), there's a big gulf between launching an immune response against a virus trying to gain a foothold in the body and against large, established tumors tucked deep in the brain.

Unlike a virus in the early stages of infecting healthy cells, for example, these tumors have many ways to block the immune system from doing its job, explained Lesley Chaboub, PhD, a member of the Weissman lab at the University of Pennsylvania that focuses on developing mRNA vaccines.

To begin with, these tumors have surrounding environments full of molecular booby traps, blocking immune cells from reaching them or disarming them, Dr. Chaboub explained. And the cells that make up the tumors tend to be very different from one another and have few shared weaknesses to be exploited.

These and other factors have made it extremely difficult "to find the right way to push the immune system to target" these tumors, she said.

Dr. Sayour and his team approached the development of their mRNA vaccine with these challenges in mind.

That required some reconfiguring of the nanoparticles themselves. The nanoparticles used in most

mRNA vaccines have a spherical core and, as a result, can only hold a small amount of mRNA. For their vaccine, Dr. Sayour and his team created a nanoparticle that—like the buttery sheets of a flaky French pastry—has layers of fat throughout it.

They could then sandwich many mRNA molecules into each layer, producing a nanoparticle with far more of these [protein](#) blueprints than those used in other mRNA vaccines, meaning it can produce far more abnormal proteins that draw the immune system's attention.

They also designed the nanoparticles so they would clump together into structures that the research team called [lipid](#) particle aggregates. This was another feature intended to communicate to the immune system that something is amiss.

And, as has been done by some other research groups, they used mRNA taken from patients' tumors as part of the vaccine "payload." The idea behind the strategy is that those mRNA molecules represent many of the potential abnormal proteins, or [antigens](#), produced by the tumor.

Taken as a whole, Dr. Sayour explained, the idea was to make this vaccine and its contents "look much more dangerous to the immune system" than has been attempted with other vaccines.

Promising findings in mice, dogs and humans

The findings reported in *Cell* also covered experiments testing a form of the vaccine in mouse models of different cancers. In mice with a uniformly deadly brain cancer called diffuse midline glioma that largely occurs in children, for example, the vaccine produced strong and rapid immune responses, shrinking tumors and allowing mice to live for long periods.

For the canine trial, all the dogs had naturally occurring brain cancers. Dogs are ideal models in this case because, like humans, they spontaneously develop brain cancers. In addition, Dr. Chaboub explained, their tumors often have the same characteristics that make glioblastoma so difficult to treat in humans.

Within a few days of the dogs receiving the first vaccine dose—given [intravenously](#), rather than into muscle—their tumors had undergone an immunological "reprogramming," the researchers reported. Specifically, before vaccination, their tumors were "cold," meaning there was little evidence of any immune system activity. But afterward, it was as if an arsonist had sparked a blaze: the tumors were now "hot" with bustling immune cells.

More importantly, the dogs lived much longer—nearly four times as long—as what is historically seen in dogs with brain cancer, they reported.

In the human trial, all four patients had glioblastoma tumors that could be surgically removed. After surgery, they were given standard treatment with chemotherapy and radiation. They then received up to four doses of the vaccine intravenously over the course of 6 weeks.

Similar to what occurred in the treated dogs, the researchers again saw multiple indicators of rapid and strong immune responses in the patients' blood samples. Those indicators included spikes in levels of proteins involved in orchestrating the immune system's response to a threat and in the levels of specific T cells involved in killing tumors cells.

Trial in children with brain tumors planned

The findings with this mRNA vaccine thus far are interesting, said James Gulley, MD, PhD, co-director of NCI's [Center for Immuno-Oncology](#).

In particular, Dr. Gulley cited the results seen in the dogs treated with the vaccine, which suggest that the vaccine appears to have activity against brain tumors. But "it's still very early," he continued, and further studies are needed to definitively show that it's safe and effective.

Dr. Sayour said his team is moving forward quickly but smartly. The upcoming trials of the vaccine, one involving adults and children and a second that would only include children, will be small (20 to 25 patients each) and still assess safety as their primary aim.

Both trials are being planned in conjunction with the international Pediatric Neuro-Oncology Consortium, which includes children's hospitals throughout the United States.

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