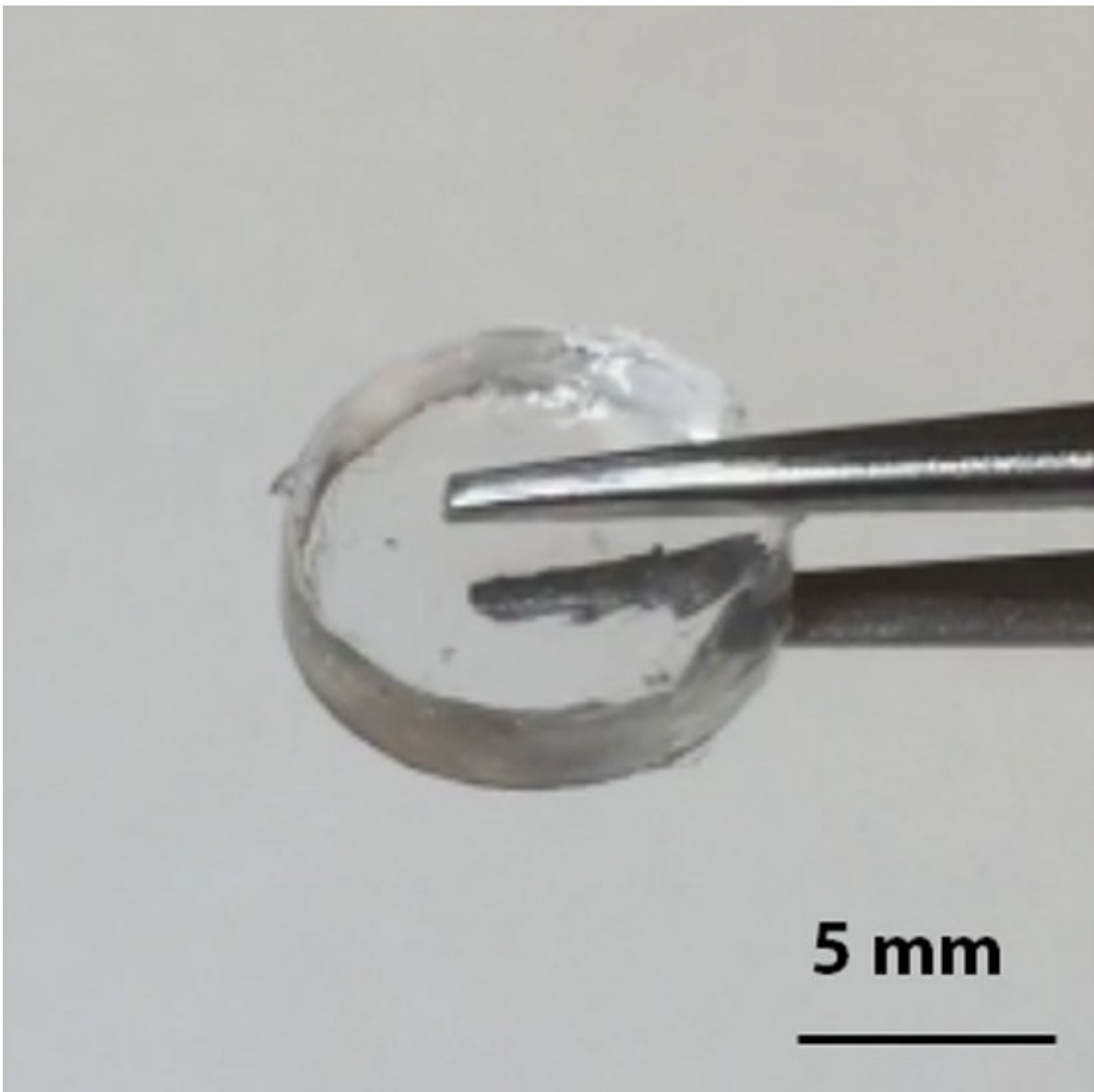


Gradual release of immunotherapy at site of tumor surgery prevents tumors from returning

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A biodegradable hydrogel representing those used in the study. Credit: C.G. Park et al., *Science Translational Medicine* (2018)

A new study by Dana-Farber Cancer Institute scientists suggests it may be possible to prevent tumors from recurring and to eradicate metastatic growths by implanting a gel containing immunotherapy during surgical removal of a tumor.

In the study, published online today by *Science Translational Medicine*, researchers removed breast tumors from mice and placed biodegradable gels containing an immune-stimulating drug in the resulting empty space. The gels released the drug, which switches on a key type of immune cell, over an extended period of time. When researchers examined the animals over the next several months, they found that this approach cured a much higher proportion of mice than delivery of the drug by other techniques. Not only did the original tumors not recur in the breast, but metastatic tumors in the lungs—far away from the site of drug delivery—were eliminated as well.

The researchers say the findings, which were duplicated in mice with lung cancer and melanoma, hold immense promise for overcoming two of the greatest obstacles to curing cancer: 1) the tendency of the disease to recur in patients who have undergone surgery to remove [solid tumors](#); and 2) the difficulty in eradicating distant metastases.

"Surgery is the main treatment option for patients with most solid tumors, but recurrence and metastasis remain significant problems," says study senior author Michael Goldberg, Ph.D., assistant professor at Dana-Farber and Harvard Medical School. "Even when an entire [tumor](#) has been removed, it is common for a small number of tumor [cells](#) to remain behind. Indeed, while half of all cancer patients undergo surgery aiming

to cure the disease, 40 percent of such patients experience a recurrence of the disease within five years. Furthermore, it has been shown that the body's natural process of healing the wound created by surgery can actually spur these residual cancer cells to metastasize to distant parts of the body and form new growths.

"The long-lasting anti-cancer effects produced by immunotherapy can be very powerful, but the percentage of patients who benefit from such drugs has been somewhat modest to date. In this study, we sought to determine whether administering immune-stimulating drugs at the place and the right time—at the site of tumor removal, before the surgical wound has been closed—could enhance the results of cancer immunotherapy."

For this approach to work, the researchers reasoned that they would need to alter the immunological conditions inside the surgical wound. When a tumor is removed, both cancer cells and neighboring cells—including immune cells and connective tissue—are removed as well. This so-called tumor microenvironment often contains cells, proteins, and other substances that deter the immune system from attacking the tumor. The removal of these components might be expected to unleash an assault by the immune system on cancer cells left after surgery. However, surgery also removes cancer-fighting immune cells and proteins that are critical for the immune system attack. Moreover, in the aftermath of surgery, the immune system concentrates most of its efforts on healing the surgical wound, lowering its guard against cancer cells. It's this "immunosuppressive" microenvironment that gives the remaining [tumor cells](#) license to metastasize and flourish in other parts of the body.

The goal of the new approach is to convert that immunosuppressive environment into an "immunostimulatory" one, Goldberg says—a condition in which the immune system is primed for an offensive against cancer cells.

In the study, the researchers loaded a hydrogel—a half-inch disc made of a biodegradable sugar naturally found in the human body—with drugs that activate [dendritic cells](#). Dendritic cells are part of the innate immune system—the body's first responders to foreign intruders or diseased cells. The hydrogel, placed in the spot where the tumor was removed, releases the drug over an extended period of time, lengthening the window of effectiveness. When the dendritic cells are activated, they train T cells—their allies in the adaptive arm of the immune system—to attack cancer cells anywhere in the body, whether at the site of the original tumor or distant metastases.

The decision to implant the hydrogel at the time of surgery was based on several considerations. "We reasoned that it would be easier to eliminate a small number of residual cancer cells by creating an immunostimulatory environment than it would be to treat an intact primary tumor, which has many means of evading an immune system attack," Goldberg notes. Moreover, administering immunotherapy prior to surgery could potentially produce immune-related side effects that could require delaying surgery. And administering the therapy after [surgery](#) and after the wound has had a chance to heal could be less effective, a previous study suggests.

The researchers confirmed that the approach succeeded in flipping the post-surgical context of the wound area from an immunosuppressive state to an immunostimulatory one. Among the treated mice, cure rates were much higher than in animals that received free drug that had not been loaded into the hydrogel, whether the drug was injected intravenously or even directly into the tumor. The animals treated with the new approach didn't appear to suffer any adverse effects from the therapy, Goldberg remarks. His group assessed the animals for changes in body weight as well as potential toxicity to the liver, kidney, and blood cells—none of which was observed.

The benefits of this approach to treatment appear to be enduring. Three months after the mice underwent the treatment, they didn't have a recurrence. When researchers injected fresh breast [cancer cells](#) in the side opposite the original tumor site, the disease didn't recur in any of the mice, as the [cancer](#) was rejected by the immune system's memory.

"This technique works particularly well with immunotherapies that are otherwise typically injected into tumors that are readily accessible, which represents a minority of solid tumors," Goldberg relates. "The ability to address any solid tumors that can be surgically removed greatly increases the number of patients who might benefit from such potent immune-stimulating agents, which can be toxic when administered throughout the body.

"This approach has the potential to deliver immunotherapy in a manner that focuses the therapy at the site of interest during a critical time window," he continues. "We are extremely encouraged by the results of this study and hope that this technology will be adapted for patients for testing in clinical trials in the not-too-distant future."

More information: C.G. Park et al., "Extended release of perioperative immunotherapy prevents tumor recurrence and eliminates metastases," *Science Translational Medicine* (2018).

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