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A Beacon to Guide Cancer Surgery

A modified virus makes cancer cells fluoresce to better identify tumors.

By Courtney Humphries

Removing tumors from cancer patients always brings uncertainty. Surgeons fear that cells they don't spot and remove might re-emerge. Researchers have been looking for ways to make cancer cells visible so that none is left behind. Some of these strategies rely on injecting fluorescent probes or nanoparticles like quantum dots that will attach to the surface of cancer cells. Now a company is working on technology that makes cancer cells fluoresce from the inside out. The approach, developed by San Diego-based company AntiCancer, in partnership with scientists at Okayama University in Japan, uses a virus that infects cancer cells to integrate a fluorescence gene into tumors. The result is cancer that permanently glows, which the company hopes would allow surgeons to remove tumors with more precision and to monitor any cancer that re-emerges.

To make cancer cells fluoresce, the researchers used a virus called OBP-401, a modified cold virus that can enter all cells but will only replicate in those that have activated telomerase, an enzyme that is expressed in cancer cells and allows them to divide indefinitely. Normally a cell can only divide a limited number of times before dying, because at every division it loses part of its telomeres, caps of DNA at the ends of chromosomes that keep the genome stable. But cancer cells can keep dividing because telomerase replaces the telomeres every time the cell divides.

The OBP-401 virus had been developed as an anticancer therapy. Here, the researchers modified the virus to carry green fluorescent protein (GFP), a protein derived from jellyfish that fluoresces in blue light. When the virus is injected into an animal, the gene becomes active in cells that express telomerase. Robert Hoffman, president of AntiCancer and a surgeon at the University of California, San Diego, explains that GFP is permanently integrated into the genome of cancer cells, making this technology fundamentally different from approaches that rely on attaching a fluorescent particle to a protein on the surface of cancer cells. Hoffman believes that by creating a genetic marker, the approach "takes advantage of the tumor biology more effectively."

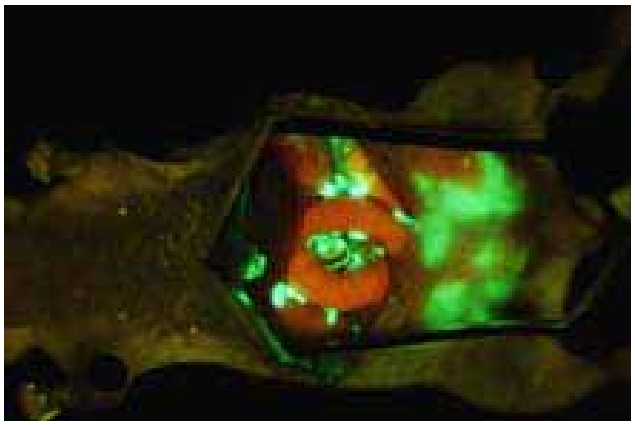
In a recent paper in the *Proceedings of the National Academy of Sciences*, Hoffman's team used the virus to illuminate tumors in mice that were scattered throughout the body. During surgery to remove the tumors, they could visualize them by exposing tumors to light of the proper wavelength and looking through a filter that picks up GFP fluorescence. "In principle it should pick up any cancer cell," says Hoffman. The team has not yet reached single-cell precision, but they are able to see and remove small cancerous areas that would otherwise be invisible.

Although new cancers that form after the virus is delivered would not be fluorescent, Hoffman says that any of the original cancer that began to grow again should still express GFP, allowing clinicians the opportunity to monitor the results of the surgery over time.

Hisataka Kobayashi, a scientist in the molecular imaging program at the National Cancer Institute, says the advantages of this method are that it very specifically targets cancer cells and makes it possible to monitor the cancer over time. The method also allows for flexibility; for instance, a gene that would cause the cancer cells to kill themselves could be added to the virus along with GFP, pairing imaging with treatment.

Kobayashi says that one of the key questions of the technology is safety. Giving patients a virus carrying a gene for imaging is very similar to giving them a gene to correct a disease, he says, and consequently "all the problems with gene therapy apply to this method." Many gene therapy approaches have been stalled because of immune reactions to the treatment. However, Lily Wu, a scientist at the University of California, Los Angeles, who develops cancer therapies, points out that similar gene therapy treatments for cancer have so far been found safe in clinical trials, whereas safety "is still not determined for other synthetic vectors such as quantum dots." Wu believes that this method offers several advantages over other ways of labeling tumors but says that it will require a more thorough quantitative analysis to demonstrate its effectiveness.

Hoffman says AntiCancer hopes to complete further safety testing that will allow it to bring the technology into clinical trials. Although fluorescence in mice can be visualized throughout the body, in humans the task will be more difficult, because the light scatters easily and doesn't penetrate very far into tissues. For that reason, the researchers envision this technique being used during surgery where the tumor can be seen directly.



A bright idea: Mice carrying tumors from human colon cancer cells were given a virus that causes cancer cells to fluoresce. Researchers were able to visualize the dispersed tumors (in green) and remove them surgically. The small intestine is shown in red. Credit: Hiroyuki Kishimoto and Robert M. Hoffman, AntiCancer