

## Using selectivity and sensitivity to detect the whole tumor

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SAN DIEGO – Removing tumors and detecting even the most slightly diseased tissue have become easier with the help of bright GFP and a GFP-expressing adenovirus. The fluorescence labeling technique, described in a recent study, will help to target and illuminate a specific tumor, along with any scattered malignant cells found in normal tissue surrounding the growth that may otherwise be hard to identify.

"The ability to selectively make tumors fluorescent will enhance the ability to detect tumors during the surgical procedure," said Dr. Robert Hoffman, lead researcher and president of the biotechnology company AntiCancer Inc. "It also has a possibility to make tumors more visible during diagnostic procedures such as fluorescence endoscopy."

Furthermore, the method could help visualize peritoneal lesions, a rare cancer that is affiliated with the delicate, thin wall of the abdomen and that can extend into the bladder and rectum. According to Hoffman and fellow researchers, peritoneal cancer comprises 20 percent of gastric, colon and pancreatic cancers. Their findings were published Aug. 25 in *Proceedings of the National Academy of Sciences*.

### Let there be GFP

To activate GFP within malignant tissue only, the researchers introduced OBP-401, a GFP-containing adenovirus that also contains a telomerase reverse transcriptase promoter.

"OBP-401 is an adenovirus that has been engineered to be expressed only in cells that express telomerase, which are essentially only cancer cells," Hoffman said. "OBP-401 also has been engineered to express the GFP gene and therefore can label tumor cells with GFP as it replicates in them."

The team expressed GFP fluorescence in A549 human lung cancer cells that had already been engineered to express red fluorescent protein (RFP). The researchers discovered that the cancer cells changed color from red to yellow, indicating that the OBP-401 had in fact delivered GFP to the infected cells, while intracellular replication of the virus intensified the fluorescence. The scientists determined that any remaining red cells were those not infected by the adenovirus.

To evaluate the effectiveness of GFP fluorescence-guided surgery, peritoneal carcinomatosis was induced into the abdominal cavity of athymic nude mice with nonfluorescent HCT-116 human colorectal cancer cells. In another experiment, the researchers injected HCT-116-RFP cells and, after the cells formed peritoneal carcinomatosis, they injected the mice with OBP-401. They observed an unmistakable color change from red to yellow in the cancer cells. Even very small tumors were visible, indicating that the adenovirus successfully targeted and labeled the entirety of the cancer.

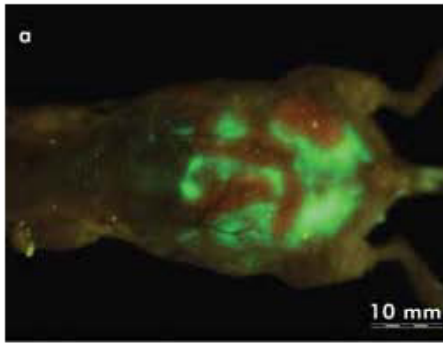
Macroscopic lesions are frequently missed because of weak contrast between tumor nodules and normal tissue. However, the study revealed that OBP-401 can be highly sensitive in detecting cancer cells. Current tumor removal procedures hinder visualization of malignant tissue in the body; however, GFP can help surgeons remove all malignant tissue. "Making the tumors fluorescent will enable the surgeon to visualize more of the tumor tissue in the body, giving the surgeon more opportunity for better resection," Hoffman said.

The parent virus of OBP-401, with no GFP expression, was recently tested and determined to be safe for clinical practice, according to Hoffman. He anticipates that the OBP-401, based on its relation to the successful parent adenovirus test, will also be safe for patient use, and he expects it to be available fairly soon. "It is hoped in the next five years that OBP-401 will be used in clinical settings," he said.

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*GFP and OBP-401 have been expressed in peritoneal lesions to reveal bright-green malignant tissue in an athymic nude mouse (a). Red fluorescence indicates cells that were not infected by the adenovirus (b). Surgeons performed a laparotomy and removed all the malignant tissue in the abdominal cavity (c).*

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