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# Detonating Tumor-Killer Drug in Cancers on Command

ScienceDaily (Nov. 18, 2009) — Experiments at the Pioneer Valley Life Sciences Institute (PVLSI) at Baystate Medical Center in Springfield, Mass., reported in a recent *British Journal of Cancer*, confirm that University of Massachusetts Amherst chemical engineer Neil Forbes' delivery and trigger system has for the first time successfully placed TRAIL, a cancer-fighting protein, directly into solid tumors and on cue, turned it on. The treatment improved the 30-day survival time of mice with mammary tumors from 0 to 100 percent.

"This is a first step, but it's the first time we've controlled delivery to the tumors and the first time we've been able to turn on production of a cytotoxic protein and kill tumors from within. With more work we should be able to fine-tune our methods," says Forbes. "As an engineer, what I've designed is transport and deployment, that is, a way to get the army in position plus a switch to signal those troops to arm themselves and attack."

It's been known for about 10 years that common bacteria such as *Salmonella* and *Escherichia* favor the microenvironment of solid tumors, says Forbes. When others engineered a non-pathogenic strain of *Salmonella*, Forbes saw an opportunity. He began to design a "troop transport" of sorts, which would be controllable in location and time, to attack tumor cells at the same time it is less harmful to patients.

Forbes designed experiments that were carried out by PVLSI surgical oncologist Sabha Ganai, who received her doctorate for the work. They report dramatic success in delivering millions of the bacterium, *S. typhimurium*, into mouse mammary tumors and triggering them to start producing tumor necrosis factor-related apoptosis-inducing ligand, or TRAIL, a peptide toxic to cancer cells. It selectively causes tumor cell death, or apoptosis, with minimal host toxicity, that is, without harming normal cells.

They began by engineering the salmonella to include the gene for TRAIL so that it gets expressed under control of the RecA promoter. Then Ganai injected 2 million *S. typhimurium* cells that carried the engineered RecA promoter and TRAIL gene into groups of genetically identical mice with mammary tumors, that is, breast cancer. The RecA promoter activates when cells experience DNA damage from any cause. In this case, Ganai and Forbes use a very low dose, 2 Grey, of gamma radiation to switch on RecA.

By about 48 hours after they are injected, the bacteria have multiplied to about 10 million per tumor. At this point, Ganai exposed the mice to either a single dose or the first of two low radiation doses.

The resulting mild damage to DNA (single-strand breaks) activates RecA and initiates the engineered production of TRAIL, which is highly toxic to cancer cells.

Mice that received two low-dose radiation treatments in conjunction with the bacterial injections to trigger the RecA promoter showed reduction in tumor volume and survived longer than control groups. TRAIL clears quickly and its release must be regularly re-stimulated for best effectiveness, Forbes says. Thus the double-dose radiation group did best of all.

Forbes and Ganai say these experiments show that they can control when the bacteria produce the anti-tumor drug by engineering *S. typhimurium* with a genetic switch that responds to radiation. This means the bacteria can be given to a future patient and once the bacteria have colonized in tumors, oncology clinicians can irradiate the tumor and start the bacteria making the drug. Irradiation makes an excellent switch because it can penetrate human tissue, is available at most cancer centers and is harmless at low doses.

Ganai and Forbes envision that, once fully developed, "this bacterial cancer therapy with spatial and temporal control of delivery will provide considerable therapeutic benefit by enhancing efficacy while limiting host toxicity."

This work was supported by grants from the National Cancer Institute and the Susan G. Komen for the Cure organization.



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**Story Source:**

Adapted from materials provided by University of Massachusetts Amherst.

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