

Can bacteria fight brain cancer?

The thinking behind an approach that has caused trouble in California.

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Last week, the *Sacramento Bee* reported that two neurosurgeons at the University of California, Davis, had been banned from research on humans after [deliberately infecting three terminally ill cancer patients with pathogenic bacteria](#) in an attempt to treat them. All three died, two showing complications from the infection. *Nature* explores what happened and the science behind it.

Who authorized the researchers to infect the patients?

All three patients consented to infection. However, anyone testing experimental drugs in the United States requires approval from their university's Institutional Review Board (IRB) and oversight by the country's Food and Drug Administration (FDA), both of which review evidence for safety and efficacy. Neurosurgeons Paul Muizelaar and Rudolph Schrot at the University of California (UC), Davis, did not obtain this approval; they say they did not think it was required. Harris Lewin, the vice-chancellor of research at UC Davis, wrote a letter to the FDA describing what had occurred as "serious and continuing noncompliance".

In 2008, working under instructions from Muizelaar, Schrot asked the FDA about the possibility of deliberately infecting a postoperative wound in a particular patient with glioblastoma with the bacterium *Enterobacter aerogenes*. He was told that animal studies were needed first. Muizelaar did not infect that patient, but arranged for a graduate student to begin tests in rats. Although bacteria were purchased as research materials not to be used in humans, they were eventually used in three other patients with glioblastoma.

The first of those asked Muizelaar about infection in 2010, and Schrot contacted the director of UC Davis's IRB asking permission to perform what Lewin's letter describes as a "one-time procedure" not intended as research. The director concluded that this procedure could be classed as "innovative care" that did not require approval by the FDA or IRB, but that subsequent work should be reviewed. Schrot and Muizelaar went on to treat two further patients and were seeking approval from an ad hoc ethics committee (not the IRB or FDA) to treat five more when the IRB director told the neurosurgeons to cease and desist, and began an internal investigation.

How is brain cancer usually treated?

Glioblastoma is an aggressive brain cancer and is usually treated with surgery, as well as with radiation and chemotherapy. However, the cancer almost always recurs after surgery. Half of patients die within 15 months of diagnosis; fewer than one in twenty lives longer than five years.



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Infections occurring after brain-tumour surgery may cause cancer regression.

Why might an infection fight cancer?

There are isolated reports of patients with various types of cancer successfully fighting off an infection only to find that the cancer has also disappeared. Presumably, the infection spurs white blood cells to attack both pathogens and malignant cells. In 1999, researchers at the University of Mississippi Medical Center in Jackson described four case studies in which the regression of malignant brain tumours co-occurred with infection. *Enterobacter aerogenes*, the same bacterium used at UC Davis, was recovered from microbial cultures taken from three of the patients¹.

What further studies have been done?

In 2004, a group led by Bert Vogelstein at the Howard Hughes Medical Institute in Maryland introduced cancer cells into mice and rabbits, allowed large tumours to form and then injected the animals with spores of the anaerobic bacterium *Clostridium novyi-NT*. About one-third of the animals' tumours disappeared, apparently as a result of an immune response².

Then, in 2011, researchers at the Catholic University of Rome examined the records of 197 patients treated for glioblastoma between 2001 and 2008, of which ten developed pathogenic infections after surgery. Those patients had a median survival rate of 30 months, whereas patients who did not become infected had a median survival rate of 16 months. However, the authors concluded that the association was “not definitive”³.

A 2009 report considered 382 patients with malignant brain cancer, 18 of whom developed infections. Infected patients lived longer on average, but the difference was not statistically significant⁴. What's more, the researchers reasoned that infection may correlate with longer survival not because infection prolongs survival but because patients who live longer are more likely to develop infections.

Are there clinical trials studying whether an immune response can fight cancer?

Yes. But rather than infecting patients with active microbes, these studies use therapeutic vaccines. The first cancer-treatment vaccine, Provenge, for prostate cancer, was approved in 2010 but is still controversial.

A US government registry of clinical trials that have attained regulatory approval lists more than three dozen studies using vaccines for glioblastoma. One, at Duke University in Durham, North Carolina, injects patients' brains with weakened, engineered poliovirus. Many of the others work by collecting a patient's white blood cells and exposing them to cancer-specific molecules.

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References

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