Can bacteria shrink tumors?

Cancer Therapy: 
The Microbial Approach

In this age of advanced medical science and technology, we still continue to hunt for innovative cancer therapies that prove effective and safe. Treatments that successfully eradicate tumors while at the same time cause as little damage as possible to normal tissue are the ultimate goal, but are also not easy to find.

The use of microorganisms in cancer therapy is not a new idea but it is currently a buzzing topic in cancer therapy research.

In the late 1800s, German physicians W. Busch and F. Fehleisen both individually observed that certain cancers began to regress when patients acquired accidental erysipelas (cellulitis) caused by *Streptococcus pyogenes*.

New York surgeon William Coley was the first to use bacteria as a form of cancer therapy in the 1890s. He injected live *Streptococcus* into cancer patients but after the recipients unfortunately died from subsequent infections, Coley decided to use heat killed bacteria. He made a mixture of two heat-killed bacterial species, *Streptococcus pyogenes* and *Serratia marcescens*. This concoction was termed “Coley’s toxins.” Bacteria were either injected into tumors or into the bloodstream.

William Coley was the first to use bacterial injections to treat cancer patients.
He treated more than 1,000 patients using this bacterial approach to cancer therapy. However, Coley’s studies were controversial and difficult to repeat. His approaches were further disregarded with the emergence of radiation and chemotherapy treatments in the 20th century.

Solid tumors contain areas of low oxygen, known as hypoxia. These regions emerge when tumor cells grow very rapidly, causing them to outpace the blood supply that delivers oxygen to the tumor. Cancer cells in hypoxic regions are highly resistant to standard chemotherapy and radiation therapies. Scientists discovered that certain anaerobic bacteria, such as *Clostridium* spp., were able to grow and live in oxygen-poor cancerous tissue but the bacteria could not survive when coming in contact with oxygenated sides of the tumor, thus causing no harm to normal tissue.

In the 1950s and 1960s, researchers used the anaerobic bacterium *Clostridium butyricum* to treat cancer patients. While the treatment was successful in diminishing tumor size, patients became sick from the toxins produced by the bacteria. Use of non-pathogenic *Clostridium* strains proved ineffective and did not result in significant tumor regression.

In the early 2000s, genetic engineering allowed scientists at Johns Hopkins University to create a strain of *Clostridium novyi* with a deleted gene that codes for the lethal toxin produced by the bacterium. They named this organism *C. novyi*-NT (NT for non-toxic). *Clostridium novyi* is an obligate anaerobe and is a ubiquitous organism, found in soil and feces. It is a pathogenic organism and is closely related to *Clostridium botulinum* types C and D.

![Image of Clostridium botulinum at 1,000X](image)

Without the ability to produce toxic proteins, *C. novyi*-NT was a good candidate for cancer treatment with the hopes of reducing tumor size while at the same time limiting side effects.

*C. novyi*-NT spores injected into the brain tumors of rats resulted in localized tumor necrosis and increased rat survival rate (2). Brain edema was common as a result of *C. novyi*-NT germination but abscess formation was not seen with the use of antibiotics. Abscess formation could be a potential side effect of this treatment but can be managed and the risk compared with the benefits may be well worth it for certain cancer types.

Furthermore, it has been shown that *C. novyi*-NT spores could result in a localized inflammatory response as well as an adaptive immune response against tumor cells (3).

The researchers that conducted these studies realized that successful results in lab rodents rarely translate to successful trials in people so they utilized canine models to demonstrate the plausibility of the treatment.

Dogs were chosen because the toxicities and effects from therapeutic agents are similar in dogs and people. Also, canine soft tissue sarcomas have clinical and histopathological features that resemble human soft tissue sarcomas. *C. novyi*-NT spores injected intra-tumorally produced robust antitumor responses and adverse effects were mild in severity.
consistent with local infection at the injection site (2).

Safety trials were started in humans and results have been positive though not perfect. The main issue with this type of treatment has to do with the fact that *C. novyi*-NT elicits a local response and does not target metastatic tumors, metastasis being the most lethal aspect of cancer. The next step for these researchers is to determine which types of tumors respond best to this type of therapy and how immune cells are stimulated to attack the tumor as well. Understanding the mechanisms at work here can lead to research on more effective cancer treatment.

Bacteria belonging to other genera have also been studied in cancer therapy. A strain of *Salmonella typhimurium* with two important genes deleted has also been developed for use in cancer treatment.

The genes the organism lacks are required for causing toxic shock in its animal hosts and for purine synthesis. Without these genes, *S. typhimurium* does not cause illness in the host and is incapable of replicating in normal tissue but can still grow in tumors where purine is available (4).

The less limiting environmental conditions required for *Salmonella* growth makes this organism useful for treatment against small tumors, unlike *Clostridium* spp. which cannot survive in aerobic environments.

Less direct ways of using bacteria in cancer treatment are also being studied, such as engineering bacteria to be vectors for gene-directed enzyme prodrug therapy use (4).

Most bacterial cancer therapies are either early in development or are still undergoing investigational research, with the exception of *Bacillus Calmette-Guérin* (BCG). BCG is the only established cancer treatment that utilizes bacteria. This is commonly recognized as the vaccine used to provide protection from tuberculosis.

The BCG Vaccine

It is an attenuated strain of *Mycobacterium bovis* that, in addition to vaccinating against tuberculosis, has been used as an effective form of immunotherapy for superficial bladder cancer. It is also commonly used to prevent recurrence of noninvasive bladder cancer.

The use of viruses in cancer therapy has also made article headlines. Significant events include a modified measles virus that was able to almost completely eradicate myeloma in a 49 year old woman, and a modified HIV-type virus used to treat leukemia in a young girl.

HIV can be modified for therapeutic purposes.

Many of these oncolytic viruses (viruses that preferentially attack and kill tumor cells) have been genetically engineered from modified viruses. Viruses utilized in these studies have included herpes viruses, pox viruses and adenovirus. The future of oncolytic viruses to be used in cancer therapy is certainly a promising one and we can look forward to upcoming research and clinical trials in this field.
Cancer patients today have a variety of mainstream treatment choices that include surgery, radiation therapy, immunotherapy, and chemotherapy. These treatments have saved many lives and continue to be the best treatment choice for certain cancers but they are also not always one hundred percent effective and some are certainly not without their damaging side effects.

The use of microorganisms in cancer therapy research has come a long way since “Coley’s toxins” and the future looks bright, not only for advances in this field, but also for cancer patients that can receive this form of treatment.

References