William Coley and Coley's Toxins - Yesterday and Today

The role of bacteria as an anticancer agent was recognized almost one hundred years ago when the German physicians W. Busch and F. Fehleisen separately observed that certain types of cancers regressed following accidental erysipelas (*Streptococcus pyogenes*) infections that occurred whilst patients were hospitalized. Independently, the American physician William Coley spent his life researching and implementing this therapy. William Coley, born 1862 in Connecticut, went to college at Yale, and graduated from Harvard Medical School in 1888. He joined the staff of Memorial Hospital in New York as a surgical intern. One of his first patients in 1890 was Bessie Dashiell, a 17-year-old girl who had a swelling in her hand which was diagnosed as a malignant bone tumor, most probably an Ewing's sarcoma in her metacarpal. Despite a forearm amputation, she died of widespread metastases within ten weeks. This rapid spread of a lethal cancer had a profound effect on Dr. Coley. He was determined to find an effective treatment. During a review of the records of New York Hospital, Dr. Coley learned about a patient who, seven years prior, had had an inoperable malignant tumor in his neck that seemed to disappear after he developed erysipelas. The patient was discharged, apparently without evidence of a residual tumor. Dr. Coley personally searched for this patient by combing the tenements of Lower Manhattan. Weeks later, he finally found the patient, a German immigrant named Stein, who had no evidence of residual cancer.

Dr. Coley developed the theory that it was the fever from the infection which had helped patients recover from their cancer. So he began to treat patients by injecting Streptococcus pyogenes directly into inoperable tumors. He found the treatment was most effective when it provoked a fever and a full-blown infection. This led physicians to understand that the increase in body temperature not only mobilized the body's own immune system, thus fighting off the infection, but also destroyed the tumor at the same time. Later Dr. Coley decided to use a mixture of dead Streptococcus pyogenes and dead Serratia marcescens bacteria. This was subsequently termed "Coley's Toxin". In 1893, the first patient to receive Coley's Toxin was John Ficken, a 16-year-old boy with a massive abdominal tumor. Every few days, Coley injected this bacterium directly into the tumor mass, which produced the symptoms of an infectious disease, but did not produce the disease itself. On each injection, there was a dramatic rise in body temperature and chills. The tumor gradually diminished in size, and after four months of

intensive treatment, the tumor was a fifth its original size. Later that year, the remains of the growth were barely perceptible.[1]

The boy received no further anticancer treatment and remained in good health until he died of a heart attack 26 years later. Over the next 40 years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. By the end of his career, Coley had written over 150 papers on this subject.[2, 3, 4]

Coley mainly used his toxins on patients with inoperable bone and soft-tissue sarcomas, observing that this treatment was less effective on other types of cancer such as melanomas and carcinomas. Beginning in 1899, Parke Davis and Company had begun to prepare the Coley's Toxins, so they were available for all physicians. Because of his widely used treatment, as well as the fact that he was publishing his work, Coley was much in the public eye. Early in his career he received small donations from the Rockefeller family to help with his research, and in 1902 he arranged a large grant from the Huntington family that supported him and other cancer researchers. This endowment was the first in the U.S. designated specifically to study cancer.[5]

Despite his reported positive results, Coley's Toxin came under a great deal of criticism because many doctors did not believe it possible. Medicine has always been, and still is, ruled by belief. Additional controversies surrounding Coley's work reflect the field of oncology struggling to stabilize its understanding of how to treat cancer. For example, James Ewing, perhaps the most famous cancer pathologist in the country, was a leading opponent of Coley's work. This was a problem for Coley because Ewing was Medical Director of Memorial Hospital, and for many years was Coley's boss. Their memos to one another reflect constant interpersonal animosity. Ewing himself had become a fanatical supporter of radiation therapy for the treatment of all bone tumors and repudiated any other theories for the treatment of cancer. Ewing therefore refused Coley permission to use his toxins at Memorial Hospital. This was ironic, because Coley had more experience than any other surgeon in the country in treating the small round blue cell sarcoma that still carries Ewing's name.

In 1934, The *Journal of the American Medical Association* acknowledged that Coley's Toxin might be of value: "It appears, that undoubtedly the combined toxins of erysipelas and prodigiosus may sometimes play a significant role in preventing or retarding malignant recurrence or metastases; occasionally they may be curative in hopelessly inoperable neoplasms; . . . The Council has, for these reasons, retained Erysipelas and Prodigiosus Toxins-Coley in New and Nonofficial Remedies, with a view to facilitating further studies with the product."

In 1935, Coley was inducted as an honorary fellow into the Royal College of Surgeons of England, becoming just the fifth American to receive that honor. After Coley's death in 1936, his son continued to prescribe and use the treatment for his patients. Coley's Toxins were widely used for the next 30 years and in the first half of the 20th century, different formulas of Coley's Toxins were manufactured by several U.S. drug companies. These formulations were used to treat patients with a variety of types of cancer until the early 1950s, when other forms of cancer treatment became more widely used, such as radiotherapy.

Unfortunately, skepticism and criticism, together with the development of radiation therapy and chemotherapy, caused Coley's Toxin to gradually disappear from use in the U.S. By 1952, the Park Davis Company no longer produced Coley's Toxin.[6] In 1962, the FDA refused to acknowledge Coley's Toxin as a proven drug and created strict regulations which rendered Coley's Toxins illegal. The FDA considered the treatment to be the introduction of a "new drug" even though it had been around for well over 50 years.

Coley's daughter, Helen Coley Nauts, deserves much credit for keeping her father's legacy relevant. After her father died, she dedicated her life to studying his toxins and reviewing his work. Although Nauts herself had no formal medical training, she published more than 18 monographs and identified more than 500 patients who were successfully treated with her father's toxin. In 1953, she founded the Cancer Research Institute, which still exists today, to honor her father and advance the field of immunotherapy research.

In retrospect, William Coley's intuitions were correct. Using fever induction therapy to stimulate the immune system is effective in treating cancer. Coley was a model of the clinician-scientist, treating patients and using his practice to initiate research and build theories. But he was a man before his time, and he met with severe criticism. During the second half of the 20th century, which is characterized by heavy use of antibiotics, fever was regarded by mainstream medicine as an unnecessary, weakening state which should be suppressed or prevented. The situation today has not changed much. The immune system is constantly repressed with anti-microbials and even mild fever is suppressed with an anti-febrile.

Within the last few years there has been ongoing research in the U.S. using certain bacteria to stimulate the immunity and attack tumors. In 2015, scientists modified or attenuated a strain of salmonella (Salmonella enterica serovar Typhimurium) to attack tumors in mice. These bacteria have been shown not only to colonize solid tumors, but also to exhibit an intrinsic antitumor effect. According to these scientists, these bacteria can also serve as tumor-targeting vectors for therapeutic molecules. However, the

pathogenic *Salmonella Typhimurium* strains used for tumor therapy need to be attenuated for safe application.[7]

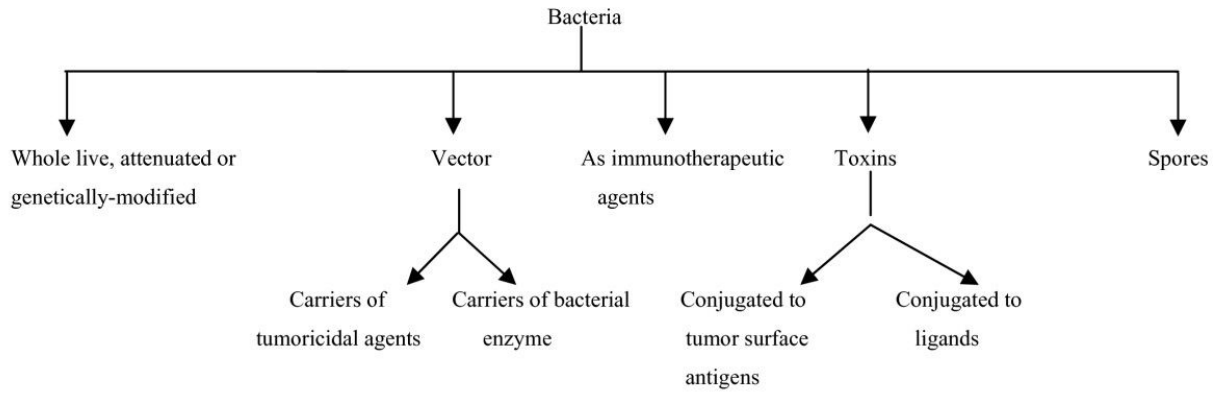
Following this research of antitumor bacterial therapy in 2017, Zheng et al. engineered a weakened strain of Salmonella typhimurium to produce the flagellin B protein from another bacterium, *Vibrio vulnificus*. The engineered bacteria induced an effective antitumor immune response, successfully treating tumors in several different mouse models with no evidence of toxicity.[8]

Another 2017 study published in *Science* by Johns Hopkins research team looked at *Clostridium novyi,* a relative of the microbe responsible for botulism. Because *C. noyvi* causes infections, the team removed its toxin-producing genes to make it safer for use. The new bacteria strain is called *C. noyvi-NT* (NT stands for non-toxic). To start testing their hypotheses, the researchers injected bacterial spores directly into rat tumors with brain cancer. They observed an antitumor response that improved the survival rates of the animals. They then injected the modified bacterial spores into the tumors of 16 dogs and observed the responses. In six dogs, the tumor sizes were reduced; in three dogs, the cancer went away completely. The researchers concluded, “Together, these results show that *C. novyi-NT* can precisely eradicate neoplastic tissues and suggest that further clinical trials of this agent in selected patients are warranted.”[9]

A major problem with using bacteria as anti-cancer agents is their toxicity at the dose required for therapeutic efficacy and reducing the dose results in diminished efficacy. Moreover, systemic infection of bacteria is rather inconvenient and carries higher risk of obvious toxicity. However, according to Shibin Zhou, M.D., Ph.D., associate professor of oncology at Johns Hopkins Medicine, "One advantage of using bacteria to treat cancer is that you can modify these bacteria relatively easily, to equip them with other therapeutic agents, or make them less toxic as we have done here.”

Saurabh Saha, senior author of the study added, “Coley injected his first patient a century ago, and what he saw was almost identical to what we saw in our first patient. Within the same time frame observed by Coley, our patient developed a fever, the tumor started swelling, and then it started to shrink. Oxygen is scarce inside tumors, and these bacteria love areas of low oxygen. They grow and divide and kill the cancer cells. A good thing about using bacteria as a therapeutic agent is that once they're infecting the tumor, they can induce a strong immune response against tumor cells themselves." The researchers hypothesized that the bacteria release enzymes that destroy the tumor cells, and eat the shreds. “It shows that what was done 120 years ago with Coley’s Toxins deserves to be revisited again today, using bacteria as an adjuvant to stimulate the immune system to fight cancer,” Saha said. “I think it’s a very important modality, and one that we should continue pressing forward on to learn more about.”

Several decades after Coley's work a variety of natural and genetically modified non-pathogenic bacterial species are being explored as potential antitumor agents, either to provide direct tumoricidal effects or to deliver tumoricidal molecules. In recent years, the use of genetically modified bacteria for selective destruction of tumors, and bacterial gene-directed enzyme prodrug therapy have shown promising potential. Studies have been numerous and ongoing. [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21] The detailed overview of these bacteria based approaches is given below.



Patyar et al. Journal of Biomedical Science 2010, 17:21 http://www.jbiomedsci.com/content/17/1/21

Today, bacteria-induced fever therapy and intertumoral injections of attenuated bacteria in the treatment of cancer is still illegal in the U.S., but these therapies continue to be researched and clinically used to treat cancer patients in many other countries, such as Germany, Switzerland, China, Japan, Mexico, Central America, and others.

For more information on bacterial induced fever therapy and hyperthermia, see Hyperthermia.

Footnotes

1. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases. Am J Med Sci. 1893 May;105:487–511.

2. Coley WB. The treatment of malignant inoperable tumors with the mixed toxins of erysipelas and bacillus prodigiosus. Brussels: M Weissenbruch; 1914.

3. Coley BL. Neoplasms of Bone. New York: Medical Book Department of Harper & Brothers; 1949. pp. 565–570.

4. Coley-Nauts H, McLaren JR. Coley Toxins – the first century. Adv Exp Med Biol. 1990;267:483.

5. Hall SS. A Commotion in the Blood. New York: Henry Holt and Company, Inc; 1997.

6. Hoption-Cann SA, van Netten JP, et al. Dr William Coley and tumour regression: a place in history or in the future. Postgrad Med J. 2003;79(938):672–680.
http://pmj.bmj.com/content/79/938/672.short

7. Frahm M, Felgner S, Kocijancic D, Rohde M, Hensel M, Curtiss R, III, Erhardt M, Weiss S. 2015. Efficiency of conditionally attenuated *Salmonella enterica* serovar Typhimurium in bacterium-mediated tumor therapy. mBio 6(2):e00254-15. doi:10.1128/mBio.00254-15.
http://mbio.asm.org/content/6/2/e00254-15.short

8. Zheng, Jin Hai et al. “Two-Step Enhanced Cancer Immunotherapy With Engineered Salmonella Typhimurium Secreting Heterologous Flagellin”. Science Translational Medicine 9.376 (2017): eaak9537. Web. 9 Feb. 2017.
http://stm.sciencemag.org/content/9/376/eaak9537.short

9. Roberts, N. J. et al. “Intratumoral Injection Of Clostridium Novyi-NT Spores Induces Antitumor Responses”. Science Translational Medicine 6.249 (2014): 249ra111-249ra111. Web. 9 Feb. 2017.
http://stm.sciencemag.org/content/6/249/249ra111.short

10. S Patyar, R Joshi, DS Prasad Byrav, A Prakash,B Medh, BK Das Bacteria in cancer therapy: a novel experimental strategy. *Journal of Biomedical Science* 2010 17:21.
https://doi.org/10.1186/1423-0127-17-21.
https://jbiomedsci.biomedcentral.com/track/pdf/10.1186/1423-0127-17-21?site=http://jbiomedsci.biomedcentral.com

11. King I, Itterson M, Bermudes D: Tumor-targeted *Salmonella typhimurium* overexpressing cytosine deaminase: a novel, tumor-selective therapy. Methods Mol Biol. 2009, 542: 649-659.
https://link.springer.com/protocol/10.1007/978-1-59745-561-9_33

12. Hagihara N, Walbridge S, Olson AW, Oldfield EH, Youle RJ: Vascular protection by chloroquine during brain tumor therapy with Tf-CRM 107. Cancer Res. 2000, 60: 230-234.
http://cancerres.aacrjournals.org/content/60/2/230.short

13. Puri RK: Development of a recombinant interleukin-4-Pseudomonas exotoxin for therapy of glioblastoma. Toxicol Pathol. 1999, 27 (1): 53-57. 10.1177/019262339902700111.
http://europepmc.org/abstract/med/10367674

14. Fan D, Yano S, Shinohara H, Solorzano C: Targeted therapy against human lung cancer in nude mice by high affinity recombinant antimesothelin single chain Fv immunotoxin. Mol Cancer Ther. 2002, 1: 595-600.
http://mct.aacrjournals.org/content/1/8/595.short

15. Fujimori M, Amano J, Taniguchi S: The genus Bifidobacterium for cancer gene therapy. Curr Opin Drug Discov Devel. 2003, 5: 200-203.
http://europepmc.org/abstract/med/11926126

16. Tjuvajev J, Blasberg R, Luo X, Zheng LM, King I, Bermudes D: Salmonella-based tumor-targeted cancer therapy: Tumor amplified protein expression therapy (TAPET) for diagnostic imaging. J Control

Release. 2001, 74: 313-315. 10.1016/S0168-3659(01)00340-6.
http://www.sciencedirect.com/science/article/pii/S0168365901003406

17. Kokai Kun JF, Benton K, Wieckowski EU, Mcclane BA: Identification of a *Clostridium perfringens*enterotoxin region required for large complex formation and cytotoxicity by random mutagenesis. Infect Immun. 1999, 67: 5634-5641.
http://iai.asm.org/content/67/11/5634.short

18. Michl P, Buchholz M, Rolke M: Claudin-4: a new target for pancreatic cancer treatment using *Clostridium perfringens* enterotoxin. Gasrtoenterology. 2001, 121: 678-684. 10.1053/gast.2001.27124.
http://www.sciencedirect.com/science/article/pii/S0016508501543498

19. Kominsky SL, Vali M, Korz D: *Clostridium perfringens* enterotoxin elicits rapid and specific cytolysis of breast carcinoma cells mediated through tight junction proteins claudin 3 and 4. Am J Pathol. 2004, 164: 1627-1633.
http://www.sciencedirect.com/science/article/pii/S0016508501543498

20. Ansiaux R, Gallez B: Use of botulinum toxins in cancer therapy. Expert Opin Investig Drugs. 2007, 16 (2): 209-218. 10.1517/13543784.16.2.209.
http://www.tandfonline.com/doi/abs/10.1517/13543784.16.2.209

21. Puri RK: Development of a recombinant interleukin-4-Pseudomonas exotoxin for therapy of glioblastoma. Toxicol Pathol. 1999, 27 (1): 53-57. 10.1177/019262339902700111.
http://europepmc.org/abstract/med/10367674

22. Xu J, Liu XS, Zhou SF, Wei MQ: Combination of immunotherapy with anaerobic bacteria for immunogene therapy of solid tumours. Gene Ther Mol Biol. 2009, 13: 36-52.
https://research-repository.griffith.edu.au/bitstream/handle/10072/30312/62336_1.pdf?sequence=1

23. Vogadri F, Martinoli C, Petrovska L, Chiodoni C, Transidico P, Bronte V, Longhi R, Colombo MP, Dougan G, Rescigno M: Cancer Immunotherapy Based on Killing of Salmonella-Infected Tumor Cells. Cancer Res. 2005, 65 (9): 3920-3927. 10.1158/0008-5472.CAN-04-3002.
http://cancerres.aacrjournals.org/content/65/9/3920.short

24. Al-Ramadi BK, Fernandez-Cabezudo MJ, El-Hasasna H, Al-Salam S, Attoub S, Xu D, Chouaib S: Attenuated Bacteria as Effectors in Cancer Immunotherapy. Ann N Y Acad Sci. 2008, 1138 (1): 351-357. 10.1196/annals.1414.036.
http://onlinelibrary.wiley.com/doi/10.1196/annals.1414.036/full

25. Loeffler M, Le'Negrate G, Krajewska M, Reed JC: Attenuated Salmonella engineered to produce human cytokine LIGHT inhibit tumor growth. Proc Natl Acad Sci. 2007, 104 (31): 12879-12883. 10.1073/pnas.0701959104.
http://www.pnas.org/content/104/31/12879.short

26. Hayashi A, Nishida Y, Yoshii S, Kim SY, Uda H, Hamasaki T: Immunotherapy of ovarian cancer with cell wall skeleton of Mycobacterium bovis Bacillus Calmette-Guérin: effect of lymphadenectomy. Cancer Sci. 2009, 100 (10): 1991-1995. 10.1111/j.1349-7006.2009.01271.x.
http://onlinelibrary.wiley.com/doi/10.1111/j.1349-7006.2009.01271.x/full

27. Yuk JM, Shin DM, Song KS, Lim K, Kim KH, Lee SH, Kim JM, Lee JS, Paik TH, Kim JS, Jo EK: Bacillus calmette-guerin cell wall cytoskeleton enhances colon cancer radiosensitivity through autophagy. Autophagy. 2010, 6 (1): 46-60.
http://www.tandfonline.com/doi/abs/10.4161/auto.6.1.10325

YouTube Videos

The History of Coley's Toxins
https://www.youtube.com/watch?v=StDpsx58Za8

Original Coley's Toxins Opening | Ralph Moss | Eric Merola
https://www.youtube.com/watch?v=bUgrDEzuiiU

Tumor Killing Bacteria
https://www.youtube.com/watch?v=y5TNRW1_VZI

Cancer & Infectious Diseases: Bacterial Proteins/Peptides for Therapy and Prevention
https://www.youtube.com/watch?v=kVs3mt71KkY

Korean scientists modify food poisoning bacteria to fight cancer
https://www.youtube.com/watch?v=Fej3RsxXquE

Genetically Modified Salmonella Destroys Brain Cancer
https://www.youtube.com/watch?v=z94yUn33Ylo

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