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## Preface: A Brief History of Bacterial Therapy of Cancer

Anecdotal records go back at least 200 years describing cancer patients going into remission after a bacterial infection [1]. In 1867, the German physician Busch reported that a cancer went into remission when the patient contracted erysipelas, now known as *Streptococcus pyogenes* [2]. Bruns intentionally injected a cancer patient in 1888 with *S. pyogenes* and the tumor regressed [1].

In the late 1890s, William B. Coley of New York Cancer Hospital, later to become Memorial Sloan-Kettering Cancer Center, treated cancer patients with *S. pyogenes*. Coley read about 47 cases of cancer where the patient became infected with bacteria and tumors regressed [3]. Coley located a former patient from his institute whose malignant tumor in his neck regressed after he became infected with erysipelas. When Coley located the patient, he had no evidence of cancer [3]. Coley also found a sarcoma patient in 1891 who had tumor regression also after infection with *S. pyogenes*. Koch, Pasteur, and von Behring recorded that cancer patients infected with *S. pyogenes* had tumor regression [1].

Coley's first patient that he infected with *S. pyogenes* recovered from head and neck cancer. Coley had excellent results infecting cancer patients with *S. pyogenes*. Coley subsequently used killed *S. pyogenes* with a second killed organism now known as *Serratia marcescens*, due to fears of infecting cancer patients with live bacteria. The killed organisms became known as Coley's Toxins. Coley's Toxins are thought to be the beginning of the field of cancer immunology, and many researchers believe that the main anticancer efficacy of bacteria is immunological, but as can be seen in this book, bacteria can directly kill cancer cells as well.

Coley was unfairly criticized by the scientific community and called a quack [3]. During Coley's time, X-rays and surgery became the main treatment of cancer, and their proponents heavily opposed Coley's bacterial therapy, especially James Ewing, a very famous cancer pathologist for whom the Ewing sarcoma is named. Ewing tried to force Coley out of the New York Cancer Hospital, even though Coley had successfully treated hundreds of cancer patients. Ewing was Medical Director of New York Cancer Hospital, therefore Coley's boss, and they hated each other. Ewing would only allow radiation therapy and surgery for all bone tumors, and Ewing did not allow Coley to use his toxins [3]. Coley died deeply disappointed in 1936 and thus ended bacterial therapy of cancer for almost 70 years.

In modern times, Hoption Cann et al. [4] compared Coley's bacterial treatment to current chemotherapy. The 10-year survival rates of Coley's patients were compared to the Surveillance Epidemiology End Result Cancer Registry [5] and found patients receiving current conventional therapies did not fare better than patients treated with bacteria over 100 years ago.

In the middle of the last century, preclinical studies began with bacterial therapy of cancer and are now very widespread. Malmgren and Flanigan [6] demonstrated that anaerobic bacteria could survive and replicate in necrotic tumor tissue with low oxygen content. Several approaches aimed at utilizing bacteria for cancer therapy were described in mice [7–19].

In the modern era, the obligate aerobes *Bifidobacterium* [19] and *Clostridium* [20], which replicate only in necrotic areas of tumors, have been developed for cancer therapy. Anaerobic bacteria cannot grow in viable tumor tissue, which limits their efficacy. Yazawa

et al. tested *Bifidobacterium longum* and found it selectively localized in mammary tumors after systemic administration [19] (please see Chapter 5). *Clostridium novyi*, without its lethal toxin (*C. novyi* no toxin [NT]), was generated by the John Hopkins group. *C. novyi*-NT spores germinated within necrotic areas of tumors in mice and even killed some viable tumor after intravenous (i.v.) injection. *C. novyi*-NT spores were administered in combination with chemotherapy, resulted in hemorrhagic necrosis and tumor regression [20]. Recently, *C. novyi*-NT was used in a patient with leiomyosarcoma and caused one metastatic lesion to regress [21]. The disadvantage of the obligate anaerobes described above is that they do not grow in viable regions of tumors due to high oxygen tension [2, 22].

*Salmonella typhimurium* (*S. typhimurium*) is a facultative anaerobe, which can grow in the viable regions as well as necrotic regions of tumors [23]. Attenuated auxotrophic mutants of *S. typhimurium* retained their tumor-targeting capabilities, but became safe to use in mice and humans [24]. *S. typhimurium* with the lipid A-mutation (*msbB*) deleted and purine auxotrophic mutations (*purI*) had antitumor efficacy in mice and swine and also had significantly reduced host TNF- $\alpha$  induction and low toxicity. *S. typhimurium* (VNP20009), attenuated by *msbB* and *purI* mutations, was safely administered to patients, in a phase I clinical trial on patients with metastatic melanoma and renal carcinoma. Efficacy was not observed, perhaps due to overattenuation [25].

The coming decade should see the resurgence of bacterial therapy of cancer begun by Coley. This book sets the stage for this upcoming revolution of cancer therapy.

After reading this book, one may wonder where cancer therapy would be if Ewing did not so cruelly end Coley's bacterial treatment and eliminate any chance for a successor.

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Bacterial Therapy of Cancer

Methods and Protocols

Hoffman, R. (Ed.)

2016, XVI, 186 p. 43 illus., 33 illus. in color., Hardcover

ISBN: 978-1-4939-3513-0

A product of Humana Press