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COMMENTARY

Bugs as Cancer Drugs: Challenges and Opportunities

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ABSTRACT The first nonsurgical cancer therapy was bacterial therapy introduced in 1891 to treat solid tumors. Because in many cases it was harmful and ineffective, and with the emergence of radiotherapy and chemotherapy, bacterial therapy was discontinued. Motivated by the need to improve targeting of solid tumors and in light of recent progress made in developing microbial therapies, the National Cancer Institute has for the first time issued funding opportunities to stimulate research on bacterium-based cancer therapies for conditions under which current cancer therapies are inadequate.

KEYWORDS therapy, cancer, microbial

William B. Coley's observation that bacterial infection was associated with tumor regression in cancer patients lead him in 1891 to inoculate patients with Fehleisen's erysipelas coccus (1) (presumably *Streptococcus pyogenes*) and other formulations containing a mixture of killed bacteria (e.g., *Streptococcus pyogenes* and *Serratia marcescens*) to shrink or eliminate solid tumors. However, his results were not reproducible and in many cases the treatments had limited effectiveness or proved to be harmful. With the development of better-understood and more-effective radiation and chemotherapy, bacterium-based cancer therapy was largely abandoned nearly 80 years ago.

In light of the tremendous gains in knowledge in the molecular biology of tumor-bacterium interactions and motivated by the need for new therapeutics for solid tumors and under conditions where current cancer therapies are inadequate, the National Cancer Institute (NCI) held the first-ever conference on microbe-based cancer therapy (2) more than a century after Coley's initial research. The conference inspired a white paper on the topic (3), and to stimulate new research in the field, NCI initiated two new funding opportunities: PAR-19-194 (4), aimed at promoting early research without preliminary data, and PAR-19-193 (5), to support more-advanced research on bacterium-based cancer therapies.

Over the past century, cancer therapy research has been focused primarily on harnessing the clinical effectiveness of chemical therapies (e.g., cytotoxic chemotherapy, hormonal therapies, and biological-pathway-targeted therapies) and radiation therapy. More recently, research has focused on exploring the promise of immunotherapy, highlighted by the use of monoclonal antibodies (6), immune checkpoint blockers for melanoma (7), and CAR-T adoptive cell therapies that reprogram the immune system to target acute lymphoblastic leukemia (8) and non-Hodgkin's lymphoma (9). Microbe-based therapies can incorporate some of the direct cytotoxic activity of chemical therapies or radiation therapy while also eliciting a therapeutic immune response. Oncolytic viruses, such as a herpesvirus modified for the treatment of melanomas (10), have been explored, but only limited research has been carried out on bacterial therapy. The single exception is the introduction of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) treatment (11) to prevent relapses of superficial bladder cancer in the late 1980s. Nevertheless, relative to research on other cancer therapy modalities, the area of bacterial therapy has remained underdeveloped. While much of

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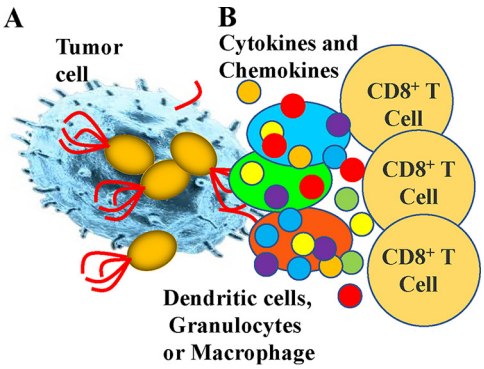

FIG 1 Mechanism of microbe-based cancer therapy. (A) Bacteria direct cell killing of tumor cells. Bacterial toxins can damage membrane structures or interfere with critical cellular functions. Intracellular bacterial replication destroys cancer cells and initiates apoptosis and autophagy. (B) Bacterial activation of the immune system. Immune cells such as dendritic cells, macrophages, or granulocytes attracted to the bacteria colonize tumors and secrete cytokines and chemokines which activate the immune cells and recruitment of $CD8^+$ T lymphocytes which eliminate other primary tumors and metastases.

the recent progress in immunotherapy has rapidly advanced the treatment of hematologic cancers, progress in treating solid tumors, which are the vast majority of cancers, has advanced more slowly. The promise of modern microbe-based cancer therapy is that it may address the gap in progress for treating solid tumors.

At the beginning of the 20th century, it was difficult to control bacterial infections and to formulate a uniform and reproducible bacterial therapeutic agent, and scientists were unable to explain the mode of action for Coley's therapy. Many of these challenges have now been addressed. Advances in knowledge of immunology, bacterial pathogenesis, and cancer biology today provide better understanding of the mode of action of bacterium-based cancer therapy, showing that bacterial infection can both kill tumor cells directly and trigger tumoricidal immune responses (12) (Fig. 1). New molecular and genetic manipulation tools have made it possible to revisit bacterial therapy from new perspectives. In the past decade, steady progress has been made to exploit and enhance the potential of microbe-based cancer therapies, several of which were recently described (3, 9).

Bacterium-based cancer therapies possess some unique properties suitable to address solid-tumor conditions where conventional cancer therapies are inadequate, such as poorly vascularized, hypoxic solid tumors; dormant or slow dividing cells resistant to treatment; or islands of microinvasive tumor cells buried within normal brain tissues. For example, it was shown that obligate or facultative anaerobic bacteria such as *Bifidobacterium*, *Clostridium*, *Salmonella*, or *Escherichia coli* specifically colonize and proliferate inside anaerobic tumor tissues (13), killing tumor cells (9) and activating an antitumor immune response (12), with potential to provide long-lasting effects and to broaden tumor targeting for prevention and treatment (14). This unique ability of anaerobic microorganisms to grow selectively in hypoxic areas of solid tumors (14, 15) that are often not accessible to cancer drugs may be exploited for therapeutic purposes. For example, an obligate anaerobic strain of *Clostridium novyi* (16) and engineered attenuated *Salmonella* (17) were shown to selectively infect hypoxic tumor tissues (18). Further research on *Salmonella* has shown that it can be used to activate dormant tumor cells normally resistant to treatment, enabling treatment of activated cells with conventional therapy (19). Other approaches include a "Trojan horse" strategy using attenuated *Salmonella* (20) or *Listeria monocytogenes* (21) to infect cancer cells and induce their expression of a "foreign" antigen or a tumor-associated antigen to incite a therapeutic immune response. Additional work has shown that *Bifidobacterium* can enhance immune cell checkpoints PD-1 and CTLA-4 (22, 23).

While bacterium-based cancer therapy has great potential to address gaps in progress against solid tumors, the field remains challenging and underdeveloped, in

part because there is a lack of a critical mass of resources and researchers who are poised to develop and translate recent discoveries. Additional factors that have limited the field include the complexity of tumor-bacterium interactions, past failures, and the development of other promising treatment modalities. To move forward requires a better understanding of the complex nature of interactions between bacteria, tumor, and host immunity and also requires collaboration between microbiologists, cancer researchers, and immunologists.

Success in developing "bugs as drugs" will rely on attracting and supporting more researchers in the field, especially microbiologists with knowledge of the host/microbe interactions that can be exploited for cancer therapy. Microbiologists can provide a better understanding of microbial genetics, virulence, physiology, and host immune responses and other relevant expertise needed to build collaborations with cancer biologists, thus creating the critical mass of researchers needed to develop the potentially rewarding scientific and clinical opportunities in the field of bacterial therapeutics, more than a century after its potential was first recognized by William B. Coley.

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