William B. Coley
His Hypothesis, His Toxin, and the Birth of Immunotherapy

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KEYWORDS

• William B. Coley • Toxin • Immunotherapy • Cancer

KEY POINTS

- At the end of the 19th century, William B. Coley introduced the concept of immunotherapy.
- He observed dramatic responses of tumor regression in some patients following would infection.
- His theories were largely discredited and ignored for over a century.

INTRODUCTION

In recent years, immunotherapy has been the focus of great interest to researchers, clinicians, and the general public. Traditionally cancer therapy has been thought to be limited to cut, burn, and poison, or surgery, radiation therapy, or chemotherapy.[1] Some clinicians have considered it the so-called fifth pillar of cancer therapy, following surgery, cytotoxic chemotherapy, radiation, and targeted therapy.[2] However, the origins of immunotherapy in cancer treatment reach back at least into the nineteenth century. This article reviews the origins, development, and future of immunotherapy.

EARLY IMMUNOTHERAPY

In the mid-1800s 2 German physicians, Busch and Fehleisen,[3] independently observed regression of tumors in patients with cancer after accidental infections by erysipelas.[2] In 1868, Busch[29] intentionally infected a patient with cancer with erysipelas and noted shrinkage of the tumor. In 1882, Fehleisen[3] repeated this treatment and identified *Streptococcus pyogenes* as the causative agent of erysipelas.

WILLIAM B. COLEY: "THE MOST OPPORTUNE TIME IN A THOUSAND YEARS"

William B. Coley was a young surgeon in New York City in 1890 who had recently graduated from Harvard Medical School. Coley[1] thought that he had entered medicine at the "most opportune time in a thousand years." He was about to meet a young female patient who would change his career and would affect the future of cancer treatment.

Elizabeth "Bessie" Dashiell was a 17-year-old friend of John D. Rockefeller Jr. In the summer of 1890, she returned from a cross-country train trip with what appeared to be a minor injury of her right hand, which she had caught in the seat lever of her Pullman rail car. Because of her ongoing pain, Rockefeller suggested that she see Doctor Coley. On examination, he noted some swelling and discoloration. He incised the mass and found no obvious infection and sent her home with a diagnosis of periostitis.

She returned when her condition did not improve, and Coley operated a second time and performed a biopsy. The biopsy returned as a sarcoma. She had a rapid downhill course with metastases to her breast, liver, and abdomen, and soon died.

Bessie's rapid demise was not only upsetting to Coley but spurred him to investigate whether this was an unusual clinical course for a sarcoma. Coley began to review the records of all the previous patient with sarcoma at New York Hospital. One record caught his attention. Seven years earlier, a 31-year-old patient named Fred Stein had been seen at New York Hospital with a large

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left neck mass that had been proved to be a sarcoma. One of the attending surgeons had operated on the mass, but it recurred. Stein underwent 5 operations over the course of 3 years. He required skin grafts, which failed, and he ultimately developed a wound infection with erysipelas (*S pyogenes*). Erysipelas was frequently the cause of virulent postoperative infections in that period and had been referred to as St Anthony's fire since the Middle Ages.[1]

Stein had never returned for follow-up and Coley was curious what had happened to him. After some medical sleuthing, Coley was ultimately able to track down Stein living on the Lower East Side of Manhattan. On examination and having Stein further evaluated at New York Hospital, it appeared that Stein was free of disease 7 years after his original diagnosis. Why had these 2 patients with sarcoma had such different outcomes? Coley wondered whether the wound infection had played a role.

In 1891, Coley saw another patient, known only as Mr Zola, with a recurrent sarcoma of the neck. It was deemed inoperable. Based on his previous experience, Coley thought that injecting Zola's tumor with erysipelas was worth a try, given the circumstances. The tumor appeared to slough, but did not totally disappear. Coley was encouraged.

Coley surmised that he needed to induce a more severe infection and that the extent of the febrile response might be a good marker. Through contacts, he was able to obtain what was thought to be a more potent bacterial brew from Robert Koch in Berlin. With further injections of the new preparation, Mr Zola's tumor totally regressed without recurrence after 8.5 years of follow-up.

These early experiences led Coley to hypothesize that the infection elaborated a substance or substances that caused the tumors to regress. One of Coley's challenges was that the preparation of his "toxin" was arbitrary without a standard formula or concentration. Coley's toxin was ultimately a mixture of *S pyogenes* and *Serratia marcescens*. Coley 's results were inconsistent: some patients responded and some did not.

At the same time, he was experiencing some political problems. The head of the New York Cancer Hospital (which would ultimately become Memorial Sloan Kettering Cancer Center), James Ewing, was skeptical of Coley's work and was also very enthusiastic about the new modality of radiation therapy. Coley's work remained controversial.

From 1923 to 1963, Parke-Davis was the only source of Coley's toxins in the United States. In 1963, the Food and Drug Administration (FDA) assigned Coley's toxin to a new-drug status, which made it illegal to prescribe it outside of clinical trials. The mechanism of action of the toxins was never fully elucidated. Because the activity of the toxins was associated with fever, it was thought that it resulted from a lipopolysaccharide that increased lymphocyte activity and boosted tumor necrosis factor (TNF).[4] However, Tsung and Norton[5] have reported that the active agent is interleukin-12, rather than TNF.

BACILLI CALMETTE-GUÉRIN: UROLOGY'S IMMUNOTHERAPY SUCCESS STORY

In the early part of the twentieth century, tuberculosis (TB) continued to be a major public health issue. TB is caused by *Mycobacterium tuberculosis* and *Mycobacterium bovis*, which are known collectively as tubercle bacilli.[6] In 1908, Albert Calmette, a bacteriologist, and Camille Guérin, a veterinarian, working together at the Pasteur Institute, began trying to develop a TB vaccine. They isolated a virulent strain of *M bovis* from an infected cow and, after passages though multiple cultures, showed gradual loss of virulence. In 1921, after 231 passages in subcultures through 13 years, they showed attenuation to a nonvirulent, but genetically stable, form in guinea pigs.[6]

This unique strain of *M bovis* was named after Calmette and Guérin and became known as bacilli Calmette-Guérin (BCG). They first tested the BCG on a baby whose mother and grandmother had TB. The baby had no side effects and did not develop TB. From 1921 to 1924, 217 Parisian children were vaccinated with BCG and were successfully immunized against TB.[6]

It had been noted that TB seemed to have antitumor effects. In 1929, Pearl,[7] through an autopsy study at Johns Hopkins Hospital, reported a lower frequency of cancer in patients with TB. He went on to show that cancer survivors had a higher incidence of active or healed TB than individuals dying of cancer. He concluded that there was some type of protection against cancer conferred by TB, but could not explain a mechanism.

In 1930, because of a laboratory error, a large number of German babies were vaccinated with contaminated BCG and died. This incident was known as the Lubeck Disaster and decreased the enthusiasm for BCG as a cancer therapy for the next 3 decades.[6]

In 1959, the next major advance in the understanding of the mechanism of action of BCG occurred. Old and colleagues[8] reported that mice infected with BCG showed increased resistance to a challenge with transplantable tumors. BCG caused general augmentation of

immunologic activity and was found to activate macrophages that inhibited or destroyed cancer cells. This finding was the first direct evidence of the antitumor effects of BCG, which became known as TNF.

In the 1970s, Zbar and colleagues[9] defined the criteria for successful BCG therapy, which included (1) close contact between BCG and the tumor cells, (2) a host capable of mounting an immunologic response to mycobacterial antigens, (3) a limited burden, and (4) adequate numbers of viable BCG organisms.

In 1972, Morales and colleagues[10] initiated the original BCG protocol for bladder cancer treatment, which was 6 weekly treatments of 120 mg in 50 mL of saline instilled via a urethral catheter. An intradermal injection of BCG was performed to assess delayed hypersensitivity injection. The initial trail of 10 patients showed no bladder cancer recurrences in the 47 patient months of follow-up after BCG treatment.[10]

In 1975, de Kernion and colleagues[11] reported that an isolated melanoma in the bladder was successfully treated with cystoscopic injection of BCG vaccine. In 1978, Morales received approval from the National Cancer Institute to fund 2 randomized trials to test the effectiveness of the combined BCG regimen against superficial bladder cancer.[12,13] More data continued to accrue to support the efficacy of BCG in the treatment of superficial bladder cancer. In 1990, the FDA approved the general use of intravesical BCG for the treatment of noninvasive bladder cancer.

THE LANDMARKS OF IMMUNOLOGIC DISCOVERY THAT PROVIDED THE FOUNDATION FOR IMMUNOTHERAPY

Over the past decades, there have been robust, fundamental scientific discoveries that have laid the foundation for the new era of immunotherapy treatment of malignancy. A summary of some of the major landmarks is provided in **Table 1**.

Table 1
Landmarks of immunotherapy and cancer treatment

1868	Wilhelm Busch reports impact of erysipelas on a tumor
1891	William B. Coley begins his investigations using his toxin
1957	Discovery of interferon by Alick Isaacs and John Lindenmann
1959	Immune surveillance cancer theory by Lewis Thomas and F.M. Burnet
1959	Chemical structure of antibodies by Gerald Edelmann and Sidney Porter
1974	Cell-mediated immunity described by Peter Doherty and Rolf Zinkermagel
1975	Monoclonal antibodies manufactured by Caser Milstein and George Koehler
1975	Discovery of TNF by Lloyd Old
1982	Discovery of T-cell receptor by James Allison, B. McIntyre, and D. Bloch
2011	First anti–CTLA-4 drug (ipilimumab). First checkpoint inhibitor approved by FDA
2012	Discovery of CRISPR/Cas9 system: more efficient method of genome editing
2018	Nobel Prize awarded to James Allison and Tasuko Honjo for discovery of cancer therapy by inhibition of negative immune regulation

Abbreviations: CRISPR, clustered regularly interspaced short palindromic repeat; CTLA, cytotoxic T lymphocyte–associated protein.

Interferon was discovered in 1957 by Issacs and Linderman.[14] Interferons are naturally occurring substances that interfere with the ability of viruses to reproduce, and they also boost the immune system. There are 3 classes of interferons: alpha, beta, and gamma. In therapeutic doses, interferons may have significant side effects. Although they only have a minor role in modern immunotherapy, their discovery provided insight into some of the natural immune responses of the body.

Besides interferon, other cytokines have generated clinical interest. Interleukin-2 (IL-2) and interferon-alpha have shown mild clinical benefits and have received FDA approval for the treatment of several cancers. IL-2 was approved for the treatment of advanced renal cell carcinoma and metastatic melanoma, and interferon-alpha was approved for hairy cell leukemia, follicular non-Hodgkin lymphoma, melanoma, and acquired immunodeficiency syndrome–related Kaposi sarcoma. The application of these cytokines was a milestone in cancer immunotherapy because it showed that immunotherapy could achieve durable, objective clinical responses.

Immune surveillance was a concept that was proposed by Burnet and Thomas[15–17] in the late 1950s. Every day, each cell in the body is estimated to experience more than 20,000 DNA-damaging events,[2,18] which are normally repaired without sequelae.[2,19] Cells that are not repaired

and that acquire malignant potential are then usually recognized and killed by the tumor immunosurveillance system.[2] This concept that the immune system is capable of identifying and killing nascent nonself malignant cells was a major milestone in thinking and was developed by Burnet[15,17] and Thomas.[16] It provided the underpinning for the construct of immunoediting processes, which are divided into elimination, equilibrium, and escape.[2] Hanahan and Weinberg[20] proposed 8 hallmarks of cancer, and the ability of cancer cells to evade immune destruction has been identified as the eighth hallmark of cancer.

Adoptive cell therapy is another form of immunotherapy that involves the isolation and in vitro expansion of tumor-specific T cells.[2] The FDA has approved anti–cluster of differentiation (CD) 19 chimeric antigen receptor (CAR) T cells[21,22] as well as cultures of tumor-infiltrating T lymphocytes.[23] These approaches apply strategies that depend on cytokines for in vitro expansion and in vivo persistence of transferred T cells.

Berraondo and colleagues[21] propose that the search for the next generation of cytokine-based drugs is based on 3 concepts. First, synergistic combinations of anti–programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) monoclonal antibodies and CAR 19 T cells. Second, improved pharmacokinetics, whereby the half-lives of cytokines could be increased in the circulation. Third, achieving higher local concentrations of cytokines into the tumor microenvironment with recombinant proteins[24] or gene therapy vectors.[25,26]

CHECKPOINT INHIBITORS

The most recent advance in cancer immunotherapy has been the discovery and clinical applications of immune checkpoint inhibitors, anticytotoxic T lymphocyte–associated protein 4 (CTLA-4), PD-1, and PD-L1, which provide a strategy to modulate the immune system to fight the malignancy. These drugs remove the “brakes” on the immune system and permit T-cell activation.[27,28]

Studies have been published and more are ongoing using a variety of immune checkpoint inhibitors in prostate cancer, renal cancer, and bladder cancer. Ipilimumab, the first monoclonal directed against CTLA-4, has been used to treat prostate cancer. T cells require 2 signals to become fully activated. CD28 and CTLA-4 are T-cell receptors that play a decisive role in initial activation and subsequent control of cellular immunity.[29] Ipilimumab has been used in several prostate cancer trials and 2 studies deserve mention. One study, CA184-095, randomized (2:1) 602 men who were chemotherapy naive to ipilimumab or placebo. Although progression-free survival was longer in the ipilimumab arm, the results showed that the therapy had no effect on overall survival.[30] A second study, CA184-043, compared ipilimumab with placebo in 799 men with metastatic castration-resistant prostate cancer previously treated with radiotherapy and docetaxel chemotherapy. There was no improvement in overall survival (hazard ratio [HR], 0.85; $P = .53$), but there was a suggestion of benefit in patients with more favorable disease.[31]

In November 2015, nivolumab (anti–PD-1) received FDA approval for the treatment of patients with metastatic renal cell carcinoma who had progressed on antiangiogenic therapy. In a phase 3 study, CheckMate 025, 821 patients with advanced renal cell carcinoma who had 1 or 2 prior tyrosine kinase inhibitors were randomized to treatment with nivolumab or everolimus. Although progression-free survival was similar between the groups, the primary end point of overall survival favored nivolumab rather than everolimus (25 months vs 19.6 months; HR, 0.73, $P = .002$). Interestingly, the survival benefit did not depend on the expression of PD-L1 on tumor cells.[32]

The most extensive experience with checkpoint inhibitor drugs in urologic oncology has been in the treatment of bladder cancer. A variety of anti–PD-1 and anti–PD-L1 agents, atezolizumab (IMvigor210), durvalumab (phase 1/2 study 1108), pembrolizumab (KEYNOTE-045), nivolumab (CheckMate-275), and avelumab (JAVELIN) have all been FDA approved for the treatment of urothelial carcinoma in patients pretreated or relapsed with platinum-based therapy since 2016 or 2017. Multiple ongoing phase 3 investigations are in progress.

The underpinnings of the scientific discoveries that have laid the foundation for the exciting era of cancer immunotherapy date back for more than a century. It is not hyperbole to state that the next decade offers the potential for clinical advances in cancer care that have never been imagined. Malignancies once thought to be incurable will realistically be curable. The potential for progress in immunotherapy is limitless.

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