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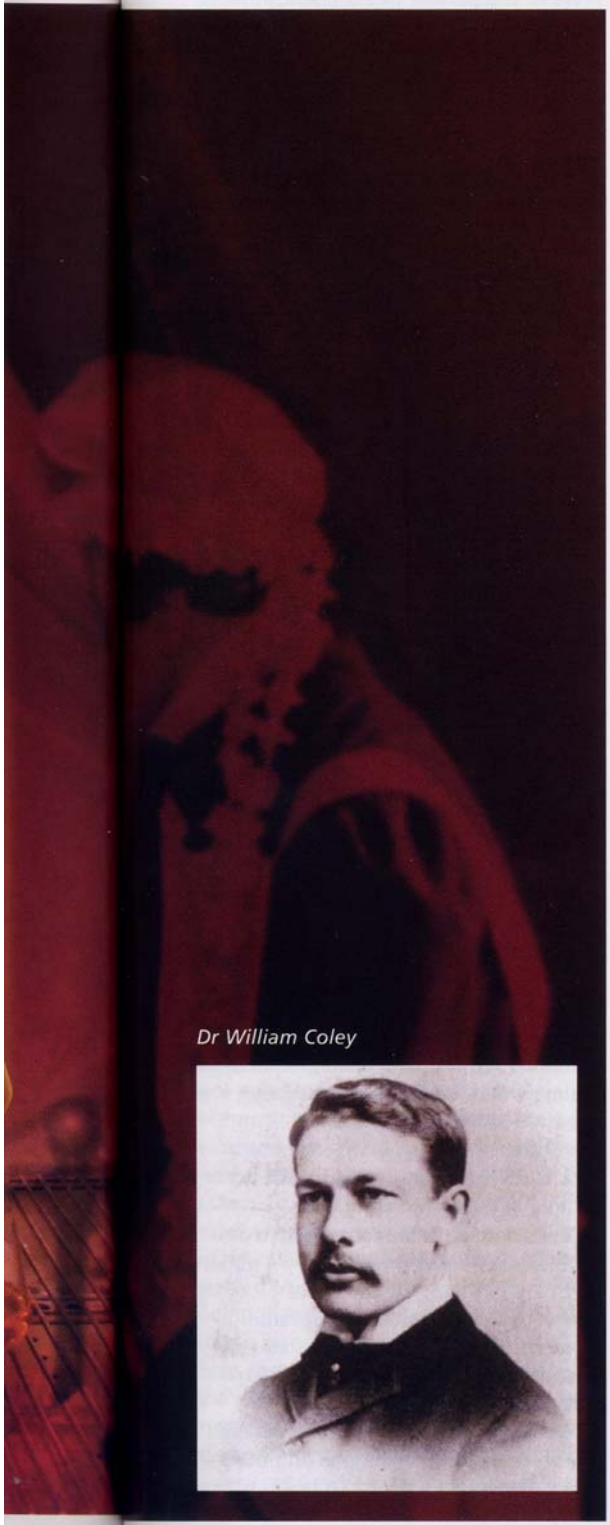
Bacterial anti-cancer vaccines:

a science frozen in time

INSIDE

Peter N Green and **Stephen A Hoption Cann** re-examine the mechanisms and methodologies associated with Dr William Coley's famous toxins



Dr William Coley

As Curator of a major national culture collection, my main purpose is to propagate and maintain a wide range of bacterial species as reference material for the scientific community. However, in the health care professions, doctors, nurses, surgeons and other health care personnel view bacteria somewhat differently, in the clinical environment at least. Bacteria are viewed as the enemy: they cause wound infections, septicaemia, post-operative trauma, and on occasion can and do kill patients. Seen in this context, they are most definitely bad news. Indeed, in hospitals throughout the world most of the focus on bacteria, from the clinician's viewpoint, is geared towards prevention of the infective agent finding a niche in which it can survive and proliferate; and ultimately its destruction.

With Lister and the advent of antiseptics at the end of the 19th century, the fight against bacteria as infective agents began in earnest. By the 1930's and 1940's with the discovery and introduction of modern antibiotic therapies, the bacterial war was seen as being largely won. Sir Alexander Fleming and his successors were to open a Pandora's box of anti-infective agents which were to form a major component in the front line of infectious disease control.

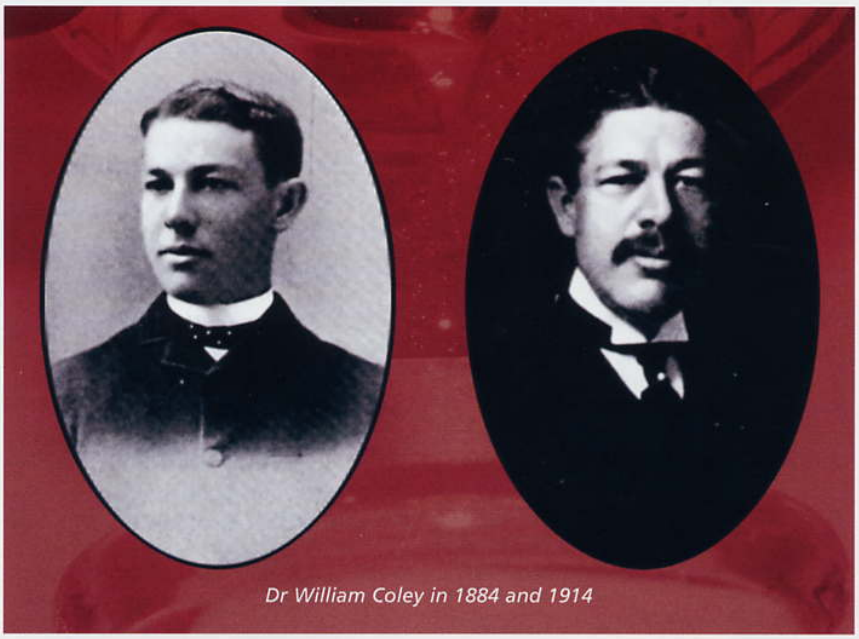
However, one should perhaps pose the question: was there a price to pay for this victory over infective agents in the hospital environment, apart from the obvious multi-drug resistance we see developing in the community today? Did anyone stop to ask themselves the simple question: are all infections by definition, bad? This article is aimed at convincing you that on some occasions they are not.

If I were to tell you that sometimes dangerous or pathogenic bacteria can benefit mankind and possibly even save lives many would think me crazy. Why? Because this is contrary to all we have been taught as scientists in terms of infection and disease control. However, every once in a while, it would be wise to have the courage to rip up the rule book and throw it away, to engage an open mind and examine new ideas. The man I am going to talk about in this article, had that courage, but like many who stray from the conventional teachings and beliefs of his peers, his efforts were scorned and largely ignored by the establishment of the day.

In the early 1890's Dr William Coley was a young surgeon at the New York Cancer Hospital (Later to become the Memorial Sloan-Kettering Cancer Center) in New York. Even at that young stage of his career, he was becoming disillusioned with the conventional medical treatment of cancer and wondered whether nature had its own cure. The first patient he was to lose as a young doctor was indirectly to lead to a huge change in his life as a practicing clinician. A young woman of 17 had injured her right hand and presented with persistent inflammation and pain. She was diagnosed as having sarcoma of the bone and her arm was amputated below the elbow. Despite no clinically evident metastases, the patient died 2.5 months after surgery. Shaken by his failure, Coley searched the hospital records for previous cases to learn more about her disease. Serendipitously, he came upon the record of an immigrant patient who presented with an egg-sized sarcoma on his left cheek. The sarcoma was operated on twice but recurred. The extensive wound after surgery could not be closed and skin grafts were unsuccessful. Ironically, this failure to close the wound was to play a crucial role in the patient's eventual recovery. The tumour progressed and a final operation only partially removed the growth. His case was considered hopeless. However, after the last operation, the wound became infected and the patient developed a high fever. The infective agent was shown to be *Streptococcus pyogenes* or erysipelas as it was known at the time. Little could be done to stop the infection, yet surprisingly, after each attack of fever, the ulcer improved, the tumour shrank and finally disappeared completely and the patient was fully discharged some 4.5 months later. Coley, eager to find this patient, spent weeks searching throughout New York's lower east side. His efforts were not in vain. The patient, still bearing a large scar from the previous surgery, had no trace of cancer and claimed excellent health since his discharge – seven years previously (Coley 1891).

During his investigations, Coley discovered a common theme. For hundreds of years, doctors had reported many cases where tumours had disappeared, apparently

spontaneously (Coley 1893). He researched more and more cases of spontaneous regression involving cancer patients and found that many of these people had something in common apart from their miraculous recovery. Most had been struck down by an acute infectious disease. It might have been flu or measles, malaria, smallpox or syphilis; or like the man in New York, erysipelas. In most cases, their fever subsided, their tumours had broken down and been absorbed or sloughed off. Indeed, infection seemed to be the key to many of these so called "miracle cures." Patients of pre-20th century surgeons, without antibiotics or antiseptics almost inevitably picked up infections from dirty hands, dirty instruments and unhygienic dressings. However, even by Coley's time, cleanliness and hygiene were the order of the day and surgeons would not entertain his seemingly bizarre notions of deliberately infecting patients. Occasionally though, a patient caught an infection by accident. Gradually, Coley began to reason with the few of his colleagues who would listen. He argued that it seemed fair to presume that if accidentally acquired infections of erysipelas could get rid of a tumour, then an artificially induced infection of the same agent would result in the same outcome. Convinced by his logic and determined to prove his sceptics wrong, Coley single-mindedly decided to inoculate the first case of inoperable sarcoma that should present itself. In May 1891, only a few months after losing his first patient, he found a willing volunteer. The man had tumours in both his neck and tonsils and despite recent surgery they had reappeared and were growing fast. Coley injected a streptococcal soup directly into the tumours, every day or two for the next two months. The tumours shrank and the man began to feel much better. In August, Coley stopped the injections and the tumours began to grow again. Coley acquired a more potent culture of streptococci and tried again. This time the patient developed a full blown fever. *"The disease ran its course and I made little effort to check it,"* reported Coley. After two weeks the tumour had completely disappeared. Almost two years later, when Coley reported his results, the tumour in the neck had not returned. Encouraged, Coley tried his treatment on more patients. His sixth patient was a middle aged cigar maker with a lumpy skin tumour on his back and a second tumour in his groin, the size of a goose egg. Surgery failed and both tumours soon grew back. Coley injected them with his streptococcal culture. They shrank but showed no sign of breaking down. He tried again with a different culture. Almost immediately, the cigar maker grew feverish and his temperature hit 40°C. The lump on his back responded immediately. A few days later, the second tumour began to break down as well. Three weeks from the start of his treatment, both tumours had entirely disappeared. Clearly, Coley had made another key discovery; namely that the infective agent had to induce a high fever in the patient to sufficiently stimulate the immune system to attack the tumours vigorously and to have any chance of resulting in their complete removal.



Dr William Coley in 1884 and 1914

Indeed, it is worth noting that fever is a highly conserved physiological response to infectious stimuli. It is more than just a rise in body temperature and not analogous to hyperthermia (that is a mechanically achieved increase in temperature). Febrile thermogenesis (e.g. chill, shivering etc.) is associated with an increase in metabolic rate of 2-3 times, while maintenance of a fever has been associated with a 30-50% increase in metabolic rate (Baracos *et al.*, 1987). It is unlikely that such a response would be conserved unless it had considerable use or adaptive value.

Historically, Coley was not the first medical practitioner to see a positive role for infective agents in wound management. Centuries beforehand the use of septic or deliberately infected bandages was practised by a few in the profession, the logic being that they either killed the patient or improved the healing of their wound (Hoption Cann *et al.*, 2003). Indeed, the earliest example of such cancer immunotherapy may be thousands of years old. In the writings of Papyrus (ca. 1550 BC), he cited the great Egyptian physician Imhotep (c 2600 BC) who recommended that the treatment for swellings (including tumours) was a poultice followed by incision. Such a regime would inevitably lead to an infection at the tumour site. Nevertheless, using live bacteria to initiate an infection was a precarious gamble between life and death.

In the pre-antibiotic era, the problems associated with Coley's initial approach, as with the medieval practices before him, soon became apparent. Erysipelas was not that easy to control once it began and, perhaps surprisingly, it was not that easy to induce in the first place. Some patients required repeated injections and others never developed a fever. To begin with, Coley believed he needed live bacteria

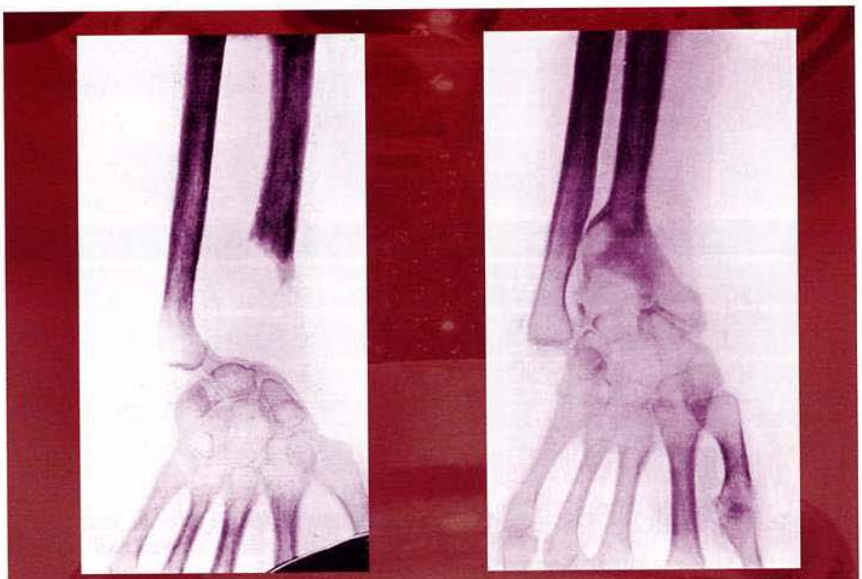
to elicit a patient response, but even daily injections sometimes failed to produce a fever, while in other patients the infection ran out of control. Coley decided that the key factors in his streptococcal soup were bacterial toxins or metabolites produced by the growing culture and that indeed dead bacteria or heat killed preparations may work just as well. After much painstaking work, he finally settled on a mix of dead erysipelas (*Strep. pyogenes*) and another bacterium, *Serratia marcescens*. This "vaccine" became known as "Coley's toxins." These had the advantage of eliciting the same response as live bacteria; importantly the fever, but without the risk of an actual infection. This was to prove a key breakthrough. Indeed, although most of his subsequent work was with Coley's toxins, he often held the view that the identity of the bacteria was less important than the method of use and the fact that they produced a febrile response in his patients. It was also highly desirable, (but not essential) to inject the toxins directly into the tumour as often as necessary to cause fever and to keep this up for weeks or even months (Hoption Cann *et al.*, 2002). It was almost as if the very high fever or "crisis" induced by Coley's toxins produced a greatly enhanced response from the body's immune system: one which, in addition to attacking the bacterial inocula, also attacked and destroyed the tumour cells.

Before summarizing Coley's remarkable work, it is perhaps worth looking in detail at some of the more important factors in Coley's treatment regimes as these are key to the success of anyone who revives his techniques in modern day medicine. Coley's work had not gone unnoticed, despite the sceptics, and his published papers on cancer regression associated with his mixed bacterial vaccine stimulated others to explore the underlying mechanisms of this phenomenon (Nauts *et al.*, 1953). Specifically, researchers strived to identify the "active" component of Coley's vaccine. This also led to investigations to determine which host factors produced in response to the vaccine could induce tumour regression. Cytokines such as tumour necrosis factor (TNF), interleukins and interferons were considered as possibilities. However, the answer is far more complex than ascribing the response to one or another of these factors. Any immune response to pathogens is associated with a multitude of cytokine cascades and a diversity of cellular responses. This immune response was readily evoked through the use of Coley's crude bacterial vaccine, but difficult to reproduce with single cytokine therapy.

After Coley's vaccine is administered, a wide range of cytokines become detectable in the urine including Interleukins 1,2, 6, 8, 10, 12 and 18; gamma-interferon, inducible protein 10, macrophage stimulating factor and TNF (Hoption Cann *et al.*, 2003). Many more cytokines are up-regulated and others down-regulated to varying degrees throughout the course of treatment, yet, this illustrates the point that individual immunomodulating cytokines are in fact only a small facet of this complex immunological response to infection, and correspondingly, tumour regression. That said, there are undoubtedly key cytokines that play a big part in the immune response to Coley's vaccine; principally Interleukin 2 which is produced by Th1 cells (a specific group of lymphocytes or specialised white blood cells often referred to as T helper cells which play an important role in all immune responses). In particular, they help activate and direct other cells within the immune system such as cytotoxic T cells and macrophages. One theory to explain the success of Coley's vaccine centres on its ability to enhance leucocyte and lymphocyte proliferation, maturation and activation. In particular, some think that lymphocytes and in particular macrophages, have a dual role in both cell and tumour production or repair and also similarly in their destruction, depending upon the cytokine expressions being exerted upon or by the immune system (van Netten *et al.*, 1992; Oleszczuk *et al.*, 1994).

Another aside perhaps worth making at this point, concerns the paradoxical influence of acute and chronic infections on tumour formation (Hoption Cann *et al.*, 2006). It is now well established that some malignancies arise in association with chronic infections of one type or another. *Helicobacter pylori* and gastric cancer, *Schistosoma haematobium* and bladder cancer and human papilloma virus (HPV) and cervical cancer are some examples. These infectious diseases generally afflict the organ where the cancer later develops. However, unlike the acute febrile response, a chronic infection generally represents a failed immune response to disease.

Acute infections, exemplified by opportunist post-operative infections or those induced using Coley's vaccine, in contrast, stimulate the immune system



Tumour regression with Coley's vaccines: October 1919 (left) and May 1920 (right)

Figure 1. Cancer: 5-Year Survival

American Cancer Society - 2004				Coley Vaccine
Type	**Localized**	**Regional**	**Distant**	**Inoperable**
Breast	97%	79%	23%	65%
Colorectal	90%	66%	9%	46%
Melanoma	97%	60%	14%	60%
Ovarian	95%	72%	31%	67%
Uterine	96%	65%	26%	73%

Figure 2. The importance of Clinical Protocol

Dependence of length of treatment on survival: 137 cases of inoperable soft tissue sarcoma

No. of Patients	Length of Therapy	Percentage 5-year survival
3	1 week	0%
7	2 weeks	14%
13	4 weeks	23%
24	2 months	42%
32	4 months	48%
15	6 months	80%
20	12 months	75%
8	24 months	50%
7	> 2 years	71%
8	unknown	63%

Figure 3. Historical case study (1999)

Cancer: 10 years survial rates

Cancer	NCI -SEER group	Coley vaccine group
Kidney	23%	33%
Ovarian	29%	55%
Sarcoma	38%	50%

to target and destroy the infective agent.

Although Coley's toxins were easiest to administer and observe on surface or easily accessible tumours by direct injection into cancerous tissue, the toxins could also be used systemically by intramuscular injection (IM) into the buttock, by intra-peritoneal (IP) injection and also by intravenous (IV) injection, although the last method was more difficult to control and monitor. Thus the beauty of Coley's vaccines, crude though they were, was that they could attack remote tumours, different types of tumours, as well as advanced metastatic progression of the disease.

There are countless other examples of success stories and also of failures as Coley strove to obtain a better understanding of his vaccine and its usage. Coley's success is all the more remarkable in that he was continually fighting the medical establishment who were highly sceptical of his non-conformist therapy. Even Coley's boss, the eminent pathologist James Ewing, became bitterly opposed to his use of the vaccine; seeing radium as the new utopian cure for cancer. In one hostile letter to Coley 1917, Ewing wrote *"gradually we shall get enough cases (treated with radium) with better results, and other institutions will report other good results, so that you will be discredited in the end."* (Hall 1997). However, continuing lacklustre results with radium stirred Ewing to later state (after Coley's death) that *"in some recoveries...there is substantial evidence that the toxins played an essential role"* (Ewing 1940). Coley died in 1936 and for a time his toxins died with him. However, Coley had a remarkable daughter; Helen Coley Nauts, and she developed a passionate desire to devote her life to proving her father's early beliefs and efforts were not to be in vain. During her life time, Helen Coley Nauts researched and documented countless numbers of her fathers' cases and forced the medical world to begin to give his work the credit it deserved (Nauts 1990). There was to be a further setback to the use of Coley's vaccine. In 1962 the FDA passed legislation outlawing the use of therapies it considered ineffective and this included Coley's toxins. This was put into place despite the fact Coley's daughter had presented evidence to show that of nearly 1000 patients treated by her father around 50% had survived in excess of five years (Nauts 1984). A quite remarkable statistic given the advanced state of many of the cancers he treated (See figure 1).

After his death in 1936, interest in Coley's toxins waned. Radiotherapy and later chemotherapy both became standard treatments. Both knock out the immune system and so infection became something to be avoided at all costs. Current researchers have focused resources on ways to trigger the production of specific types of anti-cancer cells or particular tumour suppressing molecules. But Coley's vaccine worked precisely because it was so crude and non-specific and thus stimulated a heightened general immune response. More importantly, the immune system works at its best during a fever, as many would now accept. In 1950, Dr M.J. Shear, an oncologist at the Children's Hospital in Boston, examined a large series of children with untreated acute leukaemia. In those that experienced spontaneous remissions, three quarters of these remissions were preceded by acute infections (Shear 1950). He made the following comment, namely: *"are pathogenic and non-pathogenic micro-organisms one of nature's controls of microscopic foci of malignant tissue? In making progress in the control of infectious disease, are we removing one of nature's controls of cancer?"* (Shear 1950). Think of it for a moment. What treatment are you offered in present

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day medicine if you seek help for a bacterial infection? You are offered antibiotics to kill the bacterial agent which is challenging the immune system and antipyretics to suppress unpleasant symptoms, like fever. The exact opposite of that which Coley's vaccine seeks to achieve; hence a possible explanation for the dramatic reduction in the number of spontaneous regressions observed today.

Although much of Coley's interest and work looked at bone sarcomas, his toxins were used to successfully treat carcinomas, lymphomas, melanomas and myelomas (Hoption Cann *et al.*, 2006). In a comprehensive evaluation of Coley's work involving 896 patients, looking at microscopically proven malignancies treated with Coley's vaccine up to 110 years ago, the five year survival for inoperable carcinomas (34% - 73%) was broadly similar to inoperable sarcomas (13 - 79%), the range varying with tumour sub-type (Nauts 1984). To determine comparable rates of 10 year survival for various cancer patients, in 1999 researchers compared Coley's vaccine patients with matched controls from the National Cancer Institute's Surveillance Epidemiology End Result or SEER database (Richardson *et al.*, 1999). The study found higher rates of 10 year survival for Coley's vaccine patients compared to modern patients in kidney cancer, ovarian cancer and sarcoma (figure 3).

When looking at treatment efficacies it is interesting to compare the effect of length of treatment on outcome or prognosis (figure 2). It is clear from much work that Coley's vaccine is not a one-shot wonder cure. It takes several months of sustained treatment to fully challenge the cancer being treated. Days, weeks, even months of repeated and sustained stimulation of the body's immune system with the vaccine.

Although clearly much more work needs to be done under controlled trial conditions on statistically larger groups of patients before these trends or findings can be more fully substantiated, in these and many other forms of cancer; the data of Coley and others cannot be dismissed out of hand. The phenomenon of spontaneous regression of a wide variety of cancers, linked to both the intentional and unintentional intervention of bacterial infective agents, is far too well documented over several decades, and indeed centuries to be dismissed (Nauts 1980).

The good news is that new small scale trials are now beginning with Coley's vaccine. A small Canadian Company MBVax has been set up and is in the process of conducting limited trials of a new vaccine based on Coley's original formulation. Treatment is at an early stage but initial results are very encouraging.

In conclusion, retrospective studies of Coley's work have shown that despite the billions of dollars spent on the development of modern conventional treatments, for many types of cancer, patients receiving current therapies fared no better than the patients receiving treatments initiated by Coley over 100 years ago. Indeed for some of the case histories I have shared with you, all that the patient would be offered in 2007 would be palliative terminal care. Ironically, had Coley been alive today, I suspect he would still have his sceptics within the profession. Nevertheless, the flame of hope, lit by Coley and indeed others who have argued that there may well be hidden mechanisms within the body's own immune system which can regress or cure many forms of cancer, was dimmed, but not extinguished by Coley's death. We may indeed rediscover what Coley had long known about the potential of the immune system. In a paper from 1920 "The Idea of Progress", Coley quoted the 1st Century Roman Philosopher Seneca who stated, *"The day will come when posterity will be amazed that we remain ignorant of things that will seem to them plain"* (Coley 1920).

The time is long, overdue to re-ignite and re-examine the mechanisms and methodologies associated with Coley's famous toxins which I earnestly believe can enrich, complement and advance modern cancer therapies.

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