Trends in Cancer Research
Vol. 9, 2013

Mini-Review

William Coley's legacy - the development of modern mycobacteria-based therapies for cancer

Androulla Elia[1], Laura Rosa Brunet[2] and Thorsten Hagemann[3]

[1]St George's, University of London, Biomedical Sciences, Cranmer Terrace, London SW17 ORE, [2]Immodulon Therapeutics Ltd., The London Clinic Cancer Centre, 22 Devonshire Place, London W1G 6JA, [3]Barts Cancer Institute, Queen Mary, University of London, John Vane Science Centre, Charterhouse Square, London EC1M 6BQ, UK

ABSTRACT

The recent successful use of immunotherapeutic agents for the treatment of cancer has provided further support for a role for the immune system in this disease and so, it is appropriate to remember the father of immunotherapy, William B. Coley, who started this journey in 1891. Coley, a surgeon with an interest in bone sarcoma, attempted to treat patients with inoperable bone and soft-tissue sarcoma with administrations of bacterial preparations. He developed a treatment that became known as Coley Toxins, which he used for over 40 years at the Bone Sarcoma Unit at Memorial Hospital, now the Memorial Sloan-Kettering Cancer Centre in New York City, surrounded by controversy and scepticism but achieving undeniable success. In this review we will outline the subsequent progress of his idea, including related adaptations, and explore alternatives such as heat-killed mycobacteria-based immunotherapies, which are being developed by the pharmaceutical industry. We will present evidence to explain the potential value of this approach and discuss its applicability to cancer immunotherapy.

KEYWORDS: immunotherapy, Coley, mycobacteria, innate immunity, tumour microenvironment

INTRODUCTION

Following his graduation from Harvard Medical School in 1888, William Coley started an internship at the New York Hospital. During these early years he came across a number of cancer patients and was struck by the fate of two in particular; Miss Dashiell, diagnosed with malignant bone tumour at the age of 17 but who died within 10 weeks despite radical surgery and Mr. Stein, a German immigrant who had been diagnosed with an inoperable neck tumour and who went into remission following a severe bout of erysipelas, an acute skin infection. Intrigued by the effect of the bacterial infection on Mr. Stein's cancer and moved by the fate of Miss Dashiell, Coley researched the literature. He catalogued a number of observations of tumour regression following natural infections associated with high fever or after intentional injections of bacteria in cancer patients. A particular organism caught his attention, *Streptococcus pyogenes*, the causative agent of erysipelas. In 1891, like Bruns, a German physician, before him [1], he injected live *S. pyogenes* in a patient and was able to induce tumour shrinkage. Further patients were injected, but because of the risk of developing lethal infections [2], Coley stopped administering the live bacteria and instead developed what became known as Coley Toxins, a heat-killed preparation of *S. pyogenes* and *Serratia marcescens* (at that time known as *Bacillus prodigiosus*) to be administered for as long as necessary [3-5]. Coley published his clinical results in a number of papers, and by the end of his career there were over 150 reports and almost 1000 treated patients. With the commercial availability of Coley Toxins

produced by Parke Davis & Co and Buxton & Tracy Pharmaceutical Co, even more patients were treated by interested physicians. However, because of variability in the various modes of administration, which included intravenous, intramuscular and intratumoral, and in the preparations themselves (up to 13 were developed), results were not consistent. Soon the increasing controversies started to overshadow the reported successes [6].

In a changing landscape of therapeutic options, that came to include radiation and chemotherapy, and following personal acrimony with leaders in the oncology field, Coley's pioneering work slowly fell into oblivion. By 1952, commercial production had stopped and 10 years later, the USA Food and Drug Administration (FDA) refused to acknowledge Coley Toxins as a proven drug, thereby limiting its use in the USA as a treatment for cancer [7]. Work did however continue in a few dedicated laboratories and clinics around the world. This has led to a re-evaluation of this therapeutic strategy in recent years. The development of alternative bacterial products, based on similar premises, and the evidences from more rigorous clinical evaluations in randomized clinical trials support a role for this approach as adjunctive therapy in current cancer management (Figure 1).

Increasing clinical evidence

Both Coley and, subsequently, his daughter, Helen Coley Nauts, compiled several reviews to provide supportive evidence for clinical use of Coley Toxins. The first clinical series comprising of about 160 patients with sarcomas, carcinomas and epitheliomas, suggested improvement in about half of the patients with sarcoma [3].

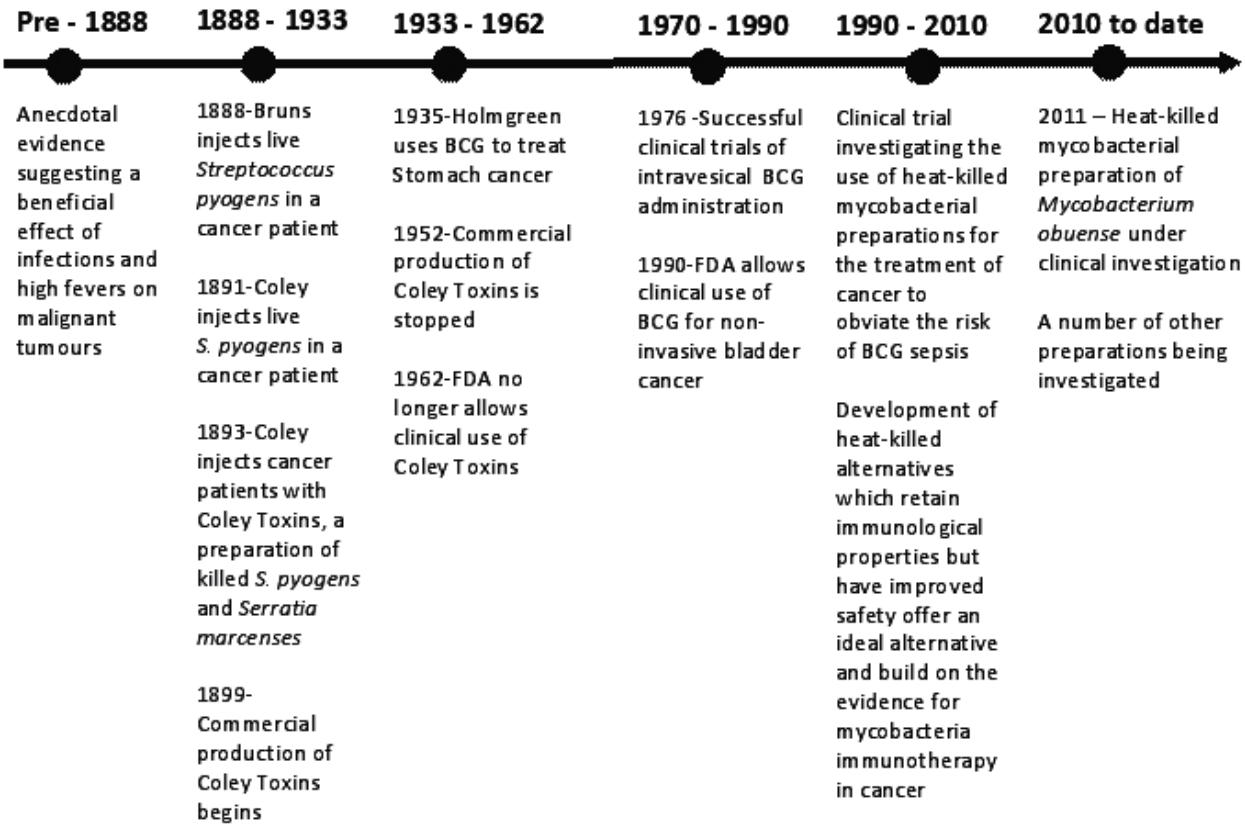

Figure 1. The development of Coley Toxins, related adaptations and the advent of heat-killed whole cell mycobacteria-based therapies.

Several papers were published later by Nauts detailing the fate of over 800 patients with microscopically confirmed diseases who were treated with Coley Toxins. Data from a selected group of these patients were accessed for inclusion in a retrospective study comparing the 10-year survival rate of patients treated with Coley Toxins with that of patients treated with modern conventional therapy (other than radiation) to determine the efficacy of treatment [8]. Based on case records, the survival of 128 patients with renal, ovarian, breast cancer or soft-tissue sarcoma who had received Coley Toxins between 1890 and 1960 was compared to that of 1675 patients diagnosed in 1983 and who had received conventional treatment, as reported by the Surveillance Epidemiology End Results population-based cancer registry in the USA. Groups were matched on the basis of age, sex, ethnicity, tumour site and stage. Interestingly, the survival rates were comparable in the two groups. Despite the obvious caveats given the use of historical data, the small number of patients in the group treated by Coley, the effects of selection biases and inherent differences over the historical period, it is of note that Coley's treatment did not appear to be associated with increased risk of mortality and patients had survival rates comparable to those receiving conventional treatments.

The best supporting evidence in clinical research comes from randomized controlled trials; over the years, there have been three randomized clinical trials testing Coley Toxins or the related preparation, mixed bacterial vaccine (MBV) [9-11]. Even though patient numbers were small, results were suggestive of effective treatment. The first trial conducted in 71 patients with advanced inoperable metastatic cancers reported objective responses in over 25% of patients treated with Coley Toxins (n = 34) compared to less than 3% in those treated with the typhoid vaccine (n = 37) [9]. The same group reported the response to Coley Toxins in a non-controlled series of 93 patients with histologically proven and progressing cancer and with no other treatment options [12]. Treatment was associated with subjective improvement in 20 patients (21.5%) who reported decreased pain, dyspnoea and cough. Moreover, 30 patients (32.3%) had objective improvement with decreased tumour lesions and nodes. The other two randomized clinical trials both used MBV, a modern adaptation of Coley Toxins, which was administered in combination with conventional treatment. One trial compared the efficacy of combination treatment of MBV with radiation and chemotherapy in 56 patients with advanced nodular lymphoma [10]. Compared to patients receiving radiation and chemotherapy alone (n = 30), those who also received MBV (n = 26) faired significantly better, reporting fewer relapses (42% vs 20%) and a higher rate of complete responses (44% vs 85%), as well as longer median survival (34.3 months, $p = 0.029$). The third trial investigated the effects of MBV in hepatocellular carcinoma [11]. The survival rate over the course of 3 years in 86 patients categorized by surgical status (palliative resection and unresectable) was assessed and showed a trend towards significant greater survival at two and three years ($p = 0.09$ and $p = 0.07$, respectively) in those patients with unresectable cancer treated with the combination of MBV, radiotherapy and Cisplatin (41% and 41%, at two and three years, respectively) compared to those treated with radiotherapy and Cisplatin alone (25% and 20% at two and three years, respectively).

The therapeutic effect of Coley Toxins and combined preparations of several bacteria was evaluated in two further uncontrolled clinical trials [13, 14]. In the trial by Waisbren, 139 patients with poor prognosis and no other treatment options were treated with a preparation of MBV and *Bacille Calmette Guerin* (BCG), transfer factor and also in some cases with lymphoblastoid lymphocytes [13]. It appeared that combination therapies aimed at immuno-modulation were well tolerated and a welcome alternative for patients with limited treatment options. In a second study conducted in Germany, 15 advanced melanoma patients received Coley Toxins: 4 patients (26.7%) improved; 3 patients had total or long lasting remission and one patient had stable disease [14].

Evidence based on the clinical studies summarized above suggests that Coley Toxins or comparable whole cell bacterial preparations can provide alternative therapeutic options especially

in combination with conventional treatments. For these reasons, further work is required to determine the mode of action and develop better characterized and more consistent preparations for clinical use and suitable combination strategies. Several issues remain to be addressed to take full advantage of this promising yet overlooked therapeutic approach (Box 1).

Current adaptations of Coley Toxins

Following on from Coley Toxins, a number of whole cell bacterial preparations have been developed and investigated for the treatment of cancer (Table 1). These are all based on the hypothesis that treatment with bacterial preparations, whether Coley Toxins, MBV, BCG, heat-killed whole cell mycobacterial preparations or pneumococcal vaccine PCV-13, boost the patient immune system and the ability to mount effective responses aimed at tumour cells, thereby limiting and inhibiting tumour growth and spread.

The most successful example to date, on this tenet, has been the use of BCG, a live attenuated strain of *Mycobacterium bovis*, originally

Table 1. Clinical trials with whole cell bacterial preparations.

	Indication	**Status**	**Reference**
BCG	*In situ* bladder carcinoma	Approved	[15, 16]
Mycobacterium indicus pranii	Invasive bladder cancer	Unknown	[21]
	Non-small cell lung cancer (NSCLC)	Unknown	[22]
	BCG refractory superficial transitional cell carcinoma of bladder	Completed	NCT00694798
	Superficial transitional cell carcinoma of bladder	Active, not recruiting	NCT00694915
	Advanced stage melanoma (Stage III, IV melanoma)	Terminated	NCT00675727
	Plus docetaxel for hormone refractory metastatic prostate cancer	Terminated	NCT00525408
	Combination with paclitaxel plus cisplatin in advanced NSCLC	Completed	NCT00680940
Mycobacterium vaccae	In conjunction with chemotherapy in the treatment of NSCLC	Development on hold	[24, 25]
Mycobacterium obuense	Adult melanoma cancer patients	Completed	NCT01308762 [26]
	A long term follow up study for patients who previously took part in the phase I study IMM-101-001	Enrolling by invitation	NCT01559818
	Combination with gemcitabine in advanced pancreatic cancer	Ongoing	NCT01303172
	Combination with radiation induced tumour necrosis in patients with previously treated colorectal cancer	Recruiting	NCT01539824
MVB	Tumours expressing NY-ESO-1 antigen	Ongoing	NCT00623831
Pneumococcal polyvalent vaccine	Early stage asymptomatic chronic lymphocytic leukemia or small lymphocytic lymphomas	Recruiting	NCT01351896
	Myeloma	Recruiting	NCT01245673

developed as a vaccine for tuberculosis. Intravesical administration of BCG has received FDA approval for use as an immunotherapeutic agent for treatment of *in situ* bladder carcinoma [15, 16]. A review of the literature has shown that, despite its toxicity, treatment with BCG is superior to Mitomycin C in reducing recurrence in high-risk patients, making BCG the treatment of choice in non-muscle invasive bladder cancer [17, 16]. BCG has been investigated in a number of other cancers with limited success, even though it is still sporadically used for the treatment of melanoma [18, 19]. Intra-lesional administration of BCG appears to enhance survival in melanoma patients with late stage disease and cutaneous metastasis [20]. More recently BCG has been investigated in renal and prostate cancer [reviewed in 16]. However, the risk of sepsis has limited further development. Hence, the use of heat-killed preparations which retain similar immunological characteristics but have improved safety profiles is now being pursued as an alternative.

A preparation of heat-killed *Mycobacterium indicus pranii*, produced by Cadila Pharmaceuticals Ltd., which has FDA approval as a vaccine for leprosy, has been shown to have promising effects in invasive bladder cancer and in non-small cell lung cancer (NSCLC) when used in conjunction with radiotherapy and chemotherapy [21, 22] and in advanced solid tumours refractory to standard treatments [23]. This product is also undergoing evaluation in superficial transitional cell carcinomas of the bladder (NCT00694798 and NCT00694915), Stage III-IV melanoma patients (NCT00675727), hormone refractory metastatic prostate cancer in combination with Docetaxel (NCT00525408), and NSCLC in combination with Paclitaxel + Cisplatin (NCT00680940).

Another saprophytic non-pathogenic mycobacteria which had been investigated for the treatment of cancer is *Mycobacterium vaccae* [18, 19]. Its good safety profile and immunomodulatory effects along with promising effects in patients [19, 24, 25] prompted the development of a related product by Immodulon Therapeutics Ltd. based on heat-killed whole cell *Mycobacterium obuense*. A phase I clinical trial (NCT01308762) using this preparation (IMM-101) in stage III/IV melanoma patients reported a good safety profile [26]. There is some preliminary evidence for therapeutic effects with 10 of the 18 patients still alive after nearly 3 years and 7 still receiving treatment (NCT01559818) as of September 2013 (Immodulon Therapeutics Ltd., data on file). *M. obuense* is currently in Phase II clinical trials in pancreatic cancer in combination with Gemcitabine (NCT01303172) and in advanced colorectal cancer (NCT01539824).

How are effective immune responses against the tumour elicited by Coley Toxins and related products?

It is likely that the anti-tumour effects of Coley Toxins, BCG and heat-killed mycobacterial preparations currently being investigated are mediated by their ability to induce or modulate systemic immune activation. Indeed, bacterial preparations, by their very nature, are potent inducers of both innate and Type-1 immunity. Their ability to elicit an immune response is based foremost on the presence of Microbe Associated Molecular Patterns (MAMP) which activate cells of the immune system, such as Natural Killer cells (NK), γδ T cells and myeloid cells through interaction with Pattern Recognition Receptors (PRR). Myeloid cells include macrophages (Mϕ), Dendritic Cells (DC); which are at the interface between innate and adaptive immunity and granulocytes. The activation of these cells and in particular that of DC, directs the development of adaptive immunity, resulting in a strong bias towards the induction of CD4+ Th1 responses and CD8+ cytotoxic cell activity. The observed therapeutic effects of Coley Toxins, and its more modern adaptations, may be due to the indiscriminate stimulation of innate immunity following treatment. It has been proposed that interleukins such as IL-1, IL-6, IL-12 and cytokines such as TNF-α are active mediators in this process, promoting a cytokine environment in which adaptive immunity specific to the bacterial antigen is induced. The resulting cytokine milieu promoting immune activation may in turn restore the ability of tumour specific Th1 and CTLs cells to recognize tumour antigens and mount tumour specific responses (Figure 2). For example, in its role as an anti-cancer non-specific immune stimulant, BCG induces a local inflammatory response in the

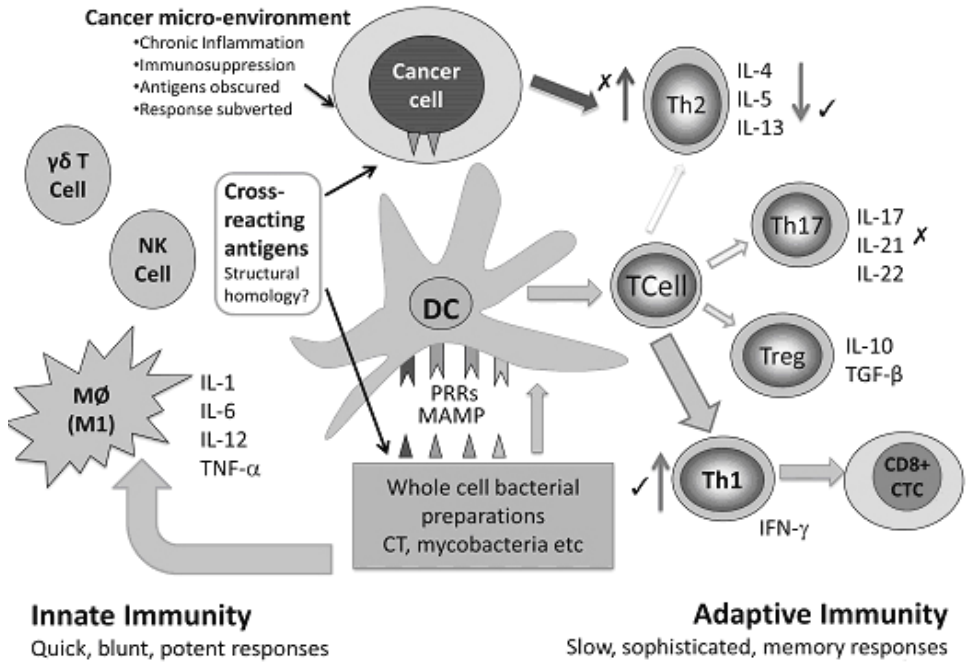

Figure 2. Effect on innate and adaptive immunity in cancer as a result of administration of Coley Toxins and related preparations. A critical issue that needs to be addressed in our efforts to induce effective anti-tumour immune responses in patients is the lack of sufficient and appropriate signals for DC costimulation at the tumour site. This leads to DC which remain immature or not suitably activated and therefore unable to induce protective anti-tumour immune responses including induction of Th1 and CD8+ CTLs. We propose that the non-specific activation of cells of the innate immune system and of DC by MAMP of Coley Toxins and related adaptations, such as mycobacterial preparations, is able to provide appropriate stimulation and promote a cytokine environment suitable for induction of Type-1 adaptive immunity.

bladder characterized by infiltration of innate immune cells, including Mϕ and of lymphocytes, in particular CD4+ Th1 cells leading to increased effector/suppressor ratio [27, 28]. The ensuing cytokine environment, which includes a wide range of mediators such as IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, GM-CSF as well as chemokines and adhesion molecules, ultimately leads to Type-1 responses mediating tumour destruction and TRAIL-induced apoptosis [29, 30].

In the last few years, the interactions between MAMP and PRR have been carefully studied, revealing that they go beyond activating innate immune cells involved in the defence against pathogen challenges and participate in a number of other processes, some of which are relevant to cancer therapy [31, 32]. The best studied PRR are the Toll-like Receptors (TLR) which recognize a variety of bacterial lipoproteins, RNA and DNA. Their involvement in mediating immune responses against cancer is exemplified by the findings that approved anti-cancer drugs such as BCG (*in situ* bladder carcinoma) and Imiquimod (basal cell carcinoma) are TLR agonists; BCG induces TLR2 and TLR4 signalling [33, 34] and Imiquimod is a TLR7 agonist [35]. Both of these, and possibly Coley Toxins as well, operate in a MYD88-dependent fashion leading to NF-κB activation and transcription of proinflammatory cytokine genes such as those coding for IFN-α, TNF-α, IL-6 and IL-12 [36, 37]. Microbes are also recognized by several other receptors including those for mannose, complement and lectin, to name a few. Although these receptors are less well characterized they are also likely to play a role in the induction of innate and adaptive immune responses against tumours. Over recent years, however, a number of PRR have been associated with a tumour promoting role which will not be further elucidated in this review [38, 39].

In the context of cancer immunity, the activation and stimulation of cells of the innate immune system, such as NK cells and Mϕ, with bacterial products or PRR agonists may restore immune function and correct the abnormalities associated with the immunosuppressive environment at the tumour site. For example, the inflammatory environment resulting from exposure to bacterial products may induce classical activation of Mϕ, associated with high IL-12 and low IL-10 and counteract the pro-tumour effects of tumour-associated Mϕ and M2 Mϕ which are associated with low IL-12 and high IL-10 [38, 40].

But the most significant effect of treatment with bacterial preparations is perhaps on DC, which are critical for the induction of adaptive immunity as, once activated, their main function is in the processing and presentation of antigens to CD4+ and CD8+ lymphocytes. Bacterial activation of DC alters their gene expression leading to up regulation of co-stimulatory markers and chemokine receptors which drive recruitment and functional interactions. In the context of cancer, however, DC fail to mature correctly and are therefore unable to appropriately induce Type-1 responses [41, 42]. Indeed, the immunosuppressive environment of the tumour site is characterized by hypoxia and increased secretion of VEGF, M-CSF, IL-6, IDO, extracellular adenosine as well as immunosuppressive cytokines such as IL-10 and TGF-β. All of the above, to differing degrees contribute to the impairment of DC functions during cancer. The immune defect of DC is even observed in the circulation as well as in the lymph nodes leading to systemic impairment of immune function [41, 42]. Because bacteria activate DC which preferentially drive Th1 development and cytotoxic immune responses, it is possible that this specific effect restores DC functionality by providing a cytokine milieu that counteracts the immunosuppression induced by the tumour (Figure 2).

CONCLUSION

The acknowledgement of an important role for the immune response in cancer has led to the recent establishment of the field of "*oncoimmunology*" [43]. This has resulted in important innovations both in therapeutic approach and in the understanding of the natural evolution of cancer. In particular, an improved appreciation of the host's ability to mount effective anti-tumour responses through both innate and adaptive immunity has promoted renewed interest in therapeutic methodologies that combine chemotherapy and/or radiotherapy with immunotherapy. It is now clear that one of the barriers to effective anti-tumour responses is mediated by the immunosuppressive environment of the tumour causing a lack of immune activation signals to innate immune cells, and inadequate immunostimulation of antigen presenting cells. We propose that these immune-suppressive effects may be overcome by using Coley Toxins or its modern adaptations, including mycobacterial preparations which, to date, have offered the greatest clinical promise. These may be able to induce systemic immune activation both through innate and adaptive immunity leading to durable anti-tumour responses through the induction of cytotoxic cells such as CD8+ CTLs.

Box 1

Unanswered questions:

- The use of live bacterial preparations, for example *Streptococcus pyogenes* and BCG, have been hampered by local reactions and even fatalities. Would the use of heat-killed preparations of mycobacteria species, which retain the immunological properties of live preparations but have improved safety, provide preferable alternatives?
- Significant problems were encountered in the manufacture of Coley Toxins which limited its development for clinical use. Manufacture of whole cell bacterial preparations needs to be carefully controlled to ensure consistent products for clinical administration. Are there bacteria which are more amenable than others to large scale manufacturing?

Box 1 continued..

- Are some bacterial preparations better suited than others at inducing anti-tumour immune response through their activation of innate and adaptive immunity?
- What are the best routes of delivery to induce appropriate systemic activation of innate and adaptive immunity?
- A more detailed understanding of schedule and 'treatment holidays' using combinations with blockade checkpoint inhibitors would be advantageous. This may address the question of whether one can exhaust the immune response by continuously stimulating both arms of the immune system. Alternatively, would the broad array of MAMPs and antigens contained within whole cell bacterial preparation prevent this stimulation by using multiple pathways?
- The combination of Coley Toxins or its modern adaptations with chemotherapy and/or radiotherapy warrants further investigation. Would the release of tumour antigens following immunogenic cell death of targeted cancer cells in the presence of increased levels of danger signals lead to improvements in the immune responses in particular boosting cytotoxic T cell functions?

ACKNOWLEDGMENTS

The authors thank Prof. John Grange, Dr. Kevin Bilyard and Mr. Charles Akle for thoughtful review of the manuscript.

CONFLICT OF INTEREST STATEMENT

Dr. Laura Rosa Brunet is a consultant for Immodulon Therapeutics Ltd. Immodulon Therapeutics Ltd. has provided research support to Prof. Thorsten Hagemann and additionally with the Ralph Bates Pancreatic Cancer Research Fund to Dr. Androulla Elia.

REFERENCES

1. Bruns, P. 1888, Beitr. Klin. Chir., 3, 443.
2. Coley, W. B. 1893, Am. J. Med. Sci., 105, 487-511.
3. Coley, W. B. 1896, Am. J. Med. Sci., 112, 251-281.
4. Coley, W. B. 1909, Practitioner, 83, 589-613.
5. McCarthy, E. F. 2006, Iowa Orthop. J., 15, 74-78.
6. JAMA Editorial. 1984, JAMA, 24, 919.
7. Hoption-Cann, S. A. and van Netten, J. P. 2003, Postgrad. Med. J., 79, 672-80.
8. Richardson, M. A., Ramirez, T., Russell, N. C. and Moye, L. A. 2003, Altern. Ther. Health Med., 200(5), 42-47.
9. Johnston, B. J. 1962, Cancer Chemother. Rep., 21, 19-68.
10. Kempin, S., Cirrencione, C. and Myers, J. 1983, Proc. Am. Soc. Clin. Oncol., 24, 56.
11. Tang, Z. Y., Zhou, H. Y., Zhao, G., Chai, L. M., Zhou, M., Lu, J. Z., Liu, K. D., Havas, H. F. and Nauts, H. C. 1991, Med. Oncol. Tumour Pharmacother, 8, 23-28.
12. Johnston, B. J. and Novales, E. T. 1962, Cancer Chemother. Rep., 21, 43-68.
13. Waisbren, B. A. 1987, J. Biol. Response Med., 6, 1-19.
14. Kölmel, K. F., Vehmeyer, K., Göhring, E., Kuhn, B. and Wieding, J. U. 1991, Onkologie, 14, 411-417.
15. Alexandroff, A. B., Jackson, A. M., O'Donnell, M. A. and James, K. 1999, Lancet, 353, 1689.
16. Gandhi, N. M., Morales, A. and Lamm, D. L. 2013, BJU Int., 112(3), 288-97.
17. Shelley, M. D., Mason, M. D. and Kynaston, H. 2010, Canc. Treat. Rev., 36, 195-205.
18. Grange, J. M., Krone, B. and Stanford, J. L. 2009, Eur. J. Cancer, 45(13), 2266-73.
19. Rook, G. A. and Dalgleish, A. 2011, Immunol. Rev., 240(1), 141-59.
20. Tan, J. K. and Ho, V. C. 1993, J. Dermatol. Surg. Oncol., 19, 985-990.
21. Chaudhuri, P. and Mukhopadhyay, S. 2003, J. Indian Med. Assoc., 101, 559-60.
22. Sur, P. K. and Dastidar, A. G. 2003, J. Indian Med. Assoc., 101, 118-20.
23. ASCO 14019, 2008, http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/14019

24. O'Brien, M. E., Anderson, H., Kaukel, E., O'Byrne, K., Pawlicki, M., Von Pawel, J. and Reck, M. 2004 Ann. Oncol., 15(6), 906-14.
25. Stanford, J. L., Stanford, C. A., O'Brien, M. E. and Grange, J. M. 2008, Eur. J. Cancer, 44, 224-7.
26. Stebbing, J., Dalgleish, A., Gifford-Moore, A., Martin, A., Gleeson, C., Wilson, G., Brunet, L. R., Grange, J. and Mudan, S. 2012, Ann. Oncol., 23, 1314-1319.
27. Prescott, S., Hargreave, T. B., Chisholm, G. D. and Smyth, J. F. 1992, J. Urol., 147, 1636-42.
28. Ratliff, T. L., Ritchey, J. K., Yuan, J. J., Andriole, G. L. and Catalona, W. J. 1993, J. Urol., 150, 1018-23.
29. Jackson, A. M., Alexandroff, A. B., Kelly, R. W., Skibinska, A., Esuvaranathan, K., Prescott, S., Chisholm, G. D. and James, K. 1993, Clin. Exp. Immunol., 99, 369-75.
30. Ludwig, A. T., Moore, J. M., Luo, Y., Chen, X., Saltsgaver, N. A., O'Donnell, M. A. and Griffith, T. S. 2004, Cancer Res., 64, 3386-90.
31. Galluzzi, L., Vacchelli, E., Eggermont, A., Fridman, W. H., Galon, J., Sautès-Fridman, C., Tartour, E., Zitvogel, L. and Kroemer, G. 2012, Oncoimmunol., 1, 699-716.
32. Vacchelli, E., Galluzzi, L., Eggermont, A., Fridmanm, W. H., Galon, J., Sautès-Fridman, C., Tartour, E., Zitvogel, L. and Kroemer, G. 2012, Oncoimmunol., 1, 894-907.
33. Heldwein, K. A., Liang, M. D., Andresen, T. K., Thomas, K. E, Marty, A. M., Cuesta, N., Vogel, S. N. and Fenton, M. J. 2003, J. Leukoc. Biol., 74, 277-86.
34. Uehori, J., Matsumoto, M., Tsuji, S., Akazawa, T., Takeuchi, O., Akira, S., Kawata, T., Azuma, I., Toyoshima, K. and Seya, T. 2003, Infect. Immun., 71, 4238-49.
35. Hemmi, H., Kaisho, T., Takeuchi, O., Sato, S., Sanjo, H., Hoshino, K., Horiuchi, T., Tomizawa, H., Takeda, K. and Akira, S. 2002, Nat. Immunol., 3, 196-200.
36. Akazawa, T., Masuda, H., Saeki, Y., Matsumoto, M., Takeda, K., Tsujimura, K., Kuzushima, K., Takahashi, T., Azuma, I., Akira, S., Toyoshima, K. and Seya, T. 2004, Cancer Res., 64, 757-64.
37. Hagemann, T., Lawrence, T., McNeish, I., Charles, K. A., Kulbe, H., Thompson, R. G., Robinson, S. C. and Balkwill, F. R. 2008, J. Exp. Med., 205, 1261-8.
38. Hagemann, T., Biswas, S. K., Lawrence, T., Sica, A. and Lewis, C. E. 2009, Blood, 113(14), 3139-46.
39. Kim, S., Takahashi, H., Lin, W. W., Descargues, P., Grivennikov, S., Kim, Y., Luo, J. L. and Karin, M. 2009, Nature, 457(7225), 102-6.
40. Biswas, S. K. and Mantovani, A. 2010, Nat. Immunol., 11(10), 889-96.
41. Palucka, K. and Banchereau, J. 2012, Nat. Rev. Cancer, 12(4), 265-77.
42. Gabrilovich, D. I., Ostrand-Rosenberg, S. and Bronte, V. 2013, Nat. Rev. Immunol., 12(4), 253-268.
43. Zitvogel, L. and Kroemer, G. 2012, Oncoimmunology, 1(8), 1223-1225.