Cytokine & Growth Factor Reviews xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Perspective

Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited

William K. Decker [a,*], Amar Safdar [b,1]

[a] Department of Stem Cell Transplantation and Cellular Therapy, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA
[b] Department of Infectious Diseases and Employee Health, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Interferon
Growth factors
Interleukin
Cancer
Leukemia
Lymphoma
Hepatitis
Tuberculosis
AIDS

ABSTRACT

In the nineteenth century, William B. Coley induced durable remission of inoperable metastatic sarcoma by repeatedly injecting live streptococcus bacilli and, subsequently, heat-killed bacterial extracts into the primary tumor. While Coley's contemporaries debated the veracity of his results, this bold treatment protocol established the new scientific field of immunology. In Coley's era, the scientific and medical communities lacked the prerequisite knowledge to validate and understand his treatment protocols. Today, a more comprehensive understanding of the human immune system, anchored by the discovery of the mammalian Toll-like receptor gene family in the 1990s, permits a mechanistic understanding of his results. Coley's cocktail of TLR agonists likely stimulated a complex cascade of cytokines, each of which plays a unique and vital role in the orchestration of the immune response. Here we explore Coley's legacy: a dissection of those cytokines which possess the immunostimulatory properties necessary to modulate the immune system and ameliorate human disease. The discussion is limited to molecules that have been able to show therapeutic promise in the clinical setting.

1. Introduction

In 1891, an inspired young surgeon named William B. Coley (Fig. 1) embarked upon an intellectual odyssey that would ultimately earn him the title "Father of Immunotherapy"; however, Coley's journey was not to be one of triumph and exultation, but rather a case study of resolve and determination in the face of implacable odds. Coley is a somewhat tragic figure whose contributions to immunology have mainly been recognized and appreciated posthumously. Haunted by the death of his first patient from metastatic sarcoma, Coley delved deeply into the historical record in search of a potential cure for cancer. What he found would entwine the seemingly unrelated conditions of cancer and infection as well as give birth to the nascent fields of immunology and immunotherapy, a remarkable achievement considering that immune cell mediators and their mechanisms of action (i.e. macrophage phagocytosis pictured in Fig. 2) were wholly unknown in his era. Coley found 47 case reports in which concomitant infection seemed to have caused the remission of an otherwise incurable neoplastic malignancy. His research even relied upon anecdotes from the pre-antiseptic era: eighteenth century surgeons reported oncologic cure rates of greater than 80% following resection or amputation, provided that the patient did not die from the inevitable infection that accompanied eighteenth century surgical procedures. Most striking to Coley was the apparent connection between erysipelas, a streptococcal skin infection, and the remission of soft tissue sarcoma.

When Coley began injecting his cancer patients with *Streptococcus pyogenes* (the causative agent of erysipelas) in 1891, he encountered some surprising impediments. Unexpectedly, it was very difficult to induce erysipelas in most patients and, once infection was established, it was difficult to cure patients of their invasive streptococcal disease. Two patients even died from disseminated septicemia. By 1893, Coley had settled upon an admixture of heat-killed *S. pyogenes* and heat-killed *Bacillus prodigious* (now reclassified as *Serratia marcecsens*). This fortuitous combination of Gram-positive and Gram-negative bacteria possessed a wide array of immunostimulatory properties that allowed Dr. Coley to achieve long-term cure rates unrivaled by medical science in the 73 years since his death (Table 1). Yet Coley's treatment protocol was doomed in his own lifetime by the contemporary development of radiotherapy and the absence of a definable, mechanistic explanation for infection-mediated tumor regression [1–5]. It is the century-long search for mechanism that today defines Coley's legacy. His initial observations have, in large part, led to the discovery of the soluble signaling factors that modulate immune function, as well as the pattern recognition receptors responsible for the detection of infectious

* Corresponding author. Tel.: +1 713 563 1896; fax: +1 713 563 1898.
E-mail addresses: wkdecker@mdanderson.org (W.K. Decker), asafdar@mdanderson.org (A. Safdar).
[1] Tel.: +1 713 792 0825; fax: +1 713 745 6839.

1359-6101/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cytogfr.2009.07.004

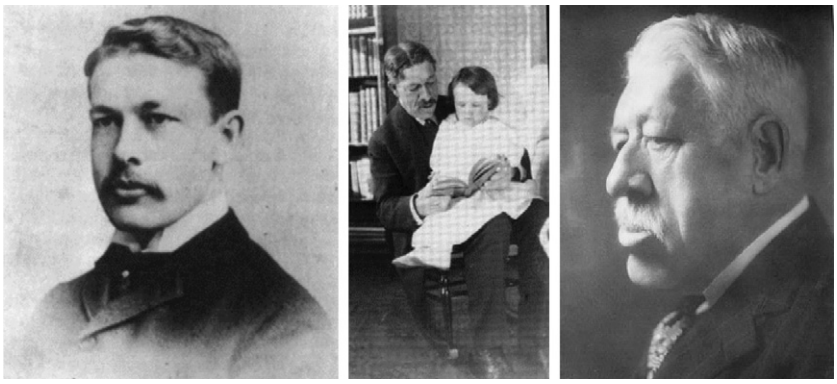

Fig. 1. The Father of Immunotherapy: William Bradley Coley, 1862–1936. Left Panel: William Coley in the early 1890s circa age 30, roughly the time period during which he formulated his original immunotherapeutic treatment for soft tissue sarcoma. Center Panel: William Coley in 1910, reading to his daughter Helen (later Helen Coley Nauts). Mrs. Nauts would later make her life's work to keep the memory of her father's treatment protocol alive. Her supreme efforts alone ensured that Coley Fluid was not consigned to the dustbin of history. With a grant from the Nelson Rockefeller Foundation, she founded the Cancer Research Institute in 1953; and in 1975, the CRI established the William B. Coley Award for Distinguished Research in Basic and Tumor Immunology. Mrs. Nauts passed away in 2001 at the age of 93. Right Panel: Dr. Coley near the end of his life, suffering from the effects of acromegaly, duodenal ulcers, pyloric stenosis, and diverticulitis. Panels reprinted with permission from Nature Publishing Group and the Hospital for Special Surgery.

organisms [6–9]. Coley's legacy is perpetuated as we empirically adapt these physiologic immune modulators and TLR agonists for the optimal treatment of human disease.

While a large number of potential biological adjuvants have demonstrated anti-tumor efficacy in experimental systems, a relatively small number of these have been successfully translated to the clinic, and a correspondingly smaller number have demonstrated meaningful efficacy in human beings. Here we attempt to limit the scope of our review to those compounds that have either demonstrated significant efficacy in the clinic or seem likely to exhibit such in the near future (Table 2). Some powerful immune mediators such as IL-12 and IFN-γ are not discussed since they have shown little promise as stand alone immune therapies. Their efficacy seems to be limited to an adjuvant role in conjunction with vaccination, a topic which may be reserved for an independent discussion.

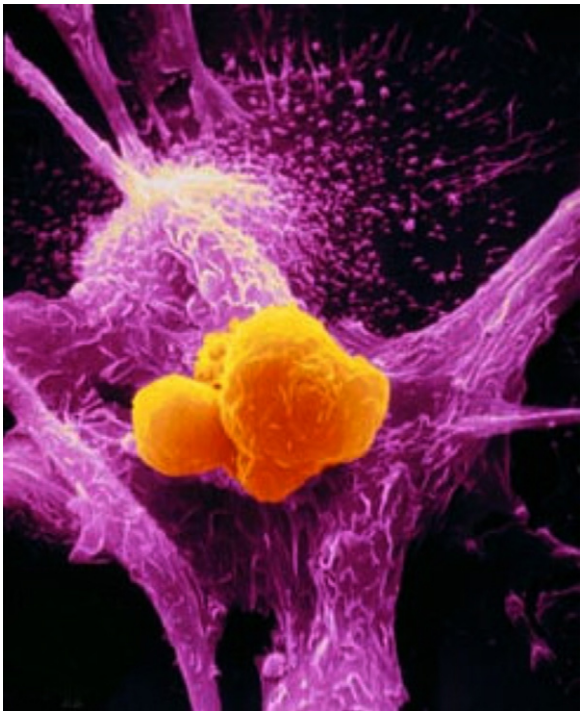

Fig. 2. Electron micrograph of a macrophage in the process of engulfing a tumor cell. Macrophages are a versatile type of immune cell that operate on the cusp of both innate and adaptive immunity, engulfing both non-specific cellular debris and the objects of antibody opsonization. Like most immune and somatic cell types, macrophage activity is enhanced by interferon-α. Macrophages are also induced to proliferate and upregulate phagocytic activity in the presence of GM-CSF. Interferon-α is secreted by the plasmacytoid DC subset in response to ligation of Toll-like receptors and other pattern recognition receptors by a wide variety of agonists. GM-CSF is secreted by activated $CD4^+$ T-cells. Faux color electron micrograph reprinted with permission from PhotoTake USA, Inc. (www.phototakeusa.com).

2. Interferon-alpha (IFN-α)

2.1. Neoplasia

IFN-α is perhaps the most widely and successfully employed bioimmunoadjuvant used for the treatment of neoplasia. *In vivo*, dendritic cells that express lymphoid-specific lineage markers, called plasmacytoid dendritic cells (DCs) or DC2, serve as accessory cells that aid in the immune response by secreting large amounts of type I interferons (IFN-α/β/ω) in response to viral infection and other types of inflammation. Consistent with an apparent role in viral defense, plasmacytoid DCs express intracellular Toll-like receptors (TLR)-7 and -9, which are important in the recognition of microbial nucleic acids, but do not express other TLRs, such as TLR-1, -2, -3, -4, -5, or -8. In response to activation by TLR ligation and/or inflammatory chemokines, plasmacytoid DCs migrate to sites of inflammation where they secrete significant amounts (up to 10 pg IFN per cell) of IFN-α *in situ* [10–14].

Table 1
Examples of Dr. Coley's clinical results.

Disease	Any response	Durable CR
Soft tissue sarcomas	63% (66/104)	52% (54/104)
Lymphomas	52% (26/50)	38% (19/50)
Osteosarcoma	33% (1/3)	0% (0/3)
Ovarian carcinoma	75% (3/4)	25% (1/4)
Cervical carcinoma	100% (2/2)	50% (1/2)
Testicular carcinoma	44% (8/18)	33% (6/18)
Renal carcinoma	50% (3/6)	50% (3/6)
Multiple myeloma	100% (1/1)	100% (1/1)
Colorectal carcinoma	50% (1/2)	0% (0/2)
Breast carcinoma	43% (6/14)	14% (2/14)
Melanoma	67% (4/6)	17% (1/6)
Total	**58% (121/210)**	**42% (88/210)**

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

Table 2
Disease indications for which cytokine therapy may be considered standard of care or has been attempted experimentally.

Cytokine therapy	Cancer indication		Infectious disease indication	
	Standard of care	Experimental	Standard of care	Experimental
IFN-α	Leukemias Lymphomas Multiple myeloma Kaposi's sarcoma RCC Melanoma	HCC Osteosarcoma Transitional cell Carcinoma Pancreatic Adenocarcinoma	HCV	HBV Flavivruses JEV SLEV WNV
IL-2	RCC Melanoma	Prostatic carcinoma		HIV
TNF-α	Soft tissue Sarcoma Melanoma	Liver metastasis Transitional cell Carcinoma		
G-CSF		HCC AML Melanoma	Febrile Neutropenia	
GM-CSF		NHL (in combination with rituximab)	Febrile Neutropenia	*Aspergillus* and *Scedosporium* infection
CD40L		Carcinomas of the Cervix Bladder Ovary Breast Squamous cell Epithelium Melanoma Lymphomas Leukemias		

IFN-α has profound immunologic effects upon target somatic cell populations, cells of the innate immune system, and cells of the adaptive immune system via its modulation of professional antigen presenting cells (APCs), principally the myeloid DC. Further, some of the anti-tumor effects of IFN-α are not strictly immune-mediated, but rather physiologic effects upon the tumor cells themselves. Schmidt et al. demonstrated that IFN-α upregulates MHC class I surface expression as well as components of the immunoproteasome in pancreatic tumor cell lines. Accordingly, IFN-α pretreatment of pancreatic tumor targets was able to mediate lysis by partially HLA-matched $CD3^+$ lymphocytes whereas untreated tumor targets could not be lysed at all. The same authors also demonstrated significant upregulation of NK killing activity following IFN-α treatment [15]. Other authors have demonstrated that IFN-α treatment significantly elevates serum TNF-α and IL-12 levels *in vivo*; upregulates dendritic cell MHC class I, MHC class II, and CD86; and increases the levels of circulating $CD40^+$ APC and $CD8^+$ T-cells [16,17]. Both IFN-α and IFN-β have also shown the ability to induce growth arrest and apoptosis of human adrenocortical carcinoma cell lines in a caspase 3, 8, and 9 dependent fashion [18]. Moreover, IFN-α/β treatment of *p*-glycoprotein overexpressing osteosarcoma cells induces growth arrest and sensitizes these cells to subsequent chemotherapeutic treatments [19,20]. One might surmise that Coley's treatment protocol induced the production of copious amounts of IFN-α via the ligation of TLR-9 by unmethylated bacterial CpG DNA present in his extract.

IFN-α therapy is used widely for the treatment of a variety of neoplastic conditions including hairy cell leukemia [21–23], chronic phase CML (until the advent of Gleevec) [21–23], a variety of lymphomas [21,23,24], multiple myeloma [22], Kaposi's sarcoma [21], renal cell carcinoma [21,22], and disseminated melanoma [21–23,25,26]. IFN-α therapy has also been used experimentally to treat pancreatic adenocarcinoma [15,17], hepatocellular carcinoma [27,28], osteosarcoma [29], and transitional cell carcinoma of the bladder [30]. The efficacy of IFN-α therapy varies significantly among disease indications for which its application may be considered standard of care. In the pre-Gleevec era, administration of IFN-α to CML patients generated clinical remissions in over 90% of cases, though such remissions were almost never durable. At the other end of the spectrum, administration of IFN-α to stage III melanoma patients at high risk of relapse results in a modest improvement of 5 year DFS to 37% in comparison to 26% among individuals in the observation group [21].

2.2. Infectious disease

Chronic hepatitis C virus (HCV) is a serious and disabling disease transmitted by high-risk sexual behavior and contaminated blood products. IFN-α therapy has led to a significant improvement in HCV-associated fibrosis, which often results from direct virus-mediated damage of hepatocytes. The goal of treating patients with chronic HCV infection is to eradicate the virus. The eradication of HCV from the serum, referred to as sustained virologic response (SVR), is now being attributed to rapid virologic response achieved within 4 weeks after the treatment with IFN-α has commenced [31]. IFN-α in concert with oral ribavirin acts synergistically to mitigate inflammatory liver damage and promote repair via mechanisms still poorly understood [32]. Treatment-induced SVR, however, is seen in only 50% of the patients with chronic HCV infection [33]. Individual body weight, ethnicity, HCV viral load at baseline, and viral genotype are important in predicting SVR in patients receiving IFN-α therapy [34]. It is suggested that HCV nonstructural 5A (NS5A) phosphoprotein plays a central role in subverting host's innate immune defense and mitigates endogenous IFN-α-mediated antiviral surveillance [35]. This mechanism has also been suggested in HCV tolerance to IFN-α therapy.

Chronic hepatitis B virus (HBV) infection is also a serious infection afflicting nearly 350 million people worldwide. Treat-

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

ment with lamivudine, a nucleoside, and adefovir dipivoxil, a nucleotide, form the backbone of therapy, which is well tolerated and associated with normalization of aminotransaminase levels and low HBV e antigen (HBeAg). Seroconversion corresponds with regression of virus-induced hepatic fibrosis [36]. Infection relapse after discontinuation of lamivudine therapy and the emergence of drug resistance are the main limitations of nucleoside/nucleotide therapy. Two phase III trials using long-acting IFN-α alone or in combination with lamivudine have shown significant promise in suppressing HBV viral load and in achieving HBeAg seroconversion [37,38]. Furthermore, in a small number of patients, loss of HBeAg was accompanied by development of HBV surface antibodies [38]. Drug costs and adverse events are the main limitations of long-acting IFN-α therapy which is currently considered appropriate only for a select group of patients with chronic HBV infection.

IFN-α also has demonstrated *in vitro* activity against most clinically important flavivirus infections [39] such as Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLEV), yellow fever, and West Nile virus (WNV) although treatment with IFN-α is considered experimental and clinical responses vary substantially. Nearly 700 million children in Asia are susceptible to JEV and, despite protection or reduced severity of disease demonstrated in animal experiments with IFN-α_{2b} treatment [40], there was no clinical benefit reported in a similar double-blinded, controlled trial in children with JEV infection [41]. Yellow fever is a mosquito-borne infection that leads to life-threatening hemorrhagic fever; and treatment with recombinant IFN-α in a primate model has been shown to markedly suppress viremia, improve liver function, and enhance survival [42]. Clinical trials have not been performed, yet IFN-α is presently used in combination with ribavirin for serious cases. IFN-α also ameliorates serious life-threatening complications associated with SLEV [43] and WNV in animal experiments, though there is a limited clinical experience [44,45]. In a patient with prolonged WNV meningoencephalitis, IFN-α_{2b} therapy was associated with a favorable response [44], which may in part have been due to interferon-mediated restriction of viral tropism, viral replication, and neuronal cell death [46].

3. Interleukin-2 (IL-2)

3.1. Neoplasia

Interleukin-2 (IL-2) is an important T-cell and NK cell growth factor secreted predominantly by activated T-cells as part of a positive autocrine feedback loop that regulates survival and expansion; however, the rationale for the use of IL-2 in cancer immunotherapy is less dependent upon any pervasive immunologic theory than it is upon the observation that systemic levels of IL-2 may serve as an independent prognostic variable for a variety of different neoplasias [47,48]. Given this observation, IL-2 supplementation has been attempted for nearly every conceivable tumor type [30,49,50], though sporadic successes have been largely confined to disseminated melanoma and renal cell carcinoma [51–55]. A very recent trial has demonstrated that the administration of low-dose IL-2 in conjunction with zoledronate may impact overall response rate and 12-month survival in patients with metastatic hormone-refractory carcinoma of the prostate; however, improvements in long-term disease-free survival have yet to be documented [56].

The prognosis for individuals with metastatic melanoma and renal cell carcinoma is especially grim, and the administration of high-dose IL-2, either alone or in combination with other agents, remains one of the few treatment alternatives for patients with stage IV disease. Overall response rates to single agent IL-2 are poor, rarely exceeding 20%, and durable long-term responses are observed in only 6–8% of patients [51,52,54,55]. Response rates when IL-2 is given in combination with other agents such as IFN-α or chemotherapy are occasionally enhanced in some reports; however, overall survival typically remains unchanged. Given the expense, high toxicity, and very low long-term response rates associated with high dose IL-2 therapy, investigators have spent much of their efforts in an attempt to predict which patients will respond meaningfully to IL-2 therapy [57]. In renal cell carcinoma, non-clear cell histology has been associated with a poor response to IL-2 therapy (6% versus 21%). Among patients with clear cell histology, the presence of alveolar features and the absence of papillary or granular features has been associated with a 39% response rate whereas patients with non-alveolar tumors exhibiting granular or papillary features demonstrate a response rate of only 3% [53,58–60]. In melanoma, higher response rates have been associated with the presence of cutaneous or subcutaneous metastases, normal serum LDH levels, the involvement of fewer than three organs, and a good performance status (ECOG 0 or 1) [61,62].

3.2. Infectious disease

In patients with HIV-AIDS, introduction of highly active antiretroviral therapy (HAART) has changed the grave dynamics of this devastating illness. IL-2 immunotherapy has been a focus of protracted research in AIDS patients with advanced CD4 lymphocytopenia; however, the use of lymphoproliferative cytokines seemed counterintuitive in the era prior to effective antiretroviral therapy. Since the introduction of HAART, decreased viral loads have been sustainable, and the introduction of IL-2 to stimulate $CD8^+$ CTL activity now makes some sense; however, IL-2 therapy has an additional, recognizable effect in promoting the growth suppressor or regulatory T-cells (Tregs) via STAT3/STAT5-mediated upregulation of transcription factor Foxp3 [63]. Tregs appear to have divergent influences on HIV disease. In lymphoid tissues, Tregs may favorably reduce the pool of potentially infectable HIV-target helper T-cells yet, negatively, limit the number of HIV-primed effector T-cells and promote retroviral immune escape. A serious concern in this setting is that IL-2-enhanced Tregs will abrogate viral clearance via downregulation of anti-retroviral immune responses, leading to the formation of viral reservoirs in the central nervous system, genital tract, and intestinal tract. Tregs can act to support retroviral infection in higher mammals via the dysregulation or suppression of virus-specific immune responses, and the ablation of Treg function with anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) monoclonal antibody therapy has resulted in effective viral tissue clearance [64]. The therapeutic role of IL-2 against an established HIV infection may rely partly upon stimulation of CD8-mediated viral containment as IL-2 activation of CTL responses has been demonstrated even in the setting of severe CD4 lymphocytopenia. Clinical studies have also shown that IL-2 along with HAART therapy is superior in maintaining CD4 cell counts whereas IL-2 alone seems less effective in accomplishing this goal [65]. Intermittent low-dose IL-2 minimizes activation of NK cells and reduces the release of TNF-α, IFN-γ, GM-CSF, and other proinflammatory cytokines that contribute to the toxicity associated with high-dose IL-2 (18 MU per day) [66]. Intermittent IL-2 therapy has also been associated with prolonged survival of CD4 T-cells [67]. Nevertheless, in a pooled analysis of 3 randomized trials, significant improvements in CD4 cell counts and plasma HIV levels did not significantly alter the clinical outcome in patients who were treated with IL-2 versus conventional therapy [68]. This was unexpected as IL-2 treated patients have demonstrated an increase in the expansion of phenotypically naïve and memory T-cells [69]. The precise role of IL-2 in controlling HIV infection remains uncertain and could possibly be related to the disease state and

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

host immunologic status. On the positive side, there remains some indication that patients treated with IL-2 plus HAART may enhance outcome in the setting of opportunistic infections.

4. Tumor necrosis factor-α (TNF-α)

4.1. Neoplasia

As evidenced by its lofty and inspiring appellation, tumor necrosis factor alpha (TNF-α) has long been expected to be a premier weapon in the fight against cancer; however its use in therapeutic protocols has been severely limited by its high systemic toxicity and by paradoxical, pleiotropic effects that favor, rather than hinder, the spread of neoplastic disease. TNF-α was originally isolated as one of the bioactive compounds that produced dramatic remissions of soft tissue sarcoma in patients treated with Coley's mixed toxins as well as the soluble factor induced by BGC that could mediate hemorrhagic necrosis in tumor-bearing mice [70–72]. It is a homotrimeric soluble cytokine secreted by inflammatory macrophages and activated T-cells, which contributes to many different aspects of the inflammatory process, particularly in the establishment of reversible micro-environments via its ability to stimulate cellular differentiation and tissue remodeling [71]. At supraphysiologic concentrations, TNF-α promotes destruction of the tumor neovasculature in a caspase-8-dependent fashion [73]; however, the accumulation of such supraphysiologic doses cannot be achieved systemically without the onset of vasoplegia, multi-organ failure, and "septic shock-like syndrome" [72]. This complication has limited the use of TNF-α therapy to closed circuit perfussive strategies [70,72,74–77]. Further, when produced chronically at physiologic levels, TNF-α appears to have a number tumor promoting effects. TNF-α is produced by a wide variety of tumor types, and TNF-α levels have been directly correlated with poor prognosis and resistance to therapy [78–81]. It appears to promote tumor growth and metastasis in a wide variety of experimental systems [70], possibly in accordance with a paradoxical but physiologic role in NF-κB-mediated proliferation [82,83]. Moreover, specific TNF-α promoter alleles that confer high levels of expression have been positively correlated with the development of a variety of neoplasias including lymphoma [84], myeloma [85], carcinoma of the prostate [86], cutaneous basal cell carcinoma [87], and cervical intraepithelial neoplasia [88].

Isolated limb perfusion in conjunction with TNF-α, melphalan, and/or INF-γ is used to treat bulky disease associated with inextirpable soft tissue sarcoma or in-transit melanoma metastases. This procedure is limb-sparing and boasts a response rate that approaches 100%; however, there is no impact upon time to progression or upon overall survival, both of which remain identical to those observed following disfiguring surgical intervention [70,72,76]. Isolated hepatic perfusion in conjunction with TNF-α, melphalan, and hyperthermia has also been used to treat colorectal or melanotic liver metastases; however, there is only scant evidence that TNF-α contributes meaningfully to successful outcomes [75,77,89,90] while the risk of TNF-induced hepatotoxicity remains unacceptably high [91]. TNF-α has also been applied topically in experimental settings to treat transitional cell carcinoma of the bladder [30,92–94].

4.2. Infectious disease

TNF blockade has provided an effective breakthrough for the treatment of patients with severe rheumatoid arthritis and psoriasis; however, TNF and interferon-γ also play a central role in the containment of intracellular pathogens such as *Mycobacterium tuberculosis*, *Listeria monocytogenes* as well as other organisms for which immune eradication depends upon robust granulomatous inflammatory responses including *Histoplama capsulatum*, *Cryptococcus neoformans,* and *Aspergillus* species. Infliximab was the first anti-TNF monoclonal antibody used for the treatment of rheumatologic disease. This agent suppressed mononuclear cells and interferon-γ production, resulting in a spike of concomitant tuberculosis infections. Greater than 40% of tuberculosis cases in infliximab treated patients occurred within 3 months of initiating therapy, and during this period the rate of infection was highest among all TNF blockers available in the US (95 cases per 100,000 person-years versus 11/100,000 patients-years with etanercept treated individuals). The median time to tuberculosis following inflixamab is 17 weeks, yet 79 weeks for patients treated with etanercept [95]. This difference in the risk of tuberculosis reflects a selective TNF blockade by etanercept whereas inflixamab leads to a multifaceted suppression of cellular immune responses [96].

5. Granulocyte colony stimulating factor (G-CSF)

5.1. Neoplasia

Granulocyte colony stimulating factor (G-CSF) is a soluble regulator of neutrophil (Fig. 3) production and is frequently used in conjunction with chemotherapeutic regimens to combat neutropenia [97,98]. In the future, an expanded use of G-CSF in cancer therapy may be evaluated upon recent speculation that neutrophilia may combat solid tumors by one of several different mechanisms. Several investigators have noted that neutrophils possess anti-tumor properties related to their capacity to generate reactive oxygen species (ROS) [99,100] as well as their ability to express TRAIL on the cell surface [101]. A more radical theory developed by non-biologists suggests that excessive neutrophilia allows neutrophils to situate themselves on the tumor periphery, impeding tumor growth by mechanical means and causing necrosis in a manner analogous to that observed following antiangiogenic therapy [102–106]. Proponents of this theory claim to have produced a durable remission in terminal hepatocellular carcinoma by treatment with G-CSF; however, no data supporting the hypothesis was provided in the case report [107]. Indeed, there

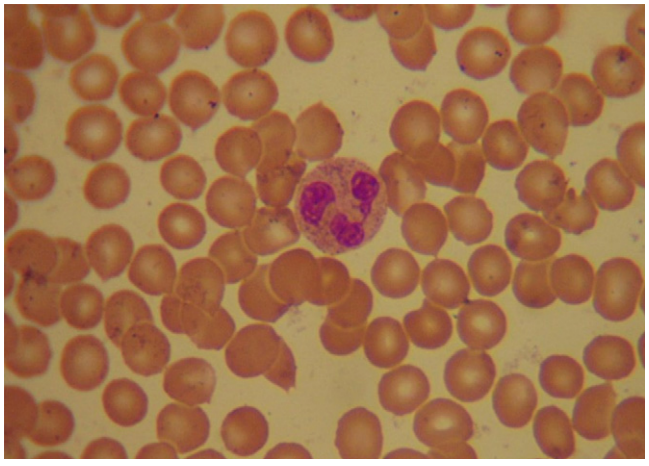

Fig. 3. Neutrophil granulocyte smear, MayGrunwal-Giemsa (40× oil immersion). Neutrophils are the principal actors of the innate immune system, responding rapidly to inflammatory stimuli in a non-specific fashion. Proliferation, phagocytic and cytotoxic activity are greatly enhanced in response to granulocyte lineage cytokines G-CSF and GM-CSF, and administration of these cytokines is a front line therapy for the prevention of febrile neutropenia that typically accompanies immunosuppressive cancer therapies. Image by Tommaso Leonardi released to the public domain through wikimedia commons.

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

exists much anecdotal evidence that G-CSF might possess a neutrophil-independent mechanism of tumor suppression; the literature contains sporadic reports of complete remissions following the administration of G-CSF for the treatment of acute myelogenous leukemia (AML) [108–111]. Recent work suggests that this effect could be mediated in part by the *HIC1* tumor suppressor gene. *HIC1* is epigenetically silenced by hypermethylation in AML, but its expression can be induced by granulocyte differentiation [112]. G-CSF has also been reported to play a role in the remission of melanotic brain metastases [113]. As with the application of other pleiotropic cytokine growth factors, enthusiasm must be tempered by G-CSF's inherent toxicity [114–116] as well as significant evidence that G-CSF can promote tumor growth and metastasis rather than cure under varying circumstances [117–120].

5.2. Infectious disease

Febrile neutropenia is the most serious complication of antineoplastic chemotherapy and risk of infection is directly related to the degree (absolute neutrophil count $<$500 cells/dl) and duration of neutropenia [121]. G-CSF is recommended to reduce the duration and severity of treatment-related neutropenia in patients with 20% or greater risk for developing fever during neutropenia [122]. Similarly, patients with a high risk of infection while undergoing chemotherapy and those with episodes of serious infections with previous chemotherapy may also benefit from the use of secondary G-CSF prophylaxis [123]. In randomized trials, G-CSF treatment-shortened duration of neutropenia was associated with a 50% reduction in the incidence of confirmed infections; 40% developed at least one episode of fever compared to 77% in patients not given growth factor. Furthermore, in these earlier trials, G-CSF was also associated with a significantly shorter duration of infection-related hospitalization, number of days of treatment with intravenous antibiotics, need for reducing the dose of chemotherapy, and delay in administration of chemotherapy [124,125]. However, when compared with broad-spectrum antibacterials and antifungals in combination, prophylaxis with G-CSF in patients with advanced breast cancer fail to show significant benefit in preventing febrile neutropenia [126].

In patients with hematologic malignancy, the use of G-CSF was also associated with a significant reduction (44%) in the incidence of severe neutropenia. The number of hospital admissions declined by 60% with a concomitant 50% reduction in the length of hospital stay and an 80% reduction in chemotherapy delay due to neutropenia [127]. These important benefits with the use of G-CSF prophylaxis are poorly correlated with improvements in overall or disease free survival in patients receiving chemotherapy, however [128]. In a recent review of 17 randomized trials enrolling 3493 patients, a significant reduction in the risk of febrile neutropenia was accompanied by reduced risk of infection-related mortality and early death in patients receiving hematopoietic growth factor [97]. Most studies show a modest improvement in the duration of neutropenia; whereas reduced severity of infection, duration of leukemia in remission, disease-free or overall survival benefit are observed inconsistently in patients treated with G-CSF prophylaxis [129].

6. Granulocyte macrophage colony stimulating factor (GM-CSF)

6.1. Neoplasia

Granulocyte/macrophage colony simulating factor (GM-CSF) is a 23 kDa cytokine that exerts a wide array of autocrine and paracrine effects upon various immune cell types. GM-CSF promotes the proliferation and differentiation of monocytes, neutrophils, lymphocytes and eosinophils [130–133]. It also enhances the differentiation of monocytes into macrophages and dendritic cells and is a potent dendritic cell chemokine [131,134,135]. Importantly, GM-CSF clearly enhances phagocytic function and ADCC (antibody-dependent cell-mediated cytotoxicity), mostly likely via the inducible upregulation of the FcαRI scavenger receptor on neutrophils and macrophages [131,136–138]. GM-CSF is also reported to upregulate MHC class II expression on cells of monocytic lineage as well as adhesion molecules such as Mo1 and LeuM5 in the granulocytic subfraction [131].

GM-CSF is typically administered to cancer patients following chemotherapy in order to manage febrile neutropenia, and with its widespread use have come occasional, anecdotal reports of GM-CSF-induced tumor regression [139–142]. Mechanistically, it has been suggested that some tumors of hematopoietic origin may be induced to proliferate following administration of GM-CSF, thereby sensitizing the tumor to subsequent or concomitant chemotherapy. Such reports notwithstanding, comprehensive reviews of the literature as well as large randomized trials have repeatedly shown that administration of GM-CSF exhibits no demonstrable effects upon the incidence of CR or upon OS [143–145], a somewhat counterintuitive result given its potent immunostimulatory properties. Conversely, when GM-CSF is administered in conjunction with antibody based therapies, specifically rituximab (anti-CD20) for the treatment of NHL (non-Hodgkins lymphoma), positive, synergistic effects have been observed in multiple trials, most likely due to the ability of GM-CSF to enhance ADCC [131,146,147].

6.2. Infectious disease

6.2.1. Prophylaxis

In contrast to its relative ineffectiveness as a cancer monotherapy, GM-CSF is a prominent cytokine used in the treatment of infectious disease. GM-CSF has been shown to reduce the duration of neutropenia, promote macrophage antimicrobial function, and prevent serious fungal and intracellular bacterial infections. A multicenter blinded trial in patients with AML randomized to receive GM-CSF versus placebo showed a significant decrease in median duration of neutropenia and life-threatening infection, including fungal infections and pneumonia; the overall survival benefit of nearly 6 months in patients given GM-CSF was encouraging [148]. Others have shown that the use of GM-CSF may also reduce the duration of hospitalization and use of intravenous antibiotic therapy. Lung cancer patients have been able to tolerate high-doses of chemotherapy when given concomitant GM-CSF; however, overall responses were not different in patients who were randomized to receive GM-CSF versus antibiotic prophylaxis alone [149]. In preterm neonates, early postnatal GM-CSF prophylaxis did not reduce sepsis or improve survival or short-term outcomes. This disappointing result was seen despite correction of neutropenia in this susceptible population [150].

6.2.2. Adjuvant therapy for infection

GM-CSF has shown promise in reducing pathogen burden and improving innate immune responses against agents of zygmomycosis [151], *Aspergillus,* and often drug resistant *Scedosporium* species [152]. Furthermore, GM-CSF in the laboratory has been shown to mitigate and ameliorate corticosteroid-induced immune dysfunction in neutralizing invading pathogenic fungi [153]. Limited clinical experience suggests that the use of GM-CSF may improve neutrophil recovery as well as responses and outcomes in

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

severely immunocompromised cancer patients with difficult-to-treat, life-threatening bacterial and fungal infections [154]. Recent data from our group also suggests a possible benefit of using GM-CSF plus interferon gamma in patients with serious opportunistic infections with or without donor granulocyte transfusions [155,156]. Adjuvant bioimmunotherapy has also been used successfully for the treatment of conventional refractory infections [157]; however, further clinical trials are needed before use of GM-CSF is recommended for the treatment of routine infections.

7. CD40 ligand (CD154)

CD40L (CD154) is a homotrimeric ligand complex found principally upon the surface of $CD4^+$ T-cells and also known to be secreted as a soluble cytokine. Its homotrimeric receptor, CD40, is expressed on the surface of a wide variety of different cell types, but most notably upon platelets, epithelial cells, professional antigen presenting cells of hematopoietic origin, and upon a wide variety of malignancies [158,159]. This interesting and diverse expression pattern provides multiple rationales for the use of CD40L in tumor therapy.

The first of these rationales relates to the physiologic role of CD40L as a proliferative and/or survival signal for non-neoplastic cell types [158,159] specifically its effects upon the maturation process of myeloid dendritic cells (Fig. 4). In their immature state, myeloid DC actively sample the surrounding antigenic milieu as part of their normal homeostatic activities. Upon detection of a danger signal such as an inflammatory cytokine or a TLR agonist, DC stabilize the most recently sampled environmental antigens on the cell surface in the context of MHC class II and migrate to the peripheral lymphoid organs to engage T-lymphocytes [160–163]. Prior to the priming of a $CD8^+$ T-cell response, DC must first become "licensed" by a specific interaction between the dendritic cell and a $CD4^+$ T-lymphocyte. Though this interaction is initially mediated in an antigen-specific fashion, licensing is ultimately promulgated via the ligation of CD40 by the homotrimeric ligand expressed on the surface of the $CD4^+$ cell [164–167]. It is at this level of regulation that the introduction of soluble CD40L or a CD40 agonist would be hypothesized to have a meaningful effect. Accordingly, there is at least one animal study which demonstrated a T-cell mediated eradication of established $CD40^-$ tumors following intratumoral administration of a CD40 agonist antibody [168]. Nevertheless, a clinical trial based upon the intratumoral administration of CD40L or other CD40 agonist has yet to be reported in the literature. The clinical exploitation of this therapeutic rationale has heretofore been limited to vaccine trials utilizing CD154-transduced cells [169].

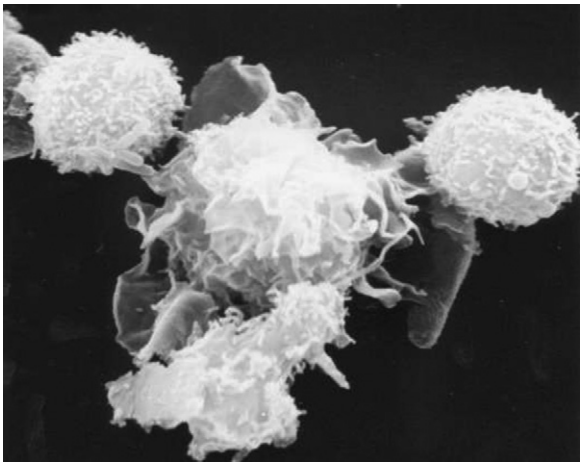

Fig. 4. Electron micrograph of lymphocytes interacting with a myeloid dendritic cell. DC, principally DC of myeloid lineage, initiate adaptive immunity by priming T- and B-cells in response to a complex and variegated array of immune stimuli. Th-1 type immune responses, i.e. the priming of cellular immunity, are characterized by DC secretion of IL-12 and downstream T-cell secretion of IL-2 and IFN-γ. Whereas the application of IL-12 and IFN-γ have been largely ineffective as stand-alone therapies, the administration of IL-2 has resulted in a modicum of therapeutic success in some settings. CD40L, both membrane-bound and soluble, is a key mediator of DC function, allowing the "licensing" of CD8 responses when delivered to DC surface CD40, typically by $CD4^+$ helper T-cells. Image derived from Tyndall et al [187] reprinted with permission.

The second rationale for the use of CD40L is based upon the physiologic cytostatic effect that it exhibits upon activated B-cells and some types of epithelial cells. This paradoxical property of CD40L has also been demonstrated experimentally for a wide variety of $CD40^+$ neoplasms including carcinomas of the bladder, ovary, cervix, lung and squamous cell epithelium [170–176]; certain types of melanoma [177]; and high-grade B-cell leukemias and lymphomas [178–182]. CD40L appears to exacerbate indolent, low-grade B-cell malignancies in accordance with its function as a stimulatory factor of resting B-cells [183,184]. In 2001, Vonderheide et al. published the results of a phase I clinical trial in which recombinant, soluble CD40L was administered subcutaneously to 32 patients with stage IV solid tumors or advanced NHL. One patient exhibited a partial response to therapy, a 50% reduction in NHL after a single course of therapy. A second patient exhibited a 50% reduction in the size of a squamous cell laryngeal tumor mass after a single course of treatment and ultimately experienced a durable, complete remission. This patient remained disease free two years after enrolling in the trial and one year after the cessation of therapy [185]. A similar trial, in which a CD40 agonist antibody is being used to target multiple myeloma, has not yet reported any results [158,186].

8. The legacy of William B. Coley

How was Dr. Coley able to produce such dramatic antitumor responses? Coley himself believed, incorrectly, that the bacterial mediators of his treatment regimen were producing a "toxic factor" that was harmful only to neoplasia but spared normal cell types. We can now surmise that Coley's Mixed Toxins, as the treatment was called at the time, delivered a "perfect storm" of TLR and other PRR agonists, marshaling the forces of both innate and adaptive immunity. Nevertheless, the exact mechanisms of action remain almost completely uncharacterized, despite the revival of the treatment in 2005 by Canadian pharmaceutical manufacturer MBVax. Given the nature of the Coley concoction, it would be reasonable to speculate that IFN-α plays a central role in tipping the balance between tolerance and immunity. Indeed, it is hard to imagine how the substantial amounts of unmethylated CpG bacterial DNA contained in the extract would not stimulate significant IFN-α production, likely via the ligation of TLR-9 in the plasmacytoid DC subset. But IFN-α is unlikely to comprise the whole story. The vast array of other bacterial components likely result in the ligation of innumerable other TLRs and PRRs including TLR-2, a PRR of lipoteichoic acid, and TLR-4, a PRR of lipopolysaccharide. The inflammatory cascade induced by such a shock would attract large numbers of neutrophils and, secondary to secretion of GM-CSF, greater numbers of dendritic cells. Neutrophil mediated damage of host tissues would cause the release of host TLR ligands like heat shock proteins (e.g. Hsp70) and hyaluronic acid, thereby generating additional inflammatory cascades resulting in further neutrophil infiltration and additional dendritic cell chemoattraction. The end result of this positive feedback loop would surely result in $CD4^+$ T-cell priming and the release of additional inflammatory mediators like IL-2 and TNF-α. Hence Coley's cure is likely to have involved the same immune mediators that comprise today's stand-alone immunotherapies; but Coley's

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

cure would have had the advantage of utilizing all these immunoadjuvants in concert and within the spatial, temporal, and chronological parameters optimally recognized by the mammalian immune system.

Why did not all of Dr. Coley's patients respond to his treatment? What accounted for his treatment failures? As most tumor immunologists recognize, immunotherapy has the potential to be a powerful weapon in the fight against cancer, yet it is not a magic bullet capable of eradicating all tumors under all circumstances. Dr. Coley's treatment regimen addressed one of the fundamental issue which allows neoplasia to develop undetected by immune surveillance: a marked dearth of danger signals. By providing such signals *in trans*, Coley fluid marshals the non-specific forces of innate immunity and allows peripheral tolerance to be broken by antigens for which high affinity T-cells, unselected by central tolerance, still remain in peripheral circulation. Yet recognition and eradication by adaptive immunity are still dependent upon optimal presentation of tumor-specific antigens by MHC class I. In some cases, HLA haplotype is suboptimal for the presentation of the critical antigens that mediate robust immune clearance. In other cases, tumors are able to escape adaptive immunity by downregulating antigen presentation or the expression of MHC class I. How such tumors generally evade detection by natural killer cells is still a matter of some conjecture, nevertheless that such evasion occurs is incontrovertible. Lastly, many tumors evolve the ability to profoundly downregulate immune function by the production of a variety of suppressive factors including TGF-β, IL-10, sCTLA-4, HLA-G as well as a multitude of other uncharacterized or poorly characterized mechanisms.

Still, many of Dr. Coley's results, particularly those achieved in the treatment of soft tissue sarcomas, remain unrivaled to this day by the modern medical establishment. Had Dr. Coley lived to his 95th birthday or even beyond, he would have enjoyed the rejuvenation of his reputation that accompanied the discovery of type I interferons in 1957 and TNF-α in 1968. The discovery and characterization of these critical immune mediators marked the beginning of an immunological renaissance which continues to this day and has assured Dr. Coley a permanent place in history.

References

[1] Burdick CG. William Bradley Coley 1862–1936. Ann Surg 1937;105(January (1)):152–5.
[2] Hoption Cann SA, van Netten JP, van NC. Dr William Coley and tumour regression: a place in history or in the future. Postgrad Med J 2003;79(December (938)):672–80.
[3] Levine DB. The hospital for the ruptured and crippled: William Bradley Coley, Third Surgeon-in-Chief 1925–1933. HSS J 2008;4(February (1)):1–9.
[4] McCarthy EF. The toxins of William B, Coley and the treatment of bone and soft-tissue sarcomas. Iowa Orthop J 2006;26:154–8.
[5] Starnes CO. Coley's toxins in perspective. Nature 1992;357(May (6373)):11–2.
[6] Gay NJ, Keith FJ. Drosophila Toll and IL-1 receptor. Nature 1991;351(May (6325)):355–6.
[7] Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA. The dorsoventral regulatory gene cassette spatzle/Toll/cactus controls the potent antifungal response in Drosophila adults. Cell 1996;86(September (6)):973–83.
[8] Medzhitov R, Preston-Hurlburt P, Janeway Jr CA. A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. Nature 1997;388(July (6640)):394–7.
[9] Poltorak A, He X, Smirnova I, et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 1998;282(December (5396)):2085–8.
[10] Colonna M, Trinchieri G, Liu YJ. Plasmacytoid dendritic cells in immunity. Nat Immunol 2004;5(December (12)):1219–26.
[11] Decker WK, Xing D, Shpall EJ. Dendritic cell immunotherapy for the treatment of neoplastic disease. Biol Blood Marrow Transpl 2006;12(February (2)):113–25.
[12] Guiducci C, Ott G, Chan JH, et al. Properties regulating the nature of the plasmacytoid dendritic cell response to Toll-like receptor 9 activation. J Exp Med 2006;203(August (8)):1999–2008.
[13] McKenna K, Beignon AS, Bhardwaj N. Plasmacytoid dendritic cells: linking innate and adaptive immunity. J Virol 2005;79(January (1)):17–27.
[14] Piccioli D, Sammicheli C, Tavarini S, et al. Human plasmacytoid dendritic cells are unresponsive to bacterial stimulation and require a novel type of cooperation with myeloid dendritic cells for maturation. Blood 2009;113(April (18)):4232–9.
[15] Schmidt J, Patrut EM, Ma J, et al. Immunomodulatory impact of interferon-alpha in combination with chemoradiation of pancreatic adenocarcinoma (CapRI). Cancer Immunol Immunother 2006;55(November (11)):1396–405.
[16] Barnes E, Salio M, Cerundolo V, et al. Impact of alpha interferon and ribavirin on the function of maturing dendritic cells. Antimicrob Agents Chemother 2004;48(September (9)):3382–9.
[17] Schmidt J, Jager D, Hoffmann K, Buchler MW, Marten A. Impact of interferon-alpha in combined chemoradioimmunotherapy for pancreatic adenocarcinoma (CapRI): first data from the immunomonitoring. J Immunother 2007;30(January (1)):108–15.
[18] van Koetsveld PM, Vitale G, de Herder WW, et al. Potent inhibitory effects of type I interferons on human adrenocortical carcinoma cell growth. J Clin Endocrinol Metab 2006;91(November (11)):4537–43.
[19] Jia SF, An T, Worth L, Kleinerman ES. Interferon-alpha enhances the sensitivity of human osteosarcoma cells to etoposide. J Interferon Cytokine Res 1999;19(June (6)):617–24.
[20] Manara MC, Serra M, Benini S, Picci P, Scotlandi K. Effectiveness of Type I interferons in the treatment of multidrug resistant osteosarcoma cells. Int J Oncol 2004;24(February (2)):365–72.
[21] Belardelli F, Ferrantini M, Proietti E, Kirkwood JM. Interferon-alpha in tumor immunity and immunotherapy. Cytokine Growth Factor Rev 2002;13(April (2)):119–34.
[22] Davis ID, Jefford M, Parente P, Cebon J. Rational approaches to human cancer immunotherapy. J Leukoc Biol 2003;73(January (1)):3–29.
[23] Pfeffer LM, Dinarello CA, Herberman RB, et al. Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. Cancer Res 1998;58(June (12)):2489–99.
[24] Petropoulos D, Worth LL, Mullen CA, Lockhart S, Choroszy M, Chan KW. Interferon-alpha after autologous stem cell transplantation in pediatric patients with advanced Hodgkin's lymphoma. Bone Marrow Transpl 2006;38(September (5)):345–9.
[25] Garbe C, Eigentler TK. Diagnosis and treatment of cutaneous melanoma: state of the art 2006. Melanoma Res 2007;17(April (2)):117–27.
[26] Riker AI, Radfar S, Liu S, Wang Y, Khong HT. Immunotherapy of melanoma: a critical review of current concepts and future strategies. Expert Opin Biol Ther 2007;7(March (3)):345–58.
[27] Kubo S, Nishiguchi S, Hirohashi K, et al. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. Ann Intern Med 2001;134(May (10)):963–7.
[28] Lo CM, Liu CL, Chan SC, et al. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. Ann Surg 2007;245(June (6)):831–42.
[29] Strander H. Interferons and osteosarcoma. Cytokine Growth Factor Rev 2007;18(October (5–6)):373–80.
[30] Perabo FG, Muller SC. Current and new strategies in immunotherapy for superficial bladder cancer. Urology 2004;64(September (3)):409–21.
[31] Poordad F, Reddy KR, Martin P. Rapid virologic response: a new milestone in the management of chronic hepatitis C. Clin Infect Dis 2008;46(January (1)):78–84.
[32] Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39(April (4)):1147–71.
[33] Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347(September (13)):975–82.
[34] Ferenci P, Fried MW, Shiffman ML, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. J Hepatol 2005;43(September (3)):425–33.
[35] Huang Y, Staschke K, De FR, Tan SL. Phosphorylation of hepatitis C virus NS5A nonstructural protein: a new paradigm for phosphorylation-dependent viral RNA replication? Virology 2007;364(July (1)):1–9.
[36] Hui CK, Leung N, Shek TW, et al. Sustained disease remission after spontaneous HBeAg seroconversion is associated with reduction in fibrosis progression in chronic hepatitis B Chinese patients. Hepatology 2007;46(September (3)):690–8.
[37] Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005; 352(June (26)):2682–95.
[38] Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351(September (12)):1206–17.
[39] Vithanomsat S, Wasi C, Harinasuta C, Thongcharoen P. The effect of interferon on flaviviruses *in vitro*: a preliminary study. Southeast Asian J Trop Med Public Health 1984;15(March (1)):27–31.
[40] Saxena SK, Mathur A, Srivastava RC. Inhibition of Japanese encephalitis virus infection by diethyldithiocarbamate is independent of its antioxidant potential. Antivir Chem Chemother 2003;14(March (2)):91–8.
[41] Solomon T, Dung NM, Wills B, et al. Interferon alfa-2a in Japanese encephalitis: a randomised double-blind placebo-controlled trial. Lancet 2003;361(March (9360)):821–6.

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

[42] Stephen EL, Sammons ML, Pannier WL, Baron S, Spertzel RO, Levy HB. Effect of a nuclease-resistant derivative of polyriboinosinic-polyribocytidylic acid complex on yellow fever in rhesus monkeys (Macaca mulatta). J Infect Dis 1977;136(July (1)):122–6.
[43] Rahal JJ, Anderson J, Rosenberg C, Reagan T, Thompson LL. Effect of interferon-alpha2b therapy on St. Louis viral meningoencephalitis: clinical and laboratory results of a pilot study. J Infect Dis 2004;190(September (6)):1084–7.
[44] Lewis M, Amsden JR. Successful treatment of West Nile virus infection after approximately 3 weeks into the disease course. Pharmacotherapy 2007;27(March (3)):455–8.
[45] Sayao AL, Suchowersky O, Al-Khathaami A, et al. Calgary experience with West Nile virus neurological syndrome during the late summer of 2003. Can J Neurol Sci 2004;31(May (2)):194–203.
[46] Samuel MA, Diamond MS. Alpha/beta interferon protects against lethal West Nile virus infection by restricting cellular tropism and enhancing neuronal survival. J Virol 2005;79(November (21)):13350–61.
[47] Herberman RB. Summary: potential of interleukin-2 for the therapy of cancer. J Biol Response Mod 1984;3(October (5)):527–32.
[48] Lissoni P, Barni S, Rovelli F, Tancini G. Lower survival in metastatic cancer patients with reduced interleukin-2 blood concentrations. Preliminary report. Oncology 1991;48(2):125–7.
[49] Grande C, Firvida JL, Navas V, Casal J. Interleukin-2 for the treatment of solid tumors other than melanoma and renal cell carcinoma. Anticancer Drugs 2006;17(January (1)):1–12.
[50] Nicolini A, Carpi A, Rossi G. Cytokines in breast cancer. Cytokine Growth Factor Rev 2006;17(October (5)):325–37.
[51] Hess V, Herrmann R, Veelken H, Schwabe M. Interleukin-2-based biochemotherapy for patients with stage IV melanoma: long-term survivors outside a clinical trial setting. Oncology 2007;73(1–2):33–40.
[52] Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2621 patients. J Clin Oncol 2007;25(December (34)):5426–34.
[53] McDermott DF. Update on the application of interleukin-2 in the treatment of renal cell carcinoma. Clin Cancer Res 2007;13(January (2 Pt 2)):716s–20s.
[54] Negrier S, Maral J, Drevon M, Vinke J, Escudier B, Philip T. Long-term follow-up of patients with metastatic renal cell carcinoma treated with intravenous recombinant interleukin-2 in Europe. Cancer J Sci Am 2000;6(February (Suppl 1)):S93–8.
[55] Petrella T, Quirt I, Verma S, Haynes AE, Charette M, Bak K. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. Cancer Treat Rev 2007;33(August (5)):484–96.
[56] Dieli F, Vermijlen D, Fulfaro F, et al. Targeting human {gamma}delta} T cells with zoledronate and interleukin-2 for immunotherapy of hormone-refractory prostate cancer. Cancer Res 2007;67(August (15)):7450–7.
[57] Jin P, Wang E, Provenzano M, Stroncek D, Marincola FM. Gene expression signatures of interleukin-2 *in vivo* and *in vitro* and their relation to anticancer therapy. Crit Rev Immunol 2007;27(5):437–48.
[58] Cangiano T, Liao J, Naitoh J, Dorey F, Figlin R, Belldegrun A. Sarcomatoid renal cell carcinoma: biologic behavior, prognosis, and response to combined surgical resection and immunotherapy. J Clin Oncol 1999;17(February (2)):523–8.
[59] Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol 2002;20(May (9)):2376–81.
[60] Upton MP, Parker RA, Youmans A, McDermott DF, Atkins MB. Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy. J Immunother 2005;28(September (5)):488–95.
[61] Keilholz U, Conradt C, Legha SS, et al. Results of interleukin-2-based treatment in advanced melanoma: a case record-based analysis of 631 patients. J Clin Oncol 1998;16(September (9)):2921–9.
[62] Phan GQ, Attia P, Steinberg SM, White DE, Rosenberg SA. Factors associated with response to high-dose interleukin-2 in patients with metastatic melanoma. J Clin Oncol 2001;19(August (15)):3477–82.
[63] Zorn E, Nelson EA, Mohseni M, et al. IL-2 regulates FOXP3 expression in human CD4+ CD25+ regulatory T cells through a STAT-dependent mechanism and induces the expansion of these cells *in vivo*. Blood 2006;108(September (5)):1571–9.
[64] Hryniewicz A, Boasso A, Edghill-Smith Y, et al. CTLA-4 blockade decreases TGF-beta, IDO, and viral RNA expression in tissues of SIVmac251-infected macaques. Blood 2006;108(December (12)):3834–42.
[65] Porter BO, Anthony KB, Shen J, et al. Inferiority of IL-2 alone versus IL-2 with HAART in maintaining CD4 T cell counts during HAART interruption: a randomized controlled trial. AIDS 2009;23(January (2)):203–12.
[66] Mier JW, Vachino G, Klempner MS, et al. Inhibition of interleukin-2-induced tumor necrosis factor release by dexamethasone: prevention of an acquired neutrophil chemotaxis defect and differential suppression of interleukin-2-associated side effects. Blood 1990;76(November (10)):1933–40.
[67] Kovacs JA, Lempicki RA, Sidorov IA, et al. Induction of prolonged survival of CD4+ T lymphocytes by intermittent IL-2 therapy in HIV-infected patients. J Clin Invest 2005;115(August (8)):2139–48.
[68] Emery S, Capra WB, Cooper DA, et al. Pooled analysis of 3 randomized, controlled trials of interleukin-2 therapy in adult human immunodeficiency virus type 1 disease. J Infect Dis 2000;182(August (2)):428–34.
[69] Sereti I, Martinez-Wilson H, Metcalf JA, et al. Long-term effects of intermittent interleukin 2 therapy in patients with HIV infection: characterization of a novel subset of CD4(+)/CD25(+) T cells. Blood 2002;100(September (6)):2159–67.
[70] Balkwill F. Tumor necrosis factor or tumor promoting factor? Cytokine Growth Factor Rev 2002;13(April (2)):135–41.
[71] Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 1975;72(September (9)):3666–70.
[72] Lejeune FJ, Lienard D, Matter M, Ruegg C. Efficiency of recombinant human TNF in human cancer therapy. Cancer Immun 2006;6:6.
[73] Lin Y, Devin A, Rodriguez Y, Liu ZG. Cleavage of the death domain kinase RIP by caspase-8 prompts TNF-induced apoptosis. Genes Dev 1999;13(October (19)):2514–26.
[74] Lienard D, Ewalenko P, Delmotte JJ, Renard N, Lejeune FJ. High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma. J Clin Oncol 1992;10(January (1)):52–60.
[75] Nakamoto T, Inagawa H, Takagi K, Soma G. A new method of antitumor therapy with a high dose of TNF perfusion for unresectable liver tumors. Anticancer Res 2000;20(November (6A)):4087–96.
[76] Rossi CR, Foletto M, Pilati P, Mocellin S, Lise M. Isolated limb perfusion in locally advanced cutaneous melanoma. Semin Oncol 2002;29(August (4)):400–9.
[77] Rothbarth J, Tollenaar RA, van dV. Recent trends and future perspectives in isolated hepatic perfusion in the treatment of liver tumors. Expert Rev Anticancer Ther 2006;6(April (4)):553–65.
[78] Foa R, Massaia M, Cardona S, et al. Production of tumor necrosis factor-alpha by B-cell chronic lymphocytic leukemia cells: a possible regulatory role of TNF in the progression of the disease. Blood 1990;76(July (2)):393–400.
[79] Herrmann F, Helfrich SG, Lindemann A, Schleiermacher E, Huber C, Mertelsmann R. Elevated circulating levels of tumor necrosis factor predict unresponsiveness to treatment with interferon alfa-2b in chronic myelogenous leukemia. J Clin Oncol 1992;10(April (4)):631–4.
[80] Vinante F, Rigo A, Tecchio C, et al. Serum levels of p55 and p75 soluble TNF receptors in adult acute leukaemia at diagnosis: correlation with clinical and biological features and outcome. Br J Haematol 1998;102(September (4)):1025–34.
[81] Warzocha K, Salles G, Bienvenu J, et al. Tumor necrosis factor ligand-receptor system can predict treatment outcome in lymphoma patients. J Clin Oncol 1997;15(February (2)):499–508.
[82] Hsu H, Shu HB, Pan MG, Goeddel DV. TRADD-TRAF2 and TRADD-FADD interactions define two distinct TNF receptor 1 signal transduction pathways. Cell 1996;84(January (2)):299–308.
[83] Song HY, Regnier CH, Kirschning CJ, Goeddel DV, Rothe M. Tumor necrosis factor (TNF)-mediated kinase cascades: bifurcation of nuclear factor-kappaB and c-jun N-terminal kinase (JNK/SAPK) pathways at TNF receptor-associated factor 2. Proc Natl Acad Sci USA 1997;94(September (18)):9792–6.
[84] Warzocha K, Ribeiro P, Bienvenu J, et al. Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin's lymphoma outcome. Blood 1998;91(May (10)):3574–81.
[85] Davies FE, Rollinson SJ, Rawstron AC, et al. High-producer haplotypes of tumor necrosis factor alpha and lymphotoxin alpha are associated with an increased risk of myeloma and have an improved progression-free survival after treatment. J Clin Oncol 2000;18(August (15)):2843–51.
[86] Oh BR, Sasaki M, Perinchery G, et al. Frequent genotype changes at 308, and 488 regions of the tumor necrosis factor-alpha (TNF-alpha) gene in patients with prostate cancer. J Urol 2000;163(May (5)):1584–7.
[87] Hajeer AH, Lear JT, Ollier WE, et al. Preliminary evidence of an association of tumour necrosis factor microsatellites with increased risk of multiple basal cell carcinomas. Br J Dermatol 2000;142(March (3)):441–5.
[88] Ghaderi M, Nikitina L, Peacock CS, et al. Tumor necrosis factor a-11 and DR15-DQ6 (B*0602) haplotype increase the risk for cervical intraepithelial neoplasia in human papillomavirus 16 seropositive women in Northern Sweden. Cancer Epidemiol Biomarkers Prev 2000;9(October (10)):1067–70.
[89] Bartlett DL, Libutti SK, Figg WD, Fraker DL, Alexander HR. Isolated hepatic perfusion for unresectable hepatic metastases from colorectal cancer. Surgery 2001;129(February (2)):176–87.
[90] Rothbarth J, Pijl ME, Vahrmeijer AL, et al. Isolated hepatic perfusion with high-dose melphalan for the treatment of colorectal metastasis confined to the liver. Br J Surg 2003;90(November (11)):1391–7.
[91] De Vries MR, Borel RI, van d V, et al. Isolated hepatic perfusion with tumor necrosis factor alpha and melphalan: experimental studies in pigs and phase I data from humans. Recent Results Cancer Res 1998;147:107–19.
[92] Glazier DB, Bahnson RR, McLeod DG, von Roemeling RW, Messing EM, Ernstoff MS. Intravesical recombinant tumor necrosis factor in the treatment of superficial bladder cancer: an Eastern Cooperative Oncology Group study. J Urol 1995;154(July (1)):66–8.
[93] Serretta V, Piazza B, Pavone C, Piazza S, Pavone-Macaluso M. Is there a role for recombinant tumor necrosis factor alpha in the intravesical treatment of superficial bladder tumors?—a phase II study. Int J Urol 1995;2(May (2)):100–3.
[94] Sternberg CN, Arena MG, Pansadoro V, et al. Recombinant tumor necrosis factor for superficial bladder tumors. Ann Oncol 1992;3(November (9)):741–5.
[95] Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006;43(September (6)):717–22.

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

[96] Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. Lancet Infect Dis 2008;8(October (10)):601–11.
[97] Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007;25(July (21)):3158–67.
[98] Lopez-Lazaro M. Granulocyte colony-stimulating factor (G-CSF): a novel anticancer therapy based on the "universal dynamics of tumor growth"? Exp Oncol 2006;28(September (3)):249–51.
[99] Dissemond J, Weimann TK, Schneider LA, et al. Activated neutrophils exert antitumor activity against human melanoma cells: reactive oxygen species-induced mechanisms and their modulation by granulocyte-macrophage-colony-stimulating factor. J Invest Dermatol 2003;121(October (4)):936–8.
[100] Zivkovic M, Poljak-Blazi M, Egger G, Sunjic SB, Schaur RJ, Zarkovic N. Oxidative burst and anticancer activities of rat neutrophils. Biofactors 2005;24(1–4):305–12.
[101] Koga Y, Matsuzaki A, Suminoe A, Hattori H, Hara T. Neutrophil-derived TNF-related apoptosis-inducing ligand (TRAIL): a novel mechanism of antitumor effect by neutrophils. Cancer Res 2004;64(February (3)):1037–43.
[102] Bosch X. Physicists describe new way to study tumours. Lancet 1999; 353(January (9146)):44.
[103] Bru A, Pastor JM, Fernaud I, Bru I, Melle S, Berenguer C. Super-rough dynamics on tumor growth. Phys Rev Lett 1998;81(November (18)):4008–11.
[104] Bru A, Albertos S, Subiza JL, Garcia-Asenjo JL, Bru I. The universal dynamics of tumor growth. Biophys J 2003;85(November (5)):2948–61.
[105] Bru A, Albertos S, Garcia-Asenjo JL, Bru I. Pinning of tumoral growth by enhancement of the immune response. Phys Rev Lett 2004;92(June (23)).
[106] Burton A. Fractal tumour contours question therapy strategies. Lancet Oncol 2001;2(May (5)):253.
[107] Bru A, Albertos S, Garcia-Hoz F, Bru I. Regulation of neutrophilia by granulocyte colony-stimulating factor: a new cancer therapy that reversed a case of terminal hepatocellular carcinoma. J Clin Res 2005;8:9–13 [Ref Type: Generic].
[108] Benz R, Goede JS, Parlier V, Muhlematter D, Jotterand M, Fehr J. G-CSF-induced remission in two cases of acute myeloid leukemia. Leuk Res 2008;32(July (7)):1148–52.
[109] Piccaluga PP, Martinelli G, Malagola M, et al. Complete remission in acute myeloid leukemia with granulocyte-colony stimulating factor without chemotherapy. Report of cytogenetic remission of a t(9;11)(p22q23) positive AML patient and review of literature. Haematologica 2003;88(August (8)):ECR28.
[110] Toki H, Matsutomo S, Okabe K, Shimokawa T. Remission in hypoplastic acute myeloid leukaemia induced by granulocyte colony-stimulating factor. Lancet 1989;1(June (8651)):1389–90.
[111] Xavier L, Cunha M, Goncalves C, et al. Hematological remission and long term hematological control of acute myeloblastic leukemia induced and maintained by granulocyte-colony stimulating factor (G-CSF) therapy. Leuk Lymphoma 2003;44(December (12)):2137–42.
[112] Britschgi C, Jenal M, Rizzi M, et al. HIC1 tumour suppressor gene is suppressed in acute myeloid leukaemia and induced during granulocytic differentiation. Br J Haematol 2008;141(April (2)):179–87.
[113] Bottoni U, Bonaccorsi P, Devirgiliis V, et al. Complete remission of brain metastases in three patients with stage IV melanoma treated with BOLD and G-CSF. Jpn J Clin Oncol 2005;35(September (9)):507–13.
[114] Adler BK, Salzman DE, Carabasi MH, Vaughan WP, Reddy VV, Prchal JT. Fatal sickle cell crisis after granulocyte colony-stimulating factor administration. Blood 2001;97(May (10)):3313–4.
[115] Gertz MA, Lacy MQ, Bjornsson J, Litzow MR. Fatal pulmonary toxicity related to the administration of granulocyte colony-stimulating factor in amyloidosis: a report and review of growth factor-induced pulmonary toxicity. J Hematother Stem Cell Res 2000;9(October (5)):635–43.
[116] O'Malley DP, Whalen M, Banks PM. Spontaneous splenic rupture with fatal outcome following G-CSF administration for myelodysplastic syndrome. Am J Hematol 2003;73(August (4)):294–5.
[117] Mueller MM, Herold-Mende CC, Riede D, Lange M, Steiner HH, Fusenig NE. Autocrine growth regulation by granulocyte colony-stimulating factor and granulocyte macrophage colony-stimulating factor in human gliomas with tumor progression. Am J Pathol 1999;155(November (5)):1557–67.
[118] Natori T, Sata M, Washida M, Hirata Y, Nagai R, Makuuchi M. G-CSF stimulates angiogenesis and promotes tumor growth: potential contribution of bone marrow-derived endothelial progenitor cells. Biochem Biophys Res Commun 2002;297(October (4)):1058–61.
[119] Segawa K, Ueno Y, Kataoka T. *In vivo* tumor growth enhancement by granulocyte colony-stimulating factor. Jpn J Cancer Res 1991;82(April (4)):440–7.
[120] Yokoyama T, Hyodo M, Hosoya Y, et al. Aggressive G-CSF-producing gastric cancer complicated by lung and brain abscesses, mimicking metastases. Gastric Cancer 2005;8(3):198–201.
[121] Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med 1966;64(February (2)):328–40.
[122] Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24(July (19)):3187–205.
[123] Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2006;42(October (15)):2433–53.
[124] Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325(July (3)):164–70.
[125] Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer 1993;29A(3):319–24.
[126] Schroder CP, de Vries EG, Mulder NH, et al. Prevention of febrile leucopenia after chemotherapy in high-risk breast cancer patients: no significant difference between granulocyte-colony stimulating growth factor or ciprofloxacin plus amphotericin B. J Antimicrob Chemother 1999;43(May (5)):741–3.
[127] Hackshaw A, Sweetenham J, Knight A. Are prophylactic haematopoietic growth factors of value in the management of patients with aggressive non-Hodgkin's lymphoma? Br J Cancer 2004;90(April (7)):1302–5.
[128] Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev 2008;4:CD003189.
[129] Frankfurt O, Tallman MS. Growth factors in leukemia. J Natl Compr Canc Netw 2007;5(February (2)):203–15.
[130] Robin G, Markovich S, Athamna A, Keisari Y. Human recombinant granulocyte-macrophage colony-stimulating factor augments viability and cytotoxic activities of human monocyte-derived macrophages in long-term cultures. Lymphokine Cytokine Res 1991;10(August (4)):257–63.
[131] Schuster SJ, Venugopal P, Kern JC, McLaughlin P. GM-CSF plus rituximab immunotherapy: translation of biologic mechanisms into therapy for indolent B-cell lymphomas. Leuk Lymphoma 2008;49(September (9)):1681–92.
[132] Steis RG, VanderMolen LA, Longo DL, et al. Recombinant human granulocyte-macrophage colony-stimulating factor in patients with advanced malignancy: a phase Ib trial. J Natl Cancer Inst 1990;82(April (8)):697–703.
[133] Young DA, Lowe LD, Clark SC. Comparison of the effects of IL-3, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor in supporting monocyte differentiation in culture. Analysis of macrophage antibody-dependent cellular cytotoxicity. J Immunol 1990;145(July (2)):607–15.
[134] Gazitt Y, Shaughnessy P, Devore P. Mobilization of dendritic cells and NK cells in non-Hodgkin's lymphoma patients mobilized with different growth factors. J Hematother Stem Cell Res 2001;10(February (1)):177–86.
[135] Shaughnessy PJ, Bachier C, Lemaistre CF, Akay C, Pollock BH, Gazitt Y. Granulocyte colony-stimulating factor mobilizes more dendritic cell subsets than granulocyte-macrophage colony-stimulating factor with no polarization of dendritic cell subsets in normal donors. Stem Cells 2006;24(July (7)):1789–97.
[136] Charak BS, Agah R, Mazumder A. Granulocyte-macrophage colony-stimulating factor-induced antibody-dependent cellular cytotoxicity in bone marrow macrophages: application in bone marrow transplantation. Blood 1993; 81(June (12)):3474–9.
[137] Connor RI, Shen L, Fanger MW. Evaluation of the antibody-dependent cytotoxic capabilities of individual human monocytes. Role of Fc gamma RI and Fc gamma RII and the effects of cytokines at the single cell level. J Immunol 1990;145(September (5)):1483–9.
[138] Keler T, Wallace PK, Vitale LA, et al. Differential effect of cytokine treatment on Fc alpha receptor I- and Fc gamma receptor I-mediated tumor cytotoxicity by monocyte-derived macrophages. J Immunol 2000;164(June (11)):5746–52.
[139] Cochran AJ, Huang RR, Lee J, Itakura E, Leong SP, Essner R. Tumour-induced immune modulation of sentinel lymph nodes. Nat Rev Immunol 2006;6(September (9)):659–70.
[140] Pinedo HM, Buter J, Luykx-de Bakker SA, et al. Extended neoadjuvant chemotherapy in locally advanced breast cancer combined with GM-CSF: effect on tumour-draining lymph node dendritic cells. Eur J Cancer 2003;39(May (8)):1061–7.
[141] Si Z, Hersey P, Coates AS. Clinical responses and lymphoid infiltrates in metastatic melanoma following treatment with intralesional GM-CSF. Melanoma Res 1996;6(June (3)):247–55.
[142] Vaquerano JE, Cadbury P, Treseler P, Sagebiel R, Leong SP. Regression of intransit melanoma of the scalp with intralesional recombinant human granulocyte-macrophage colony-stimulating factor. Arch Dermatol 1999;135(October (10)):1276–7.
[143] Becker PS. Growth factor priming in therapy of acute myelogenous leukemia. Curr Hematol Rep 2004;3(November (6)):413–8.
[144] Bohlius J, Reiser M, Schwarzer G, Engert A. Impact of granulocyte colony-stimulating factor (CSF) and granulocyte-macrophage CSF in patients with malignant lymphoma: a systematic review. Br J Haematol 2003;122(August (3)):413–23.
[145] Rini BI, Stadler WM, Spielberger RT, Ratain MJ, Vogelzang NJ. Granulocyte-macrophage—colony stimulating factor in metastatic renal cell carcinoma: a phase II trial. Cancer 1998;82(April (7)):1352–8.
[146] Cartron G, Zhao-Yang L, Baudard M, et al. Granulocyte-macrophage colony-stimulating factor potentiates rituximab in patients with relapsed follicular lymphoma: results of a phase II study. J Clin Oncol 2008;26(June (16)):2725–31.
[147] Olivieri A, Lucesole M, Capelli D, et al. A new schedule of CHOP/rituximab plus granulocyte-macrophage colony-stimulating factor is an effective rescue for patients with aggressive lymphoma failing autologous stem cell transplantation. Biol Blood Marrow Transpl 2005;11(August (8)):627–36.

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004

[148] Rowe JM, Andersen JW, Mazza JJ, et al. A randomized placebo-controlled phase III study of granulocyte-macrophage colony-stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia: a study of the Eastern Cooperative Oncology Group (E1490). Blood 1995;86(July (2)):457–62.
[149] Sculier JP, Paesmans M, Lecomte J, et al. A three-arm phase III randomised trial assessing, in patients with extensive-disease small-cell lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. Br J Cancer 2001;85(November (10)):1444–51.
[150] Carr R, Brocklehurst P, Dore CJ, Modi N. Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised controlled trial. Lancet 2009;373(January (9659)):226–33.
[151] Gil-Lamaignere C, Simitsopoulou M, Roilides E, Maloukou A, Winn RM, Walsh TJ. Interferon-gamma and granulocyte-macrophage colony-stimulating factor augment the activity of polymorphonuclear leukocytes against medically important zygomycetes. J Infect Dis 2005;191(April (7)):1180–7.
[152] Gil-Lamaignere C, Winn RM, Simitsopoulou M, Maloukou A, Walsh TJ, Roilides E. Inteferon gamma and granulocyte-macrophage colony-stimulating factor augment the antifungal activity of human polymorphonuclear leukocytes against Scedosporium spp.: comparison with Aspergillus spp.. Med Mycol 2005;43(May (3)):253–60.
[153] Roilides E, Blake C, Holmes A, Pizzo PA, Walsh TJ. Granulocyte-macrophage colony-stimulating factor and interferon-gamma prevent dexamethasone-induced immunosuppression of antifungal monocyte activity against Aspergillus fumigatus hyphae. J Med Vet Mycol 1996;34(January (1)):63–9.
[154] Bodey GP, Anaissie E, Gutterman J, Vadhan-Raj S. Role of granulocyte-macrophage colony-stimulating factor as adjuvant treatment in neutropenic patients with bacterial and fungal infection. Eur J Clin Microbiol Infect Dis 1994;13(Suppl 2):S18–22.
[155] Safdar A, Rodriguez G, Rolston KV, et al. High-dose caspofungin combination antifungal therapy in patients with hematologic malignancies and hematopoietic stem cell transplantation. Bone Marrow Transpl 2007;39(February (3)):157–64.
[156] Safdar A, Rodriguez GH, Lichtiger B, et al. Recombinant interferon gamma1b immune enhancement in 20 patients with hematologic malignancies and systemic opportunistic infections treated with donor granulocyte transfusions. Cancer 2006;106(June (12)):2664–71.
[157] Lewis R, Hogan H, Howell A, Safdar A. Progressive fusariosis: unpredictable posaconazole bioavailability, and feasibility of recombinant interferon-gamma plus granulocyte macrophage-colony stimulating factor for refractory disseminated infection. Leuk Lymphoma 2008;49(January (1)):163–5.
[158] Loskog A, Totterman TH. CD40L—a multipotent molecule for tumor therapy. Endocr Metab Immune Disord Drug Targets 2007;7(March (1)):23–8.
[159] Tong AW, Stone MJ. Prospects for CD40-directed experimental therapy of human cancer. Cancer Gene Ther 2003;10(January (1)):1–13.
[160] Banchereau J, Paczesny S, Blanco P, et al. Dendritic cells: controllers of the immune system and a new promise for immunotherapy. Ann NY Acad Sci 2003;987(April):180–7.
[161] Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. Nat Rev Immunol 2005;5(April (4)):296–306.
[162] Hartgers FC, Figdor CG, Adema GJ. Towards a molecular understanding of dendritic cell immunobiology. Immunol Today 2000;21(November (11)):542–5.
[163] Steinman RM, Hawiger D, Nussenzweig MC. Tolerogenic dendritic cells. Annu Rev Immunol 2003;21:685–711.
[164] Behrens G, Li M, Smith CM, et al. Helper T cells, dendritic cells and CTL immunity. Immunol Cell Biol 2004;82(February (1)):84–90.
[165] Bennett SR, Carbone FR, Karamalis F, Miller JF, Heath WR. Induction of a CD8+ cytotoxic T lymphocyte response by cross-priming requires cognate CD4+ T cell help. J Exp Med 1997;186(July (1)):65–70.
[166] Bennett SR, Carbone FR, Karamalis F, Flavell RA, Miller JF, Heath WR. Help for cytotoxic-T-cell responses is mediated by CD40 signalling. Nature 1998;393(June (6684)):478–80.
[167] Schoenberger SP, Toes RE, van d V, Offringa R, Melief CJ. T-cell help for cytotoxic T lymphocytes is mediated by CD40-CD40L interactions. Nature 1998;393(June (6684)):480–3.
[168] van Mierlo GJ, den Boer AT, Medema JP, et al. CD40 stimulation leads to effective therapy of CD40(−) tumors through induction of strong systemic cytotoxic T lymphocyte immunity. Proc Natl Acad Sci USA 2002;99(April (8)):5561–6.
[169] Wierda WG, Cantwell MJ, Woods SJ, Rassenti LZ, Prussak CE, Kipps TJ. CD40-ligand (CD154) gene therapy for chronic lymphocytic leukemia. Blood 2000;96(November (9)):2917–24.
[170] Eliopoulos AG, Davies C, Knox PG, et al. CD40 induces apoptosis in carcinoma cells through activation of cytotoxic ligands of the tumor necrosis factor superfamily. Mol Cell Biol 2000;20(August (15)):5503–15.
[171] Gallagher NJ, Eliopoulos AG, Agathangelo A, Oates J, Crocker J, Young LS. CD40 activation in epithelial ovarian carcinoma cells modulates growth, apoptosis, and cytokine secretion. Mol Pathol 2002;55(April (2)):110–20.
[172] Ghamande S, Hylander BL, Oflazoglu E, Lele S, Fanslow W, Repasky EA. Recombinant CD40 ligand therapy has significant antitumor effects on CD40-positive ovarian tumor xenografts grown in SCID mice and demonstrates an augmented effect with cisplatin. Cancer Res 2001;61(October (20)):7556–62.
[173] Hirano A, Longo DL, Taub DD, et al. Inhibition of human breast carcinoma growth by a soluble recombinant human CD40 ligand. Blood 1999;93(May (9)):2999–3007.
[174] Posner MR, Cavacini LA, Upton MP, Tillman KC, Gornstein ER, Norris Jr CM. Surface membrane-expressed CD40 is present on tumor cells from squamous cell cancer of the head and neck *in vitro* and *in vivo* and regulates cell growth in tumor cell lines. Clin Cancer Res 1999;5(August (8)):2261–70.
[175] Tong AW, Papayoti MH, Netto G, et al. Growth-inhibitory effects of CD40 ligand (CD154) and its endogenous expression in human breast cancer. Clin Cancer Res 2001;7(March (3)):691–703.
[176] Wingett DG, Vestal RE, Forcier K, Hadjokas N, Nielson CP. CD40 is functionally expressed on human breast carcinomas: variable inducibility by cytokines and enhancement of Fas-mediated apoptosis. Breast Cancer Res Treat 1998;50(July (1)):27–36.
[177] Von LA, van der BP, Pahl HL, Aruffo A, Simon JC. Stimulation of CD40 on immunogenic human malignant melanomas augments their cytotoxic T lymphocyte-mediated lysis and induces apoptosis. Cancer Res 1999;59(March (6)):1287–94.
[178] Funakoshi S, Longo DL, Beckwith M, et al. Inhibition of human B-cell lymphoma growth by CD40 stimulation. Blood 1994;83(May (10)):2787–94.
[179] Hess S, Engelmann H. A novel function of CD40: induction of cell death in transformed cells. J Exp Med 1996;183(January (1)):159–67.
[180] Marches R, Racila E, Tucker TF, et al. Tumour dormancy and cell signalling—III: role of hypercrosslinking of IgM and CD40 on the induction of cell cycle arrest and apoptosis in B lymphoma cells. Ther Immunol 1995;2(June (3)):125–36.
[181] Schultze JL, Cardoso AA, Freeman GJ, et al. Follicular lymphomas can be induced to present alloantigen efficiently: a conceptual model to improve their tumor immunogenicity.. Proc Natl Acad Sci USA 1995;92(August (18)):8200–4.
[182] Schultze JL, Michalak S, Seamon MJ, et al. CD40-activated human B cells: An alternative source of highly efficient antigen presenting cells to generate autologous antigen-specific T cells for adoptive immunotherapy. J Clin Investig 1997;100(December (11)):2757–65.
[183] Johnson PW, Watt SM, Betts DR, et al. Isolated follicular lymphoma cells are resistant to apoptosis and can be grown *in vitro* in the CD40/stromal cell system. Blood 1993;82(September (6)):1848–57.
[184] Kluin-Nelemans HC, Beverstock GC, Mollevanger P, et al. Proliferation and cytogenetic analysis of hairy cell leukemia upon stimulation via the CD40 antigen. Blood 1994;84(November (9)):3134–41.
[185] Vonderheide RH, Dutcher JP, Anderson JE, et al. Phase I study of recombinant human CD40 ligand in cancer patients. J Clin Oncol 2001;19(July (13)):3280–7.
[186] Law CL, Gordon KA, Collier J, et al. Preclinical antilymphoma activity of a humanized anti-CD40 monoclonal antibody. SGN-40. Cancer Res 2005;65(September (18)):8331–8.
[187] de Vere Tyndall A, Knight SC, Edwards AJ, Clarke JB. Veiled (dendritic) cells in synovial fluid. Lancet 1983;1(8322):472–3.

William K. Decker is a Senior Research Scientist in the Department of Stem Cell Transplantation and Cellular Therapy at the University of Texas MD Anderson Cancer Center in Houston, Texas. He received an undergraduate degree in Biology from Tufts University in Boston, Massachusetts and a PhD in Molecular and Human Genetics from Baylor College of Medicine in Houston. After further postdoctoral study at Baylor and a brief stint in industry, he returned to academia and has been working at M.D. Anderson since 2004. His research has focused upon dendritic cell regulation of the Th-1 immune response, and his work has demonstrated that dendritic cells possess the ability to compare MHC class I and class II antigenic sequences via a novel regulatory complex involving tRNA molecules and their associated tRNA synthetases. He has also focused upon the soluble signaling mediators used by these so-called "Th-1" dendritic cells to mediate cellular immune responses.

Amar Safdar is an associate professor of Medicine and Director of the Immunology Research Program in the Department of Infectious Diseases, Infection Control, and Employee Health at the University of Texas MD Anderson Cancer Center in Houston, Texas. He received his MD degree from Dow Medical College in Karachi, Pakistan and completed his Internal Medicine training at New York Medical College and the New York Downtown Hospital, Cornell University Medical Center, New York, NY. He then received both clinical and research training in Infectious Diseases as a Fellow at the Memorial Sloan Kettering Cancer Center and Weill Medical College of Cornell University, New York, NY. His clinical research has focused upon vaccine preventable illnesses in immunocompromised cancer patients as well as the role that small molecule cytokine adjuvants may play in the perpetuation of adaptive immune responses. He is a Fellow of both the American College of Physicians and the Infectious Disease Society of America.

Please cite this article in press as: Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. Cytokine Growth Factor Rev (2009), doi:10.1016/j.cytogfr.2009.07.004