Published in final edited form as:
*Future Oncol*. 2009 April ; 5(3): 379–390. doi:10.2217/FON.09.6.

# Dendritic cell-based therapeutic cancer vaccines: what we have and what we need

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## Abstract

Therapeutic cancer vaccines rely on the immune system to eliminate tumor cells. In contrast to chemotherapy or passive (adoptive) immunotherapies with antibodies or *ex vivo*-expanded T cells, therapeutic vaccines do not have a direct anti-tumor activity, but aim to reset patients' immune systems to achieve this goal. Recent identification of effective ways of enhancing immunogenicity of tumor-associated antigens, including the use of dendritic cells and other potent vectors of cancer vaccines, provide effective tools to induce high numbers of circulating tumor-specific T cells. However, despite indications that some of the new cancer vaccines may be able to delay tumor recurrence or prolong the survival of cancer patients, their ability to induce cancer regression remains low. Recent reports help to identify and prospectively remove the remaining obstacles towards effective therapeutic vaccination of cancer patients. They indicate that the successful induction of tumor-specific T cells by cancer vaccines is not necessarily associated with the induction of functional cytotoxic T lymphocytes, and that current cancer vaccines may promote undesirable expansion of Treg cells. Furthermore, recent studies also identify the tools to counteract such phenomena, in order to assure the desirable induction of Th1-cytotoxic T lymphocytes, NK-mediated type-1 immunity and appropriate homing of effector cells to tumors.

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**Keywords**

breast cancer; cancer; clinical trials; colorectal cancer; CTL; dendritic cells; immunotherapy; melanoma; NK cells; ovarian cancer; prostate cancer; signal 3; signal 4; Th1; vaccines

## Immune system as a means to fight cancer

Despite an overall progress in cancer therapy, substantial groups of cancer patients lack effective treatment options, and even larger groups lack curative therapies. Combined use of surgery, radio- and chemo-therapy is often highly active in eliminating the major tumor mass, but is less effective in eliminating residual cancer cells and in preventing disease recurrence. This particular deficit of the current treatments provides the rationale for the utilization of the immune system, specialized in eliminating such 'rare events' in our bodies as invading bacteria or the individual host's cells hijacked by viruses, in order to identify and destroy cancer cells.

The goal of therapeutic cancer vaccines (or active immunotherapy) is to instruct the patient's own immune system to kill cancer cells. Compared with chemotherapy, the theoretical advantages of such an approach are its higher ability to selectively eliminate the transformed cells, resulting in low toxicity, and the ability to recognize and attack multiple target molecules, even the newly arising antigens on rapidly mutating tumor cells (due to the phenomenon of epitope spreading).

The use of the immune system to fight tumors was proposed in the late 19th century by William Coley at the Memorial Sloan–Kettering Cancer Center in New York (NY, USA), who noted sporadic cases of spontaneous regression of advanced cancer attributable to infections (reviewed in [1]). Throughout the following century, repeated attempts to utilize the immune system to fight cancer in a systematic approach were met with limited success, prompting a century-long debate on the relevance of the immune system to cancer surveillance and therapy [2,3].

At the beginning of the 21st century, it has become evident that the immune system can be utilized to fight cancer, but it is also clear that the spontaneously arising responses against cancer are relatively ineffective [3], and that the effectiveness of currently available immunotherapies for cancer still trails the effectiveness of vaccination against infective agents [4–9].

The reasons for the above gap include the use of cancer vaccines in therapeutic settings (rather than as a preventive mode, relevant to antimicrobial vaccines), relative antigenic similarity of tumor cells to healthy cells from the same tissues (with only a low percentage of cell-associated antigenic epitopes being overexpressed on tumor cells and an even smaller percentage being unique to the tumor), and paucity of tissue damage and distress signals at early phases of tumor growth. Additionally, the high adaptability of tumors, such as their ability to discard highly immunogenic antigens and key molecules needed for antigen recognition and to produce multiple immunosuppressive factors [10,11], allows evasion from the immune response.

While the high number of active mechanisms used by tumors to evade the immune system and to induce immune dysfunction predict the difficulties in the development of effective cancer immunotherapies, it also points to the active role of the immune system in selecting the resistant tumor cell variants, and thus to the ability of immune cells to eliminate tumor cells. In accordance with this notion, even if the immune system often fails to prevent the initial tumor growth, different forms of immunotherapy have been shown to reduce tumor incidence, promote tumor regression and prolong the survival of experimental animals and patients with cancer, suggesting that a proper method of activating the immune system can be used to

eliminate or control the residual disease and possibly to treat, or even cure, patients with macroscopic lesions.

## Vaccines versus adoptive immunotherapies of cancer

Available immunotherapies of cancer can be roughly divided into adoptive immunotherapies that rely on administration of *ex vivo* prepared immune cells or antibodies, and active immunotherapies or vaccines **(**Table 1).

In contrast to passive (adoptive) immunotherapies that aim to directly destroy tumor cells using preformed immune effector molecules or cells, cancer vaccines aim to induce endogenous immune surveillance by exposing the patients' immune system to tumor-relevant antigens delivered in an immunogenic form in the context of adjuvants, such as pathogen-derived pathogen-associated molecular patterns, proinflammatory cytokines or activated antigen-presenting cells (APCs). As expected, since the immune system specializes in eliminating 'rare events' while sparing the overall tissue, current cancer vaccines trail adoptive immunotherapies in inducing regression of bulky tumors [8], but show promise in inducing disease stabilization and prolonging patients' survival [9,12–15].

While adoptive immunotherapies, particularly those involving preformed antibodies (that can be mass-produced and easily distributed in a lyophilized form), are highly feasible, their limitations include the need for their continued/repetitive administration in order to sustain the therapeutic effects and their relatively narrow specificity limited to individual tumor-related antigens. For these reasons, they are both relatively expensive and can be applied only to the patients with tumors that display a particular antigenic composition, limiting the scope of their applicability.

The intrinsic advantage of vaccines is the feasibility of targeting multiple antigenic targets, or even the whole antigenic repertoire of tumor cells, by including in the vaccines multiple tumor-related epitopes or whole tumor cells as sources of cancer-related antigens. In addition, recent observations of the induction of responses to tumor-relevant epitopes that are not included in the original vaccine, particularly relevant to dendritic cell (DC)-based vaccines [16,17], further support the ability of vaccines to target a wide population of tumor cells, despite the heterogeneity and adaptability of tumor cells within the individual cancer patient. In addition to the longevity of the vaccination-induced T-cell responses, the above findings indicate that vaccines may offer an advantage to adoptive immunotherapies with regard to inducing responses to the most relevant antigens in the individual patients, and limit the ability of tumors to escape immune surveillance by adapting their antigenic profiles.

Of importance for the feasibility of active immunotherapies for use in patients with reduced performance status, and older patients who are particularly prevalent in oncology clinics, is the fact that previous cancer vaccines have all been very well tolerated. This is in contrast to adoptive immunotherapies with tumor-infiltrating lymphocytes, which are associated with a high incidence of adverse side effects (mostly organ-specific autoimmune phenomena).

## 'Off-the-shelf' vaccines versus customized cell-based active immunotherapies

Two general approaches have been applied to the development of new immunotherapeutic interventions. The 'off-the-shelf' approach utilizes standardized vaccines, which are antigenic preparations capable of activating endogenous APCs, such as DCs, then being presented by DCs to tumor-specific T cells, and ultimately inducing T cell activation. The advantages of standardized vaccines (usually recombinant proteins, recombinant viruses or synthetic peptides

containing one or several tumor-relevant epitopes) are that they can be mass-produced, and are easily stored and distributed. However, their limitation is the predetermined, usually limited, antigenic repertoire (making them applicable to only limited subsets of patients whose tumors express the particular tumor-related antigens), and in the case of the peptide-based vaccines, their applicability is often limited to an even narrower subset of patients who express a particular HLA type (usually HLA-A2 in the USA and Europe). Their applicability to the treatment of cancer is still limited by the current lack of universally over-expressed tumor rejection antigen(s) on many types of cancer. In addition, the limitation of both protein-based and peptide-based vaccines is their poor ability to include balanced activation of the $CD4^+$ and $CD8^+$ subsets of T lymphocytes, which is thought to be essential for the effectiveness of anti-tumor immunity [6,18–22]. The existing peptide-based vaccines preferentially induce (HLA-A2-restricted) $CD8^+$ T-cell responses (able to directly kill tumor cells, but with limited lifespan in the absence of $CD4^+$ T-cell help), while protein-based vaccines effectively induce MHC II-restricted $CD4^+$ T-cell responses, but are less effective in inducing $CD8^+$ cytotoxic T lymphocytes (CTLs) [6,18–22]. Furthermore, the ability of such vaccines to activate patients' T cells depends on the characteristics and level of activation of local DCs, known to be negatively affected by the presence of tumor [23]. Despite these intrinsic limitations, recent studies in breast cancer demonstrated the ability of a standardized Her2/Neu peptide-based vaccine to delay the recurrence of completely resected breast cancer [15].

Many of the above limitations can be avoided by applying customized, patient-specific vaccines, involving a patient's own tumor cells, which display the unique antigenic repertoire that is relevant to each particular patient, both with regard to the patient's HLA type and the unique profile of the tumor-associated antigens expressed on the patient's tumor cells. In addition, cell-based approaches that involve patients' *ex vivo*-generated APCs (such as DC-based vaccines) also avoid the reliance on endogenous APCs, which are frequently dysfunctional in patients with advanced cancer [23].

## Impaired functions of endogenous dendritic cells in cancer

Endogenous DCs in cancer-bearing patients are a target of tumor-associated suppressive factors, resulting in their aberrant functions and impaired development of effector functions in tumor-specific lymphocytes [24,25]. The mediators of such tumor-induced DC dysfunction include IL-10, TGF-β, VEGF, IL-6 and prostanoids, such as $PGE_{2–6}$ [26–29], leading to impaired ability of DCs developing in their presence to undergo maturation, to elevate the expression of costimulatory molecules needed for T-cell activation and to produce cytokines needed to support survival and effector functions in tumor-specific T cells [30–33].

The dysfunction of endogenous DCs has been noted in patients with ovarian, breast, melanoma, renal cell and prostate carcinoma [34–37]. Similar findings have been reported in the blood of patients with head and neck, lung and breast cancer [31,38]. Tumor-derived factors were shown to modulate STAT-3 activity and disturb key intracellular signaling pathways required for DC activation and final maturation, including NF-κB activation [39,40].

The absence of adequate costimulation and cytokine secretion by DCs leads to anergy of naïve, memory and effector T cells, and their conversion into regulatory T(reg) cells, favoring tumor evasion. In addition to inducing aberrant functions of tumor-infiltrating DCs, tumor-derived factors also induce DC apoptosis [41,42], which can also promote T-cell unresponsiveness [43]. Such DC apoptosis-inducing factors include ceramides, gangliosides, nitric oxide and IL-10, all of which are capable of inducing DNA fragmentation in DCs and suppressing anti-tumor immunity [44–46].

## *Ex vivo* -generated dendritic cells in cancer treatment: dendritic cell-based cancer vaccines

The deficit of endogenous DCs frequently observed in cancer patients, manifested by an overall reduction in stimulatory capacity or selective impairment in the ability to induce the desirable type-1 immune responses [24,25], suggested the use of *ex vivo*-generated DCs as carriers of cancer vaccines [47]. DCs, first identified by Ralph Steinman at the Rockefeller University in New York (NY, USA) in the 1970s [48–51], are APCs uniquely specialized in inducing primary immune responses, supporting the survival and effector functions in previously primed T cells, and mediating overall communication within the immune system [52,53].

Since, in contrast to the DCs that develop in the context of tumor-related suppressive factors, fully mature DCs acquire at least partial resistance to such factors [54–56], the attempts to restore normal immune functions in cancer-bearing patients led to the use of fully functional *ex vivo*-generated DCs from cancer patients as a therapeutic tool.

Following the initial success of the DC-based immunotherapy trials in follicular lymphoma and melanoma in the mid-1990s [57,58], DCs have been successfully used to treat patients with melanoma, lymphoma and renal cell carcinoma [4,6,7,22,59]. However, overall clinical response rates do not exceed the usual 10–15% observed in various types of immunotherapies [22,59–63], arguing for the need to improve the design of DC-based vaccines – notably the selection of the most appropriate types of DCs.

## Fine-tuning of dendritic cell-based vaccines: polarized dendritic cells as carriers of signal 1, 2 & 3

DCs provide T cells with antigenic ‘signal 1’ and costimulatory ‘signal 2’ [64–66], needed for the activation and expansion of pathogen-specific T cells. DCs also provide an additional polarizing ‘signal 3’, driving the development of immune responses towards type-1 or type-2 immunity [53], associated with differential involvement of particular effector mechanisms and different abilities to induce cancer rejection [53,64–73]. Potentially, an additional signal (tentatively-termed ‘signal 4’) regulating organ-specific trafficking of immune cells [74–80] is also delivered by the DCs. In addition to their role as the initiators of Ag-specific responses of $CD4^+$ and $CD8^+$ T cells, DCs have also been shown to support the tumoricidal activity of natural killer (NK) cells [81].

Several features of DCs, including their maturation status, migratory potential and cytokine production, were shown to be important for the ability of DC-based cancer vaccines to induce high numbers of Th1-type $CD4^+$ T cells and $CD8^+$ CTLs. Effective induction of anti-tumor CTL responses requires mature DCs that express high levels of costimulatory molecules and can migrate in response to CCL19 or CCL21 – the lymph-node-produced CCR7 ligands [82–84]. In addition, high IL-12p70 secretion has been shown to dramatically enhance the ability of DCs to induce tumor-specific Th1 cells and CTLs, and to promote tumor rejection in therapeutic mouse models [85–87].

Unfortunately, obtaining DCs that possess the three desired features (high immuno-stimulatory function, high migratory activity and high capacity to produce IL-12p70) has been difficult. ‘First-generation’ DC-based vaccines utilized relatively immature or only partially mature DCs, which were immunogenic [57,58], but suboptimal with regard to their lymph-node homing ability and T-cell-stimulating potential [82,88]. ‘Second-generation’ DC-based vaccines, matured in the presence of an IL-1β/TNFα/IL-6/$PGE_2$-containing cytokine cocktail [89], showed a desirable fully mature status, but a reduced ability to produce bioactive IL-12p70, also referred to as DC exhaustion [54,90,91]. Thus, although the ‘second-generation’

DC-based vaccines are clearly superior to immature DCs with respect to their immunostimulatory capacity [82,88] and migratory responses to lymph node-associated chemokines [84,92,93], the desirable combination of all the above three features has not been attained.

In accordance with the possibility of boosting the clinical efficacy of cancer vaccines, we and other groups have demonstrated the feasibility of inducing 'nonexhausted' mature DCs, by exposing immature DCs to type-1 and type-2 interferons and Toll-like receptor ligands, or alternatively, to properly-activated NK cells or memory-type $CD8^+$ T cells [55,91,94–99]. The resulting 'type-1 polarized' DCs (DC1s) show dramatically enhanced capacity to induce long-lived tumor-specific T cells with strongly pronounced anti-tumor effector functions in human *in vitro* and mouse *in vivo* models, and high activity in enhancing tumoricidal functions in resting NK cells. Our original observations [55] and the data from the laboratory of Brian Czerniecki in Philadelphia (PA, USA) [97] and Marieke van Ham in Amsterdam (The Netherlands) [100] demonstrated that the combination of IFN-γ with LPS (including its clinical-grade form, MPLA) or DC maturation-inducing cytokines TNFα and IL-1β overcomes the maturation-associated DC 'exhaustion', yielding stable DC1s that produce highly elevated levels of IL-12p70 upon interaction with CD40L-expressing $CD4^+$ Th cells and induce much stronger Th1-type and CTL responses [55,97]. DC1s with similar properties can be effectively induced by 'two-signal-activated' autologous NK cells or memory-type $CD8^+$ T cells ([95, 96,99] and our unpublished data).

Further addition of IFNα and poly-inosinic:polycytidylic acid (poly-I:C) to the DC-maturation cocktail enhances the ability of maturing DCs to acquire CCR7 expression [91], and instruct the DCs to preferentially interact with naïve, memory and effector T cells, rather than with the undesirable T Treg cells [101]. These latest data suggest that polarized DCs may be able to avoid the undesirable expansion of Treg cells observed with the previously used vaccines [102–106]. In accordance with the ability of polarized DCs to induce qualitatively improved immune responses, 'α-type-1-polarized DCs' (αDC1s) induce up to 40-fold higher numbers of long-lived melanoma-specific CTLs in a single round of *in vitro* sensitization [91], when directly compared with standard (s)DCs matured by IL-1β/TNFα/IL-6/$PGE_2$ [89], which are frequently used in 'second-generation' DC-based vaccines.

So far, our data from melanoma [91], CLL [107], follicular lymphoma, cervical, endometrial, ovarian and prostate cancer uniformly demonstrate the feasibility of generating polarized DC1s from patients with multiple forms of cancer and their loading with peptide antigens or autologous tumor cells [107]. These DCs showed a fully mature phenotype (as CD83, CD86 and CD80 expression), and also expressed moderate levels of CCR7 on their surface. Regardless of the source of antigen loaded (peptide antigens or apoptotic tumor cells), αDC1s were also superior to sDCs in *in vitro* expansion of tumor antigen-specific functional CTLs, and were also able to cross-present tumor epitopes, as tested by IFNγ enzyme-linked immunosorbent spot (ELISPOT) assays.

Our recently published data describe the first murine model of polarized DC1s [108], which provides a tool to further our understanding of the immune responses generated by DC1 vaccines *in vivo.* Murine bone marrow-derived DCs that are matured in IL-4/IFNγ/lipopoly-saccharide/granulocyte macrophage-colony stimulating factor (GM-CSF) have a mature phenotype and retain the capacity for high IL-12 production *in vitro*. Unlike many mouse models that use nonphysiologically high numbers of DCs for vaccinations, our data demonstrate that DC1s are superior inducers of antitumor immunity, even when used at extremely low numbers of DCs [108].

In accordance with the early indications of clinical activity of cancer vaccines incorporating polarized DCs in the clinical trials currently implemented at the University of Pittsburgh (PA, USA), these data suggest that the effectiveness of cancer vaccines may be increased by the use of DCs that selectively activate the desirable type of immune responses. Our additional efforts aim at the development of strategies to boost the ability of the vaccination-induced effector cells to enter into tumors.

## *In vivo* polarization of endogenous dendritic cells in cancer vaccination

While the use of *ex vivo* generated DCs provides a unique opportunity to avoid tumor-induced DC dysfunction and allows for very precise manipulation of DC properties, the associated requirement for the *ex vivo* manipulation of patients' cells and the resulting need for specialized cell culture facilities prompted attempts to develop cell-free vaccines capable of targeting endogenous DCs, and their subsets, within the bodies of cancer patients. The reported advantage of the combined use of tumor-specific antigen with therapies activating NKT cells, for example using α-galactosylceramide [47,52,109–113] in enhancing the IL-12p70-production by endogenous DCs [112], raises the possibility that vaccines engineered to deliver the antigens selectively to DCs can be coupled with strategies to induce DC polarization *in vivo*.

We have previously shown that two types of immune cells can promote type-1 polarization of DCs. Resting NK cells that are activated in the presence of IL-18 and IFNα or IL-2 can induce DC maturation and enhance IL-12p70 production, in a TNFα-mediated manner [96,114]. Memory $CD8^+$ T cells interacting with DCs in an antigen-specific manner can also secrete TNFα to promote the polarization and maturation of the DCs [95,115,116]. These observations suggest that by combining the delivery of tumor-relevant antigen to endogenous DCs with the strategies aimed to promote the interaction of those DCs with either NK cells or memory $CD8^+$ T cells (rather than effector cells prevailing among tumor-specific cells in cancer patients), endogenous DCs that take up the vaccine-associated antigens *in vivo* could be type-1 polarized without any *ex vivo* manipulation. In support of this possibility, our recent observations show that cancer vaccines, including additional elements to promote the interaction of DCs with TNFα and IFNγ-producing tumor-unrelated viral- or xeno-antigen-specific memory type $CD8^+$ T cells, enhances the immunogenic and therapeutic effects of vaccination against different tumors, in an IL-12-dependent mechanism [117]. While these experiments in a murine model did use *ex vivo* manipulated DCs, it is possible to target antigens to DCs *in vivo*. One example of such an approach is the targeting of endogenous DCs using tumor-relevant antigens physically linked to DC-specific antibodies, an approach that showed promise in mouse experiments [118,119].

In remains to be tested if the strategies aimed at *in vitro* polarization of DCs may show therapeutic synergism with the previously proposed strategies to enhance the DC numbers, such as Flt3-ligand treatment, known to increase the DC numbers in mouse [120], favoring antigen cross-presentation [121]. Interestingly for potential clinical translation of such strategies, Flt3-ligand was shown to support the induction of immunogenic DCs from human peripheral blood [122,123].

## DCs regulate the migratory pattern of T cells: modulation of the ability of DCs to deliver 'signal 4' as a tool to boost the effectiveness of cancer vaccines?

While the differences in homing properties of different T-cell subsets have been known for over 15 years [124–130], a series of more recent studies demonstrated the key role of DCs in regulating T-cell homing properties [74–76,78,131]. Depending upon the tissue origin, DCs use such metabolites as vitamin D or vitamin A to induce CCR10 [132] or CCR9 [133] on T

cells to preferentially home to skin or the intestine, respectively. DCs isolated from Peyers' patches or treated with retinoids show the ability to induce gut-homing properties in naïve T cells [74–76,78]. Similarly, migratory APCs have recently been shown to imprint the ability of T cells to home to the CNS [80].

In further support of the notion that the migratory capacity of human melanoma-specific T cells can be affected by DC-related factors (delivery of 'signal 4'), it was shown that enhanced expression of functional CLA (cutaneous homing receptor; ligand for skin endothelium-expressed ELAM) and enhanced migration of effector CTLs to metastatic melanoma lesions in the skin can be induced by the treatment of patients with systemic IL-12 [134]. Berger and colleagues have recently reported that vaccination with monocyte-derived DCs can induce melanoma-specific T cells that home to both the skin and to visceral metastases [135].

The possibility that improved tumor homing may translate into better outcomes of active immunotherapies is supported by the observations that the level of T-cell infiltration is a strong independent prognostic marker of the survival of cancer patients with melanoma [136] and colorectal cancer [137–139]. A recent report suggested that the numbers of melanoma-infiltrating T cells are a better prognostic factor of response to tumor vaccination than the mere numbers of melanoma-specific T cells in circulation [140], suggesting that the ability of vaccines to induce melanoma-relevant homing properties is key to successful immunotherapy. Another recent report demonstrated a dramatic survival advantage of the CTL-associated CXCR3 expression for patients with advanced melanoma [141]. Moreover, high expression of CXCR3 on circulating $CD8^+$ T cells was shown to be a strong positive prognostic factor predicting long-term survival of patients with stage III melanoma.

Therefore, the ability of DC vaccines to induce CXCR3-expressing CTLs is likely to be an important factor contributing to their ability to act as effective vaccines against melanoma and other tumors. Furthermore, it remains to be tested if the efficacy of cancer immunotherapy can be enhanced by modulating the pattern of chemokines at tumor sites to facilitate the tumor entry of the effector-type T cells induced by vaccines.

## Dealing with regulatory T(reg) cells

In addition to the ability of DC-based vaccines to induce a desirable set of homing receptors on tumor-specific T cells, another aspect that requires a thorough evaluation is the possibility of manipulating tumor-infiltrating DC vaccines to selectively express chemokines that attract (and thus preferentially activate) the desirable types of immune cells, such as Th1, NK and CTL, while avoiding the interaction with suppressor/regulatory cells. Recently, we observed that the conditions of DC maturation imprint the ability of mature DCs to secrete different classes of chemokines and thus, selectively attract and interact with functionally distinct specific types of T cells [101]. DCs matured in the presence of $PGE_2$ preferentially secrete CCL22/SDF1 and attract Tregs, possibly explaining the previously reported preferential expansion of undesirable Treg cells in cancer patients vaccinated with $PGE_2$-matured 'standard' DCs [105]. In contrast, the inclusion of interferons in the DC maturation cocktails, particularly when combined with elimination of $PGE_2$, suppressed CCL22 production and promoted the secretion of effector T-cell-attracting chemokines, such as CCL5 and CXCL10 (and other CXCR3 ligands). This ability to produce specific chemokines seems to be imprinted during their maturation, as the chemokine expression remains stable even after removal of original maturation factors. Therefore, it is possible that the use of DCs matured in different environments, such as $PGE_2$-matured 'standard' DCs and type-1-polarized αDC1s, matured in the presence of IFNs and other NK cell-replacing factors, mimicking the conditions of acute infection, will preferentially amplify functionally different types of immunity.

Since tumor microenvironments are rich in $PGE_2$ [26–29] and CCL22 [142] and have been shown to effectively recruit Tregs [142], it remains to be tested whether treatment may reduce CCL22 levels and Treg infiltration. The potential advantage of such tumor-specific chemokine modulation is supported by studies that show that DCs present in regressing tumors have particularly high expression of CXCL9 and show elevated ability to attract $CXCR3^+$ T cells to tumor tissue [143,144].

## Future perspective: towards effective therapeutic cancer vaccines

Despite their relatively limited size, recent clinical studies have suggested a potential advantage of current cancer vaccines in reducing the rate of tumor recurrence and prolonging survival of patients with advanced cancer [12,15]. However, their activity in inducing tumor regression is still limited.

In addition to the constant need for the identification of additional antigens uniquely or preferentially expressed on cancer cells, and effective ways of bypassing the dysfunction of endogenous DCs in cancer patients, the areas that are critical for vaccine efficacy are the ability of DCs to induce T cells with the desirable effector functions and with the ability to enter tumor tissues (ability to deliver signal 3 and signal 4; Figure 1). Of additional impact can be the development of strategies of selectively, or at least preferentially, enhancing the effector arm of immune responses, without hyperactivating the regulatory cells.

While we are clearly ‘not there yet’, it is likely that the road to the development of effective cancer vaccines will be measured in years, rather than decades. While current clinical trials are mostly conducted in the setting of advanced disease, the confirmation of even a limited advantage of such treatments for the survival of these groups of patients will pave the road to testing their activity in adjuvant or neoadjuvant settings in patients with resectable or resected tumors, or in patients with precancerous lesions, with the goal of establishing immune surveillance and preventing the onset of macroscopic disease or its recurrence.

**Executive summary**

- Recent identification of effective ways of enhancing immunogenicity of tumor-associated antigens, including the use of dendritic cells as potent vectors of cancer vaccines, provide effective tools to induce high numbers of circulating tumor-specific T cells.
- Despite the indications that some cancer vaccines may be able to delay tumor recurrence or prolong the survival of cancer patients, their ability to induce cancer regression remains low.
- Recent reports indicate that the successful induction of tumor-specific T cells by cancer vaccines is not necessarily associated with the induction of functional cytotoxic T lymphocytes, but instead lead to undesirable activation and expansion of regulatory T cells.
- In the current review, we discuss the possible ways of counteracting such negative phenomena using selected types of dendritic cells, in order to assure the desirable induction of cytotoxic T lymphocytes, Th1- and natural killer cells, their appropriate homing to tumor tissues and therapeutic effectiveness.

## Acknowledgments

**Financial & competing interests disclosure**

This work was supported by the NIH grants CA095128, CA114931, CA101944, EA055944 and by the institutional funds in support of CA137214. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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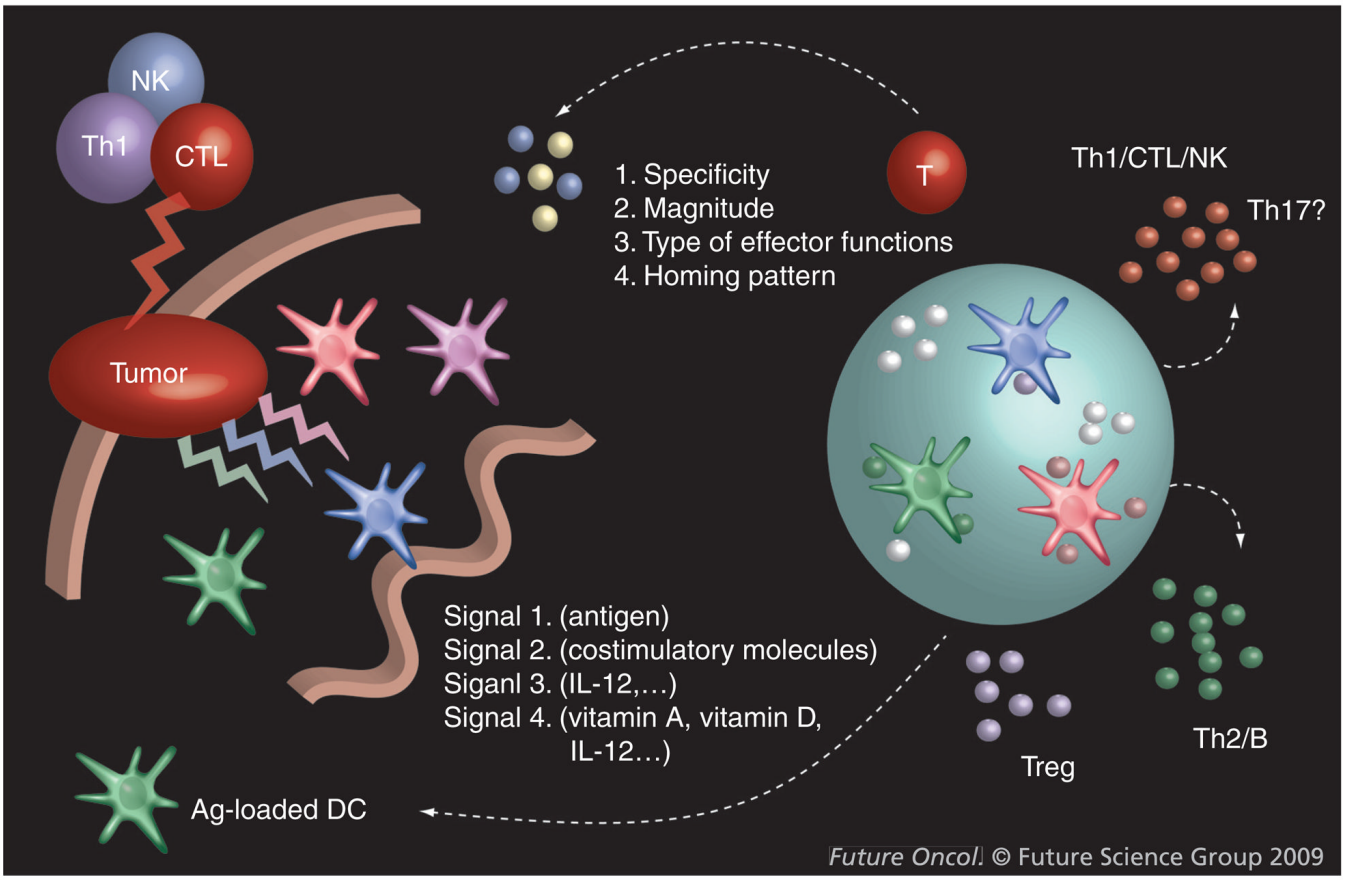


**Figure 1. Current model of anticancer immunity: roles of dendritic cells**

DCs provide T cells with antigenic ‘signal 1’ and costimulatory ‘signal 2’ [64–66], needed for the activation and expansion of pathogen-specific T cells. DCs also provide an additional polarizing ‘signal 3’, driving the development of immune responses towards type-1 or type-2 immunity [53], associated with differential involvement of particular effector mechanisms and different abilities to induce cancer rejection [53,64–73]. Furthermore, recent studies indicate that DCs may also provide T cells with an additional signal (tentatively-termed ‘signal 4’) regulating organ-specific trafficking of immune cells [74–80]. The key role of DCs in regulating the expansion, acquisition of effector functions and or tumor-relevant homing properties suggest the possibility of exploiting these properties in the development of effective cancer immunotherapeutics.

Ag: Antigen; CTL: Cytotoxic T lymphocyte; DC: Dendritic cell; NK: Natural killer.

**Table 1**

Vaccines versus ‘passive’ immunotherapies with antibodies and adoptively transferred T cells.

| Therapy | Vaccines | Antibodies | Adoptive T-cell transfer |
|---|---|---|---|
| Direct cytotoxic effects | No | Yes | Yes |
| T cell effectors able of tumor entry | ? | ? | Yes |
| ADCC | ? | Yes | No |
| Induction of immune surveillance | Yes | ? | ? |
| Induction of clinical responses | ? (Low) | Yes | Yes |
| Survival benefit | Likely (limited data) | Yes | ? |
| Toxicity | No | Yes | Yes |
| Targeting patient/tumor-unique Ags | Yes | No | Yes |

?: Inconclusive data.

ADCC: Antibody-dependent cell-mediated cytotoxicity; Ags: Antigens.