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Dendritic cells and immunity against cancer

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SUMMARY

T cells can reject established tumors when adoptively transferred into patients, thereby demonstrating the power of the immune system for cancer therapy. However, it has proven difficult to maintain adoptively transferred T cells in the long term. Vaccines have the potential to induce tumor-specific effector and memory T cells. However, clinical efficacy of current vaccines is limited, possibly because tumors skew the immune system by means of myeloid-derived suppressor cells, inflammatory type 2 T cells and regulatory T cells (Tregs), all of which prevent the generation of effector cells. To improve the clinical efficacy of cancer vaccines in patients with metastatic disease, we need to design novel and improved strategies that can boost adaptive immunity to cancer, help overcome Tregs and allow the breakdown of the immunosuppressive tumor microenvironment. This can be achieved by exploiting the fast increasing knowledge about the dendritic cell (DC) system, including the existence of distinct DC subsets which respond differentially to distinct activation signals, (functional plasticity), both contributing to the generation of unique adaptive immune responses. We foresee that these novel cancer vaccines will be used as monotherapy in patients with resected disease, and in combination with drugs targeting regulatory/suppressor pathways in patients with metastatic disease.

Keywords

dendritic cells; cancer; vaccines; T cells

INTRODUCTION

The immune system is able to control cancer both in mice (1,2) and humans (reviewed in (3)). Perhaps the most compelling evidence of tumor immunosurveillance is provided by the studies in breast cancer and paraneoplastic diseases. Onconeural antigens, which are normally expressed on neurons, immune privileged sites, are also expressed in some cases of breast cancer (4). In these patients, a strong antigen-specific $CD8^+$ T cell response is generated, which provides effective tumor control but also an autoreactive neurologic disease, paraneoplastic cerebellar degeneration (5). In another example of tumor immunosurveillance, patients with pre-malignant monoclonal gammopathy of undetermined significance (MGUS) frequently display immune response against SOX2 (a gene critical for

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Jacques Banchereauis employed by Roche.

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self-renewal in embryonal stem cells) (6). On the contrary, patients with malignancy such as multiple myeloma (MM) lack anti-SOX2 immunity (6).

Nevertheless, in the majority of cases, natural immunity to cancer is not protective, highlighting the need to develop strategies to boost patient resistance to cancer. This has been facilitated by the molecular identification of human cancer antigens, which in turn allowed the development of antigen specific immunotherapy (7–9). One strategy is adoptive T cell therapy (reviewed in (10,11)). There, autologous antigen specific T cells are expanded ex vivo and reinfused to patients. Adoptive T cell therapy has been shown to be an effective treatment for EBV-associated lymphomas (12) and has induced tumor regression in patients with solid tumors (13,14). Another strategy is to expand T cells in vivo by means of vaccination.

CANCER VACCINES: LESSONS FROM THE PAST AND KEY RECENT PROGRESS

Active immunization has been a successful strategy for the prevention of infectious diseases (15). One example showing great promise with regards to cancer is the prevention of HPV-positive cervical cancer by vaccinating with a recombinant viral capsid protein (16). Therapeutic vaccination is more difficult possibly because most cancer antigens are non-mutated self-proteins and thus the repertoire is depleted of high avidity clones through negative selection (17,18). Numerous approaches for the therapeutic vaccination of humans with cancer have been developed including: autologous and allogeneic tumor cells (which are often modified to express various cytokines), peptides, proteins and DNA vaccines (reviewed in (19)). The observed results have been variable, yet in many cases, a tumor-specific immune response could be measured. The clinical efficacy of therapeutic vaccination in cancer has been questioned (20) because of the limited rate of objective tumor regressions observed in clinical trials. At least two issues need to be considered: 1) the quality of immune responses that these early cancer vaccines were capable of eliciting; this will be discussed later; and 2) definitions of clinical endpoints allowing assessment of the clinical efficacy of immunotherapy. The latter ones have been challenged by recent clinical trials testing anti-CTLA4 (ipilumimab) in patients with stage IV melanoma. There, in a randomized phase III clinical trial an improved overall survival in patients who received anti-CTLA4 was observed (21). In another indication an active immunotherapy product, sipuleucel-T (APC8015), based on the PBMCs activated with a fusion protein of prostate cancer antigen such as prostatic acid phosphatase PAP with GM-CSF, resulted in approximately 4 month-prolonged median survival in phase III trials in patients with prostate cancer (22). In both studies, the analysis of survival curves shows the separation only after 4–6 months suggesting a certain delay in the treatment effect. These clinical trials, therefore, bring forward basic principles of active immunotherapy which set this treatment modality apart from chemotherapy, radiotherapy, targeted therapies and even adoptive T cell transfer. Thus, during the time in which it takes to build tumor immunity tumors might progress before they actually regress; and tumors might appear clinically enlarged due to inflammation associated with active immune responses and lymphocyte infiltration. Thus, one of the lessons is that overall survival might be the only true parameter of clinical efficacy.

Nevertheless, cancer vaccines are entering a renaissance era prompted by a series of recent clinical trials showing promising clinical outcomes. Thus, sipuleucel-T discussed above has been approved by the FDA for treatment of metastatic prostate cancer thereby paving the clinical development and regulatory path for the next generation of active immunotherapy products. A randomized phase II trial of a poxviral-based vaccine targeting PSA (PROSTVAC) in men with metastatic castration-resistant prostate cancer showed improved

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overall survival in patients who received PROSTVAC compared to patients receiving control vectors (23). The list also includes positive reports from phase III trials in 1) follicular lymphoma testing idiotype vaccine therapy (BiovaxID); and 2) melanoma testing peptide vaccine in combination with IL-2 (24,25). While these first generation positive randomized phase II/III clinical trials need further analysis and mechanistic studies, they underline the therapeutic potential of cancer vaccines.

Vaccines act through DCs which induce, regulate and maintain T cell immunity (15,26). Therefore, understanding the DC system is essential for the design of novel cancer vaccines with improved clinical efficacy. Ex vivo-generated DCs have been used as therapeutic vaccines in patients with metastatic cancer for over a decade and early studies have been reviewed elsewhere (27,28). Importantly, a number of studies have shown that DCs can expand in patients T cells specific for non-mutated self proteins that are over-expressed in cancer. As we will discuss below, the past five years have brought key findings relevant to DC biology and increased our understanding of how DCs regulate immune responses. This together with key progresses in tumor immunology and unraveling molecular pathways regulating T cell immunity (for example, CTLA-4 (29) and PD1 (30)), will allow us to refine and improve the immunogenicity and clinical efficacy of DC vaccination.

BUILDING ON DENDRITIC CELL SUBSETS FOR IMPROVED CANCER VACCINES

T cell priming is under the control of DCs (Figure 1). In the steady state, non-activated (immature) DCs present self-antigens to T cells, which leads to tolerance (31,32). DCs induce immune tolerance in a number of ways including i) T cell deletion (33–35); ii) the induction of T cell unresponsiveness (36); and iii) the activation of regulatory T cells (Tregs) (37–40). Once activated (mature), antigen-loaded DCs are geared towards the launching of antigen-specific immunity (41,42) leading to T cell proliferation and differentiation into helper and effector cells (Figure 1). DCs are also important in launching humoral immunity partly due to their capacity to directly interact with B cells (43,44) and to present unprocessed antigens (45–48).

DCs are endowed with two critical features: subsets and functional plasticity (15). This diversity permits the adaptive immune system to mount functionally distinct types of responses (Figure 2). The two major DC subsets are the myeloid DCs (mDCs) and the plasmacytoid DCs (pDCs). pDCs are considered the front line in anti-viral immunity owing to their capacity to rapidly produce high amounts of type I interferon in response to viruses (49,50). Human pDCs, in fact, are composed of two subsets with different functional properties, distinguished by the expression of CD2 (51). $CD2^{high}$ pDCs and $CD2^{low}$ pDCs display distinct transcription profiles, differential secretion of IL12 p40 and differential expression of co-stimulatory molecule CD80 on activation. The role of pDCs in active immunotherapy of cancer is largely undefined. mDCs are also composed of subsets displaying different phenotype and functions. For example, in human skin, epidermis hosts only Langerhans Cells (LCs) while the dermis contains two mDC subsets, $CD1a^+$ DCs and $CD14^+$ DCs, as well as macrophages (52–55). $CD14^+$ dermal DCs specialize in the generation of humoral immunity with IL-12 being the major cytokine involved (53,56–58), whereas LCs specialize in the priming of high avidity antigen-specific $CD8^+$ T cells (53). Another mDC subset, BDCA-3^+ DCs, present in blood and secondary lymphoid organs, was recently proposed to be the equivalent of mouse $CD8^+$ DC subset (59–62). Accordingly, BDCA-3^+ DCs can secrete IL-12, and cross-present exogenous antigens to $CD8^+$ T cells. In line with this, the combination of cytokines used to differentiate monocytes into DCs, for the purpose of vaccination, play a critical role in determining the quality of the elicited T cell responses. For example, DCs generated with GM-CSF and IL-15 display the phenotype and

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characteristics of LCs. In particular, they are more efficient in priming melanoma-antigen specific $CD8^+$ T cells in vitro than DCs derived with GM-CSF and IL-4 (63,64). Thus, vaccination with IL15-DCs might elicit stronger $CD8^+$ T cell responses that may lead to improved clinical responses. The selection of methods for activating DCs also represents a critical parameter in the design of DC vaccines. For example, IL-4 DCs activated with a cocktail of IFN-α, poly:IC, IL-1β, TNF, and IFN-γ induce up to 40 times more melanoma-specific CTLs in vitro than DCs matured with the "standard" cocktail of IL-1β/TNF/IL-6/ prostaglandinE_2 (PGE_2)(65–67). Studies with the new generation of ex vivo DC vaccines will permit us to assess the type of immune responses elicited by human DCs generated in different cytokine environments in vivo.

Characterization of distinct DC subsets is in turn essential for building a novel in vivo approach to vaccination where antigens are directly delivered to DCs using chimeric proteins made of an anti-DC receptor antibody fused to a selected antigen (DC targeting). Pioneering studies in mice demonstrated that the specific targeting of model antigens to DCs in vivo results in considerable potentiation of antigen-specific $CD4^+$ and $CD8^+$ T cell immunity. The induction of immunity is observed only when the DC maturation signal is provided (31,68,69), and otherwise, tolerance ensues (31). These studies have already been extended to demonstrate the generation of therapeutic anti-tumor immunity (70,71) in animal models through the targeting of tumor antigens to mDCs including LCs (72) (73). Furthermore, targeting both tumor and control antigens to human DCs ex vivo can lead to efficient antigen presentation and generation of $CD4^+$ T cell (74,75) and $CD8^+$ T cell (76,77) responses.

DENDRITIC CELLS IN TUMOR ENVIRONMENT

Essential to the success of next generation cancer vaccines based on fusion proteins targeting DCs in vivo is the understanding of the biology of DCs in the tumor environment. Numerous studies in humans have concluded that DCs can infiltrate tumors. We found that breast cancer tumor beds are infiltrated with immature DCs. In contrast, mature DCs are found in the peri-tumoral areas in ~60% of cases (78). A number of studies have suggested that DCs can contribute to tumor development. Our studies in breast cancer indicate that tumor cells polarize mDCs into a state that drives the differentiation of naïve $CD4^+$ T cells into IL-13-secreting T cells (79). These Type 2 T cells in turn facilitate breast tumor development in xenograft model as it can be partly inhibited by administration of IL-13 antagonists (Figure 3). The role of Th2 cells was further established in a spontaneous mouse breast cancer model, where Th2 cells facilitate the development of lung metastasis through macrophage activation (80). In several other mouse tumor models, IL-13 produced by NKT cells induces myeloid cells to make TGF-β that inhibits CTL functions (81). Thus, type 2 cytokines are involved in tumorigenesis through various mechanisms. mDCs can also have direct interactions with tumor cells as shown in multiple myeloma where they directly promote the survival and clonogenicity of tumor cells (82,83).

pDCs have been found in approximately 10% of breast carcinomas and are associated with poor prognosis (84). The infiltrating pDCs produce little type I IFN upon TLR ligation (85). This inhibition appears to depend on the ligation of ILT7 on pDCs binding by BST2 expressed on tumor cells (86). Likewise, in ovarian carcinoma, tumor-infiltrating pDCs do not induce effector $CD8^+$ T cell responses, but rather promote the differentiation of $IL10^+$ $CCR7^+$ $CD8^+$ Tregs (87). Finally, pDCs may promote tumor angiogenesis by the secretion of proangiogenic cytokines (88,89).

DC can fight back tumors at least through two pathways: an indirect one with the induction of potent CTL responses, and a direct one through DC-dependent tumor cytotoxicity. For

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example, pDCs appear to directly contribute to the anti-tumor activity of in vivo-administered Imiquimod (TLR7 ligand), which is used for the treatment of basal cell carcinoma (90–92).

Clearly, understanding the functions of DCs in the tumor bed represents an important area of future investigations and exploitation for therapy. An interesting strategy would be to rewire their molecular pathways from “pro-tumor” DCs into “anti-tumor” DCs.

THE QUALITY OF IMMUNE RESPONSES

Four components of the immune response emerge as critical to whether the induced response will be therapeutic: 1) the quality of elicited CTLs; 2) the quality of induced $CD4^+$ helper T cells; 3) the elimination and/or non-activation of Tregs; and 4) the breakdown of the immunosuppressive tumor microenvironment. Indeed, the immune responses elicited by the first generation DC vaccines might not be of the quality required to allow the rejection of bulky tumors. For example, the induced $CD8^+$ T cells might not migrate into the tumor lesions (18,93). Furthermore, low avidity $CD8^+$ T cells might not be able to recognize peptide-MHC class I complexes on tumor cells and/or to kill them (18). Finally, the tumor micro-environment might inhibit effector $CD8^+$ T cell functions, for example, by action of myeloid-derived suppressor cells and Tregs as summarized in recent reviews, respectively (94,95). Besides the quality of $CD8^+$ T cells, the quality of $CD4^+$ T cells is one of the key parameters of immune efficacy. $CD4^+$ T cells have long been known to be involved in anti-tumor immunity (96) and can act through different mechanisms including i) provision of help in the expansion of tumor antigen-specific CTLs (97), ii) activation of macrophages at tumor sites (98,99), and iii) active killing of tumor cells (100,101). Furthermore, it is now well established that antigen-specific $CD4^+$ T cells are fundamental for the induction of long-term memory $CD8^+$ T cells (102). However, $CD4^+$ T cells can also be detrimental, be it in the form of regulatory/suppressor T cells that might dampen elicited $CD8^+$ T cell responses (103) (104), or pro-tumor type 2 cytokine secreting $CD4^+$ T cells that counteract anti-tumor immunity by promoting tumor development (79) and/or by polarizing tumor associated macrophages (80), as discussed above.

Furthermore, there is a need for the development and validation of tools to identify patients who can benefit from a particular form of immunotherapy including vaccination. Indeed, only a fraction of patients eligible for treatment responds to adoptive transfer of tumor-infiltrating lymphocyte (TIL) cells (105). Along the same lines, only a fraction of patients achieves durable regressions in response to vaccination (106).

COMBINING CANCER VACCINES WITH OTHER THERAPIES

In view of the remarkable diversity of regulatory/suppressive pathways present in patients with metastatic cancer, any durable clinical response elicited by vaccination is already an achievement. However, to improve the outcomes, DC vaccines need to be combined, in particular for patients at advanced stages, with other therapies that offset the suppressive tumor environment (19). Such combination regimens will involve several intervention strategies that target different pathways (Figure 4).

In particular, blocking antibodies or soluble receptors can be exploited for the blockade of suppressive cytokines in the tumor microenvironment such as IL-10 (107), IL-13 (108), TGF-β (109,110) and VEGF (111,112). Such strategies can be used to block immune-inhibitory signals in lymphocytes as illustrated by anti-CTLA-4 (29,113) and/or anti-PD1 (30,114,115), or to block their ligands expressed on tumors or DCs (for example anti-PD-L1). In contrast, agonistic antibodies (111,112) might further potentiate the function of effector T cells, for example, with anti-CD137 (116), a ligand for 4-1BB (117). Just as

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different tumors are currently treated with different combinations of cytostatic drugs and targeted therapies, we foresee the development of clinical protocols combining DC vaccines with individualized adjunct therapies.

CONCLUSIONS

There has never been a better and more exciting time to work on developing cancer vaccines. The considerable progress made in the understanding of DC biology as well as effector/regulatory T cell biology clearly has opened avenues for the development of vastly improved clinical protocols. These optimized DC vaccines eliciting strong and long-lived antigen-specific $CD8^+$ and $CD4^+$ T cell immunity will be offered to patients with early stage disease. For patients with late stage disease, strategies that combine novel highly immunogenic DC-based vaccines and immunomodulatory antibodies will have high impact on enhancing therapeutic immunity in cancer by simultaneously enhancing the potency of beneficial immune arms and offsetting immunoregulatory pathways.

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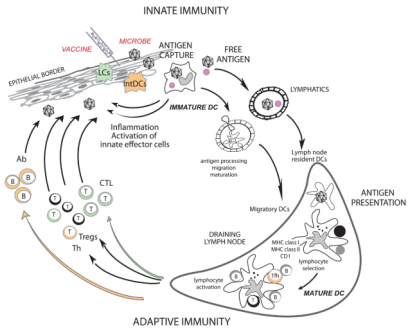

Figure 1. Dendritic cells

DCs reside in the tissue where they are poised to capture antigens (118), be it microbes or vaccines. DCs recognize microbes/vaccines, and secrete cytokines (e.g. IFN-α), directly through pattern recognition receptors, or indirectly through stromal cells that sense microbes/vaccines. Cytokines secreted by DCs in turn activate effector cells of innate immunity such as eosinophils, macrophages and NK cells. Activation triggers DCs migration towards secondary lymphoid organs and simultaneous activation (maturation). These migratory DCs display antigens in the context of classical MHC class I and class II or non-classical CD1 molecules, which allow selection of rare antigen-specific T lymphocytes. Activated T cells drive DCs towards their terminal maturation, which induces further expansion and differentiation of lymphocytes. Activated T lymphocytes traverse inflamed epithelia and reach the injured tissue, where they eliminate microbes and/or microbe-infected cells. B cells, activated by DCs and T cells, differentiate into plasma cells that produce antibodies against the initial pathogen. Antigen can also drain into lymph nodes without involvement of peripheral tissue DCs and be captured and presented by lymph node resident DCs (119). Antigen capture by interstitial DCs (intDCs; orange) will preferentially lead to generation of humoral immunity whereas antigen capture by Langerhans cells (LCs; green) will preferentially lead to generation of cellular immunity (53).

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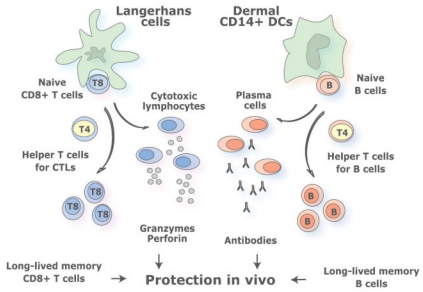

Figure 2. Distinct DC subsets generate distinct types of T cell immunity

DC system has two cardinal features: 1) subsets; and 2) plasticity. This yields distinct types of immunity thereby allowing DCs to cope with protection against a variety of microbes and maintenance of tolerance to self. Understanding these two features is fundamental to develop vaccines that elicit the desired type of immune responses. Novel vaccines rely on rational immunological approaches and aim at activating both the cellular and the humoral arm. We envision that targeting antigens and activation of distinct mDC subsets, with different specializations, will result in the generation of a broad and long lived immune protection. Thus, the most efficient vaccines might be those that will target both LCs and dermal $CD14^+$ DCs thereby allowing the maximal stimulation of cellular and humoral immune responses and the generation of long-term memory protection.

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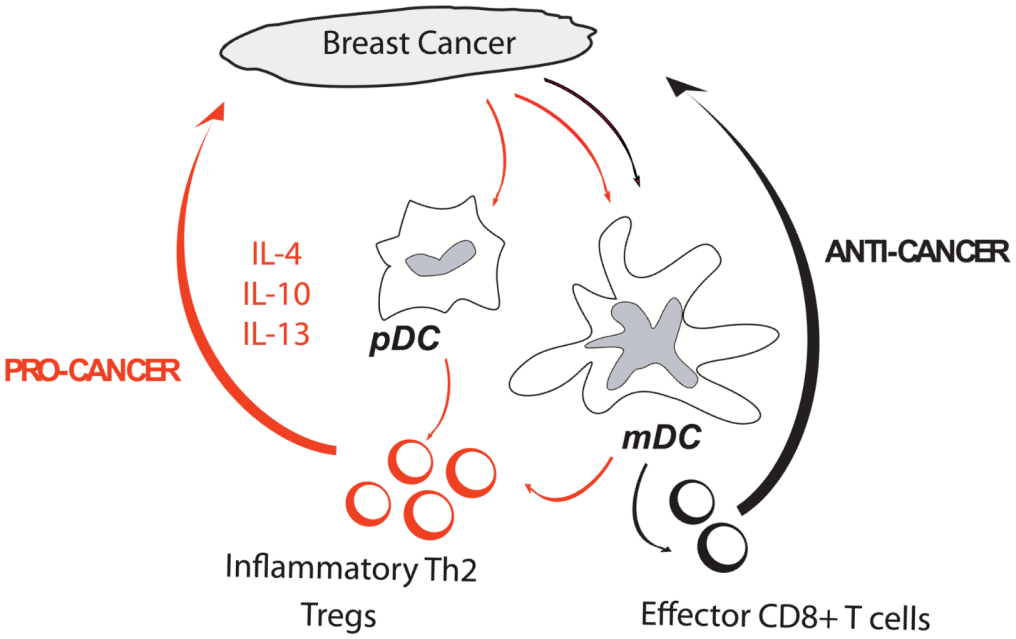

Figure 3. DCs in tumor environment

Cancer cells attract immature DC possibly through chemokines such as MIP3 alpha and/or SDF-1. The DC can then be either blocked or skewed in their maturation, for example by VEGF, leading to induction of polarized CD4+T cells that promote the expansion of cancer cells (pro-cancer) at the expense of CD8+T cells that can cause tumor regression (anti-cancer). An interesting strategy would be to rewire their molecular pathways from “pro-cancer” DCs into “anti-cancer” DCs for example with antibodies or DC activators.

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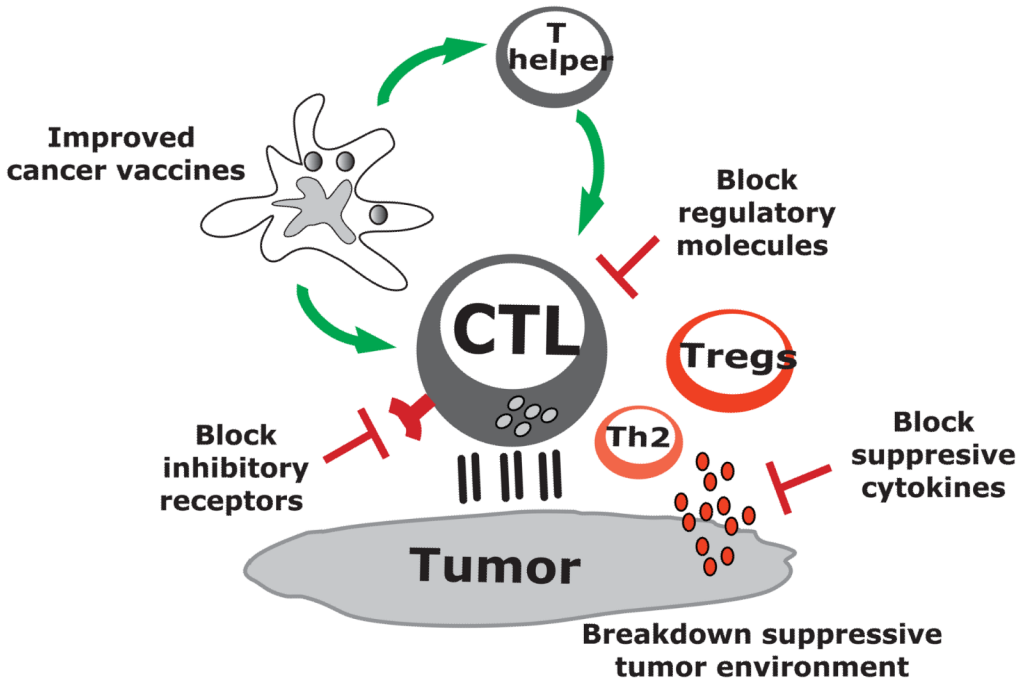

Figure 4. DC vaccines in combination therapies

Current active immunotherapy trials have shown durable tumor regressions in a fraction of patients. However, clinical efficacy of current approaches is limited, possibly because tumors invade the immune system by means of myeloid-derived suppressor cells, inflammatory type 2 T cells and regulatory T cells (Tregs). To improve the clinical efficacy of immunotherapies, we need to design novel and improved strategies that can boost adaptive immunity to cancer, help overcome Tregs and allow the breakdown of an immunosuppressive tumor microenvironment. This can be achieved by developing combination therapies targeting these three major components.