FOCUS: VACCINES

Optimizing Dendritic Cell-Based Approaches for Cancer Immunotherapy

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Dendritic cells (DC\textsuperscript{†}) are professional antigen-presenting cells uniquely suited for cancer immunotherapy. They induce primary immune responses, potentiate the effector functions of previously primed T-lymphocytes, and orchestrate communication between innate and adaptive immunity. The remarkable diversity of cytokine activation regimens, DC maturation states, and antigen-loading strategies employed in current DC-based vaccine design reflect an evolving, but incomplete, understanding of optimal DC immunobiology. In the clinical realm, existing DC-based cancer immunotherapy efforts have yielded encouraging but inconsistent results. Despite recent U.S. Federal and Drug Administration (FDA) approval of DC-based sipuleucel-T for metastatic castration-resistant prostate cancer, clinically effective DC immunotherapy as monotherapy for a majority of tumors remains a distant goal. Recent work has identified strategies that may allow for more potent "next-generation" DC vaccines. Additionally, multimodality approaches incorporating DC-based immunotherapy may improve clinical outcomes.

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†Abbreviations: IL, interleukin; GM-CSF, granulocyte macrophage colony-stimulating factor; TAP, transporter associated with antigen processing; IRAP, insulin-regulated aminopeptidase; FcyRIIB, Fc gamma receptor IIb; DNA, deoxyribonucleic acid; HLA, human leukocyte antigen; CpG, cytosine-phosphate-guanine; TGF-\(\beta\), transforming growth factor-\(\beta\); EGF, epidermal growth factor; CXCL, C-X-C chemokine ligand; KLH, keyhole limpet hemocyanin; TNF, tumor necrosis factor; PGE\(_2\), Prostaglandin E\(_2\); MYD88, myeloid differentiation primary response gene-88; SOCS1, suppressor of cytokine signaling-1; HER2, human epidermal growth factor receptor-2; ELISPOT, enzyme-linked immunospot assay; WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; FoxP3, Forkhead box P3; MDSC, myeloid-derived suppressor cells; ATRA, all trans-retinoic acid; PD-1, programmed death-1; HMGB1, high mobility group box-1; GIST, Gastrointestinal Stromal Tumor; c-KIT, mast/stem cell growth factor receptor; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; Flt-3, fms-related tyrosine kinase-3; BRAF, v-Raf murine sarcoma viral oncogene homolog-B.

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INTRODUCTION

As professional antigen-presenting cells (APC), dendritic cells (DC) function at the interface of the innate and adaptive immune systems. DCs serve as sentinel members of the innate immune arm, responding to “danger” signals by elaborating protective cytokines (e.g., IL-6, IL-12). In their role as master APCs, DCs induce adaptive responses by processing and presenting antigens to naïve T-lymphocytes at lymphoid organs in the context of major histocompatibility (MHC) molecules [1]. Due to these bridging functions, significant effort has been invested in targeting DCs directly or indirectly for the induction of tumor-specific immune responses in cancer patients.

Following the initial promise of DC-based vaccines in lymphoma and melanoma patients in the 1990s [2,3], autologous DCs have been employed in immunotherapy for several tumor types, including prostate cancer (PC), malignant glioma, and renal cell carcinoma (RCC) with varying success [4]. FDA approval of sipuleucel-T — prostatic acid phosphatase GM-CSF fusion protein-pulsed blood DCs — for metastatic castration-resistant PC [5] has energized efforts to replicate and improve upon the success of such DC-based strategies in other tumor types. However, clinically effective DC-based immunotherapy as monotherapy for a majority of tumors remains a distant goal.

In this review, we summarize the rationale for recruiting DCs in immunotherapy, discuss relevant DC immunobiology, critically evaluate DC-based vaccine design and clinical efficacy of DC vaccines in human trials, and explore multimodality strategies to optimize the benefit of current DC-based immunotherapy.

RATIONALE FOR DC USE IN IMMUNOTHERAPY

Effective APCs

DCs are “master” APCs. Their potency for inducing T-cell proliferation is 10 to 100 times that of B-cells or monocytes [6,7]. DCs sensitize antigen-specific responses in both CD4+ [8] and CD8+ T-cells [9]. CD8+ T-cells differentiate into cytotoxic T-lymphocytes (CTLs) and contribute to direct tumoricidal activity. CD8+ T-cell memory is more effectively maintained when stimulated by DCs [6]. While CD8+ T-cells have historically been valued as the primary effectors of anticancer immunity, increasing evidence supports the importance of CD4+ T-cell help in potentiating CTL responses [10], facilitating immunologic memory and displaying direct cytotoxicity of their own [11].

Cross-Presentation

DCs induce CD8+ T-cell responses, in part, due to their ability to cross-present — re-route exogenous antigens, typically presented on MHC class II molecules, into pathways for class I presentation [6]. Although evidence initially suggested that certain activated human blood DC subsets (i.e., CD141+/BDCA3+) are specialized for cross-presentation [12], emerging data indicate that all lymphoid organ-resident DCs (CD141+/BDCA3+, CD1c+/BDCA1+, or plasmacytoid) cross-present efficiently [13]. Two intracellular pathways are utilized for cross-presentation: a) cytosolic (proteasome-dependent), whereby internalized proteins escape intracellular trafficking and are transported to endoplasmic reticulum by TAP1/2 transporters for class I loading; and b) vacuolar (proteasome/TAP-independent), wherein exogenous antigens are degraded in endocytic compartments by lysosomal proteases, cathepsins, or IRAP, and loaded onto class I molecules [14]. Augmentation of cross-presentation is increasingly utilized in DC-based vaccine design [15].

Impact on Humoral Immunity

The role of the humoral system in antitumor immunity is increasingly appreciated, and several mechanisms via which antibodies mediate these effects have been elucidated. These include interfering or altering transmembrane signaling, inducing antibody-dependent cellular cytotoxicity, or participating in complement-mediated cytotoxicity [16]. DCs indirectly facilitate humoral im-
munity by activating follicular CD4+ T-helper (Th) cells, which contribute to germinal center formation and regulate differentiation of B-cells into plasma cells and memory B-cells [17]. DCs directly influence differentiation and survival of B-cells, generation of antibody-secreting plasma cells, and stimulation of memory B-cells via subset-specific cytokine production [18]. Moreover, using a non-degradative intracellular pathway via FcγRIIB, DCs directly present antigen to B-cell receptors, resulting in antibody production [19,20].

DCs can potentiate antitumor humoral immune effects. In a BALB neuT-transgenic murine model, vaccination with bone marrow-derived DCs modified by a recombinant adenovirus-expressing truncated neu oncoprotein (DC\textsubscript{Ad.Neu}) induced potent serum anti-neu antibodies and IFN-γ secretion by CD4+ and CD8+ T-cells. More importantly, DC\textsubscript{Ad.Neu} prevented autochthonous breast cancers and inhibited growth of transplantable neu-expressing breast cancers [21]. In a separate study, HER2-expressing recombinant adenoviral vaccination alone in the BALB neuT-transgenic model also induced anti-neu antibodies, which were both necessary and sufficient for antitumor protection. Antibody effectiveness was also subtype-dependent, with IgG2a being most effective [22].

**Induction of Natural Killer (NK) and NK T-Cell (NKT) Responses**

DCs favorably condition the tumor microenvironment (TME) via their interactions with NK and NKT-cells. DCs attract NK cells to the TME by secreting CXCR3 ligands, thereby stimulating NK effector functions [23]. Once NKs are recruited, interactions between NKs and DCs reciprocally enhance antitumor immunity. NK cells can induce DC activation, facilitate DC maturation to a type 1-polarizing phenotype (DC1), and edit DCs by eliminating tolerogenic subtypes [24].

While NKT-cells mediate direct tumor lysis, their antitumor effects depend in large part on their ability to activate NK cells and DCs [25]. Targeting NKT-DC interactions have clinical implications: Activating NKT cells with α-galactosylceramide-loaded DCs (with low-dose lenalidomide) resulted in clinical regression and broad immune activation in myeloma [26].

**Direct DC Tumoricidality**

Evidence supports DCs’ capacity for direct antitumor cytotoxicity [27]. This is achieved when DCs take up apoptotic tumor cells and present tumor antigens to other effector elements, thereby eliciting a tumor-specific immune response.

**DC IMMUNOBIOLOGY**

DC-based vaccines differ from conventional (peptide, protein, DNA) vaccines in that a dynamic component of the immune system is harnessed to affect immunization [16]. DCs are governed by a pre-programmed life cycle as well as a range of constitutive and inducible functions that have been exploited for vaccine development. This section briefly explores the immunobiology of DCs pertinent to their use in immunotherapy.

**DC Activation and Function**

DCs primarily exist in immature (non-activated) and mature (activated) states. Immature DCs (iDC) are responsible for capture, transport, and processing of antigens [28] while awaiting infectious/inflammatory signals, which commences maturation. Upon maturation, DCs lose their phagocytic and antigen-processing capabilities [28,29] and upregulate chemokine receptors, allowing migration to sites of eventual activity [30]. The ability of DCs to induce T-cell responses is augmented in a number of ways: increased expression of surface MHC [31,32] and co-stimulatory [33] molecules and elaboration of soluble factors that influence polarization of the ensuing immune response [34,35].

**DC Subsets and Plasticity**

Two major subsets of DCs are described: classical (cDC; myeloid or mDC) and plasmacytoid (pDC) DCs. cDCs have historically been distinguished from pDCs on the basis of CD11c expression [36] and myeloid markers [37]. cDCs highly express class II molecules and are efficient at inducing T-cell prolifera-
tion [38]. Although cDCs are referred to as lymphoid-organ “resident” due to their frequent occurrence in the thymus, spleen, and lymph nodes, a subpopulation was discovered in circulating blood and are termed migratory DCs [38]. Migratory DCs are further subdivided on the basis of reciprocal CD141/BDCA3 and CD1c/BDCA1 expression [1]. CD1c+/BDCA1+ DCs are predominantly found in the blood compartment, are similar to murine CD11b+ DCs, and are potent activators of CD4+ T-cells [1]. Human CD141+/BDCA3+ DCs are similar to murine CD8α+DCs in their ability to generate robust CD8+ T-cell responses and cross-present exogenous antigens on MHC class I [12,39].

pDCs differ from cDCs by virtue of CD303+ and CD11c- status, low class II expression, and relatively poor ability to stimulate T-cells [36]. Despite these shortcomings, pDCs’ ability to respond to viral infections, via increased Toll-like receptor (TLR)-7/-9 expression and vigorous IFN-α/β production [40,41], may be harnessed in DC vaccine design.

Classification schemes of DC lineage have proven remarkably complex to define. Early classification attempts based on surface marker expression or transcription factors assumed that myeloid- and lymphoid-derived progenitor populations developed into distinct DC subsets [42-46]. However, there is substantial plasticity in these populations; it is now clear that both myeloid- and lymphoid-derived progenitors can develop into cDC/mDC or pDC subsets via intermediary progenitors under the influence of Flt3 ligand [38,47,48]. This plasticity has been exploited by various activation protocols in DC vaccine design [6].

**DC Activation via TLR Signaling**

Although the innate immune system is considered more non-specific compared to the adaptive system, it possesses the ability to respond to countless microbial threats while discriminating them from self-antigens [49]. This was explained by the discovery of receptors such as TLRs on immune cells that recognized molecular patterns common to many pathogens, termed pathogen-associated molecular patterns [49]. Eleven TLRs with homology to invertebrate counterparts have been identified in humans [50]. Examples include TLR2 (ligand: lipoteichoic acid [LTA]); TLR3 (double-stranded RNA); TLR4 (lipopolysaccharide [LPS]); TLR7/8 (single-stranded RNA); and TLR9 (unmethylated CpG-containing DNA) [51]. TLRs initiate downstream molecular events by recruiting MyD88 and TRAF6, thereby inducing expression of cytokine genes relevant to inflammation via two disparate pathways: a) NF-κB and AP-1 (involving the canonical IκB-kinase complex [IKK-α, IKK-β, and IKK-γ]); and b) MAP kinases (including ERK, JNK, p38) [52].

TLRs are found on various DC subsets and direct their respective immunogenic capacities. For instance, pDCs (expressing TLR7/9) and cDC/mDCs (TLR8) respond to certain infections but not others [53]. Furthermore, different signaling pathways are activated depending on the TLR(s) stimulated and adaptor proteins involved. For example, simultaneous activation of MyD88-dependent and MyD88-independent (TRIF-mediated) pathways synergizes to generate DC phenotypes that secrete IL-12 more potently than when either pathway is activated individually [54]. Finally, TLR-primed DCs induce antigen-specific high-avidity CD8+ [55,56] and type 1-polarized CD4+ Th (Th1) responses [57], providing a compelling rationale for TLR agonism in DC-based immunization.

**DC1-Mediated Th1**

The plasticity of DC lineage and influence of external signals impacts DC maturation to disparate phenotypes. In turn, these phenotypes polarize the immune response (i.e., induce diverse Th subsets) via cytokine elaboration [6]. The DC1 phenotype, so named because it induces CD4+ Th1 immunity [58], is the primary phenotype utilized in vaccination for several reasons. DC1-secreted IL-12p70 polarizes naive CD4+ T-cells to IFN-γ-secreting Th1; IFN-γ is critically important for tumor rejection in a number of models [59]. Importantly, Th1-driven CTLs detect class I-tumor antigen complexes with
higher affinity than Th2-driven counterparts [60]. Finally, Th1 subsets are instrumental in B-cell responses by inducing antibody class-switching and IgG production [6]. IL-12p70 contributes to host anti-tumor responses by promoting NK cell activation [61] and displaying anti-angiogenic properties by hindering tumor neovascularization [62]. In our studies, CD8⁺ T-cells could only recognize HLA-A2⁺ cancer cells if the sensitizing DCs secreted IL-12p70. Moreover, IL-12p70 sensitized T-cells recognized antigen at significantly lower concentrations during recall responses compared with non-IL-12p70-sensitized T-cells [55]. Taken together, incorporation of IL-12p70-producing DC1 in vaccine design appears warranted.

**DC2-Mediated Th2**

DCs that promote CD4⁺ Th type-2 (Th2) differentiation are referred to as DC2. Cytokines that favor production of Th2 subsets include IL-4 and anti-IFN-γ; Th2, in turn, produce IL-4, IL-5, IL-6, and IL-10 [6]. Th2, primarily involved in promoting allergic reactions, defending against parasitic infection, and inducing B-cell differentiation, are considered less effective than their Th1 counter-
parts in combating cancer. While earlier reports posited an antitumor effect for Th2 [63], more recent evidence suggests that Th2 may be pro-tumorigenic. In a murine mammary carcinoma model, DC2-derived Th2 facilitated tumor development by generation of IL-4 and IL-13 [64]. In another study, IL-4-expressing Th2 promoted pulmonary metastasis of mammary carcinoma by enhancing TGF-β and EGF production by tumor-associated macrophages [65]. These data have engendered a bias against the use of DC2 in vaccine design.

**DC17-Mediated Th17**

DCs conditioned to drive Th17 differentiation are termed DC17. DC17s are characterized by IL-23, IL-1β, IL-6, and TGF-β production, although controversy exists regarding which of these is truly necessary for Th17 induction [66,67]. Interestingly, Th1-favoring IFN-γ and IL-4 inhibit IL-23-dependent Th17 production [68]. Our group has previously demonstrated that DC activation with single TLR ligands (LTA, LPS, or R848) can polarize Th17 responses compared with two signals required for DC1 activation [69]. Conversely, our collaborators utilize a combination of adenosine triphosphate (ATP) and LTA to promote Th17 differentiation [70].

The anticancer role of Th17 cells, characterized by IL-17, IL-21 and IL-22 secretion, remains controversial [71,72]. Initially, Th17 cells were considered protumorigenic due to increased IL-17 expression/function in several tumors [73]. More recently, however, studies have demonstrated an antitumor role for Th17 cells. In murine B16 melanoma, adoptive transfer of Th17 (vs. Th1 or non-polarized Th0) was most effective at inducing tumor regression. Intriguingly, Th17-mediated effects were dependent on IFN-γ production, and IFN-γ neutralization abrogated tumor rejection [74]. Indeed, IL-17 synergizes with IFN-γ to induce CXCL9/10 secretion by tumor cells, attracting effector T-cells (T_{eff}) [75]. Widespread utilization of DC17 in cancer immunotherapy will depend on continued understanding of Th17 immunobiology and its interplay with Th1 immunity.

**DC-BASED VACCINE DESIGN STRATEGIES**

Given the diverse anticancer armamentarium offered by DC immunobiology, an intense search for the optimal vaccine construction strategy has emerged in recent years. Two strategies (Figure 1) are widely accepted: a) direct targeting of antigens to DC receptors in vivo; and b) ex vivo-generated antigen-loaded DCs.

**DC-Targeting In Vivo**

In this approach, chimeric antigen-antibody complexes targeted to DC surface molecules are internalized into endosomal compartments for MHC loading and stimulation of T-cell responses [76]. While a comprehensive review of DC receptors is presented elsewhere [76,77], a discussion of the most promising molecules follows.

The most comprehensively characterized DC receptor is DEC-205 — a multi-lectin receptor mediating ligand binding and internalization [76]. Antigens complexed with anti-DEC-205 monoclonal antibodies (mAb) have shown promise in preclinical studies [78-80]; HIVgag-DEC-205-targeting vaccine in primates generated robust Th1 immunity in a prime-boost model [80]. In murine models, conjugation of anti-DEC-205 mAb to TRP-2 [78] or survivin [79] generated antigen-specific immunity and tumor regression. Interestingly, targeting self-antigens to DEC-205 induces tolerance — conjugation of proteolipid protein to anti-DEC-205 mAb tolerized T-cells and reduced IL-17 secretion by Th17 [81].

Another promising target is the mannose receptor (MR). Antigen mannosylation enhances uptake by APCs, particularly DCs, with subsequent presentation on class I/II molecules [76]. Interestingly, chemical modification of the mannan conjugate can skew the ensuing immune response; oxidized mannan stimulates Th1 immunity, whereas reduced mannan favors predominantly Th2 responses [82]. Targeting MR/DEC-205 holds clinical promise. Antibody-targeted NY-ESO-1 to MR/DEC-205 elicited human CD8+ and CD4+ T-cell immunity with broad antigen specificity; whereas non-targeted and
mAb-targeted NY-ESO-1 similarly activated CD4+ T cells, cross-presentation to CD8+ T-cells was efficiently induced only by receptor-targeted antigen [83]. Accordingly, phase I/II clinical trials involving β-hCG-MR mAb conjugates (CDX-1307) and NY-ESO-1-DEC-205 (CDX-1401) have been initiated [77,84]. In its first in-human application, CDX-1401 administered to 45 patients with treatment-refractory advanced malignancy generated potent anti-NY-ESO-1 immunity, as well as encouraging clinical results [85].

DC-SIGN is a membrane lectin with significant implications for antigen targeting. Via its high-affinity interactions with ICAM-2/ICAM-3, DC-SIGN mediates DC signaling and trafficking [76]. DC-SIGN-ligand complexes are channeled into late endosomes and presented on class II molecules, generating robust CD4+ immunity [86]. KLH-DC-SIGN mAb potentiated naïve T-cell responses and inhibited tumor growth in a murine model [87]. Lastly, DCIR is a versatile tyrosine-based receptor with immunomodulatory properties. Targeting DCIR not only activates T-cell responses, but also inhibits TLR8- (IL-12, TNF-α) and TLR9- (IFN-α) related signaling [88]. Antigens targeted to anti-DCIR mAb (e.g., influenza matrix protein, MART-1) potently stimulated CD8+ T-cell responses in vitro and in vivo [89].

A few salient features of in vivo DC-targeting deserve mention. First, antigen must be delivered to mature/activated DCs, since antigen presentation by immature DCs induces tolerance rather than immunity [18]. Vaccine constructs must rely on the retained ability of mature DCs to present antigen taken up via endocytic receptors [90]. Functionally, this is achieved by accompanying antigen-mAb conjugates with molecular adjuvants (e.g., anti-CD40 mAb, poly-I:C, CpG) [77]. Second, targeting receptors on distinct DC subsets may bias the immunologic outcome. CD8α+ DCs targeted using anti-DEC-205-ovalbumin (OVA) favored the generation of CD8+ immunity, whereas CD8α- DCs targeted using anti-DCIR-OVA or anti-Dectin-1-OVA more efficiently induced CD4+ immunity [91]. Third, engaging different DC receptors may deliver distinct signals to the same DC, polarizing their function accordingly. Targeting DC-ASGPR (without adjuvant) generated IL-10-secreting regulatory T-cells, whereas targeting DCs with anti-LOX1 mAb resulted in Th1 polarization [92]. Fourth, the choice of adjuvant may be critical in skewing immune responses to a desired phenotype. Potent Th1 responses were induced by anti-Clec9A-OVA mAb delivered to CD8α+ DCs in the presence of poly-I:C (TLR3 agonist). When curdlan (β-glucan) was used as adjuvant, immunization with anti-Clec9A induced Th17 responses [93]. Finally, the ubiquitous expression of some molecules (e.g., DEC-205, MR) on non-DC APCs (monocytes, B-cells) may dissipate the antigen-targeting efficiency of this approach. Given these complexities, and the uncertainty associated with translating preclinical evidence into clinical success, moving in vivo DC-targeting to human trials requires considerable work yet.

**Ex Vivo-Generated Antigen-Loaded DCs**

Pioneering studies describing the ability to culture murine DCs ex vivo from bone marrow precursors galvanized DC vaccine development in the 1990s [94]. Human applications followed soon thereafter. Human DCs could be generated from peripheral blood-derived monocytes or CD34+ hematopoietic progenitors [95]. Ex vivo-manipulated autologous DCs could be expanded, loaded with antigen, and administered back to patients to generate antitumor immunity [1]. This approach had two ostensible advantages: a) bypassing endogenous DC dysfunction in cancer-bearing patients; and b) streamlining immune responses to recognize and eliminate tumor cells in an antigen-specific fashion.

Although a majority of clinical trials have utilized ex vivo-generated DC vaccines, several controversies linger. First, the maturation state of DCs has been a matter of debate. Despite moderate clinical benefit in trials using IL-4-immature DCs [4], a meta-analysis revealed a significant association between DC maturation and improved clinical responses in PC [96]. These findings have been reproduced in melanoma [97] and
glioblastoma [98]. These disparities in clinical efficacy reflect lessons learned in the laboratory. By virtue of their low co-stimulatory and class II molecule expression (and intermediate class I expression), iDCs induce suboptimal T-cell priming and generate T-cell tolerance. Fully activated DCs (e.g., matured with TLR agonists) can abrogate such tolerance [6]. Furthermore, maturation can be performed rapidly in 2 to 3 day protocols (versus ≥1 week) [99]. These “rapid-activation” systems obviate longer culture times without compromising DC functionality [16].

Second, the optimal DC phenotype, and the maturation strategy utilized therein, remains contentious. It is increasingly recognized that abundant production of IL-12p70 during DC maturation ex vivo, as well as “burst” secretion during DC activation in vivo (via CD40-CD40L in lymphoid organs), is critical for the induction of CTL responses [99,100]. Moreover, DC1-derived IL-12p70 drives Th1-polarized immunity and is predictive of favorable outcomes in melanoma [101] and glioblastoma [102]. In addition to IL-12p70 elaboration, other desirable functions of immunogenic DCs include non-exhaustive capacity, expression of chemokines enhancing TME infiltration of Teff (e.g., CXCL9/10), low IL-10 secretion following restimulation with CD40L, and enhanced migratory ability to lymph nodes. Several cytokine cocktails have been proposed to achieve optimal DC characteristics. The “gold-standard” system in clinical trials comprises TNF-α, IL-1β, IL-6, and PGE2 [4,16]. Limitations of this technique (i.e., low IL-12p70 “burst,” Treg chemoattraction/exansion, increased expression of pro-tolerogenic indoleamine-2,3-dioxygenase [99]) prompted a search for viable alternatives. Combinations of IFN-α, IL-1β, TNF-α, IFN-γ, and poly-I:C yielded non-exhaustive DCs with improved IL-12p70 “burst” in vivo [103], while IL-1β, TNF-α, IFN-γ, low-dose PGE2, and R848 (TLR7/8 agonist) enhanced lymph node homing [104]. Our group [105], as well as others [106], utilizes a streamlined recipe of IFN-γ and LPS to activate DCs. LPS-induced TLR4 agonism results in activation of highly immunogenic DCs [16] and yield an IFN-producing tumor-“killing” phenotype [105]. Finally, compared with four other cytokine cocktails, IFN-γ/LPS generated the highest relative IL-12:IL-10 ratio and elicited the strongest antigen-specific CTL response [107].

Third, the ideal strategy for DC antigen-loading is not universally agreed upon. The most common approach has been loading with tumor-associated peptides or whole recombinant tumor proteins [1]. While these non-mutated self-antigens may break self-tolerance at the cellular level, they rarely do so at the host level [108], accounting for disappointing clinical results. Putative reasons for this phenomenon include negative selection of high-avidity clones with ensuing self-tolerance to low-avidity clones [109] and maintenance of host level self-tolerance via pre-programmed immunosuppressive elements (e.g., Treg) [108]. Strategies have been proposed to overcome these pitfalls: a) co-administration of TLR agonists, as discussed earlier [6]; b) silencing of antigen presentation “attenuators” (e.g., SOCS1) may enhance in vivo DC function by augmenting immunogenicity [108]; c) using homologous xenogeneic (e.g., murine) antigens to break self-tolerance [110]; and d) engineering DCs loaded with mutated neo-antigens from patient-specific tumors, which may activate a T-cell repertoire without pre-programmed Treg [111]. Other modalities of DC loading (engineered fusion proteins, autologous/allogeneic tumor cells, tumor cell-lysate, DC-tumor hybrids, and DNA- or mRNA-transfected) have emerged and are reviewed elsewhere [99].

Fourth, the optimal route for DC administration remains controversial. Historically, with intradermal/subcutaneous injection techniques, DC trafficking to regional lymph nodes was considered critically important to their function. Indeed, maturation cocktails (e.g., PGE2-containing) were designed to optimize trafficking ability [112]. The growing popularity of IFN-γ/LPS maturation regimens, with their incident lack of CCR7/CXCR-4 (“trafficking” chemokines) expression [99], dictated a search for alternative techniques to over-
come this limitation. Ultrasound-guided intranodal injection, which co-localizes DC1-derived IL-12p70 “burst” with the anatomic site of T-cell sensitization, has emerged as a feasible solution [113].

Finally, the opportunity for DC vaccination in early disease settings remains underexplored, with most trials focusing on locally advanced/metastatic settings [4]. Immunization in early disease or reduced-tumor states may circumvent tumor- and patient-induced immune dysfunction inherent in advanced disease settings [6]. Indeed, our group has conducted phase I/II neoadjuvant HER2/neu-pulsed autologous DC1 trials in early (Stage I) HER2"neg"-invasive breast cancer and HER2"pos"-ductal carcinoma in situ (DCIS) with encouraging results. In the initial phase I study, 5/27 (18.5 percent) subjects had no evidence of residual DCIS (complete response [CR]) at surgery, with a substantial loss of target antigen in the remainder of patients [114]. In the subsequent phase I/II study, nearly 25 percent of

| Malignancy                  | Phase III trials | Phase II trials | Phase I trials       |
|-----------------------------|------------------|-----------------|----------------------|
| Solid*                      | --               | 4               | 9 (includes 1 phase I/II) |
| Brain                       | 2                | 10 (includes 1 phase II/III) | 18 (includes 2 phase I/II) |
| Breast                      | 1                | 9 (includes 1 phase II/III) | 8 (includes 3 phase I/II) |
| Cervical                    | --               | --              | 1                    |
| Colorectal                  | --               | 8               | 6 (includes 4 phase I/II) |
| Gastric                     | --               | 1               | 1 (includes 1 phase I/II) |
| Hepatocellular Carcinoma    | --               | 1               | 2 (includes 1 phase I/II) |
| Hematologic Malignancies    | 1                | 14              | 11 (includes 4 phase I/II) |
| Lung                        | 1                | 7 (includes 1 phase II/III) | 4 (includes 1 phase I/II) |
| Melanoma                    | 2                | 28              | 38 (includes 14 phase I/II) |
| Mesothelioma                | --               | --              | 2                    |
| Ovarian                     | --               | 8               | 4 (includes 2 phase I/II) |
| Pancreatic                  | --               | 1               | 3 (includes 1 phase I/II) |
| Peritoneal                  | --               | 1               | 1 (includes 1 phase I/II) |
| Prostate                    | 4                | 19              | 14 (includes 8 phase I/II) |
| Renal cell                  | 1                | 14              | 13 (includes 9 phase I/II) |
| Sarcoma                     | --               | 7               | 5 (includes 3 phase I/II) |

*includes multiple solid organ cancers
HER2\textsuperscript{pos}-DCIS patients have achieved CR [unpublished results]. In another study, a Wilms’ tumor-1 (WT1) mRNA-electroporated DC vaccine was effective in acute myeloid leukemia patients with minimal residual disease, but not in those with relapsed or progressive disease [115]. Finally, ongoing trials in resected glioma (NCT00045968) and RCC (NCT01582672) are exploiting reduced-tumor states to evaluate DC vaccine efficacy [4].

CLINICAL EFFICACY OF DC-BASED IMMUNOTHERAPY

As mentioned earlier, DC-based immunotherapy has produced inconsistent clinical results. In this section, the clinical efficacy of “traditional” ex vivo antigen-loaded DC immunotherapy is summarized.

In a pilot study, four B-cell lymphoma patients administered autologous idiotype-specific DCs demonstrated promising clinical responses [2]. Soon thereafter, a randomized phase III trial comparing autologous DC vaccination with dacarbazine as first-line therapy for advanced melanoma was initiated but closed prematurely due to the lack of meaningful objective response rates (ORR) on interim analysis [3]. Its failure was attributed to several factors, including suboptimal DC maturation, inadequate dosage, and subcutaneous route of injection. Despite this setback, DC-based approaches have been adopted for a wide range of tumor types, including PC, lung cancer, melanoma, RCC, non-Hodgkin’s lymphoma, breast cancer, and malignant glioma (Table 1, Supplement). Encouragingly, the FDA recently approved sipuleucel-T — autologous APCs (including DCs) activated with prostatic acid phosphatase-GM-CSF fusion protein — for metastatic castration-resistant PC. In two placebo-controlled randomized trials, sipuleucel-T prolonged overall survival (OS) by nearly four months compared with placebo, with a 22 percent relative mortality risk reduction [5,116].

Clinical experience with DC-based vaccination underscores a few distinct advantages. First, DC immunotherapy is safe; injection site reaction, fever, and fatigue are the most commonly reported adverse effects in phase I trials; systemic grade 3-4 toxicity is rare [4]. Additionally, concerns regarding immunotherapy-induced autoimmunity appear less worrisome for DC-based approaches compared with mAb (e.g., anti-CTLA-4) or cytokine (e.g., IL-2) therapies [4,114]. Moreover, DC therapies are expected to adequately preserve quality of life in immunized patients [117]. Finally, regardless of the immune monitoring technique (ELISPOT, tetramer assays, skin biopsy of delayed-type hypersensitivity reactions), a majority of DC-based trials indicate that this approach is highly immunogenic, even in advanced malignancy [4]. In metastatic PC and RCC, antigen-specific immunity was induced in 77 percent and 61 percent of patients, respectively [96]. DCs’ immunogenicity in early disease settings is more readily discernible. Our phase I/II HER2-pulsed DC1 trial demonstrated durable (up to 48 months post-immunization) anti-HER2 Th1 immunity in a majority of HER2\textsuperscript{pos}-DCIS patients [114].

While tolerable and immunogenic, DC-based approaches have been criticized for their disappointing ORRs (partial/complete response by WHO/RECIST criteria) [118]; a recent systematic review concluded that ORR in melanoma, PC, glioma, and RCC were 8.5 percent, 7.1 percent, 15.6 percent, and 11.5 percent, respectively [4]. A more longitudinal endpoint of treatment efficacy (e.g., OS) may be more appropriate than measuring short-term tumor regression. This paradigm is exemplified by the IMPACT trial, wherein a survival benefit for sipuleucel-T was observed over placebo despite its lack of improvement in time to biochemical failure or progression-free survival [5]. OS is increasingly utilized as an end-point in newer DC-based vaccine trials (Supplement).

This discordance between robust immunogenicity, poor ORR, and measurable survival benefit seen with DC-based approaches can be explained by the fact that immune potentiation against advanced cancer is an indolent, not immediate, process. Furthermore, an initial increase in radi-
ographic tumor burden, which would be considered progressive disease by RECIST, often reflects a protective vaccine-induced peritumoral immune infiltrate [119]. As such, tumor regression following immunotherapy has been documented even after initial progression or appearance of new lesions [120]. In an effort to capture these atypical response patterns, novel surrogates for vaccine-induced efficacy were proposed — so-called immune-related response criteria (IRRC). IRRC includes index as well as new lesion(s) in measuring tumor burden and emphasizes the need for longitudinal surveillance to confirm progression [121]. Adoption of IRRC-defined endpoints in future clinical trials may uncover the true merit of DC-based vaccination.

**OPTIMIZING DC-BASED APPROACHES**

The maximal benefit of DC-based immunotherapy may be realized in combinatorial approaches with other anticancer therapies that synergistically enhance DC function. This section will illustrate the rationale for such approaches (Table 2, Figure 1).

**“Next Generation” DCs**

Our growing understanding of DC biology sheds light on strategies to optimize vaccine efficacy. First, exploiting the diversity of DC lineage may prove advantageous. For instance, although pDCs have a proclivity toward Th2 polarization, their ability to produce IFN-α/β during viral infection can activate other DCs, augment T-cell cross-priming, and generate potent CTL responses [122]. CD141+/BDCA3+ DCs, when activated by poly-I:C, produce abundant amounts of IL-12p70 and IFN-β, excel at antigen cross-presentation, and result in stronger Th1 induction than CD1c+ DCs [123]. Second, manipulating ex vivo culture conditions may generate more immunogenic DCs. Langerhans cell-type DCs — derived from CD34+ progenitors or IL-15-monoocytes [124] — are more efficient at priming antigen-specific CTLs than GM-CSF/IL-4-DCs [125]. Trials employing Langerhans-type DCs are under way in melanoma [4]. Third, modified expression of co-stimulatory molecules could enhance DC potency. CD40L overexpression in murine DCs via mRNA-electroporation enhanced B7/IL-12p70 production, critical for Th1 immunity. Moreover, mRNA-electroporated DCs encoding CD40L, CD70, and TLR4 generated durable tumor responses in chemorefractory metastatic melanoma [126].

**Muting Immunosuppressive Phenotypes**

Tumors create immunosuppressive networks (Treg, MDSCs) that mediate escape from immune surveillance. Two broad strategies to mute Treg/MDSCs are plausible and may improve DC potency. First, DCs can be harnessed to directly target immunosuppressive elements. We recently demonstrated that TLR4-activated DC1 not only inhibits Treg effects but also converts regulatory cells into IFN-γ-secretory Th1 [127]. Alternatively, loading DCs with immunogenic FoxP3 epitopes may generate FoxP3-specific CTLs capable of eliminating Treg. Melanoma-bearing mice vaccinated with FoxP3 mRNA-transfected DCs reduced in-tratumoral FoxP3+ Treg by 85 percent and augmented TRP2-specific CTL responses following co-vaccination with TRP2-DCs [128]. While promising, such approaches must consider the risk of depleting Treg systemically, which may promote irreversible autoimmunity.

Second, DCs can be synergized with several Treg/MDSC-targeting therapies. Anti-CD25 mAb (daclizumab, basiliximab), targeting IL-2 receptor α-chains, transiently deplete Treg and augment tumor rejection in murine models. In metastatic melanoma, addition of daclizumab to tumor antigen/KLH-pulsed DCs depleted Treg, but undesirably suppressed tumor-specific CD25+ effectors. No differences in progression-free survival were observed between daclizumab-treated or untreated groups [129]. A recombinant IL-2-diphtheria toxin conjugate — denileukin diftitox — is another CD25-targeting strategy demonstrating Treg depletion and persistent antigen-specific CTL responses in RCC [130] and CEA-overexpressing malig-
Table 2. Optimizing dendritic cell-based vaccination via multimodality approaches. Clinical trials utilizing the respective approach are listed, if applicable.

| Strategy                        | Agent/technique utilized | Proposed advantage(s)                                         | Clinical trial(s) completed/under way, if applicable |
|---------------------------------|--------------------------|----------------------------------------------------------------|-----------------------------------------------------|
| "Next-generation" DC vaccines   | Plasmacytoid DC          | IFN-α/β production, enhances cross-presentation               | Melanoma (NCT01690377)                                |
|                                 | CD141+/BDCA3+ DC Langerhans cell DC | Improves cross-presentation                               | N/A                                                  |
|                                 | mRNA-electroporated DC encoding CD40L/CD70/TLR4 (Trimix) | Increases antigen-specificity                              | Melanoma (NCT01456104, NCT00700167, and NCT01189383) |
|                                 |                           | Durable antitumor Th1 immunity                              | Melanoma (NCT01066390)                                |
| Muting immunosuppression        | Anti-CD25 (basiliximab, daclizumab) mAb | Deplete T<sub>reg</sub>                                       | Brain (NCT00626483); Melanoma (NCT00847106); Ovarian (NCT01132014) |
|                                 | Denileukin diftitox      | Target CD25, deplete T<sub>reg</sub>                         | Melanoma (NCT00056134); Ovarian (NCT00703105); Solid (NCT00128622) |
|                                 | 1-methyl-D-tryptophan    | Inhibits indoleamine-2,3-dioxygenase                         | Breast (NCT01042535, NCT01302821)                    |
|                                 | all-trans retinoic acid  | MDSC differentiation into non-suppressive cells              | Lung (NCT00617409)                                    |
|                                 | COX-2 inhibitors (celecoxib, meloxicam) | Inhibit CCL2, upregulate CXCL10                             | Melanoma (NCT00197912); Head & Neck (NCT00589186); Brain (NCT01759810); Lung (NCT00442754, NCT01782287); Breast (NCT01782274) |
|                                 | Lenalidomide             | Inhibit MDSC                                                 | Myeloma (NCT00698776)                                 |
|                                 | Anti-VEGF                | Inhibit MDSC                                                 | Renal (NCT00913913); Prostate (NCT00027599); Ovarian (NCT00683241 NCT01132014) |
| Targeting immune checkpoint pathways | Anti-CTLA4               | Inhibit CTLA-4:B7                                            | Melanoma (NCT00090896)                                |
|                                 | Anti-PD-1                | Impair PD-1:CTL interaction                                  | Renal (NCT01441765); Prostate (NCT01420965); Hematological (NCT01096602, NCT01067287) |
| Cytokines and TLR agonists      | IL-2                     | Protect CTL effectors from tumor-mediated dysfunction        | Brain (NCT01235845); Breast (NCT00197925, Colorectal (NCT00176761, NCT0001959); Lung (NCT00442754); Melanoma (NCT00197912, NCT00338377, NCT00910650, NCT00279058, NCT00006113, NCT00004025, NCT01339663, NCT00003229, NCT00019214, NCT00704938); Renal (NCT00197960, NCT00913913, NCT00085436, NCT00704938); Sarcoma (NCT00001566); Lymphoma (NCT00006434) |
|                                 | IFN-α                    | Induce apoptosis of tumor                                    | Melanoma (NCT00278018, NCT00610389), Renal (NCT00913913, NCT00085436, NCT00610389) |
|                                 | IFN-γ                    | Cytotoxic, polarize Th1                                      |                                                     |
|                                 | IL-7                     | Maintenance of DCs                                           | Myeloma (NCT00616720)                                 |

Continued on next page.
nancies [131]. More recent evidence, however, suggests that denileukin paradoxically induces a tolerogenic DC phenotype, promotes survival of non-activated T_{reg} [132], and depletes tumoricidal NK cells [133]. To overcome these limitations, a non-CD25-based alternative — I-methyl-D-tryptophan — which inhibits indoleamine-2,3-dioxygenase is currently being trialed in combination with DC vaccines [4]. The inhibition of T_{reg} functional activity may complement DC vaccination. In a murine model of graft-versus-host disease, mAbs targeting OX40 or GITR (TNF family receptors influencing T_{reg} function) abrogated T_{reg}-mediated suppression [134]. Anti-GITR mAb in conjunction with HER2/neu-expressing DC vaccines displayed potent anti-tumor immunity in a tolerogenic murine model [135]. A synthetic

| Strategy | Agent/technique utilized | Proposed advantage(s) | Clinical trial(s) completed/under way, if applicable |
|----------|--------------------------|------------------------|-----------------------------------------------------|
| Cytokines and TLR agonists | IL-12 | Polarize Th1, anti-angiogenic | Pediatric Solid Tumors (NCT00923351) |
| | Imiquimod (TLR7) | Induced type 1-IFN by pDC | Breast (NCT00622401); Brain (NCT01808820, NCT01792505, NCT01171469); Lung (NCT00442754); Ovarian (NCT00799110); Sarcoma (NCT01803152, NCT01241162, NCT00944580) |
| | Poly-IC (TLR3) | DC activation, T_{eff} infiltration | Brain (NCT01204684, NCT00766753); Melanoma (NCT01783431); Pancreatic (NCT01677962, NCT01410968); Solid (NCT01734564) |
| | Resiquimod (TLR7/8) thymosin-α-1 (TLR9) | T_{eff} infiltration, inhibit T_{reg}; Potentiate CTL responses | Brain (NCT01204684); Renal (NCT00197860) |
| Chemotherapy | Cyclophosphamide ±fluorarabine | Lymphodepleting, re-boots immune system | Solid (NCT01697527); Brain (NCT00323115, NCT02010606); Melanoma (NCT00338377, NCT00910650, NCT01946373, NCT00313508, NCT00704938); Renal (NCT00704938, NCT0093522) |
| | Metronomically dosed cyclophosphamide | Depletes T_{reg}/MDSC, potentiates Th1/Th17 | Head & Neck (NCT01149902); Lung (NCT01159288); Melanoma (NCT00197912, NCT00683670, NCT00722098, NCT00978913, NCT00313235, NCT01339663; NCT00610389), Mesothelioma (NCT01241682); Ovarian (NCT00683241, NCT00478452); Prostate (NCT01339663); Renal (NCT00610389) |
| | Gemcitabine | Improves cross-presentation, T_{eff} infiltration | Pancreatic (NCT00547144); Sarcoma (NCT01803152) |
| Radiotherapy | Radiotherapy | Enhances tumor immunogenicity, releases TLR agonists, targets stroma | Brain (NCT00323115, NCT01213407, NCT01567202); Breast (NCT00082641); Esophageal (NCT01691625); Melanoma (NCT00278018); Pancreatic (NCT00547144, NCT00843830); Sarcoma (NCT00365872, NCT01347034) |
| Targeted therapies | Sunitinib; Dasatinib; Trastuzumab | Inhibits MDSC, depletes CTLA-4/PD-1; Potentiate CTLs, enhance ADCC | Renal (NCT01582672, NCT01582672); Melanoma (NCT01876212); Breast (NCT00089895, NCT00266110) |
peptide inhibiting nuclear translocation of FoxP3 protected mice undergoing CD8+ peptide immunization against tumor implantation [136]. Finally, disrupting Treg trafficking to tumors/lymph nodes may boost DC function at these sites. CCR4 antagonists, which block CCL22/CCL17-mediated Treg recruitment, induced antigen-specific CTLs when combined with peptide vaccination in murine models [137].

MDSCs have emerged as key tumor-induced suppressors of T-cell responses. Owing to evidence that MDSCs may directly impair DC vaccine quality [138], concomitantly targeting MDSCs may be warranted. Three strategies exist: a) promoting MDSC differentiation into non-suppressive cells (ATRA, vitamin D3); b) depleting MDSC levels (sunitinib, gemcitabine, 5-FU), or c) inhibiting MDSC function (PDE-5 inhibitors, cyclooxygenase-2 inhibitors) [139]. Cyclooxygenase-2 (COX-2) inhibitors favorably predispose the TME for DC immunotherapy by diminishing the MDSC-attracting chemokine CCL2 while upregulating CXCL10 [140]. Other MDSC-targeted interventions that could be used with DC vaccines include VEGF inhibitors (bevacizumab), lenalidomide, and tyrosine kinase inhibitors (TKI; e.g., sunitinib, vemurafenib) [4].

**Targeting Immune Checkpoint Pathways**

CTLA-4 and PD-1 are the best understood immune checkpoint receptors that negatively regulate activated CTL function, resulting in an “exhausted” T-cell phenotype. Monoclonal antibodies targeting CTLA-4/PD-1 are immunostimulatory therapies aimed at recovering T-cell cytotoxicity [141]. Anti-CTLA-4 is tumor non-specific, preventing downregulation of CTL function by inhibiting CTLA-4:B7 interaction [142]. Preliminary clinical evidence suggests that combination of DC immunotherapy and anti-CTLA-4 may be synergistic in their benefit. In advanced melanoma patients, co-administration of MART1-pulsed DCs and anti-CTLA-4 mAb ( tremelimumab) yielded durable antitumor responses at a higher rate than with either agent alone [143]. The non-specific mechanism of CTLA-4 blockade, however, manifests as dose-limiting toxicity in many patients. Conversely, anti-PD-1 antibodies, which impair the inhibitory CTL:PD-1 ligand interaction on tumors, potentiate tumor-specific immunity and demonstrate a more favorable toxicity profile [144]. Administration of anti-PD-1 antibody (pidelizumab) enhanced activated-CTL responses following stimulation with an autologous myeloma-DC fusion vaccine [145]. Pidelizumab is currently being investigated in combination with DC vaccination in hematologic, renal, and prostate malignancies [4].

**Cytokines and TLR Agonists**

Cytokines and TLR agonists are attractive adjuncts for DC vaccines due to their critical role in regulating lymphocyte homeostasis and potentiating CTL function. Concomitant administration of systemic IL-2 with DCs proved effective in preclinical studies. In a murine sarcoma model, IL-2 potentiated antitumor effects of tumor lysate-pulsed DCs *in vivo* and induced protective immunity to lethal tumor challenge; this combination also mediated regression of established pulmonary metastases [146], suggesting its applicability in advanced malignancy. In advanced melanoma patients, however, tumor lysate-pulsed DCs plus IL-2, albeit well tolerated and variably immunogenic, failed to induce meaningful clinical responses [147,148]. Despite these results, several trials employing adjunctive cytokine therapy (GM-CSF, IL-2, IFN-γ, pegylated-IFN-α, IL-12) with DC vaccination are under way [4].

Topical/intra-lesional administration of TLR agonists could be explored as adjuncts to DC immunotherapy. Imiquimod (TLR7/8 agonist) stimulates type-1 IFN production by tumor-resident pDCs, engaging them in an inflammatory milieu and improving tumoricidality [149]. Synthetic CpG-containing oligodeoxynucleotides induce innate and adaptive immune responses by triggering TLR9 expressed by pDCs and B-cells. In a phase I trial, intra-lesional PF-3512676 demonstrated clinical activity in basal cell
carcinoma and subcutaneous melanoma metastasis [150]. The combination of IFN-α and poly-I:C, used in a tissue explant culture system in colorectal tumors, upregulated Teff-attracting chemokines CXCL10 and CCL5 [151]. Several clinical trials utilizing novel TLR agonists (e.g., picibanil [TLR4], resiquimod [TLR7/8], thymosin-α-1 [TLR9]) are currently under way [4].

**Chemotherapy**

The traditional view of chemotherapy as immunosuppressive has been challenged, prompting a re-evaluation of its utility as an adjunct to immunotherapy. In recent years, successful “chemoimmunotherapy” combinations have emerged [152]. Such clinical effects may be explained by the mechanistic synergism between these two modalities, the heightened sensitization of tumor cells to chemotherapy during vaccination-invoked immune siege [153] or provocation of immune responses induced by chemotherapy-induced cell death [154]. The impact of chemotherapeutic agents on antitumor immunity varies by their unique immunologic repercussions. Three effects are recognized: a) increasing Teff stimulation (e.g., cyclophosphamide, paclitaxel); b) enhancing tumor immunogenicity (e.g., doxorubicin, cisplatin, 5-FU); and c) decreasing tumor-induced immunosuppression (e.g., gemcitabine, cyclophosphamide, paclitaxel/carboplatin) [152]. Ultimately, chemotherapy-specific immune effects should guide selection of optimal agent(s) for chemoimmunotherapy.

In this regard, a few chemotherapeutic agents/regimens deserve mention. Lymphodepleting regimens (cyclophosphamide or temozolomide±fludarabine) can reboot the immune system by eliminating immunosuppressive elements and creating an immunostimulatory cytokine (e.g., IL-7, IL-15) environment [155]. This prompts an immune-recovery state ideal for DC vaccination [4]. Metronomically dosed cyclophosphamide inhibits angiogenesis, depletes Treg/MDSC populations, increases tumor cell permeability to CTL-derived cytolytic factors, and potentiates antitumor Th1/Th17 responses [99]. Finally, gemcitabine: a) augments antitumor immunity by increasing tumor antigen cross-presentation, T-lymphocyte expansion, and T eff infiltration [156]; b) selectively induces MDSC apoptosis in several preclinical models, without detrimental effects on T-, B-, or NK-cells [139]; and c) selectively inhibits splenic MDSCs and augments *in vitro* expansion of antigen-specific splenic T-cells in 4T1 mammary carcinoma-bearing BALB/c mice [157].

While the immune benefits of various chemotherapeutic agents are increasingly recognized, optimal sequencing of chemoinmunotherapy is yet to be conclusively established. Although patients heavily pretreated with chemotherapy are less responsive to subsequent immune manipulations [158], less aggressive regimens administered prior to immunization may potentiate antitumor immunity. Dacarbazine treatment before peptide vaccination broadened the T-cell receptor diversity of melan-A-specific CTL clones in melanoma patients, with a trend toward longer survival [159]. Conversely, DC vaccination may effectively prime the immune system before cytotoxic insult. Indeed, patients with advanced small cell lung cancer demonstrated notable clinical responses to second-line chemotherapy following vaccination with DCs transduced with adenoviral-delivered wild-type p53 [160]. To confound matters, concurrent chemotherapy and DC vaccination may be a viable strategy in certain tumor types; a majority of colon cancer patients concomitantly receiving adjuvant oxaliplatin/capecitabine and KLH/CEA-pulsed DCs demonstrated CEA-specific T-cell responses [161]. Several trials attempting to elucidate the optimal dosing/timing of chemoimmunotherapy are under way [4, 99].

**Radiotherapy**

There has been a recent paradigm shift from viewing radiotherapy as merely cytoreductive to appreciating its varied immunomodulatory effects. While these effects are quite complex [51], a simplified rationale for combining DC immunotherapy and radiotherapy follows. Irradiation of tumor cells enhances their immunogenicity via upregulating class I molecules (e.g., in melanoma [162]) or tumor-associated antigen expression (e.g., CEA on gastric adenocarcinoma cells [163]). Radiation-
induced release of proinflammatory cytokines (TNF-α, IL-1β) or endogenous TLR agonists (HMGB1 [TLR4]) activate DCs and prime antigen-specific T-cell responses [51]. Moreover, radiation exposure alters the TME favorably, selectively inhibiting Treg [164] and inducing CTL-mediated targeting of tumor stroma [165]. In light of this dynamic interplay between irradiated tumor, DCs, and effector/suppressor immune fractions, combinatorial approaches of DC vaccination with radiotherapy are currently being explored in several tumor types [4].

**Targeted Therapies**

Targeted molecular therapies can be utilized in combination with DC immunotherapy. A promising agent is sunitinib, a TKI targeting c-KIT, VEGFR, PDGFR, and Flt-3, primarily applied in GIST/RCC patients [166]. In preclinical models, sunitinib effectively decreases TME accumulation of MDSC, restores Th1/CTL functionality, inhibits PD-1L expression on pDCs/MDCs, depletes CTLA-4/PD-1 expression on activated-CTLs, and mutes the expression of inhibitory IL-10, TGF-β, and FoxP3 from tumor-infiltrating leukocytes [167,168]. Likewise, the immune effects of vemurafenib, a BRAFV600E-targeting TKI in melanoma, are increasingly appreciated. In conjunction with its inhibitory effects on Treg and MDCs, vemurafenib reduces tumor-induced CCL2 expression and enhances TME Teff infiltration [169]. Interestingly, vemurafenib reversed BRAFV600E melanoma-induced DC dysfunction without deleterious effects on DC viability or ability to prime T-cell responses, making it an exciting candidate for combination immunotherapy [4,170]. Indeed, we are actively examining the efficacy of this combination in a murine model of BRAFV600E/PTEN-/- melanoma.

**CONCLUSIONS AND OUTLOOK**

Realistically, tangible benefits with DC immunotherapy will likely be realized by employing a multifaceted strategy of DC delivery (e.g., uniting *in vivo* DC-targeting and *ex vivo*-manipulated DCs in individual trials), rationally combining multivalent DC-based vaccines with established anticancer agents, and utilizing these multimodality approaches in early disease or reduced-tumor settings. Furthermore, the repeatedly proven safety of DC vaccination places the onus on regulatory agencies to allow investigators to bypass resource-intensive phase I testing and focus the majority of efforts in evaluating DCs’ therapeutic efficacy. These developments might expedite the availability of clinically effective DC approaches for cancer immunotherapy.

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Datta et al.: Optimizing dendritic cell-based cancer immunotherapy

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Supplement. Clinical trials employing dendritic cell-based immunization approaches. Trials are grouped by phase of development (I-III) and malignancy type. Trial endpoints are indicated (i.e., safety, immunogenicity, tumor/disease response, and overall survival). Trials that were withdrawn or terminated were excluded from this list. Data was obtained using the search terms “dendritic cells” and “cancer” on www.clinicaltrials.gov.

| clinicaltrials.gov identifier | Malignancy       | Status      | Dendritic cell product                                                                 | Safety | Immune Response | Tumor/Disease Response | Survival |
|-------------------------------|------------------|-------------|---------------------------------------------------------------------------------------|--------|-----------------|------------------------|----------|
| NCT01759810*                 | Brain            | ongoing     | Dendritic vaccine, allogeneic hematopoietic stem cells, cytotoxic lymphocytes          |        | x               | x                      |          |
| NCT00045968                 | Brain            | recruiting  | DC-Vect-HL (Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen)              |        | x               | x                      |          |
| NCT01782274*                 | Breast (* Brain metastasis) | ongoing  | Dendritic vaccine, allogeneic hematopoietic stem cells, cytotoxic lymphocytes          |        | x               | x                      |          |
| NCT0178288*                  | Lung (* Brain metastasis) | ongoing  | Dendritic vaccine, allogeneic hematopoietic stem cells, cytotoxic lymphocytes          |        | x               | x                      |          |
| NCT01875653                 | Melanoma         | not yet open | Autologous DCs Loaded With Irradiated Autologous Tumor Cells In GM-CSF                 |        | x               | x                      |          |
| NCT0183748                  | Melanoma         | not yet open | Autologous DCs Loaded With Autologous Tumor RNA                                     |        | x               | x                      |          |
| NCT00066434                 | Non-Hodgkin's lymphoma | completed | Tumor-pulsed DCs + IL2                                                               |        | x               | x                      |          |
| NCT00065442                 | Prostate         | completed   | SpikeVec-T (Autologous Antigen Presenting Cells Loading With PA2024)                  |        | x               | x                      |          |
| NCT0133704                 | Prostate         | completed   | SpikeVec-T (Autologous Antigen Presenting Cells Loading With PA2024)                  |        | x               | x                      | x        |
| NCT0005647                  | Prostate         | completed   | SpikeVec-T (Autologous Antigen Presenting Cells Loading With PA2024)                  |        | x               | x                      |          |
| NCT00779402                 | Prostate         | ongoing     | SpikeVec-T (Autologous Antigen Presenting Cells Loading With PA2024)                  |        | x               | x                      |          |
| NCT01582672                 | Renal cell       | recruiting  | AGS-003 (Autologous DC Immunotherapy)                                               |        | x               | x                      |          |

| clinicaltrials.gov identifier | Malignancy       | Status      | Dendritic cell product                                                                 | Safety | Immune Response | Tumor/Disease Response | Survival |
|-------------------------------|------------------|-------------|---------------------------------------------------------------------------------------|--------|-----------------|------------------------|----------|
| NCT00019084                  | Solid*           | completed   | Mutant PS3 or RAS peptides pulsed DC vaccine +/- IL2                                  |        | x               | x                      |          |
| NCT0191420                   | Solid*           | invitation only | Wilms' Tumor Gene (WT1) mRNA-electroporated Autologous DC Vaccine                     |        | x               | x                      |          |
| NCT01917557                  | Solid*           | recruiting  | NY-ESO-1 TCR Engineered PBMCs + NY-ESO-1157-165 Pulsed DCs + IL2                      |        | x               | x                      |          |
| NCT01829466**                | Solid*           | recruiting  | DCVac-Direct (Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen)            |        | x               | x                      | x        |
| NCT01373515**                | AML completed    | DC-Peptide (Leukemic DC Vaccine)                                                      |        | x               | x                      | x        |
| NCT00510133                  | AML ongoing      | GRN182 (Autologous Mature DCs Transfected With mRNA Encoding Human Telomerase Reverse Transcriptase) |        | x               | x                      | x        |
| NCT01066602                  | AML recruiting   | DC AML vaccine + CT-011 (investigational monoclonal antibody)                         |        | x               | x                      | x        |
| NCT01865334                 | AML recruiting   | Wilms' Tumor (WT1) Antigen-targeted DC Vaccine                                         |        | x               | x                      | x        |
| NCT0174304**                 | AML recruiting   | Autologous DCs Transfected With RNA Encoding Leukemia-associated Antigens              |        | x               | x                      | x        |
| NCT00976837                  | Brain completed  | Tumor Lysate-Pulsed DC vaccine                                                         |        | x               | x                      | x        |
| NCT0084454**                 | Brain completed  | DC with mRNA from tumor stem cells                                                    |        | x               | x                      | x        |
| NCT00322115                  | Brain completed  | Intra-nodal DC/Tumor Lysate Vaccination + Radiotherapy (RT) + temozolomide (TMZ)      |        | x               | x                      | x        |
| NCT00706753**                | Brain ongoing    | Type 1 DCs Pulsed With Multiple Peptides                                              |        | x               | x                      | x        |
| NCT01006044                  | Brain ongoing    | Autologous DC Vaccine                                                                 |        | x               | x                      | x        |
| NCT01280552                  | Brain ongoing    | DC-T-07 (Autologous DCs pulsed with immunogenic antigens)                              |        | x               | x                      | x        |
| NCT0165283                  | Brain recruiting | Tumor Lysate-Pulsed autologous DC vaccine                                              |        | x               | x                      | x        |
| NCT01240684                  | Brain recruiting | Tumor Lysate-Pulsed autologous DC vaccine +/- Toll-like Receptor Agonist              |        | x               | x                      | x        |
| NCT01262104                  | Brain recruiting | Total tumor RNA (TTRNA)-loaded DCs +/- Autologous Lymphocyte Transfer                  |        | x               | x                      | x        |
| NCT00088885                  | Breast completed | Multipeptide DC Vaccine + Trastuzumab/Monoclonal antibody                            |        | x               | x                      | x        |
| NCT0022405*                  | Breast ongoing   | DC/Tumor Fusion Vaccine + IL-12                                                        |        | x               | x                      | x        |
| NCT01431196                  | Breast ongoing   | Autologous DC vaccine                                                                 |        | x               | x                      | x        |
| NCT00266110                  | Breast ongoing   | Multipeptide DC Vaccine + Trastuzumab/Monoclonal antibody                            |        | x               | x                      | x        |
| NCT00326841                  | Breast ongoing   | Autologous DC-amybacntrix p53 vaccine                                                 |        | x               | x                      | x        |
| NCT01042535**                | Breast recruiting | DC-adenovirus p53 vaccine + 1-methyl-D-ribose                                         |        | x               | x                      | x        |
| NCT02018455**                | Breast recruiting | Cytisine, 1E7-1CEF-loaded DC vaccine + neoadjuvant chemotherapy +/- IL-1 blockade w enkriks |        | x               | x                      | x        |
| NCT0291533**                 | Breast recruiting | HER-2 Pulsed DC Vaccine                                                                |        | x               | x                      | x        |
| NCT0311272                  | Colorectal       | completed   | MetCanCancerVac (Autologous DCs Pulsed With Allogeneic Melanoma Lysate)               |        | x               | x                      | x        |
| NCT01010342                  | Colorectal       | completed   | Vaccine-carboxyembryonic antigen (CEA)-mucin 1 (MUC-1) Triad of costimulatory molecules TRICOM vaccine (PANNAC-V) and falcorp-CEA-MUC-1-TRICOM Vaccine (PANNAC-F) administered with autologous dendritic cells or with sargramostim (GM-CSF) |        | x               | x                      |          |
| NCT00019581**                | Colorectal       | completed   | Mutant Ras Peptide-Pulsed DCs +/- IL-2                                                |        | x               | x                      | x        |
| NCT00228189**                | Colorectal       | completed   | CEA-loaded DC vaccine                                                                 |        | x               | x                      | x        |
| NCT01413295 | Colorectal | ongoing | Autologous DCs pulsed with autologous tumour antigens | x | x |
|-------------|------------|---------|-----------------------------------------------------|----|----|
| NCT01867092** | Colorectal | recruiting | Vaccination with frameshift-derived neoantigen-loaded DC | x | x | x |
| NCT01340256 | Colorectal | recruiting | Autologous DCs loaded with autologous tumour antigens | x | x | x |
| NCT00013433** | Colorectal | completed | DC Vaccine with GM-CSF | x | x | x |
| NCT01783921** | Gastric | recruiting | S-1 plus DC activated Cytokine Induced Killer treatment (DC-CIK) | x | x | x |
| NCT00223344** | DC | completed | DC Vaccine With Four AEP Peptides | x | x | x |
| NCT00239110** | Hematologic Malignancies | completed | WT1-Pulsed DCs | x | x | x |
| NCT01215126 | Lymphoma | not yet open | EBV Defined DC Vaccine +/- TLR9 Agonist, DUK-CPS-001 | x | x | x |
| NCT01926839 | Lymphoma | recruiting | Radiation Combined With Intratumoral Injections of DC and Rituximab | x | x | x |
| NCT00846450 | Melanoma | completed | Autologous tumor cells + DC + GMCSF | x | x | x |
| NCT00120984** | Melanoma | completed | Autologous DC + GMCSF | x | x | x |
| NCT01979122** | Melanoma | completed | Tumor antigen loaded autologous DC | x | x | x |
| NCT01042560 | Melanoma | completed | Antigen-loaded autologous DC vaccine | x | x | x |
| NCT00245539** | Melanoma | completed | DC Vaccine Preventing HLA Class I and II Restricted Tumor Epitopes Either by Peptide-pulsing or mRNA Transfection | x | x | x |
| NCT00436930 | Melanoma | completed | Adjuvant GM-CSF + Proliferating Tumor Cells vs GM-CSF + DCs Loaded With Proliferating Tumor Cells | x | x | x | x |
| NCT01278490** | Melanoma | completed | mRNA-Transfected DCs | x | x | x |
| NCT01071519 | Melanoma | completed | Autologous DC-allogeneic Melanoma tumor cell lysate vaccine | x | x | x |
| NCT00339323** | Melanoma | completed | Dendritic cell-MART-1 peptide vaccine | x | x | x |
| NCT00647190** | Melanoma | completed | Dendritic Cell Based Vaccines With an Anti-COX2 Monoclonal Antibody (Baidumim) | x | x | x |
| NCT00019690 | Melanoma | completed | CD4+ Derived or Peripheral Monocyte Derived DCs Pulsed With MART-1 and gp100 Melanoma Antigens + sargramostim | x | x | x |
| NCT01325749** | Melanoma | completed | DCs Loaded With Heat Treated Killed Allogeneic Melanoma Cells | x | x | x |
| NCT0058134 | Melanoma | completed | Dendritic cells, recombinant CD40-Ligand, therapeutic autologous DCs | x | x | x | x |
| NCT02344778 | Melanoma | completed | MART-1+gp100+prostates Peptide-Pulsed DC Vaccine | x | x | x |
| NCT00245944** | Melanoma | completed | Peptide-Pulsed DCs | x | x | x |
| NCT00032255** | Melanoma | completed | Autologous cultured DCs pulsed with gp100 and tyrosinase peptides or autologous melanoma tumor cell lysates +/- IL-2 | x | x | x | x |
| NCT00019214** | Melanoma | completed | DCs Presenting Epitopes Derived From Melanoma Associated Antigens MART-1 and gp 100 +/- IL-2 | x | x | x |
| NCT00315255 | Melanoma | completed | DC Vaccine Loaded With Killed Allogeneic Melanoma Cells + Cyclophosphamide | x | x | x | x |
| NCT00074320 | Melanoma | ongoing | Mature, Autologous Monocyte-Derived DCs Transfected With RNAs Encoding for Mage-3, MelanA, and Survivin Antigens | x | x | x | x |
| NCT09940004** | Melanoma | ongoing | Autologous DC vaccination | x | x | x |
| NCT01193553** | Melanoma | ongoing | IL-12 DC Vaccine | x | x | x |
| NCT01929017** | Melanoma | recruiting | Autologous DCs electroporated with mRNA | x | x | x |
| NCT19173322 | Melanoma | recruiting | Autologous tumor lysate loaded DC vaccine in combination with IFN-α/IFN-β and/or radiotherapy | x | x | x | x |
| NCT01676212 | Melanoma | recruiting | Type 1-Polarized Autologous DC Vaccines Incorporating Tumor Blood Vessel Antigen (TBVA)-Derived Peptides + Dasatinib | x | x | x | x |
| NCT00238377 | Melanoma | recruiting | Chemotherapy + IL-2 plus T-Cells + DC vaccine | x | x | x | x |
| NCT00944650 | Melanoma | recruiting | MART-1250-35-Pulsed DCs and IL-2 | x | x | x | x |
| NCT02129075 | Melanoma | recruiting | CDX-141 (DC Targeting My-EGFR+Vacine) + Neoantigen-based Melanoma-poly-ICCLC vaccine + Recombinant CDX-301 (Recombinant Human FES Ligand) | x | x | x | x | x |
| NCT01676779 | Melanoma | recruiting | mRNA Electroporated Autologous DCs | x | x | x | x |
| NCT00003538 | Melanoma | completed | Autologous idotype or tumor lysate-pulsed DCs | x | x | x | x |
| NCT06616720 | Multiple myeloma | completed | DC-Based Idiotype Vaccine With Adjutant Cytokines | x | x | x | x |
| NCT01656141 | Multiple myeloma | completed | Allogeneic DC vaccines + cyclophosphamide, melphalan, cyclosporin, mycophenolate mofetil | x | x | x | x |
| NCT01985318** | Multiple myeloma | completed | Idiotype-pulsed allogeneic DCs | x | x | x | x |
| NCT00665224 | Multiple myeloma | initiation | DCs electroporated with mRNA coding for the full-length Wilms tumor antigen (WT1) | x | x | x | x |
| NCT01067287 | Multiple myeloma | recruiting | DC fusion vaccine and CT-011 (mononclonal ab) | x | x | x | x |
| NCT00427254 | NSCLC | completed | Autologous DCs pulsed with allogeneic melanoma cells lysate (IMCancerVac) | x | x | x | x |
| NCT00199629 | NSCLC | completed | Mutant p53 peptide pulsed DC vaccine | x | x | x | x |
| NCT00103118 | NSCLC | ongoing | Autologous DC Vaccines | x | x | x | x |
| NCT11152588 | NSCLC | recruiting | DC vaccine loaded with Tumor Antigen | x | x | x | x |
| NCT1617629 | Ovarian | completed | Cvic (Autologous DCs Pulsed With Recombinant Human Fusion Protein Coupled to Oxidized Polyaminoacids) | x | x | x | x |
| NCT04784452** | Ovarian | completed | Cyclophosphamide With Peptide Pulsed Mature DCs | x | x | x | x |
| NCT01063505 | Ovarian | ongoing | Cvic (MUC1 DC Vaccine) | x | x | x | x |
| NCT00799110 | Ovarian | ongoing | DC-Tumor Fusion Vaccine + gmcsf +/- iniquimod | x | x | x | x |
| NCT00703105 | Ovarian | recruiting | Autologous tumor lysate-loaded DC vaccine +/- Ontak | x | x | x | x |
| NCT01334047** | Ovarian recruiting | Autologous DCs Loaded With Amplified Ovarian Cancer Stem Cell mRNA, hTERT and SV40 | x | x | x | x |
| NCT03033616 | Ovarian not yet open | Gvdpusdlenc-T (autologous DCs loaded with irradiated autologous tumor cells in GM-CSF) | x | x | x | x |
| NCT01521143 | Ovarian recruiting | Onc (Autologous DCs Pulsed With Recombinant Human Fusion Protein [Macul 1-GLutathione S Transferase] Coupled to Cidofovir Polyammines) | x | x | x | x |
| NCT01578530** | Pancreatic recruiting | S1 plus DC activated Cytokine induced killer treatment (DC-CIK) | x | x | x | x |
| NCT02151446** | Peritoneal not yet open | Triple combination of ceciloub, interferon alfa (IFN), and rituximab + DC vaccine | x | x | x | x |
| NCT01687207** | Prostate completed | Antigen loaded DC Vaccine | x | x | x | x |
| NCT01276914** | Prostate completed | mRNA, Transfection DCs | x | x |
| NCT00027599 | Prostate completed | Prostatic Acid Phosphatase-Pulsed DCs (Provenge) In Combination With Bevacizumab | x | x |
| NCT01171729** | Prostate completed | Creativa-PC consisted of antigen (PSA, FAP and KLH) primed DC | x | x | x | x |
| NCT00859341** | Prostate completed | Autologous DCs Pulsed With Apoptotic Tumor Cells (DC/IL13NCAP) | x | x | x | x |
| NCT00024211** | Prostate completed | Autologous DCs Pulsed With RNA Encoding Prostate Specific Antigen, PSA | x | x | x | x |
| NCT00646290 | Prostate completed | Sipuleucel-T | x | x | x | x |
| NCT00552097** | Prostate ongoing | Autologous DCs expressing Trn-MUC1 | x | x | x | x |
| NCT00345293** | Prostate ongoing | Autologous DC vaccine (DC/PC3) | x | x | x | x |
| NCT00013242 | Prostate ongoing | Sipuleucel-T | x | x | x | x |
| NCT01353012 | Prostate ongoing | Sipuleucel-T | x | x | x | x |
| NCT01467663 | Prostate ongoing | Sipuleucel-T With Concurrent Versus Sequential Administration of Aziostereone Acetate Plus Prednisone | x | x | x | x |
| NCT00715078 | Prostate ongoing | Sipuleucel-T | x | x | x | x |
| NCT01412181 | Prostate ongoing | Sipuleucel-T + Imiquod acetate | x | x | x | x |
| NCT01472749 | Prostate ongoing | Sipuleucel-T | x | x | x | x |
| NCT00715104 | Prostate ongoing | Sipuleucel-T | x | x | x | x |
| NCT01446731 | Prostate recruiting | Docetaxel + mRNA transfected DC | x | x | x | x |
| NCT01976255** | Prostate recruiting | DC-vaccination with tumor mRNA | x | x | x | x |
| NCT01981122 | Prostate recruiting | Sipuleucel-T + Epirubicin | x | x | x | x |
| NCT00876944** | Renal cell completed | Unselected, Autologous, Amplified Tumor Total RNA Transfected, DC Vaccine (MB-003) | x | x | x | x |
| NCT00197680** | Renal cell completed | Autologous DCs pulsed with peptides or tumor lysate in combination with adjuvant cytokines | x | x | x | x |
| NCT00050325** | Renal cell completed | Allogeneic DCs | x | x | x | x |
| NCT00625795** | Renal cell completed | Allogeneic DCs | x | x | x | x |
| NCT00272649** | Renal cell completed | AGS-003 DC Immunotherapy | x | x | x | x |
| NCT00913613 | Renal cell completed | VEGF Blockade With Bevacizumab Combined With Autologous TumorDC Vaccine, Interleukin-2 (IL-2) and Interferon-a-2b (IFN-2b) | x | x | x | x |
| NCT00065456 | Renal cell completed | Autologous Tumor DC Vaccine Combined With Interleukin-2 (IL-2) And Interferon-a-2b (IFN-2b) | x | x | x | x |
| NCT00678119 | Renal cell completed | Autologous DC Immunotherapy (AGS-003) + sandimib | x | x | x | x |
| NCT01482949 | Renal cell incomplete | Autologous DC Immunotherapy (AGS-003) + sandimib | x | x | x | x |
| NCT00456539** | Renal cell ongoing | DC Tumor Fusion Vaccine + granfo | x | x | x | x |
| NCT00141311** | Renal cell ongoing | Autologous DCs derived w irradiated tumor cells | x | x | x | x |
| NCT01924156** | Renal cell ongoing | Adenovirus-transfected autologous DC + CIK cells | x | x | x | x |
| NCT00823203** | Renal cell recruiting | Autologous DCs pulsed with tumor lysate in combination with Cytokine-Induced Killer Cell (CIK) | x | x | x | x |
| NCT01447165 | Renal cell recruiting | PD-1 Blockade Alone or In Conjunction With the DC (DC)Renal cell Carcinoma (RCC) Fusion Cell Vaccine | x | x | x | x |
| NCT00001566 | Sarcoma completed | Autologous T-Cell Transplantation With Vaccine Driven Expansion of Anti-Tumor Effectors | x | x | x | x |
| NCT00050677 | Sarcoma completed | DCs | x | x | x | x |
| NCT00923531** | Sarcoma ongoing | Tumor Purged/CD35 Depleted Lymphocytes With Tumor Lysate/KLH Pulsed DC Vaccine | x | x | x | x |
| NCT00405227 | Sarcoma ongoing | Tumor Lysate-pulsed DC Vaccine | x | x | x | x |
| NCT01347034 | Sarcoma ongoing | Autologous DCs | x | x | x | x |
| NCT01063516** | Sarcoma recruiting | Autologous DC vaccine (ADK) loaded with allogeneic tumor lysate expression of cancer-estis antigens (CTA) | x | x | x | x |
| NCT01988832** | Sarcoma recruiting | Adenovirus-transfected autologous DCs + CIK cells | x | x | x | x |
| NCT00049218** | SCLC completed | Autologous DC adenovirus p53 vaccine after chemo | x | x | x | x |
| NCT00671409 | SCLC ongoing | DCs Transduced With An Adenoviral Vector Containing the p53 Gene +p53asl + p53 pten recom biotic acid | x | x | x | x |

** Phase I**

| NCT00027534 | Solid completed | Autologous DCs Infected With CEA-6D Expressing C600, -Thioc | x | x |
| NCT00841002 | Solid completed | CDX-1307 | x | x |
| NCT00004004 | Solid completed | Carcinoidembryonic Antigen RNA-Pulsed, Autologous Human Cultured DCs | x | x |
| NCT number | Study title | Phase | Study design | Objectives | Key characteristics |
|------------|-------------|-------|--------------|------------|---------------------|
| NCT0183518** | Sarcoma recruiting | Autologous DC vaccine (ADK) loaded with allogeneic tumor lysate expression of cancer-testis antigens (CTA) | x x x x | |
| NCT0188882** | Sarcoma recruiting | Adenovirus-transduced autologous DCs + CIK cells | x | |
| NCT0049218** | SCLC completed | Autologous DCs-equivin p53 vaccine after chemop | x x x x | |
| NCT00617409 | SCLC ongoing | DCs Transduced With an Adenoviral Vector Containing the p53 Gene +3palifera+ + retinoic acid | x x | |

**Phase I**

| NCT00027534 | Solid completed | Autologous DCs Infected With CEA-ID Expressing Foxp3-TiCon | x | |
| NCT0084102 | Solid completed | CDX-1A | x x | |
| NCT0000604 | Solid recruiting | Carcinoembryonic Antigen RNA-Pulsed, Autologous Human Cultured DCs | x x | |
| NCT00122622 | Solid completed | Regulatory T-Cell Depletion With Denileukin Diftox Followed by Active Immunotherapy With Autologous DCs Infected With CEA-ID Expressing Foxp3-TiCon | x x | |
| NCT00059715 | Solid completed | CDAP-1 (BD) and CMV Ipp56 Peptide-Pulsed, Autologous DCs | x x | |
| NCT0027406 | Solid recruiting | Cyclophosphamide/Fludarabine + NY-ESO-1 TCR Engineered Adoptive TCell Transfer Therapy + NY- ESO-1(157-165) pE 3 peptide pulsed DC vaccine + ramipril + 1.5 | x x x | |
| NCT01501118 | Solid recruiting | Autologous AdHER2 DC vaccine | x | |
| NCT01922820 | Solid recruiting | DEC-25A-NY-ESO-1 fusion protein vaccine + stramum | x x x | |
| NCT00834402 | AML completed | Wilms Tumor Gene (WTG) mRNA-transfected Autologous DC Vaccine | x x | |
| NCT00835321 | AML completed | Autologous DC vaccine | x x x | |
| NCT01453274 | AML recruiting | Vaccine DCs are pulsed with overlapping peptides derived from MAGE-A1, MAGE-A3, and NY-ESO-1 | x x x | |
| NCT0117149 | Brain completed | Autologous DCs loaded with allogeneic Brain tumor stem cells = immunitor | x x | |
| NCT00839894 | Brain completed | Autologous DCs Pulsed With Autologous Apoptotic Tumor Cells (EOCART) | x x x | |
| NCT01107815 | Brain completed | Autologous Tumor Lysate-Pulsed DC vaccine | x x | |
| NCT0578446 | Brain completed | Surgical Resection With Gladed Wafer Placement Followed by Vaccination With DCs Pulsed With Tumor Lysate | x x x x | |
| NCT0078589 | Brain completed | Tumor Associated Antigen Pulsed DC Immunotherapy | x | |
| NCT00812001 | Brain completed | Gloma-associated antigen peptide-pulsed autologous DC vaccine | x x x | |
| NCT00855510 | Brain completed | Autologous Tumor Lysate-Pulsed DC vaccine | x x x x | |
| NCT00839869 | Brain ongoing | Anti-Tumor Immunotherapy Targeted Against Cytomegalovirus | x x x | |
| NCT00806032 | Brain ongoing | BTSC mRNA-loaded DCs | x x | |
| NCT00860095 | Brain ongoing | CMV, VACV, and CMV, DCs | x x | |
| NCT02010806 | Brain recruiting | DC vaccine + temozolomide chemotherapy and involved field radiation therapy | x x x x | |
| NCT0188820 | Brain recruiting | DC Vaccine + Imiquimod | x x x x | |
| NCT01902771 | Brain recruiting | DC Vaccine/Tumor lysate = imiquimod | x x x | |
| NCT01792305 | Brain recruiting | DC Vaccine in combination with Imiquimod cream | x x x x | |
| NCT0204489 | Brain recruiting | Autologous ICT-121 DC Vaccine | x x x x | |
| NCT0656483 | Brain recruiting | RNA-loaded DC vaccine + basiliximab | x x | |
| NCT00197522 | Breast completed | Autologous CD34+ Derived DCs Transduced With an Adenoviral Vector Expressing Inactivated HER- 2 Neu | x x | |
| NCT0205724 | Breast recruiting | HER-2 pulsed DC Vaccine | x x | |
| NCT0018423 | Breast recruiting | HER-2 pulsed DC Vaccine | x x | |
| NCT07158582 | Breast recruiting | Autologous DCs Loaded With Oncoreat Antigens | x x x x | |
| NCT0106292 | Breast completed | AdHer-2Neu transduced DCs | x | |
| NCT0000307 | Cervical completed | Immunization With Altering Human Papillomavirus E7 Lipoepitope Epitope Vaccine and DCsPresenting the E7 Epitope | x x x | |
| NCT01715992 | Colorectal completed | Alpha-type-1 DC Vaccines | x x x | |
| NCT0054901 | Colorectal ongoing | Tumor-loaded DCs | x x | |
| NCT0174601 | HCC recruiting | COMBDCDC (allogeneic DCs) Cancer Vaccine | x x x x | |
| NCT07700167 | Melanoma completed | Antigen-Bearing DCs | x x | |
| NCT0067524 | Melanoma completed | Mature Autologous DCs Transfected With Tumor Antigen RNA and Small Inhibitory RNAs | x x x | |
| NCT00313558 | Melanoma completed | MART-1 tetanus Vaccine + NY-ESO-1 Peptide-Pulsed DCs + Fludarabine | x x | |
| NCT00798829 | Melanoma completed | Adenovirus C571 Transduced MART-1 tetanus Peptide-Pulsed DCs | x x | |
| NCT0085458 | Melanoma completed | Autologous tumor cell lysate-pulsed DCs | x x | |
| NCT00008989 | Melanoma completed | CP-775, 206 (CTLA4) Blocking monoclonal antibody In Combination With MART-1 Peptide- Pulsed DCs | x | |
| NCT0003985 | Melanoma completed | DC-MART-1 peptide vaccine | x x | |
| NCT0515983 | Melanoma completed | Autologous DCs Loaded With Allogeneic Apoptotic Tumor Cells | x x | |
| NCT01339563 | Melanoma completed | Autologous T- Antigen-Presenting Cells (T-APC) + CD8+ Antigen-Specific T Cells (CTL) + Cyclophosphamide | x x | |
| NCT0015067 | Melanoma | completed | Adenoviral Transduced Autologous DCs Engineered to Express hIL-12 (NCT00112485) | x | x | x |
| NCT0005867 | Melanoma | completed | DC-MART-1 peptide vaccine | x | x | x |
| NCT0186380 | Melanoma | completed | Autologous Triflav DC vaccine | x | x | x |
| NCT0003792 | Melanoma | completed | IL-2 + DCs, and then pulsed with MART-1-gpl100, lymphocytes, MAGE-3 peptides and CD134 Antibody | x | x | x |
| NCT0014824 | Melanoma | completed | NY-ESO-1 Protein Vaccination + Imiquimod | x | x | x |
| NCT1838257 | Melanoma | not yet recruiting | Infusion of activated Tumor Infiltrating Lymphocytes (TILs) followed by Low-Dose Interleukin-2 | x | x | x |
| NCT00260338 | Melanoma | ongoing | Alpha-IFN-Based and cDC-Based Intratumoral Vaccines | x | x | x |
| NCT00124124 | Melanoma | ongoing | melanoma vaccine (5 melanoma peptides) with either Montanide or DCs | x | x | x |
| NCT00074320 | Melanoma | ongoing | Mature Autologous Monocyte-Derived DCs Transfected With RNAs Encoding for Mage-3, MelanA, and Survivin Antigens | x | x | x |
| NCT01465104 | Melanoma | recruiting | Autologous Lungingase-type DCs Electroporated With mRNA Encoding a Tumor-associated Antigen | x | x | x |
| NCT01863108 | Melanoma | recruiting | Peptide-loaded Polymethylated DC Line (GenusVac-Merk) | x | x | x |
| NCT01945373 | Melanoma | recruiting | Chemotherapy (Cyclophosphamide/Rudabine) + T cells + IL-2 + DCs pulsed with autologous tumor lysate and NY-ESO-1 peptide | x | x | x |
| NCT01735089 | Melanoma | recruiting | DC Activating Scaffold Incorporating Autologous Melanoma Cell Lysate (WDVAX) | x | x | x |
| NCT00893777 | Melanoma | recruiting | Peptide-coated DCs (pDC) | x | x | x |
| NCT0083870 | Melanoma | recruiting | Mature DC Vaccine Against gp100 + cyclophosphamide | x | x | x |
| NCT00208082 | Mesothelioma | completed | Tumor lysate-loaded autologous DCs | x | x | x |
| NCT01241852 | Mesothelioma | completed | DC-Based Immunotherapy Combined With Low-Dose Cyclophosphamide | x | x | x |
| NCT00495969 | Multiple myeloma | completed | DC Tumor Fusion Vaccine | x | x | x |
| NCT00458563 | Multiple myeloma | completed | DC Tumor Fusion | x | x | x |
| NCT00498512 | Multiple myeloma | completed | Autologous idotype-protein pulsed DCs | x | x | x |
| NCT01995701 | Multiple myeloma | recruiting | CT: MAGE-A3, and WT1 mRNA-electroporated Autologous Lungingase-type DCs | x | x | x |
| NCT00023805 | NSSLCL | completed | Autologous Tumor Lysate-Pulsed DCs | x | x | x |
| NCT00120984 | NSSLCL | completed | Autologous DC-adenovirus CC1.21 vaccine | x | x | x |
| NCT01574222 | NSSLCL | ongoing | Autologous DC-adenovirus CC1.21 vaccine | x | x | x |
| NCT00063241 | Ovarian | completed | Autologous DC Vaccine Loaded With Autologous Tumor Cells Lysate (DC-Vax-C) + intravenous bevacizumab and oral metronomic cyclophosphamide | x | x | x |
| NCT0184585 | Ovarian | ongoing | Fully Mature, TERTmRNA and Survivin - Peptide Double Loaded DCs | x | x | x |
| NCT00547114 | Pancreatic | completed | Intratumoral DC Immunotherapy in Combination With Gemcitabine and Stereotactic Radiosurgery | x | x | x |
| NCT01491080 | Pancreatic | completed | PolyI:Clc and Peptide-pulsed DCs vaccine | x | x | x |
| NCT00108268 | Prostate | completed | Tumor RNA transfected DCs | x | x | x |
| NCT00089551 | Prostate | completed | PSA-Based Vaccine | x | x | x |
| NCT0097309 | Prostate | ongoing | Elopole-Enriched TARP Peptide and TARP Peptide-Pulsed DCs | x | x | x |
| NCT00374049 | Prostate | ongoing | MYC1 Vaccine + Poly-I:Clc (Polylysine-polylysine Acid Stabilized With Polylysine and Carboxymethylcellulose) or HibernTM | x | x | x |
| NCT00970203 | Prostate | recruiting | Autologous 1 DC-Based Vaccines Loaded With Allogeneic Prostate Cancer Cells Lines + Androgen Ablation | x | x | x |
| NCT01823778 | Prostate | recruiting | DC vaccine, BPX-201 + activating agent, AP1903 | x | x | x |
| NCT0005816 | Renal cell | completed | Autologous Dendritic Cells Transfected With Autologous TotalTumor RNA | x | x | x |
| NCT00185474 | Renal cell | completed | Multi-Antigen Loaded DC Vaccine | x | x | x |
| NCT0152017 | Renal cell | ongoing | Cemog-DC (allogeneic DCs) Cancer Vaccine | x | x | x |
| NCT01828777 | Renal cell | recruiting | Autologous DCs Transfected With Ad-GMCAVX | x | x | x |
| NCT01031512 | Sarcoma | recruiting | DC Vaccination With and Without Injection of Myeloid Derived Suppressor Cells by Geminabine + Imiquimod | x | x | x |
| NCT01241162 | Sarcoma | recruiting | Autologous cancer testis antigen specific DC vaccine + docetaxel (demethylating chemotherapy) | x | x | x |