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FOCUS: VACCINES

Optimizing Dendritic Cell-Based Approaches for Cancer Immunotherapy

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Dendritic cells (DC†) 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; CD, cluster of differentiation; TAP, transporter associated with antigen processing; IRAP, insulin-regulated aminopeptidase; FcγRIIB, Fc gamma receptor IIB; DNA, deoxyribonucleic acid; IFN, interferon; RNA, ribonucleic acid; HLA, human leukocyte antigen; CpG, cytosine-phosphate-guanine; TGF-β, transforming growth factor- β; EGF, epidermal growth factor; CXCL, C-X-C chemokine ligand; KLH, keyhole limpet hemocyanin; TNF, tumor necrosis factor; PGE2, Prostaglandin E2; 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 tumoricidality. $CD8^+$ 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 *neu*T-transgenic murine model, vaccination with bone marrow-derived DCs modified by a recombinant adenovirus-expressing truncated neu oncoprotein ($DC_{Ad.Neu}$) induced potent serum anti-*neu* antibodies and IFN-γ secretion by $CD4^+$ and $CD8^+$ T-cells. More importantly, $DC_{Ad.Neu}$ 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 *neu*T-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 $CD8\alpha^+$ 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 naïve $CD4^+$ 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

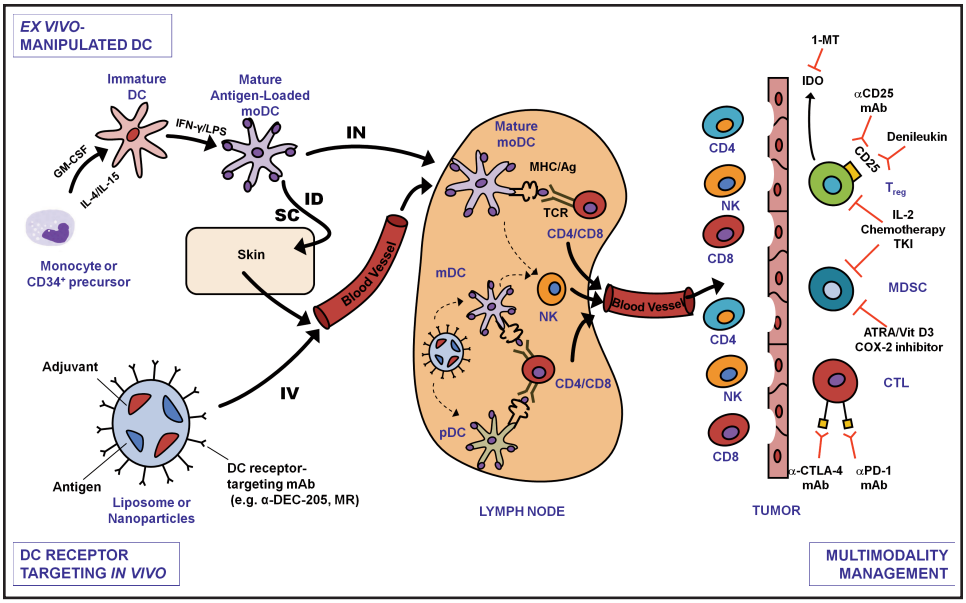

Figure 1. Global view of a multimodality approach to optimizing DC immunotherapy. Antigen-specific T-cell responses can be induced by traditional *ex vivo*-manipulated DCs or DC receptor targeting *in vivo*. In *ex vivo* manipulation, monocyte or CD34$^+$ precursors are sequentially matured with proinflammatory cytokines, loaded with antigen, and injected (either IN or ID/SC). Liposomes or nanoparticles comprising monoclonal DC receptor-targeting antibody-antigen chimera (± adjuvant) can also be delivered to lymph nodes via IV routes. Within the lymph node, DCs present antigen to CD8$^+$/CD4$^+$ T-cells in the context of MHC Class I/II molecules, triggering antigen-specific CTLs. Natural DC subsets, such as mDCs and pDCs, can be targeted with DC targeting liposomes/nanoparticles, which in turn stimulate antigen-specific CD8$^+$/CD4$^+$ T-cell production. Cross-talk between DC-delivering mechanisms can induce other immune cells, such as NK cells. These effector populations migrate to the tumor bed, where they directly attack tumor cells. Multimodality optimization of DC immunotherapy involves preventing antigen-specific CTL exhaustion and depleting tumor-elaborated T_{reg} and MDSCs. Anti-CTLA-4 and anti-PD-1 mAb are immunostimulatory therapies aimed at recovering T-cell cytotoxicity. A variety of agents, including IL-2, chemotherapy, and TKIs can mute T_{reg}/MDSCs. COX-2 inhibitors, ATRA, and vitamin D3 can specifically target MDSCs, whereas anti-CD25 mAbs and denileukin diftitox target CD25 on T_{reg}. Non-CD25-based alternatives, such as 1-MT, inhibit T_{reg}-generated IDO.

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^{pos} 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 endosomic 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. $CD8\alpha^+$ DCs targeted using anti-DEC-205-ovalbumin (OVA) favored the generation of $CD8^+$ immunity, whereas $CD8\alpha^-$ 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 $CD8\alpha^+$ 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-activated Th interaction *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 T_{eff} (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," T_{reg} chemoattraction/expansion, 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 PGE_2, 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., T_{reg}) [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 T_{reg} [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., PGE_2-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-

Table 1. Number of clinical trials employing DC immunotherapy, organized by involved organ and phase of development. Data was obtained using the search terms "dendritic cells" and "cancer" on www.clinicaltrials.gov.

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

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) $HER2^{pos}$-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

HER2^{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^{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-monocytes [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 (T_{reg}, MDSCs) that mediate escape from immune surveillance. Two broad strategies to mute T_{reg}/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 T_{reg} effects but also converts regulatory cells into IFN-γ-secreting Th1 [127]. Alternatively, loading DCs with immunogenic FoxP3 epitopes may generate FoxP3-specific CTLs capable of eliminating T_{reg}. Melanoma-bearing mice vaccinated with FoxP3 mRNA-transfected DCs reduced intratumoral $FoxP3^+$ T_{reg} 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 T_{reg} systemically, which may promote irreversible autoimmunity.

Second, DCs can be synergized with several T_{reg}/MDSC-targeting therapies. Anti-CD25 mAb (daclizumab, basiliximab), targeting IL-2 receptor α-chains, transiently deplete T_{reg} and augment tumor rejection in murine models. In metastatic melanoma, addition of daclizumab to tumor antigen/KLH-pulsed DCs depleted T_{reg}, 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 T_{reg} 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_{reg}	Brain (NCT00626483); Melanoma (NCT00847106); Ovarian (NCT01132014)
	Denileukin diftitox	Target CD25, deplete T_{reg}	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 (NCT00197860, 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.

Table 2. Optimizing dendritic cell-based vaccination via multimodality approaches. Continued.

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-I:C (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 ±fludarabine	Lymphodepleting, reboots immune system	Solid (NCT01697527); Brain (NCT00323115, NCT02010606); Melanoma (NCT00338377, NCT00910650, NCT01946373, NCT00313508, NCT00704938); Renal (NCT00704938, NCT00093522)
	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 (NCT00088985, NCT00266110)

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 — 1-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

peptide inhibiting nuclear translocation of FoxP3 protected mice undergoing $CD8^+$ peptide immunization against tumor implantation [136]. Finally, disrupting T_{reg} trafficking to tumors/lymph nodes may boost DC function at these sites. CCR4 antagonists, which block CCL22/CCL17-mediated T_{reg} 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 (pidilizumab) enhanced activated-CTL responses following stimulation with an autologous myeloma-DC fusion vaccine [145]. Pidilizumab 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 T_{eff}-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 T_{eff} 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 T_{reg}/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 chemoimmunotherapy 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 T_{reg} [164] and inducing CTL-mediated targeting of tumor stroma [165]. In light of this dynamic interplay between irradiated tumor, DCs, and effector/suppressive 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/MDSCs, 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 $BRAF^{V600E}$-targeting TKI in melanoma, are increasingly appreciated. In conjunction with its inhibitory effects on T_{reg} and MDSCs, vemurafenib reduces tumor-induced CCL2 expression and enhances TME T_{eff} infiltration [169]. Interestingly, vemurafenib reversed $BRAF^{V600E}$ 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 $BRAF^{V600E}/PTEN^{-/-}$ 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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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
Phase III							
NCT01759810*	Brain	ongoing	Dendritic vaccine, allogeneic hematopoietic stem cells, cytotoxic lymphocytes			x	x
NCT00045968	Brain	recruiting	DCVax(R)-L (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
NCT01782287*	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
NCT01983748	Melanoma	not yet open	Autologous DCs Loaded With Autologous Tumor RNA		x	x	x
NCT00006434	Non-Hodgkin's lymphoma	completed	Tumor-pulsed DCs + IL2		x		
NCT00065442	Prostate	completed	Sipuleucel-T (Autologous Antigen Presenting Cells Loading With PA2024)			x	x
NCT01133704	Prostate	completed	Sipuleucel-T (Autologous Antigen Presenting Cells Loading With PA2024)			x	x
NCT00005947	Prostate	completed	Sipuleucel-T (Autologous Antigen Presenting Cells Loading With PA2024)			x	x
NCT00779402	Prostate	ongoing	Sipuleucel-T (Autologous Antigen Presenting Cells Loading With PA2024)			x	x
NCT01582672	Renal cell	recruiting	AGS-003 (Autologous DC Immunotherapy)			x	x
Phase II							
NCT00019084	Solid+	completed	Mutant P53 or RAS peptides pulsed DC vaccine +/- IL2		x		
NCT01291420	Solid+	invitation only	Wilms' Tumor Gene (WT1) mRNA-electroporated Autologous DC Vaccine		x		
NCT01697527	Solid+	recruiting	NY-ESO-1 TCR Engineered PBMCs + NY-ESO-1157-165 Pulsed DCs + IL2			x	
NCT01882946**	Solid+	recruiting	DCVax-Direct (Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen)	x		x	x
NCT01373515**	AML	completed	DCP 001 (Leukemic DC Vaccine)	x	x		
NCT00510133	AML	ongoing	GRNVAC1 (Autologous Mature DCs Transfected With mRNA Encoding Human Telomerase Reverse Transcriptase)	x	x		
NCT01096602	AML	recruiting	DC AML vaccine + CT-O11 (investigational monoclonal antibody)	x	x	x	
NCT01686334	AML	recruiting	Wilms' Tumor (WT1) Antigen-targeted DC Vaccine		x	x	x
NCT01734304**	AML	recruiting	Autologous DCs Transfected With RNA Encoding Leukemia-associated Antigens	x	x	x	
NCT00576537	Brain	completed	Tumor Lysate-Pulsed DC vaccine	x			
NCT00846456**	Brain	completed	DC vaccine with mRNA from tumor stem cells	x	x	x	x
NCT00323115	Brain	completed	Intra-nodal DC/Tumor Lysate Vaccination + Radiotherapy (RT) + temozolomide (TMZ)	x	x	x	x
NCT00766753**	Brain	ongoing	Type 1 DCs Pulsed With Multiple Peptides	x	x		
NCT01006044	Brain	ongoing	Autologous DC Vaccine	x	x	x	x
NCT01280552	Brain	ongoing	ICT-107 (Autologous DCs pulsed with immunogenic antigens)	x	x	x	x
NCT01635283	Brain	recruiting	Tumor Lysate-Pulsed autologous DC vaccine		x	x	x
NCT01204684	Brain	recruiting	Tumor Lysate-Pulsed autologous DC vaccine +/- Toll-like Receptor Agonists			x	x
NCT01326104	Brain	recruiting	Total tumor RNA (TTRNA)-loaded DCs +/- Autologous Lymphocyte Transfer			x	
NCT00088985	Breast	completed	Multiepitope DC Vaccine + Trastuzumab/Vinorelbine		x	x	
NCT00622401**	Breast	ongoing	DC/Tumor Fusion Vaccine + IL12	x	x	x	
NCT01431196	Breast	ongoing	Autologous DC vaccine	x	x	x	x
NCT00266110	Breast	ongoing	Multiepitope DC Vaccine + Trastuzumab/Vinorelbine		x		
NCT00082641	Breast	ongoing	Autologous DC-adenovirus p53 vaccine	x	x		
NCT01042535**	Breast	ongoing	DC-adenovirus p53 vaccine + 1-methyl-D-tryptophan	x	x	x	x
NCT02018458**	Breast	recruiting	Cyclin B1/WT-1/CEF-loaded DC vaccine + preoperative chemotherapy +/- IL-1 blockade w anakinra	x		x	
NCT02061332**	Breast	recruiting	HER-2 Pulsed DC Vaccine	x	x	x	
NCT00311272	Colorectal	completed	MelCancerVac (Autologous DCs Pulsed With Allogenous Melanoma Lysate)			x	
NCT00103142	Colorectal	completed	Vaccinia-Carcinoembryonic antigen (CEA)-mucin 1 (MUC-1)- Triad of costimulatory molecules TRICOM vaccine (PANVAC-V) and fowlpox-CEA-MUC-1-TRICOM Vaccine (PANVAC-F) administered with autologous dendritic cells or with sargramostim (GM-CSF).	x	x		
NCT00019591**	Colorectal	completed	Mutant Ras Peptide-Pulsed DCs +/- IL 2		x	x	
NCT00228189**	Colorectal	completed	CEA-loaded DC vaccine	x	x		

NCT01413295	Colorectal	ongoing	Autologous DCs pulsed with autologous tumour antigens			x	x
NCT01885702**	Colorectal	recruiting	Vaccination with frameshift-derived neoantigen-loaded DC	x	x	x	
NCT01348256	Colorectal	recruiting	Autologous DCs loaded with autologous tumor antigens			x	x
NCT00003433**	Colorectal	completed	CEA RNA-pulsed DC cancer vaccine		x		x
NCT01783951**	Gastric	recruiting	S-1 plus DC activated Cytokine induced killer treatment (DC-CIK)	x		x	x
NCT00022334**	HCC	completed	DC Pulsed With Four AFP Peptides	x	x	x	
NCT00923910**	Hematologic Malignancies	completed	WT1 Peptide-Pulsed DCs	x			
NCT02115126	Lymphoma	not yet open	EBV Derived DC Vaccine +/- TLR9 Agonist, DUK-CPG-001	x	x	x	
NCT01926639	Lymphoma	recruiting	Radiotherapy Combined With Intratumoral Injections of DC and Rituximab		x	x	
NCT00948480	Melanoma	completed	Autologous tumor cells + DC + GMCSF			x	x
NCT00012064**	Melanoma	completed	Autologous DC + GMCSF	x	x	x	
NCT00197912**	Melanoma	completed	Tumor antigen loaded autologous DC	x	x	x	
NCT01042366	Melanoma	completed	Antigen-loaded autologous DC vaccine		x		
NCT00243529**	Melanoma	completed	DC Vaccines Presenting HLA Class I and II Restricted Tumor Epitopes Either by Peptide-pulsing or mRNA Transfection	x	x		
NCT00436930	Melanoma	completed	Adjuvant GM-CSF + Proliferating Tumor Cells vs GM-CSF + DCs Loaded With Proliferating Tumor Cells	x	x	x	x
NCT01278940**	Melanoma	completed	mRNA- Transfected DCs	x	x	x	
NCT00107159	Melanoma	completed	Autologous DC-allogeneic Melanoma tumor cell lysate vaccine	x	x	x	
NCT00039325**	Melanoma	completed	Dendritic cell-MART-1 peptide vaccine	x	x	x	
NCT00847106**	Melanoma	completed	Dendritic Cell Based Vaccines With an Anti-CD25 Monoclonal Antibody (Daclizumab)		x	x	
NCT00019890	Melanoma	completed	CD34+ Derived or Peripheral Monocyte Derived DCs Pulsed With MART-1 and gp100 Melanoma Antigens + sargramostim	x			
NCT00125749**	Melanoma	completed	DCs Loaded With Heat Treated Killed Allogeneic Melanoma Cells	x	x	x	
NCT00056134	Melanoma	completed	Denileukin diftitox, recombinant CD40-ligand, therapeutic autologous DCs	x	x	x	x
NCT00334776	Melanoma	completed	MART-1gp100/Tyrosinase Peptide-Pulsed DC Vaccine		x	x	
NCT00243594**	Melanoma	completed	Peptide-Pulsed DCs		x	x	
NCT00003229**	Melanoma	completed	Autologous cultured DCs pulsed with gp100 and tyrosinase peptides or autologous melanoma tumor cell lysates+ IL2	x	x	x	x
NCT00019214**	Melanoma	completed	DCs Presenting Epitopes Derived From Melanoma Associated Antigens MART-1 and gp 100 +/- IL2	x			
NCT00313235**	Melanoma	completed	DC Vaccine Loaded With Killed Allogeneic Melanoma Cells + Cyclophosphamide	x	x	x	
NCT00074230	Melanoma	ongoing	Mature, Autologous Monocyte-Derived DCs Transfected With RNAs Encoding for Mage-3, MelanA, and Survivin Antigens	x	x	x	x
NCT00940004**	Melanoma	ongoing	Autologous DC vaccination	x	x	x	
NCT01189383**	Melanoma	ongoing	IL15-DC Vaccine		x		
NCT00929019**	Melanoma	recruiting	Autologous DC electroporated with mRNA		x	x	
NCT01973322	Melanoma	recruiting	Autologous tumor lysate loaded DC vaccine in combination with IFN-alfa and/or radiotherapy	x	x	x	
NCT01876212	Melanoma	recruiting	Type I-Polarized Autologous DC Vaccines Incorporating Tumor Blood Vessel Antigen (TBVA)-Derived Peptides + Dasatinib	x	x	x	x
NCT00338377	Melanoma	recruiting	Chemotherapy + IL-2 plus T-Cells + DC Vaccine			x	
NCT00910650	Melanoma	recruiting	MART-126•35-Pulsed DCs and IL-2	x		x	
NCT02129075	Melanoma	recruiting	CDX-1401 (DC Targeting NY-ESO-1 Vaccine) + neoantigen-based Melanoma-poly-ICLC vaccine + Recombinant CDX-301 (Recombinant Human Flt3 Ligand)	x	x	x	x
NCT01676779	Melanoma	recruiting	mRNA Electroporated Autologous DCs	x			x
NCT00083538	Multiple myeloma	completed	Autologous idiotype or tumor lysate-pulsed DCs		x		
NCT00616720	Multiple myeloma	completed	DC-Based Idiotype Vaccine With Adjuvant Cytokines		x	x	
NCT00185614	Multiple myeloma	completed	Allogenic DC vanccines + cyclophosphamide, melphalan, cyclosporin, mycophenolate mofetil	x			x
NCT00186316**	Multiple myeloma	completed	Idiotype-pulsed allogeneic DCs		x		
NCT00965224	Multiple myeloma	invitation only	DCs electroporated with mRNA coding for the full-length Wilms' tumor antigen (WT1)		x	x	x
NCT01067287	Multiple myeloma	recruiting	DC fusion vaccine and CT-011 (monoclonal ab)	x	x	x	
NCT00442754	NSCLC	completed	Autologous DCs pulsed with allogeneic melanoma cell lysate (MelCancerVac)		x	x	x
NCT00019929	NSCLC	completed	Mutant p53 peptide pulsed DC vaccine	x	x	x	x
NCT00103116	NSCLC	ongoing	Autologous DC Vaccines		x	x	
NCT01159288	NSCLC	recruiting	DC vaccine loaded with Tumor Antigen			x	
NCT01617629	Ovarian	completed	Cvac (Autologous DCs Pulsed With Recombinant Human Fusion Protein Coupled to Oxidized Polymannose)	x			x
NCT00478452**	Ovarian	completed	Cyclophosphamide With Peptide Pulsed Mature DCs	x	x		
NCT01068509	Ovarian	ongoing	Cvac (MUC1 DC Vaccine)	x	x	x	x
NCT00799110	Ovarian	ongoing	DC/Tumor Fusion Vaccine + gmcsf +/- imiquimod	x	x	x	
NCT00703105	Ovarian	recruiting	Autologous tumor lysate-loaded DC vaccine +/- Ontak	x	x		

NCT01334047**	Ovarian	recruiting	Autologous DCs Loaded With Amplified Ovarian Cancer Stem Cell mRNA, hTERT and Survivin	x	x	x	x
NCT02033616	Ovarian	not yet open	ovapuldencel-T (autologous DCs loaded with irradiated autologous tumor cells in GM-CSF)	x		x	x
NCT01521143	Ovarian	recruiting	Cvac (Autologous DCs Pulsed With Recombinant Human Fusion Protein [Mucin 1-Glutathione S Transferase] Coupled to Oxidized Polymannose)	x		x	x
NCT01781520**	Pancreatic	recruiting	S-1 plus DC activated Cytokine induced killer treatment (DC-CIK)	x		x	x
NCT02151448**	Peritoneal	not yet open	Triple combination of celecoxib, interferon alfa (IFN), and rintatolimod + DC vaccine	x	x	x	x
NCT01897207**	Prostate	completed	Antigen loaded DC Vaccine	x	x	x	x
NCT01278914**	Prostate	completed	mRNA- Transfected DCs	x	x		
NCT00027599	Prostate	completed	Prostatic Acid Phosphatase-Pulsed DCs (Provenge) In Combination With Bevacizumab	x	x		
NCT01171729**	Prostate	completed	CreaVax-PC consisted of antigen (PSA, PAP and KLH) primed DC		x	x	x
NCT00289341**	Prostate	completed	Autologous DCs Pulsed With Apoptotic Tumor Cells (DC/LNCaP)	x	x	x	
NCT00004211**	Prostate	completed	Autologous DCs Pulsed With RNA Encoding Prostate Specific Antigen, PSA	x	x	x	
NCT00849290	Prostate	completed	Sipuleucel-T	x		x	
NCT00852007**	Prostate	ongoing	Autologous DCs expressing Tn-MUC1	x	x	x	x
NCT00345293**	Prostate	ongoing	Autologous DC vaccine (DC/PC3)	x	x	x	
NCT00901342	Prostate	ongoing	Sipuleucel-T	x	x		x
NCT01338012	Prostate	ongoing	Sipuleucel-T	x	x		x
NCT01487863	Prostate	ongoing	Sipuleucel-T With Concurrent Versus Sequential Administration of Abiraterone Acetate Plus Prednisone	x	x		
NCT00715078	Prostate	ongoing	Sipuleucel-T		x		x
NCT01431391	Prostate	ongoing	Sipuleucel-T + leuprolide acetate	x	x	x	
NCT01477749	Prostate	ongoing	Sipuleucel-T	x	x		
NCT00715104	Prostate	ongoing	Sipuleucel-T		x		
NCT01446731	Prostate	recruiting	Docetaxel +/- mRNA transfected DC	x	x	x	x
NCT01197625**	Prostate	recruiting	DC-vaccination with tumor mRNA	x		x	
NCT01981122	Prostate	recruiting	Sipuleucel-T + Enzalutamide	x	x	x	x
NCT00087984**	Renal cell	completed	Unselected, Autologous, Amplified Tumor Total RNA-Transfected, DC Vaccine (MB-002)	x		x	
NCT00197860**	Renal cell	completed	autologous DCs pulsed with peptides or tumor lysate in combination with adjuvant cytokines	x	x	x	
NCT00050323**	Renal cell	completed	Allogeneic DCs	x	x	x	
NCT00625755**	Renal cell	completed	Allogeneic DCs	x	x	x	
NCT00272649**	Renal cell	completed	AGS-003 DC Immunotherapy		x	x	
NCT00913913	Renal cell	completed	VEGF Blockade With Bevacizumab Combined With Autologous Tumor/DC Vaccine, Interleukin-2 (IL-2) and Interferon-α-2b (IFNα-2b)	x	x	x	
NCT00085436	Renal cell	completed	Autologous Tumor/DC Vaccine Combined With Interleukin-2 (IL-2) And Interferon-α-2a (IFNα-2a)		x	x	
NCT00678119	Renal cell	completed	Autologous DC Immunotherapy (AGS-003) + sunitinib		x	x	
NCT01482949	Renal cell	invitation only	Autologous DC Immunotherapy (AGS-003) + sunitinib	x	x	x	x
NCT00458536**	Renal cell	ongoing	DC Tumor Fusion Vaccine + gmcsf	x	x		
NCT00014131**	Renal cell	ongoing	Autologous DCs admixed w irradiated tumor cells		x	x	x
NCT01924156**	Renal cell	ongoing	Adenovirus-transfected autologous DC + CIK cells	x		x	
NCT00862303**	Renal cell	recruiting	Autologous DCs pulsed with tumor lysate in combination with Cytokine-Induced Killer Cell (CIK)		x	x	
NCT01441765	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
NCT00365872	Sarcoma	completed	DCs	x	x	x	
NCT00923351**	Sarcoma	ongoing	Tumor Purged/CD25 Depleted Lymphocytes with Tumor Lysate/KLH Pulsed DC Vaccine	x	x		
NCT00405327	Sarcoma	ongoing	Tumor Lysate-pulsed DC Vaccine		x	x	
NCT01347034	Sarcoma	ongoing	Autologous DCs	x	x		
NCT01883518**	Sarcoma	recruiting	Autologous DC vaccine (ADKV) loaded with allogeneic tumor lysate expression of cancer-testis antigens (CTA)	x	x	x	x
NCT01898663**	Sarcoma	recruiting	Adenovirus-transfected autologous DCs + CIK cells	x		x	
NCT00049218**	SCLC	completed	Autologous DC-adenovirus p53 vaccine after chemo	x	x	x	x
NCT00617409	SCLC	ongoing	DCs Transduced With an Adenoviral Vector Containing the p53 Gene +/-paclitaxel +/- retinoic acid			x	x

Phase I							
NCT00027534	Solid+	completed	Autologous DCs Infected With CEA-6D Expressing Fowlpox -Tricom	x	x		
NCT00648102	Solid+	completed	CDX-1307	x		x	
NCT00004604	Solid+	completed	Carcinoembryonic Antigen RNA-Pulsed, Autologous Human Cultured DCs	x	x		

NCT01883518**	Sarcoma	recruiting	Autologous DC vaccine (ADKV) loaded with allogeneic tumor lysate expression of cancer-testis antigens (CTA)	x	x	x	x
NCT01898663**	Sarcoma	recruiting	Adenovirus-transfected autologous DCs + CIK cells	x		x	
NCT00049218**	SCLC	completed	Autologous DC-adenovirus p53 vaccine after chemo	x	x	x	x
NCT00617409	SCLC	ongoing	DCs Transduced With an Adenoviral Vector Containing the p53 Gene +/-paclitaxel +/- retinoic acid			x	x

Phase I							
NCT00027534	Solid^{+}	completed	Autologous DCs Infected With CEA-6D Expressing Fowlpox -Tricom	x	x		
NCT00648102	Solid^{+}	completed	CDX-1307	x		x	
NCT00004604	Solid^{+}	completed	Carcinoembryonic Antigen RNA-Pulsed, Autologous Human Cultured DCs	x	x		
NCT00128622	Solid^{+}	completed	Regulatory T Cell Depletion With Denileukin Diftitox Followed by Active Immunotherapy With Autologous DCs Infected With CEA-6D Expressing Fowlpox-Tricom	x	x		
NCT00057915	Solid^{+}	completed	CAP-1 (6D) and CMVpp65 Peptide-Pulsed, Autologous DCs	x	x		
NCT02070406	Solid^{+}	not yet recruiting	Cyclophosphamide/Fludarabine + NY-ESO-1 TCR Engineered Adoptive TCell Transfer Therapy + NY-ESO-1(157-165) peptide pulsed DC vaccine + ipilimumab + IL2	x	x	x	
NCT01730118	Solid^{+}	recruiting	Autologous Ad HER2 DC vaccine	x			
NCT01522820	Solid^{+}	recruiting	DEC-205-NY-ESO-1 fusion protein vaccine + sirolimus	x	x	x	
NCT00834002	AML	completed	Wilms Tumor Gene (WT1) mRNA-transfected Autologous DC Vaccine	x	x		
NCT00963521	AML	completed	Autologous DC vaccine	x	x	x	
NCT01483274	AML	recruiting	Vaccine DCs are pulsed with overlapping peptides derived from MAGE-A1, MAGE-A3, and NY-ESO-1	x	x	x	
NCT01171469	Brain	completed	Autologous DCs loaded with allogeneic Brain tumor stem cells + Imiquimod	x		x	
NCT00893945	Brain	completed	Autologous DCs Pulsed With Autologous Apoptotic Tumor Cells (DC/AAT)	x	x	x	
NCT00107185	Brain	completed	Autologous Tumor Lysate-Pulsed DC vaccine	x			x
NCT00576446	Brain	completed	Surgical Resection With Gliadel Wafer Placement Followed by Vaccination With DCs Pulsed WithTumor Lysate		x	x	x
NCT00576641	Brain	completed	Tumor Associated Antigen Pulsed DC Immunotherapy	x			
NCT00612001	Brain	completed	Glioma-associated antigen peptide-pulsed autologous DC vaccine	x		x	x
NCT00068510	Brain	completed	Autologous Tumor Lysate-Pulsed DC vaccine	x	x	x	x
NCT00639639	Brain	ongoing	Anti-Tumor Immunotherapy Targeted Against Cytomegalovirus	x	x	x	
NCT00890032	Brain	ongoing	BTSC mRNA-loaded DCs	x	x		
NCT00693095	Brain	ongoing	CMV/ALT + CMV-DCs	x	x	x	
NCT02010606	Brain	recruiting	DC vaccine+ temozolomide chemotherapy and involved field radiation therapy	x	x	x	x
NCT01808820	Brain	recruiting	DC Vaccine + imiquimod	x	x	x	x
NCT01902771	Brain	recruiting	DC Vaccine/tumor lysate + imiquimod	x	x	x	
NCT01792505	Brain	recruiting	DC Vaccine in combination with Imiquimod cream	x		x	
NCT02049489	Brain	recruiting	Autologous ICT-121 DC Vaccine	x	x	x	x
NCT00626483	Brain	recruiting	RNA-loaded DC vaccine + basiliximab	x	x		
NCT00197522	Breast	completed	Autologous CD34+ Derived DCs Transduced With an Adenovirus Vector Expressing Inactivated HER-2/Neu	x		x	
NCT02063724	Breast	recruiting	HER-2 pulsed DC Vaccine	x	x	x	
NCT02061423	Breast	recruiting	HER-2 pulsed DC Vaccine	x	x	x	
NCT00715832	Breast	recruiting	Autologous DCs Loaded With Oncofetal Antigen/iLRP	x	x	x	x
NCT00162929	Breast	completed	AdHer-2/neu transduced DCs	x		x	
NCT00003977	Cervical	completed	Immunization With Alternating Human Papillomavirus E7 Lipopeptide Epitope Vaccine and DCsPresenting the E7 Epitope	x	x	x	
NCT01671592	Colorectal	completed	Alpha-type-1 DC Vaccines	x	x	x	x
NCT00558051	Colorectal	ongoing	Tumor-loaded DCs	x	x		
NCT01974661	HCC	recruiting	COMBIG-DC (allogeneic DCs) Cancer Vaccine	x	x	x	x
NCT00700167	Melanoma	completed	Antigen-Bearing DCs	x	x		
NCT00672542	Melanoma	completed	Mature Autologous DCs Transfected WithTumor Antigen RNA and Small Inhibitory RNAs	x	x	x	
NCT00313508	Melanoma	completed	MART-1/gp100/Tyrosinase/NY-ESO-1 Peptide-Pulsed DCs +/- Fludarabine			x	x
NCT00798629	Melanoma	completed	Adenovirus CCL-21 Transduced MART-1/gp100 Peptide-Pulsed DCs	x	x		
NCT00085488	Melanoma	completed	Autologous tumor cell lysate-pulsed DC	x	x		
NCT00090896	Melanoma	completed	CP-675,206 (CTLA 4 Blocking monoclonal antibody) In Combination With MART-1 Peptide-Pulsed DCs	x			
NCT00003665	Melanoma	completed	DC-MART-1 peptide vaccine	x		x	
NCT00515983	Melanoma	completed	Autologous DCs Loaded With Allogeneic ApoptoticTumor Cells	x	x		
NCT01339663	Melanoma	completed	Autologous T- Antigen-Presenting Cells (T-APC) + CD8+ Antigen-Specific T Cells (CTL) + Cyclophosphamide	x	x	x	

NCT00815607	Melanoma	completed	Adenoviral Transduced Autologous DCs Engineered to Express hIL-12(INXN-3001)	x	x	x	
NCT00005617	Melanoma	completed	DC MART-1 peptide vaccine	x	x	x	
NCT01066390	Melanoma	completed	Autologous TriMix-DC vaccine		x	x	
NCT00003792	Melanoma	completed	IL2 + DCs, and then pulsed with MART-1, gp100, tyrosinase, MAGE-3 peptides and flu matrix	x	x	x	
NCT00142454	Melanoma	completed	NY-ESO-1 Protein Vaccination + imiquimod	x	x	x	
NCT01883297	Melanoma	not yet recruiting	Infusion of "Re-Stimulated" Autologous Tumor-Infiltrating Lymphocytes (TILs) Followed by Low-Dose Interleukin-2	x	x	x	
NCT00390338	Melanoma	ongoing	Alpha-Type-1 DC-Based and cDC-Based Intralymphatic Vaccines	x	x		
NCT00124124	Melanoma	ongoing	melanoma vaccine (5 melanoma peptides) with either Montanide or DCs	x	x		
NCT00074230	Melanoma	ongoing	Mature, Autologous Monocyte-Derived DCs Transfected With RNAs Encoding for Mage-3, MelanA, and Survivin Antigens	x	x	x	x
NCT01456104	Melanoma	recruiting	Autologous Langerhans-type DCs Electroporated With mRNA Encoding a Tumor-associated Antigen	x	x		
NCT01863108	Melanoma	recruiting	Peptide-loaded Plasmacytoid DC Line (GeniusVac-Mel4)	x	x	x	
NCT01946373	Melanoma	recruiting	Chemotherapy (Cyclophosphamide/fludarabine) + T cells + IL-2 + DCs pulsed with autologous tumor lysate and NY-ESO-1 peptide	x	x		
NCT01753089	Melanoma	recruiting	DC Activating Scaffold Incorporating Autologous Melanoma Cell Lysate (WDVAX)	x	x	x	x
NCT01690377	Melanoma	recruiting	Plasmacytoid DCs (pDC)	x	x		
NCT00683670	Melanoma	recruiting	Mature DC Vaccine Against gp100 + cyclophosphamide	x	x	x	
NCT00280982	Mesothelioma	completed	Tumor lysate-loaded autologous DCs	x			
NCT01241682	Mesothelioma	completed	DC-based Immunotherapy Combined With Low-dose Cyclophosphamide	x	x		
NCT00459069	Multiple myeloma	completed	DC Tumor Fusion Vaccine	x	x	x	
NCT00458653	Multiple myeloma	completed	DC Tumor Fusion	x	x	x	
NCT00988312	Multiple myeloma	completed	Autologous idiotype-protein pulsed DCs		x		
NCT01995708	Multiple myeloma	recruiting	CT7, MAGE-A3, and WT1 mRNA-electroporated Autologous Langerhans-type DCs	x	x		
NCT00023985	NSCLC	completed	Autologous Tumor Lysate-Pulsed DCs	x	x		
NCT00601094	NSCLC	ongoing	Autologous DC-adenovirus CCL21 vaccine	x	x	x	
NCT01574222	NSCLC	ongoing	Autologous DC-adenovirus CCL21 vaccine	x	x	x	
NCT00683241	Ovarian	completed	Autologous DC Vaccine Leaded With Autologous Tumor Cell Lysate (DCVax-L) + intravenous bevacizumab and oral metronomic cyclophosphamide	x	x		
NCT01456065	Ovarian	ongoing	Fully Mature, TERT-mRNA and Survivin - Peptide Double Loaded DCs	x	x	x	x
NCT00547144	Pancreatic	completed	Intratumoral DC Immunotherapy in Combination With Gemcitabine and Stereotactic Radiosurgery	x	x	x	
NCT01410968	Pancreatic	completed	Poly-ICLC and Peptide-pulsed DCs vaccine	x	x	x	x
NCT00108264	Prostate	completed	Tumor RNA transfected DCs	x	x		
NCT00096551	Prostate	completed	PSA-Based Vaccine	x	x	x	
NCT00972309	Prostate	ongoing	Epitope-Enhanced TARP Peptide and TARP Peptide-Pulsed DCs	x		x	
NCT00374049	Prostate	ongoing	MUC1 Vaccine + Poly-ICLC (Polyinosinic-polycytidylic Acid Stabilized With Polylysine and Carboxymethylcellulose) or HiltonolTM	x	x		
NCT00970203	Prostate	recruiting	Alpha-Type 1 DC-Based Vaccines Loaded With Allogeneic Prostate Cell Lines + Androgen Ablation	x	x	x	
NCT01823978	Prostate	recruiting	DC vaccine, BPX-201 + activating agent, AP1903	x		x	
NCT00005816	Renal cell	completed	Autologous DCs Transfected With Autologous TotalTumor RNA	x	x	x	x
NCT00004880	Renal cell	completed	Multi-Antigen Loaded DC Vaccine	x	x	x	
NCT01525017	Renal cell	ongoing	Combig-DC (allogeneic DCs) Cancer Vaccine	x	x	x	
NCT01826877	Renal cell	recruiting	Autologous DCs Transduced With Ad-GMCAIX	x	x	x	
NCT01803152	Sarcoma	recruiting	DC Vaccination With and Without Inhibition of Myeloid Derived Suppressor Cells by Gemcitabine + imiquimod	x	x	x	x
NCT01241162	Sarcoma	recruiting	Autologous cancer testis antigen specific DC vaccine + decitabine (demethylating chemotherapy)	x	x	x	