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REVIEW

Trial watch: dendritic cell vaccination for cancer immunotherapy

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ABSTRACT

Dendritic- cells (DCs) have received considerable attention as potential targets for the development of anticancer vaccines. DC-based anticancer vaccination relies on patient-derived DCs pulsed with a source of tumor-associated antigens (TAAs) in the context of standardized maturation-cocktails, followed by their reinfusion. Extensive evidence has confirmed that DC-based vaccines can generate TAA-specific, cytotoxic T cells. Nonetheless, clinical efficacy of DC-based vaccines remains suboptimal, reflecting the widespread immunosuppression within tumors. Thus, clinical interest is being refocused on DC-based vaccines as combinatorial partners for T cell-targeting immunotherapies. Here, we summarize the most recent preclinical/clinical development of anticancer DC vaccination and discuss future perspectives for DC-based vaccines in immunooncology.

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Introduction

The presentation of antigenic material to cells of the adaptive immune system, notably $CD4^+$ helper T cells and $CD8^+$ cytotoxic T lymphocytes (CTLs), is a crucial function of myeloid cells,[1,2] as it stands at the basis of both antigen-specific immune activation and tolerance.[3–11] Professional antigen-presenting cells (APCs) are specialized at executing this function, and dendritic cells (DCs) are largely viewed as the most proficient of APCs.[7,8,12–18] Indeed, DCs not only present extracellular antigens on MHC Class II molecules to $CD4^+$ T cells,[19,20] in thus far resembling macrophages and B cells,[21–23] but they also efficiently mediate cross-presentation, i.e., the presentation of extracellular antigens on MHC Class I molecules to $CD8^+$ CTLs, which is key for anticancer immunity.[8,24–31] Pioneering research by the team of the Canadian physician Ralph Steinman uncovered the existence of DCs in 1973, an achievement for which he was eventually awarded the 2011 Nobel Prize in Physiology or Medicine.[32–35] The name DC reflects the distinguishing morphology of these cells, which can acquire a tree-like shape (from the Greek term "dendron", translating to "tree").[36–38] Following the discovery of DCs by the Steinman laboratory, considerable efforts have been dedicated to characterize their unique phenotypic and functional features, which firmly position DCs at the interface between innate and adaptive immunity.[8,13,39–51]

DCs are common throughout the body, although they are relatively more abundant in tissues that are in contact with the external environment, such as epithelial tissues.[5,16,52–66] DCs are highly heterogeneous in terms of ontogeny,[67–69] function, responsiveness to selected stimuli and preference for specific sources of antigens for presentation.[16,70–77] These features have been harnessed to generate ever more refined biological classifications of DCs into different subsets.[76,78–81] In particular, both human and mouse DCs can be morphologically classified into 2 major subsets: myeloid DCs, which are also known as conventional or classical DCs (cDCs) and (prior to activation) resemble circulating monocytes,[82–84] and plasmacytoid DCs (pDCs), which resemble plasma cells.[85–88] Two other DC subsets have been described: $CD16^+$ monocyte-derived (or inflammatory) DCs, and Langerhans cells (LCs), a skin-resident population of DCs with potent immunosuppressive activity.[86,89–92] Here, cDCs

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derive from a common myeloid precursor and can be further classified into two subsets: (1) cDC1, which express CD8α or CD103 in mice, or CD141 in humans; and (2) cDC2, which express CD11b in mice, or CD1c in humans.[93] In contrast, pDCs are believed to originate from a poorly defined lymphoid precursor, and are characterized by co-expression of CD45R/B220 and Ly-6C in mice, or CD123 and CD304 in humans.[85] An alternative classification for DCs reflects the differential expression of master transcription factors like basic leucine zipper transcription factor ATF-like 3 (BATF3), which is critical for the development of $CD8\alpha^+$ DCs in lymphoid tissues and $CD103^+CD11b^-$ DCs in peripheral tissues.[94–97] High-dimensional analysis techniques (*e.g.*, mass cytometry, single-cell RNA sequencing) have further expanded our understanding on the complexity of DCs, while casting some doubts on the accuracy of the aforementioned classifications.[85,86,98]

Different DC subsets exhibit functional specialization on a number of immunological levels, including: (1) capturing, processing and presenting antigens (*e.g.*, human $CD141^+$ DCs and mouse $CD8\alpha^+$ DCs are highly proficient at cross-presentation, while $CD11b^+$ DCs efficiently mediate conventional MHC Class II presentation);[97,99–105] (2) preferential engagement of adaptive immune cell populations (*e.g.*, $CD14^+$ DCs enriched in the dermis and LCs tend to specifically drive humoral responses and $CD8^+$ T cell effectors, respectively);[106,107] and (3) secretion of antiviral and immunomodulatory cytokines such as type I interferon (IFN) (*e.g.*, pDCs mount stronger type I IFN responses as compared to other DC subsets).[108–112]

In homeostatic conditions, blood-borne as well as tissue-resident DCs exist in an immature functional state, which is key for the preservation of peripheral tolerance to self antigens.[113] In particular, immature DCs (iDCs) potently suppress the activity (or even promote the clonal deletion) of self-reactive T cells,[45,114] and favor the proliferation of immunosuppressive $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells.[27,115–117] The most salient features of iDCs are: (1) prominent potential for the uptake of extracellular material, especially cell corpses, vesicles and other small non-soluble entities, coupled to the secretion of homeostatic cytokines and chemokines; (2) expression of specific chemokine receptors that enable rapid chemotaxis to sites of inflammation; (3) retention of MHC Class II molecules within late endosomes; and (4) minimal surface expression of co-stimulatory molecules like CD40, CD70, CD80, CD83, CD86 and tumor necrosis factor (ligand) superfamily, member 4 (TNFSF4, also known as OX40L).[118]

In pathological settings, a plethora of microbial cues commonly known as microbe-associated molecular patterns (MAMPs)[8,119–121] and endogenous danger signals cumulatively referred to as damage-associated molecular patterns (DAMPs)[58,122–128] drive the rapid phenotypic and functional conversion of iDCs into mature DCs (mDCs).[129–137] Here, mDCs differ from their immature counterparts as they display: (1) limited phagocytic activity; (2) altered profile of chemokine receptors including high levels of chemokine (C-C motif) receptor 7 (CCR7), which favors DC homing and persistence in lymph nodes; (3) robust exposure of peptide-bound MHC molecules and co-stimulatory ligands on the cell surface; and (4) secretion of pro-inflammatory cytokines such as interleukin 12 (IL12) and T cell-targeting chemokines such as C-X-C motif chemokine ligand 10 (CXCL10).[38,116,118,138–149] Thus, mDCs acquire the anatomical location and all the functional properties that are required for optimal T cell priming.[150–153]

Since the cross-priming of $CD8^+$ CTLs against tumor-associated antigens (TAAs) is critical for the elicitation of robust and durable anticancer immune responses, and this process is often disabled in developing tumors (by a multitude of immunosuppressive strategies deployed by cancer cells),[154,155] DCs have attracted considerable attention as potential targets for the development of therapeutic cancer vaccines.[156–159] This approach generally involves the differentiation of DCs from autologous, patient-derived monocytes, followed by *ex vivo* DC exposure to an appropriate source of TAAs in the context of potent maturation cocktails,[160] and culminating with the reinfusion of mDCs to the patient. Accumulating clinical evidence demonstrates that this approach often promotes at least some degree of TAA-specific CTLs-driven immunity in patients.[8,156,157,161] However, the efficacy of therapeutic DC vaccination is often limited by the robust immunosuppressive circuits that are in place in the microenvironment of most tumors.[98,162]

Therapeutic DC vaccines developed so far can be broadly classified in different groups based on the approach for TAA-delivery or molecular modifications imposed on DCs before reinfusion.[163,164] These groups are: (1) DCs not pulsed with TAAs and employed either in an immature form or used upon maturation with pro-inflammatory cytokines and/or MAMPs or DAMPs;[138,165–169] (2) DCs pulsed *ex vivo* with tumor lysates or tumor-derived mRNA (both of which cover either a broad array of TAAs), specific TAA-based peptides (generally consisting of one or a few selected peptides), or precise TAA-coding mRNAs;[59,170–221] (3) DCs provided *in vivo* with TAAs;[222–233] (4) DCs stimulated *in situ* by immunostimulatory agents applied peritumorally or intratumorally;[234] (5) DCs transfected (virally or biochemically) with a genetic vector coding for one or a few TAAs and/or immunostimulatory factors;[235] or (6) DC-derived exosomes.[236–240] That said, the most common approach to therapeutic cancer vaccination with DCs consists of DCs pulsed with TAAs or tumor lysates and stimulated with standard maturation cocktails.[241] Herein, iDC pulsing is usually achieved by: (1) co-incubation with autologous or allogeneic tumor lysates;[170–179,242–244] (2) co-incubation with recombinant TAAs or peptides thereof;[59,180–186] (3) transfection of TAA-encoding plasmids or mRNAs;[187–211,245–248] and, (4) fusion of DCs with inactivated malignant cells, resulting in the generation of so-called "dendritomes".[177–179,212–219,249] The possibility of creating DC vaccines *in situ* or *in vivo* by direct TAA delivery has been explored with DC-targeting immunoliposomes,[250–252] DC-targeting genetic vectors,[253–256] or TAAs fused to monoclonal antibodies or other moieties targeting DC surface receptors.[222–228,230,231,233,257,258] The possibility of creating DC vaccines exploiting specific (naturally available) DC subsets has also been explored.[259,260] Particularly, specific DC subsets including pDCs, LCs and $CD1c^+$ DCs have been successfully utilized in the clinic for the vaccination of cancer patients.[259–261] Notably, sipuleucel-

T (commercially sold as Provenge®) is the sole tumor-targeting cellular therapy involving (but not restricted to) DCs that is currently approved by the US Food and Drug Administration (FDA) for use in individuals with asymptomatic or minimally-symptomatic metastatic castration-resistant prostate cancer.[262–264]

Here, we summarize preclinical and clinical progress in the development of therapeutic cancer vaccines based on DCs. As the cancer immunotherapy landscape is currently dominated by other therapeutic modalities[265–269] such as immune checkpoint blockers (ICBs) and adoptive T-cell transfer (ACT),[270,271] interest is being refocused on implementing DC-based vaccines as part of multimodal (immuno)therapeutic regimens.[15,43,272–278] That said, the number of clinical trials currently open to investigate the safety and therapeutic profile of DC vaccination in cancer patients remains high.

Recent preclinical developments

Several preclinical reports dealing with anticancer DC vaccines were published since our last Trial Watch on this topic (February 2017).[279] Of this abundant preclinical literature, we found of particular interest the following selected studies, which are largely representative of the overall trends in the field (not discussed in any specific order). Nimanong *et al.* (from Medical School Hannover, Hannover, Germany) combined DC vaccination with a co-stimulatory cocktail consisting of a CD40 agonistic antibody,[280] an agonist of Toll-like receptor 3 (TLR3) (and different combinations of neoantigen-based or TAA-based peptides) and achieved successful remission of large murine subcutaneous MC38 tumors, accompanied by robust antigen-specific T-cell responses.[281] Moreno Ayala *et al.* (from Universidad de Buenos Aires, Buenos Aires, Paraguay) reported that combining DC vaccines with a FOXP3-targeting synthetic peptide (P60) that inhibits T_{REG} cells results in superior antitumor efficacy against murine LM3 or 4T1 mammary carcinomas.[282] Liu *et al.* (from Chinese PLA General Hospital, Beijing, China) tested the efficacy of DC vaccines involving DCs pulsed with glioma-derived exosomes and α-galactosylceramide (α-GalCer), an agonist for invariant natural killer T (iNKT) cells, in combination with adoptively transferred iNKT cells, in an orthotopic rat glioma model, observing efficient induction of antitumor immunity.[283] Similarly, Escriba-Garcia *et al.* (from Hospital de la Santa Creu i Sant Pau, Barcelona, Spain) found that DC vaccines combined with α-GalCer enabled 100% tumor-free survival in a murine model of B-cell lymphoma, correlating with increased effector T-cell functions and expansion of iNKT cells secreting interferon gamma (IFNG).[284] Vo *et al.* (from Chonnam National University Hwasun Hospital, Jeollanamdo, Republic of Korea) successfully combined TAA-based DC vaccination with the immunomodulatory drug lenalidomide, achieving potent antitumor immunity against murine MC38 colorectal carcinoma tumors, which was accompanied by reduction in myeloid-derived suppressor cells (MDSCs)[285] and induction of lymphoid effector functions.[286] Dammeijer *et al.* (from Erasmus MC, Rotterdam, Netherlands) documented that the pharmacological inhibitor of colony stimulating factor 1 receptor (CSF1R), PLX3397 (also known as pexidartinib),[287,288] which causes depletion of tumor-associated macrophages (TAMs), synergizes with DC vaccines to achieve eradicating immunity in mouse models of mesothelioma.[289] Moreno Ayala *et al.* (from Universidad de Buenos Aires, Buenos Aires, Paraguay) combined DC vaccines with different TLR7 or TLR9 agonists, observing that whereas DCs activated through TLR9 enabled prolonged tumor- and metastasis-free survival, dual TLR7/TLR9 activation impaired vaccination efficacy, a disparity that could be ameliorated by inhibiting nitric oxide synthase (NOS) and indoleamine-pyrrole-2,3-dioxygenase 1 (IDO1).[290,291] Ebrahimi-Nik *et al.* (from University of Connecticut, Farmington, CT, USA) reported DCs to be superior to macrophages at eliciting neoantigen-targeted eradicating immunity in a DC vaccination setup, but surprisingly found $CD11c^{+}MHC\text{-}II^{low}$ DCs to be the best APCs in this particular setting.[26] Montico *et al.* (from Centro di Riferimento Oncologico, Aviano, Italy) pulsed human DCs with mantle cell lymphoma (MCL) or diffuse large B-cell lymphoma (DLBCL) cells undergoing immunogenic cell death (ICD)[292,293] in response to 9-*cis*-retinoic acid plus type I IFN, which mediated robust anticancer immunity upon inoculation in immunodeficient tumor-bearing mice reconstituted with human peripheral blood mononuclear cells (PBMCs).[42] Antonios *et al.* (from University of California, Los Angeles, California, USA) treated orthotopic glioma-bearing mice with DC vaccines combined with antibodies against programmed cell death 1 (PDCD1, best known as PD-1) and PLX3397, reporting therapeutic benefits only in the context of vaccination.[294] Arab *et al.* (from Tehran University of Medical Sciences, Tehran, Iran) achieved pronounced inhibition of tumor growth and antitumor immunity upon combining DC vaccination with blockade of adenosine A2A receptor (ADORA2A) and 5′-nucleotidase ecto (NT5E, best known as CD73).[295] Komorowski *et al.* (from Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA) achieved robust therapeutic effects against murine neuroblastomas by combining DC vaccines with an oncolytic vaccinia virus[296,297] expressing a C-X-C chemokine receptor type 4 (CXCR4) antagonist.[298] Stefanski *et al.* (from University of Minnesota, Minneapolis, Minnesota, USA) pulsed DCs genetically-engineered to overexpress CCL21 with TAAs, and reported the induction of efficient anticancer immunity in mouse models of leukemia.[299] Van Woensel *et al.* (from KU Leuven, Leuven, Belgium) found that combining DC-based vaccines with the intranasal administration of chitosan nanoparticles loaded with small interfering RNAs targeting galectin 1 (LGALS1) drives robust tumor-targeting immune responses in a murine model of orthotopic glioma, correlating with dramatic changes in the tumor microenvironment in favor of M1-polarized macrophages and effector T cells.[300] Huang *et al.* (from Xinhua Hospital and Shanghai Jiaotong University School of Medicine, Shanghai, China) observed that vaccines obtained by pulsing DCs with exosomes from transforming growth factor beta 1 (TGFB1)-defective cancer cells induce superior anti-leukemia immunity *in vivo*.[301] Lu *et al.* (from Tianjin Medical University, Tianjin, China) found that DC-derived exosomes from DCs expressing a hepatocellular carcinoma (HCC)-associated antigen are very efficient at eliciting $CD8^{+}$ T cell-dependent eradicating immunity in 3 different

mouse models of the disease.[302] Bryson *et al.* (from University of Southern California, Los Angeles, CA, USA) used a Sindbis virus-based method to deliver breast cancer-associated antigens to tumor-resident DCs, resulting in a potent vaccination effect *in situ* that amplified $CD8^+$ CTL-dependent immunity against murine breast cancer.[303] Liu *et al.* (from University of North Carolina at Chapel Hill, Chapel Hill, NC, USA) formulated a nanoparticle-based method to deliver mucin 1 (MUC1)-coding mRNA to lymph node-resident DCs in a mannose receptor-dependent fashion, culminating with expansion of MUC1-reactive T cells and regression of MUC1-expressing 4T1 mammary carcinomas, especially in the context of cytotoxic T-lymphocyte associated protein 4 (CTLA4) blockage.[304] Oberli *et al.* (from Harvard Medical School, Boston, Massachusetts, USA) created a cancer vaccine consisting of DCs, macrophages and neutrophils transfected with an mRNA coding for melanoma antigens and delivered with lipid nanoparticles, which effectively eradicated B16 melanomas in a $CD8^+$ CTL-dependent manner.[305] Wennhold *et al.* (from University Hospital of Cologne, Cologne, Germany) compared the efficacy of antigen-pulsed and CD40-activated B cell and DC vaccines against B16 melanoma and E.G7 lymphoma, observing that B cell-based vaccines perform as efficiently as DC vaccines at inducing antitumor immunity.[306] Wculek et al. (from Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain) showed that splenic cDC1s pulsed with cancer cells undergoing ICD were able to induce therapeutic immune responses that synergized with PD-1 blockade,[307] supporting a mechanistic link between ICD-inducing systemic anticancer therapies and cDC1-dependent antigen cross-presentation.[307–320] This finding extends prior observations indicating that human $CD1c^+$ DCs are critical for the presentation of tumor antigens from cancer cells succumbing to ICD.[8,103,321–323] Finally, Ventura *et al.* (Yale University School of Medicine, New Haven, CT, USA) identified a novel approach to generate potent, cytokine-independent DCs, that involves the physical interaction of circulating monocytes with platelets, potentially opening a completely unexplored avenue to DC-based vaccine.[324]

These are only a few examples of the abundant preclinical literature on therapeutic DC vaccines with oncological applications, demonstrating a persistent interest in this promising but only partially realized therapeutic paradigm.

Completed clinical studies

We identified 34 peer-reviewed papers published since the release of our latest Trial Watch on therapeutic DC-based vaccines for oncological indications (February 2017)[279] reporting safety and efficacy data from clinical trials assessing this therapeutic paradigm in patients with cancer.

The majority of these studies (Figure 1) tested autologous DCs pulsed with: TAAs or peptides thereof,[325–342] autologous cancer cell lysates,[343–348] or TAA-coding RNAs.[276,349–352] The predominant use of these TAA sources for the generation of DC-based vaccines is in line with previous trends, as documented in our previous Trial Watch on this subject,[279] *de facto* reflecting a broad consensus in the field. Additional TAA sources explored in recent clinical studies include (Figure 1): lysates of autologous (tumor) stem cells, lysates of allogeneic cancer cell lines, and TAA-encoding viral vectors.[353–355] Of note, one of these clinical studies involved DC vaccines based on personalized antigenic peptides.[335] Moreover, a Phase I clinical study investigated an acute myeloid leukemia (AML)-derived cell line as allogeneic DC vaccine (DCP-001), owing to its DC-like behavior and expression of AML-relevant antigens.[356] Finally, autologous DCs have been investigated in combination with cytokine-induced killer (CIK) cells[357] for the therapy of advanced pancreatic carcinoma.[358]

Most of the aforementioned clinical studies based on specific TAAs focused on WT1 transcription factor (WT1),[327,328,337,342,349] acid phosphatase, prostate (ACPP),[276,325,329] telomerase reverse transcriptase (TERT)[276,333,351] or baculoviral IAP repeating containing 5 (BIRC5, best known as survivin)[276,333,340] (Figure 1). This configuration partly deviates from the trend identified in our latest Trial Watch dealing with DC-based vaccines.[279] Indeed, while WT1 remains amongst the most commonly targeted TAAs, interest in melanoma-associated differentiation antigens has decreased,[337] irrespective of melanoma remaining among the most common indications for experimental DC vaccination (Figure 1).

While most of these clinical studies were basket trials enrolling patients with multiple solid tumors (Figure 1),[326,331,336,348] studies focusing on single indications most commonly enrolled patients with melanoma,[332,337,339,343] prostate cancer,[276,325,329,353] or glioblastoma (GBM).[341,346,350,352] This was followed by pancreatic cancer,[327,333,358] non-small cell lung carcinoma (NSCLC),[338,340,354] and myeloma[330,334,345] (Figure 1). This trend was very similar to the one we described in 2017,[279] with the single exception of studies enrolling subjects with renal cell carcinoma (RCC), which declined over the past 2 years.

In most clinical studies, DC vaccines were administered in combination with standard-of-care[348] or off-label chemotherapeutics (*e.g.*, gemcitabine, cyclophosphamide, S-1, temozolomide, carboplatin, paclitaxel or docetaxel),[276,326–328,337,338,341,344,346,350,358] radiotherapy,[335,341,346] targeted anticancer agents (*e.g.*, tyrosine kinase inhibitors),[328,344] or specific immunotherapeutic regimens, including recombinant colony stimulating factor 2 (CSF2, best known as GM-CSF), recombinant IL2, ACT, and TL3 agonists.[326,333,344,352,353]

Importantly, the vast majority of these clinical studies confirmed that DC-based vaccines are safe for cancer patients,[359] causing mild-to-moderate side effects including fever, erythema, flu-like symptoms, rash and/or fatigue, in a small proportion of patients.[328,333,335,340,341,348] Signs of ongoing TAA- or tumor-targeting effector responses upon vaccination, including (but not limited to) increased antigen-specific T- or B-cell activity and tumor infiltration by $CD8^+$ CTLs, were consistently documented.[327,332,355] Moreover, multiple clinical studies reported promising clinical responses to vaccination, including disease stabilization[326,328,333,342,344,354] as well as a few partial and complete responses.[330,335,345,347–349] Encouragingly, a few cases of robust extension in patient survival were also documented.[327,351,356,358] For example, DCs pulsed with TAAs from GBM stem cells provided significant progression-free and overall survival advantage (as compared to placebo) to a cohort

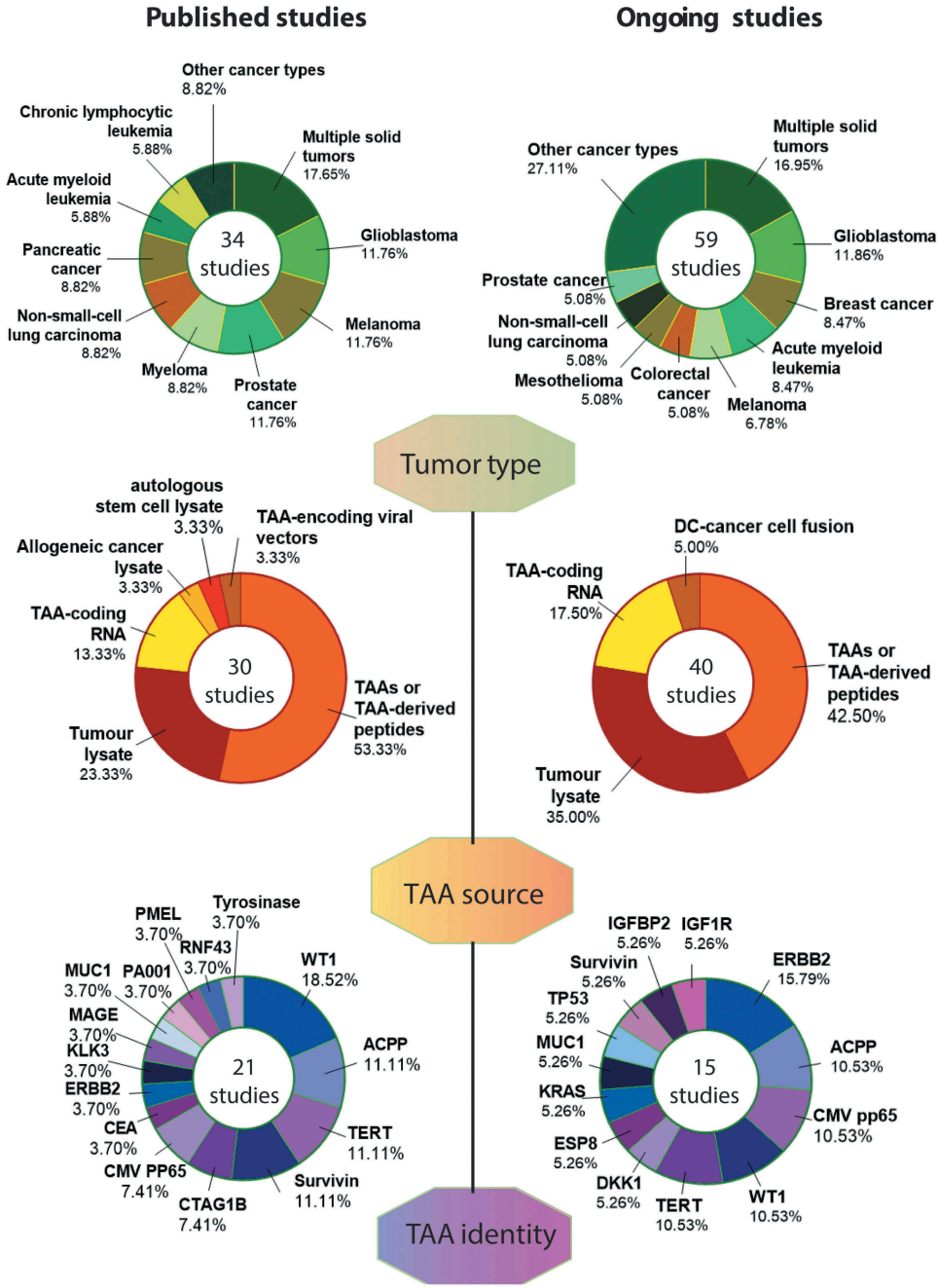

Figure 1. Overview of current strategies of dendritic cell vaccination for cancer therapy. ACPP, acid phosphatase, prostate; AML, acute myeloid leukemia; CEA, carcinoembryonic antigen; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; DC, dendritic cell; DKK1, dickkopf WNT signaling pathway inhibitor 1; EPS8, epidermal growth factor receptor pathway substrate 8; HCC, hepatocellular carcinoma; KRAS, KRAS proto-oncogene, GTPase; MUC1, mucin 1, cell surface associated; NSCLC, non-small cell lung cancer; NY-ESO-1 (official name: CTAG1B), cancer/testis antigen 1B; CMV pp65, cytomegalovirus 65 kDa phosphoprotein; PSA (official name: KLK3), kallikrein related peptidase 3; RCC, renal cell carcinoma; RNF43, ring finger protein 43; TAA, tumor-associated antigen; TERT, telomerase reverse transcriptase; WT1, WT1 transcription factor.

of 43 patients with GBM enrolled in a Phase II clinical trial.[341] Similarly, AML patients at very high risk of relapse receiving DCs transfected with *WT1* mRNA exhibited a higher 5-year overall survival rate as compared to historical controls.[349] Altogether, these publications capture the promise offered by DC vaccination in specific oncological settings.

Ongoing clinical trials

For the period between February 2017 to February 2019, official sources (http://www.clinicaltrials.gov/) list no less than 59 clinical trials evaluating the safety and therapeutic profile of DC-based vaccines in cancer patients. The specifics of these clinical trials are summarized in Table 1.

In these studies, the most common approaches consist of autologous DCs pulsed with TAAs or peptides thereof, lysates from autologous tumor cells, or TAA-coding RNA (Figure 1 and Table 1). The clinical trials targeting specific TAAs focus on WT1, erb-b2 receptor tyrosine kinase 2 (ERBB2), ACPP, and the human cytomegalovirus protein 65 kDa phosphoprotein (pp65) (Figure 1 and Table 1). As an alternative, multiple ongoing clinical trials favor the use of TAA or TAA-derived peptide mixtures, including

Table 1. Overview of clinical trials currently testing dendritic cell-based immunotherapy in cancer patients.

Strategy	Indication	Phase	Status	TAA(s)	Combinatorial treatment	Reference
Autologous DCs	Breast cancer	I/II	Recruiting	n.a.	Neoadjuvant chemotherapy	NCT03450044
	Colorectal carcinoma	I/II	Recruiting	n.a.	Avelumab	NCT03152565
	Hepatocellular carcinoma	I/II	Recruiting	n.a.	Trans-arterialchemoembolization	NCT03086564
	NSCLC	I	Recruiting	n.a.	Pembrolizumab	NCT03546361
	Prostate cancer	I/II	Recruiting	n.a.	GNRH1 agonist and central memory T cells	NCT03085966
	Solid tumors	I	Not yet recruiting	n.a.	Single agent	NCT03638765
		I	Recruiting	n.a.	Avelumab, ipilimumab and nivolumab	NCT03707808
		I	Not yet recruiting	n.a.	Anti-PD1 antibody	NCT03815084
Autologous DCs loaded with tumor cell lysate	Breast cancer	I	Unknown	Tumor lysate	Single agent	NCT03113019
	Colorectal carcinoma	I	Recruiting	Tumor lysate	Single agent	NCT03214939
	Glioblastoma	II	Recruiting	Tumor lysate	Standard therapy	NCT03395587
		I	Not yet recruiting	Tumor lysate	Single agent	NCT03360708
	Gastric cancer	II	Recruiting	Tumor lysate	Single agent	NCT03410732
	Melanoma	I	Not yet recruiting	Tumor lysate	Anti-PD-1 antibody	NCT03743298
		I/II	Recruiting	Tumor lysate	Pembrolizumab	NCT03325101
		I	Not yet recruiting	Tumor lysate	Single agent	NCT03803397
	Mesothelioma	II/III	Recruiting	Tumor lysate.	Best supportive care	NCT03610360
		I	Not yet recruiting	Tumor lysate	Pembrolizumab and IL2	NCT03546426
	Ovarian cancer	I/II	Not yet recruiting	Tumor lysate	Autologous NK cell-like CTLs	NCT03735589
		II	Active, not recruiting	n.a.	Standard of care chemotherapy	NCT03657966
	Renal cell carcinoma	II	Withdrawn	Tumor lysate	Boost radiotherapy and high-dose IL2	NCT03226236
	Solid tumors	I	Recruiting	Tumor lysate	Single agent	NCT03671720
Autologous DCs transfected or pulsed with TAA-coding RNA(s)	Acute myeloid leukemia	I/II	Recruiting	WT1	Single agent	NCT03083054
	Glioblastoma	I	Recruiting	Tumor-derived mRNA	TTRNA-xALT, temozolomide, and autologous hematopoietic stem cells	NCT03334305
		I	Recruiting	Tumor-derived mRNA	TTRNA-xALT, temozolomide, lymphodepletive conditioning and autologous hematopoietic stem cells	NCT03396575
		II/III	Recruiting	Survivin and TERT	Temozolomide	NCT03548571
		I	Active, not recruiting	CMV pp65	Tetanus toxoid	NCT03615404
		II	Not yet recruiting	CMV pp65	Temozolomide, varlilumab, and tetanus-diphtheria vaccine	NCT03688178
	NSCLC	I	Recruiting	TERT	Single agent	NCT03371485
Autologous DCs loaded with recombinant TAAs or TAA-derived peptide(s)	Acute myeloid leukemia	I	Recruiting	WT1 or EPS8	CAR-expressing T cells	NCT03291444
	Breast cancer	I	Recruiting	ERBB2	Neoadjuvant chemotherapy	NCT03387553
		II	Recruiting	IGFBP2, ERBB2, and IGF1R	DNA-based vaccine	NCT03384914
		II	Recruiting	ERBB2	Single agent	NCT03630809
	Colorectal carcinoma	I	Recruiting	Mutated peptides	Single agent	NCT03730948
	Gastric cancer	I	Not yet recruiting	Tumor peptide pool	Anti-PD-1 antibody	NCT03393416
	Glioblastoma	II	Recruiting	Autologous TAAs	Single agent	NCT03400917
	Hepatocellular carcinoma	I	Recruiting	Personalized neoantigen	Microwave ablation	NCT03674073
	Lung Cancer	II	Recruiting	TP53	Nivolumab and Ipilimumab	NCT03406715
	Melanoma	I	Recruiting	Melanoma tumor-specific peptides	Cyclophosphamide and pembrolizumab	NCT03092453
	Myeloma	I	Not yet recruiting	DKK1-derived peptide	Single agent	NCT03591614
	Nasopharyngeal cancer	I	Recruiting	EBV proteins	Single agent	NCT03282617
	Pancreatic cancer	I	Recruiting	Mutant KRAS peptides	Single agent	NCT03592888
	Prostate cancer	I/II	Active, not recruiting	MUC1- and WT1-derived peptides	Standard therapy	NCT03114631
		III	Recruiting	ACPP	Single agent	NCT03686683
		I/II	Recruiting		*Pdcd1*$^{-/-}$ T Cells	NCT03525652
	Solid tumors	n.a.	Not yet recruiting	TAAs	Cyclophosphamide	NCT03185429
		II	Recruiting	Immunogenic neoantigens	Single agent	NCT03300843

(*Continued*)

Table 1. (Continued).

Strategy	Indication	Phase	Status	TAA(s)	Combinatorial treatment	Reference
Autologous DC-CIK combinations	Lung cancer	I/II	Recruiting	n.a.	Anti-PD-1 antibody	NCT03360630
	Mesothelioma	I/II	Recruiting	n.a.	Anti-PD-1 antibody and hyperthermia	NCT03393858
	Neoplasms	I/II	Recruiting	n.a.	Anti-PD-1 antibody	NCT03190811
	NSCLC	I	Not yet recruiting	Dribbles	Single agent or with imiquimod/GM-CSF	NCT03057340
	Renal cell carcinoma	II	Recruiting	n.a.	Axitinib and anti-PD-1 antibody	NCT03736330
	Solid tumors	I/II	Recruiting	n.a.	Chemotherapy	NCT03047525
		I	Not yet recruiting	n.a.	Anti-PD-1 antibody	NCT03815630
Allogenic DCs	Acute myeloid leukemia	II	Recruiting	n.a.	Single agent	NCT03697707
	Solid tumors	I/II	Recruiting	n.a.	Pembrolizumab	NCT03735290
DC-cancer cell fusions	Acute myeloid leukemia	II	Recruiting	n.a.	Single agent	NCT03059485
		I	Recruiting	n.a.	Decitabine	NCT03679650
	Multiple myeloma	II	Not yet recruiting	n.a.	Nivolumab	NCT03782064

Abbreviations: ACPP, acid phosphatase, prostate; CAR, chimeric antigen receptor; CIK, cytokine-induced killer; CMV pp65, cytomegalovirus 65 kDa phosphoprotein; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DKK1, dickkopf WNT signaling pathway inhibitor 1; EBV, Epstein-Barr virus; EPS8, epidermal growth factor receptor kinase substrate 8; ERBB2, erb-b2 receptor tyrosine kinase 2; GNRH1, gonadotropin releasing hormone 1; IGF1R, insulin like growth factor 1 receptor; IGFBP2, insulin-like growth factor binding protein 2; IL, interleukin; KRAS, KRAS proto-oncogene, GTPase; MUC1, mucin 1, cell surface associated; n.a., not applicable; NK, natural killer; NSCLC, non-small cell lung cancer; PD-1 (official name PDCD1), programmed cell death 1; TAA, tumor-associated antigen; TERT, telomerase reverse transcriptase; TTRNA-xALT, total tumor RNA-autologous lymphocyte transfer; WT1, WT1 transcription factor.

blends of mutated peptides or neoantigens (pre-defined or personalized), or melanoma-specific TAA-derived peptides (Table 1).

As for indication, most of ongoing clinical studies focusing on DC vaccines are basket trials and enroll patients with multiple solid tumors (Figure 1 and Table 1). Restricted studies most commonly accrue patients with breast carcinoma and GBM, followed by patients with colorectal carcinoma, melanoma, mesothelioma and prostate cancer (Figure 1 and Table 1). Notably, there are at least three advanced-phase clinical trials testing therapeutic DC-based vaccines in cancer patients: a Phase II/III study enrolling GBM patients (NCT03548571), a Phase II/III trial enrolling patients with mesothelioma (NCT03610360), and a Phase III study open to individuals with prostate cancer (NCT03686683) (Table 1). This indicates that at least some DC-based vaccines have reached advanced clinical development, and may soon be evaluated for approval by regulatory authorities.[158,278]

Interestingly, the majority of the ongoing clinical trials administer DC-based vaccines in combination with ICBs targeting PD-1, such as pembrolizumab or nivolumab, CD274 (best known as PD-L1), such as avelumab, or CTLA4, like ipilimumab, alone or in different combinations (Table 1). Alternatively, DC vaccination is performed in combination with other immunotherapeutic modalities, including adoptively transferred chimeric antigen receptor (CAR)-expressing T cells, CIK cells or autologous NK cells,[360] recombinant cytokines,[361,362] immunostimulatory antibodies (*e.g.*, varlilumab),[363,364] or MAMP-based immunostimulants (*e.g.* tetanus toxoid or tetanus-diphtheria vaccine).[250,365,366] Additional combinatorial partners for DC-based vaccines in clinical development include: (1) standard-of-care neoadjuvant chemotherapy based on ICD inducers like cyclophosphamide or non-ICD inducers like temozolomide and decitabine;[291,367] (2) radiotherapy;[368] or (3) targeted therapies (*e.g.* the tyrosine kinase inhibitor axitinib).[289,369,370] Finally, some clinical studies are testing innovative strategies that may support immunity, such as hyperthermia.[371,372]

In summary, as compared to the clinical trials we discussed in the previous Trial Watch dealing with DC-based vaccination,[279] the tendency for currently described studies is to combine DC-based vaccines with other forms of immunotherapy (rather than traditional treatments), which largely reflects the progress of immuno-oncology for the past 2 years.[270,271]

Status update on clinical trials

These following clinical trials have changed status since the publication of our latest Trial Watch on DC-based vaccination for cancer therapy (February 2017):[279] NCT02432846, NCT02366728, NCT02405338, NCT02529072, NCT02692976 and NCT02728102 were previously listed as "Recruiting" but are now listed as "Active, not recruiting"; NCT02993315 shifted from "Active" to "Recruiting"; NCT02709993 and NCT02775292 are now "Recruiting"; and NCT02248402 was previously listed as "Completed" but is now "Unknown". Moreover, NCT02615574, NCT02745756 and NCT02705703 have been "Withdrawn", the latter following the decision of the study sponsor to discontinue development, whereas NCT02548169 was "Terminated" due to loss of funding and NCT02851056 is "Suspended", pending interim analyses.

Concluding remarks

The number of published and ongoing clinical trials testing DC vaccination as a therapeutic approach to malignant disorders suggest that there is a persisting interest in identifying indications for which this immunotherapeutic regimen would offer a good alternative to (or improve the efficacy of) ICBs and ACT. Current efforts in this sense appear to focus on GBM, which is known to be particularly susceptible to DC vaccination.[158,373,374]

In a scenario in which several new immunotherapies are constantly entering clinical development, such as the current one,[270,375–383] it is evident that only clinical trials demonstrating a clear survival advantage may drive the approval of DC-

based vaccines by regulatory authorities. It is therefore encouraging to note that there are at least three advanced (Phase II/III-III) clinical trials currently testing DC-based vaccines in patients with cancer. The results of these studies are eagerly awaited, especially since data from another highly anticipated Phase III trial testing DC-based vaccines in subjects with GBM were not as promising as expected.[384]

The clinical development of DC-based vaccines for oncological indications has been negatively impacted by the commercial failure of Sipuleucel-T as well as by disappointing efficacy in multiple (sometimes poorly designed) clinical studies completed so far.[385–387] Indeed, although DC-based vaccines have demonstrated at least some degree of clinical activity in some studies,[158] their long-term efficacy depends on a number of parameters that are often underestimated, encompassing the immunosuppressive circuitries that are in place in the microenvironment of most solid tumors,[130,271,363,388] the evolution of antigen-loss variants,,[389] and the overall immunological competence of the patient.[156,157] Furthermore, manufacturing DC-based vaccines involves elevated production costs and robust regulatory scrutiny, which constitute additional obstacles to development.[157]

Finally, the lack of robust predictive biomarkers of response to DC-based vaccines limit enthusiasm, in particular when production costs are considered.[342,390–394] At odds with ICBs,[267] DC-based vaccines are indeed associated with mild side effects,[156,157] implying that current efforts to identify predictive biomarkers are mainly aimed at increasing signal-to-noise ratio and support the design of clinical trials focused on patient subsets that are most likely to benefit from treatment. Our hope is that such efforts will soon be successful and drive the development of safe and effective DC-based vaccines for oncological indications.

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