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1638-1648	1649-1658	1659-1668	1669-1678	1679-1688	1689-1698	1699-1708	1709-1718	1719-1728	1729-1738	1739-1748	1749-1758	1759-1768	1769-1778	1779-1788	1789-1798	1799-1808	1809-1818	1819-1828	1829-1838	1839-1848	1849-1858	1859-1868	1869-1878	1879-1888	1889-1898	1899-1908	1909-1918	1919-1928	1929-1938	1939-1948	1949-1958	1959-1968	1969-1978	1979-1988	1989-1998	1999-2008	2009-2018	2019-2028	2029-2038	2039-2048	2049-2058	2059-2068	2069-2078	2079-2088	2089-2098	2099-2108	2109-2118	2119-2128	2129-2138	2139-2148	2149-2158	2159-2168	2169-2178	2179-2188	2189-2198	2199-2208	2209-2218	2219-2228	2229-2238	2239-2248	2249-2258	2259-2268	2269-2278	2279-2288	2289-2298	2299-2308	2309-2318	2319-2328	2329-2338	2339-2348	2349-2358	2359-2368	2369-2378	2379-2388	2389-2398	2399-2408	2409-2418	2419-2428	2429-2438	2439-2448	2449-2458	2459-2468	2469-2478	2479-2488	2489-2498	2499-2508	2509-2518	2519-2528	2529-2538	2539-2548	2549-2558	2559-2568	2569-2578	2579-2588	2589-2598	2599-2608	2609-2618	2619-2628	2629-2638	2639-2648	2649-2658	2659-2668	2669-2678	2679-2688	2689-2698	2699-2708	2709-2718	2719-2728	2729-2738	2739-2748	2749-2758	2759-2768	2769-2778	2779-2788	2789-2798	2799-2808	2809-2818	2819-2828	2829-2838	2839-2848	2849-2858	2859-2868	2869-2878	2879-2888	2889-2898	2899-2908	2909-2918	2919-2928	2929-2938	2939-2948	2949-2958	2959-2968	2969-2978	2979-2988	2989-2998	2999-3008	3009-3018	3019-3028	3029-3038	3039-3048	3049-3058	3059-3068	3069-3078	3079-3088	3089-3098	3099-3108	3109-3118	3119-3128	3129-3138	3139-3148	3149-3158	3159-3168	3169-3178	3179-3188	3189-3198	3199-3208	3209-3218	3219-3228	3229-3238	3239-3248	3249-3258	3259-3268	3269-3278	3279-3288	3289-3298	3299-3308	3309-3318	3319-3328	3329-3338	3339-3348	3349-3358	3359-3368	3369-3378	3379-3388	3389-3398	3399-3408	3409-3418	3419-3428	3429-3438	3439-3448	3449-3458	3459-3468	3469-3478	3479-3488	3489-3498	3499-3508	3509-3518	3519-3528	3529-3538	3539-3548	3549-3558	3559-3568	3569-3578	3579-3588	3589-3598	3599-3608	3609-3618	3619-3628	3629-3638	3639-3648	3649-3658	3659-3668	3669-3678	3679-3688	3689-3698	3699-3708	3709-3718	3719-3728	3729-3738	3739-3748	3749-3758	3759-3768	3769-3778	3779-3788	3789-3798	3799-3808	3809-3818	3819-3828	3829-3838	3839-3848	3849-3858	3859-3868	3869-3878	3879-3888	3889-3898	3899-3908	3909-3918	3919-3928	3929-3938	3939-3948	3949-3958	3959-3968	3969-3978	3979-3988	3989-3998	3999-4008	4009-4018	4019-4028	4029-4038	4039-4048	4049-4058	4059-4068	4069-4078	4079-4088	4089-4098	4099-4108	4109-4118	4119-4128	4129-4138	4139-4148	4149-4158	4159-4168	4169-4178	4179-4188	4189-4198	4199-4208	4209-4218	4219-4228	4229-4238	4239-4248	4249-4258	4259-4268	4269-4278	4279-4288	4289-4298	4299-4308	4309-4318	4319-4328	4329-4338	4339-4348	4349-4358	4359-4368	4369-4378	4379-4388	4389-4398	4399-4408	4409-4418	4419-4428	4429-4438	4439-4448	4449-4458	4459-4468	4469-4478	4479-4488	4489-4498	4499-4508	4509-4518	4519-4528	4529-4538	4539-4548	4549-4558	4559-4568	4569-4578	4579-4588	4589-4598	4599-4608	4609-4618	4619-4628	4629-4638	4639-4648	4649-4658	4659-4668	4669-4678	4679-4688	4689-4698	4699-4708	4709-4718	4719-4728	4729-4738	4739-4748	4749-4758	4759-4768	4769-4778	4779-4788	4789-4798	4799-4808	4809-4818	4819-4828	4829-4838	4839-4848	4849-4858	4859-4868	4869-4878	4879-4888	4889-4898	4899-4908	4909-4918	4919-4928	4929-4938	4939-4948	4949-4958	4959-4968	4969-4978	4979-4988	4989-4998	4999-5008
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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 immunology.

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## Introduction

The presentation of antigenic material to cells of the adaptive immune system, notably CD4<sup>+</sup> helper T cells and CD8<sup>+</sup> cytotoxic T lymphocytes (CTLs), is a crucial function of myeloid cells,<sup>1,2</sup> as it stands at the basis of both antigen-specific immune activation and tolerance.<sup>3–11</sup> Professional antigen-presenting cells (APCs) are specialized at executing this function, and dendritic cells (DCs) are largely viewed as the most proficient of APCs.<sup>7,8,12–18</sup> Indeed, DCs not only present extracellular antigens on MHC Class II molecules to CD4<sup>+</sup> T cells,<sup>19,20</sup> in thus far resembling macrophages and B cells,<sup>21–23</sup> but they also efficiently mediate cross-presentation, i.e., the presentation of extracellular antigens on MHC Class I molecules to CD8<sup>+</sup> CTLs, which is key for anticancer immunity.<sup>8,24–31</sup> 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.<sup>32–35</sup> 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”).<sup>36–38</sup> 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.<sup>8,13,39–51</sup>

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.<sup>5,16,52–66</sup> DCs are highly heterogeneous in terms of ontogeny,<sup>67–69</sup> function, responsiveness to selected stimuli and preference for specific sources of antigens for presentation.<sup>16,70–77</sup> These features have been harnessed to generate ever more refined biological classifications of DCs into different subsets.<sup>76,78–81</sup> 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,<sup>82–84</sup> and plasmacytoid DCs (pDCs), which resemble plasma cells.<sup>85–88</sup> Two other DC subsets have been described: CD16<sup>+</sup> monocyte-derived (or inflammatory) DCs, and Langerhans cells (LCs), a skin-resident population of DCs with potent immunosuppressive activity.<sup>86,89–92</sup> Here, cDCs

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derive from a common myeloid precursor and can be further classified into two subsets: (1) cDC1, which express CD8 $\alpha$  or CD103 in mice, or CD141 in humans; and (2) cDC2, which express CD11b in mice, or CD1c in humans.<sup>93</sup> 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.<sup>85</sup> 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 $\alpha$ <sup>+</sup> DCs in lymphoid tissues and CD103<sup>+</sup>CD11b<sup>-</sup> DCs in peripheral tissues.<sup>94–97</sup> 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.<sup>85,86,98</sup>

Different DC subsets exhibit functional specialization on a number of immunological levels, including: (1) capturing, processing and presenting antigens (*e.g.*, human CD141<sup>+</sup> DCs and mouse CD8 $\alpha$ <sup>+</sup> DCs are highly proficient at cross-presentation, while CD11b<sup>+</sup> DCs efficiently mediate conventional MHC Class II presentation);<sup>97,99–105</sup> (2) preferential engagement of adaptive immune cell populations (*e.g.*, CD14<sup>+</sup> DCs enriched in the dermis and LCs tend to specifically drive humoral responses and CD8<sup>+</sup> T cell effectors, respectively);<sup>106,107</sup> 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).<sup>108–112</sup>

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.<sup>113</sup> In particular, immature DCs (iDCs) potently suppress the activity (or even promote the clonal deletion) of self-reactive T cells,<sup>45,114</sup> and favor the proliferation of immunosuppressive CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup> regulatory T (T<sub>REG</sub>) cells.<sup>27,115–117</sup> 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).<sup>118</sup>

In pathological settings, a plethora of microbial cues commonly known as microbe-associated molecular patterns (MAMPs)<sup>8,119–121</sup> and endogenous danger signals cumulatively referred to as damage-associated molecular patterns (DAMPs)<sup>58,122–128</sup> drive the rapid phenotypic and functional conversion of iDCs into mature DCs (mDCs).<sup>129–137</sup> 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).<sup>38,116,118,138–149</sup> Thus, mDCs acquire the anatomical location and all the functional properties that are required for optimal T cell priming.<sup>150–153</sup>

Since the cross-priming of CD8<sup>+</sup> 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),<sup>154,155</sup> DCs have attracted considerable attention as potential targets for the development of therapeutic cancer vaccines.<sup>156–159</sup> 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,<sup>160</sup> 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.<sup>8,156,157,161</sup> 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.<sup>98,162</sup>

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.<sup>163,164</sup> 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;<sup>138,165–169</sup> (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;<sup>59,170–221</sup> (3) DCs provided *in vivo* with TAAs;<sup>222–233</sup> (4) DCs stimulated *in situ* by immunostimulatory agents applied peritumorally or intratumorally;<sup>234</sup> (5) DCs transfected (virally or biochemically) with a genetic vector coding for one or a few TAAs and/or immunostimulatory factors;<sup>235</sup> or (6) DC-derived exosomes.<sup>236–240</sup> 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.<sup>241</sup> Herein, iDC pulsing is usually achieved by: (1) co-incubation with autologous or allogeneic tumor lysates;<sup>170–179,242–244</sup> (2) co-incubation with recombinant TAAs or peptides thereof;<sup>59,180–186</sup> (3) transfection of TAA-encoding plasmids or mRNAs;<sup>187–211,245–248</sup> and, (4) fusion of DCs with inactivated malignant cells, resulting in the generation of so-called “dendritomes”.<sup>177–179,212–219,249</sup> The possibility of creating DC vaccines *in situ* or *in vivo* by direct TAA delivery has been explored with DC-targeting immunoliposomes,<sup>250–252</sup> DC-targeting genetic vectors,<sup>253–256</sup> or TAAs fused to monoclonal antibodies or other moieties targeting DC surface receptors.<sup>222–228,230,231,233,257,258</sup> The possibility of creating DC vaccines exploiting specific (naturally available) DC subsets has also been explored.<sup>259,260</sup> Particularly, specific DC subsets including pDCs, LCs and CD1c<sup>+</sup> DCs have been successfully utilized in the clinic for the vaccination of cancer patients.<sup>259–261</sup> 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.<sup>262–264</sup>

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<sup>265–269</sup> such as immune checkpoint blockers (ICBs) and adoptive T-cell transfer (ACT),<sup>270,271</sup> interest is being refocused on implementing DC-based vaccines as part of multimodal (immuno)therapeutic regimens.<sup>15,43,272–278</sup> 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).<sup>279</sup> 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,<sup>280</sup> 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.<sup>281</sup> 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<sub>REG</sub> cells results in superior antitumor efficacy against murine LM3 or 4T1 mammary carcinomas.<sup>282</sup> Liu *et al.* (from Chinese PLA General Hospital, Beijing, China) tested the efficacy of DC vaccines involving DCs pulsed with glioma-derived exosomes and  $\alpha$ -galactosylceramide ( $\alpha$ -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.<sup>283</sup> Similarly, Escriba-Garcia *et al.* (from Hospital de la Santa Creu i Sant Pau, Barcelona, Spain) found that DC vaccines combined with  $\alpha$ -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).<sup>284</sup> 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)<sup>285</sup> and induction of lymphoid effector functions.<sup>286</sup> 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),<sup>287,288</sup>

which causes depletion of tumor-associated macrophages (TAMs), synergizes with DC vaccines to achieve eradicating immunity in mouse models of mesothelioma.<sup>289</sup> 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).<sup>290,291</sup> 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<sup>+</sup>MHC-II<sup>low</sup> DCs to be the best APCs in this particular setting.<sup>26</sup> 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)<sup>292,293</sup> 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).<sup>42</sup> 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.<sup>294</sup> 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).<sup>295</sup> 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<sup>296,297</sup> expressing a C-X-C chemokine receptor type 4 (CXCR4) antagonist.<sup>298</sup> 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.<sup>299</sup> 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.<sup>300</sup> 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 (TGFBI)-defective cancer cells induce superior anti-leukemia immunity *in vivo*.<sup>301</sup> 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<sup>+</sup> T cell-dependent eradicating immunity in 3 different

mouse models of the disease.<sup>302</sup> 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<sup>+</sup> CTL-dependent immunity against murine breast cancer.<sup>303</sup> 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.<sup>304</sup> 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<sup>+</sup> CTL-dependent manner.<sup>305</sup> 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.<sup>306</sup> 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,<sup>307</sup> supporting a mechanistic link between ICD-inducing systemic anticancer therapies and cDC1-dependent antigen cross-presentation.<sup>307–320</sup> This finding extends prior observations indicating that human CD1c<sup>+</sup> DCs are critical for the presentation of tumor antigens from cancer cells succumbing to ICD.<sup>8,103,321–323</sup> 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.<sup>324</sup>

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)<sup>279</sup> 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,<sup>325–342</sup> autologous cancer cell lysates,<sup>343–348</sup> or TAA-coding RNAs.<sup>276,349–352</sup> 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,<sup>279</sup> *de facto* reflecting a broad consensus in the field. Additional TAA sources explored in recent clinical studies include

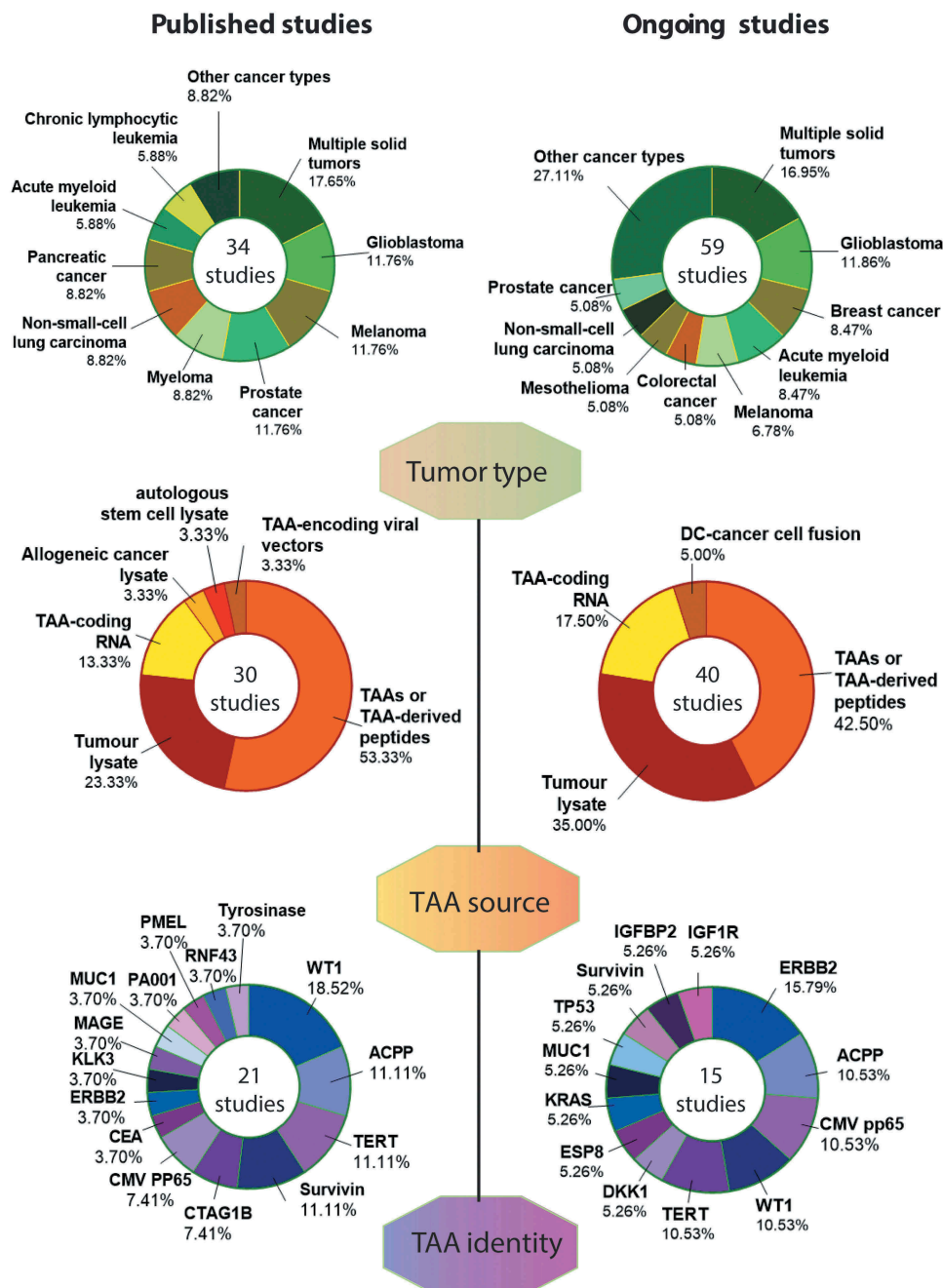
(Figure 1): lysates of autologous (tumor) stem cells, lysates of allogeneic cancer cell lines, and TAA-encoding viral vectors.<sup>353–355</sup> Of note, one of these clinical studies involved DC vaccines based on personalized antigenic peptides.<sup>335</sup> Moreover, a Phase I clinical study investigated 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.<sup>356</sup> Finally, autologous DCs have been investigated in combination with cytokine-induced killer (CIK) cells<sup>357</sup> for the therapy of advanced pancreatic carcinoma.<sup>358</sup>

Most of the aforementioned clinical studies based on specific TAAs focused on WT1 transcription factor (WT1),<sup>327,328,337,342,349</sup> acid phosphatase, prostate (ACPP),<sup>276,325,329</sup> telomerase reverse transcriptase (TERT)<sup>276,333,351</sup> or baculoviral IAP repeating containing 5 (BIRC5, best known as survivin)<sup>276,333,340</sup> (Figure 1). This configuration partly deviates from the trend identified in our latest Trial Watch dealing with DC-based vaccines.<sup>279</sup> Indeed, while WT1 remains amongst the most commonly targeted TAAs, interest in melanoma-associated differentiation antigens has decreased,<sup>337</sup> 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),<sup>326,331,336,348</sup> studies focusing on single indications most commonly enrolled patients with melanoma,<sup>332,337,339,343</sup> prostate cancer,<sup>276,325,329,353</sup> or glioblastoma (GBM).<sup>341,346,350,352</sup> This was followed by pancreatic cancer,<sup>327,333,358</sup> non-small cell lung carcinoma (NSCLC),<sup>338,340,354</sup> and myeloma.<sup>330,334,345</sup> (Figure 1). This trend was very similar to the one we described in 2017,<sup>279</sup> 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<sup>348</sup> or off-label chemotherapeutics (*e.g.*, gemcitabine, cyclophosphamide, S-1, temozolomide, carboplatin, paclitaxel or docetaxel),<sup>276,326–328,337,338,341,344,346,350,358</sup> radiotherapy,<sup>335,341,346</sup> targeted anticancer agents (*e.g.*, tyrosine kinase inhibitors),<sup>328,344</sup> or specific immunotherapeutic regimens, including recombinant colony stimulating factor 2 (CSF2, best known as GM-CSF), recombinant IL2, ACT, and TL3 agonists.<sup>326,333,344,352,353</sup>

Importantly, the vast majority of these clinical studies confirmed that DC-based vaccines are safe for cancer patients,<sup>359</sup> causing mild-to-moderate side effects including fever, erythema, flu-like symptoms, rash and/or fatigue, in a small proportion of patients.<sup>328,333,335,340,341,348</sup> 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<sup>+</sup> CTLs, were consistently documented.<sup>327,332,355</sup> Moreover, multiple clinical studies reported promising clinical responses to vaccination, including disease stabilization<sup>326,328,333,342,344,354</sup> as well as a few partial and complete responses.<sup>330,335,345,347–349</sup> Encouragingly, a few cases of robust extension in patient survival were also documented.<sup>327,351,356,358</sup> 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.<sup>341</sup> 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.<sup>349</sup> 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
Autologous DCs loaded with tumor cell lysate	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
	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
Mesothelioma	I	Not yet recruiting	Tumor lysate	Single agent	NCT03803397	
	II/III	Recruiting	Tumor lysate.	Best supportive care	NCT03610360	
Ovarian cancer	I	Not yet recruiting	Tumor lysate	Pembrolizumab and IL2	NCT03546426	
	I/II	Not yet recruiting	Tumor lysate	Autologous NK cell-like CTLs	NCT03735589	
Renal cell carcinoma	II	Active, not recruiting	n.a.	Standard of care chemotherapy	NCT03657966	
	II	Withdrawn	Tumor lysate	Boost radiotherapy and high-dose IL2	NCT03226236	
Autologous DCs transfected or pulsed with TAA-coding RNA(s)	Solid tumors	I	Recruiting	Tumor lysate	Single agent	NCT03671720
	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, varilumab, and tetanus-diphtheria vaccine	NCT03688178
	NSCLC	I	Recruiting	TERT	Single agent	NCT03371485
		I	Recruiting	WT1 or EPS8	CAR-expressing T cells	NCT03291444
	Autologous DCs loaded with recombinant TAAs or TAA-derived peptide(s)	Breast cancer	I	Recruiting	ERBB2	Neoadjuvant chemotherapy
II			Recruiting	IGFBP2, ERBB2, and IGF1R	DNA-based vaccine	NCT03384914
Colorectal carcinoma		II	Recruiting	ERBB2	Single agent	NCT03630809
		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
	I	Recruiting	EBV proteins	Single agent	NCT03282617	
Nasopharyngeal cancer	I	Recruiting	Mutant KRAS peptides	Single agent	NCT03592888	
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	
Solid tumors	I/II	Recruiting		<i>Pcd1<sup>-/-</sup></i> T Cells	NCT03525652	
	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
	leukemia	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.<sup>158,278</sup>

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,<sup>360</sup> recombinant cytokines,<sup>361,362</sup> immunostimulatory antibodies (e.g., varlilumab),<sup>363,364</sup> or MAMP-based immunostimulants (e.g. tetanus toxoid or tetanus-diphtheria vaccine).<sup>250,365,366</sup> 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;<sup>291,367</sup> (2) radiotherapy;<sup>368</sup> or (3) targeted therapies (e.g. the tyrosine kinase inhibitor axitinib).<sup>289,369,370</sup> Finally, some clinical studies are testing innovative strategies that may support immunity, such as hyperthermia.<sup>371,372</sup>

In summary, as compared to the clinical trials we discussed in the previous Trial Watch dealing with DC-based vaccination,<sup>279</sup> 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.<sup>270,271</sup>

### 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):<sup>279</sup> 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.<sup>158,373,374</sup>

In a scenario in which several new immunotherapies are constantly entering clinical development, such as the current one,<sup>270,375–383</sup> 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.<sup>384</sup>

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.<sup>385–387</sup> Indeed, although DC-based vaccines have demonstrated at least some degree of clinical activity in some studies,<sup>158</sup> 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,<sup>130,271,363,388</sup> the evolution of antigen-loss variants,<sup>389</sup> and the overall immunological competence of the patient.<sup>156,157</sup> Furthermore, manufacturing DC-based vaccines involves elevated production costs and robust regulatory scrutiny, which constitute additional obstacles to development.<sup>157</sup>

Finally, the lack of robust predictive biomarkers of response to DC-based vaccines limit enthusiasm, in particular when production costs are considered.<sup>342,390–394</sup> At odds with ICBs,<sup>267</sup> DC-based vaccines are indeed associated with mild side effects,<sup>156,157</sup> 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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