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Trial Watch

Dendritic cell-based interventions for cancer therapy

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Abbreviations: AML, acute myeloid leukemia; APC, antigen-presenting cell; ASCO, American Society of Clinical Oncology; cDC, conventional DC; CEA, carcinoembryonic antigen; CLEC, C-type lectin domain family; CRC, colorectal carcinoma; CTLA4, cytotoxic T lymphocyte-associated protein 4; CXCL21, chemokine (C-C motif) ligand 21; DAMP, damage-associated molecular pattern; DC, dendritic cell; ERBB2, *v-erb-b2* erythroblastic leukemia viral oncogene homolog 2; GM-CSF, granulocyte macrophage colony-stimulating factor; ICOS, inducible T-cell co-stimulator; ICOSL, ICOS ligand; iDC, immature DC; IFN, interferon; IL, interleukin; LY75, lymphocyte antigen 75; MAMP, microbe-associated molecular pattern; mDC, mature DC; MRI, magnetic resonance imaging; NKT, natural killer T; PAP, prostate acid phosphatase; pDC, plasmacytoid DC; RCC, renal cell carcinoma; TAA, tumor-associated antigen; TBVA, tumor blood vessel antigen; TLR, Toll-like receptor; TRA, tumor-rejection antigen; Treg, regulatory T cell; WT1, Wilms' tumor 1

Dendritic cells (DCs) occupy a privileged position at the interface between innate and adaptive immunity, orchestrating a large panel of responses to both physiological and pathological cues. In particular, whereas the presentation of antigens by immature DCs generally results in the development of immunological tolerance, mature DCs are capable of priming robust, and hence therapeutically relevant, adaptive immune responses. In line with this notion, functional defects in the DC compartment have been shown to etiologically contribute to pathological conditions including (but perhaps not limited to) infectious diseases, allergic and autoimmune disorders, graft rejection and cancer. Thus, the possibility of harnessing the elevated immunological potential of DCs for anticancer therapy has attracted considerable interest from both researchers and clinicians over the last decade. Alongside, several methods have been developed not only to isolate DCs from cancer patients, expand them, load them with tumor-associated antigens and hence generate highly immunogenic clinical grade infusion products, but also to directly target DCs in vivo. This intense experimental effort has culminated in 2010 with the approval by the US FDA of a DC-based preparation (sipuleucel-T, Provenge®) for the treatment of asymptomatic or minimally symptomatic metastatic castration-refractory prostate cancer. As an update to the latest Trial Watch dealing with this exciting field of research (October 2012), here we summarize recent advances in DC-based anticancer regimens, covering both high-impact studies that have been published during the last 13 mo and clinical trials that have been launched in the same period to assess the antineoplastic potential of this variant of cellular immunotherapy.

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Introduction

"Dendritic cells" (DCs) is the term introduced in 1973 by the Canadian immunologist Ralph Steinman to describe a small subset of murine splenic cells characterized by a peculiar tree-like morphology (from the Greek "dendron," meaning tree).[1] Setting the stage for a brand new era in immunology, this discovery granted Ralph Steinman the 2011 Nobel Prize for Medicine and Physiology.[2–4] Indeed, after an initial lag period, the publication rate of scientific articles dealing with DCs has incessantly grown throughout the last 4 decades, nowadays approximating

4000 units/year (all article types confounded, source http://www.ncbi.nlm.nih.gov/pubmed/). Thus, thanks to the work of several pioneers in the field, such as Anna Karolina Palucka, Jacques Banchereau and others, the unique functional profile of DCs, placing them at the hub of innate and adaptive immune responses, has been characterized with increasing precision.[5–21]

DCs differentiate from common myeloid bone marrow progenitors and can be found in virtually all tissues, although they accumulate at sites of intense antigen exposure, such as lymphoid organs, the skin as well as external and internal mucosae.[22–24] Generally, tissue-resident DCs are immature, meaning that they are very efficient at engulfing extracellular material but not at releasing cytokines. In addition immature DCs (iDCs) express (1) MHC class II molecules mostly in the late endosomal compartment; (2) reduced levels of co-stimulatory molecules (e.g., CD40, CD70, CD86, OX40L); and (3) a particular set of chemokine receptors.[25] Importantly, in the absence of appropriate maturation stimuli (see below), iDCs present antigens to T cells in the context of inhibitory signals, hence promoting peripheral tolerance.[26–28] Such an immunosuppressive response relies on at least two distinct mechanisms, i.e., the deletion of antigen-specific T-cell clones (clonal deletion) and the expansion of $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs).[26]

Several stimuli can promote the maturation of iDCs, including (but presumably not limited to) microbe-associated molecular patterns (MAMPs), damage-associated molecular patterns (DAMPs), immune complexes as well as a wide panel of cytokines and chemokines.[5,22,25,29–31] A detailed description of the signal transduction cascades that underpin the maturation of iDCs exceeds the scope of the present Trial Watch and can be found in references 24 and 32–37. As opposed to their immature counterparts, mature DCs (mDCs) exhibit a limited ability to engulf antigens, but (1) express elevated levels of MHC class II molecules at the cell surface; (2) become capable of migrating toward lymph nodes, owing to the expression of specific chemokine receptors (e.g., CCR7); and (3) secrete high quantities of cytokines/chemokines.[24,25] Thus, mDCs are highly efficient at triggering adaptive immune responses, much more than other professional antigen-presenting cells (APCs) including B cells and macrophages.[38] Of note, the immunostimulatory potential of DCs is not restricted to the elicitation of cellular immune responses, but also impacts humoral immunity.[39–41]

DCs exist in several phenotypically and morphologically distinct subsets.[10,42–46] Thus, epidermal Langerhans cells efficiently stimulate $CD8^+$ T-cell responses by secreting interleukin (IL)-15, whereas human $CD14^+$ dermal DCs produce high levels of IL-12, thus promoting the differentiation of naïve B cells into antibody-producing plasma cells.[10,47] Murine $CD8\alpha^+$ DCs (and their circulating $CD141^+$ human homologs) are highly efficient at cross-presentation,[48–52] and appear to be required for optimal responses to foreign (and perhaps tumor-associated) antigens in vivo.[53] Plasmacytoid DCs (pDCs) constitute a morphologically peculiar subset of DCs (named after their resemblance to plasma cells) that produces high levels of Type I interferon (IFN) upon viral infection, hence eliciting robust T_H1 immune responses.[54–56] Such an ability–which is shared by "conventional" DCs (cDCs) only in part–presumably originates from the fact that pDCs express a large panel of pattern recognition receptors, including several members of the Toll-like receptor (TLR) family. Thus, as compared with cDCs, pDCs are endowed with a superior ability to detect MAMPs and DAMPs.[57–59]

Not surprisingly, given their critical position at the interface between innate and adaptive immunity, DCs have been implicated in the pathophysiology of several human disorders, including a wide panel of infective, inflammatory, autoimmune and allergic conditions.[23,60–62] Moreover, along with the realization that the immune system is not a mere bystander of oncogenesis, tumor progression and therapeutic responses,[63,64] an ever more important role has been ascribed to DCs in the context of natural and therapy-elicited anticancer immunosurveillance.[30,65,66] Accumulating preclinical evidence suggests indeed that numeric or functional defects in specific DC subsets facilitate oncogenesis, tumor progression and chemoresistance.[30,67–75] In support of this notion, elevated intratumoral levels of mDCs have been associated with improved clinical outcomes in cohorts of patients affected by a large panel of solid neoplasms.[32,76–95] Moreover, the accumulation of tolerogenic DCs, including $CD208^+$ mDCs and $CD123^+$ pDCs, within neoplastic lesions has been shown to constitute a negative prognostic factor in multiple clinical settings.[32,96–101]

During the last decade, along with the recognition of DCs as central regulators of responses as diverse as the induction of peripheral tolerance and the elicitation of robust antigen-specific immunity, the interest of researchers and clinicians for DCs has progressively turned from observational to interventional.[23,32,102–104] Thus, dozens–if not hundreds–of strategies have been devised for harnessing the immunogenic potential of DCs as a means to treat several human disorders, including infectious, autoimmune, asthmatic and malignant conditions.[9,23,32,61,102,105–109] Perhaps the climax of such an effort has been reached in 2010, when sipuleucel-T, a DC-enriched autologous cell preparation expanded ex vivo in the presence of a prostate acid phosphatase/granulocyte macrophage colony-stimulating factor (PAP/GM-CSF) fusion protein (also known as Provenge®), has been approved by the US FDA for use in patients with asymptomatic or minimally symptomatic metastatic castration-refractory prostate cancer.[110–112]

For illustrative purposes, DC-based anticancer interventions can be classified into 4 major groups, based on the underlying therapeutic principle: (1) reinfusion of unloaded DCs;[113–119] (2) reinfusion of DCs loaded ex vivo with preparations enriched to various extents in tumor-associated antigens (TAAs);[120–171] (3) in vivo DC loading with TAAs;[6,172–184] and (4) DC-derived exosomes.[185–188] Interestingly, DCs can be loaded with TAAs ex vivo in several different ways (near to invariably in the presence of appropriate maturation signals) including (1) the exposure of iDCs to autologous cancer cell lysates;[120–129,189–192] (2) the incubation of iDCs with recombinant TAAs;[130–137] (3) the transfection of DCs with bulk RNA extracted from malignant cells, TAA-coding RNAs or TAA expression vectors;[138–163,193,194] and (4) the fusion of DCs with inactivated cancer cells, to form so-called "dendritomes."[127–129,164–171,195] Along similar lines, multiple methods are nowadays available for delivering TAAs to DCs in vivo,

including (1) the administration of TAA fused to monoclonal antibodies specific for DC surface markers such as lymphocyte antigen 75 (LY75, also known as CD205 or DEC-205), CD209 (best known as DC-SIGN), C-type lectin domain family 4, member A (CLEC4A, also known as DCIR) and C-type lectin domain family 9, member A (CLEC9A);[6,172–182] and (2) the administration of TAAs encapsulated in DC-targeting immunoliposomes.[196–198] Importantly, to avoid the establishment of peripheral tolerance, all approaches of in vivo DC targeting require the co-delivery of adequate maturation signals.[173,174]

Each of these general and specific strategies brings about unique advantages and drawbacks.[32,199,200] However, in spite of such a heterogeneity of approaches, all DC-based anticancer interventions aim at eliciting novel (or boosting pre-existing) immune responses against an established neoplasm, de facto representing a therapeutic (as opposed to prophylactic) clinical paradigm. While the antigenic specificity of antitumor responses cannot be controlled when unloaded DCs are employed, one or more TAAs can be specifically targeted with TAA-loaded DCs and DC-derived exosomes. Obviously, both the safety and the efficiency of targeted DC-based interventions are largely influenced by the choice of therapeutically relevant TAAs.[201–203] As discussed in detail in several recent reviews,[204–209] ideal TAAs should not only be specifically expressed/overexpressed by malignant cells (to avoid, or at least minimize, autoimmune reactions against non-transformed tissues),[210–214] but also behave as tumor-rejection antigens (TRAs), i.e., allow for the elicitation of an immune response that results in tumor eradication.[215] Of note, multiple relatively unspecific immunostimulatory agents including TLR agonists as well as commonly used vaccine adjuvants operate by promoting the maturation of DCs in vivo. However, as these agents have been the topic of dedicated Trial Watches,[216–219] they will not be further discussed here.

As it stands, DCs orchestrate immunological functions as diverse as the establishment of peripheral tolerance and the elicitation of antigen-specific (humoral and cellular) immune responses, de facto occupying a privileged position at the interface between the innate and the adaptive immune system.[220] At least in part, this is due to the following DC prerogatives: (1) their preferential accumulation at anatomical sites of continuous antigen exposure; (2) their ability to efficiently take up high amounts of extracellular material, process it and present the corresponding antigenic epitopes to T and B lymphocytes; (3) their propensity to sense a wide panel of exogenous and endogenous signals of danger, and (4) their capacity to mature into multiple, phenotypically and functionally distinct, subsets.[23]

Along the lines of our monthly Trial Watch series,[32,216–219,221–233] here we summarize the latest developments in the use of DCs as a means to elicit novel (or boost existing) anticancer immune responses, focusing on high-impact studies that have been published and clinical trials that have been launched during the last 13 mo.

Literature Update

During the last 13 mo (July 2012–July 2013, both included), no less than 4,400 articles dealing with DCs have been published in peer-reviewed scientific journals (all types of publication confounded, source http://www.ncbi.nlm.nih.gov/pubmed/). Several of these papers reported the results of recently completed clinical trials assessing the clinical profile of DC-based vaccines in cancer patients. In particular, autologous DCs pulsed ex vivo with purified TAAs or TAA-derived peptides, administered as a standalone intervention or combined with chemo- or immunotherapeutic agents, have been investigated for their ability to elicit tumor-specific immune responses, and hence exert antineoplastic effects, in glioma,[234,235] glioblastoma,[236,237] multiple myeloma,[238] melanoma,[239–241] ductal carcinoma in situ,[242] and hepatocellular carcinoma patients.[243] Along similar lines, the safety and efficacy of autologous DCs loaded ex vivo with tumor lysates, alone or combined with other chemo- or immunotherapeutic regimens, have been tested in cohorts of patients affected by glioblastoma,[244] osteosarcoma,[245] renal cell carcinoma (RCC),[246] and other solid tumors.[247] The clinical profile of DCs engineered to express one or several TAAs (alone or together with co-stimulatory molecules such as CD40 ligand, CD70 and a constitutively active variant of TLR4) has been explored in nasopharyngeal carcinoma,[248] melanoma,[249] small cell lung cancer[250] and colorectal carcinoma (CRC) patients.[251] Finally, (1) autologous DCs expanded ex vivo (but neither genetically modified nor pulsed with TAAs or tumor lysates) have been tested for their ability to improve the clinical responses of newly diagnosed glioblastoma to induction radiotherapy and maintenance chemotherapy;[252] (2) the safety and therapeutic efficacy of autologous DCs loaded ex vivo with the natural killer T (NKT)-cell activator α-galactosylceramide,[253,254] given in combination with low-dose lenalidomide (an immunostimulatory agent),[255] have been evaluated in patients with asymptomatic myeloma;[256] (3) dendritomes have been investigated as an adjuvant therapy upon autologous stem cell transplantation in multiple myeloma patients;[257] and (4) the clinical profile of DCs electroporated ex vivo with mRNAs encoding two distinct TAAs (i.e., gp100 and tyrosinase) has been assessed in individual bearing Stage III/IV melanoma.[258]

Taken together, these studies demonstrate that the administration of multiple distinct DC-based vaccines to cancer patients not only is safe, but also elicits a tumor-specific immune response that—at least in a fraction of patients—translates into objective clinical benefits. Measures aimed at broadening and potentiating vaccination-elicited immune responses, such as the simultaneous targeting of $CD8^+$ and $CD4^+$ T cells[239] or the co-administration of immunostimulatory chemotherapeutic agents (e.g., cyclophosphamide, lenalidomide)[65,66] may extend such clinical benefits to a larger patient population. Nonetheless, the identification of surrogate biomarkers of efficacy remains a critical obstacle against the development of DC-based anticancer interventions (see below). Among the abovementioned clinical studies, we have found of particular interest the work by Ten et al., reporting that the administration of a pDC-based vaccine to melanoma patients is safe and exerts robust immunostimulatory functions.[240] Al least apparently, this is at odds with the association between high intratumoral levels of pDCs and poor disease outcome, which holds true in patients affected by several tumor types.[32,96,99,100,259] Thus, contrarily to previous beliefs, it may be

possible to harness not only cDCs, but also pDCs, for anticancer immunotherapy.[260–263]

Along with such an intense wave of clinical investigation, vast efforts have been dedicated to the elucidation of fundamental aspects of the immunobiology and pathophysiological/therapeutic relevance of DCs, including (but not limited to): (1) how DCs regulate cellular and humoral immune responses;[264–275] (2) which specific subsets of DCs promote the establishment of tolerance and by which molecular and cellular circuitries;[27,276–284] (3) which signals regulate the persistence and maturation of DCs;[285–288] (4) how cross-presentation and other DC functions (in particular, antigen uptake, intracellular trafficking and phagosomal degradation) mutually interact with (and hence regulate) each other;[289–294] (5) which cellular precursors and which cell-extrinsic and cell-intrinsic signals are required for the development of distinct DC subsets;[295–305] (6) what are the phenotypic and functional differences between DC subset, in mice and humans;[306–314] (7) which signal transduction pathways underpin the immunomodulatory activity of pDC, in preclinical and clinical settings;[96,259–261,315–321] (8) how iDCs and mDCs migrate from tissues to lymph nodes;[322–326] and (9) how DCs influence the initiation of autoimmune diabetes,[327] HIV-1 infection,[328,329] and the response of cancer patients to chemo- and immunotherapeutic regimens.[330–332]

Of the extensive literature generated during the last 13 mo around the immunobiology and clinical relevance of DCs, we have found of particular interest the works by Idoyaga et al., Vitali et al. and Weber et al., which altogether identified migratory (as opposed to tissue-resident) DCs as major inducers of peripheral tolerance and attributed to chemokine (C-C motif) ligand 21 (CXCL21) a prominent role in this setting.[27,281,323] Moreover, by establishing the clinical relevance of the inducible T-cell costimulator ligand (ICOSL)-dependent ability of intratumoral pDCs to drive the accumulation of $ICOS^+$ Tregs, Conrad et al., Faget et al. and Yu et al. have provided a strong rationale for the development of immunotherapeutic regimens based on ICOS- or ICOSL-targeting antibodies.[96,317,318,320,333,334] Along similar lines, the research group lead by Nadege Goutagny (Léon Bérard Research Center, Lyon, France) has demonstrated that the intratumoral administration of TLR7 agonists can restore the ability of pDCs to drive a robust, Type I IFN-dependent tumor-specific immune response.[259] Together with the clinical and preclinical results published by Tel and colleagues,[240,260] these results might pave the way toward harnessing the immunostimulatory potential of pDCs for anticancer immunotherapy.[261,263,335,336]

Update on Clinical Trials

When our latest Trial Watch dealing with DC-based anticancer interventions was submitted for publication to *OncoImmunology* (July, 2012), official sources listed 114 recent (started after 2008, January 1st) clinical trials (all statuses included) that would assess the safety and efficacy of this immunotherapeutic strategy in cancer patients.[32] Of these studies, 35 involved DCs loaded ex vivo with purified TAAs, 34 DCs transfected with tumor-derived RNA or engineered to express TAAs, 22 DCs loaded ex vivo with tumor lysates, 9 dendritomes and 14 other DC-based approaches (including in vivo DC targeting). The status of the vast majority of these trials has remained unchanged since, with the exception of NCT00678119, NCT00683241, NCT00722098 and NCT01373515 (all of which have been completed), as well as NCT01216436 (which has been suspended for funding issues) (source www.clinicaltrials.gov). Preliminary results from NCT01373515, a Phase I/IIa clinical trial investigating the safety and therapeutic potential of DCP-001, a preparation of mDCs obtained from an acute myeloid leukemia (AML)-derived cell line that expresses multiple TAAs (so-called "DCOne" cells), have been disclosed at the meeting of the American Society of Clinical Oncology (ASCO) held last June in Chicago (IL, USA). DCP-001 was well tolerated by AML patients, with most common toxicities being moderate (grade < 2) injection site reactions. In addition, DCP-001 not only elicited robust cellular and humoral immune responses, but also was associated with clinical activity (at least to some extent), warranting the initiation of a randomized Phase II study.[337] To the best of our knowledge, the results of NCT00678119 (testing DCs transfected ex vivo with tumor-derived RNA in prostate cancer patients), NCT00683241 (assessing the clinical profile of DCs pulsed ex vivo with cancer-cell lysates in women affected by ovarian carcinoma) and NCT00722098 (investigating the safety and therapeutic activity of DCs loaded ex vivo with multiple recombinant TAAs in melanoma patients) have not yet been disclosed.

At present (July 2013), official sources list 29 clinical trials launched after 2012, July 1st that would investigate the safety and therapeutic profile of DC-based anticancer interventions (source www.clinicaltrials.gov). The most common approach in this sense is represented by the administration of autologous DCs expanded ex vivo in the presence of one or more recombinant TAAs or peptides thereof (8 trials). Thus, DCs loaded with *v-erb-b2* erythroblastic leukemia viral oncogene homolog 2 (ERBB2)-, carcinoembryonic antigen (CEA)-, tumor blood vessel antigen (TBVA)-, or NY-ESO-1-derived peptides are being tested in cohorts of patients affected by breast carcinoma, CRC, melanoma or other solid neoplasms, respectively, either as standalone immunotherapeutic interventions (NCT01730118; NCT01885702) or combined with IL-2 plus autologous lymphocytes genetically engineered to express a NY-ESO-1-targeting T-cell receptor (NCT01697527) or dasatinib, an FDA approved multitarget tyrosine kinase inhibitor[338–342] (NCT01876212). Along similar lines, the safety and clinical profile of autologous DCs pulsed ex vivo with not better specified TAAs or TAA-derived peptides, administered in combination with the hitherto experimental TLR3 agonist Hiltonol® [219,343] or with hematopoietic stem cells plus cytotoxic T lymphocytes, are being assessed in advanced or unresectable melanoma patients (NCT01783431) as well as in subjects bearing primary glioblastoma multiforme (NCT01759810) or brain metastases from breast or lung carcinoma (NCT01782274; NCT01782287) (**Table 1**).

Seven trials initiated after 2012, July 1st to assess the safety profile and efficacy of DC-based anticancer interventions involve sipuleucel-T. In particular, sipuleucel-T is being tested (invariably in cohorts of advanced, castration-resistant prostate carcinoma

Table 1. Clinical trials recently started to assess the safety and therapeutic profile of DC-based vaccines in cancer patients*

Approach	Tumor type	Phase	Status	TAA	Notes	Ref.
Autologous DCs	Melanoma	III	Not yet recruiting	n.a.	As single agent	NCT01875653
	Pancreatic cancer	0	Recruiting	n.a.	Combined with Hiltonol®	NCT01677962
	Prostate cancer	I	Recruiting	n.a.	Genetically modified DCs, combined with AP1903	NCT01823978
	RCC	I	Recruiting	n.a.	Genetically modified DCs, as single agent	NCT01826877
	Solid tumors	I/II	Recruiting	n.a.	As single agent	NCT01882946
		II	Active not recruiting	n.a.	Combined with Hiltonol®	NCT01734564
DCs pulsed with tumor lysates	Brain cancer	I	Not yet recruiting	n.a.	Combined with imiquimod	NCT01808820
	CRC	I	Recruiting	n.a.	As single agent	NCT01671592
	Melanoma	I	Recruiting	n.a.	As single agent	NCT01753089
	Sarcoma	I	Recruiting	n.a.	Combined with imiquimod ± gemcitabine	NCT01803152
		I/II	Recruiting	n.a.	As single agent	NCT01883518
DCs pulsed with TAAs or TAA-derived peptides	Breast carcinoma	I	Recruiting	ERBB2	As single agent	NCT01730118
		II/IIII	Active not recruiting	n.s.	Combined with CTLs and HSCT	NCT01782274
	CRC	I/II	Recruiting	CEA	As single agent	NCT01885702
	Glioblastoma	II/IIII	Active not recruiting	n.s.	Combined with CTLs and HSCT	NCT01759810
	Lung cancer	II/IIII	Active not recruiting	n.s.	Combined with CTLs and HSCT	NCT01782287
	Melanoma	II	Not yet recruiting	TBVA	Combined with dasatinib	NCT01876212
		n.a.	Recruiting	n.s.	Combined with Hiltonol®	NCT01783431
	Advanced tumors	II	Recruiting	NY-ESO-1	Combined with IL-2 + autologous PBLs genetically modified to express a NY-ESO-1-targeting TCR	NCT01697527
DCs transfected with TAA-coding RNA	AML	I/II	Not yet recruiting	Multiple LAAs	As single agent	NCT01734304
		II	Not yet recruiting	WT1	As single agent	NCT01686334
	Melanoma	II	Recruiting	n.s.	As single agent	NCT01676779
Sipuleucel-T	Prostate cancer	I	Recruiting	PAP	Combined with ipilimumab	NCT01832870
		II	Not yet recruiting	PAP	As single agent or in combination with EBRT	NCT01807065
		II	Recruiting	PAP	Combined with a DNA-based vaccine and GM-CSF	NCT01706458
		II	Active not recruiting	PAP	Combined with ipilimumab	NCT01804465
		II	Not yet recruiting	PAP	Combined with SABR	NCT01818986
		II	Not yet recruiting	PAP	Combined with glycosylated rhIL-7	NCT01881867
		n.a.	Not yet recruiting	PAP	Combined with radiotherapy	NCT01833208

Abbreviations: AML, acute myeloid leukemia; CEA, carcinoembryonic antigen; CRC, colorectal carcinoma; CTL, cytotoxic T lymphocyte; DC, dendritic cell; EBRT, external beam radiation therapy; ERBB2, *v-erb-b2* erythroblastic leukemia viral oncogene homolog 2; GM-CSF, granulocyte macrophage colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; LAA, leukemia-associated antigens; n.a., not applicable/not available; n.s., not specified; PAP, prostatic acid phosphatase; PBL, peripheral blood lymphocyte; RCC, renal cell carcinoma; rh, recombinant human; SABR, stereotactic ablative radiation therapy; TAA, tumor-associated antigen; TBVA, tumor blood vessel antigen; TCR, T-cell receptor; WT1, Wilms' tumor 1. *Started after 2012 July, 1st and not withdrawn, terminated or suspended at the day of submission (source www.clinicaltrials.gov).

patients) in combination with a wide panel of immunotherapeutic interventions, including: (1) various forms of radiotherapy[233,344–346] (NCT01807065, NCT01833208, NCT01818986); (2) ipilimumab, an FDA approved monoclonal antibody targeting cytotoxic T lymphocyte-associated protein 4 (CTLA4)[347–350] (NCT01804465; NCT01832870); (3) glycosylated recombinant human IL-7[227,230,351,352] (NCT01881867); and (4) a DNA-based anticancer vaccine administered together with recombinant GM-CSF[225,227,230,353,354] (NCT01706458). Five studies have recently been launched to investigate the clinical profile of autologous DCs pulsed ex vivo with tumor lysates. This approach, is being evaluated either as a standalone therapeutic intervention or combined with gemcitabine (an immunostimulatory nucleoside analog)[65,66,355,356] and/or the FDA-approved TLR7 agonist

imiquimod,[218,357–361] in cohorts of individuals bearing various forms of sarcoma (NCT01803152, NCT01883518), brain cancer (NCT01808820), melanoma (NCT01753089) or CRC (NCT01671592). Of note, NCT01671592 is an investigational, as opposed to interventional, clinical trial, aimed at following—by magnetic resonance imaging (MRI)—the distribution of DCs loaded ex vivo with tumor lysates upon reinfusion (**Table 1**).

Six distinct clinical trials have been launched after 2012, July 1st to evaluate the safety and efficacy of autologous DCs. Four of these studies involve the reinfusion of autologous DCs expanded ex vivo (in the presence of appropriate maturation signals, but not genetically modified), either as a standalone therapeutic interventions or in combination with Hiltonol®, to individuals affected by Stage III melanoma (NCT01875653), unresectable pancreatic carcinoma (NCT01677962) or other solid neoplasms (NCT01734564; NCT01882946). In addition, two clinical trials are testing the therapeutic profile of DCs genetically engineered to express a GM-CSF-carbonic anhydrase IX fusion protein or an exogenously activatable variant of CD40, given as single agent or in combination with the chemical CD40 activator, respectively, in metastatic RCC (NCT01826877) and castration-resistant prostate carcinoma (NCT01823978) patients. Finally, the efficacy of DCs transfected ex vivo with tumor-derived or TAA-coding RNAs, invariably as standalone therapeutic interventions, is being investigated in 3 clinical trials. In particular, DCs transfected with mRNAs coding for Wilms' tumor 1 (WT1) or several other leukemia-associated antigens are being explored as a treatment for AML patients undergoing remission (NCT01686334; NCT01734304), whereas DCs electroporated with not better specified mRNAs (presumably bulk mRNAs derived from neoplastic lesions) are being tested in individuals affected by Stage III/IV melanoma (NCT01676779) (**Table 1**).

Concluding Remarks

On 2011, October 3rd, the Nobel Committee for Physiology or Medicine awarded the Nobel Prize in Physiology or Medicine to Bruce Beutler (an American immunologist) and Jules A. Hoffmann (a Luxembourgish-born French biologist), "for their discovery concerning the activation of innate immunity," and to Ralph Steinman, for "his discovery of the dendritic cell and its role in adaptive immunity." The Nobel Committee was unaware that Ralph Steinman had deceased from pancreatic cancer 3 d earlier, on September 30th. Although the statute of the Nobel Foundation stipulates that the Noble Prize cannot be awarded posthumously, the Nobel Committee eventually announced that the decision would remain unchanged, as it "was made in good faith."[2–4]

Steinman's discovery, dating back to 1973,[1] opened a new exciting era in experimental immunology, inspiring the work of several other research groups worldwide. Such an intense wave of investigation has not yet come to an end, as demonstrated by the high amount of top quality scientific reports published each year around the immunobiology of DCs, providing us with profound insights into the molecular and cellular mechanisms whereby DCs regulate peripheral tolerance and elicit potent adaptive immune responses.[5–21] Moreover, starting with the late 1990s, great interest has been raised by the possibility to employ DCs as therapeutic agents. Since then, dozens of different approaches have been devised to harness the immunostimulatory potential of DCs against a wide panel of neoplasms.[9,23,32,102,106–108] Nowadays, several of these DC-based anticancer interventions have entered the clinical phase of development. Official sources list indeed more than 120 clinical trials recently (after 2008, January 1st) initiated to test the safety and efficacy of DC-based anticancer immunotherapy (source www.clinicaltrials.gov). Of these studies, 29 were launched during the last 13 mo, indicating that the interest of clinicians in the therapeutic potential of DCs remains very high.

However, with the notable exception of sipuleucel-T, which is currently approved by FDA and other international regulatory agencies for the treatment of metastatic castration-refractory prostate cancer,[110,362,363] the clinical progress of DC-based anticancer immunotherapy appears to be problematic, with the majority of strategies failing to proceed beyond Phase II studies. As we have exhaustively discussed in the latest Trial Watch dealing with DC-based anticancer immunotherapeutic regimens,[32] several issues may contribute to such a reduced success rate, including (1) the poor availability of clinical grade TLR agonists, calling for the use of surrogate compounds; (2) the fact that only a few TAAs constitute bona fide TRAs; (3) the limited capacity of systemically administered DCs to relocalize to neoplastic lesions; (4) our insufficient understanding of the functional heterogeneity of distinct DC subsets; (5) the absence of reliable molecular or cellular biomarkers that predict the propensity of cancer patients to favorably respond to DC-based interventions; and (6) the lack of appropriate criteria for evaluating clinical responses in immunotherapy-based trials.

We anticipate that circumventing these issues, for instance by means of novel, highly selective TLR agonists that are compatible with clinical applications,[364] strategies to specifically direct the migration of DCs toward tumor nests, and surrogate markers of therapeutic efficacy,[365–368] will significantly accelerate the development of the next generation of DC-based anticancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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