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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; CEA, carcinoembryonic antigen; CIK, cytokine-induced killer; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CRC, colorectal carcinoma; CTCL, cutaneous T-cell lymphoma; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T-lymphocyte antigen 4; DAMP, damage-associated molecular pattern; DC, dendritic cell; DTH, delayed Type IV hypersensitivity; Gb_3, globotriaosylceramide; GBM, glioblastoma multiforme; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HNC, head and neck cancer; iDC, immature DC; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; KLH, keyhole limpet hemocyanin; mDC, mature DC; MAMP, microbe-associated molecular pattern; MM, multiple myeloma; NLR, NOD-like receptor; NK, natural killer; NSCLC, non-small cell lung carcinoma; PAP, prostate acid phosphatase; pDC, plasmacytoid DC; polyIC, polyinosinic-polycytidylic acid; PRR, pattern recognition receptor, PSA, prostate-specific antigen; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria In Solid Tumors; SCLC, small cell lung carcinoma; SLE, systemic lupus erythematosus; TAA, tumor-associated antigen; hTERT, human telomerase reverse transcriptase; TLR, Toll-like receptor; TNFα, tumor necrosis factor α; TRA, tumor-rejection antigen; Tregs, $CD4^+CD25^+FOXP3^+$ regulatory T cells; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor; WT1, Wilms' tumor 1

Dendritic cells (DCs) occupy a central position in the immune system, orchestrating a wide repertoire of responses that span from the development of self-tolerance to the elicitation of potent cellular and humoral immunity. Accordingly, DCs are involved in the etiology of conditions as diverse as infectious diseases, allergic and autoimmune disorders, graft rejection and cancer. During the last decade, several methods have been developed to load DCs with tumor-associated antigens, ex vivo or in vivo, in the attempt to use them as therapeutic anticancer vaccines that would elicit clinically relevant immune responses. While this has not always been the case, several clinical studies have demonstrated that DC-based anticancer vaccines are capable of activating tumor-specific immune responses that increase overall survival, at least in a subset of patients. In 2010, this branch of clinical research has culminated with the approval by FDA of a DC-based therapeutic vaccine (sipuleucel-T, Provenge®) for use in patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer. Intense research efforts are currently dedicated to the identification of the immunological features of patients that best respond to DC-based anticancer vaccines. This knowledge may indeed lead to personalized combination strategies that would extend the benefit of DC-based immunotherapy to a larger patient population. In addition, widespread enthusiasm has been generated by the results of the first clinical trials based on in vivo DC targeting, an approach that holds great promises for the future of DC-based immunotherapy. In this Trial Watch, we will summarize the results of recently completed clinical trials and discuss the progress of ongoing studies that have evaluated/are evaluating DC-based interventions for cancer therapy.

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Introduction

In 1973, Ralph Steinman and colleagues were the first to report that murine lymphoid organs, notably the spleen, contain a small population of cells exhibiting a very peculiar tree-like morphology, which they named (after the Greek term "dendron," meaning tree) dendritic cells (DCs).[1] Since then, thanks to the work of other pioneers of the field including (but not limited to) Anna Karolina Palucka and Jacques Banchereau,[2-18] the structural and functional features of murine and human DCs have been characterized with increasing precision, and DCs have turned out to

occupy a central position in the immune system. Indeed, DCs are able to orchestrate a wide repertoire of immune responses, spanning from the development of self-tolerance to the elicitation of potent cellular and humoral antigen-specific immunity. This is due to 4 main features that are a prerogative of DCs: (1) their localization at sites of intense antigen exposure; (2) their competence to engulf, process and present to T cells large amounts of antigens; (3) their ability to respond to a plethora of stimuli, and (4) their capacity to mature into multiple, functionally-distinct subsets.[19] Due to its pioneer discoveries on DCs, Ralph Steinman has been awarded—posthumously, for the first time in history—the 2011 Nobel Prize for Medicine and Physiology.[20]

DCs derive from bone marrow progenitors and can be found in virtually all tissues, but are highly enriched where antigen exposure is more intense such as in lymphoid organs, at the body surface (i.e., skin, pharynx, esophagus, vagina, ectocervix and anus) as well as at internal mucosae (i.e., respiratory system and gastrointestinal tract).[19,21] DCs exhibit peculiar probing movements (relentlessly forming and retracting cellular processes from distinct areas of the cell body), which allow them to continuously monitor the microenvironment for the presence of antigens. Antigen uptake can occur in situ, followed by the migration of DCs to draining lymph nodes via afferent lymphatics,[22] or directly within lymph nodes, when soluble antigens reach resident DCs through the lymph.[23] Of note, distinct immune responses can be elicited by DCs depending on the specific site at which antigens are taken up.[23] This reflects the remarkable functional heterogeneity of DCs (see below).

Tissue-resident DCs normally are immature, i.e., they have a high capacity for antigen uptake but a limited potential for releasing cytokines, and they express (1) MHC Class II molecules mostly in the late endosome-lysosomal compartment, (2) low levels of co-stimulatory molecules (e.g., OX40L, CD40, CD70, CD86) and (3) particular chemokine receptors.[20] Of note, immature DCs (iDCs) do not necessarily mature once they take up antigens, as maturation requires a complementary set of signals from the microenvironment. Importantly, in the absence of such signals, iDCs efficiently present antigens to T cells in the context of inhibitory interactions. This response, which appears to be critical for the development of peripheral self tolerance, can be mediated by two distinct mechanisms, namely, the deletion of antigen-specific T cell clones (clonal deletion) and the expansion of $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs).[24] The former has been shown to depend on the expression by DCs of surface cell death-inducing molecules such as FASL[25,26] and PD-L1.[27] Conversely, the latter appears to proceed (at least in part) indirectly, following the release of interleukin (IL)-2 by conventional $CD4^+$ cells that would interact—in a MHC Class II-dependent fashion—with DCs.[28]

iDCs can mature, hence becoming able to elicit adaptive T cell-based immunity, in response to a wide array of environmental signals including microbe-associated molecular patterns (MAMPs, e.g., lipopolysaccharide, unmethylated CpG DNA, double-stranded RNA), damage-associated molecular patterns (DAMPs, e.g., ATP, uric acid, HMGB1, heat-shock proteins), immune complexes as well as cytokines/chemokines released by neighboring immune or stromal cells. These paracrine mediators include, but are not limited to, interferon (IFN) γ, which can be secreted by γδ T cells as well as by natural killer (NK) cells; IL-4 and tumor necrosis factor α (TNFα), both of which are stored in the granules of mast cells; IL-15 and thymic stromal lymphopoietin (TSLP), which are secreted by stromal cells.[29,30] Another signal that is critical for DCs to acquire the ability to launch T-cell immune responses involves the ligation of the co-stimulatory receptor CD40 (also known as TNFRSF5).[31,32] The capacity of DCs to respond to so many stimuli reflect a functional elasticity that can be explained by the large panel of molecular sensors found in these cells. Indeed, DCs not only express multiple pattern-recognition receptors (PRRs) including cell surface C-type lectins, cell surface and endosomal Toll-like receptors (TLRs), intracellular helicases and NOD-like receptors (NLRs), but also a diversified array of cytokine/chemokine receptors.[33,34] Of note, most—if not all—adjuvants that are currently employed in vaccine formulations primarily act by triggering the maturation of DCs.

As compared with iDCs, mature DCs (mDCs) exhibit (1) a largely compromised ability to capture antigens, (2) increased exposure of MHC Class II molecules at the cell surface, (3) the expression of chemokine receptors that are required for their migration to lymphoid organs upon antigen uptake (e.g., CCR7), and (4) an increased capacity to secrete cytokines/chemokines.[20] In addition, mDCs are highly efficient at eliciting adaptive immune responses, much more than other antigen-presenting cells (APCs) such as macrophages.[35] In this context, different DC subsets appear to regulate not only humoral vs. cellular immunity, but also more refined aspects of the latter.[36-38] Thus, while human $CD14^+$ dermal DCs mainly stimulate naïve B cells to differentiate into antibody-producing plasma cells and memory B cells, via an IL-12-dependent mechanism, epidermal Langerhans cells preferentially stimulate $CD8^+$ T-cell responses through the production of IL-15.[7,39] At present, it remains unclear to which extent the induction of $CD8^+$ T-cell responses by Langerhans cells is mediated by the direct cross-presentation of antigens on MHC Class I molecules as opposed to the stimulation of $CD4^+$ T-cell helper functions. Of note, it has recently been suggested that Langerhans cells also mediate tolerogenic functions, at least in some settings including allergic contact dermatitis, by directly inhibiting $CD8^+$ T cells and/or by activating a specific subset of Tregs.[40] Irrespective of these unresolved issues, it appears that circulating $CD141^+$ DCs (the human homologs of murine $CD8\alpha^+$ DCs) would constitute the DC subset most efficient at cross-presentation.[41-44] Gene knockout studies in mice have demonstrated that $CD8\alpha^+$ DCs not only are critical for antigen cross-presentation in vivo, but also promote humoral immunity, perhaps by releasing IL-12.[45] In line with this notion, targeting antigens to $CD8\alpha^+$ DCs in vivo via antibodies that specifically recognize their surface marker CLEC9A has been shown to elicit potent cytotoxic T lymphocyte (CTL) and antibody responses, even in the absence of adjuvants.[46]

One particular subset of DCs is constituted by plasmacytoid DCs (pDCs), which—opposed to their myeloid (or "conventional") counterparts—have been first identified in humans.[1,47,48] pDCs were named after their morphological resemblance to

antibody-producing plasma cells and were soon recognized as potent stimulators of Th1 responses, owing to their ability to secrete high quantities of Type I IFN (in both mice and humans) and IL-12 (only in mice).[49-51] Actually, both mDCs and pDCs are known to secrete Type I IFN in response to an array of stimuli, but for the latter this array is much larger than for the former, encompassing live and inactivated viruses as well as self-nucleic acids. Most likely, this is due to the fact that—at odds with their myeloid counterparts—pDCs express both TLR7 and TLR9 in the endosomal compartment, providing them with a superior capacity to detect MAMPs and DAMPs.[52-54]

Given their critical role at the interface between innate and adaptive immune responses, it is not surprising that DCs are involved in the pathophysiology of multiple human diseases involving immunity, including (though perhaps not limited to) infection, chronic inflammation, autoimmunity and allergy.[19,55] For instance, the specific depletion of DCs has been experimentally associated with an increased susceptibility to *Mycobacterium tuberculosis*,[56] *Toxoplasma gondii*,[57] herpes simplex virus Type I and II,[58] cytomegalovirus,[59] and lymphocytic choriomeningitis virus infection.[59,60] In addition, several pathogens have devised strategies for avoiding the activation of DCs,[61-64] hijacking DC functions toward the establishment of a non-protective Th2 response[65,66] or even exploiting DCs for replication.[19,67] Along similar lines, the tolerogenic functions of iDCs appears to be compromised in several autoimmune disorders including, but not limited to, psoriasis,[68,69] systemic lupus erythematosus (SLE),[70] dermatomyositis,[71,72] and inflammatory bowel disease,[73-75] as well as in allergic conditions, a setting in which TSLP may play a prominent role.[76,77] Of note, recent results indicate that pDCs may actively contribute to the pathogenesis of SLE, owing to their capacity to respond to the so-called neutrophil extracellular traps (i.e., complexes containing self DNA and pro-inflammatory molecules that are released by neutrophils in the course of SLE) by secreting large amounts of Type I IFN.[78,79]

According to the currently accepted model of immunoediting, neoplasms acquire the ability to develop and grow in spite of a proficient immune system in three sequential steps.[80,81] Initially, the growth of cancer cells is efficiently controlled, owing to the elicitation of robust tumor-specific immune responses (elimination). As the elimination phase is normally unable to completely eradicate malignant cells, some of them may acquire alterations that either reduce their immunogenicity or increase their resistance to the cytotoxic functions of the immune system (equilibrium). Such cells eventually grow out uncontrolled (escape), leading to clinically manifest cancer.[80,81] Often, the equilibrium/escape phases occur along with the establishment of an immunosuppressive local microenvironment that involves, among multiple mechanisms,[82,83] the conditioning of tumor-infiltrating DCs toward a tolerogenic phenotype.[84,85] Thus, similar to invading pathogens, malignant cells evolve mechanisms for the subversion of DC-mediated responses.

Nevertheless, during the last two decades, DCs have been shown to provide a prominent contribution to the efficacy of multiple chemotherapeutic and immunotherapeutic anticancer regimens.[86] Thus, the therapeutic efficacy of conventional chemotherapeutics including, though probably not limited to, anthracyclines (e.g., doxorubicin, mitoxantrone), cyclophosphamide and oxaliplatin, has turned out to rely, at least in part, on the induction of immunogenic cancer cell death,[87-91] a functionally distinct type of apoptosis leading to DC-mediated priming of a potent antitumor CTL response.[92] Along similar lines, multiple targeted anticancer agents including monoclonal antibodies (e.g., trastuzumab, cetuximab, panitumumab, rituximab)[93] as well as receptor tyrosine kinase inhibitors (e.g., imatinib)[94] appear to mediate therapeutic effects, at least in part, via off-target immune mechanisms that involve DCs.[86]

In the same period, a consistent amount of preclinical and clinical results has been gathered indicating that DCs underlie a very promising immunotherapeutic approach to cancer themselves.[95] Thus, a large array of cancer vaccination strategies based on DCs have been developed, which can be subdivided into three main categories.[20] The first group of DC-based anticancer vaccines encompasses strategies whereby DCs are generated by culturing patient-derived hematopoietic progenitor cells or monocytes with specific cytokine combinations, loaded with tumor-associated antigens (TAAs) ex vivo (by multiple distinct means yet invariably in the presence of an adjuvant, to promote DC maturation), and eventually re-infused into the patient, most often intradermally and in combination with several local courses of an adjuvant.[20,30] The most common means for the ex vivo loading of DCs with TAAs include: (1) the co-incubation of DCs with whole tumor cell lysates or with apoptotic tumor cell corpses;[96] (2) the co-incubation of DCs with purified TAAs (encompassing both full-length proteins and short peptides); (3) the transfection of DCs with tumor cell-derived mRNA; (4) the genetic manipulation of DCs for the endogenous expression of TAAs; and (5) the fusion of DCs with tumor cells.[97-99] As an alternative, autologous DCs are expanded ex vivo (in the absence of TAAs), sometimes genetically engineered for the self-provision of proliferation/activation signals,[100] and then re-infused intratumorally, either before or after a therapeutic intervention.[101-104] Each of these approaches is associated with specific advantages and drawbacks whose detailed discussion exceeds the scope of this trial watch and can be found elsewhere.[98,105]

Ex vivo-generated DC-based preparations have been tested in cancer patients for more than a decade.[30] While objective clinical responses have been recorded only in some settings,[106] taken together these studies demonstrate that DC-based vaccines exhibit a good safety profile and can elicit the expansion of circulating TAA-specific $CD4^+$ and $CD8^+$ cells.[20,30] Importantly, the clinical success of DCs as an anticancer intervention has been sealed in 2010 with the approval by FDA of a DC-based therapeutic vaccine (sipuleucel-T) for use in patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer.[107-109]

The second group of DC-based anticancer vaccines comprises strategies whereby TAAs are delivered to DCs in vivo.[98,105,110] Such an approach can be achieved by coupling TAAs to monoclonal antibodies or other vectors that specifically recognize DC surface receptors like CLEC9A, DEC205, DC-SIGN, DCIR or globotriaosylceramide (Gb_3) but requires the co-delivery of DC maturation signals (as otherwise DCs would drive tolerance).[3,111-121] In

Table 1. Clinical trials evaluating DCs loaded ex vivo with tumor cell lysates or apoptotic tumor cells as an immunotherapeutic intervention against cancer.*

Approach	Indications	Trials	Phase	Status	Notes	Ref.
DCs pulsed with apoptotic bodies	AML	1	I-II	Recruiting	As single agent	NCT01146262
	Brain tumors	1	I	Active, not recruiting	As single agent	NCT00893945
DCs pulsed with tumor cell lysates	B-cell lymphoma Multiple myeloma	1	I-II	Unknown	As single agent	NCT00937183
	Brain tumors	2	I	Suspended	Combined with imiquimod	NCT01171469
			II	Recruiting	Combined with imiquimod or polyIC	NCT01204684
	Breast cancer	1	II	Recruiting	As single agent	NCT01431196
	Colorectal cancer	2	II	Recruiting	As single agent	NCT01348256 NCT01413295
	Ewing's sarcoma Neuroblastoma Rhabdomyosarcoma	1	I-II	Suspended	Combined with IL-4	NCT00923351
	Glioblastoma	2	II	Recruiting	Combined with radiotherapy, surgery and temozolomide	NCT01213407 NCT01567202
	Glioma	1	I-II	Not yet recruiting	Combined with CIK cells and IL-2	NCT01235845
	Melanoma	1	II	Active, not recruiting	As single agent	NCT01042366
	Mesothelioma	1	I	Recruiting	Combined with cyclophosphamide	NCT01241682
	Ovarian cancer	3	0	Recruiting	As single agent	NCT01132014
			I	Active, not recruiting		NCT00683241
			II	Recruiting		NCT00703105
	Prostate cancer	1	I	Active, not recruiting	Combined with androgen ablation	NCT00970203
	Renal cell carcinoma	2	II	Recruiting	Combined with bevacizumab, IFNα and IL-2	NCT00913913
			I-II		Combined with CIK cells	NCT00862303
	Reproductive tract cancer	1	I	Recruiting	Combined with anti-CD3/anti-CD28-stimulated autologous T-cells, bevacizumab, cyclophosphamide and fludarabine	NCT01312376
	Solid tumors	1	II	Unknown	Combined with GM-CSF and IFNα-2a	NCT00610389

AML, acute myeloid leukemia; CIK, cytokine-induced killer; DC, dendritic cell; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; polyIC, polyinosinic-polycytidylic acid. *Started after January, 1st 2008.

vivo DC targeting is advantageous in that it does not require the expensive and time-consuming generation of clinical grade DC preparations, but so far has been explored to limited extents, especially in the clinical setting. Another advantage of this approach, at least on theoretical grounds, is that chimeric proteins can be designed allowing for the simultaneous delivery of antigens to DCs and for the provision of specific activation signals (for instance upon the engagement of CLEC7A or CD40).[20] This said, further insights into the mechanisms that precisely regulate immune responses elicited by the in vivo delivery of TAAs to DCs are required for this promising strategy to be translated into a clinical reality.[20]

The third class of DC-based immunotherapeutic interventions against cancer includes approaches based on DC-derived exosomes.[122-124] Exosomes are small (30–90 nm in diameter), membrane-surrounded vesicles that are released by a wide range of mammalian cell types, including neoplastic cells and DCs.[125-127] Originating from the fusion of multivesicular bodies with the plasma membrane, exosomes have been shown to modulate multiple biological functions, including cell-to-cell communication and membrane dynamics.[125-127] DC-derived exosomes are not only highly enriched in MHC Class II molecules (100-fold, as compared with DCs), but also can be produced in conditions that result in the expression of high levels of co-stimulatory molecules including CD40, CD80 and CD86.[128] In line with these biological properties, DC-derived exosomes are fully capable of activating adaptive immune responses once loaded with TAAs and inoculated in vivo in suitable animal models.[122,129-131]

For the development of efficient antitumor vaccines, great efforts have been dedicated at the identification of antigens

that would yield to robust, therapeutically beneficial immune responses. This is obviously an important parameter, potentially influencing (though perhaps not entirely dictating) the outcome of DC-based (as well as of other forms of) immunotherapy. Candidates include mutated antigens, which—at least theoretically—can be recognized as non-self by the immune system, as well as wild type self antigens.[132,133] The latter have often been selected as they may lead to the development of broadly applicable anticancer vaccines. Still, T-cell clones with a high avidity for common self antigens are likely to be deleted via negative selection, and often memory T cells recognizing these antigens include immunosuppressive Tregs.[134,135] Importantly, the use of mutated antigens may circumvent these limitations, yet it requires the identification of antigens on a fully personalized basis, an approach that only now starts to become feasible thanks to the development of efficient RNA sequencing technologies.

Along the lines of our Trial Watch series,[136-141] here we will discuss recently completed or ongoing clinical trials that have evaluated/are evaluating DC-based preparations as therapeutic anticancer vaccines.

DCs Loaded Ex Vivo with Tumor Cell Lysates or Apoptotic Bodies

By the late 1990s/early 2000s, the capacity of DCs matured ex vivo in the presence of whole tumor cell lysates or apoptotic tumor cells to elicit therapeutic antitumor immunity in vivo had been firmly established.[142-147] Since then, great experimental efforts have been dedicated to the identification of factors that may influence the immunological outcome of this approach.[20] Of note, it has been suggested that DCs loaded with apoptotic tumor cells would be superior to DCs pulsed with tumor cell lysates, to DCs fused with tumor cells as well as to DCs transfected with tumor-derived mRNA in eliciting immune responses in vivo.[148-151]

During the last decade, a wide array of Phase I/II clinical trials has been launched to test the safety and efficacy of this therapeutic strategy in cancer patients. These studies have been performed in a very wide range of settings, encompassing B-cell lymphoma,[152] chronic lymphocytic leukemia (CLL),[148,153-156] cutaneous T-cell lymphoma (CTCL),[157] glioma,[158-161] glioblastoma multiforme (GBM),[162-165] thyroid carcinoma,[166,167] non-small cell lung carcinoma (NSCLC),[168-170] breast carcinoma,[171,172] mesothelioma,[173] hepatocellular carcinoma (HCC),[174,175] intrahepatic cholangiocarcinoma,[176] melanoma,[177-193] pancreatic carcinoma,[194] colorectal carcinoma (CRC),[195-200] renal cell carcinoma (RCC),[171,201-210] prostate cancer,[211,212] pediatric malignancies,[213-215] and mixed advanced cancers.[216-219] Taken together, the results of these studies were very encouraging as they indicated that (1) DCs pulsed ex vivo with tumor cell lysates or with cancer cells succumbing to apoptosis can be administered to patients in the absence of particular toxicity, and that (2) this approach leads to the activation of an immune response in a very large proportion of cases. This said, objective clinical responses were reported in a relatively limited number of studies,[152,160,164,165,175,179,180,187,189,191,194,195,198,200,202,209,219,220] perhaps linked to the fact that the Response Evaluation Criteria In Solid Tumors (RECIST) have recently been shown to be inappropriate for assessing the clinical efficacy of immunotherapeutic interventions.[20,221,222] In spite of this (perhaps only apparently) moderate rate of clinical success, some studies were able to correlate the development of antitumor immune responses (as assessed by the appearance of delayed Type IV hypersensitivity, DTH) with improved clinical outcomes,[164,179,187,219,220] thus maintaining the interest in this immunotherapeutic strategy high.

DCs matured ex vivo in the presence of apoptotic tumor cells are being tested, as a single immunotherapeutic intervention in acute myeloid leukemia (AML) patients (NCT01146262) as well as in subjects affected by brain neoplasms (NCT00893945). In addition, DCs loaded ex vivo with tumor cell lysates (alone or in the presence of the immunostimulatory protein keyhole limpet hemocyanin, KLH) are being employed in B-cell lymphoma and MM patients, as a standalone intervention (NCT00937183); in individuals affected by brain tumors, combined with the TLR3 agonist polyinosinic-polycytidylic acid (polyIC) and/or the TLR7 agonist imiquimod (NCT01171469, NCT01204684); in neuroblastoma and sarcoma patients, combined with IL-4 (NCT00923351); in GBM patients, associated with the standard therapeutic approach involving radiotherapy, surgery and temozolomide (NCT01567202, NCT01213407); in subjects affected by glioma, in combination with cytokine-induced killer (CIK) cells and IL-2 (NCT01235845); in breast carcinoma (NCT01431196), melanoma (NCT01042366), CRC (NCT01348256; NCT01413295) and ovarian cancer (NCT00683241, NCT00703105, NCT01132014) patients, as a single immunotherapeutic intervention; in mesothelioma patients, combined with cyclophosphamide (NCT01241682); in prostate cancer patients, combined with androgen ablation (NCT00970203); in individuals affected by RCC, combined with either CIK cells or with the vascular endothelial growth factor (VEGF)-targeting monoclonal antibody bevacizumab plus an immunostimulatory cocktail including IL-2 and IFNα (NCT00862303, NCT00913913); in patients with tumors of the reproductive tract, together with bevacizumab, cyclophosphamide, fludarabine and anti-CD3/anti-CD8-stimulated autologous T cells (NCT01312376); and in patients with multiple solid tumors, combined with granulocyte macrophage colony-stimulating factor (GM-CSF) plus IFNα (NCT00610389). Two of these trials (NCT01171469, NCT00923351) have been suspended, for unspecified reasons, while all the others are listed as active (source www.clinicaltrials.gov). Intriguingly, two of these trials involve the use of autologous DCs loaded with oxidized tumor cell lysates, a procedure that has been associated with increased immunogenicity in preclinical settings.[223]

Table 1 reports recent (studies registered at www.clinicaltrials.gov later than 2008, January 1st) clinical trials evaluating, in oncological settings, the safety and efficacy of DCs loaded ex vivo with tumor cell lysates or apoptotic tumor cells.

DCs Pulsed Ex Vivo with Purified TAAs

The notion that DCs exposed ex vivo to purified/recombinant TAAs (be them full-length proteins or short peptides) can elicit

Table 2. Clinical trials evaluating DCs loaded ex vivo with purified TAAs as an anticancer immunotherapeutic intervention.*

Indications	Trials	Phase	Status	TAA	Notes	Ref.
AML	1	I	Recruiting	MAGE-A1 MAGE-A3 NY-ESO-1	Combined with decitabine	NCT01483274
Breast cancer	4	I	Recruiting	iLRP	As single agent	NCT00715832
		I-II		HER-2		NCT00923143
			Unknown	iLRP		NCT00879489
		II	Withdrawn	p53	Combined with an aromatase inhibitor, IL-2 and thymosin α1	NCT00935558
Glioblastoma	1	II	Recruiting	Multiple	As single agent	NCT01280552
Glioma	2	I	Active, not recruiting	GAAs	As single agent	NCT00612001
		I-II				NCT00766753
Hematological malignancies	1	I-II	Recruiting	KLH WT1	Combined with IL-4	NCT00923910
Hepatocellular carcinoma	1	I-II	Unknown	AFP	As single agent	NCT01128803
Melanoma	6	I-II	Completed	Various	Combined with daclizumab	NCT00847106
			Recruiting	MAGE-A1 MAGE-A3 MART-1	As single agent	NCT01082198
				Various		NCT01189383
				gp100	Combined with cyclophosphamide	NCT00683670
		II	Active, not recruiting	Various	As single agent	NCT00722098
			Unknown	MART-1	Combined with IL-2, non-myeloablative chemotherapy and transgenic T cells	NCT00910650
Neuroblastoma Sarcoma	2	I	Recruiting	MAGE-A1 MAGE-A3 NY-ESO-1	Combined with decitabine and imiquimod	NCT01241162
			Terminated	MAGE-A1 MAGE-A3 NY-ESO-1	As single agent	NCT00944580
NSCLC	1	n.a.	Not yet recruiting	Cyclin B1	As single agent	NCT01398124
Ovarian cancer	3	I	Recruiting	Survivin	As single agent	NCT01456065
		II	Active, not recruiting	MUC1		NCT01068509
		II	Enrolling by invitation			NCT01617629
Pancreatic cancer	3	I	Recruiting	Multiple	As single agent	NCT01410968
			Suspended	KLH	Combined with radiotherapy	NCT00843830
		II	Active, not recruiting		Alone or combined with a TNFα-encoding vector and radiotherapy	NCT00868114
Prostate cancer	10	I	Active, not recruiting	TARP	As single agent	NCT00972309
		I-II	Completed	KLH PAP PSA		NCT01171729
		II	Active, not recruiting	PAP fused to GM-CSF	Sipuleucel-T, as single agent	NCT00715078
						NCT00715104
						NCT00901342
						NCT01338012
			Recruiting			NCT01477749
					Sipuleucel-T, combined with hormonotherapy	NCT01487863
						NCT01431391
		III	Active, not recruiting		Sipuleucel-T, as single agent	NCT00779402

AML, acute myeloid leukemia; DC, dendritic cell; GM-CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; KLH, keyhole limpet hemocyanin; n.a., not available; NSCLC, non-small cell lung carcinoma; PAP, prostate acid phosphatase; PSA, prostate-specific antigen; TAA, tumor-associated antigen; TNF, tumor necrosis factor; WT1, Wilms' tumor 1. *Started after January, 1st 2008.

both protective and therapeutic anticancer immune responses in vivo was first demonstrated in 1995, independently, by the laboratories of Michael Lotze and Cornelius Melief.[224,225] In the following few years, the therapeutic potential of antigen-pulsed DCs was confirmed in additional tumor models,[226,227] the underlying molecular and cellular circuitries begun to the characterized,[228-231] and several strategies for increasing the immunogenicity of this approach were devised, encompassing the genetic manipulation of DCs for the emission of immunostimulatory (e.g., IL-12),[232] proliferative (e.g., GM-CSF),[233] or chemotactic signals (e.g., lymphotactin).[234,235] These research threads have never been dismissed since, leading to an ever increasing understanding of the biology that underlie the immunogenicity of antigen-pulsed DCs and to an ever more refined arsenal of protocols for ex vivo antigen loading.[20,105,236] As a standalone example, protein transduction (achieved by fusing TAAs to protein transduction domains such as that of HIV-1 Tat) has been developed as a means to increase the accumulation of purified proteins/peptides in the cytosol of DCs, resulting in the preferential processing of antigens by the proteasome and their presentation on MHC Class I molecules.[237] Of note, some B-cell neoplasms including follicular, non-Hodgkin's and mantle cell lymphoma as well as multiple myeloma (MM) produce tumor-specific immunoglobulins that, owing to their idiotypic determinants, can be exploited as TAAs.[238,239] Although DC-based interventions against such TAAs have been called "anti-idiotypic vaccines," they are conceptually equivalent to other approaches employing DCs as a means to elicit a tumor-specific immune response, the only difference being the nature and specificity of the TAA.[238,239]

The results of the first pilot study testing the safety of DCs loaded ex vivo with purified TAAs (in this case, idiotypic determinants) in cancer patients were published in 1996, and were fairly encouraging: all four follicular B-cell lymphoma patients developed measurable antitumor cellular immune responses, and clinical responses were observed in three of them (one complete regression, one partial regression, and one complete resolution of disease, as assessed by the disappearance of disease-specific molecular markers).[240] Since then, this approach has been tested in a consistent number of Phase I/II clinical trials that enrolled patients affected by a wide array of neoplasms including chronic myeloid leukemia (CML),[241,242] myeloma,[243-249] sarcoma,[218,250] glioma,[251,252] GBM,[253-255] breast carcinoma,[256-261] NSCLC,[262-265] melanoma,[179,184,191,193,266-282] HCC,[283] pancreatic carcinoma,[284,285] gastrointestinal malignancies,[286,287] biliary tract cancer,[284] CRC,[262,264,288-290] RCC,[291-293] ovarian carcinoma,[218,256,294,295] cervical carcinoma,[296,297] prostate cancer,[259,298-311] and other advanced malignancies.[312] Altogether, these clinical studies demonstrated that the use of DCs loaded ex vivo with purified TAAs is safe and results in the activation of TAA-specific immunity in a large proportion of patients, some of whom also exhibit partial or complete clinical responses.

In spite of these encouraging results and perhaps linked to the lack of appropriate surrogate markers to assess the clinical efficacy of immunotherapy-based clinical trials,[221,222] the vast majority of studies investigating the anticancer activity of DCs loaded ex vivo with purified TAAs have not yet reached Phase III (see below), and perhaps never will. One notable exception to this trend is provided by prostate cancer. Indeed, DCs loaded ex vivo with specific TAAs, in particular prostate acid phosphatase (PAP), were soon demonstrated to elicit clinical responses in a consistent fraction of prostate carcinoma patients,[298-304] fostering the launch of multiple Phase III clinical trials,[107,313,314] including a large, randomized, double-blind, placebo-controlled multicenter study.[107] This latter trial unequivocally demonstrated that autologous DCs loaded and activated ex vivo with recombinant PAP fused to GM-CSF (an immunotherapeutic preparation known as sipuleucel-T) are capable of extending the overall survival of patients affected by asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer by approximately 4 mo.[107] Shortly after the release of these results, sipuleucel-T was approved by the FDA for use in humans and begun to be commercialized under the label Provenge®, even though a meticulous phenotypic characterization of the cellular component of this product has not been performed to date.[109]

Recently (studies registered at www.clinicaltrials.gov later than 2008, January 1st), DCs loaded ex vivo with purified TAAs have been (and, often, are still being) tested in AML, neuroblastoma and sarcoma patients (targeted TAAs: MAGE-A1, MAGE-A3, and NY-ESO-1), as a single intervention (NCT00944580), in combination with decitabine (NCT01483274) or associated with decitabine plus imiquimod (NCT01241162); in individuals affected by various hematological malignancies, combined with IL-4 (NCT00923910); in breast carcinoma patients (targeted TAAs: iLRP, HER2 and p53), either as a standalone intervention (NCT00715832, NCT00879489, NCT00923143) or combined with an aromatase inhibitor, IL-2 and thymosin α1 (NCT00935558); in individuals affected by GBM (targeted TAAs: multiple; NCT01280552) and glioma (targeted TAAs: GAA and others; NCT00612001, NCT00766753), as a single immunotherapeutic approach; in melanoma patients (targeted TAAs: gp100, MAGE-A1, MAGE-A3, MART-1, tyrosinase and others, sometimes in combination with viral peptides), as a standalone intervention (NCT00722098, NCT01082198, NCT01189383) or combined with cyclophosphamide (NCT00683670), daclizumab (NCT00847106), or IL-2, non-myeloablative conditioning chemotherapy and transgenic T cells (NCT00910650); in subjects affected by NSCLC (targeted TAA: cyclin B1), as a single therapeutic agent (NCT01398124); in HCC patients (targeted TAA: AFP), as a standalone intervention (NCT01128803); in ovarian cancer patients (targeted TAAs: MUC1, survivin), as a single immune therapeutic intervention (NCT01068509, NCT01456065, NCT01617629); in patients bearing pancreatic cancer (targeted TAAs: multiple, loaded in combination with polyIC or KLH), either as a single agent (NCT00868114, NCT01410968) or combined with an adenoviral vector encoding TNFα and/or radiotherapy (NCT00868114, NCT00843830); and in prostate cancer patients (targeted TAAs: PAP, PSA, TARP, sometimes loaded in combination with KLH), as a standalone anticancer measure (NCT00972309, NCT01171729). All these clinical trials are Phase I/II studies, and the vast majority of them are currently ongoing. A few exceptions are constituted by NCT00935558, which has been withdrawn due to the lack of patients enrolled, NCT00843830, which has been suspended

Table 3. Clinical trials evaluating DCs transfected ex vivo with tumor-derived mRNA or engineered to express TAAs*

Approach	Indications	Trials	Phase	Status	TAA/RNA	Notes	Ref.
DCs engineered to express TAAs	Breast cancer	1	n.a.	Recruiting		Combined with 1-MT	NCT01302821
	Metastatic solid tumors	1	II	Terminated	p53	Combined with anti-p53 TCR-transduced lymphocytes, cyclophosphamide, fludarabine, G-CSF and IL-2	NCT00704938
	Prostate cancer	1	I-II	Recruiting	MUC1	As single agent	NCT00852007
			II	Active, not recruiting		Combined with paclitaxel ± ATRA	NCT00617409
	SCLC	3	II	Recruiting	p53	Combined with ATRA	NCT00618891
			II	Terminated		Combined with ex vivo expanded T cells	NCT00776295
DCs transfected with TC-derived mRNA	AML	1	I	Completed	WT1	As single agent	NCT00834002
	AML CML MM	1	II	Enrolling by invitation	WT1	As single agent	NCT00965224
	Brain tumors	1	I-II	Enrolling by invitation	TSC-derived RNA	As single agent	NCT00846456
	Breast cancer Melanoma	1	I	Recruiting	hTERT p53 Survivin	Combined with cyclophosphamide	NCT00978913
	Glioblastoma	4	I	Active, not recruiting	CMV p65	As single agent	NCT00639639
						Combined with adoptive T-cell adoptive transfer	NCT00693095
				Recruiting	TSC-derived RNA	Combined with bevacizumab	NCT00890032
			I-II	Active, not recruiting	CMV p65	Combined with adoptive T-cell transfer, daclizumab and imiquimod	NCT00626483
	Medulloblastoma Neuroectodermal tumors	1	I-II	Recruiting	TC-derived RNA	Combined with adoptive T-cell transfer	NCT01326104
	Melanoma	9		Active, not recruiting	CD40L CD70 TLR4	As single agent	NCT01066390
			I			As single agent	NCT00672542
				Recruiting	gp100 MAGE-3 MART-1 Tyrosinase	Combined DCs transfected with GITRL-encoding RNA	NCT01216436
					TRP2	As single agent	NCT01456104
			I-II		gp100 Tyrosinase	As single agent	NCT00940004
				Active, not recruiting	CD40L CD70 TLR4		NCT01530698
					hTERT Survivin TC-derived RNA	Combined with temozolomide	NCT00961844
				Completed	TC-derived RNA	As single agent	NCT01278940
				Recruiting	gp100 Tyrosinase		NCT00929019

AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; CML, chronic myeloid leukemia; CMV, cytomegalovirus; DC, dendritic cell; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; MM, multiple myeloma; PAP, prostate acid phosphatase; PSA, prostate-specific antigen; SCLC, small cell lung carcinoma; TAA, tumor-associated antigen; TC, tumor cell; TCR, T-cell receptor; hTERT, human telomerase reverse transcriptase; TLR, Toll-like receptor; TSC, tumor stem cell; WT1, Wilms' tumor 1. *Started after January, 1st 2008.

Table 3. Clinical trials evaluating DCs transfected ex vivo with tumor-derived mRNA or engineered to express TAAs* (continued)

Approach	Indications	Trials	Phase	Status	TAA/RNA	Notes	Ref.
DCs transfected with TC-derived mRNA	Ovarian cancer	2	I	Recruiting	hTERT Survivin	As single agent	NCT01456065
			I-II		hTERT Survivin TSC-derived RNA		NCT01334047
	Prostate cancer	4	II	Recruiting	hTERT PAP PSA Survivin	Combined with docetaxel	NCT01446731
				Completed	TC-derived RNA		NCT01278914
			I-II	Recruiting	hTERT Survivin TC-derived RNA	As single agent	NCT01197625
				Withdrawn	hTERT		NCT01153113
	Renal cell carcinoma	2	II	Active, not recruiting			NCT00678119
				Enrolling by invitation	CD40L TC-derived RNA	Combined with sunitinib	NCT01482949
			III	Not yet recruiting			NCT01582672
	Solid tumors		I-II	Enrolling by invitation	WT1	As single agent	NCT01291420

AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; CML, chronic myeloid leukemia; CMV, cytomegalovirus; DC, dendritic cell; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; MM, multiple myeloma; PAP, prostate acid phosphatase; PSA, prostate-specific antigen; SCLC, small cell lung carcinoma; TAA, tumor-associated antigen; TC, tumor cell; TCR, T-cell receptor; hTERT, human telomerase reverse transcriptase; TLR, Toll-like receptor; TSC, tumor stem cell; WT1, Wilms' tumor 1. *Started after January, 1st 2008.

(listed as temporarily closed to accrual), NCT00944580, which has been prematurely terminated (due to unexpectedly low screening results leading to poor accrual) and NCT01171729, which has been completed (though results have not been released yet).

Sipuleucel-T has recently been/is currently being tested, either as a single intervention or combined with hormonotherapy, in eight distinct clinical trials (including seven Phase II and one Phase III studies) enrolling prostate cancer patients (NCT00715078, NCT00715104, NCT00779402, NCT00901342, NCT01338012, NCT01431391, NCT01477749, NCT01487863). These trials aim at assessing the clinical reliability of different protocols for the derivation of sipuleucel-T from autologous DCs as well as the use of sipuleucel-T as a (partially) off-label medication, for instance in patients affected by hormone-sensitive, rather than hormone-refractory, prostate cancer (source www.clinicaltrials.gov).

Table 2 collects recent clinical trials evaluating the safety and efficacy of DCs loaded ex vivo with purified TAAs in cancer patients.

DCs Pulsed with Tumor-Derived mRNA or Engineered for the Expression of TAAs

The interest in using RNA (be it total RNA extracted from bulk tumor cells or the mRNA coding for a specific TAA synthesized in vitro) as a means to load DCs for the development of anticancer vaccines begun to rise in the late 1990s, thanks to the pioneer work of Eli Gilboa and colleagues at the Duke University.[315-317] Approximately in the same period, the efficacy of naked DNA-based vaccines (most often consisting in the electroporation-mediated delivery of constructs for the expression of TAAs) turned out to be enormously increased by protocols resulting in the preferential transfection of DCs, in vivo.[318-320] Following this discovery, several laboratories worldwide demonstrated that the infusion of DCs engineered ex vivo with (often—but not always—adenoviral)[321] vectors for the expression of TAAs elicits superior immune responses, in vivo, as compared with the direct electroporation of DNA-based vaccines, a notion that in a few years was extended to a wide array of different TAAs and tumor models.[322-332] Along similar lines, in the 2000–2010 decade, several reports provided unequivocal proof that—upon re-infusion—DCs pulsed ex vivo with tumor-derived RNA are capable of eliciting both protective and therapeutic anticancer immune responses.[333-343]

During the last decade, RNA-pulsed DCs as well as DCs engineered for the endogenous expression of TAAs have been evaluated as anticancer immunotherapeutics in a few Phase I/II clinical trials. In particular, DCs electroporated with the mRNA coding for full-length Wilms' tumor 1 (WT1) have been tested in AML patients;[344,345] DCs loaded with the mRNA encoding

Table 4. Clinical trials evaluating dendritomes as an immunotherapeutic intervention in cancer patients*

Indications	Trials	Phase	Status	Notes	Ref.
AML	1	II	Recruiting	Combined with CT-011 or GM-CSF	NCT01096602
B-cell lymphoma Multiple myeloma	1	I-II	Unknown	As single agent	NCT00937183
Breast cancer	1	I-II	Recruiting	Alone or combined with IL-12	NCT00622401
Melanoma	2	I-II	Unknown	As single agent	NCT00626860
		II	Active, not recruiting		NCT01042366
Non-Hodgkin lymphoma	1	n.a.	Recruiting	Combined with cryotherapy and a pneumococcal polyvalent vaccine	NCT01239875
Renal cell carcinoma	2	I-II	Completed	As single agent	NCT00625755
		II	Recruiting	Combined with CT-011	NCT01441765
Reproductive tract cancer	1	II	Active, not recruiting	Combined with GM-CSF ± imiquimod	NCT00799110

AML, acute myeloid leukemia; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-12, interleukin-12; n.a., not available. *Started after January, 1st 2008.

the carcinoembryonic antigen (CEA) have been used in CRC patients[289] as well as in patients with advanced CEA-expressing malignancies;[346] DCs transduced with the mRNA coding for the human telomerase reverse transcriptase (hTERT) have been tested in a subject bearing pancreatic cancer,[347] and in prostate cancer patients;[348] the safety and efficacy of DCs transfected with the mRNA encoding the prostate-specific antigen (PSA)[349] or with RNA derived from allogeneic prostate cancer cell lines[350,351] have been investigated in prostate cancer patients; and DCs pulsed with autologous tumor RNA (alone or combined with KLH) have been tested in patients affected by various brain tumors,[352] glioma,[353] neuroblastoma,[354] melanoma,[350,355] CRC,[356] and RCC.[357] In addition, DCs stably expressing TAAs (most often upon adenoviral transduction) have been tested in patients with advanced (breast, pancreatic and papillary) cancers (expressed TAA: mucin 1),[358] small cell lung carcinoma (SCLC, expressed TAA: mucin p53),[359,360] and melanoma (expressed TAAs: tyrosinase, melan A and gp100).[361,362] Taken together, these studies demonstrated that RNA-loaded as well genetically-modified DCs can be safely administered to cancer patients, leading (in a fraction of cases) to the activation of an antitumor immune response.

Recently (studies registered at www.clinicaltrials.gov later than 2008, January 1st), DCs transduced (most often by electroporation) with RNA have been (and, often, are still being) tested in patients affected by hematological malignancies encompassing acute myeloid leukemia (AML), CML and MM (transduced TAA-encoding RNA: WT1), as a single immunotherapeutic intervention (NCT00834002, NCT00965224); in individuals affected by brain tumors (including GBM) and neuroectodermal tumors (transduced RNAs: CMV p65 or tumor stem cell-derived RNA), either as a single agent (NCT00639639, NCT00846456) or combined with adoptive T-cell transfer (NCT00626483, NCT00693095, NCT01326104), bevacizumab (given as an adjuvant, NCT00890032) or with the tetanus toxoid (NCT00639639); in breast cancer patients (transduced TAA-encoding RNAs: hTERT, p53 and survivin), combined with cyclophosphamide (NCT00978913); in melanoma patients (transduced RNAs: gp100, hTERT, MAGE-3, MART-1, p53, survivin, TRP2, tyrosinase and tumor cell-derived RNA, sometimes in combination with RNAs coding for immunostimulatory proteins including CD40L, CD70 and TLR4), as a standalone intervention (NCT00672542, NCT00929019, NCT00940004, NCT01066390, NCT01278940, NCT01456104, NCT01530698) or in combination with cyclophosphamide (NCT00978913), temozolomide (NCT00961844) or DCs transfected with RNAs encoding immune modulators such as GITRL (NCT01216436); in subjects affected by ovarian cancer (transduced RNAs: hTERT, survivin and tumor cell-derived RNA), as a single agent (NCT01334047, NCT01456065); in prostate cancer patients (transduced RNAs: PAP, PSA, hTERT, survivin and tumor cell-derived RNA), as a standalone intervention (NCT01153113, NCT01197625, NCT01278914) or combined with docetaxel (NCT01446731); in RCC patients (transduced RNAs: tumor cell-derived RNA plus the mRNA encoding CD40L), invariably in combination with the tyrosine kinase inhibition sunitinib (NCT00678119, NCT01482949, NCT01582672); and in patients affected by advanced solid tumors (transduced TAA-encoding RNA: WT1), as a single immunotherapeutic intervention (NCT01291420).

In addition, DCs engineered to stably express p53 as a TAA have been/are being tested in combination with 1-methyl-d-tryptophan (an inhibitor of indoleamine 2,3-dioxygenase, IDO) in breast cancer patients (NCT01302821), combined with chemotherapy, IL-2, granulocyte colony-stimulating factor (G-CSF, filgrastim) and anti-p53 TCR-transduced lymphocytes in patients with progressive or recurrent metastatic cancer (NCT00704938), and in combination with all-trans retinoic acid, paclitaxel, all-trans retinoic acid plus paclitaxel or ex vivo expanded T cells in SCLC (NCT00617409, NCT00618891, NCT00776295). Along similar lines, MUC1-expressing DCs are being investigated as a single immunotherapeutic intervention against prostate cancer (NCT00852007). Most of these studies are currently ongoing, with a few exceptions. These include NCT00704938 and

NCT00776295, which have been prematurely terminated (the latter due to low accrual), NCT01153113, which has been withdrawn (due to the status of investigational new drug being withdrawn by FDA), as well as NCT00834002 and NCT01278940, which have been completed. These results of these latter two studies, however, have not yet been released. Of note, exception made for one sipuleucel-T-based study (NCT00779402), NCT01582672 is the sole clinical trial currently assessing the efficacy of DC-based immunotherapy in a Phase III setting (source www.clinicaltrials.gov).

Table 3 collects recent clinical trials testing the safety and efficacy, as anticancer immunotherapeutics, of DCs transfected ex vivo with tumor-derived mRNA or engineered to express TAAs.

DCs Fused Ex Vivo with Tumor Cells

The first indications that DCs fused to cancer cells would induce therapeutic antitumor responses in vivo date back to the late 1990s/early 2000s.[363-366] Such cell hybrids, also known as "dendritomes," form spontaneously when DCs are co-cultured with both living and apoptotic tumor cells, though at a very low frequency.[363] Thus, multiple protocols have been devised to promote the formation of dendritomes, including approaches based on polyethylene glycol, fusogenic viral glycoproteins and electrofusion.[367-370] It has been proposed that—up re-infusion—dendritomes exert a lower immunogenic potential than DCs pulsed ex vivo with apoptotic tumor cells,[149-151] perhaps owing to comparatively lower expression levels of co-stimulatory surface markers and/or IL-12.[371] Of note, dendritomes have been proposed as a means to drive the activation and expansion ex vivo of antitumor T cell clones for adoptive cell transfer approaches.[372]

During the last decade, Phase I/II clinical trials have investigated the safety and efficacy of dendritomes[373] in patients affected by AML,[374] MM,[375,376] glioma,[377] breast carcinoma,[378,379] melanoma,[380-385] adrenocortical carcinoma,[386] RCC,[379,387-391] and mixed solid tumors.[392,393] Taken together, these clinical studies demonstrated that the administration of dendritomes to cancer patients is safe and associated with the development of DTH responses (indicative of the activation of the immune system) in a very large proportion of cases. In addition, objective clinical benefits (including disease stabilization as well as partial and complete responses) were reported—at least for a fraction of patients—in the vast majority of the studies, with two notable exceptions. In the first one, none of the 11 metastatic melanoma patients treated with dendritomes plus IL-2 developed DTH, pointing to a problem with the vaccination protocol itself.[381] The second one was based on a patient cohort way too small for drawing reliable conclusion. Indeed, only two adrenocortical carcinoma patients were treated with dendritomes and, while they did develop immunological responses, no clinical benefits were observed.[386]

Recently (studies registered at www.clinicaltrials.gov later than 2008, January 1st), dendritomes have been (and, often, are still being) tested in AML patients, in combination with the anti-PD1 monoclonal antibody CT-011 or with GM-CSF (NCT01096602); in B-cell lymphoma and MM patients, as a single immunotherapeutic agent (NCT00937183); in breast carcinoma patients, alone or combined with recombinant IL-12 (NCT00622401); in melanoma patients, as a standalone intervention (NCT00626860, NCT01042366); in non-Hodgkin lymphoma patients, in combination with cryotherapy and a pneumococcal polyvalent vaccine (NCT01239875); in RCC patients, alone or together with CT-011 (NCT00625755, NCT01441765); as well as in subjects affected by neoplasms of the reproductive tract, combined with GM-CSF alone or GM-CSF plus imiquimod (NCT00799110). Only one of these studies is listed by official sources as completed (NCT00625755), yet its results have not been released yet (source www.clinicaltrials.gov).

Table 4 reports recent clinical trials evaluating the safety and efficacy of dendritomes for cancer therapy.

Other DC-Based Approaches

In addition to the strategies described above, several other approaches have been undertaken, with variable rates of success, to harness the immunogenic potential of DCs for cancer therapy.[30,394] These include, but are not limited to, the intratumoral administration of DCs expanded ex vivo (but not loaded with TAAs), either preceding or ensuing a therapeutic intervention,[101-104] the use of DC-based exosomes,[124,126] as well as the direct administration of TAAs fused to DC-specific monoclonal antibodies (in vivo DC targeting).[111-113,395] We were unable to find in the literature any clinical report on the safety and efficacy of this latter approach for cancer therapy. Conversely, the safety and efficacy of DC-derived exosomes have already been investigated in two Phase I clinical trials, involving advanced melanoma and NSCLC patients.[263,396] The results of these studies indicate that DC-derived exosomes loaded with TAAs can be safely administered to cancer patients, yielding—at least in a fraction of cases—immunological and (partial) clinical responses.[263,396]

Along similar lines, the intratumoral administration of ex vivo expanded DCs has already been tested in a few Phase I/II clinical trials. Obviously, this approach cannot be undertaken in the wide range of tumors for which an intratumoral injection is associated with a high rate of intervention-associated morbidity, though technical advances are expected to resolve this issue, at least in some cases[397] Of note, elevated intratumoral amounts of DCs have often, but not always, associated with an improved clinical outcome,[398-402] most likely due to the fact that DCs exist in several functionally distinct subsets, which cannot be appropriately discriminated by means of the common markers detected by immunohistochemistry. Indeed, studies in which DCs were quantified based on maturation-specific markers invariably unveiled a positive correlation between infiltration by mDCs and clinical outcome,[403-406] with a single exception provided by CRC patients.[407] This is paralleled by the fact that high intratumoral levels of Tregs positively (rather than negatively, as in all other cancers)[86] affect CRC prognosis,[408] and de facto reflects the very peculiar oncogenesis of CRC, which involves a prominent pro-inflammatory component.[409]

Irrespective of these issues, intratumoral DCs so far have been tested in small cohorts of breast carcinoma,[410] melanoma,[410,411] hepatoma,[412] soft tissue sarcoma,[413] resectable pancreatic carcinoma,[104]

Table 5. Clinical trials evaluating antigen-naïve DCs, DC-derived exosomes and in vivo DC targeting as immunotherapeutic interventions for cancer therapy*

Approach	Indications	Trials	Phase	Status	Notes	Ref.
Allogeneic DCs	Renal cell carcinoma	1	I	Recruiting	As single agent	NCT01525017
Autologous DCs	AML	2	I	Completed	As single agent	NCT00963521
			I	Recruiting	Irradiated DCs, as a single agent	NCT01373515
	HNC	1	I	Unknown	iDCs, combined with cyclophosphamide, docetaxel and picibanil	NCT01149902
	Multiple myeloma	1	I-II	Unknown	Combined with lenalidomide	NCT00698776
	Pancreatic cancer	1	I-II	Active, not recruiting	iDCs, alone or combined with picibanil	NCT00795977
	Prostate cancer	2	I-II	Active, not recruiting	iDCs, as single agent	NCT00753220
			II	Suspended	Combined with allogeneic tumor-cell vaccine	NCT00814892
	Soft tissue sarcoma	1	II	Recruiting	Combined with radiotherapy	NCT01347034
DC-derived exosomes	NSCLC	1	II	Recruiting	As a single agent	NCT01159288
Genetically engineered autologous DCs	Melanoma	1	I	Active, not recruiting	IL-12-expressing DCs, as single agent	NCT00815607
	NSCLC	2	I	Recruiting	CCL21-expressing DCs, as single agent	NCT00601094 NCT01574222
In vivo DC targeting	NY-ESO-1-expressing solid tumors	1	I	Recruiting	Alone or combined with sirolimus	NCT01522820

AML, acute myeloid leukemia; DC, dendritic cell; HNC, head and neck cancer; iDC, immature DC; IL-12, interleukin-12; mDC, mature DC; NSCLC, non-small cell lung carcinoma. *Started after January, 1st 2008.

and advanced cancer patients.[414] Cumulatively, the results of these studies further confirmed the notion that the administration of DCs is safe and—at least in fraction of patients—can elicit therapeutic immune responses. Recently (studies registered at www.clinicaltrials.gov later than 2008, January 1st), the safety and efficacy of genetically-unmodified DCs have been (and, often, are still being) investigated in several distinct settings and following multiple strategies. These include: (1) allogeneic DCs employed as a single agent in RCC patients (NCT01525017); (2) autologous DCs used alone against AML (NCT00963521), in combination with radiotherapy in soft tissue sarcoma patients (NCT01347034), or with an allogeneic prostate cancer cell vaccine in patients with non-metastatic prostate cancer (NCT00814892); (3) irradiated autologous DCs tested as a single intervention in AML patients (NCT01373515); (4) autologous iDCs used as standalone agent against pancreatic (NCT00795977) and prostate cancer (NCT00753220), or combined with chemotherapy and/or an experimental TLR4 agonist (picibanil) in head and neck cancer (HNC) (NCT01149902) or pancreatic cancer (NCT00795977) patients; and (5) mDCs in combination with lenalidomide for the therapy of MM (NCT00698776). In addition, a few trials are testing autologous DCs that have been genetically engineered for the production of IL-12 or CCL21 as standalone interventions in melanoma (NCT00815607) and NSCLC (NCT00601094, NCT01574222) patients, respectively. With a single exception (NCT00963521), for which—however—results are not yet available, all these clinical studies have not yet been completed. When this Trial Watch was being redacted (July 2012), official sources listed one single Phase I clinical trial what would test in cancer patients the concept of in vivo DC delivery (NCT01522820). Following recent, encouraging preclinical data,[395] this study was enrolling patients affected by a wide spectrum of NY-ESO-1-expressing solid tumors for investigating the safety and efficacy of the TAA NY-ESO-1 fused to a monoclonal antibody specific for the DC surface marker DEC-205. In addition, we found only one (Phase II) clinical study investigating the use of DC-based exosomes against cancer (NCT01159288). In this latter trial, unresectable NSCLC patients responding to induction chemotherapy are allocated to receive or not DC-derived exosomes pulsed with multiple TAAs including, but not limited to, MAGE-A1, MAGE-A3, MART-1 and NY-ESO-1 (source www.clinicaltrials.gov).

Table 5 summarizes recent clinical trials evaluating the safety and efficacy of antigen-naïve DCs, DC-derived exosomes and in vivo DC targeting strategies for cancer therapy.

Concluding Remarks

Following the discovery that—in the presence of appropriate stimulatory signals—DCs are able to elicit robust (and hence potentially therapeutic) antitumor immune responses, multiple strategies have been devised to harness the potential of this functionally heterogeneous immune cell population for cancer therapy. The efficacy of these approaches, encompassing the re-infusion into patients of autologous DCs expanded, (sometimes) genetically modified and loaded with TAAs ex vivo as well as the administration of TAAs fused with monoclonal antibodies

allowing for in vivo DC targeting, has been promptly demonstrated in murine tumor models, encouraging the launch of several Phase I/II clinical trials. In the vast majority of these studies, the administration of DCs was found to be safe and—at least in a fraction of patients—to stimulate detectable antitumor responses. Clinical benefits ranging from disease stabilization to complete responses have also been observed in a variable percentage of cases. However, with the notable exception of FDA-approved sipuleucel-T, whose efficacy against asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer has been amply documented in multiple, double-blind, placebo-controlled, multicenter Phase III trials,[107,313,314] the clinical development of DC-based anticancer vaccines appears to be challenging, with most approaches failing to enter Phase III testing.

There are several reasons behind the relatively slow development of DC-based immunotherapeutic interventions. First, until recently, the availability of clinical grade TLR agonists (which are required for DC maturation) was limited. This has been partially circumvented by the use of surrogate compounds, such as clinically approved prophylactic vaccines.[415,416] Second, a limited fraction (~10%) of TAAs appears to be immunogenic, and, among these, only a few constitute bona fide tumor-rejection antigens (TRAs), i.e., antigens that elicit an immune response resulting in tumor eradication.[417] Thus, great efforts will have to be dedicated to the identification of bona fide TRAs, a highly personalized process that involves single cell exome sequencing followed by functional validation assays.[418,419] Of note, contrarily to expectations, it seems that TRAs do not preferentially arise from "driver" oncogenic mutations, suggesting that the oncogenic potential of TAAs does not correlate with their immunogenicity.[420] Third, DCs administered to patients may not efficiently localize at the tumor site.[421] Thus, even though extratumoral DCs may also provide therapeutic benefits, strategies to direct the migration of DCs toward tumor nests are under development. Forth, owing to the elevated heterogeneity (as well as to the hitherto partial characterization) of the DC system, it remains unclear which specific formulation (i.e., which specific route for the loading of TAAs and which specific subset of DCs) has the highest likelihood to result in the activation of therapeutic anticancer immune responses. Recently, great expectations have been generated by the discovery of CD141$^+$ DCs (the human homologs of murine CD8α$^+$ DCs), which would constitute the DC subset most efficient at cross-presentation.[41-44] In addition, the potential of pDCs as professional APCs is being re-evaluated.[422] Future investigations will clarify if the specific use of CD141$^+$ DCs or pDCs results in improved therapeutic outcomes.

Finally, one major issue that has hampered the development of DC-based interventions is represented by the fact that, until a few years ago, clinical efficacy in immunotherapy-based trials was assessed by the RECIST.[423] These criteria, which have been developed to monitor chemotherapy-based clinical studies, have recently been shown to be inappropriate for the assessment of immunomodulatory interventions, as the activation of antitumor responses is slow and initially may even be paralleled by an increased tumor mass (reflecting the infiltration of immune cells).[20,221,222] In line with this notion, the administration of a monoclonal antibody targeting the immunosuppressive receptor cytotoxic T-lymphocyte antigen 4 (CTLA4) has been shown—in a randomized Phase III clinical trial—to double the survival of Stage IV melanoma patients in the absence of early tumor shrinkage.[424] These observations suggest that overall survival might be the sole objective parameter to assess the clinical efficacy of immunotherapeutic interventions. As the evaluation of clinical trials based on overall survival may be excessively long (and hence discourage the development of potentially valuable immunotherapies), there is an urgent need for the identification of surrogate markers of efficacy. While it has been suggested that the clinical outcome of anticancer vaccines might correlate with the expansion of TAA-specific CTLs,[220,425-427] several other factors are involved in the elicitation of therapeutically beneficial immune responses. A better understanding of the molecular and cellular mechanisms whereby efficient immunotherapy translates into objective responses will surely lead to the identification of novel biomarkers that predict the clinical efficacy of DC-based interventions.

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