HHS Public Access

Author manuscript

J Immunol. Author manuscript; available in PMC 2019 January 15.

Published in final edited form as:

J Immunol. 2018 January 15; 200(2): 443–449. doi:10.4049/jimmunol.1701024.

Dendritic Cell-Based Cancer Vaccines[1]

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Abstract

Dendritic cells (DC) are specialized immune cells that play a critical role in promoting an immune response against antigens, which can include foreign pathogenic antigens and self-tumor antigens. DC are capable of boosting a memory T cell response but most importantly they are effective initiators of naïve T cell responses. Many years of studies have focused on the use of DC vaccines against cancer to initiate and shape an anti-tumor specific immune response and/or boost existing spontaneous anti-tumor T cell responses. Here we give a brief overview of DC biology, function and cellular subsets, and review the current status of the field of DC as cancer vaccines.

Dendritic cells (DC) are well known as the optimal antigen presenting cell (APC) for the priming of T cell responses. They are rare cells in the circulation and in tissues, and were very challenging to study for many years (1). When methods for *ex vivo* culture were developed, DC became much more actively investigated. More recently, with technologies that allow interrogation of single cells, insights into DC subsets and their biology have been made possible. Before DC, cellular cancer vaccines were often based on genetic engineering of tumor cells, both autologous and allogeneic cells and cell lines. Tumor cells engineered with cytokines like granulocyte-macrophage colony stimulating factor (GM-CSF), allogeneic HLA molecules, or other xenoantigens have been a focus of preclinical and Phase I clinical trials, but their mechanisms of immunogenicity are thought to require antigen uptake and presentation by endogenous DC. Since the ability to culture DC in sufficient numbers, DC vaccines for cancer have been tested in Phase I, II and III clinical trials. In this review, we present the biology of DC and the successes and failures to date with their use as vaccines against cancer.

[1]**Financial Support**

This work was supported by research funding from the University of Pittsburgh Cancer Institute and National Cancer Institute grant P50 CA121973 Skin SPORE (Kirkwood; Project 2 L. H. Butterfield) and National Cancer Institute grant 5T32CA175294 Training Program in Skin Biology and Cancer (P. Santos). This study utilized the University of Pittsburgh Cancer Institute's Immunologic Monitoring Laboratory shared facility (Director, L. H. Butterfield) supported in part by award National Cancer Institute grant P30 CA047904.

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DC Biology

Ralph Steinman first described and identified DC as a distinct cell type different from macrophages, due to their unique stellate shape and high expression of major histocompatibility molecules (MHC) in 1973 (1, 2). Since then the field has greatly progressed and DC are often described as professional APC because of several key features (Figure 1) (2–4). DC are mostly localized in tissues, acting as sentinels until antigen encounter. The specialized characteristics of DC allow for efficient antigen capture, internalization and processing into peptides that are then presented in the context of MHC Class I and II molecules. These complexes are subsequently able to be recognized by the T cell receptor (TCR) of $CD8^+$ and $CD4^+$ T cells (5, 6). DC that have captured antigens then migrate to lymphoid organs such as the spleen and lymph node to encounter and activate antigen-specific T cells through the TCR (“signal 1”) (7, 8). DC also provide costimulatory signals to T cells through the B7 family of molecules, (“signal 2”), transducing signals which result in expansion and clonal selection (4, 9, 10). Furthermore, DC can regulate and control the type and quality of T cell response elicited, via production of cytokines such as IL-12 p70 for Th1, IL-4 for Th2 or IL-17 for induction of a Th17 response (“signal 3”) (11–13).

Prior to antigen encounter, DC exist as immature DC. This is characterized by high expression of intracellular MHC II in late endosome-lysosomal compartments, low expression of costimulatory molecules and low expression of chemokine receptors. On the other hand, immature DC are biologically equipped for antigen capture and uptake through receptor-mediated endocytosis, pinocytosis and phagocytosis (14–17). After antigen uptake and capture, antigen-loaded DC upregulate chemokine receptors like CCR7 to migrate to the draining lymph nodes (7, 18), allowing for occurrence of DC-T cell interaction critical for the initiation of T cell responses (19).

Conversion of DC from immature to mature DC is important for initiation of antigen-specific T cell responses. Effective induction of T cell response by DC can be functionally demonstrated *in vitro* through allogeneic mixed lymphocyte reaction (MLR) experiments. In addition, DC require very small amounts of antigen to stimulate T cell proliferation and are also shown to be superior stimulators of T cells, such that 100-fold more macrophages and B cells are needed to induce a proliferative MLR response (20, 21). During maturation, DC undergo physiologic changes resulting in increased expression of surface MHC I and MHC II molecules, increased expression of costimulatory molecules, expression of chemokine receptors, and secretion of cytokines to regulate the type of T cell response elicited (22, 23). DC maturation also results in lowering of the pH of endocytic vacuoles to activate proteolysis, and transport of peptide-MHC molecules to the cell surface while decreasing the capacity for antigen capture (6).

DC maturation can also be triggered by environmental stimuli because DC express a variety of receptors for sensing of viral and microbial pathogens as well as damaged, stressed, apoptotic and necrotic cells, including autologous cells (4, 24, 25). DC can detect microbial and viral pathogens via pattern recognition receptors such as Toll-like receptors, c-type lectin receptors, NOD-like receptors and DNA/RNA receptors RIG-I and MDA5 (26). They

can detect immune complexes via activating and inhibitory Fc receptors. DC respond to immunogenic and tolerogenic signals from other immune cells via receptors for TNF, interferon, IL-10, TSLP and CD40L. Sensing of damaged cells and tissues by DC is possible due to release of molecules normally found intracellularly, such as ATP, heat shock proteins and HMGB proteins. The recognition mechanisms that DC use to recognize endogenous and non-endogenous signals are also another strategy currently utilized to generate more effective DC vaccines against cancer, by taking advantage of highly immunogenic signals resulting from cell death (27).

Another important feature exhibited by certain types of DC is the ability to cross-present intracellular antigens. As a result, DC can take up exogenous antigen which can result in the DC presenting an antigenic peptide-MHC I complex which can elicit a $CD8^+$ cytolytic response against immune complexes, non-replicating microbes and dying cells (28, 29). While the mechanisms involved are still incompletely elucidated, it is clear that during cross-presentation, protein antigens that are endocytosed and most efficiently move towards MHC class II presentation are also able to reach the cytoplasm where proteasome processing occurs prior to peptide-MHC I presentation (29).

Major DC subsets

Blood and skin derived DC are the focus of the majority of studies on human DC due to tissue accessibility. The different DC subsets are defined and classified based on characteristics such as morphology, tissue localization, function, developmental origin and expression of surface markers (Table 1). All DC progenitors originate from $CD34^+$ hematopoietic progenitors localized in the bone marrow (30) and they proliferate in response to Flt3L (31). In addition, monocytes grown in culture with GM-CSF and IL-4 also result in differentiation into monocyte-derived DC (32), which allows for generation of large-scale dendritic cells in culture. Recently, Lee et.al has shown that the specification of the DC lineage is established as early as the hematopoietic stem cell stage through lineage bias exerted by a combinatorial dose of expression of transcription factors IRF8 and PU.1, and that Flt3L reinforces IRF8 expression throughout DC lineage differentiation (33).

Blood DC are classified into 3 different subtypes (Table 1). Plasmacytoid DC are characterized by expression of IL-3 receptor α-chain (CD123), BDCA-2 (CD303), and BDCA-4 (Neuropilin) molecules (34). Plasmacytoid DC are well-equipped to rapidly produce type I interferons in response to viral infections due to high expression of TLR7 and TLR9 (35). They are also capable of immediate activation of memory cytotoxic CD8 T cells as well as expansion of viral antigen-specific CD8 effector T cells (36–38).

Conventional DC, also known as myeloid DC, are further subdivided into 2 types based on differential expression of BDCA-1 ($CD1c^+$) and BDCA-3 ($CD141^+$) (34). $CD1c^+$ DC express various lectins, Toll-like receptors 1–8 (39) and can produce high levels of IL-12p40 and p70 (40). $CD1c^+$ DC are also believed to play a role in anti-mycobacterial immunity because CD1c is a non-classical MHC molecule that presents mycobacterial isoprenoid glycolipids to T cells (41). Furthermore, $CD1c^+$ DC can phagocytose *Mycobacterium tuberculosis* and produce IL-6 and TNF (42).

The second type of myeloid DC subset is $CD141^+$ DC, best described as cross-presenting DC, similar to murine $CD8^+$ DC, because of their ability to capture antigen ultimately presented in the context of MHC Class I (43). They are particularly suited for cross presentation of cellular antigens, immune complexes and antigen targeted to late endosomes due to expression of CLEC9A and TLR3 (44, 45) (46). $CD141^+$ DC also express the receptor XCR1, which binds to chemokine lymphotactin/XCL1 produced by NK cells and activated CD8 T cells indicating role of $CD141^+$ DC in anti-viral and anti-tumor immunity (47, 48). More recently, the importance of tumor-resident DC, which express transcription factor BATF3 and can also express CD141, has been described as an important source of T cell recruiting chemokines CXCL9 and CXCL10 (49–51). These findings have important implications for cancer immunotherapy by leveraging recruitment and/or activation of BATF3+ DC in the tumor microenvironment to promote T cell infiltration, especially in a T cell-poor tumor microenvironment, also known as a “cold tumor” (50).

Two major DC subsets have been characterized in human skin: dermal interstitial DC (dermal DC) and epidermal Langerhans cells (LC). Dermal DC subsets can be further classified into $CD1a^+$ DC and $CD14^+$ DC (52). While not much is currently known about $CD1a^+$ DC, several studies suggest that $CD14^+$ DC are specialized in the development of humoral responses primarily by the differentiation of naïve CD4 T cells into follicular helper T cells and by providing direct help to activated B cells (43, 53). In comparison to $CD14^+$ DC, Langerhans cells are more efficient in cross-presentation of protein antigens and can prime naïve CD8 T cells to differentiate into effector CTL (43, 53). Thus, the continued study of DC biology can improve our understanding of the diverse functionality of DC leading to better strategies in designing more effective DC vaccines against cancer.

These findings and the paucity of studies on non-skin resident DC suggest that further studies are needed to fully understand different DC subsets and their functional specializations. The complexities of phenotyping myeloid cells have made characterizing the diverse cells in tumors quite challenging. Some limited overlap in cell surface markers between human and murine DC has added difficulties. However, more recent data have identified key surface and intracellular markers of human DC that now allow subsets to be identified. $CD103^+$ DC in tumors and their role in allowing T cell infiltration is an example (see above) (49, 50).

Overview of early DC vaccine trials

Based on the potent antigen presentation and T cell activation activity of DC, and the development of straightforward *in vitro* culture conditions to promote DC differentiation from monocytes (54–56), DC were subsequently tested as cancer vaccines (57) (Figure 2). Between 1995 and 2004, the first series of clinical trials testing monocyte-derived DC cultured in GM-CSF + IL-4 reached the clinic. They were loaded with tumor antigens in a variety of ways and used to promote tumor antigen-specific antitumor T cell immunity. Many were tested in melanoma patients based on the known “immunogenicity” of that tumor, as well as the characterization of shared tumor antigens like MART-1/Melan-A and gp100 (58–60). Other tumor types which served as early tests of DC vaccines were B cell lymphoma (61), and, later, AML (62), myeloma (63), HCC (58). The one FDA approved

cancer vaccine, Provenge, is based on GM-CSF-activated APC targeting prostate cancer (64, 65), (although the extent to which this vaccine is based on DC and not other constituents is much discussed). These early trials showed that DC vaccines were both safe and immunogenic. Tumor-specific $CD8^+$ T cell responses were detected in vaccinated patients as quickly as 7 days after a single DC injection (58). Most trials have been tested in late stage cancer patients who have progressed after standard of care treatments, and who may not have optimally functioning immune systems due to tumor-induced immune suppression and previous treatments. Regardless, up to 10% of vaccinated patients can have durable tumor regressions. *Ex vivo* cultured monocytes are not the only clinically tested DC platform. $CD34^+$ stem cells from mobilized donors cultured in GM-CSF, FLT3-L and TNF have been tested in melanoma with positive immunologic response and clinical results (66). Plasmacytoid DC have also been tested successfully (67). More detailed knowledge of DC subsets with both unique and shared functional capabilities is a more recent development; hence, the majority of trials tested the DC most easily prepared for clinical testing: $CD14^+$ peripheral blood monocyte-derived DC.

Lessons learned from early trials

Because DC are highly sensitive environmental sensors, the reagents they are exposed to can strongly impact their function; hence, the culture conditions are critical. The starting cell population: $CD14^+$ monocytes, $CD34^+$ stem cells, $CD123^+$ plasmacytoid DC, BDCA-1^+ circulating myeloid DC (68–71) are all immunogenic, but all distinct. The cytokines used for *in vitro* differentiation (GM-CSF plus IL-4 vs. IL-15 for monocyte-derived DC) (72) can impact downstream T cell responses *in vitro*, though the distinctions *in vivo* can be challenging to determine above the “noise” of human variation. The area of DC maturation signals has been an active area of investigation for many years. *In vitro* (73) and in *in vivo* models, immature DC were found to be less effective activators of immunity, expressing lower levels of MHC I and II and of costimulatory molecules, having reduced cytokine production, and being less able to traffic to lymph nodes for T cell activation (74, 75). Several studies of *in vivo* labeling of DC have shown that a small minority travel to lymph nodes, and maturation state at the time of injection may not be the most critical element (76). Therefore, in an effort to promote DC traffic to lymph nodes, potent T cell activation, and type 1-skewed immune responses, a variety of cocktails have been tested. They have been tested for the ability to upregulate surface CD83 (indicating maturation) and CCR7 (indicating the ability to traffic to lymph nodes) and have high IL-12p70 production (to skew T cells to type 1 immunity), and strong *in vitro* T cell activation (often using healthy donor blood). Because a potency assay for DC vaccines has yet to be identified which would predict *in vivo* activity, identifying an optimal maturation cocktail remains a challenge. In addition, data obtained from healthy donor cells is not always replicated in patient cells. A novel DC delivery approach to direct DC to lymph nodes via lymphatic ports and intralymphatic injection has recently been shown to be feasible (77).

Antigen loading

Another critical area of DC vaccine design and translation is antigen loading. Many sources of antigen have been tested *ex vivo*: MHC Class I restricted peptides (78), synthetic long

peptides (79), full length proteins, tumor heat shock proteins, containing peptides (80) autologous tumor cells (lysates and cells), as well as killed allogeneic tumor cells (81). In addition, transfection with DNA and RNA or transduction with viral vectors (82, 83) has been tested. All of these approaches have been successful in that they provide antigen, and are immunogenic *in vitro*, particularly when combined with maturation signals. Identification of the superior approach remains unknown. Short (8–11 aa) peptides are limited by the ability to only activate $CD8^+$ T cells, which could be more limited in function ("helpless" (84)), and the heterogeneity of HLA types in patients might support an overlapping long peptide or full length antigen approach, but addition of antigenically heterologous 'help' in the form of keyhole limpet hemocyanan (KLH) has been used by many groups. There are data suggesting tumor antigen-specific help is superior (85, 86); there are also data indicating the utility of KLH addition (87).

Two recent studies have directly compared whole tumor cell-based loading: DC-tumor hybrids (which can be accomplished by several methods) or DC-tumor cell mixtures, one in an *in vitro* study (88) showing electroporation-mediated fusion to be superior for T cell activation. A second report of a clinical trial in melanoma compared DC-tumor co-culture, PEG-mediated tumor-DC fusion and tumor lysate-loading of DC (L. Geskin, 2017, submitted). This trial indicated that a mixture of tumor cells plus DC may be inferior to the fusion and lysate loading (however, small numbers precluded a significant correlation). The optimal approach for antigen loading to produce the strongest CTL response has yet to be identified. *In vivo* DC targeting has also been investigated, particularly targeting antigens to the DEC-205 DC surface receptor (89). This area has been limited to date by specificity and efficiency of targeting (90).

Recent studies with DC for cancer: The state of the art

There have been several high profile DC based vaccine reports in the last 2–3 years that highlight the state of the art. In one proof-of-principle study focused on neoantigens, three stage III resected melanoma patients received mature autologous DC pulsed with peptides derived from mutated neoantigens (91). Identification of the patient-specific neoantigen peptides (which were short, HLA-A2 binding MHC class I restricted epitopes) required substantial effort due to current limitations in epitope prediction software and *in vitro* testing. Notably, all three had previously received CTLA-4 blockade. In the blood of the vaccinated patients (after brief *in vitro* stimulation), peptide-specific T cell responses were identified. Importantly, the post-vaccine blood samples showed a more diverse T cell receptor repertoire, which suggests the promotion of determinant/epitope spreading (58). In a study of 12 glioblastoma patients that addressed DC vaccine injection, pre-conditioning the DC vaccine injection site with a potent recall antigen (tetanus toxoid) vs. empty DC (without antigen) was tested (92). The subsequent DC vaccines were loaded with CMVpp65 RNA (expressed in a large percentage of glioblastoma tumors), and the DC injected in tetanus toxoid preconditioned sites resulted in superior lymph node trafficking of DC and superior patient survival. While a very small study should not be over-interpreted, the companion murine model studies implicated the chemokine CCL3 as mediating superior DC migration and efficacy.

Another recent trial testing DC transfected with HSP70 mRNA was investigated in HCV^+ hepatocellular cancer (HCC) patients (93). The trial was a dose escalation, with 1, 2 and 3x10e7 DC delivered per injection. What was remarkable were the objective clinical responses in this disease setting (2 CR, 5 SD of 12 patients who were SD at enrollment). While some tumor histologies like melanoma might be expected to show responses like this, in HCC, it is unusual (94).

Promoting tumor-specific immunity with a vaccine and then amplifying it with checkpoint blockade is an attractive hypothesis that is being tested in different ways. In a larger, 39 melanoma patient DC vaccine and checkpoint CTLA-4 combination trial, autologous, standard monocyte-derived DC were loaded with several shared melanoma antigen mRNAs and functionally enhanced with adding costimulation mRNAs by electroporation (95). In this study, based on previous trials in the same electroporated DC platform, the vaccines given both i.v. and i.d., were combined with simultaneous CTLA-4 blockade (with ipilimumab). There was an encouraging overall response rate with 8 CR and 7 PR from the 39 advanced melanoma patients, suggesting that this is a combination setting worthy of further testing. Given the previous study of vaccination after CTLA-4 blockade, the combination schedule will need to be investigated in future trials. Such testing is complicated by the FDA approvals of CTLA-4 and PD-1 blocking antibodies; hence, many patients will now receive these therapies after initial diagnosis.

Another trial tested the use of primary circulating $CD1c^+$ blood DC (70). These cells we cultured for only 16 hours, and the 14 stage IV melanoma patients in this study received 3 x 10e6 to 1 x 10e7 DC. Four of the 14 patients showed strong antitumor T cell responses that correlated with favorable PFS (12–35 mo.). This trial showed that harvesting these primary DC from blood is feasible, the cells are immunogenic and could be tested further.

DC vaccines for infectious disease and transplantation

There are many disease settings in addition to cancer where activation of antigen-specific immunity or skewing of spontaneous immunity towards a more therapeutic immune response is desirable. One of the first DC trials was in an infectious disease prevention setting, and examined Flu M1 peptide-pulsed DC (96), showing strong Flu-specific $CD8^+$ T cell responses as soon as 7 days after vaccination. While a reasonably efficacious Flu vaccine exists, a very active infectious disease investigative clinical setting for vaccination is chronic HIV infection. DC vaccines for HIV have been developed (67) and tested *in vitro* (97, 98) and *in vivo* in several clinical trials (99, 100). These studies, demonstrating safety and immunogenicity of type-1 immunity promoting DC, are sufficiently promising to lead to a new series of next generation clinical trials which are in preparation. The lessons learned in cancer and in chronic infection may help inform each other.

The following examples provide another useful counterpoint to stimulatory DC vaccines for cancer. Based on the studies on DC maturation and tolerance induction from immature DC, culture conditions were developed for induction of an immune suppressive state in DC with the goal of specifically inducing suppression or prevention of immune responses against self-antigens (like those targeted in autoimmunity) or highly immunogenic allogeneic

antigens (in settings of transplantation). Some of these strategies involve specifically down-regulating key molecules of co-stimulation (testing antisense oligonucleotides against CD80, CD86 and CD40 (101). Others are based on culture conditions (including Vitamin D3 (NFkB inhibition) and IL-10 (tolerance promotion) designed to skew DC to a stable suppressive state (102, 103). These modulations of DC culture and resultant phenotype are stable enough to resist strong maturation signals from the TLR ligand LPS and can increase inhibitory checkpoint molecule expression (104) including PD-L1 on the surface of DC.

Future directions with DC vaccines and conclusions

DC have been known as the environmental sensors and potent APC for decades now. The over 200 clinical trials testing DC vaccines have shown that DC are safe vaccines, highly immunogenic, and periodically able to activate an antitumor immune response capable of inducing a durable, objective tumor regression and clinical response in a previously treated, late stage cancer patient. That is why DC will continue to be tested as cancer vaccines in new stages of cancer (earlier stages), new tumor histologies (melanoma is not the only potentially responsive tumor), and new combinations (preceding simultaneously with checkpoint blockade or after checkpoint therapy). Research into DC remains critical. We do not yet know which DC subsets are optimal for clinical translation, nor do we yet know the best antigens, loading strategies, doses, routes of administration or potency assays.

Abbreviations

AML	acute myelogenous leukemia
APC	antigen presenting cells
APL	antigen presenting cell
CD	cluster of differentiation
CR	complete clinical response
DC	dendritic cells
Flu	influenza virus
GM-CSF	granulocyte macrophage colony stimulating factor
HCC	hepatocellular cancer
HIV	human immunodeficiency virus
IL	interleukin
PR	partial clinical response
PFS	progression free survival

References

1. Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med. 1973; 137:1142–1162. [PubMed: 4573839]
2. Steinman RM. Decisions about dendritic cells: past, present, and future. Annu Rev Immunol. 2012; 30:1–22. [PubMed: 22136168]
3. Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature. 1998; 392:245–252. [PubMed: 9521319]
4. Steinman RM, Banchereau J. Taking dendritic cells into medicine. Nature. 2007; 449:419–426. [PubMed: 17898760]
5. Nussenzweig MC, Steinman RM, Gutchinov B, Cohn ZA. Dendritic cells are accessory cells for the development of anti-trinitrophenyl cytotoxic T lymphocytes. J Exp Med. 1980; 152:1070–1084. [PubMed: 6968335]
6. Trombetta ES, Mellman I. Cell biology of antigen processing in vitro and in vivo. Annu Rev Immunol. 2005; 23:975–1028. [PubMed: 15771591]
7. Cyster JG. Chemokines and the homing of dendritic cells to the T cell areas of lymphoid organs. J Exp Med. 1999; 189:447–450. [PubMed: 9927506]
8. Itano AA, Jenkins MK. Antigen presentation to naive CD4 T cells in the lymph node. Nat Immunol. 2003; 4:733–739. [PubMed: 12888794]
9. Guermonprez P, Valladeau J, Zitvogel L, Thery C, Amigorena S. Antigen presentation and T cell stimulation by dendritic cells. Annu Rev Immunol. 2002; 20:621–667. [PubMed: 11861614]
10. Chen L. Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. Nat Rev Immunol. 2004; 4:336–347. [PubMed: 15122199]
11. Pulendran B, Smith JL, Caspary G, Brasel K, Pettit D, Maraskovsky E, Maliszewski CR. Distinct dendritic cell subsets differentially regulate the class of immune response in vivo. Proc Natl Acad Sci U S A. 1999; 96:1036–1041. [PubMed: 9927689]
12. Seder RA, Boulay JL, Finkelman F, Barbier S, Ben-Sasson SZ, Le Gros G, Paul WE. CD8+ T cells can be primed in vitro to produce IL-4. J Immunol. 1992; 148:1652–1656. [PubMed: 1347305]
13. LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, Schweighoffer E, Tybulewicz V, Brown GD, Ruland J, Reis e Sousa C. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. Nat Immunol. 2007; 8:630–638. [PubMed: 17450144]
14. Figdor CG, van Kooyk Y, Adema GJ. C-type lectin receptors on dendritic cells and Langerhans cells. Nat Rev Immunol. 2002; 2:77–84. [PubMed: 11910898]
15. Sallusto F, Cella M, Danieli C, Lanzavecchia A. Dendritic cells use macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products. J Exp Med. 1995; 182:389–400. [PubMed: 7629501]
16. Reis e Sousa C, Stahl PD, Austyn JM. Phagocytosis of antigens by Langerhans cells in vitro. J Exp Med. 1993; 178:509–519. [PubMed: 8393477]
17. Svensson M, Stockinger B, Wick MJ. Bone marrow-derived dendritic cells can process bacteria for MHC-I and MHC-II presentation to T cells. J Immunol. 1997; 158:4229–4236. [PubMed: 9126984]
18. Randolph GJ, Angeli V, Swartz MA. Dendritic-cell trafficking to lymph nodes through lymphatic vessels. Nat Rev Immunol. 2005; 5:617–628. [PubMed: 16056255]
19. Shakhar G, Lindquist RL, Skokos D, Dudziak D, Huang JH, Nussenzweig MC, Dustin ML. Stable T cell-dendritic cell interactions precede the development of both tolerance and immunity in vivo. Nat Immunol. 2005; 6:707–714. [PubMed: 15924144]
20. Steinman RM, Witmer MD. Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice. Proc Natl Acad Sci U S A. 1978; 75:5132–5136. [PubMed: 154105]

21. Bhardwaj N, Young JW, Nisanian AJ, Baggers J, Steinman RM. Small amounts of superantigen, when presented on dendritic cells, are sufficient to initiate T cell responses. J Exp Med. 1993; 178:633–642. [PubMed: 8340760]
22. Reis e Sousa C. Dendritic cells in a mature age. Nat Rev Immunol. 2006; 6:476–483. [PubMed: 16691244]
23. Fujii S, Liu K, Smith C, Bonito AJ, Steinman RM. The linkage of innate to adaptive immunity via maturing dendritic cells in vivo requires CD40 ligation in addition to antigen presentation and CD80/86 costimulation. J Exp Med. 2004; 199:1607–1618. [PubMed: 15197224]
24. Gallucci S, Matzinger P. Danger signals: SOS to the immune system. Curr Opin Immunol. 2001; 13:114–119. [PubMed: 11154927]
25. Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. Immunity. 2010; 33:492–503. [PubMed: 21029960]
26. Desmet CJ, Ishii KJ. Nucleic acid sensing at the interface between innate and adaptive immunity in vaccination. Nat Rev Immunol. 2012; 12:479–491. [PubMed: 22728526]
27. Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2017; 17:97–111. [PubMed: 27748397]
28. Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature. 1998; 392:86–89. [PubMed: 9510252]
29. Heath WR, Belz GT, Behrens GM, Smith CM, Forehan SP, Parish IA, Davey GM, Wilson NS, Carbone FR, Villadangos JA. Cross-presentation, dendritic cell subsets, and the generation of immunity to cellular antigens. Immunol Rev. 2004; 199:9–26. [PubMed: 15233723]
30. Caux C, Dezutter-Dambuyant C, Schmitt D, Banchereau J. GM-CSF and TNF-alpha cooperate in the generation of dendritic Langerhans cells. Nature. 1992; 360:258–261. [PubMed: 1279441]
31. Maraskovsky E, Daro E, Roux E, Teepe M, Maliszewski CR, Hoek J, Caron D, Lebsack ME, McKenna HJ. In vivo generation of human dendritic cell subsets by Flt3 ligand. Blood. 2000; 96:878–884. [PubMed: 10910900]
32. Sallusto F, Lanzavecchia A. Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha. J Exp Med. 1994; 179:1109–1118. [PubMed: 8145033]
33. Lee J, Zhou YJ, Ma W, Zhang W, Aljoufi A, Luh T, Lucero K, Liang D, Thomsen M, Bhagat G, Shen Y, Liu K. Lineage specification of human dendritic cells is marked by IRF8 expression in hematopoietic stem cells and multipotent progenitors. Nat Immunol. 2017; doi: 10.1038/ni.3789
34. Dzionek A, Fuchs A, Schmidt P, Cremer S, Zysk M, Miltenyi S, Buck DW, Schmitz J. BDCA-2, BDCA-3, and BDCA-4: three markers for distinct subsets of dendritic cells in human peripheral blood. J Immunol. 2000; 165:6037–6046. [PubMed: 11086035]
35. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, Cao W, Wang YH, Su B, Nestle FO, Zal T, Mellman I, Schroder JM, Liu YJ, Gilliet M. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature. 2007; 449:564–569. [PubMed: 17873860]
36. Siegal FP, Kadowaki N, Shodell M, Fitzgerald-Bocarsly PA, Shah K, Ho S, Antonenko S, Liu YJ. The nature of the principal type 1 interferon-producing cells in human blood. Science. 1999; 284:1835–1837. [PubMed: 10364556]
37. Asselin-Paturel C, Trinchieri G. Production of type I interferons: plasmacytoid dendritic cells and beyond. J Exp Med. 2005; 202:461–465. [PubMed: 16103406]
38. Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol. 2005; 23:275–306. [PubMed: 15771572]
39. Hemont C, Neel A, Heslan M, Braudeau C, Josien R. Human blood mDC subsets exhibit distinct TLR repertoire and responsiveness. J Leukoc Biol. 2013; 93:599–609. [PubMed: 23341538]
40. Nizzoli G, Krietsch J, Weick A, Steinfelder S, Facciotti F, Gruarin P, Bianco A, Steckel B, Moro M, Crosti M, Romagnani C, Stolzel K, Torretta S, Pignataro L, Scheibenbogen C, Neddermann P, De Francesco R, Abrignani S, Geginat J. Human CD1c+ dendritic cells secrete high levels of IL-12 and potently prime cytotoxic T-cell responses. Blood. 2013; 122:932–942. [PubMed: 23794066]

41. Moody DB, Ulrichs T, Muhlecker W, Young DC, Gurcha SS, Grant E, Rosat JP, Brenner MB, Costello CE, Besra GS, Porcelli SA. CD1c-mediated T-cell recognition of isoprenoid glycolipids in Mycobacterium tuberculosis infection. Nature. 2000; 404:884–888. [PubMed: 10786796]
42. Lozza L, Farinacci M, Bechtle M, Staber M, Zedler U, Baiocchini A, Del Nonno F, Kaufmann SH. Communication between Human Dendritic Cell Subsets in Tuberculosis: Requirements for Naive CD4(+) T Cell Stimulation. Front Immunol. 2014; 5:324. [PubMed: 25071784]
43. Palucka K, Banchereau J, Mellman I. Designing vaccines based on biology of human dendritic cell subsets. Immunity. 2010; 33:464–478. [PubMed: 21029958]
44. Sancho D, Joffre OP, Keller AM, Rogers NC, Martinez D, Hernanz-Falcon P, Rosewell I, Reis e Sousa C. Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. Nature. 2009; 458:899–903. [PubMed: 19219027]
45. Schulz O, Diebold SS, Chen M, Naslund TI, Nolte MA, Alexopoulou L, Azuma YT, Flavell RA, Liljestrom P, Reis e Sousa C. Toll-like receptor 3 promotes cross-priming to virus-infected cells. Nature. 2005; 433:887–892. [PubMed: 15711573]
46. O'Keeffe M, Mok WH, Radford KJ. Human dendritic cell subsets and function in health and disease. Cell Mol Life Sci. 2015; 72:4309–4325. [PubMed: 26243730]
47. Bachem A, Guttler S, Hartung E, Ebstein F, Schaefer M, Tannert A, Salama A, Movassaghi K, Opitz C, Mages HW, Henn V, Kloetzel PM, Gurka S, Kroczek RA. Superior antigen cross-presentation and XCR1 expression define human CD11c+CD141+ cells as homologues of mouse CD8+ dendritic cells. J Exp Med. 2010; 207:1273–1281. [PubMed: 20479115]
48. Crozat K, Guiton R, Contreras V, Feuillet V, Dutertre CA, Ventre E, Vu Manh TP, Baranek T, Storset AK, Marvel J, Boudinot P, Hosmalin A, Schwartz-Cornil I, Dalod M. The XC chemokine receptor 1 is a conserved selective marker of mammalian cells homologous to mouse CD8alpha+ dendritic cells. J Exp Med. 2010; 207:1283–1292. [PubMed: 20479118]
49. Pfirschke C, Siwicki M, Liao HW, Pittet MJ. Tumor Microenvironment: No Effector T Cells without Dendritic Cells. Cancer Cell. 2017; 31:614–615. [PubMed: 28486102]
50. Spranger S, Dai D, Horton B, Gajewski TF. Tumor-Residing Batf3 Dendritic Cells Are Required for Effector T Cell Trafficking and Adoptive T Cell Therapy. Cancer Cell. 2017; 31:711–723. e714. [PubMed: 28486109]
51. Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, Barczak A, Rosenblum MD, Daud A, Barber DL, Amigorena S, Van't Veer LJ, Sperling AI, Wolf DM, Krummel MF. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. Cancer Cell. 2014; 26:638–652. [PubMed: 25446897]
52. Valladeau J, Saeland S. Cutaneous dendritic cells. Semin Immunol. 2005; 17:273–283. [PubMed: 15953735]
53. Klechevsky E, Morita R, Liu M, Cao Y, Coquery S, Thompson-Snipes L, Briere F, Chaussabel D, Zurawski G, Palucka AK, Reiter Y, Banchereau J, Ueno H. Functional specializations of human epidermal Langerhans cells and CD14+ dermal dendritic cells. Immunity. 2008; 29:497–510. [PubMed: 18789730]
54. Inaba K, Steinman RM, Pack MW, Aya H, Inaba M, Sudo T, Wolpe S, Schuler G. Identification of proliferating dendritic cell precursors in mouse blood. J Exp Med. 1992; 175:1157–1167. [PubMed: 1569392]
55. Markowicz S, Engleman EG. Granulocyte-macrophage colony-stimulating factor promotes differentiation and survival of human peripheral blood dendritic cells in vitro. J Clin Invest. 1990; 85:955–961. [PubMed: 2179270]
56. Romani N, Gruner S, Brang D, Kampgen E, Lenz A, Trockenbacher B, Konwalinka G, Fritsch PO, Steinman RM, Schuler G. Proliferating dendritic cell progenitors in human blood. J Exp Med. 1994; 180:83–93. [PubMed: 8006603]
57. Butterfield LH. Dendritic cells in cancer immunotherapy clinical trials: are we making progress? Front Immunol. 2013; 4:454. [PubMed: 24379816]
58. Butterfield LH, Ribas A, Dissette VB, Amarnani SN, Vu HT, Oseguera D, Wang HJ, Elashoff RM, McBride WH, Mukherji B, Cochran AJ, Glaspy JA, Economou JS. Determinant spreading associated with clinical response in dendritic cell-based immunotherapy for malignant melanoma. Clin Cancer Res. 2003; 9:998–1008. [PubMed: 12631598]

59. Mukherji B, Chakraborty NG, Yamasaki S, Okino T, Yamase H, Sporn JR, Kurtzman SK, Ergin MT, Ozols J, Meehan J, et al. Induction of antigen-specific cytolytic T cells in situ in human melanoma by immunization with synthetic peptide-pulsed autologous antigen presenting cells. Proc Natl Acad Sci U S A. 1995; 92:8078–8082. [PubMed: 7644541]
60. Nestle FO, Alijagic S, Gilliet M, Sun Y, Grabbe S, Dummer R, Burg G, Schadendorf D. Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells. Nat Med. 1998; 4:328–332. [PubMed: 9500607]
61. Hsu FJ, Benike C, Fagnoni F, Liles TM, Czerwinski D, Taidi B, Engleman EG, Levy R. Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells. Nat Med. 1996; 2:52–58. [PubMed: 8564842]
62. Van Tendeloo VF, Van de Velde A, Van Driessche A, Cools N, Anguille S, Ladell K, Gostick E, Vermeulen K, Pieters K, Nijs G, Stein B, Smits EL, Schroyens WA, Gadisseur AP, Vrelust I, Jorens PG, Goossens H, de Vries IJ, Price DA, Oji Y, Oka Y, Sugiyama H, Berneman ZN. Induction of complete and molecular remissions in acute myeloid leukemia by Wilms' tumor 1 antigen-targeted dendritic cell vaccination. Proc Natl Acad Sci U S A. 2010; 107:13824–13829. [PubMed: 20631300]
63. Rosenblatt J, Avivi I, Vasir B, Uhl L, Munshi NC, Katz T, Dey BR, Somaiya P, Mills H, Campigotto F, Weller E, Joyce R, Levine JD, Tzachanis D, Richardson P, Laubach J, Raje N, Boussiotis V, Yuan YE, Bisharat L, Held V, Rowe J, Anderson K, Kufe D, Avigan D. Vaccination with dendritic cell/tumor fusions following autologous stem cell transplant induces immunologic and clinical responses in multiple myeloma patients. Clin Cancer Res. 2013; 19:3640–3648. [PubMed: 23685836]
64. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF, Investigators IS. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010; 363:411–422. [PubMed: 20818862]
65. Beer TM, Bernstein GT, Corman JM, Glode LM, Hall SJ, Poll WL, Schellhammer PF, Jones LA, Xu Y, Kylstra JW, Frohlich MW. Randomized trial of autologous cellular immunotherapy with sipuleucel-T in androgen-dependent prostate cancer. Clin Cancer Res. 2011; 17:4558–4567. [PubMed: 21558406]
66. Paczesny S, Banchereau J, Wittkowski KM, Saracino G, Fay J, Palucka AK. Expansion of melanoma-specific cytolytic CD8+ T cell precursors in patients with metastatic melanoma vaccinated with CD34+ progenitor-derived dendritic cells. J Exp Med. 2004; 199:1503–1511. [PubMed: 15173207]
67. Benitez-Ribas D, Adema GJ, Winkels G, Klasen IS, Punt CJ, Figdor CG, de Vries IJ. Plasmacytoid dendritic cells of melanoma patients present exogenous proteins to CD4+ T cells after Fc gamma RII-mediated uptake. J Exp Med. 2006; 203:1629–1635. [PubMed: 16785312]
68. Tel J, Aarntzen EH, Baba T, Schreibelt G, Schulte BM, Benitez-Ribas D, Boerman OC, Croockewit S, Oyen WJ, van Rossum M, Winkels G, Coulie PG, Punt CJ, Figdor CG, de Vries IJ. Natural human plasmacytoid dendritic cells induce antigen-specific T-cell responses in melanoma patients. Cancer Res. 2013; 73:1063–1075. [PubMed: 23345163]
69. Prue RL, Vari F, Radford KJ, Tong H, Hardy MY, D'Rozario R, Waterhouse NJ, Rossetti T, Coleman R, Tracey C, Goossen H, Gounder V, Crosbie G, Hancock S, Diaz-Guilas S, Mainwaring P, Swindle P, Hart DN. A phase I clinical trial of CD1c (BDCA-1)+ dendritic cells pulsed with HLA-A*0201 peptides for immunotherapy of metastatic hormone refractory prostate cancer. J Immunother. 2015; 38:71–76. [PubMed: 25658616]
70. Schreibelt G, Bol KF, Westdorp H, Wimmers F, Aarntzen EH, Duiveman-de Boer T, van de Rakt MW, Scharenborg NM, de Boer AJ, Pots JM, Olde Nordkamp MA, van Oorschot TG, Tel J, Winkels G, Petry K, Blokx WA, van Rossum MM, Welzen ME, Mus RD, Croockewit SA, Koornstra RH, Jacobs JF, Kelderman S, Blank CU, Gerritsen WR, Punt CJ, Figdor CG, de Vries IJ. Effective Clinical Responses in Metastatic Melanoma Patients after Vaccination with Primary Myeloid Dendritic Cells. Clin Cancer Res. 2016; 22:2155–2166. [PubMed: 26712687]
71. Bol KF, Schreibelt G, Gerritsen WR, de Vries IJ, Figdor CG. Dendritic Cell-Based Immunotherapy: State of the Art and Beyond. Clin Cancer Res. 2016; 22:1897–1906. [PubMed: 27084743]

72. Dubsky P, Saito H, Leogier M, Dantin C, Connolly JE, Banchereau J, Palucka AK. IL-15-induced human DC efficiently prime melanoma-specific naive CD8+ T cells to differentiate into CTL. Eur J Immunol. 2007; 37:1678–1690. [PubMed: 17492620]
73. Dieu MC, Vanbervliet B, Vicari A, Bridon JM, Oldham E, Ait-Yahia S, Briere F, Zlotnik A, Lebecque S, Caux C. Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. J Exp Med. 1998; 188:373–386. [PubMed: 9670049]
74. Sozzani S, Allavena P, D'Amico G, Luini W, Bianchi G, Kataura M, Imai T, Yoshie O, Bonecchi R, Mantovani A. Differential regulation of chemokine receptors during dendritic cell maturation: a model for their trafficking properties. J Immunol. 1998; 161:1083–1086. [PubMed: 9686565]
75. de Vries IJ, Lesterhuis WJ, Scharenborg NM, Engelen LP, Ruiter DJ, Gerritsen MJ, Croockewit S, Britten CM, Torensma R, Adema GJ, Figdor CG, Punt CJ. Maturation of dendritic cells is a prerequisite for inducing immune responses in advanced melanoma patients. Clin Cancer Res. 2003; 9:5091–5100. [PubMed: 14613986]
76. Barratt-Boyes SM, Zimmer MI, Harshyne LA, Meyer EM, Watkins SC, Capuano S 3rd, Murphey-Corb M, Falo LD Jr, Donnenberg AD. Maturation and trafficking of monocyte-derived dendritic cells in monkeys: implications for dendritic cell-based vaccines. J Immunol. 2000; 164:2487–2495. [PubMed: 10679086]
77. Radomski M, Zeh HJ, Edington HD, Pingpank JF, Butterfield LH, Whiteside TL, Wieckowski E, Bartlett DL, Kalinski P. Prolonged intralymphatic delivery of dendritic cells through implantable lymphatic ports in patients with advanced cancer. J Immunother Cancer. 2016; 4:24. [PubMed: 27096100]
78. Takahashi H, Nakagawa Y, Yokomuro K, Berzofsky JA. Induction of CD8+ cytotoxic T lymphocytes by immunization with syngeneic irradiated HIV-1 envelope derived peptide-pulsed dendritic cells. Int Immunol. 1993; 5:849–857. [PubMed: 8398980]
79. Rosalia RA, Quakkelaar ED, Redeker A, Khan S, Camps M, Drijfhout JW, Silva AL, Jiskoot W, van Hall T, van Veelen PA, Janssen G, Franken K, Cruz LJ, Tromp A, Oostendorp J, van der Burg SH, Ossendorp F, Melief CJ. Dendritic cells process synthetic long peptides better than whole protein, improving antigen presentation and T-cell activation. Eur J Immunol. 2013; 43:2554–2565. [PubMed: 23836147]
80. Binder RJ, Anderson KM, Basu S, Srivastava PK. Cutting edge: heat shock protein gp96 induces maturation and migration of CD11c+ cells in vivo. J Immunol. 2000; 165:6029–6035. [PubMed: 11086034]
81. Palucka AK, Ueno H, Connolly J, Kerneis-Norvell F, Blanck JP, Johnston DA, Fay J, Banchereau J. Dendritic cells loaded with killed allogeneic melanoma cells can induce objective clinical responses and MART-1 specific CD8+ T-cell immunity. J Immunother. 2006; 29:545–557. [PubMed: 16971810]
82. Arthur JF, Butterfield LH, Roth MD, Bui LA, Kiertscher SM, Lau R, Dubinett S, Glaspy J, McBride WH, Economou JS. A comparison of gene transfer methods in human dendritic cells. Cancer Gene Ther. 1997; 4:17–25. [PubMed: 9012447]
83. Meng WS, Butterfield LH. Activation of antigen-presenting cells by DNA delivery vectors. Expert Opin Biol Ther. 2005; 5:1019–1028. [PubMed: 16050780]
84. Janssen EM, Droin NM, Lemmens EE, Pinkoski MJ, Bensinger SJ, Ehst BD, Griffith TS, Green DR, Schoenberger SP. CD4+ T-cell help controls CD8+ T-cell memory via TRAIL-mediated activation-induced cell death. Nature. 2005; 434:88–93. [PubMed: 15744305]
85. Wong SB, Bos R, Sherman LA. Tumor-specific CD4+ T cells render the tumor environment permissive for infiltration by low-avidity CD8+ T cells. J Immunol. 2008; 180:3122–3131. [PubMed: 18292535]
86. Bos R, Sherman LA. CD4+ T-cell help in the tumor milieu is required for recruitment and cytolytic function of CD8+ T lymphocytes. Cancer Res. 2010; 70:8368–8377. [PubMed: 20940398]
87. Lesterhuis WJ I, de Vries J, Schreibelt G, Lambeck AJ, Aarntzen EH, Jacobs JF, Scharenborg NM, van de Rakt MW, de Boer AJ, Croockewit S, van Rossum MM, Mus R, Oyen WJ, Boerman OC, Lucas S, Adema GJ, Punt CJ, Figdor CG. Route of administration modulates the induction of dendritic cell vaccine-induced antigen-specific T cells in advanced melanoma patients. Clin Cancer Res. 2011; 17:5725–5735. [PubMed: 21771874]

88. Pinho MP, Sundarasetty BS, Bergami-Santos PC, Steponavicius-Cruz K, Ferreira AK, Stripecke R, Barbuto JA. Dendritic-tumor cell hybrids induce tumor-specific immune responses more effectively than the simple mixture of dendritic and tumor cells. Cytotherapy. 2016; 18:570–580. [PubMed: 26971685]

89. Bonifaz LC, Bonnyay DP, Charalambous A, Darguste DI, Fujii S, Soares H, Brimnes MK, Moltedo B, Moran TM, Steinman RM. In vivo targeting of antigens to maturing dendritic cells via the DEC-205 receptor improves T cell vaccination. J Exp Med. 2004; 199:815–824. [PubMed: 15024047]

90. Cruz LJ, Tacken PJ, Rueda F, Domingo JC, Albericio F, Figdor CG. Targeting nanoparticles to dendritic cells for immunotherapy. Methods Enzymol. 2012; 509:143–163. [PubMed: 22568905]

91. Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, Ly A, Lie WR, Hildebrand WH, Mardis ER, Linette GP. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015; 348:803–808. [PubMed: 25837513]

92. Mitchell DA, Batich KA, Gunn MD, Huang MN, Sanchez-Perez L, Nair SK, Congdon KL, Reap EA, Archer GE, Desjardins A, Friedman AH, Friedman HS, Herndon JE 2nd, Coan A, McLendon RE, Reardon DA, Vredenburgh JJ, Bigner DD, Sampson JH. Tetanus toxoid and CCL3 improve dendritic cell vaccines in mice and glioblastoma patients. Nature. 2015; 519:366–369. [PubMed: 25762141]

93. Maeda Y, Yoshimura K, Matsui H, Shindo Y, Tamesa T, Tokumitsu Y, Hashimoto N, Tokuhisa Y, Sakamoto K, Sakai K, Suehiro Y, Hinoda Y, Tamada K, Yoshino S, Hazama S, Oka M. Dendritic cells transfected with heat-shock protein 70 messenger RNA for patients with hepatitis C virus-related hepatocellular carcinoma: a phase 1 dose escalation clinical trial. Cancer Immunol Immunother. 2015; 64:1047–1056. [PubMed: 25982372]

94. Butterfield LH, Ribas A, Dissette VB, Lee Y, Yang JQ, De la Rocha P, Duran SD, Hernandez J, Seja E, Potter DM, McBride WH, Finn R, Glaspy JA, Economou JS. A phase I/II trial testing immunization of hepatocellular carcinoma patients with dendritic cells pulsed with four alpha-fetoprotein peptides. Clin Cancer Res. 2006; 12:2817–2825. [PubMed: 16675576]

95. Wilgenhof S, Corthals J, Heirman C, van Baren N, Lucas S, Kvistborg P, Thielemans K, Neyns B. Phase II Study of Autologous Monocyte-Derived mRNA Electroporated Dendritic Cells (TriMixDC-MEL) Plus Ipilimumab in Patients With Pretreated Advanced Melanoma. J Clin Oncol. 2016; 34:1330–1338. [PubMed: 26926680]

96. Dhodapkar MV, Steinman RM, Sapp M, Desai H, Fossella C, Krasovsky J, Donahoe SM, Dunbar PR, Cerundolo V, Nixon DF, Bhardwaj N. Rapid generation of broad T-cell immunity in humans after a single injection of mature dendritic cells. J Clin Invest. 1999; 104:173–180. [PubMed: 10411546]

97. Mailliard RB, Smith KN, Fecek RJ, Rappocciolo G, Nascimento EJ, Marques ET, Watkins SC, Mullins JI, Rinaldo CR. Selective induction of CTL helper rather than killer activity by natural epitope variants promotes dendritic cell-mediated HIV-1 dissemination. J Immunol. 2013; 191:2570–2580. [PubMed: 23913962]

98. Smith KN, Mailliard RB, Larsen BB, Wong K, Gupta P, Mullins JI, Rinaldo CR. Dendritic cells restore CD8+ T cell reactivity to autologous HIV-1. J Virol. 2014; 88:9976–9990. [PubMed: 24942586]

99. Macatangay BJ, Riddler SA, Wheeler ND, Spindler J, Lawani M, Hong F, Buffo MJ, Whiteside TL, Kearney MF, Mellors JW, Rinaldo CR. Therapeutic Vaccination With Dendritic Cells Loaded With Autologous HIV Type 1-Infected Apoptotic Cells. J Infect Dis. 2016; 213:1400–1409. [PubMed: 26647281]

100. Gandhi RT, Kwon DS, Macklin EA, Shopis JR, McLean AP, McBrine N, Flynn T, Peter L, Sbrolla A, Kaufmann DE, Porichis F, Walker BD, Bhardwaj N, Barouch DH, Kavanagh DG. Immunization of HIV-1-Infected Persons With Autologous Dendritic Cells Transfected With mRNA Encoding HIV-1 Gag and Nef: Results of a Randomized, Placebo-Controlled Clinical Trial. J Acquir Immune Defic Syndr. 2016; 71:246–253. [PubMed: 26379068]

101. Giannoukakis N, Phillips B, Finegold D, Harnaha J, Trucco M. Phase I (safety) study of autologous tolerogenic dendritic cells in type 1 diabetic patients. Diabetes Care. 2011; 34:2026–2032. [PubMed: 21680720]

102. Ezzelarab M, Thomson AW. Tolerogenic dendritic cells and their role in transplantation. Semin Immunol. 2011; 23:252–263. [PubMed: 21741270]

103. Ezzelarab MB, Zahorchak AF, Lu L, Morelli AE, Chalasani G, Demetris AJ, Lakkis FG, Wijkstrom M, Murase N, Humar A, Shapiro R, Cooper DK, Thomson AW. Regulatory dendritic cell infusion prolongs kidney allograft survival in nonhuman primates. Am J Transplant. 2013; 13:1989–2005. [PubMed: 23758811]

104. Thomson AW, Zahorchak AF, Ezzelarab MB, Butterfield LH, Lakkis FG, Metes DM. Prospective Clinical Testing of Regulatory Dendritic Cells in Organ Transplantation. Front Immunol. 2016; 7:15. [PubMed: 26858719]

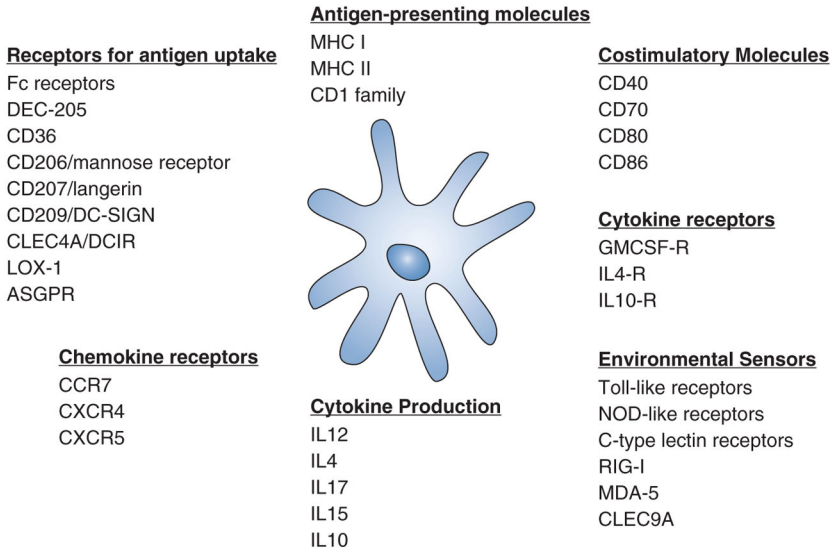

Figure 1.

DC are effective initiators of immune responses against self and non-self-antigens. In addition to phagocytosis and macropinocytosis, DC are equipped with a variety of receptors for antigen uptake. Pathogens, tumor cells and dying cells can be detected by DC through different molecules that serve as environmental sensors. After antigen uptake and processing, peptide antigens are presented to T cells via MHC I and MHC II complexes, while lipid antigens are presented through CD1 family molecules. The expression of chemokine receptors allows DC to migrate to secondary lymphoid organs containing T cells. In addition to antigen presentation, DC also provide costimulatory signals for effective T cell activation. Furthermore, DC can also produce cytokines that not only influence the type of T cell response generated, but also allow for cross-talk with other immune cells such as NK cells, macrophages and B cells.

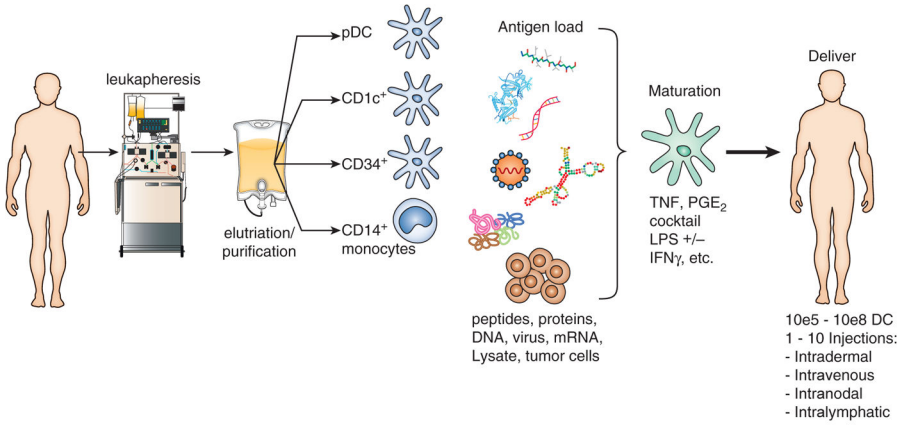

Figure 2.

The state of the art in translating DC vaccines to the clinic. A schematic is shown which describes the key steps in preparation of DC vaccines for cancer therapy, including large scale blood draw, generally via a leukapheresis procedure, followed by elutriation into monocyte and lymphocyte fractions, or other magnetic bead-based purification of subsets. The desired progenitor cells are cultured with growth factors and differentiation factors to obtain the immature cells ready for antigen loading. The antigen can take many forms, including peptides, proteins, nucleic acids and cells. The antigen loaded DC are often matured with other cytokines, growth factors or toll-like receptor ligands, and then prepared for injection, which can be via many different routes.

Table 1

Major human DC subsets and key features

I. Blood DC subsets	**Phenotype**	**Key Function and Features**	**References**
A. Plasmacytoid DC (pDC)	Lineage$^-$ CD14$^-$ CD11c$^-$ MHC Class II$^+$ CD123$^+$ BDCA-2 (CD303)$^+$ BDCA-4 (Nrp)$^+$	Produce type 1 interferons in response to viral pathogens Express high TLR7 and TLR9	(34–36)
B. Conventional/Myeloid DC			
1. CD1c+ myeloid DC	Lineage$^-$ CD11c$^+$ MHC Class II$^+$ CD86$^+$ BDCA-1 (CD1c)$^+$	T cell priming and activation IL-12 secretion	(34, 40)
2. CD141+ myeloid DC	Lineage$^-$ CD11c$^+$ MHC Class II$^+$ CD86$^+$ BDCA-3 (CD141)$^+$ CLEC9A$^+$ XCR1$^+$	Cross-presentation of exogenous antigens to CD8 T cells Express high TLR3 and TLR8	(34, 44, 45, 47, 48)
II. Skin DC			
A. Langerhans Cells (LC)	Lin$^-$ CD11c+ HLA-DR+ CD1a+ Langerin+ E-cadherin+	Main antigen presenting cell in epidermis CD4 and CD8 T cell priming and activation Contains Birbeck granules Self-renewing at steady state Th17-driven skin inflammation	(52, 53, 105, 106)
B. Dermal Dendritic Cells (DDC)			
1. CD1a+ Dermal DC	CD1a$^+$ CD14$^-$HLA-DR$^+$	Can prime and activate CD8 T cells	(52, 53)
2. CD14+ Dermal DC	CD1a–CD14+HLA-DR+	Specialized in activating humoral response	(52, 53)