Received: 24 August 2020 | Accepted: 11 March 2021

DOI: 10.1002/imed.1022

RESEARCH ARTICLE

WILEY

Therapeutic dendritic cell cancer vaccines in hematologic malignancies

Poorva Bindal MD | **Jacalyn Rosenblatt MD** | **David Avigan MD**

Department of Medicine, Division of Hematology and Hematologic Malignancies, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

Correspondence
David Avigan, 330 Brookline Ave, Kirstein 132, Boston, MA 02215, USA.
Email: davigan@bidmc.harvard.edu

Abstract

Tumor cells present antigen in the context of negative costimulation and immunosuppressive factors, resulting in the inhibition of T cell activation and immune tolerance. Dendritic cells (DCs) are a complex network of antigen presenting cells that play a critical role in maintaining the equilibrium between immune activation directed against pathogens and tolerance necessary to prevent damage mediated by autoreactive T cell clones. DCs uniquely induce primary immune responses through the constitutive and enhanced expression of positive costimulatory molecules and inflammatory cytokines necessary for T cell activation. In this context, the design of a cancer vaccine is based on the effective presentation tumor associated antigens to evoke an antigen specific activated T cell response, and importantly, immune memory. As such, DCs have played a major role in the development of cancer vaccine therapy as critical mediators of antigen presentation reversing a major component of tumor mediated immune suppression. DC based vaccines have involved the loading of individual tumor associated antigens or the use of whole tumor cells and have demonstrated potent induction of tumor specific immunity. The correlation of immune response with clinical outcome and integration of DC vaccines with other immune based therapy is currently being explored.

KEYWORDS
cancer vaccines, immunotherapy, tumor immunology

Relevance:

The authors review the available approaches for therapeutic dendritic cell vaccination in hematologic malignancies that have demonstrated the ability to evoke immune and clinical responses.

1 | INTRODUCTION

Tumor cells present antigens in the context of negative co-stimulation and immunosuppressive factors, resulting in the inhibition of T cell activation and immune tolerance. Dendritic cells (DCs) are a complex network of antigen-presenting cells within tumors and lymphoid organs that play a critical role in maintaining the equilibrium between immune activation directed against pathogens and tolerance necessary to prevent damage mediated by autoreactive T cell clones. DCs uniquely induce primary immune responses through the constitutive and enhanced expression of positive co-stimulatory molecules and inflammatory cytokines necessary for T cell activation. In this context, the design of a cancer vaccine is based on the effective presentation of tumor-associated antigens to evoke an antigen-specific activated T cell response, and importantly, immune memory. As such, DCs have played a major role in the development

of cancer vaccine therapy as critical mediators of antigen presentation reversing a major component of tumor-mediated immune suppression.

2 | IMMUNE SURVEILLANCE AND IMMUNE EDITING

Immune surveillance plays a critical role in protecting against the development and progression of cancer.[1,2] Malignant cells harbor a myriad of somatic gene mutations whose products can be immunologically recognized as non-self-antigens, by both innate and adaptive immunity providing a barrier for evolving tumors before they become clinically apparent.[3] Tumor clones that survive immune elimination can be held in a state of equilibrium, where its unopposed growth is prevented by adaptive immunity.[3,4] In contrast, a hallmark of malignancy is progressive immune dysfunction leading to a loss of immune surveillance and immune escape.[2,5] Immune selection during the equilibrium phase results in the editing of tumor immunogenicity, leading to the emergence of clonal malignant populations with decreased immunogenicity.[3–5]

Immune escape is further supported by the immunosuppressive milieu of the tumor microenvironment.[6,7] Accessory cell populations, such as regulatory T cells and myeloid-derived suppressor cells (MDSCs) suppress immune mediated killing of malignant cells. In addition, activation of immune-regulatory pathways in the surrounding stroma induces T cell exhaustion and inhibits migration of tumor-specific T cells, permitting immune evasion by the malignant clone.[8,9] In designing immune-based therapy for hematological malignancies, it is critical to understand and overcome the factors that permit immune escape.[4] The field of cancer vaccines fundamentally seeks to effectively present tumor antigen in the context of functionally potent antigen-presenting cells while overcoming the immunosuppressive milieu of the microenvironment. DCs serve as a backbone to cancer vaccine development as potent antigen-presenting cells that play a critical role in immune stimulation in response to a foreign antigen.

3 | DC BIOLOGY

DCs are potent antigen presenting cells with the ability to induce robust antigen-specific primary immune responses.[10,11] DCs are localized in tissues where they uptake and internalize foreign antigens. After antigen processing, peptides are presented in the context of major histocompatibility complexes (MHCs) on the surface of DCs.[12,13] DCs then undergo maturation and migrate to lymphoid organs to activate antigen-specific T cells.[14] Mature DCs express co-stimulatory molecules that can be upregulated to allow DCs to activate either CD4-positive helper or CD8-positive cytotoxic T-lymphocytes.[15] They have the ability to "cross prime" foreign antigens to CD8-positive cytotoxic T cells via MHC-Class I.[16,17] Thus, DCs play a critical part in immune stimulation and cytotoxic response to exogenous antigens. DCs have been classified into distinct subtypes based on morphology, function, cell origin, and surface marker expression.[18,19] Myeloid DCs [also known as conventional DCs (cDCs)], plasmacytoid DCs, dermal DCs, and epidermal Langerhans DCs are characterized by distinguishing patterns of cytokine production, antigen processing, and the induction of T cell polarization towards Th1, Th2, Th17, or regulatory T cells.[20–23] Myeloid/cDCs have been further classified into type 1 cDCs (cDC1s) and type 2 cDCs (cDC2s) that demonstrate distinct functions and density within tumors. Recent studies have indicated that a vaccine generated from cDC1s elicits long-lasting systemic T-cell mediated cytotoxic response.[24] Several immunophenotypic subsets of DCs have also been identified with cDCs consisting of either $CD141^+$ or $CD1c^+$ cells.[25] Prior studies have demonstrated that expression of associated receptors of antigen presentation determines the effectiveness of antigen cross presentation[26] and targeting these receptors influences immune response.[27] These advances in our understanding of DC biology have led to novel vaccination strategies that utilize antigen-conjugated antibodies targeting antigens to human DCs with DEC-205 and Clec9A emerging as promising targets.[28] More recently, single-cell RNA sequencing has been utilized to define DC subsets more precisely and this approach has led to the identification of new DC subsets and progenitors that may represent new therapeutic targets.[29]

Strategies for the ex vivo isolation, generation, and expansion of the DC subsets have been developed. Most commonly, protocols for myeloid DC generation have been developed involving the use of cytokine driven differentiation of monocyte precursors with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-4 (IL-4), and maturation agents such as tumor necrosis factor-α (TNFα), lipopolysaccharide (LPS), or prostaglandin-E2 (PG-E2). FMS like tyrosine kinase 3 ligand (FLT3L) has also been investigated as a means to enhance the immune response to DC vaccine therapy in non-hematologic malignancies and needs to be further examined in hematologic malignancies.[30] There have been several reports demonstrating functional competency of ex vivo generated DCs in contrast to deficiencies noted in the in vivo populations in cancer patients. There has been an ongoing debate as to the optimal DC platform for vaccine generation and the functional and migratory properties of DC populations once reintroduced in vivo in the setting of malignancy. There have been recent reports suggesting that Langerhans cells may exhibit more effective properties as mediators of vaccine response.[31]

Phenotypic and functional deficiencies have been observed in circulating and intra-tumor DCs isolated from patients with malignancy, characterized by increased expression of indoleamine 2,3-dioxygenase (IDO), and secretion of inhibitory cytokines.[32–34] DCs in the tumor bed are skewed toward an immature phenotype, less effective in eliciting an immune response due to reduced cytokine production, lower levels of MHC, co-stimulatory molecules, and decreased trafficking to lymph nodes to allow T cell activation.[35,36] Strategies to enhance DC maturation and to upregulate CCR7 to enhance trafficking to lymph nodes have been studied in an effort

to enhance the potency of native DC populations in patients with malignancy.[19,37]

4 | IDENTIFICATION OF ANTIGENIC TARGETS

Choosing the optimal antigenic target forms a vital component of cancer vaccine development. The optimal antigen must have (1) tumor-specificity allowing the generation of an immune response that spares the normal host tissues, (2) clonal breadth to capture the clonal diversity within the tumor, (3) functionality to be necessary for cancer cell survival to minimize chances of down-regulation, (4) memory for development of a sustained immune response to protect against relapse, and (5) high immunogenicity to elicit a robust immune response.[38,39]

Tumor-associated antigens (TAAs) are self-antigens that are abnormally expressed by tumor cells and have largely been the focus of vaccine development in hematological malignancies.[40] These include (1) cancer-testis antigens whose physiologic expression is restricted to fetal development (e.g., MAGE1, MAGE3, NY-ESO, PRAME in acute leukemia and multiple myeloma[41–43]), 2) lineage-specific antigens [e.g., CD138[44] in plasma cells and B-cell maturation antigen (BCMA)[45] in B-lymphocytes and plasma cells], 3) antigens derived from aberrantly expressed oncogenes or tumor suppressor genes (e.g., MUC1[46] and WT1[47,48] in leukemia). Tumor-specific antigens (TSAs) are antigens that are truly unique to tumors and may include 1) idiotype derived peptides (e.g., in B cell lymphomas[49] and multiple myeloma[50]), 2) antigens resulting from tumor-derived chromosomal translocations (e.g., BCR-ABL in chronic myeloid leukemia[51]), and 3) tumor neoantigens[52] generated by somatic alterations in tumor cell genome that may arise from a point or nonsense mutations, chromosomal translocation, splicing variants or epigenetic alteration in antigen expression.

Neoantigen epitopes have been determined through computational bioinformatics platforms that predict for mutationally derived peptides presented in the appropriate human leukocyte antigen (HLA) context. Results can be confirmed via mass spectrometry of cell surface antigen expression and via interrogation of the T cell repertoire for capacity for recognition and clonal expansion. Identified antigens may be introduced as peptides or proteins characteristically introduced with immune adjuvants or loaded onto antigen-presenting cells. The use of heteroclitic peptides may enhance the immunogenicity of self-derived antigens. Recent studies suggest that the intrinsic nature of short and long peptides may drive the nature of the CD4 and CD8 mediated response. Another strategy involves the use of antigen-specific genomic material including RNA or DNA. An alternative strategy is the use of the whole tumor as a source of antigen including tumor cell lysates[53], tumor apoptotic bodies[16,54] whole tumor RNA/DNA transfection[55], or the creation of tumor/DC hybridomas. These strategies support the potential for a broader immune response without previously identifying the critical antigens required for response. However, there is a potential concern for the presentation of self-antigens in a format that would induce autoimmunity. The nature of antigen may induce changes in the antigen-presenting cell facilitating immune activation or inhibition.

5 | CANCER VACCINE PLATFORMS

Cancer vaccine platforms have included strategies to recruit and potentiate native DCs in vivo as well as the generation of functional DCs ex-vivo. Initial approaches for cancer vaccine design characteristically involved the introduction of TAAs in the context of immunostimulatory adjuvants to induce the recruitment of native antigen-presenting cells, uptake of antigen in the vaccine bed, and subsequent stimulation of antigen-specific T cell responses. One prominent example has been vaccination with idiotype protein linked to a carrier protein KLH designed to enhance responses targeting non-Hodgkin's lymphoma or multiple myeloma. While initial studies demonstrated expansion of idiotype-specific T cells, large randomized trials that were conducted to study the efficacy of idiotype-based vaccination in B cell malignancies did not demonstrate a significant impact on outcomes despite the initial promising results seen in earlier phase studies.[56–58] The use of WT1-based vaccination has been explored in patients with acute myeloid leukemia (AML) demonstrating the expansion of antigen-specific T cells but further studies are required to assess clinical efficacy.[59,60] The use of heteroclitic peptides has been explored to enhance activation of T cells by targeting multiple antigens to decrease the risk of resistance by the emergence of single antigen-negative variants. In one example, a multi-peptide vaccine targeting XBP1, CS1, and CD138 has been shown to induce memory T cell responses in patients with smoldering myeloma.[61]

Neoantigen-based vaccination involves the identification of peptide antigens derived from clonally specific tumor mutations that are potentially seen as non-self-antigens and are recognizable by high-affinity T cells. Neoepitopes can be identified by computational platforms that sequence these unique mutational events by genomic analysis. This technique has been used to design dendritic cell vaccines in solid tumors.[62,63] Vaccination resulted in the expansion of T cells recognizing the mutated as compared to the wild type peptides and the targeting of tumor cells ex vivo. The clinical significance of these findings is currently being studied. A major challenge to this approach is the complexity of neoantigen identification for each patient and tumor type. Furthermore, the determination of the immunogenicity of these antigens with respect to the T cell repertoire remains an active area of investigation.

Another approach has been the use of the whole tumor as a source of antigen for in vivo loading of DCs recruited to the site of vaccination. The GVAX platform involves the use of autologous tumor cells to induce DC recruitment through the production of GM-CSF.[64] The GVAX vaccine was evaluated in a phase II clinical trial in patients with AML and demonstrated a

complete remission (CR) rate of 85% with a 3-year overall survival of 57.4% in patients who achieved a complete response.[65] In chronic lymphocytic leukemia (CLL), vaccination with GVAX in the adjuvant setting after reduced-intensity transplant was found to be safe, and a 2-year progression-free survival (PFS) of 82% was observed.[66]

6 | CANCER VACCINE PLATFORMS USING EX VIVO GENERATED DCS

Phenotypically and functionally potent DCs can be generated ex vivo through the cytokine-mediated differentiation of mature DCs from precursor populations in the peripheral blood or bone marrow.[67] The starting cell populations for ex vivo DC vaccine production include $CD14^+$ monocytes, $CD34^+$ stem cells, $CD123^+$ plasmacytoid DCs, and BDCA-1^+ circulating myeloid DC which are all distinct.[68] Ex vivo maturation of DCs is attained by culturing them in a cytokine cocktail including TNFα, IL-1β, IL-6, prostaglandins, GM-CSF, and IL-4.[69,70] While DCs derived from $CD34^+$ stem cells[71] and $CD123^+$ plasmacytoid DCs[72] have been studied, monocyte-derived precursor populations are most frequently utilized as a source for ex vivo DC tumor vaccine production.

The induction of tumor-specific immunity was demonstrated with an autologous DC-based vaccine pulsed with tumor-specific idiotype protein in patients with follicular lymphoma.[49,73] In the larger study with 35 patients with follicular lymphoma, 65% of patients developed a T cell or humoral anti-idiotype immune response, and 70% of patients remained without tumor progression at a median of 43 months prior chemotherapy.[49] Idiotype-based vaccine development has also been studied in multiple myeloma using a modified antigen-presenting cell platform (myelovenge) following autologous stem cell transplantation with potential improvement observed in overall survival (5.3 years versus 3.4 years) when compared to historical control group.[74]

The development of DC-based vaccine against myeloid malignancies and multiple myeloma has involved DNA or RNA coding for particular antigens that can be loaded onto DCs by ex vivo electropolation (Table 1). A vaccine against AML was developed by electropolating autologous DCs with mRNA of WT1 and an increased population of WT1-specific T cells and WT1-specific interferon-gamma producing $CD8^+$ T lymphocytes was seen in a small trial evaluating its efficacy. In addition, 50% of the patients in this trial developed molecular remission of their AML following vaccination.[60] When studied in a larger trial, 43% of 30 patients were noted to develop an anti-leukemic clinical response after vaccination with WT1 mRNA electropolated DCs following induction chemotherapy for AML.[59] Chung et al. have demonstrated that WT1 mRNA electropolated Langerhans cells elicit a more robust immune response when compared to monocyte-derived DCs.[31] This finding has significant implications for DC-based immunotherapies and suggests that the type of DCs used for mRNA electropolation has an impact on immunogenicity. Table 1 provides a summary of selected clinical trials of vaccines generated by loading antigens onto DCs ex vivo.

7 | DC/TUMOR FUSION VACCINES

Our group has developed a personalized whole-cell vaccine approach whereby patient-derived myeloma or leukemia cells are fused to ex vivo generated autologous DCs (Figure 1). The DC/tumor cell fusion vaccines allow a broad spectrum of tumor-associated antigens and neo-antigens to be presented in the context of DC-mediated co-stimulation. A phase I study evaluating DC/multiple myeloma (DC/MM) fusion cells vaccination in patients with multiple myeloma demonstrated the expansion of myeloma reactive T cells in 11 out of 15 evaluable patients. Disease stabilization was observed in 66% of patients.[78] A subsequent phase II trial assessed if this DC/MM fusion vaccine can be used in the post-autologous stem cell transplantation (SCT) setting to target post-transplant residual disease.[79] It was noted that although the period of lymphopoietic reconstitution was associated with the general suppression of cellular immunity, there was a transient expansion of the myeloma-specific T cells that was further boosted following vaccination with DC/MM fusion cells. Vaccination was also associated with a complete response/near complete response rate of 47% in the absence of maintenance therapy.[79] Based on these encouraging results, a multi-center trial evaluating DC/MM fusion cell vaccination in conjunction with maintenance lenalidomide versus lenalidomide alone is being conducted through the BMT CTN (NCT02728102).[83]

Immunologic and clinical potency of DC/tumor fusion vaccines has also been demonstrated in patients with AML. In a pilot study, 17 AML patients who achieved remission following chemotherapy were vaccinated with DC/AML fusion vaccine.[80] The results demonstrated that the vaccine was safe and elicited a significant expansion of leukemia-specific T cells. Clinically, 71% of patients remained in remission after a mean follow-up of 57 months.[80] Based on this study, a randomized phase II clinical trial is underway, in which 75 patients who achieve remission will be randomized 2: 1 to vaccine versus standard of care (NCT03059485).[84] In a phase I trial, the safety and potency of DC/AML vaccination administered alone and in conjunction with decitabine following allogeneic SCT is being assessed (NCT03679650)[85]

8 | DEFINING THE OPTIMAL DISEASE SETTING

Choosing the appropriate setting in which to incorporate a cancer vaccine is vital for optimizing the potential immunologic and clinical impact of vaccination. The development of vaccine-mediated immune response and clinical efficacy is more likely in the state of low disease burden as compared to rapidly proliferating disease.[38] This setting allows for sufficient time for the generation

TABLE 1 Selected clinical trials of vaccine generated by loading antigens onto DCs ex vivo

Disease	DC source	Tumor antigen	Antigen loading	Number of patients	Setting	Immunologic findings	Clinical findings
Multiple myeloma[50]	PBMCs	Tumor idiotype	Ex vivo pulse	12	Post-transplant	2/12 patients developed idiotype-specific immune response	2/12 patients maintained CR at 17 and 30 months
Multiple myeloma[75]	PBMCs	Tumor idiotype	Ex vivo pulse	26	Post-transplant	4/26 patients developed idiotype-specific immune response	17/20 patients alive at median follow up of 30 months
Multiple myeloma[76]	PBMCs	Tumor idiotype	Ex vivo pulse	27	Post-transplant	Not reported	Median OS in trial patients was 5.3 years compared to 3.4 years in the control group
Multiple myeloma[77]	PBMCs	mRNA from MAGE3, BCMA or survivin	Electropolated with mRNA	12	Post-transplant	2/12 patients developed vaccine-specific immune response	5/12 patients had stable disease at median follow up of 55 months
Multiple myeloma[78]	PBMCs	Whole tumor cell	Ex vivo DC/tumor cell fusion	18	Active disease with at least 1 prior treatment regimen	11/15 evaluable patients had a expansion of myeloma-reactive T cells	11/16 evaluable patients had stable disease
Multiple myeloma[79]	PBMCs	Whole tumor cell	Ex vivo DC/tumor cell fusion	36	Post-transplant	All evaluable patients developed twofold increase in myeloma reactive T lymphocytes	78% of patients achieved CR or VGPR
AML[60]	PBMCs	Whole tumor cell	Ex vivo pulse and electropolation with mRNA	10	Post-complete or partial remission after polychemotherapy	Vaccinated patients had increased levels of WT1-specific $CD8^+$ T lymphocytes	Three patients with a sustained complete response and two patients in partial response converted to complete response
AML[80]	PBMCs	Whole tumor cell	Ex vivo DC-tumor cell fusion	17	Post-remission after chemotherapy	5.4 fold increase in AML-specific $CD4^+$ T cells, and 15.7-fold increase in AML-specific $CD8^+$ T cells	71% of patients alive at 57 months without AML recurrence
AML[81]	PBMCs	mRNA construct encoding hTERT amino acids	DCs electropolated with hTERT	22	First or second complete remission after chemotherapy	58% of patients with hTERT T cell response	58% of patients in remission after 52 months
AML[59]	PBMCs	WT1 mRNA construct by in vitro transcription	DCs electropolated with WT–1 mRNA	30	Post remission treatment	1.5 fold increase in WT1-specific tetramer $CD8^+$ T cells in 50% of evaluable patients	30% of patients with molecular remission and 13% with disease stabilization
Follicular Lymphoma[73]	PBMCs	Tumor Idiotype	Idiotype pulsed DCs	4	Post chemotherapy	4/4 patients with anti-tumor immune response	1/4 patient with complete response
Follicular Lymphoma[49]	PBMCs	Tumor idiotype	Idiotype pulsed DCs	35	Post chemotherapy	65% of patients in remission with T cell or humoral response	70% of patients with PFS at 43 months
Follicular lymphoma[82]	PBMCs	Antigen unloaded	Intranodal unloaded IFN-DC plus rituximab	8	Previously heavily treated refractory disease	All patients showed induction or enhancement of T cell responses	3/8 patients converted from active disease to CR with 2/8 ongoing CR at 22 and 27 months

Abbreviations: AML, acute myeloid leukemia; BCMA, B-cell maturation antigen; CR, complete response; IFN, Interferon; OS, overall survival; PBMCs, peripheral blood mononuclear cells; PFS, Progression-Free Survival; VGPR, very good partial response.

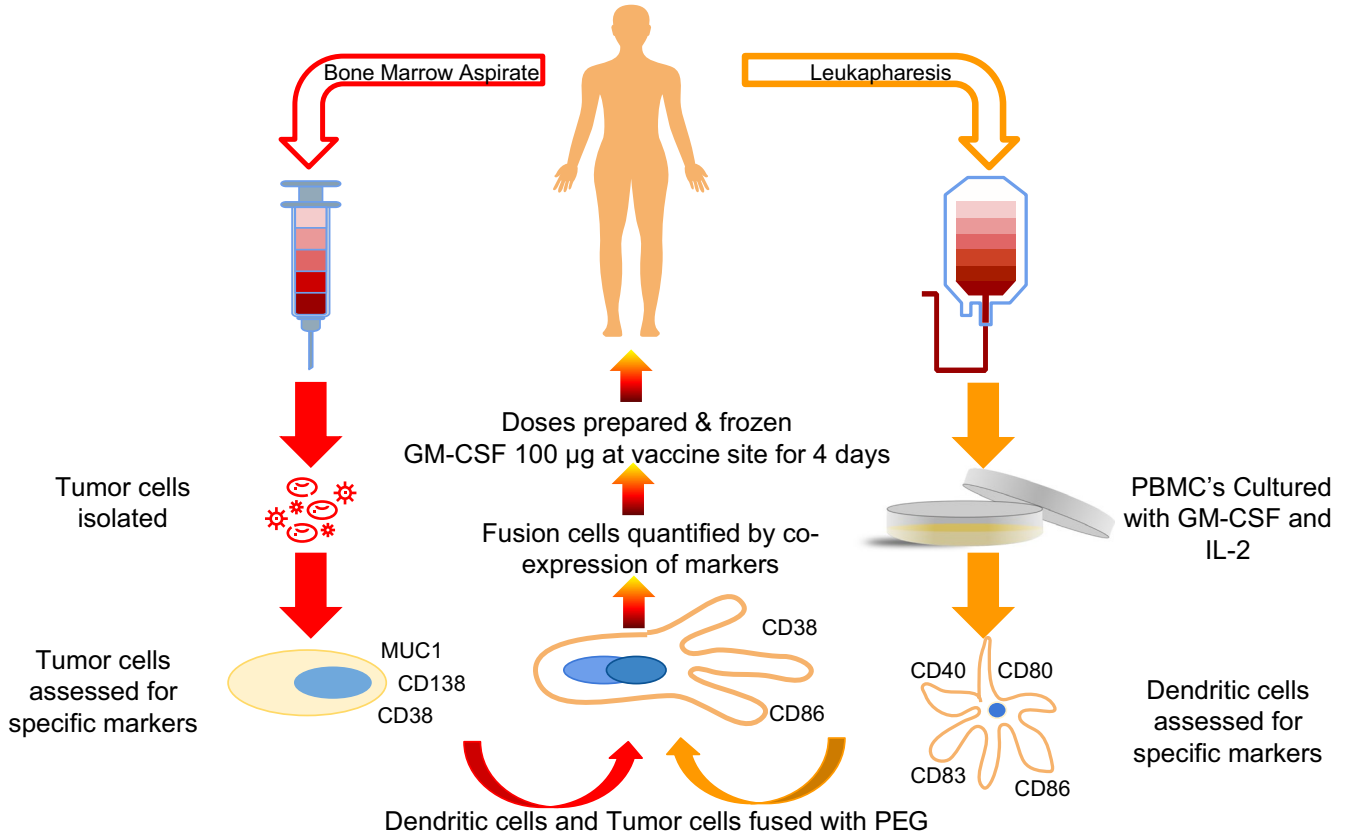

FIGURE 1 Production process ofdendritic cell-tumor fusion vaccines involves leukapheresis ofpatient's peripheral blood mononuclear cells (PBMCs) that are cultured withcytokines (IL-4, GM-CSF and TNF-alpha to facilitate differentiation andmaturation to dendritic cells. The dendritic cells are assessed for specific immunophenotypic markers and then fused with tumor cells obtained from the patient usingpolyethylene glycol (PEG). The resultant fusions are then quantified usingco-expression of immunophenotypic markers of both tumor cells and dendritic cells using flow cytometry andimmunohistochemistry. The fusion cells are then stored in frozen form untilready to be subcutaneously injected into the patient with GM-CSF

of an immune response that is less compromised by the immunosuppressive milieu of the tumor microenvironment associated with more advanced disease. Another factor is that the pattern of antigen expression may vary dependent on the disease setting and prior therapy. For instance, the expression of cancer-testis antigens (NY-ESO-1, MAGE3 in AML, and NXF2 in CLL) increases after treatment with decitabine.[86,87] Vaccine efficacy is also dependent on the functional potency of the effector cell population that exhibits progressive dysfunction as a consequence of disease evolution. As such, optimal settings for DC-based vaccine therapy may include pre-malignant disease states, post-chemotherapy or radiotherapy-induced pro-inflammatory state of remission, and the state of post-transplant immune reconstitution where a reversal of tumor tolerance is seen that allows for skewing of T cells towards tumor-reactive T-cell clones. Among the pre-malignant disease states, smoldering myeloma is currently being evaluated as a possible avenue for vaccination using a multi-peptide-based vaccine in combination with Citarinostat (CC-96241) or Citarinostat and lenalidomide (NCT02886065).[88] Another planned pilot trial is evaluating the safety and preliminary efficacy of dendritic cell DKK1 vaccine in monoclonal gammopathy and smoldering myeloma (NCT03591614).[89]

The post-transplant state of immune reconstitution also provides an opportunity for enhanced vaccine response due to depletion of regulatory T cells as demonstrated by in vitro studies.[90] Several early phase studies (Table 1) in post-transplant multiple myeloma and AML patients have shown that vaccination in this setting is safe and associated with significant immunological and clinical responses.[64,76,79] Several ongoing trials are also studying if vaccination is efficacious in the post-transplant setting.[83,85] Allogeneic transplant period offers unique aspects that may allow for enhanced response to vaccine therapy.[91] Following conditioning therapy, patients have a state of low disease burden and the engraftment of donor-derived antigen-presenting and effector cells that may exhibit greater functional potency. Potential toxicities, in particular the development of graft versus host disease (GVHD), must be considered when using vaccines in the post-transplant setting.

9 | COMBINATORIAL STRATEGIES

A major area of investigation for vaccine therapy is the use of immunostimulatory agents to augment vaccine effect by overcoming the immunosuppressive milieu of the microenvironment.

Activation of immunoregulatory pathways in the growing tumor's stroma induces T cell exhaustion and senescence, in addition to inhibiting migration of tumor-specific T cell populations. This leads to tumor proliferation by secretion of suppressive cytokines such as IL-10, and TGFβ; recruitment of regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSC); increased expression of inhibitory receptors; and production of suppressive enzymes like IDO.[8,9] A better understanding of the impact of the tumor microenvironment on immune modulation and tumor progression has led to the development of several therapeutic strategies such as vaccines targeting the production of TGFβ.[92,93] IL2 has been shown to protect effector $CD8^+$ T cells from tumor cell-induced immune dysfunction and has been most widely studied as a counter mechanism to these immunosuppressive cytokines.[68,94] Preclinical studies demonstrated that combining IL2 with DC-based vaccination potentiate the anti-tumor efficacy in murine models.[95] Clinical studies in solid tumors[96,97] have not demonstrated a clinical or immunologic benefit and this has not been extensively studied in hematologic malignancies.

The combination of DC-based vaccinations with chemotherapy affords many immune-potentiating effects by reversing the immune-suppressive tumor microenvironment in addition to lowering the tumor burden. Lenalidomide has been shown to enhance the function of DCs, reverse tumor immune suppression and enhance anti-tumor cellular immunity.[98–100] Hypomethylating agents have also been shown to alter the tumor microenvironment and enhance the immunogenic efficacy of DC/AML vaccine in pre-clinical studies and are being evaluated in a clinical trial.[101]

The combination of immune checkpoint inhibitors and tumor vaccines has the potential for unique potency. Single-agent immune checkpoint blockade has demonstrated disappointing results in hematological malignancies outside of Hodgkin's disease. This is potentially due to the lack of a native T cell response such that blocking negative co-stimulatory signals alone is insufficient. In contrast, combining immune checkpoint blockade with strategies, such as vaccines, that potently induce tumor-reactive T cell populations, have demonstrated promise pre-clinically[102] and is being studied in a clinical trial (NCT03782064).

Another potential powerful combinatorial strategy involves the use of vaccination with effector cell therapies such as chimeric antigen receptor (CAR) T cells. CAR T cells are genetically manipulated to express the variable chain of an antibody targeting a surface protein on tumor cells such as CD19 or BCMA that is linked to a costimulatory molecule and the zeta chain of the T cell receptor (TCR) resulting in T cell activation, expansion, and TCR mediated killing of the antigen-expressing target cells. While CAR T cells have demonstrated high levels of potency, disease progression can occur due to premature elimination or tolerization of the CAR T population, or the emergence of antigen-negative variants. Preclinical studies combining CAR T cell therapy with vaccination have also demonstrated potential activity.[103,104] In animal models, our group has examined the capacity of the DC/tumor vaccine to enhance CAR T cell activity potentially through the broadening of the antitumor T cell response via the native TCR and the cyclic re-expansion and activation of the CAR population via vaccine-mediated stimulation.[105]

10 | CONCLUSION

There have been significant advances in the development of DC-tumor vaccines against hematologic malignancies. DCs provide a critical platform for antigen presentation via the concurrent expression of co-stimulatory signals and inflammatory cytokines necessary for the induction of primary immune responses. As such, they offer an important strategy to overcome tumor-associated tolerance and targeting shared tumor antigens by low and medium affinity T cells. Responses may be further amplified towards neoantigens that are seen as foreign by the T cell repertoire.

While vaccine-mediated immunologic responses have been consistently observed, clear evidence of clinical efficacy has been more limited. Vaccination appears to be most effective in the setting of low volume disease as a strategy to prevent disease recurrence through the expansion of tumor-reactive lymphocytes for immune surveillance. Strategies that target multiple antigens are more potentially advantageous limiting immunologic escape through the emergence of antigen-negative variants. Vaccine responses have demonstrated the durable expansion of tumor-reactive lymphocytes with the presence of memory cells capable of longer-term protection. However, overcoming the immunosuppressive milieu of the tumor microenvironment and the associated functional deficiencies of the T cell repertoire remain significant challenges. In addition, the kinetics of vaccine response likely manifest over weeks and are likely ineffective in the setting of advanced disease with more rapid tumor growth. These characteristics are in contrast with CAR T cells in which the infusion of activated effector cells demonstrates high levels of initial potency but durability is limited by clearance or tolerization of the effector cell populations.

Future directions have focused on the development of combinatorial strategies in which vaccine-mediated T cell expansion is complemented by the use of immunomodulatory agents targeting the critical mediators of the tumor microenvironment including negative co-stimulatory signals and TGFβ. Integration of vaccination with adoptive T cell therapy is being explored in an effort to provide competent effector cells targeting tumor cells with strategies for durable T cell expansion and activation.

ORCID

Poorva Bindal https://orcid.org/0000-0002-3186-0113
David Avigan https://orcid.org/0000-0003-4624-6017

REFERENCES

1. Mohme M, Riethdorf S, Pantel K. Circulating and disseminated tumour cells — mechanisms of immune surveillance and escape. Nat Rev Clin Oncol. 2017;14(3):155–67.

2. Miller JFAP, Sadelain M. The journey from discoveries in fundamental immunology to cancer immunotherapy. Cancer Cell. 2015;27(4):439–49.
3. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565–70.
4. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol. 2011;29(1):235–71.
5. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3(11):991–8.
6. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science. 2015;348(6230):74–80.
7. Gurusamy D, Clever D, Eil R, Restifo NP. Novel "Elements" of immune suppression within the tumor microenvironment. Cancer Immunol Res. 2017;5(6):426–33.
8. Thommen DS, Schumacher TN. T cell dysfunction in cancer. Cancer Cell. 2018;33(4):547–62.
9. Suen H, Brown R, Yang S, Weatherburn C, Ho PJ, Woodland N, et al. Multiple myeloma causes clonal T-cell immunosenescence: identification of potential novel targets for promoting tumour immunity and implications for checkpoint blockade. Leukemia. 2016;30(8):1716–24.
10. Steinman RM, Adams JC, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. IV. Identification and distribution in mouse spleen. J Exp Med. 1975;141(4):804–20.
11. Mellman I, Steinman RM. Dendritic cells: specialized and regulated antigen processing machines. Cell. 2001;106(3):255–8.
12. Steinman RM, Banchereau J. Taking dendritic cells into medicine. Nature. 2007;449(7161):419–26.
13. Steinman RM. Decisions about dendritic cells: past, present, and future. Annu Rev Immunol. 2012;30:1–22.
14. Cyster JG. Chemokines and the homing of dendritic cells to the T cell areas of lymphoid organs. J Exp Med. 1999;189(3):447–50.
15. Young JW, Koulova L, Soergel SA, Clark EA, Steinman RM, Dupont B. The B7/BB1 antigen provides one of several costimulatory signals for the activation of CD4+ T lymphocytes by human blood dendritic cells in vitro. J Clin Invest. 1992;90(1):229–37.
16. Albert ML, Sauter B, Bhardwaj N. Dendritic cells acquire antigen from apoptotic cells and induce class I-restricted CTLs. Nature. 1998;392(6671):86–9.
17. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nat Rev Immunol. 2020;20(1):7–24.
18. Collin M, Bigley V. Human dendritic cell subsets: an update. Immunology. 2018;154(1):3–20.
19. Santos PM, Butterfield LH. Dendritic cell-based cancer vaccines. J Immunol. 2018;200(2):443–9.
20. Dudziak D, Kamphorst AO, Heidkamp GF, Buchholz VR, Trumpfheller C, Yamazaki S, et al. Differential antigen processing by dendritic cell subsets in vivo. Science. 2007;315(5808):107–11.
21. Mohamadzadeh M, Olson S, Kalina WV, Ruthel G, Demmin GL, Warfield KL, et al. Lactobacilli activate human dendritic cells that skew T cells toward T helper 1 polarization. Proc Natl Acad Sci USA. 2005;102(8):2880–5.
22. Gori S, Vermeulen M, Remes-Lenicov F, Jancic C, Scordo W, Ceballos A, et al. Acetylcholine polarizes dendritic cells toward a Th2-promoting profile. Allergy. 2017;72(2):221–31.
23. George MM, Subramanian Vignesh K, Landero Figueroa JA, Caruso JA, Deepe GS. Zinc induces dendritic cell tolerogenic phenotype and skews regulatory T cell-Th17 balance. J Immunol. 2016;197(5):1864–76.
24. Zhou Y, Slone N, Chrisikos TT, Kyrysyuk O, Babcock RL, Medik YB, et al. Vaccine efficacy against primary and metastatic cancer with in vitro-generated CD103 $^{+}$ conventional dendritic cells. J Immunother Cancer. 2020;8(1):e000474.
25. Schraml BU, Reis e Sousa C. Defining dendritic cells. Curr Opin Immunol. 2015;32:13–20.
26. Bachem A, Güttler S, Hartung E, Ebstein F, Schaefer M, Tannert A, et al. Superior antigen cross-presentation and XCR1 expression define human CD11c+CD141+ cells as homologues of mouse CD8+ dendritic cells. J Exp Med. 2010;207(6):1273–81.
27. Fossum E, Tesfaye DY, Bobic S, Gudjonsson A, Braathen R, Lahoud MH, et al. Targeting antigens to different receptors on conventional type 1 dendritic cells impacts the immune response. J Immunol. 2020. http://www.jimmunol.org/content/early/2020/06/25/jimmunol.1901119. Accessed 29 Jan 2021.
28. Macri C, Dumont C, Johnston AP, Mintern JD. Targeting dendritic cells: a promising strategy to improve vaccine effectiveness. Clin Transl Immunol. 2016;5(3):e66.
29. Villani AC, Satija R, Reynolds G, Sarkizova S, Shekhar K, Fletcher J, et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. Science. 2017;356(6335):eaah4573. http://science.sciencemag.org/content/356/6335/eaah4573
30. Research AA for C. FLT3 ligand boosts immune response and may enhance anticancer vaccines. Cancer Discov. 2020;11(2):219. http://cancerdiscovery.aacrjournals.org/content/early/2020/12/03/2159-8290.CD-RW2020-171
31. Chung DJ, Romano E, Pronschinske KB, Shyer JA, Mennecozzi M, St Angelo ET, et al. Langerhans-type and monocyte-derived human dendritic cells have different susceptibilities to mRNA electroporation with distinct effects on maturation and activation: implications for immunogenicity in dendritic cell-based immunotherapy. J Transl Med. 2013;11:166.
32. Brown RD, Pope B, Murray A, Esdale W, Sze DM, Gibson J, et al. Dendritic cells from patients with myeloma are numerically normal but functionally defective as they fail to up-regulate CD80 (B7–1) expression after huCD40LT stimulation because of inhibition by transforming growth factor-beta1 and interleukin-10. Blood. 2001;98(10):2992–8.
33. Choe J-Y, Yun JY, Jeon YK, Kim SH, Park G, Huh JR, et al. Indoleamine 2,3-dioxygenase (IDO) is frequently expressed in stromal cells of Hodgkin lymphoma and is associated with adverse clinical features: a retrospective cohort study. BMC Cancer. 2014;14:335.
34. Brimnes MK, Svane IM, Johnsen HE. Impaired functionality and phenotypic profile of dendritic cells from patients with multiple myeloma. Clin Exp Immunol. 2006;144(1):76–84.
35. Sozzani S, Allavena P, D'Amico G, Luini W, Bianchi G, Kataura M, et al. Differential regulation of chemokine receptors during dendritic cell maturation: a model for their trafficking properties. J Immunol. 1998;161(3):1083–6.
36. de Vries IJM, Lesterhuis WJ, Scharenborg NM, Engelen LP, Ruiter DJ, Gerritsen MJ, et al. Maturation of dendritic cells is a prerequisite for inducing immune responses in advanced melanoma patients. Clin Cancer Res. 2003;9(14):5091–100.
37. Barratt-Boyes SM, Zimmer MI, Harshyne LA, Meyer EM, Watkins SC, Capuano S, et al. Maturation and trafficking of monocyte-derived dendritic cells in monkeys: implications for dendritic cell-based vaccines. J Immunol. 2000;164(5):2487–95.
38. Avigan D, Rosenblatt J. Vaccine therapy in hematologic malignancies. Blood. 2018;131(24):2640–50.
39. Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. npj Vaccines. 2019;4:7.
40. Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. npj Vaccines. 2019;4(1):7. https://doi.org/10.1038/s41541-019-0103-y
41. Atanackovic D, Hildebrandt Y, Jadczak A, Cao Y, Luetkens T, Meyer S, et al. Cancer-testis antigens MAGE-C1/CT7 and MAGE-A3

promote the survival of multiple myeloma cells. Haematologica. 2010;95(5):785–93.
42. Batchu RB, Moreno AM, Szmania SM, Bennett G, Spagnoli GC, Ponnazhagan S, et al. Protein transduction of dendritic cells for NY-ESO-1-based immunotherapy of myeloma. Cancer Res. 2005;65(21):10041–9.
43. Ding K, Wang X-M, Fu R, Ruan E-B, Liu H, Shao Z-H. PRAME gene expression in acute leukemia and its clinical significance. Cancer Biol Med. 2012;9(1):73–6.
44. Hoyos V, Borrello I. The immunotherapy era of myeloma: monoclonal antibodies, vaccines, and adoptive T-cell therapies. Blood. 2016;128(13):1679–87.
45. Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res. 2013;19(8):2048–60.
46. Brossart P, Schneider A, Dill P, Schammann T, Grünebach F, Wirths S, et al. The epithelial tumor antigen MUC1 is expressed in hematological malignancies and is recognized by MUC1-specific cytotoxic T-lymphocytes. Cancer Res. 2001;61(18):6846–50.
47. Pronier E, Bowman RL, Ahn J, Glass J, Kandoth C, Merlinsky TR, et al. Genetic and epigenetic evolution as a contributor to WT1-mutant leukemogenesis. Blood. 2018;132(12):1265–78.
48. Di Stasi A, Jimenez AM, Minagawa K, Al-Obaidi M, Rezvani K. Review of the results of WT1 peptide vaccination strategies for myelodysplastic syndromes and acute myeloid leukemia from nine different studies. Front Immunol. 2015;6:36.
49. Timmerman JM, Czerwinski DK, Davis TA, Hsu FJ, Benike C, Hao ZM, et al. Idiotype-pulsed dendritic cell vaccination for B-cell lymphoma: clinical and immune responses in 35 patients. Blood. 2002;99(5):1517–26.
50. Reichardt VL, Okada CY, Liso A, Benike CJ, Stockerl-Goldstein KE, Engleman EG, et al. Idiotype vaccination using dendritic cells after autologous peripheral blood stem cell transplantation for multiple myeloma–a feasibility study. Blood. 1999;93(7):2411–9.
51. Cathcart K, Pinilla-Ibarz J, Korontsvit T, Schwartz J, Zakhaleva V, Papadopoulos EB, et al. A multivalent bcr-abl fusion peptide vaccination trial in patients with chronic myeloid leukemia. Blood. 2004;103(3):1037–42.
52. Linette GP, Carreno BM. Neoantigen vaccines pass the immunogenicity test. Trends Mol Med. 2017;23(10):869–71.
53. González FE, Gleisner A, Falcón-Beas F, Osorio F, López MN, Salazar-Onfray F. Tumor cell lysates as immunogenic sources for cancer vaccine design. Hum Vaccines Immunother. 2014;10(11):3261–9.
54. Kokhaei P, Choudhury A, Mahdian R, Lundin J, Moshfegh A, Österborg A, et al. Apoptotic tumor cells are superior to tumor cell lysate, and tumor cell RNA in induction of autologous T cell response in B-CLL. Leukemia. 2004;18(11):1810–5.
55. McCann KJ, Godeseth R, Chudley L, Mander A, Di Genova G, Lloyd-Evans P, et al. Idiotypic DNA vaccination for the treatment of multiple myeloma: safety and immunogenicity in a phase I clinical study. Cancer Immunol Immunother. 2015;64(8):1021–32.
56. Freedman A, Neelapu SS, Nichols C, Robertson MJ, Djulbegovic B, Winter JN, et al. Placebo-controlled phase III trial of patient-specific immunotherapy with mitumprotimut-T and granulocyte-macrophage colony-stimulating factor after rituximab in patients with follicular lymphoma. J Clin Oncol. 2009;27(18):3036–43.
57. Schuster SJ, Neelapu SS, Gause BL, Janik JE, Muggia FM, Gockerman JP, et al. Vaccination with patient-specific tumor-derived antigen in first remission improves disease-free survival in follicular lymphoma. J Clin Oncol. 2011;29(20):2787–94.
58. Levy R, Ganjoo KN, Leonard JP, Vose JM, Flinn IW, Ambinder RF, et al. Active idiotypic vaccination versus control immunotherapy for follicular lymphoma. J Clin Oncol. 2014;32(17):1797–803.
59. Anguille S, Van de Velde AL, Smits EL, Van Tendeloo VF, Juliusson G, Cools N, et al. Dendritic cell vaccination as postremission treatment to prevent or delay relapse in acute myeloid leukemia. Blood. 2017;130(15):1713–21.
60. Van Tendeloo VF, Van de Velde A, Van Driessche A, Cools N, Anguille S, Ladell K, et al. Induction of complete and molecular remissions in acute myeloid leukemia by Wilms' tumor 1 antigen-targeted dendritic cell vaccination. Proc Natl Acad Sci USA. 2010;107(31):13824–9.
61. Bae J, Prabhala R, Voskertchian A, Brown A, Maguire C, Richardson P, et al. A multiepitope of XBP1, CD138 and CS1 peptides induces myeloma-specific cytotoxic T lymphocytes in T cells of smoldering myeloma patients. Leukemia. 2015;29(1):218–29.
62. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547(7662):217–21.
63. Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015;348(6236):803–8.
64. Ho VT, Kim HT, Bavli N, Mihm M, Pozdnyakova O, Piesche M, et al. Vaccination with autologous myeloblasts admixed with GM-K562 cells in patients with advanced MDS or AML after allogeneic HSCT. Blood Adv. 2017;1(24):2269–79.
65. Borrello IM, Levitsky HI, Stock W, Sher D, Qin L, DeAngelo DJ, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting cellular immunotherapy in combination with autologous stem cell transplantation (ASCT) as postremission therapy for acute myeloid leukemia (AML). Blood. 2009;114(9):1736–45.
66. Burkhardt UE, Hainz U, Stevenson K, Goldstein NR, Pasek M, Naito M, et al. Autologous CLL cell vaccination early after transplant induces leukemia-specific T cells. J Clin Invest. 2013;123(9):3756–65.
67. Weinstock M, Rosenblatt J, Avigan D. Dendritic cell therapies for hematologic malignancies. Mol Ther Methods Clin Dev. 2017;5:66–75.
68. Bol KF, Schreibelt G, Gerritsen WR, de Vries IJM, Figdor CG. Dendritic cell-based immunotherapy: state of the art and beyond. Clin Cancer Res. 2016;22(8):1897–906.
69. de Vries IJM, Eggert AAO, Scharenborg NM, Vissers JLM, Lesterhuis WJ, Boerman OC, et al. Phenotypical and functional characterization of clinical grade dendritic cells. J Immunother. 2002;25(5):429–38.
70. Curti A, Isidori A, Ferri E, Terragna C, Neyroz P, Cellini C, et al. Generation of dendritic cells from positively selected CD14+ monocytes for anti-tumor immunotherapy. Leuk Lymphoma. 2004;45(7):1419–28.
71. Ueno H, Tcherepanova I, Reygrobellet O, Laughner E, Ventura C, Palucka AK, et al. Dendritic cell subsets generated from CD34+ hematopoietic progenitors can be transfected with mRNA and induce antigen-specific cytotoxic T cell responses. J Immunol Methods. 2004;285(2):171–80.
72. Meyer-Wentrup F, Benitez-Ribas D, Tacken PJ, Punt CJA, Figdor CG, de Vries IJM, et al. Targeting DCIR on human plasmacytoid dendritic cells results in antigen presentation and inhibits IFN-α production. Blood. 2008;111(8):4245–53.
73. Hsu FJ, Benike C, Fagnoni F, Liles TM, Czerwinski D, Taidi B, et al. Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells. Nat Med. 1996;2(1):52–8.
74. Lacy MQ, Mandrekar S, Dispenzieri A, Hayman S, Kumar S, Buadi F, et al. Idiotype-pulsed antigen presenting cells following autologous transplantation for multiple myeloma may be associated with prolonged survival. Am J Hematol. 2009;84(12):799–802.
75. Liso A, Stockerl-Goldstein KE, Auffermann-Gretzinger S, Benike CJ, Reichardt V, van Beckhoven A, et al. Idiotype vaccination using dendritic cells after autologous peripheral blood progenitor cell transplantation for multiple myeloma. Biol Blood Marrow Transplant. 2000;6(6):621–7.

76. Lacy MQ, Mandrekar S, Dispenzieri A, Hayman S, Kumar S, Buadi F, et al. Idiotype-pulsed antigen-presenting cells following autologous transplantation for multiple myeloma may be associated with prolonged survival. Am J Hematol. 2009;84(12):799–802.
77. Hobo W, Strobbe L, Maas F, Fredrix H, Greupink-Draaisma A, Esendam B, et al. Immunogenicity of dendritic cells pulsed with MAGE3, Survivin and B-cell maturation antigen mRNA for vaccination of multiple myeloma patients. Cancer Immunol Immunother. 2013;62(8):1381–92.
78. Rosenblatt J, Vasir B, Uhl L, Blotta S, MacNamara C, Somaiya P, et al. Vaccination with dendritic cell/tumor fusion cells results in cellular and humoral antitumor immune responses in patients with multiple myeloma. Blood. 2011;117(2):393–402.
79. Rosenblatt J, Avivi I, Vasir B, Uhl L, Munshi NC, Katz T, et al. 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(13):3640–8.
80. Rosenblatt J, Stone RM, Uhl L, Neuberg D, Joyce R, Levine JD, et al. Individualized vaccination of AML patients in remission is associated with induction of antileukemia immunity and prolonged remissions. Sci Transl Med. 2016;8(368):368ra171.
81. Khoury HJ, Collins RH, Blum W, Stiff PS, Elias L, Lebkowski JS, et al. Immune responses and long-term disease recurrence status after telomerase-based dendritic cell immunotherapy in patients with acute myeloid leukemia. Cancer. 2017;123(16):3061–72.
82. Cox MC, Castiello L, Mattei M, Santodonato L, D'Agostino G, Muraro E, et al. Clinical and antitumor immune responses in relapsed/refractory follicular lymphoma patients after intranodal injections of IFNα-dendritic cells and rituximab: a phase I clinical trial. Clin Cancer Res. 2019;25(17):5231–41.
83. Clinical Trials.gov. Dendritic cell/myeloma fusion vaccine for multiple myeloma (BMT CTN 1401). 2016. https://clinicaltrials.gov/ct2/show/record/NCT02728102
84. Clinical Trials.gov. DC/AML fusion cell vaccine vs observation in patients who achieve a chemotherapy-induced remission. 2017. https://clinicaltrials.gov/ct2/sho/NCT03059485
85. Clinical Trails.gov. Dendritic cell/AML fusion cell vaccine following allogeneic transplantation in AML patients. 2018. https://clinicaltrials.gov/ct2/show/record/NCT03679650
86. Srivastava P, Paluch BE, Matsuzaki J, James SR, Collamat-Lai G, Blagitko-Dorfs N, et al. Induction of cancer testis antigen expression in circulating acute myeloid leukemia blasts following hypomethylating agent monotherapy. Oncotarget. 2016;7(11):12840–56.
87. Dubovsky JA, McNeel DG, Powers JJ, Gordon J, Sotomayor EM, Pinilla-Ibarz JA. Treatment of chronic lymphocytic leukemia with a hypomethylating agent induces expression of NXF2, an immunogenic cancer testis antigen. Clin Cancer Res. 2009;15(10):3406–15.
88. Clinical Trials.gov. A study of PVX-410, a cancer vaccine, and citarinostat +/- lenalidomide for smoldering MM. 2016. https://clinicaltrials.gov/ct2/show/record/NCT02886065
89. Clinical Trials.gov. Dendritic cell DKK1 vaccine for monoclonal gammopathy and stable or smoldering myeloma. 2018. https://clinicaltrials.gov/ct2/show/record/NCT03591614
90. Chung DJ, Pronschinske KB, Shyer JA, Sharma S, Leung S, Curran SA, et al. T-cell exhaustion in multiple myeloma relapse after autotransplant: optimal timing of immunotherapy. Cancer Immunol Res. 2016;4(1):61–71.
91. Hosen N, Maeda T, Hashii Y, Tsuboi A, Nishida S, Nakata J, et al. Vaccination strategies to improve outcome of hematopoietic stem cell transplant in leukemia patients: early evidence and future prospects. Expert Rev Hematol. 2014;7(5):671–81.
92. Nemunaitis J, Dillman RO, Schwarzenberger PO, Senzer N, Cunningham C, Cutler J, et al. Phase II study of belagenpumatucel-L, a transforming growth factor beta-2 antisense gene-modified allogeneic tumor cell vaccine in non-small-cell lung cancer. J Clin Oncol. 2006;24(29):4721–30.
93. Giaccone G, Bazhenova LA, Nemunaitis J, Tan M, Juhász E, Ramlau R, et al. A phase III study of belagenpumatucel-L, an allogeneic tumour cell vaccine, as maintenance therapy for non-small cell lung cancer. Eur J Cancer. 2015;51(16):2321–9.
94. Rosenberg SA, Spiess P, Lafreniere R. A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science. 1986;233(4770):1318–21.
95. Shimizu K, Fields RC, Giedlin M, Mulé JJ. Systemic administration of interleukin 2 enhances the therapeutic efficacy of dendritic cell-based tumor vaccines. Proc Natl Acad Sci USA. 1999;96(5):2268–73.
96. Escobar A, López M, Serrano A, Ramirez M, Perez C, Aguirre A, et al. Dendritic cell immunizations alone or combined with low doses of interleukin-2 induce specific immune responses in melanoma patients. Clin Exp Immunol. 2005;142(3):555–68.
97. Redman BG, Chang AE, Whitfield J, Esper P, Jiang G, Braun T, et al. Phase Ib trial assessing autologous, tumor-pulsed dendritic cells as a vaccine administered with or without IL-2 in patients with metastatic melanoma. J Immunother. 2008;31(6):591–8.
98. Vo M-C, Anh-NguyenThi T, Lee H-J, Nguyen-Pham T-N, Jaya Lakshmi T, Jung S-H, et al. Lenalidomide enhances the function of dendritic cells generated from patients with multiple myeloma. Exp Hematol. 2017;46:48–55.
99. Luptakova K, Rosenblatt J, Glotzbecker B, Mills H, Stroopinsky D, Kufe T, et al. Lenalidomide enhances anti-myeloma cellular immunity. Cancer Immunol Immunother. 2013;62(1):39–49.
100. Sakamaki I, Kwak LW, Cha S, Yi Q, Lerman B, Chen J, et al. Lenalidomide enhances the protective effect of a therapeutic vaccine and reverses immune suppression in mice bearing established lymphomas. Leukemia. 2014;28(2):329–37.
101. Nahas MR, Stroopinsky D, Rosenblatt J, Cole L, Pyzer AR, Anastasiadou E, et al. Hypomethylating agent alters the immune microenvironment in acute myeloid leukaemia (AML) and enhances the immunogenicity of a dendritic cell/AML vaccine. Br J Haematol. 2019;185(4):679–90.
102. Rosenblatt J, Glotzbecker B, Mills H, Vasir B, Tzachanis D, Levine JD, et al. PD-1 blockade by CT-011, anti PD-1 antibody, enhances ex-vivo T cell responses to autologous dendritic/myeloma fusion vaccine. J Immunother. 2011;34(5):409–18.
103. Tanaka M, Tashiro H, Omer B, Lapteva N, Ando J, Ngo M, et al. Vaccination targeting native receptors to enhance the function and proliferation of chimeric antigen receptor (CAR)-modified T cells. Clin Cancer Res. 2017;23(14):3499–509.
104. Slaney CY, von Scheidt B, Davenport AJ, Beavis PA, Westwood JA, Mardiana S, et al. Dual-specific chimeric antigen receptor T cells and an indirect vaccine eradicate a variety of large solid tumors in an immunocompetent, self-antigen setting. Clin Cancer Res. 2017;23(10):2478–90.
105. Nagle SJ, Garfall AL, Stadtmauer EA. The promise of chimeric antigen receptor engineered T cells in the treatment of hematologic malignancies. Cancer J. 2016;22(1):27–33.

How to cite this article: Bindal P, Rosenblatt J, Avigan D. Therapeutic dendritic cell cancer vaccines in hematologic malignancies. *ImmunoMedicine*. 2021;00:e1022. https://doi.org/10.1002/imed.1022