International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 10, Issue 1, pp: (144-152), Month: April 2022 - September 2022, Available at: www.researchpublish.com

Cancer vaccine treatment for Melanoma

Supavee Piyapanpong[1*]

[1]Mahidol University International Demonstration School, Salaya, Phutthamonthon, Nakhon Pathom, Thailand 73170

DOI: https://doi.org/ 10.5281/zenodo.6832997

Published Date: 14-July-2022

Abstract: **Generally, cancer is a serious problem no matter what type of cancer, even though we have many types of medication, including vaccination. Most vaccines are created to prevent or boost immunity. However, the vaccine that this literature review mentioned was made to treat cancer. As the medical professionals wanted to treat the cancer patients precisely, a cancer vaccine was developed, not for prevention but as a cure by tricking the immune system. The vaccines have been developed using four melanoma antigens groups: overexpressed antigens, cancer-testis antigens, mutant oncogenes, and patient-specific mutated neoantigens. In addition, two technologies, Tumor antigens and Stimulation of anti-tumour immunity, have advanced based on the mechanism of cancer vaccines. Most importantly, the critical potential of cancer vaccine treatment for Melanoma has some clinical studies about the vaccinations that have been advanced and existed in much research, plus, it has been tested with humans. The history of melanoma skin cancer immunizations is extensive. It can stimulate immunological responses. An efficient vaccination platform is examined in this dynamic sector. This includes immunizations based on neoantigens and skin cancer virus inclusions.**

Keywords: **Cancer vaccines, Melanoma antigens, Melanoma, Tumor antigens.**

I. INTRODUCTION

Over the last decade, there has been a renaissance of interest in therapeutic cancer vaccines. A better understanding of the range of tumor-related antigens, the natural immune response, and the development of innovative antigen delivery systems has resulted in improved vaccine design [1, 2]. The objective of therapeutic cancer vaccines is to promote tumor regression, eradicate minimal residual disease, establish permanent antitumour memory, and prevent non-specific or undesirable side effects [3, 4]. For decades, it has been recognized that the immune system may be spontaneously activated against melanoma [5].The presence of tumor infiltrating lymphocytes (TIL) in tumor deposits is associated with a favorable prognosis [6, 7]. Cancer vaccination involves approaches to generate, enhance, or distort antitumor immunity [8, 9]. To achieve this goal, tested approaches include administration of tumor antigens, antigen-presenting cells (APCs) or other immune modulators, or direct regulation of the tumor [10-12]. Cancer vaccination may play an important role in the future combination therapies, as successful checkpoint blockade may be partially dependent on established anti tumor responses [13, 14]. This review aims to explore the advancement of cancer vaccines for melanoma treatment, plus, to inspect what current evidence is and what technology that can be an alternative for patients.

II. CANCER VACCINE BACKGROUND

Vaccines have opened up new avenues for preventing and treating infectious illnesses [15, 16]. The earliest vaccine was discovered in 1796 by Edward Jenner, who found that the cowpox vaccine protects against smallpox infection [17]. As the vaccine developed, it was used to treat more diseases, including cancers [3, 18]. In 1980, the initial cancer vaccine based on tumor cells and tumor lysates was developed [19]. In order to treat colorectal cancer, researchers used autologous tumor cells [7, 20]. The discovery of the first human tumor antigen, melanoma-associated antigen 1, in the early 1990s opened a new chapter in the use of tumor antigens in cancer vaccines [21, 22]. In 2010, a dendritic cell-based vaccine (Sipuleucel-T) was effectively utilized to treat prostate cancer, demonstrating the viability of cancer vaccines and igniting interest in the topic [23-25]. The COVID-19 epidemic has accelerated the development of vaccine technologies and pushed cancer vaccines back into the public eye [26]. To stimulate the patient's immune system, cancer vaccines primarily use tumor-

associated antigens (TAAs) and tumor-specific antigens (TSAs) [24, 27]. In theory, the vaccine might induce both specific cellular immunity and humoral immune response, preventing tumor development and eventually eradicating tumor cells [28, 29]. Most cancer vaccines are currently in the preclinical and clinical stages of development [30]. More specific antigens and vaccine development platforms need to be developed [31].

Cancer vaccines vary from ordinary vaccinations in that they attempt to destroy tumor cells via tumor antigen-specific cellular immune responses [32]. Only two FDA-approved prophylactic vaccinations have been used to prevent viral cancers (Hepatitis B virus and human papillomavirus) [33, 34]. Furthermore, unlike typical vaccinations that use antigens from external diseases, tumor antigens are endogenous and have minimal immunogenicity [35]. It is frequently difficult to trigger an efficient immune response to tumor antigens. Traditional vaccinations also produce humoral immunity [1, 24]. However, for cancer vaccines, CD8+ cytotoxic T cell-mediated cellular immunity is critical in eradicating malignant cells [36, 37]. Platforms for cancer vaccines are classified into four categories based on their preparation methods: cell-based vaccines, viruses-based vaccines, peptide-based vaccines, and nucleic acids-based vaccines [18]. Cell-based cancer vaccines are vaccinations that utilize entire cells as antigen carriers [38]. Cell-based vaccinations are the most common type of pre-clinical cancer vaccine, with dendritic cells (DCs) vaccines showing promising outcomes in clinical studies [24, 39]. Virus-based cancer vaccines cure and prevent cancers by using viruses as vectors [28]. Peptide-based vaccinations are made up of tumor antigen epitopes that are known or anticipated. Peptide-based vaccines are frequently less immunogenic, necessitating the use of adjuvants to improve immunogenicity [40]. DNA and RNA vaccines are nucleic vaccinations that contain the encoding gene and a carrier group of pathogen antigens [41, 42]. DNA cancer vaccines are closed circular DNA plasmids that encode TAAs or immunomodulatory compounds to stimulate tumor-specific responses [43, 44]. *In vitro*, mRNA vaccines can encode antigens and express proteins after internalization to trigger an immune response [38]. Combining cancer vaccinations with other immunotherapies or standardized treatments has shown to be a successful technique for overcoming tumor resistance and improving clinical outcomes in recent years [18, 45]. Cancer vaccinations have been thoroughly researched throughout the last decade [46]. The widespread availability and low cost of high-throughput sequencing methods have resulted in the discovery of multiple tumor neoantigens [47]. The comprehensive knowledge of immunological mechanisms and the development of several novel vaccination platforms has greatly aided cancer vaccine research [17, 39].

III. MECHANISM OF CANCER VACCINES

A. Tumor antigens

Antigen selection is a virtual step in the development of cancer vaccines [48]. Tumor antigens identified by T cells are critical to cancer vaccination effectiveness [49, 50]. The ideal antigen for a cancer vaccination should be highly immunogenic, specifically expressed in all cancer cells (but not in normal cells) and required for the cancer cells survival [44]. Tumor antigens are classified as TAAs or TSAs [39]. TAAs are often referred to as tumor-shared antigens [18]. TAAs are “self-antigens” such as differentiated antigens, overexpressed antigens, cancer-testicular antigens, and viral-derived “non-self” antigens [17, 27]. Human epidermal growth factor receptor 2 (HER2) and human telomerase reverse transcriptase are two well-known examples of overexpressed tumor antigens [51]. Tissue differentiation antigens are expressed by tumor cells as well as normal cells derived from the same tissue as tumor cells, such as prostate-specific antigen (PSA) expressed in the prostate gland and prostate cancer, melanoma antigens tyrosinase expressed by normal melanocytes, and melanoma cells [52]. TAAs are versatile and may be used on a variety of patients. TAAs were the primary target of early cancer vaccinations [53]. However, because of the thymus’s central immunological tolerance, activated T cells that detect TAAs or other autoantigens may be destroyed throughout development, reducing the vaccines’s potency [49]. As a result, TAA-based cancer vaccines must be appealing enough to “break the tolerance” [54]. Despite the fact that TAAs have been studied for many years, clinical studies of TAA-based cancer vaccines have had minimal success [43]. Furthermore, TAAs are expressed in non malignant tissues, raising the possibility of vaccine-induced autoimmune damage [44].

TSAs are a kind of protein that is only found in tumor cells [24]. TSAs are frequently referred to as neoantigens [55]. The individual-specific non-autogenous proteins created by tumor cell mutations [18]. Neoantigens are solely produced by tumor cells, eliciting a genuine tumor-specific T-cell response with minimal “off-target” harm [53]. Neoantigens are more immunogenic than TAAs and have a stronger affinity for the major histocompatibility complex (MHC) [38, 56]. They are also unaffected by central immune tolerance [18]. The widespread use of next-generation sequencing technology enables the identification of individualized neoantigens in a fast and cost-effective manner [24, 30]. Furthermore, the advent of algorithms for predicting MGC I class binding epitopes has tremendously aided in the identification of possible novel

immunogenicity epitopes [57]. Cancer vaccines targeting neoantigens have become the primary focus of tumor vaccine research in recent years [58]. Several clinical trials utilizing neoantigen vaccinations have recently generated positive results, including enhanced patient survival [28, 59]. A classic example is an mRNA neoantigen melanoma vaccination, which triggered T cell infiltration and neoantigen-specific death of autologous tumor cells [41, 42]. Following immunization, the occurrence of metastatic events was dramatically decreased, resulting in long-term progression-free survival [60]. Furthermore, the neoantigen-loaded DC immunization might induce a T cell-specific response, leading to antigen dissemination in melanoma patients [38]. Although tailored cancer vaccines based on neoantigens have yielded promising outcomes, a vast percentage of projected neoantigens tend to elicit very few anti-tumor responses. Furthermore, variances in tumor types and people restrict the use of mutant neoantigen-targeted cancer vaccines. As a result, finding high-quality neoantigens for the development of neoantigen vaccines is critical.

The high-quality neoantigens should have the following characteristics: First, they must have a high affinity for human leukocyte antigen (HLA); second, they must be highly heterologous compared to the wild type; third, they must be expressed by the majority of tumor cells; and fourth, they must be produced as a result of mutations that influence survival [61]. These neoantigens might elicit a strong immune response and limit the formation of tumor-immune escape [62]. At the moment, no research has determined the appropriate amount of neoantigens for a tumor vaccination [38]. A neoantigen vaccination often comprises hundreds of neoantigens [63]. For instance, a customized neoantigen DNA vaccine (GNOS-PV02) encodes up to 40 neoantigens, encompassing every discovered neoantigens in the vast majority of hepatocellular carcinoma patients [64]. Scientists have recently expanded the antigen pool for immunization by fusing common antigens with neoantigens with neoantigens to boost vaccine efficacy [64]. For instance, the APVAC1/2 vaccines can successfully trigger the T-cell response in the treatment of glioblastoma because they include both common tumor antigens and patient-specific neoantigens [64, 65]. The combination of tailored neoantigen vaccinations with PD- 1 or PD-L1 inhibitors has also shown anti-tumor effectiveness in preliminary clinical investigations [66].

B. Stimulation of anti-tumor immunity

Antigen-presenting cells (APCs) are essential for tumour-induced immune activation. DCs, the crucial link between innate immunity and adaptive immunity, are the most crucial [67]. DCs are the first antigen presenters, able to acquire antigens and cross-present them on MHC I molecules [68]. Immature DCs can recognise and capture antigens by phagocytosis and micropinocytosis [68, 69]. The stimulation of immature DCs by Toll-like receptor ligands in the tumour microenvironment (TME) may temporarily boost antigen-specific micropinocytosis, which may increase DCs' ability to trap antigens with toll-like receptor ligand adjuvants [69]. MHC I, MHC II, and costimulatory molecules on the surface of DCs will be elevated following antigen uptake, and DCs will gradually lose their capacity to take up antigens. Antigen-laden DCs move to drain lymph nodes, the prominent location of T cell priming [70]. Mature DCs provide CD4+ and CD8+ T lymphocytes with processed antigen epitopes on MHC I and MHC II molecules [30]. In addition, DCs release IL-12 and interferon (IFN) to boost the synthesis of costimulatory factors. The interaction of MHC–peptide complex–T cell receptor and costimulatory "signal 2" activate tumour-specific T lymphocytes [17, 71]. Activated T cells develop into memory T cells with a long lifespan and effector T cells [31]. Effector tumor-specific T lymphocytes proliferate and migrate to the tumour microenvironment (TME) to trigger tumour cell death via cytotoxicity and the production of effector cytokines [31]. Activated B cells also enhance tumour death via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity [31, 67].

Additionally, immunogenic cell death results in the release of tumour antigens and damage-associated molecular patterns [34]. In turn, the tumour antigens released by lysed tumour cells can be collected, processed, and re-presented by APCs to activate polyclonal T cell responses, therefore expanding the antigenic breadth of antitumor immune responses [48]. The term for these processes is the cancer-immunity cycle [48]. CD4+ T cells collaborate with other types of immune cells [72]. CD4+ T cells induce ongoing T cell initiation, growth, and antigen dissemination, extending the repertoire of antitumor T cells [72]. IFN-γ produced by Th1 CD4+ T cells upregulates MHC I on tumour cells, enhancing CD8+ T cell cytotoxicity [72]. In addition, Th1 CD4+ T cells increase the inflammatory microenvironment by interacting with diverse immune cells within tumours [8]. CD4+ T cells also regulate CD8+ T effector cell development [72]. Cytotoxic T lymphocytes (CTLs) are essential for eliminating tumour cells and presenting their corresponding antigen [73]. After activation by antigen receptors, CD8+ T cells multiply and develop into CTL effector cells [73]. To eliminate tumour cells, activated CTLs will enter the core of the tumour or infiltrate the location [72, 73]. The quantity of CTLs in TME is a crucial indicator of cancer prognosis [72, 73]. CTLs identify tumour cells displaying target antigens and attack target cells in several ways [19]. CTLs might eliminate cancer cells by generating and releasing cytotoxic particles such as perforin and granzymes. In addition,

CTLs trigger death in target cells via FasL-mediated interactions [18]. In addition, the release of IFN-γ and tumour necrosis factor (TNF-α) by CTLs causes cancer cell cytotoxicity [74]. IFN-γ may decrease the angiogenesis of cancer cells and induce M1-polarized macrophages [74]. IFN-generated by CTLs facilitates their maturation into effector CTLs [74]. In conclusion, cancer vaccines primarily eliminate tumour cells by stimulating cellular immunity and initiating the cancer-immunity cycle to play a permanent antitumor function [74].

IV. MELANOMA ANTIGENS

There are four groups of melanoma antigens: overexpressed antigens, cancer-testis antigens, mutant oncogenes, and patient-specific mutated neoantigens [55]. All have demonstrated effectiveness as targets in vitro and murine models and have been evaluated in clinical trials with certain solid tumours [52]. Melanoma lineage antigens such as MART-1/Melan-A, tyrosinase, and gp100 (expressed in > 90% of melanoma tumours) are overexpressed antigens [22]. The most remarkable avidity T cells specific to these typical "self" antigens may have been eliminated or depleted by persistent antigen stimulation, leaving only less efficient, lower avidity T cells activated [75]. Cancer testis antigens are expressed in a fraction of most tumour tissue types and germ cells typically overlooked by the immune system due to their physiological position [21]. The vast MAGE-A, MAGE-B, and MAGE-C families and NY-ESO-1 (expressed in 9 to 51% of melanomas) are examples of such antigens [12, 76]. These antigens have been implicated in treatment responses in human clinical studies. Neoantigens are antigens that develop from random somatic alterations in tumour cells [24]. Mutant oncogenes have been discovered in recent decades, as have frequently occurring shared mutations in the RAS family of oncogenes (NRAS is mutated in 15 to 25% of melanomas) [77]. Still, people used to think it was unlikely that such mutations would be present in a processed, shown, and immunogenic MHC limited epitope in a defined MHC class I or II molecule. This made it hard to target shared mutations by vaccination in a clinical trial [77].

V. TUMOR-INFILTRATING LYMPHOCYTE THERAPY IN MELANOMA

Cellular therapy has transformed the treatment of hematologic malignancies, but applying these methods to solid tumours has proven to be rather difficult [78]. There are currently no authorised cellular treatments for solid tumour patients [78]. The recent success of lifileucel in treating melanoma resistant to checkpoint inhibitors was welcomed with tremendous enthusiasm [39]. In addition to continuing trials using lifileucel, substantial research is being conducted on innovative commercial TIL treatment products (NCT05050006, NCT03997474) [79]. Numerous institutes have begun to prepare for the regulatory licencing of commercial TIL agents [79]. Coordination of care might be complicated because of the interdisciplinary nature of TIL therapy [79, 80]. Communication across numerous care teams necessitates substantial preparation and the employment of qualified staff [79]. An outpatient oncologist may treat a patient, a surgeon, an inpatient cellular therapy/bone marrow transplant/disease-specific team, and subspecialists necessary to address toxicity during TIL treatment [79, 80]. To guarantee the correct management of resected tumour tissue for cell collection, further coordination is required between the surgeon, operating room personnel, pathologists, and TIL producer [79]. Transitions between the referring medical oncologist, surgeon, cellular therapy physician, and inpatient and outpatient teams must be carefully organised, and measures must be implemented to prevent catastrophic patient safety blunders [72]. Researchers have done the majority of care coordination in clinical trials, and the expenses of care coordination are included in clinical trial budgets [81]. However, to expand access to TIL outside of clinical trials, individual hospitals will need to educate and retain care coordination personnel [81]. This will be conceivable for major facilities that want to treat many patients with cellular therapy, but it is uncertain how smaller institutions will manage the associated costs and human resources needs [81]. Further practical concerns involving the generation and delivery of TILs impede the therapy's broad application [24]. TILs need the surgical excision of a suitably big tumour or a collection of tumours [24]. The patient selection might be hampered by the inaccessibility of tumours and the morbidity of surgical excision [24]. Therefore, there is a great deal of interest in the possibility of collecting and growing TILs from biopsies, which would be a significant step toward enhancing patient access [44, 81].

The necessity for hospitalisation and specialised knowledge in delivering IL-2 is another significant hurdle to the widespread adoption of TIL treatment [7]. Experience in delivering IL-2 and treating its toxicities is diminishing due to the widespread use of checkpoint inhibitors, which prompted many clinics to cease offering IL-2 treatment [7]. Expert outpatient facilities may safely administer lymphodepleting chemotherapy and cell infusions, but IL-2 delivery requires continual monitoring [80]. Alternative IL-2 formulations safe for outpatient administration are being investigated, although their effectiveness for TIL treatment remains uncertain [62]. Alternative dosage regimens, or even the removal of IL-2, have been proposed to minimise toxicity [62]. However, there is presently no data indicating the effectiveness of this strategy with contemporary TIL products [62, 82].

VI. CONCLUSION

Cancer vaccination has a lengthy history in melanoma, with efficacy in inducing immune responses, although only a minority of patients have ever seen objective clinical responses. This dynamic field of study examines effective vaccination platforms, including, more recently, neoantigen-based vaccination and oncolytic virus combination.

REFERENCES

[1] W. S. Bowen, A. K. Svrivastava, L. Batra, H. Barsoumian, and H. Shirwan, "Current challenges for cancer vaccine adjuvant development," Expert review of vaccines, vol. 17, no. 3, pp. 207-215, 2018.

[2] M. Yazdani, M. R. Jaafari, J. Verdi, B. Alani, M. Noureddini, and A. Badiee, "Ex vivo-generated dendritic cell-based vaccines in melanoma: the role of nanoparticulate delivery systems," Immunotherapy, vol. 12, no. 5, pp. 333-349, 2020.

[3] C. O. Franck, L. Fanslau, A. Bistrovic Popov, P. Tyagi, and L. Fruk, "Biopolymer-based carriers for DNA vaccine design," Angewandte Chemie International Edition, vol. 60, no. 24, pp. 13225-13243, 2021.

[4] Z. Liu et al., "Gastrodin, a traditional Chinese medicine monomer compound, can be used as adjuvant to enhance the immunogenicity of melanoma vaccines," International Immunopharmacology, vol. 74, p. 105699, 2019.

[5] I. Falcone et al., "Tumor microenvironment: Implications in melanoma resistance to targeted therapy and immunotherapy," Cancers, vol. 12, no. 10, p. 2870, 2020.

[6] M. Antohe et al., "Tumor infiltrating lymphocytes: The regulator of melanoma evolution," Oncology letters, vol. 17, no. 5, pp. 4155-4161, 2019.

[7] M. W. Rohaan, J. H. van den Berg, P. Kvistborg, and J. B. A. G. Haanen, "Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option," Journal for immunotherapy of cancer, vol. 6, no. 1, pp. 1-16, 2018.

[8] L. H. Butterfield et al., "Multiple antigen-engineered DC vaccines with or without IFNα to promote antitumor immunity in melanoma," Journal for immunotherapy of cancer, vol. 7, no. 1, pp. 1-15, 2019.

[9] L. Liu, M. J. Wannemuehler, and B. Narasimhan, "Biomaterial nanocarrier-driven mechanisms to modulate anti-tumor immunity," Current Opinion in Biomedical Engineering, vol. 20, p. 100322, 2021.

[10] I. Date et al., "Interferon-α-induced dendritic cells generated with human platelet lysate exhibit elevated antigen presenting ability to cytotoxic T lymphocytes," Vaccines, vol. 9, no. 1, p. 10, 2020.

[11] R. Mortarini et al., "Autologous Dendritic Cells Derived from CD34+ Progenitors and from Monocytes Are Not Functionally Equivalent Antigen-presenting Cells in the Induction of Melan-A/Mart-l27_35-specific CTLs from Peripheral Blood Lymphocytes of Melanoma Patients with Low Frequency of CTL Precursors1."

[12] B. K. Patel, C. Wang, B. Lorens, A. D. Levine, N. F. Steinmetz, and S. Shukla, "Cowpea Mosaic Virus (CPMV)-Based Cancer Testis Antigen NY-ESO-1 Vaccine Elicits an Antigen-Specific Cytotoxic T Cell Response," (in eng), ACS Appl Bio Mater, vol. 3, no. 7, pp. 4179-4187, Jul 20 2020, doi: 10.1021/acsabm.0c00259.

[13] A. Mougel, M. Terme, and C. Tanchot, "Therapeutic cancer vaccine and combinations with antiangiogenic therapies and immune checkpoint blockade," Frontiers in immunology, vol. 10, p. 467, 2019.

[14] Y.-C. Chuang, J.-C. Tseng, L.-R. Huang, C.-M. Huang, C.-Y. F. Huang, and T.-H. Chuang, "Adjuvant effect of toll-like receptor 9 activation on cancer immunotherapy using checkpoint blockade," Frontiers in Immunology, vol. 11, p. 1075, 2020.

[15] R. Luthra, S. Datta, and A. Roy, "Role of Different Peptides for Cancer Immunotherapy," International Journal of Peptide Research and Therapeutics, vol. 27, no. 4, pp. 2777-2793, 2021.

[16] A. J. Fike, O. K. Kumova, and A. J. Carey, "Dissecting the defects in the neonatal CD8+ T-cell response," Journal of leukocyte biology, vol. 106, no. 5, pp. 1051-1061, 2019.

[17] R. E. Hollingsworth and K. Jansen, "Turning the corner on therapeutic cancer vaccines," npj Vaccines, vol. 4, no. 1, pp. 1-10, 2019.

[18] J. Liu, M. Fu, M. Wang, D. Wan, Y. Wei, and X. Wei, "Cancer vaccines as promising immuno-therapeutics: platforms and current progress," Journal of Hematology & Oncology, vol. 15, no. 1, pp. 1-26, 2022.

[19] M. A. Gleisner et al., "A heat-shocked melanoma cell lysate vaccine enhances tumor infiltration by prototypic effector T cells inhibiting tumor growth," Journal for immunotherapy of cancer, vol. 8, no. 2, 2020.

[20] S. Yunger et al., "Tumor-infiltrating lymphocytes from human prostate tumors reveal anti-tumor reactivity and potential for adoptive cell therapy," Oncoimmunology, vol. 8, no. 12, p. e1672494, 2019.

[21] A. Fanipakdel, M. Seilanian Toussi, F. Rezazadeh, N. Mohamadian Roshan, and S. A. Javadinia, "Overexpression of cancer-testis antigen melanoma-associated antigen A1 in lung cancer: a novel biomarker for prognosis, and a possible target for immunotherapy," Journal of Cellular Physiology, vol. 234, no. 7, pp. 12080-12086, 2019.

[22] Q. Meng, G. Luo, B. Liu, Y. Sun, and Z. Yan, "Melanoma-associated antigen A2 is overexpressed in glioma and associated with poor prognosis in glioma patients," Neoplasma, vol. 65, no. 4, pp. 604-609, 2018.

[23] L. Schachter, "Dendritic Cell Vaccines," in Blood and Marrow Transplant Handbook: Springer, 2021, pp. 895-903.

[24] R.-Y. Pan et al., "Recent development and clinical application of cancer vaccine: targeting neoantigens," Journal of immunology research, vol. 2018, 2018.

[25] C. R. Bora, I. N. Carrera, F. S. Rampersad, A. M. Richardson, and P. S. Dhembare, "Efficacious Dendritic Cell Based Immunotherapy for Advanced Solid Tumors: Three Case Studies. Medical & Clinical Research 6 (4): 495-503," ed: ISSN: 2577-8005 Abstract, 2021.

[26] K. Lundstrom, "Self-amplifying RNA viruses as RNA vaccines," International journal of molecular sciences, vol. 21, no. 14, p. 5130, 2020.

[27] C. Ragone et al., "Identification and validation of viral antigens sharing sequence and structural homology with tumor-associated antigens (TAAs)," Journal for immunotherapy of cancer, vol. 9, no. 5, 2021.

[28] S.-C. Pao, M.-T. Chu, and S.-I. Hung, "Therapeutic Vaccines Targeting Neoantigens to Induce T-Cell Immunity against Cancers," Pharmaceutics, vol. 14, no. 4, p. 867, 2022.

[29] H. T. T. Duong et al., "Smart vaccine delivery based on microneedle arrays decorated with ultra-pH-responsive copolymers for cancer immunotherapy," Biomaterials, vol. 185, pp. 13-24, 2018.

[30] J. Retseck et al., "Long term impact of CTLA4 blockade immunotherapy on regulatory and effector immune responses in patients with melanoma," Journal of Translational Medicine, vol. 16, no. 1, pp. 1-11, 2018.

[31] Y. Wang et al., "Dendritic cell biology and its role in tumor immunotherapy," Journal of hematology & oncology, vol. 13, no. 1, pp. 1-18, 2020.

[32] M. Abd Hamid, Y. Peng, and T. Dong, "Human cancer germline antigen-specific cytotoxic T cell—what can we learn from patient," Cellular & Molecular Immunology, vol. 17, no. 7, pp. 684-692, 2020.

[33] S. Beyaert, J.-P. Machiels, and S. Schmitz, "Vaccine-based immunotherapy for head and neck cancers," Cancers, vol. 13, no. 23, p. 6041, 2021.

[34] O. J. Finn, "The dawn of vaccines for cancer prevention," Nature Reviews Immunology, vol. 18, no. 3, pp. 183-194, 2018.

[35] B. Mangla, P. Kumar, K. Goyal, K. Kohli, and S. Jindal, "Product development and scale-up challenges in cancer vaccine development," in Nanotherapeutics in Cancer Vaccination and Challenges: Elsevier, 2022, pp. 313-324.

[36] R. Watkins-Schulz et al., "A microparticle platform for STING-targeted immunotherapy enhances natural killer cell- and CD8+ T cell-mediated anti-tumor immunity," Biomaterials, vol. 205, pp. 94-105, 2019.

[37] S. Dey et al., "Peptide vaccination directed against IDO1-expressing immune cells elicits CD8+ and CD4+ T-cell-mediated antitumor immunity and enhanced anti-PD1 responses," Journal for immunotherapy of cancer, vol. 8, no. 2, 2020.

[38] J. Jou, K. J. Harrington, M.-B. Zocca, E. Ehrnrooth, and E. E. W. Cohen, "The Changing Landscape of Therapeutic Cancer Vaccines—Novel Platforms and Neoantigen IdentificationThe Changing Landscape of Therapeutic Cancer Vaccines," Clinical Cancer Research, vol. 27, no. 3, pp. 689-703, 2021.

[39] Z. Ye, Q. Qian, H. Jin, and Q. Qian, "Cancer vaccine: learning lessons from immune checkpoint inhibitors," Journal of Cancer, vol. 9, no. 2, p. 263, 2018.

[40] C. D. Funk, C. Laferrière, and A. Ardakani, "Target Product Profile Analysis of COVID-19 Vaccines in Phase III Clinical Trials and Beyond: An Early 2021 Perspective," (in eng), Viruses, vol. 13, no. 3, 03 05 2021, doi: 10.3390/v13030418.

[41] A. L. Huff, E. M. Jaffee, and N. Zaidi, "Messenger RNA vaccines for cancer immunotherapy: progress promotes promise," The Journal of Clinical Investigation, vol. 132, no. 6, 2022.

[42] M. S. Copur, "Messenger RNA Vaccines: Beckoning of a New Era in Cancer Immunotherapy," Oncology (08909091), vol. 35, no. 4, 2021.

[43] L. Lu et al., "Targeting Tumor-Associated Antigens in Hepatocellular Carcinoma for Immunotherapy: Past Pitfalls and Future Strategies," Hepatology (Baltimore, Md.), 2020.

[44] Q.-T. Wang et al., "Tumor-associated antigen-based personalized dendritic cell vaccine in solid tumor patients," Cancer Immunology, Immunotherapy, vol. 69, no. 7, pp. 1375-1387, 2020.

[45] G. Fotaki et al., "Cancer vaccine based on a combination of an infection-enhanced adenoviral vector and pro-inflammatory allogeneic DCs leads to sustained antigen-specific immune responses in three melanoma models," Oncoimmunology, vol. 7, no. 3, p. e1397250, 2018.

[46] J. G. Pol, B. W. Bridle, and B. D. Lichty, "Detection of tumor antigen-specific T-cell responses after oncolytic vaccination," in Oncolytic Viruses: Springer, 2020, pp. 191-211.

[47] T. Rezaei et al., "Strategies in DNA vaccine for melanoma cancer," Pigment Cell & Melanoma Research, vol. 34, no. 5, pp. 869-891, 2021.

[48] G. Ehx and C. Perreault, "Discovery and characterization of actionable tumor antigens," Genome Medicine, vol. 11, no. 1, pp. 1-3, 2019.

[49] M. Poorebrahim et al., "Genetically modified immune cells targeting tumor antigens," Pharmacology & therapeutics, vol. 214, p. 107603, 2020.

[50] L. Buonaguro and M. Tagliamonte, "Selecting target antigens for cancer vaccine development," Vaccines, vol. 8, no. 4, p. 615, 2020.

[51] H. S. Budi et al., "Human epidermal growth factor receptor 2 (HER2)-specific chimeric antigen receptor (CAR) for tumor immunotherapy; recent progress," Stem Cell Research & Therapy, vol. 13, no. 1, pp. 1-21, 2022.

[52] A. G. Dalgleish and W. M. Liu, "The role of immune modulation and anti-inflammatory agents in the management of prostate cancer: A case report of six patients," Oncology Letters, vol. 24, no. 2, pp. 1-4, 2022.

[53] Z. Liao et al., "Leveraging biomaterials for enhancing T cell immunotherapy," ed: Elsevier, 2022.

[54] M. O. Mohsen, D. E. Speiser, A. Knuth, and M. F. Bachmann, "Virus-like particles for vaccination against cancer," Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, vol. 12, no. 1, p. e1579, 2020.

[55] D. J. Verdon and M. R. Jenkins, "Identification and targeting of mutant peptide neoantigens in cancer immunotherapy," Cancers, vol. 13, no. 16, p. 4245, 2021.

[56] C. M. Ayres and B. M. Baker, "Peptide-dependent tuning of major histocompatibility complex motional properties and the consequences for cellular immunity," Current Opinion in Immunology, vol. 76, p. 102184, 2022.

[57] Z. Yazdani, A. Rafiei, H. Irannejad, M. Yazdani, and R. Valadan, "Designing a novel multiepitope peptide vaccine against melanoma using immunoinformatics approach," Journal of Biomolecular Structure and Dynamics, vol. 40, no. 7, pp. 3312-3324, 2022.

[58] A. Safavi, A. Kefayat, A. Abiri, E. Mahdevar, A. H. Behnia, and F. Ghahremani, "In silico analysis of transmembrane protein 31 (TMEM31) antigen to design novel multiepitope peptide and DNA cancer vaccines against melanoma," Molecular immunology, vol. 112, pp. 93-102, 2019.

[59] B. Wolfson, S. E. Franks, and J. W. Hodge, "Stay on Target: Reengaging Cancer Vaccines in Combination Immunotherapy," Vaccines, vol. 9, no. 5, p. 509, 2021.

[60] C. Nardin et al., "Naturally occurring telomerase-specific CD4 T-cell immunity in melanoma," Journal of Investigative Dermatology, vol. 142, no. 2, pp. 435-444, 2022.

[61] C. Wang, C. Xiong, Y.-C. Hsu, X. Wang, and L. Chen, "Human leukocyte antigen (HLA) and cancer immunotherapy: HLA-dependent and-independent adoptive immunotherapies," Ann. Blood, vol. 5, no. 14, pp. 10-21037, 2020.

[62] K. Davari et al., "Development of a CD8 co-receptor independent T-cell receptor specific for tumor-associated antigen MAGE-A4 for next generation T-cell-based immunotherapy," (in eng), J Immunother Cancer, vol. 9, no. 3, Mar 2021, doi: 10.1136/jitc-2020-002035.

[63] X. Yang et al., "Synthetic multiepitope neoantigen DNA vaccine for personalized cancer immunotherapy," Nanomedicine: Nanotechnology, Biology and Medicine, vol. 37, p. 102443, 2021.

[64] S. Turajlic, "Case Builds for Booster Shots for People with Cancer," J Med, vol. 381, pp. 2416-28, 2019.

[65] M. Khan, X. Li, M. Yan, Z. Li, H. Yang, and G. Liao, "Efficacy and Safety of Actively Personalized Neoantigen Vaccination in the Management of Newly Diagnosed Glioblastoma: A Systematic Review," International Journal of General Medicine, vol. 14, p. 5209, 2021.

[66] K. C. Hicks et al., "Epigenetic priming of both tumor and NK cells augments antibody-dependent cellular cytotoxicity elicited by the anti-PD-L1 antibody avelumab against multiple carcinoma cell types," Oncoimmunology, vol. 7, no. 11, p. e1466018, 2018.

[67] K. Ye et al., "An armed oncolytic virus enhances the efficacy of tumor-infiltrating lymphocyte therapy by converting tumors to artificial antigen presenting cells in situ," Molecular Therapy, 2022.

[68] E. Ylösmäki et al., "Personalized cancer vaccine platform for clinically relevant oncolytic enveloped viruses," Molecular therapy, vol. 26, no. 9, pp. 2315-2325, 2018.

[69] A. Avagliano et al., "Metabolic plasticity of melanoma cells and their crosstalk with tumor microenvironment," Frontiers in Oncology, vol. 10, p. 722, 2020.

[70] D. Blumenthal, V. Chandra, L. Avery, and J. K. Burkhardt, "Mouse T cell priming is enhanced by maturation-dependent stiffening of the dendritic cell cortex," Elife, vol. 9, 2020.

[71] C. S. Garris et al., "Successful anti-PD-1 cancer immunotherapy requires T cell-dendritic cell crosstalk involving the cytokines IFN-γ and IL-12," Immunity, vol. 49, no. 6, pp. 1148-1161, 2018.

[72] J. R. Richardson, A. Schöllhorn, C. Gouttefangeas, and J. Schuhmacher, "CD4+ T cells: multitasking cells in the duty of cancer immunotherapy," Cancers, vol. 13, no. 4, p. 596, 2021.

[73] N. R. Maimela, S. Liu, and Y. Zhang, "Fates of CD8+ T cells in tumor microenvironment," Computational and structural biotechnology journal, vol. 17, pp. 1-13, 2019.

[74] H. Jimbo, H. Nagai, S. Fujiwara, N. Shimoura, and C. Nishigori, "Fas-FasL interaction in cytotoxic T cell-mediated vitiligo: The role of lesional expression of tumor necrosis factor-α and interferon-γ in Fas-mediated melanocyte apoptosis," Experimental Dermatology, vol. 29, no. 1, pp. 61-70, 2020.

[75] C. Kumar et al., "Substantial remission of prostate adenocarcinoma with dendritic cell therapy APCEDEN® in combination with chemotherapy," Future science OA, vol. 5, no. 10, p. FSO435, 2019.

[76] M. D. Kerr, D. A. McBride, A. K. Chumber, and N. J. Shah, "Combining therapeutic vaccines with chemo-and immunotherapies in the treatment of cancer," Expert Opinion on Drug Discovery, vol. 16, no. 1, pp. 89-99, 2021.

[77] M. Nagasaka, B. Potugari, A. Nguyen, A. Sukari, A. S. Azmi, and S.-H. I. Ou, "KRAS Inhibitors–yes but what next? Direct targeting of KRAS–vaccines, adoptive T cell therapy and beyond," Cancer Treatment Reviews, vol. 101, p. 102309, 2021.

[78] A. Jiménez-Reinoso, D. Nehme-Álvarez, C. Domínguez-Alonso, and L. Álvarez-Vallina, "Synthetic TILs: engineered tumor-infiltrating lymphocytes with improved therapeutic potential," Frontiers in Oncology, vol. 10, p. 593848, 2021.

[79] A. Betof-Warner, R. J. Sullivan, and A. Sarnaik, "Adoptive Cell Transfer and Vaccines in Melanoma: The Horizon Comes Into View," American Society of Clinical Oncology Educational Book, vol. 42, pp. 1-8, 2022.

[80] J. S. Granhøj, A. Witness Præst Jensen, M. Presti, Ö. Met, I. M. Svane, and M. Donia, "Tumor-infiltrating lymphocytes for adoptive cell therapy: recent advances, challenges, and future directions," Expert Opinion on Biological Therapy, vol. 22, no. 5, pp. 627-641, 2022.

[81] M. A. Anwar, M. Shah, J. Kim, and S. Choi, "Recent clinical trends in Toll-like receptor targeting therapeutics," Medicinal research reviews, vol. 39, no. 3, pp. 1053-1090, 2019.

[82] D. Sakellariou-Thompson et al., "Potential clinical application of tumor-infiltrating lymphocyte therapy for ovarian epithelial cancer prior or post-resistance to chemotherapy," Cancer Immunology, Immunotherapy, vol. 68, no. 11, pp. 1747-1757, 2019.