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Therapeutic tumour vaccines: A review

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Abstract
As the time progressed immunotherapy has become one of the best modalities of cancer treatment, along with chemotherapy and radiation; under which comes the promising field of "therapeutic tumour vaccines". The therapeutic cancer vaccines theoretically have the potential to stimulate specific immunity against tumours while sparing normal tissues, leading not only to tumour lysis but also to the induction of a long lasting, systemic immunological memory that protects against recurrent disease and metastasis. Although the challenge of developing an effective cancer vaccine remains, several therapeutic vaccination strategies are being evaluated in clinical trials. Based on their content, the cancer vaccines may be classified into several major categories, which include cell (tumour or immune cell) vaccines, protein/peptide vaccines and genetic (DNA, RNA, and viral) vaccines. The overwhelmingly immunosuppressive tumour microenvironment that reduces the clinical efficacy of vaccines can now be modified by different approaches.

Keywords: Cancer, immunotherapy, tumour vaccine

Introduction
Cancer is one of the major reasons of mortality in most of the countries and is the second leading cause of death globally, where about one in six deaths is attributed to it. The commonly adopted procedures for cancer therapy include chemotherapy, radiotherapy and surgery. Although they have shown favourable results in some patients, the mortality rate still remains high in most cases (Akbari *et al.*, 2017) [1]. This led to the development of new strategies to that specifically target cancer cells with minimal adverse effects on normal tissues. One of the strategies was to elicit immune response against tumour cells by administering tumour specific antigens as tumour vaccines.

Tumour vaccines
A tumour vaccine is an agent used either for treatment of cancer or for prevention of cancer incidence by eliciting an immune response there by inducing a protective immunity against specific molecules (antigens) expressed on tumour cells. Cancer vaccines are sub-classified as therapeutic and prophylactic vaccines. Comparatively an effective vaccine-based immune response against tumour may be the only cancer treatment with the potential to last a lifetime. Theoretically, vaccinated patients could develop an immune response that is able to either cure tumour or keep it under constant restraint, delaying tumour recurrence and prolonging survival (Vergati *et al.*, 2010) [25].

Prophylactic tumour vaccines
About 15-25% of cancers worldwide are believed to be contributed by microbes including bacteria, viruses, and parasites. Preventive vaccines are used to block development or recurrence of cancer. There are currently two types of FDA-approved cancer preventive vaccines: Hepatitis B virus vaccines for liver cancer prevention and human papillomavirus (HPV) vaccines for cervical and other cancer prevention (Finn and Forni, 2002) [8].

HPV vaccine: This vaccine protects against the HPV. The FDA has approved HPV vaccines to prevent cervical, vaginal, vulvar cancers, anal cancer and genital warts. HPV can also cause other cancers against which the FDA has not approved the vaccine for, such as oral cancer (DeMaria and Bilusic, 2019) [7].

Hepatitis B vaccine: In 1981, the hepatitis B vaccine for liver cancer became the first FDA-approved vaccine to prevent cancer. This vaccine protects against the hepatitis B virus (HBV) which is reported to cause hepatocellular carcinoma. The anti-HBV vaccine is based on 22-nm particles containing the recombinant HBV surface antigen (HBsAg), is highly immunogenic and has shown to provide lifelong immunity (Yaddanapudi *et al.,* 2013) [29].

Therapeutic tumour vaccines

Therapeutic vaccines represent a viable option for active immunotherapy of cancers that aim to treat late stage disease by using a patient's own immune system. Unlike prophylactic vaccines that are generally administered to healthy individuals, therapeutic cancer vaccines are administered to cancer patients to treat late stage disease by using a patient's own immune system. Theoretically, a therapeutic cancer vaccine is expected to stimulate specific immunity against tumours sparing normal tissues, finally leading to tumour lysis and induction of a long lasting, systemic immunological memory systemic protection against tumour recurrence or metastatic disease (Vermaelen, 2019) [26].

The idea of therapeutic tumour vaccine emerged in 1891 when Dr. William Coley made the first attempt to use intratumoural injections of inactivated *Streptococcus pyogenes* and *Serratia marcescens* (Coley's toxin) to stimulate the immune system for improving the cancer patient's condition and had reported effective response in patients (Guo *et al.,* 2013) [10].

Spectrum of therapeutic tumour vaccine targets

The choice of antigen is the single most important component of cancer vaccine design. Tumour antigens are of two types, tumour associated antigens (TAAs) and tumour specific antigens (TSAs) (Wong *et al.,* 2016) [27]. The TAAs are proteins that are expressed even in normal host cells, but are highly expressed in tumour cells. These are the result of uncontrolled genetic amplification or variation in post-translational modifications. These mainly include oncofetal antigens and tissue differentiation antigens. Oncofetal antigens are foetal proteins that are normally silenced in adult tissues but become aberrantly re-expressed in tumours due to epigenetic alterations. Tissue differentiation antigens are normal cellular proteins overexpressed in tumour tissues. The TSAs are not commonly present in normal host cells but are specific to tumour tissue. These are the result of mutation and they include personalized antigens or neoantigens and viral antigens. Viral antigens are the antigens expressed in cancers of viral origin whereas the neoantigens are the result of somatic mutations. With the improvement in technology, more and more tumour antigens are being found (Song *et al.,* 2018) [24]. The tumour antigens must prove to be immunogenic before being exploited as cancer vaccines. Therefore, the T cell assays are used to validate the immunogenicity of identified tumour antigens.

Types of therapeutic tumour vaccines

There are various therapeutic vaccination strategies under development or being evaluated in clinical trials, even though the task of developing an effective and efficient cancer vaccine remains. Based on their format/content, they may be classified into several major categories, as cellular vaccines, dendritic cell vaccines, protein/peptide vaccines, and genetic (DNA, RNA and viral) vaccines (Hollingsworth and Jasen, 2019) [12].

Cellular vaccines (Whole tumour cell vaccines)

The entire tumour cells are isolated, modified in the laboratory and are used as whole tumour cell vaccines. The common method for cell-based immunotherapy is to use a single representative cancer cell as a universal vaccine for all patients with that type of cancer. These vaccines can be broadly classified as autologous tumour cell vaccines and allogeneic tumour cell vaccines (Guo *et al.,* 2013) [10].

Autologous tumour cell vaccines

Autologous tumour cell vaccines are prepared using patient-derived tumour cells (Hanna and Peters, 1978) [11]. These tumour cells are modified in laboratory by irradiation or genetic modification to reduce the toxic effect, then are combined with immunostimulatory adjuvants (e.g., BCG) and are administered back to the patient from whom the cells were isolated. Autologous tumour cell vaccines have been tested in various cancers including lung cancer, colorectal cancer, melanoma, renal cell cancer and prostate cancer (Guo *et al.,* 2013) [10]. One major advantage of this vaccine is its potential to present the entire spectrum of tumour-associated antigens (TAAs) to the patient's immune system. However, preparation of such vaccines requires sufficient tumour specimen, which limits its use only to certain tumour types or stages.

Allogeneic tumour cell vaccines

Unlike autologous tumour cell vaccine, the allogeneic whole tumour cell vaccines typically contain two or three established human tumour cell lines. This was developed to overcome many limitations of autologous tumour cell vaccines (Lopes *et al.,* 2019) [18]. These provide limitless sources of tumour antigens and have potential to produce large scale, standardized, and cost effective vaccine. The major drawback is that during clinical trials they have been observed to develop poor immunogenicity and some are completely ineffective (DeMaria and Bilusic, 2019) [7].

Dendritic cell vaccines

The dendritic cells (DCs) are professional antigen-presenting cells (APCs) that activate T-lymphocytes through major histocompatibility complex (MHC) signaling. Here the patient's DCs are extracted and immune cell stimulants are used to reproduce them in large amounts in the lab (Banchereau & Palucka, 2005) [3]. Then these cells are exposed to antigens from the patient's cancer cells. This combination of DCs and antigens is then injected into the patient to elicit immune response by activating the T cells (Figure 1). Sipuleucel-T an autologous DC vaccine that expresses a fusion protein of prostatic acid phosphatase (PAP) and GM-CSF in 2010 and is the only therapeutic tumour vaccine approved by FDA (PROVENGE®) for metastatic castration-resistant prostate cancer (mCRPC) (Kantoff *et al.,* 2010) [15].

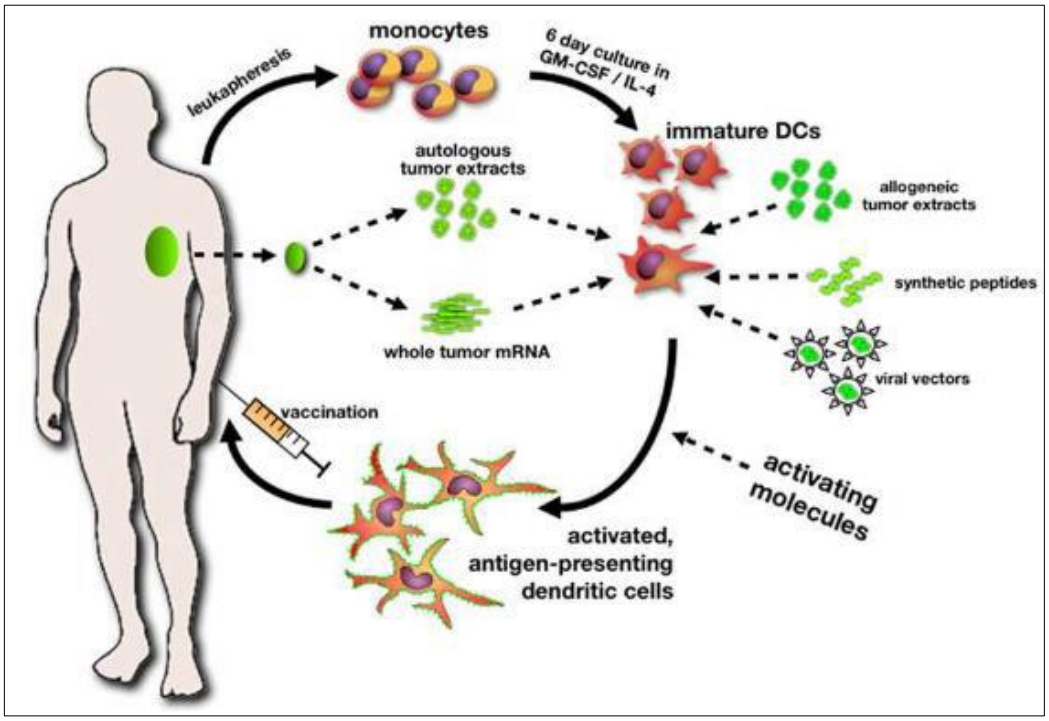

Fig 1: Production of autologous dendritic cell vaccines for cancer. Adapted from Creative Biolabs, https://www.creative-biolabs.com/vaccine/personalized-neoantigen-cancer-vaccine.htm.

Protein/peptide-based cancer vaccines

These are specific to tumour antigens and are combined with immune-stimulatory adjuvants (Buonaguro *et al.,* 2011) [4]. In this technology the vaccines are made only from TAA proteins or small fragments of TAA proteins called TAA-derived peptides, instead of being generated from the whole cell (Vergati *et al.,* 2010) [25]. These peptides contain epitopes that can be presented by MHC molecules at the cell surface and recognized by T cells as target tumour antigen there by eliciting immune response. The protein based cancer vaccines can be readily synthesized and purified at low cost, are stable and safe for usage. Their major drawback is the weak immunogenicity of a single protein/ single epitope as cancer vaccine and during clinical trials these have demonstrated to get rapidly degraded by serum/tissue peptidases (Lopes *et al.,* 2019) [18].

Genetic vaccines

Nucleic acid immunization is a promising approach in cancer therapeutic development. Here non-live, non-replicating, non-spreading DNA formulations that encode tumour antigens are injected to patients, which utilize the host's cellular machinery for expression of proteins (antigens). Such novel delivered and expressed antigens become recognized by the host immune response and induce specific T and B cell responses against the gene encoded proteins. The major advantage of genetic vaccines is the easy delivery of multiple antigens in one immunization and activation of various arms of immunity (Aurisicchio & Ciliberto, 2012) [2].

DNA vaccines are constructed of bacterial plasmids that can encode antigens to induce tumour specific host immunity. The ability to incorporate multiple genes into the vector provides opportunities to modulate intracellular routing and modification of antigens and immune outcome (Liu, 2011) [17]. In addition, DNA vaccines can be rationally combined with other immunostimulatory agents to optimize antibody responses. Despite the successful immune response of DNA vaccine achieved in animal models, the clinical trials in human are relatively ineffective when used standalone. The main trouble for DNA vaccines is their failure to induce efficient immune responses in large animals, including human bodies, which is mainly due to the poor localization into resident cells and lack of co-stimulatory molecules in local APCs (Xiang *et al.,* 2008) [28].

RNA vaccines are alternative - to DNA vaccines. Here messenger RNA (mRNA) are directly injected into the host to elicit the immune response. These are safer than DNA vaccines because of their localization in cytoplasm without any contact with nucleus (Song *et al.,* 2018) [24]. However, due to instability and short half-life of mRNA, the development of RNA vaccines falls behind that of DNA vaccines.

Viral-based vaccines are another set of genetic vaccines that use viruses as tumour antigen vehicles to stimulate an antigen-specific immune response. A good viral vector can efficiently present TAAs and stay a long term in the host with low intrinsic immunogenicity and low disease- causing potential. The first and most widely studied viral-based vectors in cancer vaccine trials are from the Poxviridae family (Guo *et al.,* 2013) [10].

Mechanism of Action of therapeutic tumour vaccines

Cancer vaccines consisting of tumour specific peptides, DNAs or RNAs when injected into the human body are captured by DCs in the tumour microenvironment or peripheral blood. On getting exposed to tumour antigens the DCs get activated and move through afferent lymph to the lymph node and present the tumour antigens or vaccine antigens to T cells (Melief *et al.,* 2015) [20]. The T cells on exposure to vaccine antigens are activated and get differentiated into effector T cells and memory T cells. Then, activated effector T cells and memory T cells migrate through the efferent lymph, thoracic duct and blood to reach tumour microenvironment and induce tumour antigen specific immune responses that lead to death of cancer cells. The memory T cells bring about long lasting systemic immunologic memory (Song *et al.,* 2018) [24].

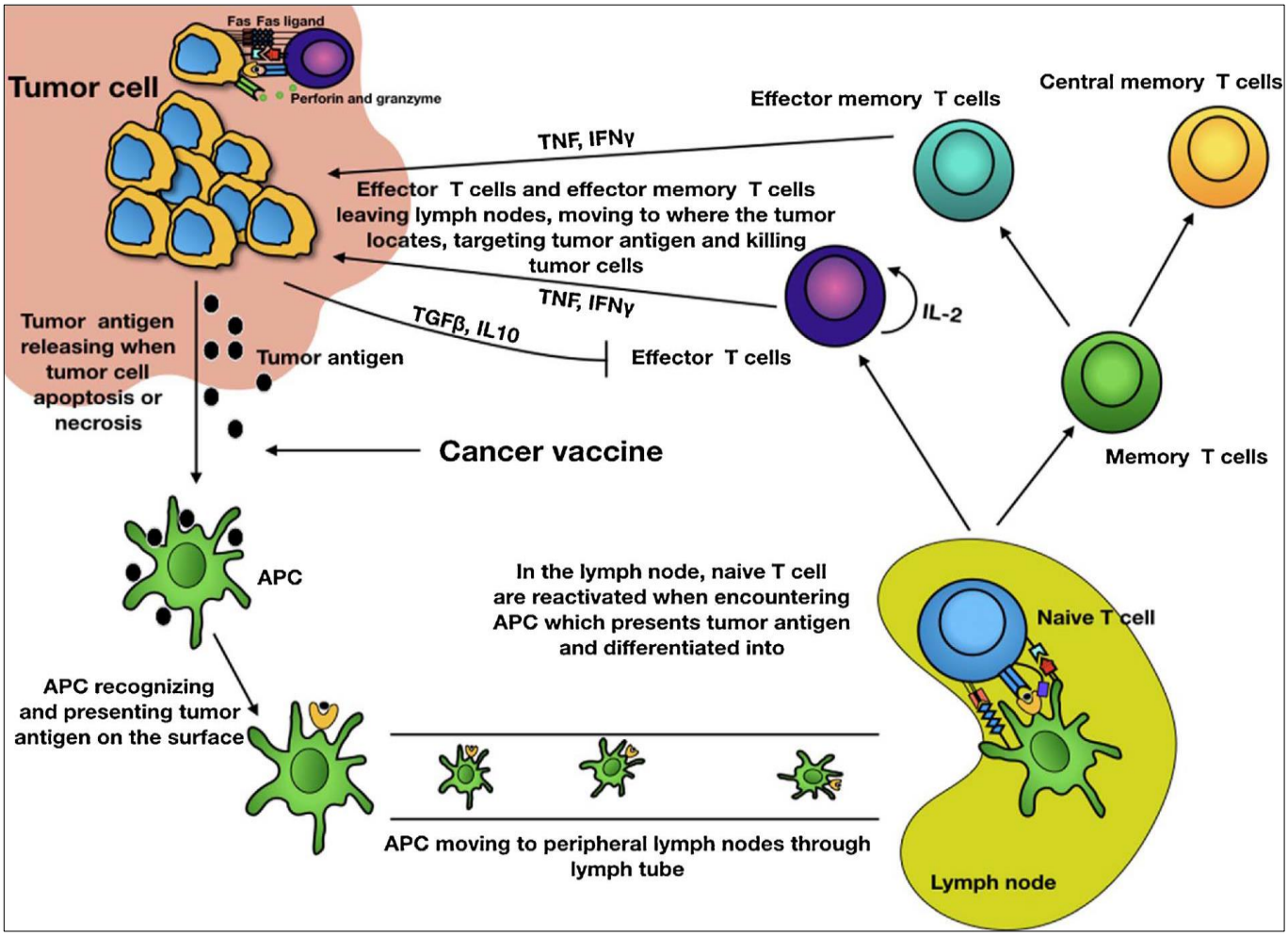

Fig 2: Mechanism of Action of therapeutic tumour vaccines. Adapted from Therapeutic cancer vaccines: From initial findings to prospects, Song, Q., Zhang, C.D. and Wu, X.H., 2018. *Immunology letters*, *196*, pp.11-21[24].

Hurdles in the development of therapeutic tumour vaccines

Although therapeutic tumour vaccines have many advantages compared to conventional methods the development of these is not that practical. Theoretically they are expected to stimulate high immune response but clinically they fail to replicate the same. The clinical studies have shown that although patients are able to produce immune responses against tumour antigens, these reactions are not significant enough to provide clinical effects. The reasons for this result are multiple. The selection of target antigen is the decisive factor of vaccine immunogenicity. In addition, the tumour microenvironment interferes with immune cell function through a variety of mechanisms (Mougel *et al.*, 2019) [21]. Therefore, the use of vaccines in combination with immunotherapy that overcomes tumour immune escape is currently a popular and effective strategy for achieving cancer treatment (Gajewski *et al.*, 2009) [9].

The tumour microenvironment contains wide range of immunosuppressive immune cell types like CD41 regulatory T cells (Tregs), myeloid derived suppressor cells (MDSCs), suppressor CD81 T cells, tumour-associated macrophages (TAMs) and regulatory natural killer (NK)/NKT. These suppressive cells and tumour cells can release a number of soluble immunosuppressive factors including TGF-β, IL-10, indoleamine-pyrrole 2,3 dioxygenase (IDO) and VEGF into the microenvironment which interferes with normal immune cell function (Yang, 2010) [30].

Recent developments in cancer vaccine platforms

Personalized vaccine strategies

With the availability of next-generation sequencing, personalized vaccine production is emerging. The sequence data from a patient's tumour biopsy are analysed to predict the possible mutations responsible for generation of tumour-specific neoantigens on the tumour cell surface in that patient. Although personalized cancer vaccines have shown encouraging results (Sahin *et al.*, 2017) [22], neoepitope prediction algorithms provide a large number of "candidates," of which only few trigger genuine anti-tumour responses.

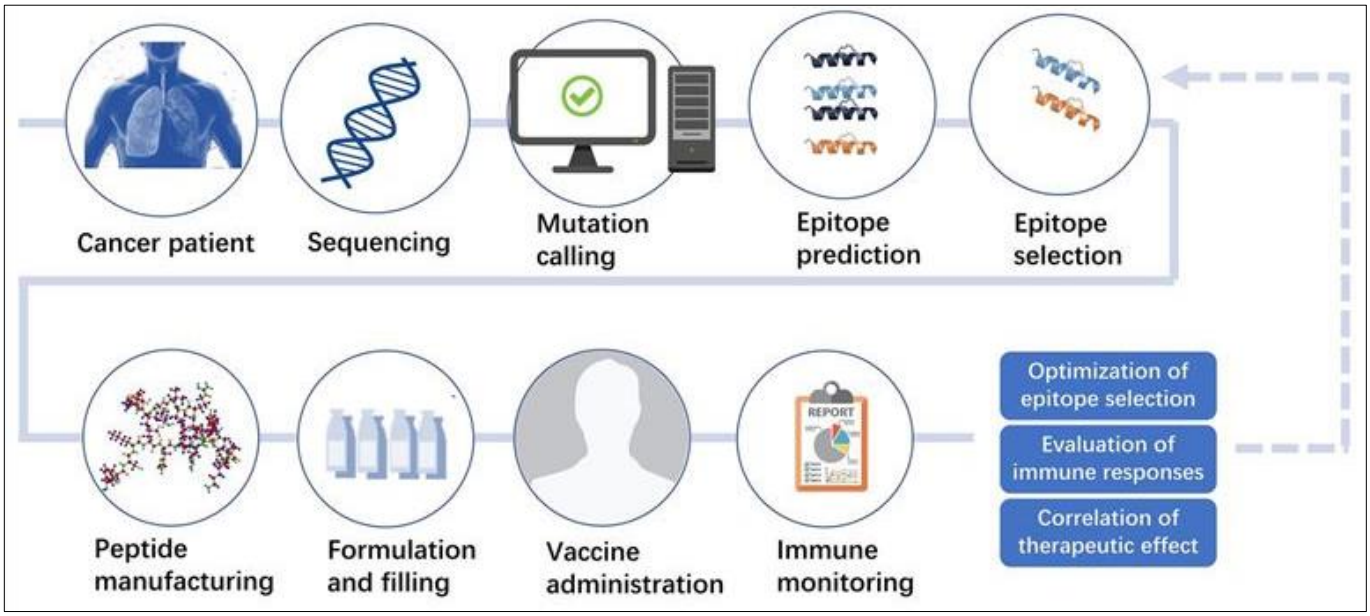

Fig 3: Workflow of the personalized neoantigen peptide vaccine. Adapted from Creative Biolabs, https://www.creative-biolabs.com/vaccine/personalized-neoantigen-cancer-vaccine.htm.

EDGE is an artificial intelligence platform used to investigate sequence data from tumour biopsies and identify tumour-specific neoantigens. ATLAS is another technology platform that uses patient's T-cell immune response machinery to identify optimal patient- and tumour specific neoantigens (Juo *et al.*, 2021) [14].

Nanoparticles as vaccine delivery systems

Nanoparticle-based cancer vaccines mainly prolong bioavailability, protect antigens from degradation and control release of antigen. Further studies are needed to address concerns of poor reproducibility with uniform size and shape, aggregation, instability and rapid clearance before widespread clinical use (Burris *et al.*, 2019) [5]. To date, only one nanoparticle vaccine, tecemotide (L-BLP25), an MUC1 antigen-specific vaccine has reached clinical trial (Butts *et al.*, 2014) [6].

Biomarker discovery for cancer vaccine

The cancer biomarkers are molecules released by a tumour or a reaction of the immune system to a tumour, which indicates the occurrence and development of cancer in the body. They play important roles in the diagnosis and prognosis of cancer. Tumour-associated biomarkers can provide guidance for the treatment of tumours, as they are related to the pathogenesis of tumours (Huang and Zhu, 2017) [13]. The patient's immune status is one major aspect in determining the disease's progression, but currently there is no single measure for assessing immunity. So, it is essential to identify the markers to predict the possible response after vaccination.

Immune combination therapies

The therapeutic tumour vaccines have failed to elicit the immune response to the expected level during the clinical trials, so the immune combination therapies have been employed (Schlom, 2012) [23]. Preclinical studies have demonstrated significant increase in the antitumour response of vaccine when combined with a wide range of immune stimulants such as IL-2, IL-15, IL-7, GM-CSF and interferon (IFN) (Mac Cheever, 2008) [19], or inhibitors of immune suppression.

Development of Tumour vaccines in India

In India, the Ministry of Science and Technology is enhancing research and development in the field of tumour vaccines to tackle the menace posed by cancer through new vaccine development for cancer prevention, nano-materials for early diagnosis, new candidate drugs and their targeted delivery as well as partnership in international research efforts. The increased expression of sperm associated antigen 9 (SPAG9) associated with various types of malignancies including cervical cancer was discovered in National Institute of Immunology (NII), New Delhi and has been a major breakthrough in cancer diagnosis. SPAG9 is a cancer antigen that could help reset the immune system and prepares it with information to target cancer cells. The DC based human clinical trials being conducted at Cancer Institute, are employing therapeutic grade SPAG9, a recombinant protein developed in NII. The vaccine developed against SPAG9 which successfully cleared the phase I clinical trials at NII, Delhi is India's first therapeutic anti-cancer vaccine to enter phase II clinical trial. The first phase took place between 2002 and 2006. In the second phase launched in 2018, the vaccine is being tested among 54 patients at Cancer Institute (WIA) at Adyar in Chennai in collaboration with NII.

Conclusion

Therapeutic cancer vaccine has gained great momentum in last decade. On comparison with conventional methods of cancer therapy, therapeutic cancer vaccines have potential safety, specificity and long-lasting response. To date, only one therapeutic tumour vaccine, Sipuleucel T, has been approved by FDA. Although such vaccines have been associated with past failures, the era of combinatorial strategies in the treatment of cancer promotes their reconsideration. A better understanding of host–tumour interactions and tumour immune escape mechanisms are required to develop effective cancer vaccines. Identification of tumour specific gene or expressed protein responsible for transformation of normal cells into tumour cells and promoting cancer progression will also discover new potential targets for vaccine therapy. Further research in the field of personalized cancer therapies using next-generation

sequencing is required. Detection of genomic and proteomic biomarkers predictive for immune response following molecular profiling of tumour and host cells, are expected to aid decision making and improve outcomes (Lee and Kulkarni, 2019) [16].

Overall, therapeutic cancer vaccines could be the future combination companion for long-term cancer treatment, with minimal toxicity and a good safety profile. The combinatorial approach of using cancer vaccine with other therapeutic methods like surgery, chemotherapy and radiotherapy has provided better clinical outcomes. In the future, research may be focused on the best combination of different personalized cancer vaccines and other therapy methods for different types of cancer patients and different disease status of the same cancer patient (Juo *et al.*, 2021) [14]. The recent success seen in several clinical trials provides motivation to overcome the challenges in the way of development of effective and efficient therapeutic tumour vaccine and provides a hope that these vaccines will soon become an important aid in cancer immunotherapy.

References

1. Akbari B, Farajnia S, Ahdi Khosroshahi S, Safari F, Yousefi M, Dariushnejad H, et al. Immunotoxins in cancer therapy: Review and update. International reviews of immunology 2017;36(4):207-19.
2. Aurisicchio L, Ciliberto G. Genetic cancer vaccines: current status and perspectives. Expert opinion on biological therapy 2012;12(8):1043-58.
3. Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. Nature Reviews Immunology 2005;5(4):296-306.
4. Buonaguro L, Petrizzo A, Tornesello ML, Buonaguro FM. Translating tumor antigens into cancer vaccines. Clinical and Vaccine Immunology 2011;18(1):23-34.
5. Burris HA, Patel MR, Cho DC, Clarke JM, Gutierrez M, Zaks TZ et al. A phase I multicenter study to assess the safety, tolerability, and immunogenicity of mRNA-4157 alone in patients with resected solid tumors and in combination with pembrolizumab in patients with unresectable solid tumors. Journal of Clinical oncology 2019;37(15):2523.
6. Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M et al. Tecemotide (L-BLP25) versus placebo after chemo radiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial. The lancet oncology 2014;15(1):59-68.
7. DeMaria PJ, Bilusic M. Cancer vaccines. Hematology/Oncology Clinics 2019;33(2):199-214.
8. Finn OJ, Forni G. Prophylactic cancer vaccines. Current opinion in immunology 2002;14(2):172-7.
9. Gajewski TF, Chesney J, Curriel TJ. Emerging strategies in regulatory T-cell immunotherapies. Clinical advances in hematology & oncology: H&O 2009;7(1):1-0.
10. Guo C, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, Wang XY. Therapeutic cancer vaccines: past, present, and future. Advances in cancer research 2013;119:421-75.
11. Hanna Jr MG, Peters LC. Specific immunotherapy of established visceral micro metastases by BCG-tumor cell vaccine alone or as an adjunct to surgery. Cancer 1978;42(6):2613-25.
12. Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. npj Vaccines 2019;4(1):1-0.
13. Huang Y, Zhu H. Protein array-based approaches for biomarker discovery in cancer. Genomics, proteomics & bioinformatics 2017;15(2):73-81.
14. Juo J, Harrington KJ, Zocca MB, Ehrnrooth E, Cohen EE. The Changing Landscape of Therapeutic Cancer Vaccines-Novel Platforms and Neoantigen Identification. Clinical Cancer Research. 2021;27(3):689-703.
15. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. New England Journal of Medicine 2010;363(5):411-22.
16. Lee EY, Kulkarni RP. Circulating biomarkers predictive of tumor response to cancer immunotherapy. Expert review of molecular diagnostics 2019;19(10):895-904.
17. Liu MA. DNA vaccines: an historical perspective and view to the future. Immunological reviews 2011;239(1):62-84.
18. Lopes A, Vandermeulen G, Préat V. Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. Journal of Experimental & Clinical Cancer Research. 2019;38(1):146.
19. Mac Cheever MA. Twelve immunotherapy drugs that could cure cancers. Immunological reviews 2008;222(1):357-68.
20. Melief CJ, van Hall T, Arens R, Ossendorp F, van der Burg SH. Therapeutic cancer vaccines. The Journal of clinical investigation 2015;125(9):3401-12.
21. Mougel A, Terme M, Tanchot C. Therapeutic cancer vaccine and combinations with antiangiogenic therapies and immune checkpoint blockade. Frontiers in immunology 2019;10:467.
22. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547(7662):222-6.
23. Schlom J. Therapeutic cancer vaccines: current status and moving forward. Journal of the National Cancer Institute 2012;104(8):599-613.
24. Song Q, Zhang CD, Wu XH. Therapeutic cancer vaccines: From initial findings to prospects. Immunology letters 2018;196:11-21.
25. Vergati M, Intrivici C, Huen NY, Schlom J, Tsang KY. Strategies for cancer vaccine development. Journal of Biomedicine and Biotechnology 2010. Available: https://pubmed.ncbi.nlm.nih.gov/20706612 [10 Feb.2021].
26. Vermaelen K. Vaccine strategies to improve anti-cancer cellular immune responses. Frontiers in immunology 2019;10:8.
27. Wong KK, Li WA, Mooney DJ, Dranoff G. Advances in therapeutic cancer vaccines. Advances in immunology 2016;130:191-249.
28. Xiang R, Luo Y, Niethammer AG, Reisfeld RA. Oral DNA vaccines target the tumor vasculature and microenvironment and suppress tumor growth and metastasis. Immunological reviews 2008;222(1):117-28.
29. Yaddanapudi K, Mitchell RA, Eaton JW. Cancer vaccines: Looking to the future. Oncoimmunology 2013;2(3):e23403.
30. Yang L. TGFβ and cancer metastasis: an inflammation link. Cancer and Metastasis Reviews 2010;29(2):263-71.