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Review

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Review

Research and Clinical Progress of Therapeutic Tumor Vaccines

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Abstract: Therapeutic cancer vaccines is a new growth point of biomedicine with broad industrial prospects in the post-COVID-19 era. Many large international pharmaceutical companies and emerging biotechnology companies are deploying different tumor therapeutic cancer vaccine projects, focusing on promoting their clinical transformation, and the vaccine industry has strong momentum for development. Such vaccines are also the core engine and pilot site for the development of new vaccine targets, new vectors, new adjuvants and new technologies, which play a key role in promoting the innovation and development of vaccines. The core technology of the mRNA novel coronavirus vaccine emerging under the new coronavirus epidemic is derived from mRNA therapeutic cancer vaccines. This review mainly systematically discusses the current research and development status and clinical research progress of various cancer treatment vaccines to reflect the development trends and challenges faced by tumor treatment vaccines.

Keywords: therapeutic tumor vaccines; clinical progress

1. Introduction

Cancer has become a major disease that seriously threatens human health and life worldwide and has always been the core focus in the field of medical research. According to the latest statistics from the International Agency for Research on Cancer (IARC), there were approximately 20 million new cancer cases worldwide in 2022, and nearly 9.7 million people died from cancer[1]. For cancer, traditional treatment methods mainly include surgery, chemotherapy and radiotherapy. Although they have improved the survival status of patients to a certain extent, their therapeutic effects still have significant limitations. Surgical methods are often difficult to cure metastatic cancers completely. While chemotherapy and radiotherapy kill tumor cells, they also severely damage normal tissues, thereby triggering many adverse reactions and having a significant impact on patients' lives. In recent years, with the continuous in-depth research on tumor immunology, immunotherapy has gradually emerged and brought new hope for tumor treatment. Such as immune checkpoint inhibitors, cell therapy and tumor vaccines, etc. have become important means of tumor immunotherapy[2-4]. Among them, tumor vaccines, as an emerging immunotherapy strategy, have been the focus of much attention in recent years. They specifically recognize and kill tumor cells by activating or enhancing the immune system of cancer patients, thereby achieving the purpose of treating tumors.

Tumor vaccines are those that deliver tumor antigens, such as lysed tumor cells, tumor-associated proteins or peptides, RNA or DNA expressing tumor antigens, into the patient's body to activate the immune response and exert anti-tumor effects[5-8]. Tumor vaccines are divided into therapeutic tumor vaccines and preventive tumor vaccines. Preventive tumor vaccines are mainly

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designed against the pathogens that cause tumors, such as the HPV vaccine for preventing cervical cancer[9, 10]. Therapeutic cancer vaccines are mainly designed for tumor antigens (tumor-associated antigens, specific antigens), stimulating the body to produce specific immune responses to kill tumors. Such vaccines have the characteristics of broad-spectrum and personalization, and have important advantages and significance. For therapeutic cancer vaccines, several marketed products have been launched, such as the BCG vaccine (TheraCys®), the dendritic cell vaccine Provenge®, the oncolytic herpesvirus vaccine (Imlygic®), and the peptide vaccine (Cimavax®), which are used to treat prostate cancer, melanoma, and renal cell carcinoma. So far, there are still many therapeutic cancer vaccines under research and development worldwide, mainly including viral vector type, bacterial vector type, cell vector type, peptide type and nucleic acid type. The main indications include prostate cancer, lung cancer, glioblastoma, melanoma, breast cancer, liver cancer, etc[7, 11-16]. With the continuous advancement of technology, tumor immunotherapy has developed rapidly and has become a research and development hotspot in the field of tumor treatment. This article will focus on systematically discussing the current research and development status of various therapeutic cancer vaccines and the updated related clinical research progress in the past five years, aiming to provide strategies and new ideas for the research and transformation of tumor therapeutic vaccines.

2. The Progress of Therapeutic Cancer Vaccines

Therapeutic cancer vaccines mainly use tumor antigens and immune adjuvants to induce specific immune responses to kill tumor cells, and anti-tumor T cells are the effector cells expected to be induced by such vaccines. Hundreds of therapeutic cancer vaccines are currently under clinical evaluation, including viral or bacterial vector vaccines, cellular vaccines, peptide vaccines and nucleic acid vaccines. Next, we will systematically discuss the research progress of different types of therapeutic tumor vaccines.

2.1. Viral and Bacterial Vectors for Therapeutic Cancer Vaccines

2.1.1. Viral Vector Tumor Vaccines

Viral vector is a tool that uses genetic engineering technology to transform viruses, and then infects cells to introduce foreign genes into cells and express genes for a long time. Instrumented viral vectors have been widely used in the field of immunotherapy due to their advantages such as high transfection efficiency, high expression level of exogenous genes, strong targeting, strong killing effect and strong immune activation ability[17]. Virus vectors mainly include lentivirus, adenoviruses and adeno-associated viruses, poxvirus，herpesvirus and oncolytic virus. Currently, there are five marketed oncolytic virus products in the world, Rigvir (Latvia), Oncorine (China), IMLYGIC (USA), Adstiladrin (USA) and DELYTACT (Japan), with indications including melanoma, head and neck squamous cell carcinoma, bladder cancer and glioma[18-22]. Next, we will systematically describe the research progress of therapeutic cancer vaccines based on viral vectors (Table 1).

Adenoviruses and Adeno-Associated Viruses

Adenovirus vectors can efficiently deliver tumor-associated antigens (TAAs) or tumor-specific neoantigens, inducing a strong T cell immune response. For example, Ad5-E1A based adenovirus vector vaccines have shown good antigen delivery in breast and ovarian cancer. Recurrent respiratory papilloma (RRP) is a stubborn neoplastic disease associated with chronic HPV6 or 11 infection, causing severe hoarseness and airway obstruction, and there is no approved therapy[23]. PRGN-2012 is a new type of gorilla adenovirus immunotherapy drug, which can enhance the specific T-cell immunity against HPV 6/11[24]. In the Phase 1 clinical trial (NCT04724980), PRGN-2012 was first used to treat severe and invasive RRP in adults and showed good clinical benefits. It was generally safe, and the complete response rate in the highest-dose group reached 50%[24].

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Adenovirus vector vaccines against cancer are a strong area of preclinical and clinical research. There are many studies on therapeutic cancer vaccines based on adenovirus vectors that have entered the clinical stage, but most of them are in the clinical phase 1-2. Adenovirus vector vaccines are mainly used for the treatment of glioblastoma (NCT05686798, NCT05914935, NCT03896568, NCT02026271, NCT02798406), Prostate Cancer (NCT02555397, NCT01931046, NCT00583024, NCT04097002, NCT00583752, NCT04374240), lung cancer (NCT06618391, NCT02879760), melanoma (NCT04217473, NCT03003676, NCT05664139, NCT05222932) and other cancers (Table 1). The adenovirus vector vaccines that have made relatively rapid progress are A and Recombinant Human Adenovirus (H101). H101 is the world's first approved virus drug and has an anti-tumor effect on liver cancer. In a phase 4 clinical trial (NCT05124002)[25], the study aimed to further verify the efficacy and safety of H101 combined with the chemotherapy drug HAIC in the treatment of intrahepatic massive cholangiocarcinoma. Previous studies have demonstrated that the progression-free survival (PFS) of HAIC in the treatment of unresectable intrahepatic cholangiocarcinoma is approximately 8 to 10 months, and the one-year progression-free rate is about 40%. The combined treatment of H101 and HAIC is expected to further enhance the therapeutic effect and increase the PFS.

Poxvirus

Poxvirus is a double-stranded DNA virus, which can replicate in cells without entering the nucleus and without the risk of gene integration, greatly improving the safety[26]. In addition, poxviruses can also insert large foreign genes (25KB), thus achieving the expression of complex eukaryotic sequences and multiple genes in mammalian cells, ensuring correct post-translational modifications[26]. Because poxviruses have strong immunogenicity and can mask the immune response to the antigens they carry when used as vaccine vectors, subsequently attenuated poxviruses with modified and deleted virulent genes have been used as vaccine vectors, such as modified vaccinia virus Ankara (MVA)[27]. In a preclinical study, the two prostate cancer-related antigens mPSCA and mSTEAP1 vaccines carried by MVA demonstrated excellent anti-tumor activity in tumor-bearing mouse models[28]. Moreover, carrying both antigens simultaneously had a stronger inhibitory effect on tumors than carrying either mPSCA or mSTEAP1, which demonstrated the advantage of poxviruses carrying multiple antigens simultaneously[28]. JX-594 (Pexa-Vec) is a vaccine based on the varicella virus. In a Phase 1 clinical trial (NCT00629759), JX-594 demonstrated significant superior complete remission and systemic efficacy for large-volume tumors compared to other similar drugs[29, 30]. Reactions at the injection site of JX-594 were observed in the tumor at all doses. However, systemic tumor responses and delivery to distant tumors through the blood require high doses[30]. In a phase 2 clinical trial (NCT00554372), researchers explored the efficacy of intratumoral injection of high-dose (10^9 PFU) and low-dose (10^8 PFU) JX-594 in patients with liver cancer[31]. The results showed that the median overall survival (OS) in the high-dose group reached 14.1 months compared with 6.7 months in the low-dose group[31]. In terms of safety, JX-594 was generally well tolerated at two doses, and no treatment-related deaths were reported[31]. There is still one study of JX-594 entering Phase 3 clinical trials. However, since the clinical benefit of JX-594 plus sorafenib in the treatment of advanced hepatocellular carcinoma (HCC) did not increase and the effect was worse compared with sorafenib alone, the interim analysis failed to reach the primary endpoint and was terminated early. The combined therapy strategy for oncolytic viruses still needs further exploration[32].

Other Virus

In addition to adenovirus vectors and poxvirus vectors, vaccines based on other viral vectors have also been applied to tumors (Table 1). In addition to adenovirus vectors and poxvirus vectors, vaccines based on other viral vectors have also been applied to tumors. For example, lentiviral vector vaccines such as Lenti-HPV-07 have been used in clinical studies to treat HPV-Associated oropharyngeal squamous cell cancer[33]. In addition, there are also some vaccines based on other

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viral vectors, such as Vvax001 (Semliki Forest Virus), HSV G207C (herpes simplex virus-1), etc., which are used in clinical studies to treat cervical intraepithelial neoplasia and brain tumors[34, 35].

Combination Therapy

For therapeutic cancer vaccines delivered by viral vectors, they are also inhibited by immunosuppressive factors (such as Treg cells and MDSCs) in the tumor microenvironment, which may weaken the therapeutic effect of the vaccine. To improve efficacy, some research has focused on developing strategies that combine viral vaccines with other therapies to address immunosuppression. In a preclinical study, adenovirus vector-delivered tumor neoantigen vaccine combined with anti-PD-1 antibodies significantly enhanced tumor immunogenic, neoantigen-specific $CD8^+$ T cell response and extended overall survival in MC38 tumor-bearing mice[36]. In addition, adenovirus vector-based tumor vaccines in combination with other therapies have been used in clinical trials to treat melanoma (NCT03003676, NCT05664139, NCT05222932)[37-39], colon cancer (NCT04166383, NCT06283134)[40, 41], glioblastoma (NCT02798406, NCT02026271)[42, 43], lung cancer (NCT06125197, NCT06618391, NCT02879760)[44-46], pancreatic cancer (NCT03281382, NCT02894944, NCT02705196)[47-49], etc. And clinical studies on combined therapy based on other viral vector vaccines are listed in Table 1.

Table 1. Clinical study of viral vector vaccines updated in recent 5 years.

Name	Cancer	ROA	Combination therapy	NCI number	Phase	Ref
Adenovirus Vector-Based Therapeutic cancer Vaccine						
Ad5-yCD/mutTKSR39rep-ADP	Glioblastoma	i.t.	/	NCT05686798	1	[50]
Recombinant L-IFN adenovirus injection (YSCH-01)	Glioblastoma	intracapsular	/	NCT05914935	1	[51]
DNX-2401	Glioblastoma	Intra-Arterial	/	NCT03896568	1	[52]
Ad-RTS-hIL-12	Glioblastoma	i.t.	Veledimex	NCT02026271	1	[43]
DNX-2401	Glioblastoma	i.t.	Anti-PD1	NCT02798406	2	[42]
Ad5PeptideTransductionDomain(PTD)(CgA-E1AmiR122)	Neuroendocrine Tumors	intrahepatic artery	/	NCT02749331	1/2	[53]
NG-641, a Tumour Selective Transgene Expressing Adenoviral Vector	Epithelial Tumours	i.v.	/	NCT04053283	1	[54]
NG-350A	Epithelial Tumor	i.v.	/	NCT03852511	1	[55]
Ad5-yCD/mutTKSR39rep-hIL12	Prostate Cancer	i.p.	/	NCT02555397	1	[56]
Ad5-SGE-REIC/Dkk3	Prostate Cancer	/	/	NCT01931046	1	[57]
Adenovirus/PSA Vaccine	Prostate Cancer	s.c.	/	NCT00583024	2	[58]
ORCA-010	Prostate Cancer	i.t.	/	NCT04097002	1/2	[59]
Adenovirus/PSA Vaccine	Prostate Cancer	s.c.	Androgen deprivation therapy	NCT00583752	2	[60]
AdNRGM	Prostate Cancer	i.t.	CB1954	NCT04374240	1	[61]
KD01	Cervical Cancer	i.t.	/	NCT06552598	1	[62]
Human Adenovirus 5 Injection (d1-d5)	Cervical Cancer	i.t.	Chemotherapy	NCT06455046	2	[63]
Adenoviral-mediated Interferon-beta (BG00001)	Pleural Malignancies	i.p.	/	NCT00299962	1	[64]
Adenovirus-hIFN-beta	Pleural Malignancies	i.p.	/	NCT00066404	1	[65]

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Ad5CMV-p53 gene	Lung Cancer	/	/	NCT00003649	1	[66]
Ad5 (CEA/MUC1/Brachyury)	Neoplasms Prostate Cancer Lung Cancer Breast Cancer Colon Cancer	s.c.	/	NCT03384316	1	[67]
Adenovirus (ColoAd1)	Colon Cancer Non-small Cell Lung Cancer Bladder Cancer Resectable Renal Cell Carcinoma	i.t./ i.v.	/	NCT02053220	1	[68]
GVAX	Sarcoma Renal Cell Carcinoma Melanoma	/	/	NCT00258687	1	[69]
Ad/PNP	Head and Neck Cancer	i.t.	/	NCT03754933	1/2	[70]
Enadenotucirev	Rectal Cancer	i.v.	Chemoradiotherap	NCT03916510	1	[71]
rAd-IFN	Pleural Mesothelioma	i.p.	Celecoxib and Gemcitabine	NCT03710876	3	[72]
SCH 721015	Mesothelioma	i.p.	Chemotherapy	NCT01119664	1	[73]
H101	Hepatocellular Carcinoma	i.t.	TACE	NCT05872841	2	[74]
H101	Hepatocellular Carcinoma	i.t.	Tislelizumab and Lenvatinib	NCT06253598	2	[75]
H101	Hepatocellular Carcinoma	hepatic arterial infusion	/	NCT06685354	2	[76]
H101	Hepatocellular Carcinoma	i.t.	Sorafenib	NCT05113290	4	[77]
HAIC of FOLFOX	Hepatocellular Carcinoma	hepatic artery	/	NCT03780049	3	[78]
SynOV1.1	Hepatocellular Carcinoma	i.t.	/	NCT04612504	1	[79]
VB-111	Colorectal Cancer	i.v.	Anti-PD-1	NCT04166383	2	[40]
BioTTT001	Colorectal Cancer	/	Anti-PD-1+ Regorafenib	NCT06283134	1	[41]
BioTTT001	Gastric Cancer	i.p.	SOX+ Anti-PD-1	NCT06283121	2	[80]
Recombinant Human Adenovirus (H101)	Cholangiocarcinoma	i.t.	FOLFOX	NCT05124002	4	[25]
Adenovirus VCN-01	Retinoblastoma	intravitreal	/	NCT03284268	Not Applicable	[81]
Ad5/3-E2F-d24-hTNFa-IRES-hIL2 (TILT-123)	Ovarian Cancer	/	Anti-PD-1	NCT05271318	1	[82]
Ad5CMV-p53 gene	Ovarian Cancer	i.p.	/	NCT00003450	1	[83]
Ad5/3-E2F-d24-hTNFa-IRES-hIL2	Melanoma	/	/	NCT04217473	1	[84]
ONCOS-102	Melanoma	i.t.	cyclophosphamide + Anti-PD-1	NCT03003676	1	[37]
Recombinant Human Adenovirus Type 5	Melanoma	/	Anti-PD-1+ Nab-paclitaxel	NCT05664139	2	[38]
Ad5/3-E2F-d24-hTNFa-IRES-hIL2	Melanoma Head and Neck Squamous Cell Carcinoma	/	Anti-PD-L1	NCT05222932	1	[39]
Recombinant human adenovirus type 5	Lung Cancer	i.t.	chemotherapy + Anti-PD-1	NCT06618391	2	[45]

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Ad-MAGEA3	Lung Cancer	i.m.	Anti-PD-1	NCT02879760	1/2	[46]
Ad5/3-E2F-d24-hTNFa-IRES-hIL2 (TILT-123)	Lung Cancer	/	Anti-PD1	NCT06125197	1	[44]
NG-641	Epithelial Tumor	i.v.	Anti-PD1	NCT05043714	1	[85]
NG-350A	Epithelial Tumours	i.v.	Anti-PD1	NCT05165433	1	[86]
NG-350A	Rectal Cancer	i.v.	Chemoradiotherapy	NCT06459869	1	[87]
Ad5-yCD/mutTKSR39rep-hIL12	Pancreatic Cancer	i.t.	chemotherap	NCT03281382	1	[47]
Ad5-yCD/mutTKSR39rep-ADP	Pancreatic cancer	/	chemotherapy	NCT02894944	1	[48]
Adenovirus serotype 5/35 encoding TMZ-CD40L and 4-1BBL (LOAd703)	Pancreatic Adenocarcinoma Ovarian Cancer Biliary Carcinoma Colorectal Cancer	i.t.	chemotherapy	NCT03225989	1/2	[88]
LOAd703	Pancreatic Adenocarcinoma Ovarian Cancer Biliary Carcinoma Colorectal Cancer	i.t.	chemotherapy or gemcitabine	NCT03225989	1/2	[88]
LOAd703	Pancreatic Cancer	i.t.	anti-PD-L1	NCT02705196	1	[49]
Theragene®,Ad5-yCD/ mutTKSR39rep-ADP	Pancreas Cancer	/	radiation	NCT04739046	2	[89]
Adenoviral p53 (Ad-p53)	Solid Tumors	i.t.	anti-PD-1/anti-PD-L1	NCT03544723	2	[90]
CAdVEC	Solid Tumors	i.t.	HER2-Specific Autologous CAR T Cells	NCT03740256	1	[91]
YSCH-01	Solid Tumors	i.t.	/	NCT05180851	1	[92]
Ad5/3-E2F-d24-hTNFa-IRES-hIL2	Solid Tumors	/	/	NCT04695327	1	[93]
AdAPT-001	Solid Tumors	i.t.	/	NCT04673942	2	[94]
Poxvirus Vector-Based Therapeutic cancer Vaccine						
PROSTVAC-V/F	Prostate Cancer	/	GM-CSF	NCT01322490	3	[95, 96]
PROSTVAC-V/F	Prostate Cancer	s.c.	Anti-PD-1	NCT02933255	1/2	[97]
TG4050	Ovarian Carcinoma	s.c.	/	NCT03839524	1	[98]
TG4050	Head and Neck Cancer	s.c.	/	NCT04183166	1/2	[99]
Other Vector-Based Therapeutic cancer Vaccine						
Lenti-HPV-07	HPV-Associated Oropharyngeal Squamous Cell Cancer, Cervical Cancer	i.m.	/	NCT06319963	1/2	[33]
Nous-209 Genetic Vaccine	Microsatellite Unstable Solid Tumors	/	Anti-PD-1	NCT04041310	1/2	[100]
Vvax001 therapeutic cancer vaccine	Cervical Intraepithelial Neoplasia	i.m.	/	NCT06015854	2	[101]
HSV G207	Recurrent Supratentorial Brain Tumors	i.t.	/	NCT02457845	1	[101]

Abbreviation: Intradermal injection (i.d.); subcutaneous injection (s.c.); intramuscular injection (i.m.); intravenous injection (i.v.). Intertumoral injection (i.t.); Intraperitoneal injection(i.p.).

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2.1.2. Bacterial Vector Tumor Vaccine

Since bacteria can naturally accumulate on tumors and regulate immune responses, it is believed that bacteria have great potential as carriers for tumor vaccines[102-105]. Redenti et al. developed a vaccine using the probiotic Escherichia coli Nissle 1917 as the tumor neoantigen vector, which significantly enhanced safety and immunogenicity, effectively activated the systemic anti-tumor immune response dominated by T cells, and killed the primary tumor and distant metastases[106]. This system utilizes the properties of living drugs to deliver tumor-specific neoantigens in the optimal environment to induce specific, effective and long-lasting systemic anti-tumor immunity, such as promoting the activation of dendritic cells, neoantigen-specific T cells and natural killer cells, as well as significantly reducing tumor-infiltrating immunosuppressive bone marrow cells and regulatory T cells and B cell populations[106]. Importantly, vaccines based on bacterial vectors have another advantage that they can be administered orally. For instance, a preclinical study found that oral administration of the modified Salmonella typhimurium VNP20009 induced a significant anti-cancer effect in B16F10 melmelanoma tumor-bearing mice. Moreover, oral administration has less toxicity and is more reversible compared to intraperitoneal administration. This study indicates that oral administration, as a new approach for bacterial application, has a high degree of safety and efficacy[107].

Nowadays, the bacteria mainly used for preparing tumor vaccines include Salmonella, Listeria, Clostridium, Bifidobacterium, etc. However, many studies are still in the preclinical stage, and few have been translated into clinical practice. ADXS11-001 is an inactivated and attenuated Listeria vector vaccine based on the HPV16 E7 antigen developed by Advaxis. In a phase 2 clinical study, ADXS11-001 demonstrated good safety and tolerability in patients with cervical cancer[108]. The median overall survival was comparable in the ADXS11-001 group (8.28 months) and the ADXS11-001+cisplatin group (8.78 months), and the progression-free survival (6.10 months vs 6.08 months) and the overall response rate (17.1% vs 14.7%) were also similar[108]. ADXS11-001 was generally well tolerated, and the severity of adverse events was mainly mild to moderate[108]. ADXS11-001 is also being used in a Phase 2 clinical study (NCT02399813) for the treatment of anorectal cancer[109]. Notably, a Phase 3 clinical trial for cervical cancer (NCT02853604) is in a terminated state (for unknown reasons)[110]. There are also some other therapeutic cancer vaccines based on bacterial vectors that have been applied in clinical trials, such as for the treatment of pancreatic cancer (NCT01417000, NCT04589234)[111, 112], breast cancer (NCT06631092)[113], and other solid tumors (Table 2).

Table 2. Clinical study of bacterial vector vaccines updated in recent 5 years.

Name	Cancer	ROA	Combination therapy	NCI number	Phase	Ref
NECVAX-NEO1	solid tumors	orally	anti-PD-1/PD-L1	NCT06631079	1/2	[114]
NECVAX-NEO1	Triple-negative Breast Cancer	orally	anti-PD-1 nab-paclitaxel chemotherapy	NCT06631092	1/2	[113]
ADXS11-001	Cervical cancer	i.v.	/	NCT01266460	2	[115]
ADXS11-001	Cervical cancer	i.v.	/	NCT02164461	1	[116]
ADXS11-001	Anal Cancer Rectal Cancer	i.v.	/	NCT02399813	2	[109]
CRS-207	Pancreatic cancer	i.v.	GVAX vaccine cyclophosphamide	NCT01417000	2	[117]
Saltikva	Pancreatic cancer	orally	/	NCT04589234	2	[112]
Clostridium Novyi-NT	Solid tumors	i.v.	/	NCT01924689	1	[118]
Clostridium Novyi-NT	Solid tumors	i.v.	anti-PD-1	NCT03435952	1	[119]
TXSVN	Multiple Myeloma	orally	/	NCT03762291	1	[120]
SGN1	Solid Tumors	i.t.	/	NCT05038150	1/2	[121]

Abbreviation: intravenous injection (i.v.); Intertumoral injection (i.t.).

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2.2. Cellular Vaccines

2.2.1. Dendritic Cell Vaccine

Dendritic cells are specialized antigen-presenting cells (APCs) that initiate effective tumor-specific immune responses by phagocytosis and processing of tumor antigens to T cells[122-125]. DC vaccine is obtained by sensitizing DC cells through tumor cell DNA, RNA, tumor cell lysate, tumor antigen protein/polypeptide and other substances, and then using the powerful presentation function of DC cells to activate the patient's T cell immune response to achieve the purpose of tumor control[126]. At present, most DC vaccine products use patients' autologous peripheral blood monocytes, which are prepared through in vitro expansion and antigen loading[127]. Dc-based vaccines have been widely selected for immunotherapy. Currently, four DC vaccine products have been approved worldwide, including Hybricell (Genoa Biotechnologia), CreaVaxPCC (CreaGene), DCVax-Brain (Northwest Biotherp), and APCEDEN (APAC Biotech), for the treatment of melanoma, prostate cancer, kidney cancer, and glioma. In addition, based on the international clinical trial register platform (http://www.clinicaltrials.gov) data showed that there are a lot of based on DC vaccine clinical trials for the treatment of cancer, partial results show good application prospect. Clinical progress of DC vaccine except for one Phase 3 clinical study (NCT00045968)[128], most of the rest are phase 1-2 clinical studies (Table 3). DC's vaccines are mainly used in clinical trials to treat liver cancer, lung cancer (NCT02688673, NCT05195619)[129, 130], breast cancer (NCT02063724, NCT02061423, NCT06435351, NCT04879888, NCT04105582)[131-135], melanoma (NCT01622933, NCT02301611, NCT01808820, NCT02678741, NCT01876212)[136-140], hematological malignancies (NCT02528682)[141] , ovarian carcinoma (NCT05714306)[142], lung cancer (NCT02956551, NCT04147078, NCT03871205, NCT03371485)[143-146], glioblastoma (NCT03914768, NCT02771301, NCT04888611, NCT02529072, NCT02366728)[147-151], gastric cancer (NCT04567069, NCT04147078)[144, 152], hepatocellular carcinoma (NCT04147078)[144], colorectal cancer (NCT04147078, NCT06545630, NCT03730948, NCT01885702)[144, 153-155], and so on.

However, the clinical efficacy of DC vaccines is very limited, and recently efforts have been made to develop new strategies to enhance the efficacy of DC vaccines. DC vaccine is developing towards individuation and precision, combination with other therapies and integration with new technologies. In personalized and precise treatment, tumor specific neoantigens with high immunogenicity can be predicted and screened according to the genetic information of patients' tumor tissues, so as to customize DC vaccines that are more in line with patients' own characteristics, improve efficacy and reduce side effects. In 2015, the first personalized neoantigen DC vaccine was tested in phase 1 clinical trials (NCT00683670)[156]. They selected seven neoantigens from melanoma patients, loaded them into DC isolated from PBMC, and injected them intravenously three times to enhance the T-cell immune response. All three patients treated survived, and no adverse reactions were observed, demonstrating the safety and feasibility of personalized neoantigen DC vaccine. Another personalized neoantigen DC vaccine trial was conducted in patients with advanced non-small cell lung cancer (NCT02956551)[157]. Similarly loading patients' personalized neoantigens into DC isolated from the PBMC showed an overall 25% objective response rate and 75% disease control rate, with only mild and transient side effects observed. In addition, there are several other neoantigen DC vaccines for the treatment of ovarian cancer[158], breast cancer (NCT04879888, NCT04105582)[134, 135], lung cancer (NCT04078269, NCT02956551, NCT03871205, NCT03205930)[143, 145, 159, 160], liver cancer (NCT03674073)[161], and so on. As technology continues to advance, DC vaccines will focus more on individualized and precise strategies. With the deepening of research on the combined application of DC vaccine with immune checkpoint inhibitors, chemotherapy and radiotherapy. Combination therapy will become the main trend of DC vaccine development. For example, a trial showed that the pp65 pulse DC vaccine combined with the chemotherapy drug temozolomide for glioma significantly extended overall survival (41.1 months)[162]. In another trial, an autologous EPHA2-targeted CAR-DC vaccine loaded with TP53 mutant peptide (TP53-EPHA-2-CAR-DC) combined with anti-PD-1 antibody/anti-CTLA4 antibody

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is used in patients with locally advanced/metastatic solid tumors or relapsed/refractory lymphoma (NCT05631886)[163]. DC vaccine combined with immune checkpoint inhibitors can enhance the immune response of T cells. When combined with chemotherapy, more tumor antigens are released by the killing effect of chemotherapy drugs on tumor cells, and DC vaccine can reactivate immune cells and improve the clearance effect of tumor cells. Based on the advantages of combination therapy, the synergies of DC vaccine and more therapies will continue to be explored and optimized to form better treatment options to overcome the limitations of tumor efficacy. In addition, with the development of nanotechnology, gene editing technology, cell engineering technology, etc., DC vaccines are also deeply integrated into these new technologies. For example, Mao et al. successfully delivered Cas9 mRNA and sgRNA to DC cells using lipid nanoparticles, achieving effective gene editing on DC cells[164]. By gene editing, the PD-L1 of DC cells was effectively knocked out, the activation and maturation of DC cells were enhanced, and the anti-tumor immune response mediated by T cells was improved, which significantly inhibited the growth of colon cancer in the tumor-bearing mouse model[164]. Another study showed that DC vaccines loaded with CircRNA encoding tumor antigens (FAPα and survivin) induced a stronger $CD8^+$ T cell response[165]. Moreover, its combination with gemcitabine significantly inhibited Panc02 tumor growth (89% inhibition rate) and extended survival in mice[165]. More efficient antigen delivery vector based on nanotechnology was developed to improve the efficiency of antigen uptake and presentation by DC cells. And DC cells were modified by gene editing technology to enhance their immune activation ability.

Although DC vaccines show great potential in cancer immunotherapy, there are still challenges in preparation techniques, individual differences, off-target effects, delivery efficiency, and immunosuppressive microenvironments. However, with the advancement of technology, the continuous development of new cell separation and preparation technology, gene editing technology, efficient delivery system, etc., will make DC vaccine is expected to become an important breakthrough in cancer immunotherapy.

Table 3. Clinical study of DC-based vaccines updated in recent 5 years.

Name	Cancer	ROA	Combination therapy	NCI number	Phase	Ref
Autologous Dendritic Cells Pulsed With Tumor Lysate Antigen	Glioblastoma	i.d.	/	NCT00045968	3	[128]
Autologous AdHER2 transduced dendritic cell vaccine	Breast Cancer	i.d.	/	NCT01730118	1	[166]
Placental or tumor-derived heat shock protein gp96 induced DCs	Solid Tumors	s.c. i.t.	/	NCT06477614	1	[167]
Autologous EphA2-targeting CAR-DC vaccine loaded with KRAS mutant peptide	Solid Tumors	i.v.	Abraxane Cyclophosphamide Anti-PD-1 Anti-CTLA4	NCT05631899	1	[168]
Autologous EphA2-targeting CAR-DC vaccine loaded with TP53 mutant peptide	Solid Tumors, Lymphomas	i.v.	Abraxane Cyclophosphamide Anti-PD-1 Anti-CTLA4	NCT05631886	1	[163]
Immune-modified DC	Multiple Myeloma, Plasmacytoma	/	/	NCT06435910	1	[169]
Tumor antigen-pulsed DC	Esophageal Squamous Cell Carcinoma	s.c.	/	NCT05317325	1	[170]
DC loaded with autologous tumor homogenate	Glioblastoma	i.d.	Temozolomide	NCT04523688	2	[171]
Autologous genetic-modification-free DC cells will be loaded with multiple tumor neoantigen peptides	Glioblastoma	s.c.	/	NCT06253234	1	[172]

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Tumor antigen-sensitized DC	Melanoma Bladder Cancer Colorectal Cancer	s.c.	/	NCT05235607	1	[173]
Tumor neoantigen peptide vaccine/neoantigen-based DC	Advanced Malignant Solid Tumors	s.c.	/	NCT05749627	Not Applicable	[174]
Autologous DC loaded with patient-specific peptides or tumor lysates	Ovarian Carcinoma	/	cyclophosphamide	NCT05714306	1/2	[175]
Dendritic-cell with tumor-associated antigen and patient specific neoantigens	Ovarian Cancer	/	/	NCT05270720	1	[176]
Tumor Antigen-sensitized DC Vaccine	Colorectal Cancer	s.c.	/	NCT06545630	1	[153]
DC vaccines loaded with HPV 16/18 E6/E7 epitopes	Cervical Intraepithelial Neoplasia	/	/	NCT03870113	1	[177]
Anti-HER2/HER3 Dendritic Cell Vaccine	Breast Cancer	i.d.	Anti-PD-1	NCT04348747	2	[178]
Autologous dendritic cell-adenovirus p53 vaccine	Breast Cancer	s.c.	/	NCT00082641	1/2	[179]
Total tumor RNA-pulsed DCs	Medulloblastoma	i.d.	Td vaccine autologous HSCs Anti-PD-1	NCT06514898	1	[180]
Immune-modified dendritic cells fused with leukemic cells (DCvac)	B-Cell Acute Lymphoblastic Leukemia	/	/	NCT05262673	1	[181]
Autologous dendritic cell	Prostate Cancer	s.c.	/	NCT05533203	1	[182]
Immune modified dendritic cell vaccine (DCvac)	T-Cell Acute Lymphoblastic Leukemia	/	/	NCT05277753	1	[183]
Peptide pulsed autologous Dendritic cell	breast cancer	i.d.	/	NCT06195618	1	[184]
HER2-Pulsed Dendritic Cell Vaccine	HER2-positive Breast Cancer	i.d.	Anti-her2 Anti-PD-1 T-Cell therapy	NCT05378464	1	[185]
Dendritic Cell Vaccine Loaded With Circular RNA Encoding Cryptic Peptide	HER2-negative Advanced Breast Cancer	i.d.	Anti-PD-1	NCT06530082	1	[186]
MIDRIX4-LUNG autologous DC vaccine	Non-small Cell Lung Cancer	i.v.	Antigen-specific DTH	NCT04082182	1	[187]
Autologous Dendritic cell (ADC) vaccine	Small Cell Lung Cancer	i.d.	Carboplatin ADC Vaccine	NCT04487756	1/2	[188]
TTRNA-DC vaccines with GM-CSF	Medulloblastoma	i.d.	Td vaccine autologous HSCs Anti-PD-1	NCT06514898	1	[180]
Tumor lysate loaded autologous DC vaccine	Colorectal Cancer	i.d.	/	NCT06522919	2	[189]
Autologous Dendritic Cell Vaccine Loaded with Personalized Peptides (PEP)	Pancreatic Adenocarcinoma	s.c.	/	NCT04627246	1	[190]
HER-2 pulsed DC1	HER2-positive Breast Cancer	/	Anti-HER2 Anti-PD-1 Paclitaxel	NCT05325632	2	[191]
allogeneic dendritic cell vaccine (DCP-001)	Ovarian Cancer	/	/	NCT04739527	1	[192]
Autologous DC loaded with autologous tumor homogenate	Mesothelioma	i.d.	Anti-PD-1 Interleukin-2	NCT03546426	1	[193]
HER2 Targeting Autologous Dendritic Cell (AdHER2DC) Vaccine	Endometrial Cancer	i.d.	Anti-PD-1 N-803 Lenvatinib	NCT06253494	1/2	[194]
Autologous dendritic cell (DC) vaccine	Liver Cancer	i.m.	Anti-PD-L1 Anti-VEGF RT	NCT03942328	1/2	[195]

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			Pneumococcal vaccine			
Multiple Signals loaded Dendritic Cells Vaccine	Hepatocellular Carcinoma	i.v.	Cyclophosphamide	NCT04317248	2	[196]
Autologous DCs pulsed with mutated peptides	Colorectal Cancer	i.v.	/	NCT03730948	1	[154]
Autologous Tumor Blood Vessel Antigen (TBVA)-Dendritic Cell Vaccine	Kidney Cancer	i.d.	Cabozantinib	NCT05127824	2	[197]
Autologous DCs pulsed with genetically modified tumor cells or tumor-related antigens including neoantigens	Glioblastoma	i.d.	/	NCT03914768	1	[147]
CCL21	non-small cell lung cancer	i.m.	Anti-PD-1	NCT03546361	1	[198]
HER2-sensitized DC	Breast Cancer	i.d.	/	NCT03630809	2	[199]
DC/multiple myeloma (MM) Fusion vaccine	Multiple Myeloma	/	Anti-PD-1	NCT03782064	2	[200]
PDC*lung01	Non Small Cell Lung Cancer	s.c. i.v.	Anti-PD-1 Antifolate agents	NCT03970746	1/2	[201]
MG-7 Antigen	Gastric Cancer	s.c.	Anti-PD-1	NCT04567069	1/2	[152]
Autologous tumor lysate pulsed dendritic cell vaccination	Glioblastoma	i.d.	Anti-PD-1 Poly ICLC	NCT04201873	1	[202]
Tumor Antigen-sensitized DC Vaccine	Esophagus Cancer	s.c.	/	NCT05023928	1	[203]
DC loaded with tri-antigens (WT1/TERT/survivin)	Acute Myeloid Leukemia	/	/	NCT05000801	Not applicable	[204]
DCs pulsed with GSC antigens (GSC-DCV)	Recurrent Glioblastoma	s.c.	Anti-PD-1	NCT04888611	2	[205]
DC vaccine loaded with personalized peptides	Non-small Cell Lung Cancer	s.c.	cyclophosphamide	NCT05195619	1	[130]
Neoantigen-loaded DC	Lung Cancer	s.c.	/	NCT06329908	1	[206]
Autologous DCs loaded with multiple tumor neoantigen peptides	Glioblastoma Multiforme of Brain	i.d	Temozolomide	NCT04968366	1	[207]
Neoantigen	Hepatocellular Carcinoma, Colorectal Cancer	i.d.	Anti-PD-1	NCT04912765	2	[208]
Neoantigen Derived Dendritic Cell	Refractory Tumor	s.c.	Anti-PD-1 Lenvatinib	NCT05767684	1	[209]
Neoantigen-primed DC	Gastric Cancer, Hepatocellular Carcinoma, Non Small Cell Lung Cancer, Colon Rectal Cancer	s.c.	/	NCT04147078	1	[144]
Neoantigen-loaded DC	Non-Small Cell Lung	s.c.	/	NCT03871205	1	[145]
Neoantigen Dendritic Cell	Breast Cancer	inguinal or axillary	Leukapheresis	NCT06435351	1	[133]
Tumor Neoantigen Based Vaccine FRAME-001	Non Small Cell Lung Cancer	s.c.	/	NCT04998474	2	[210]
Neo-antigen pulsed Dendritic cell	Breast Cancer	/	/	NCT04105582	1	[135]
Autologous Neoantigen-targeted Dendritic Cell	Non small Cell Lung Cancer	i.v.	Antigen-specific DTH	NCT04078269	1	[159]
Peptide pulsed Dendritic cell	Breast Cancer	i.d.	/	NCT04879888	1	[134]
Neo-antigen pulsed Dendritic cell	Breast Cancer	/	/	NCT04105582	1	[135]
Personalized DC Vaccine	Gastric Cancer Hepatocellular Carcinoma	s.c.	/	NCT04147078	1	[144]

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	Non Small Cell Lung Cancer Colon Rectal Cancer					
Neoantigen-loaded DC vaccine	Colorectal Cancer	/	/	NCT01885702	1/2	[155]

Abbreviation: Intradermal injection (i.d.); subcutaneous injection (s.c.); intramuscular injection (i.m.); intravenous injection (i.v.); Intertumoral injection (i.t.).

2.2.2. Tumor Cell Vaccine

Based on the characteristics of tumor cells carrying all tumor antigen information, the use of tumor cells as vaccines can provide adequate antigen information to the patient's immune system, eliminating the need to identify the optimal antigen in a specific type of cancer, overcoming the problem of tumor antigen loss, and thus helping to better activate the anti-tumor immune response[211]. The types of tumor cell-based vaccines mainly include autologous tumor cell vaccine and allogeneic tumor cell vaccine.

Autologous Tumor Cell Vaccine

Autologous tumor cell vaccines belong to the category of personalized tumor therapeutic vaccines, which are mainly tumor cells obtained from patients, and the tumorigenic ability of tumor cells is removed by irradiation while retaining their immune activity. The treated tumor cells contain tumor-associated antigens, which can activate the patient's own immune system after being transfused into the patient, prompting the body to produce a specific immune response against tumor cells, and achieve the purpose of tumor treatment. It is worth noting that vaccines prepared by directly inactivating tumor cells have poor immunogenicity and very limited efficacy. To address the problem, current strategies are to genetically modify tumor cells and combine them with adjuvants or other therapies to improve the anti-tumor efficacy of vaccines. For example, Chang et al. developed a tumor cell vaccine that overexpresses mesothelin (a new tumor antigen for ovarian cancer), which in combination with IL-12 significantly increased the proportion of mesothelin-specific T cells and prolonged mouse survival[212]. Currently, more research is on autologous tumor cell vaccine expressing GM-CSF (GVAX). In a variety of mouse tumor models, GVAX has been shown to promote the antigen presentation and activation of DC, and has good curative effect[213-215]. GVAX have been used in clinical trials for the treatment of pancreatic cancer (NCT02243371, NCT03153410, NCT00389610)[216-218], prostate cancer (NCT00140374)[219], and other tumors (Table 4). In addition, GVAX has also been selected for use in combination with other therapies to improve efficacy in clinical trials. For example, combination with nivolumab and ipilimumab for Neuroblastoma (NCT04239040)[220], combination with Cyclophosphamide for Pancreatic Cancer (NCT01417000)[111], and combination with Pembrolizumab for Colorectal Cancer (NCT02981524)[221], and so on (Table 4). In Table 2, we systematically list the updated clinical studies of autologous tumor cell-based vaccines in the past five years.

Allogeneic Tumor Cell Vaccines

Allogeneic whole tumor cell vaccines usually contain two or three established human tumor cell lines to overcome the limitations of antigen source, molecular expression, and standardization of production and preparation of autologous tumor cell vaccines[222]. For allogeneic tumor cell vaccines, batch preparation of tumor cell lines or allogeneic cells can be achieved, and their cost is much lower than that of individualized vaccines. Moreover, allogeneic tumor cell vaccines usually carry multiple tumor-associated antigens, increasing the probability of covering more patients. For tumors with low immunogenicity, the immunogenicity of vaccines can be enhanced through genetic modification to demonstrate better therapeutic effects. Like VACCIMEL, a therapeutic cancer vaccine approved in Argentina composed of four allogeneic melanoma cell lines, effectively induces T-cell immune responses against neoantigens, allogeneic antigens and tumor-associated antigens[223]. In a Phase 2 clinical study (NCT01729663), VACCIMEL demonstrated significant benefits in distant

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metastasis-free survival (DMFS) in patients with cutaneous melanoma receiving adjuvant therapy[224, 225]. VACCIMEL combined with Bacillus Calmette-Guerin (BCG) and recombinant human granulocyte macrophage-colony stimulating factor (rhGM-CSF) adjuvants induced a strong specific immune response to TAA in patients and significantly enhanced the therapeutic effect of the vaccine[224-227]. Few allogeneic tumor cell therapeutic cancer vaccines have entered clinical research and are basically in the 1-2 stage, mainly used for the treatment of glioblastoma (NCT03360708, NCT04642937, NCT06305910, NCT04388033)[228-231].

Table 4. Clinical study of tumor cells-based vaccines updated in recent 5 years.

Target	Cancer	ROA	Combination therapy	NCI number	Phase	Ref
Autologous tumor cellular vaccine						
GM-CSF Secreting Autologous Neuroblastoma Cell Vaccine (GVAX)	Neuroblastoma	/	Anti-PD-1 Anti-CTL4	NCT04239040	1	[220]
GVAX Pancreas Vaccine	pancreatic cancer	i.d.	Anti-PD-1 CRS-207	NCT02243371	2	[216]
GVAX Pancreas Vaccine	Pancreatic Cancer	i.d.	Anti-PD-1 IMC-CS4	NCT03153410	1	[217]
GVAX pancreas vaccine	Pancreatic Cancer	i.d.	/	NCT00389610	2	[218]
GVAX Pancreas Vaccine	Pancreatic Cancer	/	Anti-PD-1	NCT03161379	2	[232]
GVAX Pancreas Vaccine	Pancreatic Cancer	/	Anti-PD-1 Anti-CTL4	NCT03190265	2	[233]
GVAX Pancreas Vaccine	Pancreatic Cancer	i.d.	Cyclophosphamide FOLFIRINOX	NCT01595321	2	[234]
GVAX Pancreatic Cancer Vaccine	Pancreatic Cancer	/	Cyclophosphamide Anti-PD-1	NCT02648282	2	[235]
GM-CSF Secreting Autologous Leukemia Cell Vaccination (GVAX)	Myelodysplastic Syndrome Acute Myeloid Leukemia Chronic Myelomonocytic Leukemia	i.d.	Chemotherapy	NCT01773395	2	[236]
GM-CSF Secreting Leukemia Cell Vaccinations	Myeloid Leukemia	s.c. or i.d.	/	NCT00426205	Not Applicable	[237]
Allogeneic Myeloma GM-CSF Vaccine	Multiple Myeloma	i.d.	Lenalidomide Pneumococcal vaccine	NCT03376477	2	[238]
GVAX Colon Vaccine	Colorectal Cancer	i.d.	Anti-PD-1 CY	NCT02981524	2	[221]

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Allogeneic Colon Cancer Cell Vaccine (GVAX)	Colorectal Cancer	i.d.	CY SGI-110	NCT01966289	1	[239]
Colon GVAX	Colorectal Cancer	/	CY	NCT00656123	1	[240]
Particle-delivered, allogeneic tumor cell lysate vaccine (PalloV-CC)	Colon Cancer	i.d.	/	NCT03827967	1	
GVAX prostate cancer vaccine	Prostate Cancer	i.d.	CY	NCT01696877	1/2	[241]
Autologous tumor cellular vaccine	Prostate Cancer	i.d.		NCT06636682	2	
GVAX	Melanoma Sarcoma/Renal Cell Carcinoma	/	/	NCT00258687	1	[69]
Personalized NeoAntigen Cancer Vaccine	Kidney Cancer	s.c.		NCT02950766	1	
Autologous Breast Cancer Cells Engineered to Secrete GM-CSF	Breast Cancer	/	/	NCT00317603	1	[242]
Autologous Breast Cancer Cells Engineered to Secrete GM-CSF	Breast Cancer	/	/	NCT00880464	1	[243]
GRT-C901,GRT-R902	Non Small Cell Lung Cancer Colorectal Cancer Gastroesophageal Adenocarcinoma Urothelial Carcinoma	/	Anti-PD-1 Anti-CTL4	NCT03639714	1/2	[244]
GRT-C901,GRT-R902	Non Small Cell Lung Cancer Colorectal Cancer Gastroesophageal Adenocarcinoma Urothelial Carcinoma	/	Anti-PD-1 Anti-CTL4	NCT03639714	1/2	[244]
OVM-200	Prostate cancer lung cancer ovarian cancer	/	/	NCT05104515	1	[245]
Allogeneic tumor cell vaccine						
Therapeutic Vaccine (ACIT-1)	pancreatic cancer other cancer	/	/	NCT03096093	1/2	[246]

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Malignant Glioma Tumor Lysate-Pulsed	Glioblastoma	s.c.	Autologous Dendritic Cell	NCT03360708	1	[228]
Allogeneic Tumor Lysate Vaccine(GBM6-AD)	Glioblastoma	/	CD200AR-L imiquimod	NCT04642937	1	[229]
Allogeneic Tumor Lysate Vaccine(GBM6-AD)	Glioblastoma	/	CD200AR-L imiquimod	NCT06305910	1	[230]
DC/tumor cell fusion vaccine	Glioblastoma	/	Anti-CTL4	NCT04388033	1/2	[231]
Therapeutic Vaccine (ACIT-1)	pancreatic cancer other cancer	/	/	NCT03096093	1/2	[246]

Abbreviation: Intradermal injection (i.d.); subcutaneous injection (s.c.);.

2.3. Peptide Vaccines

Peptide tumor vaccine uses synthetic peptide fragments as antigens to stimulate the body to produce anti-tumor immune response. Peptide vaccines have been paid more and more attention because they are completely synthetic, with high safety (no complete pathogen), high specificity, flexible design and low cost[126]. Currently, three peptide vaccines are marketed worldwide, vitespen, EGF-P64K and racotumomab, for the treatment of glioma, renal cell carcinoma, cervical cancer and non-small cell lung cancer. Furthermore, many peptide tumor vaccines are in the clinical trial stage. We summarize the clinical research progress of the updated peptide tumor vaccines in the past five years in Table 5.

Traditional peptide tumor vaccine has some defects, such as poor immunogenicity, low efficacy and short half-life, which affect its therapeutic effect in clinical application. To address the very limited efficacy of peptide tumor vaccines, many studies have focused on screening highly specific neoantigen peptides, optimizing immune-stimulating adjuvants, developing more effective delivery systems and exploring combination therapy strategies to enhance immune response and tumor suppression.

Personalized neoantigen vaccines have been regarded as an effective method for inducing, enhancing and diversifying anti-tumor T-cell responses[247]. For example, a personalized neoantigen polypeptide vaccine demonstrated clinical feasibility, safety, and immunogenicity for the first time in a Phase I clinical trial in melanoma patients[248]. The vaccine can target up to 20 predicted individual tumor neoantigens, increasing the number of antigen-specific T cells, such as induced $CD4^+$ and $CD8^+$ T cells targeting 58 (60%) and 15 (16%) of 97 unique neoantigens, respectively[248]. It is well known that there is still no better treatment method for patients with glioblastoma. After standard treatment, there are often problems of recurrence, poor treatment effect and limited survival period. In a study, through somatic mutation analysis of the tumors of 173 glioblastoma patients, personalized peptide vaccines targeting tumor-specific neoantigens were produced[249]. Among the blood samples of 97 (90%) monitored patients, vaccine-induced immune responses to at least one vaccination peptide were detected in 87 cases[249]. Most patients developed persistent specific T-cell responses, and the survival period (53 months) of patients with multiple vaccine-induced T-cell responses was significantly longer than that of patients with no or low induced responses (27 months)[249]. This study demonstrated the feasibility of individualized neoantigen-targeted peptide vaccines, which provides promising potential treatment options for the treatment of glioblastoma patients[249]. With advances in high-throughput sequencing technology, genomics, synthesis technology and data science, rapid screening, optimization and preparation of personalized antigens can be achieved. Based on the optimization of tumor neoantigen personalized vaccine design strategy, many related types of vaccines have been used in clinical trials to treat melanoma (NCT05098210, NCT01970358, NCT03929029), lung cancer (NCT04397926, NCT02897765, NCT04487093, NCT03380871), and other cancers (Table 5).

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GM-CSF is a powerful immune adjuvant that can increase the maturation and function of dendritic cells, thereby enhancing antigen presentation[250]. In a preclinical study, local injection of GM-CSF, IL-2, and HPV16 E7 peptide enhanced vaccine-specific immune responses and induced higher CTL and cytokine release without increasing immunosuppressive Treg cells, more effectively inhibiting the growth of TC-1 tumor cells[251]. In a clinical study (Phase 2, NCT02636582), a peptide vaccine composed of HER2-derived MHC Class I peptide E75 (nelipepimut-S, NPS) combined with GM-CSF adjuvant in the treatment of patients with ductal carcinoma in situ (DCIS) showed good vaccine tolerance and relatively good safety[252]. Moreover, vaccination enhances the NPS-specific cytotoxic T lymphocyte (CTL) response, and the increase in the proportion of specific T cells produced in the NPS+GM-CSF group exceeds that in the NPS alone treatment group[252]. Cytosine-guanosine oligodeoxynucleotide (CpG) also is a strong adjuvant that promotes the production of pro-inflammatory cytokines, stimulates DC and B cell activation, and induces and enhances Th1 type immune response[253-260]. In a study, all 8 melanoma patients with HLA-A2$^+$ showed rapid and intense antigen-specific T-cell responses after receiving treatment with a low-dose CpG 7909 combined with melanoma antigen A analogue peptide and incomplete Freund's adjuvant vaccine[261]. The number of antigen-specific T cells produced by patients in the CPG treatment group was significantly higher than that in the CpG treatment group[261]. The mechanism is achieved by the increased T cells recognizing and killing melanoma cells in an antigen-specific manner[261]. Other different antigen-peptide vaccines combined with adjuvants have also been used in clinical trials to treat melanoma (NCT00471471, NCT00112242, NCT00112229, NCT05098210)[261-266], breast cancer (NCT02593227, NCT05232916, NCT03012100, NCT05098210)[266-269], lung cancer (NCT02818426, NCT03380871, NCT01949701, NCT06472245)[270-273], glioma (NCT02193347)[274], pancreatic cancer (NCT03645148, NCT05013216)[268, 275], and other cancers (Table 5).

Although neoantigen peptide vaccines have great potential in tumor immunotherapy, their progress in clinical trials has been hindered due to the limitations of antigen cell uptake and cross-presentation. Based on the development of delivery technology, nanovaccines co-delivered with neoantigens and adjuvants have been regarded as a very promising approach to personalized cancer immunotherapy, with encouraging results in several preclinical animal models[276-280]. For example, Moon et al. designed a high-density lipoprotein-mimicking nanodiscs delivery strategy that co-delivered neo-epitopes and the adjuvant CPG, significantly improved the delivery efficiency of antigen in vivo, improving delivery efficiency and enhancing the frequency of neoantigen-specific CD8α+ cytotoxic T lymphocytes (47 times higher)，and effectively inhibiting the tumor growth of B16F10 and MC38 tumor-bearing mice[277]. In addition, some nanovaccines based on co-delivery antigens and adjuvants have also been used to treat melanoma[279, 281] , breast cancer, colon cancer[279, 280, 282, 283] , liver cancer[284], lung cancer[285], gliomas[286], etc. However, neoantigen and adjuvant tumor vaccines loaded based on new delivery technologies are still mainly preclinical studies.

In addition to strategies such as optimizing adjuvants and developing new delivery systems to enable peptide tumor vaccines, combination with other therapies is also an important approach. In a phase 2 clinical trial (NCT02455557), the peptide vaccine SurVaxM plus temozolomide in glioblastoma patients showed a good safety profile, a strong antigen-specific CD8$^+$ T cells response, and 95.2% of patients remained progression-free six months after diagnosis[287]. Glioblastoma is a very high mortality tumor, and in clinical trials evaluating standard radiation and chemotherapy, the median survival of most patients was only 14.6 to 16.0 months, and it is exciting to see that SurVaxM plus temozolomide treatment significantly improved the median overall survival of patients (25.9 months) [287-289]. For patients with metastatic melanoma, improving overall survival has been a formidable challenge to overcome. In a Phase 3 clinical trial (NCT00094653), the median overall survival of patients with metastatic melanoma treated with glycoprotein 100 (gp100) peptide vaccine alone was 6.4 months. To improve survival, the combination of gp100 peptide vaccine and ipilimumab (an anti-CTLA-4 antibody) showed good clinical expectations, extending survival to 10.0 months[290]. In another phase 1b clinical study (NCT02897765), NEO-PV-01, a neoantigen vaccine

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tailored to a patient's tumor gene mutation, was shown to be effective in combination with PD-1 antibodies in patients with advanced melanoma, non-small cell lung cancer and bladder cancer[291]. In addition, some other clinical studies related to peptide tumor vaccines combined with other therapies in recent years are summarized in Table 5.

At present, the research progress of peptide tumor vaccines mainly revolves around the research of personalized peptide vaccines, tumor-associated antigens, and adjuvant (such as TLR agonists, STING agonists, cytokines) and delivery systems (such as nanoparticles, liposomes and other novel delivery systems) to enhance immune response. With the development of sequencing technology and bioinformatics, new adjuvants, new delivery systems and other technologies, the trend of personalized and combination therapy of peptide vaccines is developing. However, peptide tumor vaccines also face many challenges, such as poor immunogenicity, tumor immunosuppressive microenvironment, individual differences, and antigen escape. It is believed that with the innovation and development of technology, peptide tumor vaccines will definitely achieve accurate vaccine design by combining multiple omics, and explore multi-mode combined treatment schemes to improve the clinical effect of vaccines.

Table 5. Clinical study of peptide tumor vaccines updated in recent 5 years.

Target antigen	Adjuvant	Cancer	RoA	Combination therapy	NCI number	Phase	Ref
GP96 Heat Shock Protein-Peptide Complex	/	Liver Cancer	/	/	NCT04206254	2/3	[292]
Tumour antigen peptides	/	Liver Cancer	s.c.	/	NCT05059821	1	[293]
ELI-002 7P	/	Solid Tumors	s.c.	/	NCT05726864	1/2	[294]
ELI-002 2P (Amph modified KRAS peptides, Amph-G12D and Amph-G12R admixed with admixed Amph-CpG-7909)	/	Kirsten Rat Sarcoma (KRAS) Mutated Pancreatic Ductal Adenocarcinoma and Other Solid Tumors	s.c.	/	NCT04853017	1	[295]
Neoantigen Peptides vaccine	/	Non Small Cell Lung Cancer	s.c.	/	NCT04397926	1	[296]
ARG1 peptides	Montanide ISA-51	Solid Tumors	s.c.	/	NCT03689192	1	[297]
HLA-A*2402 or A*0201 restricted peptides	Montanide ISA 51	Solid Tumors	s.c.	/	NCT01949688	1/2	[298]
HLA-A*0201restricted URLC10 peptides	Montanide ISA 51	Non-small Cell Lung Cancer	s.c.	/	NCT01949701	1/2	[272]
Two peptides called UCP2 and	Montanide ISA 51	Non-small Cell Lung Cancer	/	/	NCT02818426	1/2	[270]

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UCP4 derived from telomerase							
OSE2101	Montanide ISA 51	Non-Small Cell Lung Cancer	s.c.	/	NCT06472245	3	[273]
Melan-A -ELA + NY-ESO-1b + MAGE-A10 peptide + Montanide + CpG	Montanide ISA 51	Melanoma	/	/	NCT00112242	1	[264]
PD-L1 peptide	Montanide ISA 51	Multiple Myeloma	s.c.	/	NCT03042793	1	[299]
IDH1 Peptide Vaccine	GM-CSF	Glioma	i.d.	/	NCT02193347	1	[274]
FRα peptide	GM-CSF	Breast Cancer	i.d.	/	NCT02593227	2	[267]
HER2/neu Peptide GLSI-100 (GP2 + GM-CSF)	GM-CSF	Breast Cancer	i.d.	/	NCT05232916	3	[268]
Multi-epitope folate receptor alpha peptide	GM-CSF	Breast Cancer	i.d.	/	NCT03012100	2	[269]
Neoantigen peptides	GM-CSF	Solid Tumors	/	/	NCT03662815	1	[300]
Neoantigen peptides	GM-CSF	Pancreatic Cancer	/	/	NCT03645148	1	[301]
Mutant Kirsten Rat Sarcoma (KRAS)-Targeted Long Peptide	Poly-ICLC	Pancreatic Cancer	/	/	NCT05013216	1	[275]
NEO-PV-01(personalized neoantigen)	Poly-ICLC	Melanoma, Non-Small Cell Lung Cancer	s.c.	/	NCT02897765	1	[291, 302]
Neoantigen peptides	Poly-ICLC	Breast Cancer, Melanoma	i.m.	/	NCT05098210	1	[266]
Neoantigen peptides	Poly-ICLC	Melanoma	/	/	NCT01970358	1	[303]
AE37 Peptide Vaccine	/	Breast Cancer	i.d.	anti-PD1	NCT04024800	2	[304]
OTSGC-A24	/	Gastric Cancer	s.c.	anti-PD1+anti-CTLA4	NCT03784040	1	[305]
Synthetic Tumor-Associated Peptide	/	Pancreatic Cancer, Colorectal Cancer	s.c.	anti-PD1, anti-PD1+ APX005M	NCT02600949	1	[306]

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Neoantigen peptide	/	Non Small Cell Lung Cancer	s.c.	EGFR-TKI, anti-angioge	NCT04487093	1	[307]
Liposomal HPV-16 E6/E7 Multipeptide Vaccine PDS0101	/	HPV-Oropharyngeal Squamous Cell Carcinoma	s.c.	anti-PD1	NCT05232851	1/2	[308]
Neo-antigen Heat Shock Protein Vaccine (rHSC-DIPGVax)	/	Glioma	/	anti-PD1 anti-CTLA4	NCT04943848	1	[309]
Survivin long peptide (SurVaxM)	Montanide ISA 51	Neuroendocrine Tumors	s.c.	Octreotide Acetate	NCT03879694	1	[310]
UCP2 and UCP4 derived from telomerase (UCPVax)	Montanide ISA 51	PapillomaVirus Positive Cancers	s.c.	anti-PDL1	NCT03946358	2	[311]
NPMW-peptide vaccine	Montanide ISA 51	Myelodysplastic Syndrome, Acute Myeloid Leukemia	/	anti-PDL1	NCT02750995	1	[312]
Personalized multi-peptide vaccine cocktails	XS15, Montanide ISA 51	Cancer	s.c.	TLR1/2 ligand XS15	NCT05014607		[313]
MVF-HER-2 (597-626) and MVF-HER-2 (266-296)	Montanide ISA 720	Advanced Solid Tumors	i.m.	/	NCT06414733	1	[314]
Neoantigen Peptides vaccine	Montanide ISA 51 + Poly-ICLC	Melanoma	/	anti-PD1+anti-CTLA4	NCT03929029	1	[315]
PVX-410 (contains four synthetic peptides)	Poly-ICLC	Smoldering Multiple Myeloma	s.c.	Citarinostat + Lenalidomide	NCT02886065	1	[316]
NEO-PV-01	Poly-ICLC	Non-small Cell Lung Cancer	s.c.	anti-PD1+ Chemotherapy	NCT03380871	1	[271]
Pooled mutant KRAS-targeted long peptide vaccine	Poly-ICLC	Colorectal Cancer Pancreatic Cancer	/	anti-PD1+ anti-CTLA4	NCT04117087	1	[317]
DNAJB1-PRKACA fusion kinase peptide	Poly-ICLC	Liver cancer	/	anti-PD1+ anti-CTLA4	NCT04248569	1	[318]

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Personalized multi-peptide	Poly-ICLC	Prostate Cancer	/	CDX-301	NCT05010200	1	[319]
KRAS peptide vaccine	Poly-ICLC	Non-Small Cell Lung Cancer	/	anti-PD1+ anti-CTLA4	NCT05254184	1	[320]
MUC1 Peptide Vaccine	Poly-ICLC	Ductal Carcinoma in Situ	s.c.	Aromatase Inhibitor	NCT06218303	1	[321]
Galinpepimut-S	GM-CSF	Acute Myelogenous Leukemia Ovarian Cancer Colorectal Cancer Breast Cancer Small-cell Lung Cancer	/	anti-PD1	NCT03761914	1/2	[322]
Neoantigen Peptide	GM-CFS	Solid Tumors	i.v.	anti-PD1	NCT05269381	1/2	[323]

Abbreviation: Intradermal injection (i.d.); subcutaneous injection (s.c.); intramuscular injection (i.m.); intravenous injection (i.v.).

2.4. Nucleic Acid Vaccines

2.4.1. DNA Tumor Vaccine

In cancer therapy, DNA cancer vaccines are considered to be a very attractive and promising means, with advantages such as low cost, cell-independent production, durable immune response, and potential to target multiple neoantigens[126, 324]. Of course, there are also defects of host gene integration risk, autoimmune reaction risk, and low transfection efficiency[126]. In order to improve efficacy and safety, different strategies are being used to optimize and improve DNA vaccines. To improve efficacy and safety, efforts have been made to optimize and improve DNA vaccines through different strategies, such as inserting optimized optimal antigens.

Previous studies have shown that selecting and inserting the optimal antigen for plasmid DNA is an ideal way to enhance vaccine immunogenicity and induce a broad immune response, which can overcome problems associated with antigen loss, modification, and tolerance[324]. DNA vaccine construction based on enhanced immunogenicity strategy mainly includes chimeric DNA vaccine, neoantigen DNA vaccine and polypeptide DNA vaccine. Chimeric DNA vaccines are heterologous antigenic vaccines that encode proteins or peptides from different species, and their sequences have significant homology with the self-ortholog[325, 326]. Since the homologous and natural protein sequences are only similar but not identical, this helps to circumvent immune tolerance while maintaining homology that can be recognized by T cells to enhance the potential immunogenic response[325-327]. Previous studies have shown that xenoantigens are more effective than autoantigens[327, 328]. For example, xenogeneic DNA vaccines targeting human tyrosinase were approved to treat canine melanoma[326], Xenovaccines designed with rhesus CEA (rhCEA) as the immunogen against human carcinoembryonic antigen (hCEACAM-5 or commonly hCEA) can activate $CD4^+$ T cells and autoreactive $CD8^+$ T cells, and produce high titer antibodies against hCEA and have significant anti-tumor effects. Furthermore, codon-optimized RhCEA cDNA (rhCEAopt) was demonstrated to have higher immune reactivity than hCEAopt in mice[329], Chimeric rat/human HER2 efficiently circumvents HER2 tolerance in cancer patients[330]. DNA vaccines encoding mouse/human chimeric proteins induce a better immune response against Erbb-2 tumors in mice[331]. DNA xenovaccines have shown encouraging results in a clinical trial for melanoma[332, 333]. Neoantigen vaccines are selected to express antigens specifically in tumor tissue, which overcomes the problem of immune tolerance deficiencies and side effects[334, 335]. For example, Li

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et al. 's optimized polypeptide neoantigen DNA vaccine induced strong neoantigen-specific T cell responses in preclinical mouse breast cancer models E0771 and 4T1, and combined with anti-PD-L1 antibody effectively inhibited the growth of E0771 tumors and maintained anti-tumor immunity [336].

In clinical trials, DNA vaccines are being used to treat Liver cancer (NCT04251117)[337], melanoma (NCT03655756)[338], breast cancer (NCT05455658, NCT04246671, NCT02780401)[339-341], non-melanoma skin cancers (NCT04160065)[342], glioblastoma (NCT04015700, NCT05743595)[343, 344], prostate cancer (NCT03532217, NCT03600350, NCT04090528)[345-347], and other cancers (Table 6), most of which were in the phase 1-2 clinical research stage. Despite efforts to improve the delivery efficiency of DNA vaccines, their immunogenicity in clinical trials remain limited. Therefore, people still need to continue exploring more strategies to enhance the immunogenicity of DNA vaccines, such as optimizing DNA vaccine vectors, combining cytokine adjuvants, and exploring innovative delivery methods, etc.[348].

Table 6. Clinical study of DNA vaccines updated in recent 5 years.

Target	Cancer	ROA	Combination therapy	NCI number	phase	Ref
Emm55 Streptococcal Antigen	Melanoma	i.t.	/	NCT03655756	1	[338]
TAEK-VAC-HerBy	Chordoma Breast Cancer	i.v.	Anti-HER2	NCT04246671	1/2	[340]
pNGVL4aCRTE6E7L2 DNA vaccine	Cervical Neoplasia	i.m.	/	NCT04131413	1	[349]
HPV	Cervical Cancer Vulvar Cancer Vaginal Cancer	/	/	NCT02653118	Observational	[350]
HPV	Cervical Cancer	/	/	NCT04588402	Observational	[351]
IGFBP-2, HER2, and IGF1R	Breast Cancer	i.d.		NCT02780401	1	[341]
Neoantigen DNA vaccine	Prostate Cancer	i.m.	Anti-PD1 or Anti-CTLA-4+ PROSTVAC	NCT03532217	1	[345]
Neoantigen DNA Vaccine (GNOS-PV02)	Hepatocellular Carcinoma	i.d.	Anti-PD1	NCT04251117	1/2	[337]
neoantigen DNA vaccine	Recurrent Brain Tumor	i.m.	/	NCT03988283	1	[352]
pAc/emm55 (pDNA)	non-melanoma skin cancers	intralesionally	/	NCT04160065	1	[342]
Prostatic Acid Phosphatase (pTVG-HP)	Prostate Cancer	i.d.	Anti-PD1	NCT03600350	2	[346]
pTVG-HP DNA Vaccine	Prostate Cancer	i.d.	Anti-PD1	NCT04090528	2	[347]

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DNA-PEI polyplex	Neuroblastoma	i.m.	/	NCT04049864	1	[353]
Personalized neoantigen DNA vaccine	Glioblastoma	/	/	NCT04015700	1	[343]
Personalized Neoantigen DNA vaccine	Glioblastoma	i.m.	/	NCT05743595	1	[344]
TriAd vaccine	Head and Neck Cancer	i.v.	Anti-PD-L1/TGF-beta Trap (M7824)	NCT04247282	1/2	[354]
GX-188E HPV DNA Vaccine	Head and Neck Cancer	i.m.	Anti-PD1	NCT05286060	2	[355]
pING-hHER3FL	Advanced Cancer	i.m.		NCT03832855	1	[356]
Neoantigen DNA vaccine	Small Cell Lung Cancer	i.m.	Anti-PD-L1	NCT04397003	2	[357]
CD105/Yb-1/SOX2/CDH3/MDM2-polyepitope Plasmid DNA Vaccine	Non-Small-Cell Lung Cancer	i.d.	/	NCT05242965	2	[358]
CD105/Yb-1/SOX2/CDH3/MDM2-polyepitope Plasmid DNA Vaccine	Breast Cancer	i.v.	/	NCT05455658	2	[339]
Glypican3 (GPC3)-targeted DNA plasmid vaccine (NWRD06)	Hepatocellular Carcinoma	i.m.	/	NCT06088459	1	[359]

Abbreviation: Intradermal injection (i.d.); subcutaneous injection (s.c.); intramuscular injection (i.m.); intravenous injection (i.v.); Intertumoral injection (i.t.).

2.4.2. RNA Vaccine

With the outbreak of COVID-19, the urgent use of two mRNA vaccines has brought mRNA vaccines back into the spotlight. like DNA, mRNA can encode an unlimited number of proteins and peptides. However, mRNA vaccines have several irreplaceable advantages, such as no risk of gene integration, repeatability, and coding flexibility and versatility, short production cycle and low cost[360-362]. Based on the editable flexibility of mRNA vaccines, they can encode tumor antigens as tumor antigen vaccines, cytokines for immunotherapy, tumor suppressors to inhibit tumor development, chimeric antigen receptors for engineered T cell therapy, and genomic proteins for gene therapy. In this section, we will focus on describing the progress of mRNA therapeutic cancer vaccines in clinical studies (Table 7).

Because mRNA is easily degraded by RNases, there is little research on naked mRNA vaccines, and the main focus is on the application of delivery systems to deliver mRNA into the body. Currently, the strategies for delivering mRNA mainly include protamine, cationic liposomes, and lipid nanoparticles (LNP). Protamin-coated mRNA vaccines use the positive charge of protamine to form a complex with negatively charged mRNA to avoid mRNA degradation[363]. For example, In

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a phase 1/2 clinical trial (NCT00204607), subcutaneous injection of protamine-stabilized mRNAs encoding Melan-A, Tyrosinase, gp100, Mage-A1, Mage-A3, and Survivin in 21 patients with metastatic melanoma demonstrated that the vaccine was safe with no grade II adverse events and activated the immune response. The frequency of $Foxp3^{+}/CD4^{+}$ immunosuppressive cells was significantly decreased, and some patient-specific T cells were increased[364]. The strategy of delivering mRNA into the body by means of an mRNA-Lipoplex complex formed by cationic liposomes with negatively charged mRNA is currently studied and paid more attention. For example, BNT-111 developed by BioNtech Company is a mRNA-lipoplex vaccine designed for melanoma antigen (MAGE-A3, NY-ESO-1, TPTE, Tyrosinase). In a Phase II clinical study (NCT02410733), BNT-111 demonstrated good clinical benefits, with 75% of patients producing an anti-tumor immune response[365]. Lipid nanoparticles are currently very mature mRNA delivery platforms, mainly composed of lipids, phospholipids and cholesterol[366, 367]. mRNA-4157, developed by Moderna, is an mRNA vaccine encoding 34 tumor neoantigens and wrapped with LNP. It is also the fastest-growing mRNA therapeutic cancer vaccine (Phase 3, NCT06077760, NCT05933577)[368, 369]. In a 2b clinical trial (NCT03897881), the recurrence-free survival of melanoma patients treated with mRNA-4157 combined with pembrolizumab was longer than that of pembrolizumab monotherapy (79% versus 62%). And it has relatively good safety, with no mRNA-4157-related grade 4/5 events[370]. Furthermore, another Phase 1 clinical study (NCT03313778) on non-small cell lung cancer or melanoma evaluated the safety, tolerability and immunogenicity of mRNA-4157[371]. The results showed that no patient had grade 4/5 adverse events or dose-limiting toxicity[371]. mRNA-4157 alone can induce consistent new generation and enhance the pre-existing T cell response to targeted neoantigens, and the combination therapy induces sustained neoantigen-specific T cell responses and the expansion of cytotoxic CD8 and CD4 T cells[371]. The relevant clinical studies of mRNA-4157 have demonstrated the great potential and significance of mRNA-4157 as an adjuvant monotherapy or in combination with other therapies.

There are also many other mRNA therapeutic cancer vaccines in the clinical stage, which are used to treat melanoma (NCT04526899, NCT03897881)[372, 373], liver cancer (NCT05981066, NCT05738447, NCT05761717)[374-376], lung cancer (NCT03164772, NCT06735508)[377, 378], pancreatic cancer (NCT06326736, NCT06577532, NCT06496373, NCT06156267, NCT06353646, NCT04161755)[379-384], and other cancers (Table 7). In addition, many studies are exploring the design and application of novel mRNA, such as self-amplified mRNA (saRNA), trans-amplified mRNA (taRNA), and circular mRNA (circRNA), as well as the long-term preservation means of mRNA nanoparticles, drug delivery routes, and organ-selective precision translation[360]. These explorations are expected to enable mRNA-based anti-cancer therapies to further cover various types of cancer and benefit a broad population of patients.

Table 7. Clinical study of mRNA vaccines updated in recent 5 years.

Name	Cancer	ROA	Combination therapy	NCI number	Phase	Ref
NY-ESO-1, MAGE-A3, tyrosinase, and TPTE	Melanoma	i.v.	Anti-PD-1	NCT04526899	2	[372]
mRNA-4157	Melanoma	/	Anti-PD-1	NCT03897881	2	[373]
mRNA-4157	Melanoma	i.m.	Anti-PD-1	NCT05933577	3	[369]
mRNA-4157	Cutaneous Squamous Cell Carcinoma	i.m.	Anti-PD-1	NCT06295809	2/3	[385]
mRNA-4157	Renal Cell Carcinoma	i.m.	Anti-PD-1	NCT06307431	2	[386]

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HBV mRNA vaccine	Liver Cancer	i.m.	/	NCT05738447	1	[375]
Neoantigen mRNA Vaccine (ABOR2014/ IPM511)	Liver Cancer	i.m.	/	NCT05981066	Not Applicable	[374]
Neoantigen mRNA Personalised Cancer vaccine	Liver Cancer	s.c.	Anti-PD-1	NCT05761717	Not Applicable	[376]
mRNA-4157	Non-small Cell Lung Cancer	i.m.	Anti-PD-1	NCT06077760	3	[368]
BI 1361849 mRNA vaccine comprises 6 drug product components (MUC1, survivin, NY-ESO-1, 5T4, MAGE-C2, MAGE-C1)	Non-small Cell Lung Cancer	i.d.	anti-PD-L1, anti-CTLA-4	NCT03164772	1/2	[377]
BI 1361849 mRNA vaccine comprises 6 drug product components	Non-small Cell Lung Cancer	i.d.	Anti-PD-L1, Anti-CTLA4	NCT03164772	1/2	[377]
Neoantigen mRNA Vaccines	Non-small Cell Lung Cancer	/	Anti-PD-L1	NCT06735508	1	[378]
Fixed combination of shared cancer antigens	Head and Neck Cancer	i.v.	Anti-PD-L1	NCT04534205	2	[387]
EBV mRNA vaccine	Malignant Tumors	i.m.	/	NCT05714748	1	[388]
Personalized Neoantigen mRNA Vaccine iNeo-Vac-R01	Digestive System Neoplasms	s.c.	/	NCT06019702	1	[389]
mRNA Neoantigen Vaccine iNeo-Vac-R01	Digestive System Neoplasms	s.c.	/	NCT06026774	1	[390]
Neoantigen mRNA Vaccines	Digestive System Neoplasms	s.c.	/	NCT03468244	Not applicable	[391]
Neoantigen mRNA Vaccines iNeo-Vac-R01	Neoantigen mRNA Vaccines	s.c.	/	NCT06026800	1	[392]
Neoantigen mRNA	Esophageal Cancer,	s.c.	/	NCT03908671	Not applicable	[393]

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	Non Small Cell Lung Cancer					
mRNA Neoantigen Vaccine (mRNA-0523-L001)	Endocrine Tumor	i.m.	/	NCT06141369	Not Applicable	[394]
Neoantigen mRNA Vaccines	Pancreatic Cancer	/	Gemcitabine+Abraxane	NCT06326736	1	[379]
KRAS Neoantigen mRNA Vaccine (ABO2102)	Pancreatic Cance	i.m.	Anti-PD-1	NCT06577532	1	[380]
Neoantigen mRNA Vaccines	Pancreatic Cancer	/	Anti-PD-1	NCT06496373	1	[381]
Neoantigen mRNA Vaccines	Pancreatic Cancer	/	Anti-PD-L1	NCT06156267	1	[382]
XH001 (Neoantigen Cancer Vaccine)	Pancreatic Cancer	/	Anti-CTLA-4+ Chemotherapy	NCT06353646	Not Applicable	[383]
Personalized Neoantigen Tumor Vaccines	Pancreatic Cancer	/	Anti-PD-L1	NCT04161755	1	[384]
mRNA 2752	Carcinoma	intralesional (IL)	Anti-PD-1	NCT02872025	1	[395]
mRNA-4157	Solid Tumors	i.m.	Anti-PD-1	NCT03313778	1	[396]
Neoantigen mRNA Vaccine	Solid Tumors	i.t.	/	NCT06195384	1	[397]
Neoantigen mRNA Vaccine SW1115C3	Solid Tumors	s.c.	/	NCT05198752	1	[398]
Neoantigen mRNA Personalised Cancer vaccine	Solid Tumors	s.c.	Anti-PD-1	NCT05949775	Not Applicable	[399]
Neoantigen mRNA Vaccines	Solid Tumors	i.m.	Anti-PD-1	NCT06497010	1	[400]
XH001 (Neoantigen Cancer Vaccine)	Solid Tumors	/	Anti-PD-1	NCT05940181	Not Applicable	[401]
Individualized NeoantigenVaccine mRNA-4157	Solid Tumors	i.m.	Anti-PD-1	NCT03313778	1	[402]
IL-7, IL-12 BNT152+153	Solid Tumors	i.v.	/	NCT04710043	1	[403]
mRNA-2752, a Lipid Nanoparticle Encapsulating mRNAs Encoding	Solid Tumors	i.m.	Anti-PD-1	NCT03739931	1	[404]

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Human OX40L, IL-23, and IL-36γ						
IL-12 MEDI1191	Solid Tumors	i.t.	/	NCT03946800	1	[405]

Abbreviation: Intradermal injection (i.d.); subcutaneous injection (s.c.); intramuscular injection (i.m.); intravenous injection (i.v.);Intertumoral injection (i.t.).

3. Challenges and Trends in Therapeutic Vaccines

Immunotherapy is an effective means of treatment following drug, surgery and radiotherapy, and its clinical role is increasingly prominent. Therapeutic cancer vaccines, as one of the main methods of immunotherapy, have become a new growth point of biomedicine with broad industrial prospects in the post-COVID-19 era. Major international vaccine companies [such as BioNTech SE, CureVac AG, Moderna TX, Merck Sharp &Dohme Corp] have laid out research and development pipelines to promote their clinical transformation.

For immunotherapy strategies, the anti-tumor process mainly consists of three links: effective antigen release, immune activation and tumor killing. These links complement each other and none can be missing. Vaccines developed in the past often had many deficiencies, resulting in slow development and limited therapeutic effects. Tumor antigens are the key factors that initiate the anti-tumor immune response and also the crucial link that tumor therapeutic vaccines need to address. For immune checkpoint inhibitors (PD-1/PD-L1 antibodies) and CAR-T cell therapy, they address the aspect of "tumor killing", and the treatment process faces the problem of immune tolerance. Recently, the development of gene sequencing technology and bioinformatics has enabled more precise identification of specific gene mutations and neoantigens in patients' tumor cells, thereby promoting the increasing precision of antigens. Therapeutic cancer vaccines will be highly customized based on the individual tumor antigen characteristics of each patient to enhance the vaccine's specificity and efficacy. However, individualized vaccines based on tumor neoantigens still face many challenges, such as tumor heterogeneity, immunogenicity, and how to scientifically and reasonably design and validate clinical trial protocols, etc. Tumor cells are highly heterogeneous, so the antigen expression of tumor cells in different patients may vary. In practical applications, it is difficult to find a universal tumor antigen for vaccine design, which also increases the difficulty for vaccines to cover all tumor cells. Furthermore, tumors progress rapidly and are prone to mutation, which requires a fast process from antigen sequencing, screening to design, undoubtedly putting pressure on vaccine production. The issue of immunogenicity is that tumor antigens usually have weak immunogenicity and are difficult to stimulate a strong immune response, and the immune system in the body may develop immune tolerance to tumor antigens, resulting in poor vaccine efficacy. For instance, a personalized neoantigen cancer vaccine based on mrna was terminated due to its clinical efficacy failing to meet expectations (Phase 1/2, NCT03480152)[406]. Therefore, in order to solve the problems in the immune activation part, many studies have been dedicated to developing more effective adjuvants and antigen presentation techniques to enhance the immunogenicity of tumor antigens and break immune tolerance. In particular, peptide vaccines are greatly affected by adjuvants. Many studies have proved the favorable effects of adjuvants on vaccines, such as adjuvants GM-CSF, CpG, etc. Moreover, adjuvants are also developing towards compound adjuvants, taking advantage of their respective strengths and complementing each other's weaknesses. It is believed that with the advantages of new adjuvants and compound adjuvants, the efficacy of vaccines is expected to be continuously improved in the future. In addition to adjuvants, new delivery technologies have also been a key focus area in recent years. So far, delivery carriers include viruses, bacteria, cells and lipid nanoparticles, etc. For viral vector vaccines, the development of genetic engineering technology has made the modification of viral vectors safer, more precise and more efficient, which can improve the targeting, immunogenicity and safety of the vectors. For instance, by designing and optimizing the structure and function of viruses through gene editing, viral vectors can infect tumor cells more specifically while reducing their impact on normal cells. There are already many therapeutic cancer

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vaccines based on viral vectors in the clinical research stage (Table 1). However, such vaccines still face many challenges, mainly the accompanying issues related to immunogenicity and safety. For example, the safety issues brought about by potential inserted gene mutations, the neutralizing antibodies produced by antiviral responses reduce the therapeutic effect, and the production complexity problems such as the high cost of large-scale production and quality control of viral vectors. Delivery technologies such as cell and lipid nanoparticles are all aimed at improving the delivery efficiency of antigens into tumors, increasing the effective concentration of antigens within the tumor to enhance the activation of immune responses, and simultaneously reducing off-target effects outside the tumor to improve safety. In addition to improving delivery technology, combination therapy is also a mainstream trend in overcoming cancer. Whether based on cells or lipid nanoparticles or other carriers, therapeutic cancer vaccines combined with immune checkpoint inhibitors, chemotherapy, radiotherapy, etc. have demonstrated significant advantages in preclinical and clinical studies to exert a synergistic effect and improve therapeutic outcomes.

Nowadays, research is focused on technological breakthroughs in various therapeutic cancer vaccines. By integrating the characteristics of multiple technologies and the continuously accumulated clinical experience, therapeutic cancer vaccine therapy has great potential and application space in the field of cancer treatment. However, future research still requires further improvement and optimization in aspects such as antigen screening, vector design, and production and preparation processes. Strive to reduce production costs, enhance the accuracy of antigens, improve the efficiency and targeting of delivery systems, and verify its long-term efficacy and good safety through large-scale clinical trials.

4. Conclusions and Future Directions

Over the past few decades, with the continuous breakthroughs in immunology and precision medicine technologies, people's understanding of how cancer cells evade immune system monitoring and their roles in the body has been greatly enhanced. This has led to significant progress in tumor immunotherapy, which is constantly developing in a favorable direction for defeating cancer. Previous immune checkpoint inhibitors and cell therapy methods have demonstrated their ability to regressed tumors in some studies on hematological malignancies and solid tumors. These advancements have shown the feasibility of applying tumor immunotherapy and therapeutic cancer vaccines. With the continuous development of technology, humans will be able to more accurately identify highly immunogenic neoantigens in the future. Combined with targeted and efficient delivery technologies, it is certain that highly personalized and general-purpose therapeutic vaccines can be developed for different situations, and through combined therapies, a synergistic effect can be achieved to maximize the therapeutic effect.

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