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REVIEW

Breaking barriers: Smart vaccine platforms for cancer immunomodulation

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Abbreviations: ABs, Antibodies; Ac_4ManNAz, N-azidoacetylmannosamine-tetraacylated; ACIT-1, Allogeneic cell immunotherapy 1; Ad.p53-DC, Adenovirus-p53 transduced dendritic cell; AML, Acute myeloid leukemia; APCs, Antigen-presenting cells; ASCC, Anal squamous cell carcinoma; Au-NPs, Gold-nanoparticles; B cell, B lymphocyte; BC, Breast cancer; Bcl-xL, B-cell lymphoma-extra-large; BCN-CNPs, Bicyclononyne-conjugated glycol chitosan nanoparticles; BPH, Benign prostatic hyperplasia; CC, Cervical cancer; CD, Cluster of differentiation; cDCs, Classical DCs; CEA, Carcinoembryonic antigen; CIK, Cytokine-induced killer cell; CLL, Chronic lymphocytic leukemia; CM, Cutaneous melanoma; CRC, Colorectal cancer; cRGD-CNPs, Cyclic RGD-conjugated chitosan nanoparticles; CRM 197, Cross-reactive material 197; cSCC, Cutaneous squamous cell carcinoma; CTAs, Cancer testis antigens; CTL, Cytotoxic T-lymphocyte; CTPs, Cell-targeting peptides; CuAAC, Copper-catalyzed azide-alkyne cycloaddition; DBCO, Dibenzocyclooctyne; DCs, Dendritic cells; DDS, Drug delivery system; DEPDC1, DEP domain containing 1; DEXs, DC-derived exosomes; DIPG, Diffuse intrinsic pontine glioma; DMG, Diffuse midline glioma; DNA, Deoxyribonucleic acid; DNAJB1, DnaJ homolog subfamily B member 1; DOTAP, 1,2-dioleoyl-3-trimethylammonium-propane; EAC, Esophageal adenocarcinoma; EGFR, Epidermal growth factor receptor; EPR, Enhanced permeability and retention; FasL, Fas ligand; FDA, Food and drug administration; FL, Follicular lymphoma; FOXM1, Forkhead box protein M1; FTC, Fallopian tube cancer; GAC, Gastric adenocarcinoma; GC, Gastric cancer; GEJC, Gastroesophageal junction adenocarcinoma; GIN, Gastrointestinal neoplasms; GM-CSF, Granulocyte-macrophage colony-stimulating factor; gp100, Glycoprotein 100; GP-NPs, Glycopolyester nanoparticles; GU, Genitourinary; HCC, Hepatocellular carcinoma; HER, Human epidermal growth factor receptor; HLA, Human leukocyte antigen; ^{1}H NMR, Hydrogen-1 nuclear magnetic resonance; HNSCC, Head and neck squamous cell carcinoma; HOXB13, Homeobox B13; HPV, Human papillomavirus; HSP, Heat shock protein; hTERT, Human telomerase reverse transcriptase; ID, Intradermal; iDC, Immature DC; IEDDA, Inverse electron demand Diels-Alder; IM, Intramuscular; IP, Intraperitoneal; IT, Intratumoral; IV, Intravenous; KIF20A, Kinesin family member 20A; KRAS, Kirsten rat sarcoma virus; LAMP, Lysosome-associated membrane protein 1; LNPs, Lipid-based nanoparticles; LPS, Lipopolysaccharide; mAB, Monoclonal antibody; MAGE, Melanoma-associated antigen; MCC, Merkel cell carcinoma; mDC, Mature DC; Melan-A, Melanoma antigen recognized by T cells 1; MHC, Major histocompatibility complex; MM, Multiple myeloma; MNPs, Magnetic nanoparticles; MOFs, Metal-organic frameworks; MPLA, Monophosphoryl lipid A; mRNA, Messenger ribonucleic acid; MSNPs, Mesoporous silica nanoparticles; MUC1, Mucin1; N/A, Not applicable; NB, Neuroblastoma; NCT, National clinical trial; NETs, Neuroendocrine tumors; NHS, N-hydroxysuccinimide; NK, Natural killer; NKG2D, Natural killer group 2 member D; NLCs, Nanostructured lipid carriers; NMSC, Non-melanoma skin cancers; NPs, Nanoparticles; NSCLC, Non-small cell lung cancer; NY-ESO-1, New York esophageal squamous cell carcinoma 1; OCAs, O-carboxyanhydrides; OMVs, Outer membrane vesicles; OV, Ovarian cancer; OX40L, OX40 ligand; p53, Tumor protein p53; PAP, Prostatic acid phosphatase; PCa, Prostate cancer; PDAC, Pancreatic ductal adenocarcinoma; PDC, Plasmacytoid dendritic cell; PD-L1, Programmed death ligand 1; PECs, Polyelectrolyte complexes; PEG, Polyethylene glycol; PEI, Polyethyleneimine; PLGA, Poly(lactic-*co*-glycolic acid); PNPs, Peptide-functionalized nanoparticles; PPC, Primary peritoneal cancer; PRKACA, Protein kinase cAMP-activated catalytic subunit alpha; PSA, Prostate-specific antigen; PSMA, Prostate-specific membrane antigen; PST, Pediatric solid tumor; PTPs, Protein tyrosine phosphatases; RBD, Receptor-binding domain; RGD, Arginine-glycine-aspartic acid; RNA, Ribonucleic acid; ROS, Reactive oxygen species; SC, Subcutaneous; SCLC, Small cell lung cancer; shRNA, Short hairpin ribonucleic acid; siRNA, Silencing ribonucleic acid; SLAMF7, Signaling lymphocytic activation molecule family 7; SLNs, Solid lipid nanoparticles; SPAAC, Strain-promoted azide-alkyne cycloaddition; SS, Synovial sarcoma; STS, Soft tissue sarcoma; SVP, Smart vaccine platform; TAAs, Tumor-associated antigens; T cell, T lymphocyte; TfR, Transferrin receptor; TGFβ, Transforming growth factor beta; Th, T-helper; TLR3, Toll-like receptor 3; TME, Tumor microenvironment; TNBC, Triple-negative breast cancer; TPTE, Transmembrane phosphatase with tensin homology; TRP-2, Tyrosinase-related protein 2; TSAs, Tumor-specific antigens; UC, Urothelial carcinoma; UCP, Universal cancer peptide; URLC10, Up-regulated lung cancer 10; VEGFR1, Vascular endothelial growth factor receptor 1; WT1, Wilms tumor 1; XBP1, X-box binding protein 1.

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Abstract

Despite significant advancements in cancer treatment, current therapies often fail to completely eradicate malignant cells. This shortfall underscores the urgent need to explore alternative approaches such as cancer vaccines. Leveraging the immune system's natural ability to target and kill cancer cells holds great therapeutic potential. However, the development of cancer vaccines is hindered by several challenges, including low stability, inadequate immune response activation, and the immunosuppressive tumor microenvironment, which limit their efficacy. Recent progress in various fields, such as click chemistry, nanotechnology, exosome engineering, and neoantigen design, offer innovative solutions to these challenges. These achievements have led to the emergence of smart vaccine platforms (SVPs), which integrate protective carriers for messenger ribonucleic acid (mRNA) with functionalization strategies to optimize targeted delivery. Click chemistry further enhances SVP performance by improving the encapsulation of mRNA antigens and facilitating their precise delivery to target cells. This review highlights the latest developments in SVP technologies for cancer therapy, exploring both their opportunities and challenges in advancing these transformative approaches.

KEYWORDS
cancer, click chemistry, mRNA vaccines, smart vaccine platforms, targeted delivery

1 | Introduction

According to the GLOBOCAN 2020 estimates, 19.3 million new cancer cases and nearly 10 million cancer-related deaths were reported worldwide in 2020. The report also predicts a 47% increase in the global cancer burden, with cases expected to reach 28.4 million by 2040 [1]. Cancer statistics published in 2023 show a rise in certain cancer types, with significant racial disparities in mortality rates [2], which will impose substantial economic challenges. In addition to gold-standard treatments such as surgery, radiotherapy, and chemotherapy, researchers are actively working to discover new treatment modalities that provide higher specificity and efficiency while minimizing side effects [3, 4]. A promising approach to combat cancer involves harnessing the immune response [5].

Cancer treatment presents significant challenges due to resistance mechanisms and the complexity of tumor cells, which evade the immune system through various mechanisms [6, 7]. Over the past decade, cancer vaccines have shown considerable promise, largely attributed to their favorable safety profiles, capacity to generate prolonged anti-tumor immune responses [8, 9], ability to modulate the immunosuppressive tumor microenvironment (TME), and increased infiltration of lymphocytes into solid tumors [10–17]. Moreover, combination therapies incorporating cancer vaccines have demonstrated success in inducing durable tumor regression, enhancing T lymphocyte (T cells) responses, and delivering measurable clinical benefits [18, 19].

Cancer vaccines are broadly categorized into prophylactic and therapeutic types, with this review focusing on therapeutic vaccines [20]. Over a decade ago, Sipuleucel-T, the first dendritic cell (DC)-based therapeutic cancer vaccine, received approval from the United States (US) Food and Drug Administration (FDA) [21]. Since then, no other therapeutic cancer vaccines have been approved by the FDA, although many are currently undergoing various stages of clinical trials (Table 1). The limited success of some therapeutic cancer vaccines in phase III clinical trials [22–25] can be attributed to several factors, including inefficient delivery systems, the selection of vaccine platforms or antigens with low immunogenicity, the immunosuppressive nature of the TME [26, 27], and the administration to patients with late-stage cancers [28].

Based on their fabrication method, cancer vaccines can be classified into several platforms: cell-based vaccines, nucleic acid-based vaccines, protein/peptide-based vaccines, and virus-based vaccines (Figure 1). Cell-based cancer vaccines are actively being investigated and often involve DCs treated with recombinant proteins, peptides, whole-tumor lysates, or whole-tumor cells loaded with

TABLE 1 Completed and ongoing clinical applications of various therapeutic cancer vaccines (covering the period from 2017-2023).

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
Cell-based					
ACIT-1	Tumor antigen	NCT03096093 (Phase 1/2)	Cancer and neoplasms	Intradermal	Active, not recruiting
Adenoviral transduced autologous HER2-neu DC vaccine	HER2-neu	NCT01730118 (Phase 1)	BC, adenocarcinomas, and solid tumors characterized by HER2-neu expression	Intradermal	Completed
Ad.p53-DC vaccines	p53	NCT00617409 (Phase 2)	SCLC	Intradermal	Completed
AST-VAC2 (embryonic stem cell-derived DCs)	hTERT/LAMP chimeric tumor antigen	NCT03371485 (Phase 1)	Advanced NSCLC	Intradermal	Completed
Autologous DCs loaded with autologous tumor homogenate	Tumor-lysate	NCT04166006 (Phase 2)	HNSCC, NETs, and STS	Intradermal	Recruiting
		NCT02919644 (Phase2)	Stage iv CRC	Intradermal	Unknown status
Autologous, tumor-lysate loaded DCs	Tumor-lysate	NCT03879512 (Phase 1/2)	Childhood glioblastoma	Intradermal	Recruiting
AlloStim (StimVax) ($CD4^+$ memory Th1-like T cells; precursor cells purified from blood of healthy unrelated donor)	AlloStim is allogeneic (donors are intentionally mis-matched to the host), and its mechanism is designed to modify and train the host immune system to kill tumors and prevent tumor growth and spread	NCT04444622 (Phase 2)	Metastatic CRC	Intradermal and Intravenous	Recruiting
Cvac (autologous DCs)	MUC1	NCT01068509 (Phase 2)	OV	Intradermal	Completed
DC/AML fusion vaccine (patient-derived AML cells are fused with autologous DCs)	Antigens that are unique to the DC and tumor population	NCT03679650 (Phase 1)	AML	Subcutaneous	Recruiting
		NCT03059485 (Phase 2)	AML	Subcutaneous	Recruiting
DC/MM fusion vaccine (patient-derived MM cells are fused with autologous DCs)	Antigens that are unique to the DC and tumor population	NCT03782064 (Phase 2)	MM	Subcutaneous	Terminated
DC vaccine (neoantigen-derived DCs)	Tumor neoantigen	NCT05767684 (Phase 1)	Solid tumor	Subcutaneous	Recruiting
DC vaccine (autologous DCs)	Tumor neoantigen peptides	NCT04968366 (Phase 1)	Glioblastoma multiforme of brain	Intradermal	Active not recruiting
DCVax-L (autologous DCs)	Tumor-lysate	NCT03014804 (Phase 2)	Advanced glioblastoma	Intradermal	Withdrawn

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
FANG (Vigil™) vaccine (autologous tumor cell)	rH *GM-CSF* transgene and the bifunctional shRNA furin (to block proprotein conversion to active TGF-β1 and TGF-β2)	NCT01505166 (Phase 2)	CRC	Intradermal	Terminated
		NCT01453361 (Phase 2)	Advanced melanoma	Intradermal	Terminated
GM.CD40L (bystander-based autologous tumor cell vaccine)	Tumor antigens	NCT00101166 (Phase 2)	Melanoma (skin)	Intradermal	Completed
GVAX (tumor cell)	*GM-CSF* gene is transfected into tumor cells	NCT03190265 (Phase 2)	PDAC	Intradermal	Completed
		NCT03153410 (Early Phase 1)	PDAC	Intradermal	Completed
		NCT03767582 (Phase 1/2)	PDAC	Intradermal	Recruiting
		NCT04239040 (Phase 1)	NB and PST	Intradermal	Recruiting
mDC3/*8-KRAS* vaccine (autologous DCs)	*KRAS* mutation peptides	NCT03592888 (Phase 1)	PDAC	Intravenous	Active, not recruiting
mDC3 vaccine (autologous DCs)	Tumor related antigens (mutated peptides)	NCT03730948 (Phase 1)	CRC	Intravenous	Terminated
Neoantigen-expanded (autologous DC-CIK cells)	Patient's tumor neoantigen	NCT05020119 (Phase 1)	Advanced solid tumor	Intravenous	Unknown status
Neoantigen-loaded DC vaccine (autologous DCs)	Tumor neoantigens	NCT04912765 (Phase 2)	HCC, CRC, and liver metastases	Intradermal	Recruiting
		NCT03871205 (Phase 1)	NSCLC and SCLC	Subcutaneous	Unknown status
Oncoquest-L vaccine (autologous tumor cell)	Tumor antigens	NCT02194751 (Phase 2)	FL	Subcutaneous	Not yet recruiting
PDC*lung01 (plasmacytoid DC)	NY-ESO-1, MAGE-A3, MAGE-A4, Multi-MAGE-A, MUC1, Survivin, and Melan-a	NCT03970746 (Phase 1/2)	NSCLC	Subcutaneous and Intravenous	Active, not recruiting
Prodencel (autologous DCs)	Targets PCa TME components	NCT05533203 (Phase 1)	Metastatic castration-resistant PCa	Subcutaneous	Recruiting
RT201 (macrophage)	Tumor antigen	NCT05930301 (Phase 1)	Advanced CC	Intravenous	Recruiting
Sipuleucel-T (autologous DCs)	PAP	NCT00715078 (Phase 2)	PCa	Subcutaneous	Completed
		NCT00779402 (Phase 3)	PCa	Subcutaneous	Completed

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
SV-BR-1-GM (a GM-CSF secreting BC cell line)	TAAs	NCT03066947 (Phase 1/2)	BC	Intradermal	Complete
		NCT03328026 (Phase 1/2)	BC	Intradermal	Enrolling by invitation
1650-G Vaccine (allogeneic tumor cells)	Tumor antigens	NCT00654030 (Phase 2)	NSCLC	Intradermal	Completed
Nucleic acid-based					
DNA					
AST-301 (Pngvl3-Hicd)	HER2	NCT05771584 (Phase 2)	GC	Subcutaneous	Recruiting
		NCT05163223 (Phase 2)	BC	Intradermal	Recruiting
Ifx-Hu2.0 (pDNA)	Streptococcal membrane protein, Emm55	NCT03655756 (Early Phase 1)	CM, stage III and IV	Intrathecal/ Intralesional	Completed
		NCT04160065 (Phase 1)	MCC, cSCC, and NMSC	Intrathecal/ Intralesional	Active, not recruiting
Invac-1 (DNA plasmid)	hTERT	NCT03265717 (Phase 2)	CLL	Intradermal	Terminated
pING-hHER3FL	HER3	NCT03832855 (Phase 1)	Advanced cancer	Intradermal/ Intramuscular	Recruiting
SCIB1	gp100 and TRP-2	NCT04079166 (Phase 2)	Malignant melanoma stage III/IV	Intramuscular	Recruiting
mRNA					
BNT111	Four melanoma TAAs: NY-ESO-1, MAGE-A3, tyrosinase, and TPTE	NCT04526899 (Phase 2)	Melanoma stage III/IV	Intravenous	Active, not recruiting
BNT112	PCa TAAs: kallikrein-2, kallikrein-3, PAP, HOXB13, and NK3 homeobox 1	NCT04382898 (Phase 1/2)	PCa	Intravenous	Terminated
BNT113	HPV 16 oncoproteins E6 and E7	NCT04534205 (Phase 2)	Unresectable, recurrent, or metastatic HNSCC	Intravenous	Recruiting
BNT116	Six different TAAs	NCT05142189 (Phase 1)	NSCLC	Intravenous	Recruiting
		NCT05557591 (Phase 2)	Advanced NSCLC	Intravenous	Recruiting

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
HRXG-K-1939	Tumor antigen	NCT05942378 (Phase 1)	Advanced solid tumors	Subcutaneous/ Intramuscular	Not yet Recruiting
mRNA-based, personalized cancer vaccine	Neoantigens expressed by the autologous cancer	NCT03480152 (Phase 1/2)	Melanoma, CC, GIN, GU cancer, and HCC	Intramuscular	Terminated
mRNA-0217/S001	Personalized tumor neoantigen	NCT05916248 (Phase 1)	Advanced solid tumor	Intramuscular	Recruiting
		NCT05916261 (Phase 1)	Advanced PDAC	Intramuscular	Recruiting
mRNA-2752 (Lipid NP encapsulating mRNAs)	OX40L, IL-23, and IL-36γ	NCT03739931 (Phase 1)	Advanced solid tumor malignancies or lymphoma	Intrathecal	Active, not recruiting
mRNA -4157	Personalized neoantigens	NCT03313778 (Phase 1)	Solid tumors	Intramuscular	Recruiting
		NCT03897881 (Phase 2)	Melanoma	Intramuscular	Recruiting
Personalized mRNA tumor vaccine	Personalized neoantigens	NCT03908671 (not applicable)	Metastatic advanced EAC and NSCLC	Subcutaneous	Recruiting
PGV002 mRNA vaccine	Personalized neoantigens	NCT05359354 (not applicable)	Advanced solid tumors	Intradermal	Recruiting
		NCT05192460 (not applicable)	GC, EAC, and HCC	Intradermal	Recruiting
RO7198457 (RNA-Lipoplex)	Up to 20 neoantigens	NCT04161755 (Phase 1)	PDAC	Intravenous	Active, not recruiting
SW1115C3 (mRNA personalized cancer vaccine)	Neoantigens	NCT05198752 (Phase 1)	Advanced malignant solid tumors	Subcutaneous	Recruiting
YS-ON-001 (synthetic double-strand RNA, a *TLR3* agonist)	TLR3	NCT03131765 (Phase 1)	Advanced solid tumors	Intramuscular	Completed
Peptide and protein-based					
AST-021p	HSP90-derived epitopes	NCT04864418 (Phase 1)	Advanced solid tumors	Intradermal	Active, not recruiting
Bcl-xL_42-CAF09b	Bcl-xL	NCT03412786 (Phase 1)	PCa	Intramuscular and Intraperitoneal	Completed
DNAJB1/PRKACA peptide vaccine	DNAJB1 and PRKACA	NCT04248569 (Phase 1)	Fibrolamellar HCC	Subcutaneous	Recruiting

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
DPX-Survivac	A cocktail of surviving HLA class I peptides	NCT01416038 (Phase 1)	Advanced stage OV, FTC or PPC	Subcutaneous	Completed
		NCT03332576 (Phase 1)	OV, FTC or PPC	Subcutaneous	Completed
		NCT02785250 (Phase 1/2)	PPC	Subcutaneous	Active, not recruiting
Dribble vaccine	Tumor-derived autophagosomes (dribbles corpuscle)	NCT03057340 (Phase 1)	NSCLC	Subcutaneous	Unknown status
Dribble vaccine (DPV-001)	Tumor-derived autophagosomes	NCT04470024 (Phase 1)	Metastatic HNSCC	Intradermal	Active, not recruiting
DSP-7888 (a novel cocktail peptide vaccine)	WT1 peptides	NCT04747002 (Phase 2)	AML in remission	Intradermal	Unknown status
Galinpepimut-S (peptide vaccine)	WT1 protein	NCT04040231 (Phase 1)	Mesothelioma, pleural mesothelioma, and Wilms tumor	Subcutaneous	Active, not recruiting
GV1001	hTERT	NCT04032067 (Phase 3)	BPH	Intradermal	Completed
HER2 tumor vaccine	HER2-neu peptides	NCT05315830 (Phase 1)	Advanced GAC or GEJC	Intramuscular	Unknown status
Histone H3.3-K27M neoantigen vaccine	Mutant histone H3 variant (H3.3)	NCT04749641 (Phase 1)	DIPG	Subcutaneous	Recruiting
IMU-131	B cell epitope peptide sequences selected from HER2-neu structure	NCT02795988 (Phase 1/2)	GIN and adenocarcinoma	Intramuscular	Active, not recruiting
iNeo-Vac-P01 (personalized neoantigen vaccine)	Neoantigen peptides	NCT05307835 (Phase 1)	EAC	Subcutaneous	Recruiting
		NCT04810910 (Phase 1)	Resectable PDAC	Subcutaneous	Recruiting
		NCT03662815 (Phase 1)	Advanced malignant solid tumor	Subcutaneous	Unknown status
		NCT03645148 (Phase 1)	PDAC	Subcutaneous	Completed

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
IO103 (PD-L1 peptide vaccine)	PD-L1	NCT03042793 (Phase 1)	MM	Subcutaneous	Completed
KRAS peptide vaccine	Mutant *KRAS*	NCT05013216 (Phase 1)	High risk cancer and PDAC	Subcutaneous	Recruiting
		NCT04117087 (Phase 1)	CRC and PDAC	Subcutaneous	Recruiting
LabVax 3(22)-23	Labyrinthin (a protein found on the surface of adenocarcinoma tumor cells)	NCT05101356 (Phase 1/2)	Advanced stage adenocarcinoma	Intradermal	Recruiting
NEO-PV-01	Personalized neoantigens (up to 20 peptides (14-35 amino acids))	NCT03380871 (Phase 1)	Metastatic non squamous NSCLC	Subcutaneous	Completed
		NCT03597282 (Phase 1)	Metastatic melanoma	Subcutaneous	Terminated
NeoVax	Personalized neoantigens (up to 20 peptides)	NCT03361852 (Phase 1)	FL	Subcutaneous	Active, not recruiting
		NCT04024878 (Phase 1)	OV	Subcutaneous	Recruiting
		NCT03219450 (Phase 1)	CLL	Subcutaneous	Recruiting
NY-ESO-1 ISCOMATRIX® vaccine	NY-ESO-1	NCT00199901 (Phase 2)	Melanoma	Intramuscular	Completed
OSE2101 (TEDOPI®)	10 synthetic peptides (modified epitopes restricted to HLA-A2^{+}) targeting 5 TAAs: CEA, HER2-neu, p53, MAGE2, and MAGE3	NCT04713514 (Phase 2)	Platinum-sensitive OV and relapsed OV	Subcutaneous	Recruiting
OTSGC-A24 (a cocktail of peptide vaccines against GC-specific antigens)	Novel specific tumor antigens: FOXM1, DEPDC1, KIF20A, URLC10, and VEGFR1	NCT03784040 (Phase 1)	Advanced GC	Subcutaneous	Unknown status
		NCT01227772 (Phase 1/2)	Advanced GC	Subcutaneous	Unknown status
OVM-200	Survivin (a protein expressed at high levels in many solid tumors)	NCT05104515 (Phase 1)	PCa, NSCLC, and OV	Subcutaneous	Recruiting
Personalized cancer vaccine	Tumor antigen peptides (alfa-fetoprotein and Glypican-3)	NCT05059821 (Phase 1)	HCC	Subcutaneous	Recruiting
Personalized neoantigen cancer vaccine	Neoantigen peptides	NCT04072900 (Phase 1)	Metastatic melanoma (skin)	Percutaneously into inguinal lymph nodes	Unknown status

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
PGV001	Tumor neoantigens	NCT03359239 (Phase 1)	Metastatic UC	Intravenous	Completed
Poly-ICLC (mutation-derived tumor antigen vaccine)	Several peptides based on each patient's own tumor sequence	NCT03223103 (Phase 1)	Glioblastoma	Intrathecal	Active, not recruiting
PolyPEPI1018	12 dominant epitopes from 7 CTAs	NCT03391232 (Phase 1/2)	Metastatic CC	Subcutaneous	Completed
		NCT05243862 (Phase 2)	Metastatic CC	Subcutaneous	Active, not recruiting
Proscavax	PSA	NCT02058680 (Phase 1)	PCa	Intradermal	Unknown status
		NCT03579654 (Phase 2)	PCa	Intradermal	Unknown status
PVX-410 (multi-peptide cancer vaccine)	MM associated antigens: XBP1, syndecan-1 (CD138), and SLAMF7	NCT04634747 (Phase 2)	Metastatic TNBC	Subcutaneous	Not yet recruiting
Radvax	Extracted autologous tumor proteins	NCT05807035 (Phase 1)	Solid tumor	N/A	Recruiting
rHSC-DIPGVax (neoantigen heat shock protein vaccine)	16 peptides reflecting neo-epitopes found in the majority of DIPG and DMG	NCT04943848 (Phase 1)	DIPG and DMG (h3 k27m-mutant)	Intrathecal	Recruiting
RV001V	*Ras* homolog gene family member C	NCT04114825 (Phase 2)	PCa recurrent	Subcutaneous	Active, not recruiting
Stimuvax® (L-BLP25)	MUC1	NCT01507103 (Phase 2)	CRC	Subcutaneous	Completed
UCPVax (two separate peptides called UCP2 and UCP4)	Telomerase-derived helper peptides	NCT04263051 (Phase 2)	Advanced NSCLC	Subcutaneous	Active, not recruiting
		NCT02818426 (Phase 1/2)	Metastatic NSCLC	Subcutaneous	Active, not recruiting
		NCT04280848 (Phase 2)	Glioblastoma	Subcutaneous	Active, not recruiting
		NCT05528952 (Phase 2)	HCC	Subcutaneous	Recruiting
		NCT03946358 (Phase 2)	HNSCC, ASCC, and CC	Subcutaneous	Active, not recruiting
UV1	hTERT	NCT03538314 (Phase 1)	Malignant melanoma	Intradermal	Active, not recruiting
		NCT04382664 (Phase 2)	Malignant melanoma	Intradermal	Completed
		NCT05075122 (Phase 2)	HNSCC	Intradermal	Recruiting
YB-01 (a recombinant fusion protein)	MUC1	NCT05986981 (Phase 2)	Solid tumor	Intramuscular	Not yet recruiting

(Continues)

TABLE 1 (Continued)

Vaccine type/Name	Antigen(s)	Identifier/ Phase	Cancer	Injection route	Status
Virus-based					
Ad-CEA	CEA	NCT03050814 (Phase 2)	CRC	Subcutaneous	Terminated
CMB305	NY-ESO-1	NCT03520959 (Phase 3)	Metastatic NY-ESO-1 positive SS	Subcutaneous and Intramuscular	Terminated
ETBX-071, ETBX-61, and ETBX-51 (adenovirus-based vaccines)	TAAs: PSA, MUC1, and brachyury	NCT03481816 (Phase 1)	PCa	Subcutaneous	Completed
GRT-C901/GRT-R902	Patient-specific neoantigen	NCT03639714 (Phase 1/2)	NSCLC, CRC, and UC	Subcutaneous	Completed
		NCT05141721 (Phase 2/3)	Metastatic CRC	Intramuscular	Active, not recruiting
		NCT05456165 (Phase 2)	Metastatic CRC	Intramuscular	Terminated
GRT-C903/GRT-R904	Shared neoantigens in solid tumors	NCT03953235 (Phase 1/2)	NSCLC, CRC, and PDAC	N/A	Completed
PANVAC-VF (falimarev-inalimarev)	MUC1 and CEA	NCT00669734 (Phase 1)	PCa	Subcutaneous	Active, not recruiting
PROSTVACV/F	PSA	NCT02933255 (Phase 1/2)	PCa	Subcutaneous	Active, not recruiting
		NCT00060528 (Phase 1/2)	PCa	Subcutaneous	Completed
Vvax001	HPV-derived tumor antigens	NCT03141463 (Phase 1)	CC	Intramuscular	Completed

Abbreviations: ACIT-1, allogeneic cell immunotherapy 1; Ad.p53-DC, adenovirus-p53 transduced dendritic cell; AML, acute myeloid leukemia; ASCC, anal squamous cell carcinoma; BC, breast cancer; Bcl-xL, B-cell lymphoma-extra-large; BPH, benign prostatic hyperplasia; CC, cervical cancer; CD, cluster of differentiation; CEA, carcinoembryonic antigen; CIK, cytokine-induced killer cell; CLL, chronic lymphocytic leukemia; CM, cutaneous melanoma; CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; CTAs, cancer testis antigens; DCs, dendritic cells; DEPDC1, DEP domain containing 1; DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; DNA, deoxyribonucleic acid; DNAJB1, DnaJ homolog subfamily B member 1; EAC, esophageal adenocarcinoma; FL, follicular lymphoma; FOXM1, forkhead box protein M1; FTC, fallopian tube cancer; GAC, gastric adenocarcinoma; GC, gastric cancer; GEJC, gastroesophageal junction adenocarcinoma; GIN, gastrointestinal neoplasms; GM-CSF, granulocyte-macrophage colony-stimulating factor; gp100, glycoprotein 100; GU, genitourinary; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; HLA, human leukocyte antigen; HNSCC, head and neck squamous cell carcinoma; *HOXB13*, homeobox B13; HPV, human papillomavirus; HSP90, heat shock protein 90; hTERT, human telomerase reverse transcriptase; IL, interleukin; KIF20A, kinesin family member 20A; KRAS, kirsten rat sarcoma virus; LAMP, lysosome-associated membrane protein 1; MAGE, melanoma antigen family; MCC, merkel cell carcinoma; Melan-*A*, melanoma antigen recognized by T cells 1; mDC, mature dendritic cell; MM, multiple myeloma; mRNA, messenger ribonucleic acid; MUC, mucin 1; N/A, not applicable; NB, neuroblastoma; NCT, national clinical trial; NETs, neuroendocrine tumors; NMSC, non-melanoma skin cancers; NP, nanoparticle; NSCLC, non-small cell lung cancer; NY-ESO-1, New York esophageal squamous cell carcinoma 1; OV, ovarian cancer; OX40L, OX40 ligand; p53, tumor protein p53; PAP, prostatic acid phosphatase; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; PDC, plasmacytoid dendritic cell; PD-L1, programmed death ligand 1; PPC, primary peritoneal cancer; PRKACA, protein kinase cAMP-activated catalytic subunit alpha; PSA, prostate-specific antigen; PST, pediatric solid tumor; SCLC, small cell lung cancer; shRNA, short hairpin ribonucleic acid; SLAMF7, signaling lymphocytic activation molecule family 7; SS, synovial sarcoma; STS, soft tissue sarcoma; TAAs, tumor-associated antigens; *TGFβ*, transforming growth factor beta; Th1, T-helper type 1 cells; TLR3, toll-like receptor 3; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TPTE, transmembrane phosphatase with tensin homology; TRP-2, tyrosinase-related protein 2; UC, urothelial carcinoma; UCP, universal cancer peptide; *URLC10*, up-regulated lung cancer 10; VEGFR1, vascular endothelial growth factor receptor 1; WT1, Wilms tumor 1; XBP1, X-box binding protein 1.

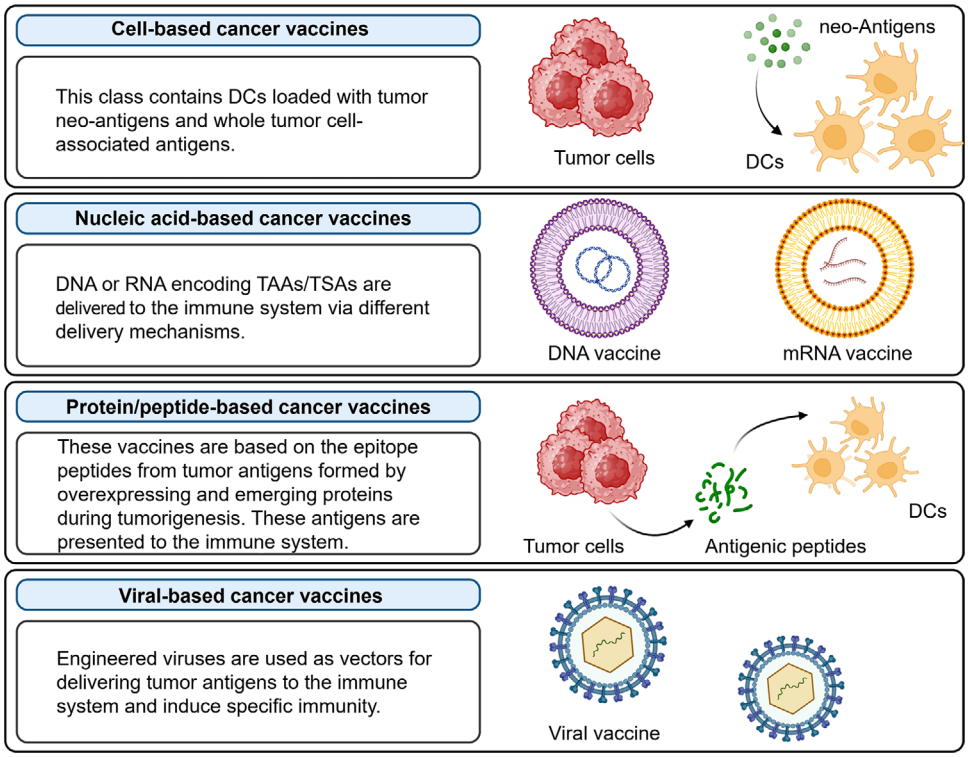

FIGURE 1 Overview of main cancer vaccine platforms. A schematic illustration of the four main cancer vaccine platforms used in humans: cell-based, nucleic acid-based, peptide/protein-based, and viral-based vaccines. Each platform offers unique advantages for targeting malignant cells. Among them, mRNA-based vaccines stand out as strong candidates for developing SVPs due to their ease of use, cost-effectiveness, and potential to induce long-term immune responses. Abbreviations: DCs, dendritic cells; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid; TAAs, tumor-associated antigens; TSAs, tumor-specific antigens; SVP, smart vaccine platform.

recombinant deoxyribonucleic acid (DNA) [29, 30]. However, the time-consuming, expensive, and labor-intensive process of preparing these genetically modified cells remains a significant limiting factor [31, 32]. Recently, mRNA-based cancer vaccines have gained considerable attention due to their benefits, such as being well-tolerated, safe for patients, non-infectious, immunogenic, and relatively inexpensive [33]. A major challenge lies in their mass production, storage, and distribution for widespread vaccination programs [34]. To address these issues, various carrier platforms have been developed to enhance mRNA stability and facilitate its uptake by antigen-presenting cells (APCs) [35, 36].

Another type of cancer vaccine, known as protein- and peptide-based vaccines, uses specific protein segments or peptides derived from tumor cells to stimulate an immune response against cancer cells that display these antigens, allowing for precise recognition and targeting of the cancer cells. This approach offers several advantages, such as targeted antigen specificity and reduced adverse effects compared to traditional therapies [37, 38]. However, challenges remain in ensuring stability, minimizing immunogenicity, and managing complex manufacturing processes [39, 40]. As a final example of cancer vaccines, viral-based vaccines use genetically altered viruses as carriers for tumor-associated antigens (TAAs). These vaccines provide greater stability than mRNA vaccines and can induce intracellular antigen expression, strong immunogenicity, and a rapid immune response [41]. However, their efficacy may be limited by pre-existing immunity to the vaccine virus, and they often rely on direct intratumoral (IT) injections to overcome dilution and neutralization in the bloodstream [42].

Recent advancements have focused on optimizing tumor-specific antigens (TSAs), developing more potent vaccine adjuvants, and exploring alternative delivery platforms, such as nanoparticles (NPs) [43]. Key parameters, including size, charge, shape, and surface modifications, can be tailored in NPs [44, 45]. This versatility allows NPs to co-deliver antigens and adjuvants, increase stability and half-life, prolong bioavailability, and control antigen release [43, 46]. NPs hold promise as tools to address challenges in mRNA vaccine design and delivery [47]. Various nanocarriers are used as delivery systems, including polymeric NPs, protein-based NPs, inorganic NPs, liposomes, and bio-nanocarriers [48]. Surface modification of

NPs helps elicit more specific adaptive immune responses [46], while polyethylene glycol (PEG) reduces nonspecific binding to serum proteins [49]. Studies using preclinical tumor models have shown that intravenous (IV) injection of a self-assembling NPs vaccine induces systemic innate immunity. This approach effectively remodels the TME, promoting the development of tumor-specific $CD8^+$ T cells and resulting in tumor regression [50, 51].

In addition to NPs, exosomes represent another promising platform for vaccine delivery [52]. Exosomes, natural vesicles secreted by cells, are ideal for vaccine delivery due to their inherent stability, biocompatibility, and ability to cross biological barriers [53]. Loaded with antigenic cargo, exosomes can efficiently target APCs, eliciting robust immune responses [54]. Their small size enhances tissue penetration and immunomodulation, while their natural origin minimizes concerns about immunogenicity. Exosome-based vaccines hold significant potential for personalized immunotherapy and the targeted delivery of antigens, adjuvants, or therapeutic molecules [55].

Click chemistry, a key component of smart vaccine platforms (SVPs), is a rapidly growing field in bioconjugation and drug discovery [56]. Awarded the 2022 Nobel Prize in Chemistry [57], it has gained popularity for functionalizing materials and enabling researchers to study cellular processes and track biological events in living organisms [58]. This approach has the potential to enhance cancer-targeted pharmaceuticals and overcome challenges such as imprecise drug activation and limited tumor penetration [59, 60]. The integration of nanotechnology with click chemistry allows for the development of targeted and stable vaccine delivery systems, known as SVPs. These systems, designed to encapsulate mRNA-encoding antigens, can be enhanced with synthetic and natural molecules to improve stability and targeted delivery. This review provides a comprehensive overview of SVP concepts, highlighting both their opportunities and challenges.

2 | mRNA-based vaccines as a key framework for SVPs

One of the major obstacles to developing an effective therapeutic cancer vaccine and SVP platform is the selection of optimal antigens. Antigens must be recognized by the patient's T cells and presented frequently and exclusively on the surface of tumor cells. Antigen selection is crucial in defining key vaccine characteristics, including the ability to generate a strong and broad immune response, precise targeting, and minimized toxicity. Additionally, it influences the targeting of cancer stem cells to prevent recurrence and supports the development of long-lasting immunologic memory that could enable cancer eradication after vaccination [61].

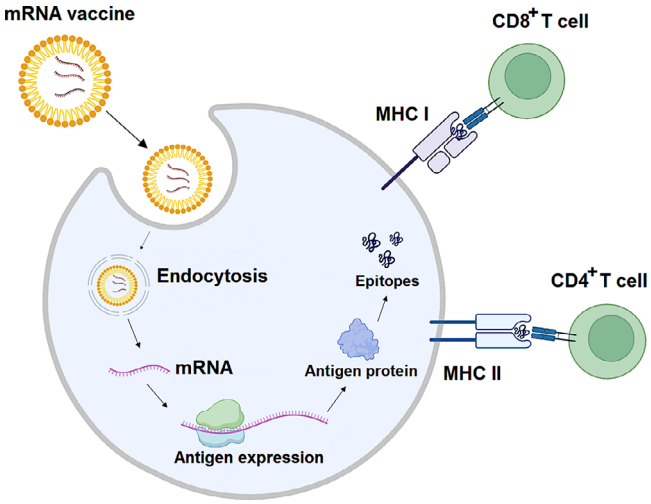

FIGURE 2 mRNA delivery systems for enhanced immune activation. Encapsulating mRNA within delivery systems enhances vaccine efficacy by effectively overcoming biological barriers. Once the delivery system merges with the cell membrane, the encapsulated mRNA is released into the cytoplasm, where it is translated into antigens. These antigens are subsequently presented by MHC-I and MHC-II complexes, activating immune responses that recruit T-helper cells ($CD4^+$) and cytotoxic T cells ($CD8^+$) to specifically target and eliminate cancer cells. Abbreviations: $CD4^+$ T cell, cluster of differentiation 4^+ T cell; $CD8^+$ T cell, cluster of differentiation 8^+ T cell; MHC, major histocompatibility complex; mRNA, messenger ribonucleic acid.

A notable advantage of mRNA-based vaccines is their ability to induce both humoral and cellular immune responses, particularly by activating $CD8^+$ T cells, which are essential for targeting and eliminating cancer cells [62]. mRNA vaccines offer unique benefits, functioning as self-adjuvants and mitigating the potential risks of genomic integration and the genetic mutations associated with DNA-based therapeutic approaches [63]. Furthermore, mRNA's ability to produce diverse tumor antigens—through processes like alternative mRNA splicing or intron retention within a single molecule—provides a distinct advantage over traditional protein- and peptide-based strategies [64]. Another key benefit of mRNA vaccines is their cost-effective manufacturing, which allows for the efficient generation of large quantities of the intended product under in vitro conditions [62]. The delivery of mRNA encoding cancer antigens to APCs initiates translation within the cytoplasm, followed by the processing of synthesized proteins into peptides. These peptides are then presented by MHC (major histocompatibility complex) class I and class II molecules (Figure 2), triggering the activation of tumor-reactive T cells specific to the antigens [65].

TABLE 2 Characteristics of various types of tumor antigens used in developing SVPs.

Feature	TAAs		TSAs		
Types of tumor antigens	Over-expressed proteins/differentiation antigens	CTAs	Oncoviral antigens	Shared neoantigens	Private neoantigens
Tumor specificity	Variable	Good	Optimal	Optimal	Optimal
Central tolerance	High	Low	None	None	None
Prevalence in patients	Frequent	Frequent	Frequent	Frequent	Low

Abbreviations: CTAs, cancer testis antigens; TAAs, tumor-associated antigens; TSAs, tumor-specific antigens; SVPs.

Nevertheless, mRNA vaccines are associated with a range of challenges that require careful consideration. A significant hurdle inherent in mRNA-based vaccines is the delivery of molecules into the cytoplasm. mRNA, being large, unstable, hydrophilic, and negatively charged, faces difficulties in crossing the lipid bilayer of target cell membranes. Additionally, when naked mRNA is injected into an organism, it is rapidly degraded due to the high levels of ribonuclease present in blood and bodily fluids [66]. As a result, various strategies have been developed to facilitate the delivery of mRNA vaccines to cells, including approaches based on viral vectors, lipids, polymers, hybrid carriers, and peptides [67]. Furthermore, there are multiple options for selecting suitable antigens for cancer vaccines, including TAAs or TSAs, also known as neoantigens (Table 2).

TAAs are present in normal cells but show preferential or abnormal expression in cancerous cells, making them promising candidates for cancer vaccine development that could be universally applied to patients with the same type of malignancy [68]. Clinical investigations have primarily focused on TAAs [61, 69], which can be broadly classified into overexpressed antigens, differentiation antigens, and cancer testis antigens (CTAs). Overexpressed antigens are found in both normal and neoplastic tissues, with markedly higher expression levels in neoplasms [70]. Differentiation antigens, another category of TAAs, are typically specific to certain tissues such as gp100 and Melan-A in melanoma [71], PAP and PSA in PCa [72], and CEA in CRC [73]. CTAs represent a unique class of TAAs that are predominantly expressed in various tumor types while largely absent in normal tissues, except in the testis and placenta. Examples include NY-ESO-1, MAGE-A1, MAGE-A3, B melanoma antigen, and gastric cancer antigen. Due to their restricted expression in normal tissues and prominent role in spermatogenesis, CTAs are viewed as particularly promising candidates for cancer vaccine development [74].

One limitation of targeting TAAs is that they are normal host proteins, which can lead to immune self-tolerance mechanisms that degrade or eliminate TAA-specific T cells with high functional avidity [75]. Additionally, TAA-specific T cells may target normal tissues, potentially causing toxicity or autoimmune diseases [76]. Therefore, targeting such antigens requires careful consideration.

Recent studies have shown that neoantigens (i.e., TSAs) arise from non-synonymous mutations or epigenetic changes and are expressed only in cancer cells (e.g., β-catenin-m, HSP70-*2*, and KRAS) [77]. These mutant peptides are more likely to be perceived as foreign by the immune system, allowing them to evade self-tolerance mechanisms and making them highly immunogenic targets [78]. Neoantigen-based vaccines have been explored in preclinical and early-phase clinical trials for various cancers [79, 80]. Several early-stage clinical studies across different cancer types have demonstrated that personalized neoantigen vaccines are safe, feasible, and capable of enhancing immune responses against predicted neoepitopes [81, 82]. For instance, the personalized neoantigen vaccine NEO-PV-01 elicited neoantigen-specific $CD4^+$ and $CD8^+$ T cell responses when used as a first-line treatment for advanced non-squamous non-small cell lung cancer (NSCLC) [83].

A particular challenge with the use of neoantigenic vaccines is that some tumors (e.g., AML) have a limited number of immunogenic epitopes due to low mutation frequency compared to solid tumors. Therefore, most clinical trials of neoantigen vaccines have been limited to cancer types with high mutation burdens [84]. However, a recent study revealed that vaccines targeting neoantigens can improve survival in patients with glioblastoma, which generally exhibits a low mutation burden [85]. Another challenge in using mutation-derived vaccine peptides is that most tumor-specific mutations are patient-specific and thus unsuitable in large-scale vaccine production, although they can be utilized for personalized approaches [86].

Overall, selecting the appropriate antigens is crucial for vaccine efficacy. While some vaccine clinical trials have shown promising results, the overall objective response rate remains low. Currently, there is insufficient clinical trial data to determine the optimal antigen or group of antigens for widespread application. Combining TAAs and neoantigens has shown promising results [40], suggesting

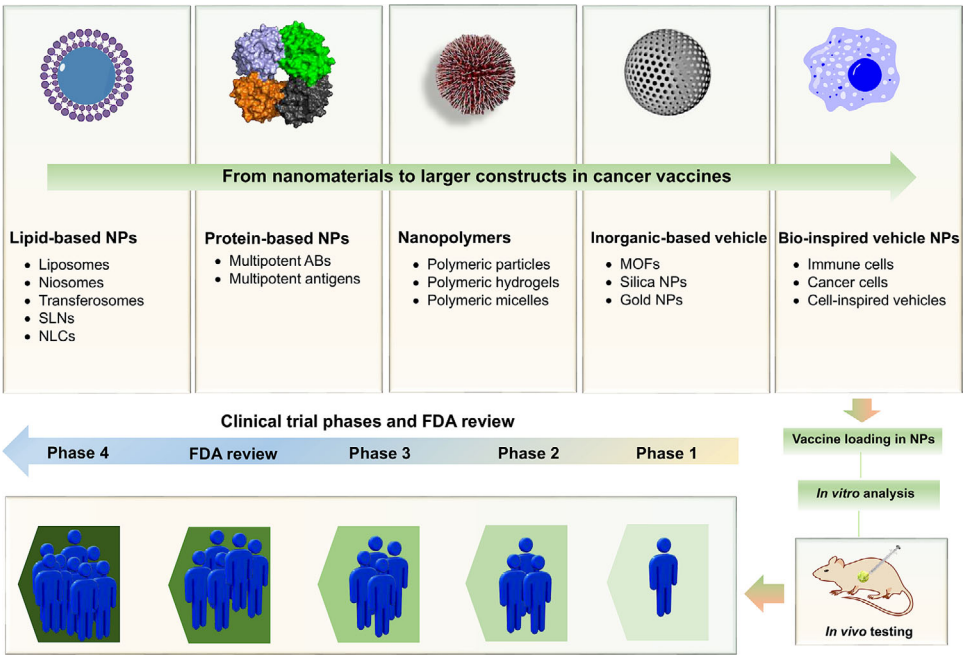

FIGURE 3 Overview of NPs in vaccine delivery. Schematic illustrating the types of NPs used in vaccine delivery, specifically in SVPs for encapsulating mRNA. Various nanomaterials, including lipid-, protein-, polymer-, and inorganic-based carriers, as well as bio-inspired systems, serve as effective delivery vehicles for cancer vaccines. These carriers enhance vaccine bioavailability, biodistribution, and half-life. Once the vaccine is encapsulated within nanocarriers, the delivery system undergoes rigorous validation through in vitro and in vivo assessments. After successful validation, the vaccine progresses through clinical trial phases: Phase 1 (evaluating safety and dosage), Phase 2 (assessing efficacy and potential side effects), and Phase 3 (expanded testing in larger populations). If the vaccine shows positive outcomes, it is submitted to the FDA for review. Upon approval, Phase 4 post-marketing studies assess long-term efficacy and safety in real-world settings, ensuring the vaccine's readiness for broad distribution. Abbreviations: ABs, antibodies; FDA, food and drug administration; MOFs, metal-organic frameworks; NLCs, nanostructured lipid carriers; NPs, nanoparticles; SLNs, solid lipid nanoparticles.

that a combination of antigenic targets may improve outcomes and facilitate the development of versatile SVPs.

3 | NPs as protective shields for SVPs

Conventional vaccine platforms, such as naked generation, face numerous obstacles including challenges such as low stability, limited immunogenicity, inadequate biodistribution, and off-target effects [87]. In recent years, there has been a rising level of interest in using NPs as delivery vehicles for vaccines (Figure 3). NPs can either encapsulate the vaccine antigen or attach it to their surface [88, 89]. Encapsulation protects antigens from degradation and ensures a sustained immune response, while surface decoration allows for antigen presentation similar to that of the pathogen, triggering a comparable immune response [90]. Furthermore, certain composite NPs enable site-specific vaccine delivery and prolonged release, maximizing exposure to the immune system. Researchers are also exploring non-traditional delivery methods such as topical application, inhalation, and optical delivery using NPs [88, 91]. Additionally, NPs offer the potential to combine multiple antigens within a single particle, providing protection against multiple diseases simultaneously [92, 93].

There are various types of nanomaterials used as delivery vehicles for cancer vaccines, including lipid-based, protein-based NPs, polymer-based, inorganic-based, and bio-inspired vehicles [94]. Each of these systems holds great potential for application in the design of therapeutic cancer vaccines [95]. Lipid-based NPs (LNPs) have emerged as promising carriers for effective cancer vaccine delivery [96]. Among these, liposomes have garnered significant attention for their potential in therapeutic cancer vaccine design [97]. Due to their structural similarity to cell membranes, liposomes provide an excellent platform for antigen encapsulation, thereby improving antigen stability. Furthermore, these LNPs can integrate with cell membranes, promote antigen presentation to APCs, and boost immunogenicity, thereby stimulating the adaptive immune response [98].

The safety and efficacy of liposomes as adjuvants in humans were first demonstrated by Allison and Gregoriadis in 1974, marking the beginning of their use as vaccine delivery systems. Since then, liposomes have gained popularity and are increasingly explored for their potential in

immunotherapies [99]. A well-known cationic liposome, 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), has been widely researched for its ability to promote antigen delivery in APCs such as DCs [100]. Research has shown that DOTAP can activate DCs, enhancing antigen delivery and endocytosis [101], leading to the induction of mitogen-activated protein kinase and chemokines that promote a response from the immune system directed at cancer cells. Furthermore, liposome-based vaccines efficiently induce functional antigen-specific $CD8^+$ and $CD4^+$ T cells, effectively eliminating tumors in mouse models [102].

Liposomes are widely used for the delivery of RNA-based vaccines, such as mRNA cancer vaccines, in animal tumor models. Incorporating different adjuvants, such as lipopolysaccharide (LPS), has been shown to enhance the effectiveness of lipid-based mRNA vaccines, resulting in tumor shrinkage and prolonged survival in tumor-bearing mice [103]. A recent breakthrough involves the development of a novel mRNA lipid NP cancer vaccine aimed at preventing cancer relapse post-stem cell transplant [104]. This innovative vaccine utilizes LNPs to deliver mRNA-encoding TSAs to APCs, eliciting an immune response against cancer cells. Another example is mRNA-4157, a lipid-encapsulated personalized vaccine encoding several neoantigens, evaluated alone and in combination with pembrolizumab in a phase 1 study on patients with solid tumors, administered via intramuscular (IM) injection [8]. Results showed mRNA-4157 to be safe and well tolerated, inducing neoantigen-specific T cells and supporting its progression to phase 2. However, the potential toxicity of these liposomes requires further validation. Ongoing research is crucial to refine their application and guarantee their safety in vaccine delivery [105].

Protein-based NPs are promising candidates for the development of SVPs due to their excellent biodistribution and biocompatibility. Researchers have developed methods to design protein-based NPs that respond to environmental cues, particularly pH changes. For example, octahedral NPs have been engineered with targeting antibodies (ABs) that disassemble below certain pH thresholds. These NPs can carry protein and nucleic acid payloads, enter cells through AB-mediated endocytosis, and release their contents in response to pH variations [106]. In vaccine applications, protein-based NPs are designed to mimic pathogens (such as multipotent antigens and ABs), enhancing immune responses while efficiently delivering antigens [106–111].

Furthermore, NPs, including nanopolymers, have emerged as a promising platform for vaccine delivery. Nanopolymers have been utilized in drug delivery since the emergence of NPs [112, 113], commonly serving as materials for drug encapsulation. They are highly biocompatible and non-toxic, making them ideal candidates for clinical applications, particularly in delivering cancer vaccines [114]. Polymeric NPs can be categorized into two main types: natural and synthetic [115]. Natural polymers such as alginate [116] are one type of polymeric NP. Another promising natural polymer for nonviral delivery platforms is chitosan, known for its biocompatibility, biodegradability, low immunogenicity, and ease of manufacturing [117]. Chitosan has been shown to effectively enhance both humoral and cellular immunity, including stimulating mucosal immune responses. Cellulose, another natural polymer, offers significant advantages for targeted and controlled release in vaccine applications [118].

Unlike natural polymeric NPs, their synthetic counterparts have been more extensively studied for vaccine delivery purposes. Synthetic polymer-based carriers come in various forms, including polymeric micro/NPs, polymeric micelles, dendrimers, nanodiscs, and hydrogels [119–136]. Polymeric micro/NPs are colloidal particles of micro or nano size that can assemble hydrophilic and hydrophobic molecules [137], enabling stable delivery of antigens with high efficacy [138]. They have an ability to effectively entrap and adsorb antigens, making them a promising avenue for drug delivery. Synthetic polymeric NPs encompass materials such as polylactic acid, poly(lactic-*co*-glycolic acid) (PLGA), polyglutamic acid, and PEG [139–142]. PLGA, for instance, is an FDA-approved synthetic polymer known for its excellent biocompatibility and biodegradability [143]. It enables controlled, sustained release of antigens and can be customized for specific purposes, such as promoting lysosomal escape [144]. PLGA NPs have demonstrated stronger immune responses compared to PEG, possibly due to their slower antigen release and ability to activate specific immune cells [145]. Another example is polyethyleneimine (PEI), used to synthesize linear and branched polymers with varying molecular weights [146]. PEI-based NPs, which are positively charged, are extensively employed in gene delivery owing to their ability to bind nucleic acids via electrostatic interactions [147].

Synthetic polymers have been successfully developed to interact with molecules on the surface of APCs and to be internalized through cell endocytosis [148–151]. Once inside the cell, the NPs disintegrate via the proton sponge effect in the acidic lysosomal environment, facilitating the cytoplasmic release of the loaded substances. Examples of such polymers include poly(methyl methacrylate), poly(ethylacrylic acid), and poly(propylacrylic acid) [99, 152, 153]. These polymers provide multiple benefits, such as potent immunological adjuvant effects, straightforward preparation, safety, and biocompatibility. Overall, synthetic polymers offer numerous advantages in vaccine

delivery, including sustained and controlled release of antigens, customizable modifications for desired functions, and efficient internalization by APCs [150, 154, 155]. However, researchers emphasize the importance of understanding the interaction between NPs and the immune system, as this interaction can influence the safety and efficacy of vaccines [156]. Further research is required to refine the design of polymeric NPs for vaccine delivery and to explore their long-term impacts on the immune system.

Despite the promising potential of polymeric NPs and other advanced vaccine delivery systems, new vaccine delivery systems continue to emerge, offering distinct advantages in specific applications. Vaccines incorporating complex biochemical behaviors, such as those utilizing inorganic-based vehicles, have shown remarkable potential in cancer immunotherapy [157, 158]. These vehicles can take the form of diverse NPs and metal-organic frameworks, including silica [159], gold [160], iron oxide [161], silver [162], carbon [163], graphene [164], selenium [165], copper oxide [166], and zinc oxide [167]. In certain scenarios, inorganic-based vaccine delivery platforms composed of mineral components are preferred over organic materials due to their potent immunostimulatory effects and their ability to maintain stability within the body [168]. This has spurred the development of numerous inorganic-based vaccine formulations, which have demonstrated promise in various medical applications [66].

Mesoporous silica NPs (MSNPs) are a type of synthetic, amorphous silica-based NP extensively studied in cancer therapy [169]. Possessing several advantageous properties such as a porous structure, high surface area, tunable surface functionality, and high loading efficiency, MSNPs are considered ideal for drug and vaccine delivery applications [170]. Additionally, MSNPs demonstrate adjuvant properties stemming from their morphology, size, and modified groups, which further enhance their therapeutic effects [171]. MSNPs have been utilized to deliver a range of therapeutics including chemotherapeutic agents, silencing ribonucleic acid (siRNA), and vaccines, showing promising results. They represent a compelling platform for cancer therapy, and their potential continues to be explored in preclinical and clinical studies [172]. However, additional studies are required to enhance the application of MSNPs in vaccine delivery and confirm their safety in clinical settings [173]. Future research should also explore the combination of MSNPs with other therapeutic modalities to improve cancer treatment outcomes.

As an additional class of NPs, bio-inspired delivery vehicles offer a promising alternative for overcoming traditional pharmaceutical challenges [174]. These innovative vehicles demonstrate remarkable potential by seamlessly integrating with biological systems and aligning more effectively with physiological processes. Compared to synthetic counterparts, bio-inspired vehicles provide several advantages, including enhanced drug and antigen transport capacity, improved immune system engagement, and more precise targeted delivery mechanisms [175]. Traditional synthetic delivery systems often face immunological barriers, as the body's defense mechanisms typically recognize these artificial carriers as foreign entities and eliminate them before therapeutic agents can reach their intended targets. This premature immune response can significantly compromise the efficacy and safety of vaccines. Bio-inspired vehicles, however, address these challenges through sophisticated biomimetic designs that emulate natural biological structures, allowing them to evade immune surveillance more successfully [176, 177].

The use of bacterial ghosts and outer membrane vesicles (OMVs) as delivery vehicles in cancer therapy has been extensively researched within the bio-inspired vehicles field [178, 179]. Bacterial ghosts are empty bacterial shells that can be effectively loaded with DNA and presented to DCs, presenting opportunities for enhanced immune activation in cancer therapy [180]. Researchers have optimized the drug delivery system (DDS) using bacterial ghost-based DNA delivery vectors and identified specific formulations for clinical studies [181, 182]. Bacterial ghosts are generated through carefully controlled biological or chemical disruption techniques that eliminate live bacteria while preserving essential antigens to provoke an immune response, thus improving vaccine safety. Ghost vaccines are produced via methods like phage-mediated lysis, in which viruses lyse bacterial cells, or through chemical techniques that remove the cell contents while leaving the envelope intact. This creates a biologically inert yet immunologically active structure, similar to a killed vaccine. Ghost vaccines offer three key advantages: (1) *Antigenicity preservation* – the mild preparation method maintains bacterial antigenic properties for an effective immune response, (2) *Flexibility* – the ability to carry multiple antigens and plasmid DNA for targeting various pathogens, and (3) *Safe delivery* – they serve as platforms for DNA vaccines and carriers for recombinant proteins and immune-enhancing adjuvants. Ghost vaccines elicit strong immune responses and show great potential against various pathogens, particularly as platforms for multi-antigen vaccine development [181–183].

OMVs originate from Gram-negative bacteria and contain unique pathogen-associated molecular patterns. These patterns include LPS, outer membrane proteins, and lipoproteins [184, 185]. OMVs can present diverse antigens on their surfaces by expressing lipoproteins like outer surface protein A and cytolysin A, which are specifically designed to be surface-exposed. In addition to

antigen presentation by DCs, OMVs can regulate the TME without side effects. OMVs are highly versatile, capable of carrying various payloads including targeted ABs, small interfering RNAs, peptide antigens, and NPs [186, 187]. Overall, bacteria-inspired delivery vehicles show great promise in vaccine development and preclinical applications for cancer therapy. The utilization of bacterial ghosts and OMVs as delivery vehicles offers a unique approach to antigen delivery, potentially improving efficacy while reducing side effects. Further research is necessary to optimize their application and ensure their safety and efficacy in clinical settings [90, 188, 189].

Briefly, the field of targeted vaccine delivery for cancer treatment is advancing quickly, and many candidates are currently undergoing clinical trials [190, 191]. Each candidate presents distinct advantages and limitations that require careful evaluation based on the specific cancer type and vaccine involved. For example, liposomes are lipid bilayer vesicles designed to encapsulate vaccine antigens, enabling targeted delivery to cells [192]. Liposomes have demonstrated potential in preclinical research as effective delivery systems for cancer vaccines, owing to their biocompatibility and ability to protect antigens from degradation. However, their relatively large size may limit deep tumor penetration and the ability to reach all desired cells [192]. On the other hand, nanopolymers are small, branched polymers that are engineered with specific functional groups to target cells. They have shown effectiveness in delivering cancer vaccines to APCs and eliciting a robust immune response [117]. However, their toxicity and potential to cause inflammation to require further evaluation. In selecting NPs for designing targeted delivery systems (like SVPs) for cancer vaccines, priority should be given to safety, biocompatibility, and the capacity to prolong vaccine half-life. The delivery system should also selectively target cells while minimizing off-target effects.

4 | Functionalizing NPs for advanced SVPs

Technological advancements have enabled the modification of NPs' surface chemistry to create particles with specific biological properties [193]. The development of smart NPs engineered and functionalized to enhance their specificity and performance in cancer therapy presents a promising alternative to conventional NPs. These smart NPs efficiently accumulate and release their payloads, creating a sophisticated delivery platform [194]. They can be guided by specific stimuli and delivered to target sites with precision [195]. Functionalized NPs (Figure 4) have diverse applications ranging from drug delivery for treatment and cure to diagnostic uses in biological imaging, cell labeling, biosensors, and medical devices like stents or lenses [196–198].

To achieve optimal therapeutic pharmacokinetics, NP surfaces are functionalized with different molecules [199]. Each category of molecules offers specific advantages. For instance, NPs coated with polymers and surfactants exhibit better chemical and thermal stability and are less prone to aggregation, enhancing their utility [200]. Ligands, on the other hand, are particularly appealing as they can significantly increase receptor binding affinity. Given that circulating NPs experience strong shearing pressures in the vasculature, achieving high binding affinity is crucial for in vivo efficacy [201]. Through a process known as active targeting delivery, targeting ligands on NPs can specifically bind to target cells upon entering the TME, facilitating the delivery of targeted therapeutic agents. Various recognition ligands include proteins, peptides, ABs, nucleic acids, carbohydrates, and small molecules [202].

4.1 | Functionalization of NPs with synthetic polymers

Polymers are prominent candidates in the strategy of functionalizing NPs [203]. When used for surface modifications, polymers can alter various properties of NPs, including stability, solvent compatibility, size, dispersion, and assembly. Additionally, polymers can endow NPs with a larger surface area and increased mechanical strength, thereby enhancing their durability. The polymer chain can be directly attached in the presence of reactive sites on the NP surface, allowing for precise control of their properties. Nevertheless, this method may not ensure a high density of polymers on NP surfaces [204, 205]. Optimization of nanocarrier modification based on the polymer-to-carrier ratio offers the possibility of grafting additional functional moieties along with the protective polymer onto the carrier surface. This approach facilitates the development of immune-specific carriers with longevity and targetability in vivo, while being sterically protected during circulation [206].

Several notable polymers are commonly used for surface functionalization. PEG is frequently employed as an adsorbent or graft material on NP surfaces due to its properties such as electrical neutrality, strong spatial repulsion, and hydrophilicity. PEGylation involves conjugating PEG to drugs or NPs to prolong circulation time and mitigate undesirable host reactions [207]. PEG can also enhance targeting delivery capability and control NP physicochemical properties, including membrane mechanical properties, stability, drug loading, and release behavior [208, 209].

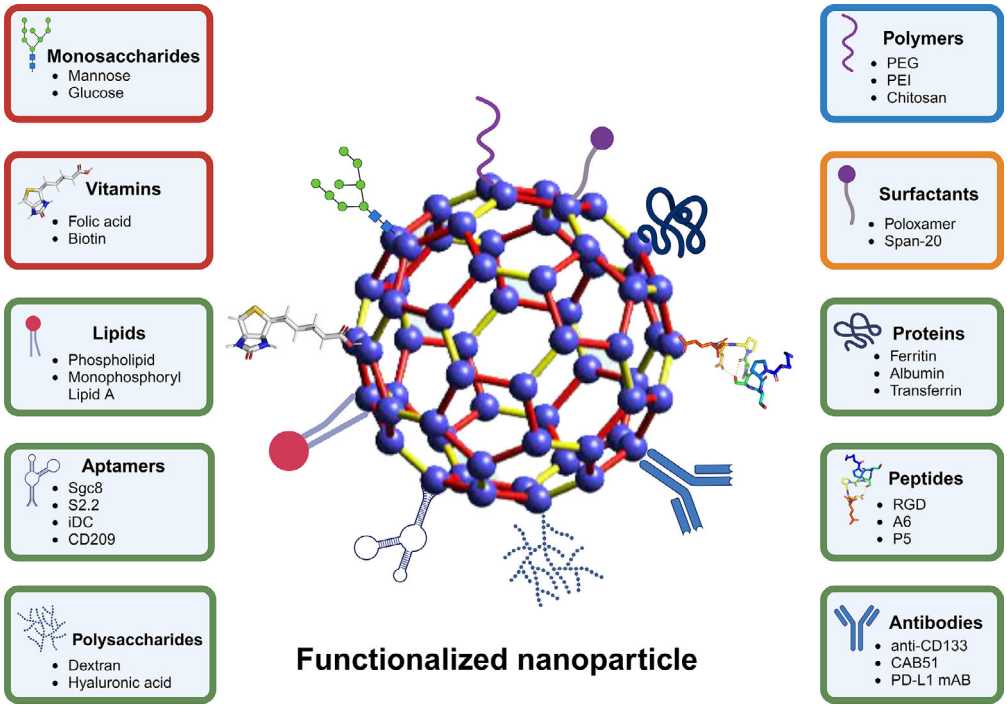

FIGURE 4 Functionalization of NPs for targeted drug delivery. Various molecules are used for NP functionalization, where NPs are chemically modified nanoscale materials designed to enhance their properties for targeted applications, particularly in drug delivery. By attaching functional groups or biologically active compounds to their surfaces, these NPs can achieve targeted distribution, greater stability, and controlled release of therapeutic agents. Several types of compounds, including polymers, peptides, proteins, ABs, polysaccharides, surfactants, vitamins, monosaccharides, lipids, and aptamers, are used in NP functionalization. These modifications improve NP performance by enabling selective binding to specific cells or tissues. The colored boxes in this picture represent different components: blue for polymers, orange for surfactants, green for macromolecules, and red for small molecules. Abbreviations: CD209, cluster of differentiation 209; iDC, immature dendritic cell; NP, nanoparticle; PD-L1 mAB, programmed death ligand 1 monoclonal antibody; PEG, polyethylene glycol; PEI, polyethyleneimine; RGD, arginine-glycine-aspartic acid.

Doxil®, the first FDA-approved nano-drug, is an example of PEGylated liposomes, which exhibit increased drug activity and have great potential as an efficient anti-cancer delivery mechanism [210]. Moreover, Ochyl et al. reported that comparing immunization with freeze-thawed lysate to vaccination with PEG-NPs generated from murine melanoma cells, antigen-specific cytotoxic T cell responses were 3.7 times higher. This underscores the possibility of generating anti-tumor immunity by encapsulating endogenous cancer cell membranes into stable vaccination nanoparticles [211].

PEI is another versatile polymer used for various purposes, including biocompatible coatings to facilitate gene delivery [212]. Known for its stability, ease of manipulation, affordability, and non-toxicity, PEI-modified liposomes have demonstrated the ability to improve the delivery of proteins to the cytoplasm [213, 214]. Jin et al. developed a vaccine incorporating polyelectrolyte complexes (PECs) and polymer-coated liposomes as self-adjuvant delivery vehicles for a B lymphocyte (B cell) peptide epitope from group A streptococcus, conjugated to a universal T-helper epitope and lipid core peptide-1. Comparing this formulation to a PEC vaccination, larger humoral immune responses were obtained [215].

4.2 | Functionalization of NPs with surfactants

A surfactant, also known as a surface-active agent, possesses both hydrophilic and hydrophobic groups within its chemical structure, making it an amphiphilic compound [216]. Surfactants can be divided into four classes based on the characteristics of their hydrophilic groups: (1) cationic surfactants, (2) anionic surfactants, (3) zwitterionic surfactants, and (4) nonionic surfactants. These compounds serve as surface modifiers on NPs, enhancing the rigidity and stability of nanocarriers.

Non-ionic surfactants, such as Poloxamer 188, Poloxamer 407, Span, and Tween, are commonly used in pharmacological research [217, 218]. Poloxamers, are water-soluble nonionic surfactants with amphiphilic properties,

forming organized structures such as micelles in solution due to their hydrophilic and hydrophobic monomers. The use of poloxamer dispersions in localized cancer treatment has been proposed as an alternative to chemotherapy, phototherapy, immunotherapy, and gene therapy [219]. Poloxamer-coated NPs have demonstrated enhanced diffusion and cellular uptake. Moreover, using poloxamer P407 (i.e., Pluronic F127) to target the tumor-draining lymphatic system, an immunotherapeutic adjuvant was transported to the tumor drainage system for lymphography. Poloxamers also show the potential to enhance adaptive immune responses in vaccine development [220]. Researchers have also demonstrated a lipid-based nanovaccine utilizing a conventional surfactant loaded with an antigenic protein and immunomodulator at its core to enhance drug delivery and immune cell activity. This nanovaccine includes a surfactant (Span-20), an antigenic protein linked with lipid-based biocompatible ionic liquids, and an immunomodulator. Compared to conventional aqueous formulations, nanovaccination offers a more efficient and focused means of delivering cancer antigens, enhancing the immune response and potentially improving therapeutics and prevention for cancer patients [221].

4.3 | Functionalization of NPs with ligands

The selection of surface ligands is a critical parameter in NP synthesis [222]. Ligands serve various functions, including regulating NP solubility and availability, minimizing surface energy post-synthesis, and encoding NP functions [223]. Functionalization with ligands exhibiting distinct affinities enables the identification of proteins, and cell surface molecules [224]. To successfully graft ligands onto NPs, several criteria must be met: (1) both the ligand and NP remain intact and functional, (2) the ligand is exposed on the particle's surface, (3) the ligand must be stabilized in blood and/or biological medium, and (4) its affinity must be preserved [225]. High ligand density enhances NP binding to targets but presents challenges, including increased hydrodynamic diameter of NPs, reduced diffusion coefficient in tumor tissue, diminished ability to avoid being detected by the immune system due to reduced display of antifouling molecules and elevated presentation of targeting moieties, potential steric hindrance of tightly packed ligands impeding NP binding, and decreased overall cellular uptake due to increased receptor and target density on cell membranes [226]. These ligands can compromise a variety of agents, such as macromolecules and small molecules, which are discussed in detail below.

4.3.1 | Functionalization of NPs with macromolecules

Proteins

Protein-coated NPs offer the potential for developing vaccines against immunoevasive pathogens. Proteins are coated onto NPs using three methods: (1) chemical conjugation, which chemically treats the NPs to bind to a reactive amino acid residue on the protein, (2) genetic fusion, which provides precise protein arrangement by genetically attaching proteins to terminals, and (3) tag coupling, where a genetically fused protein receptor or protein catcher is combined with one component, allowing the remaining component to bind to it through the genetically fused tag [227]. Ferritin-based vaccines exemplify protein-functionalized NPs with properties that are safe, easily produced, and cost-effective. They have proven to be able to elicit immune responses against various pathogens. Despite being an emerging technology, three clinical trials testing ferritin particles began between 2020 and 2021, indicating a growing interest in this platform [228]. In a recent study, ferritin-coated NPs were found to act as new cancer cell-targeted magnetic NPs (MNPs) for BC TME [229].

Albumin has proven effective in the fabrication and modification of nanomaterials. A study concluded that albumin NPs can be used passively, via the enhanced permeability and retention (EPR) effect, to target cancer tissues. Albumin adsorption prevents NP nucleation and aggregation, increases colloidal stability, and maximizes in vivo NP utilization [230]. Recent applications of albumin-coated MNPs include multimodal imaging and theranostics, achieved by modifying albumin surfaces with reporter or address groups, enabling better imaging procedures and tissue targeting simultaneously [231]. The versatility of albumin-based DDSs allows for the covalent or chemical binding of a wide range of compounds, offering opportunities for various therapeutics and theranostics. MNPs combined with albumin coating and modification provide exceptional properties for the system [232].

Another notable example is transferrin (Tf), which mediates the cellular uptake of anti-cancer drugs through transferrin receptor (TfR)-mediated endocytosis. TfR is often overexpressed in a large number of cancers, which makes it a desirable target for anti-cancer agents and delivery vehicles [233, 234]. Several studies have explored *Tf* and ABs against their receptors (e.g., R17217 and OX26 monoclonal ABs). Tf-conjugated NPs enhance brain delivery due to the presence of the TfR in the blood-brain barrier. The increased cellular uptake of drugs likely contributes to the enhanced efficacy of NPs with conjugated Tf. Consequently, Tf-conjugated NPs have a particular interaction

with cells, entering cells through caveolar pathways [235]. This process of functionalization holds the capacity to improve the infiltration and accumulation of vaccines within the TME.

Peptides

Peptide-functionalized NPs (PNPs) show considerable promise in cancer vaccine development. By integrating specific tumor-associated peptides onto NP surfaces, they can selectively target cells, activate the immune system, and elicit an anti-tumor immune response [38]. Numerous PNPs have been synthesized and applied across various domains, including biodetection, drug delivery, and cellular uptake [236]. Regarding nanocarrier surface modification, two types of peptides are identifiable. The first type, cell-penetrating peptides, are short, water-soluble, cationic peptides with nonspecific binding affinities. These peptides enhance NP penetration into target cells, such as APCs, and improve vaccine accumulation and persistence in target tissues, thereby enhancing the efficacy of cancer vaccines [237, 238]. The second type, cell-targeting peptides (CTPs), bind to specific receptors and enhance internalization [239].

An effective vaccine platform can be constructed using CTPs that selectively interact with target cells. Several peptide examples exist, with the arginine-glycine-aspartic acid (RGD) sequences notably facilitating cancer-targeted drug delivery by recognizing overexpressed integrin receptors on target cells [240]. Recent studies highlight RGD peptide-engineered nanoparticulate systems, which specifically interact with integrins expressed by tumor neovasculature or facilitate drug delivery across the blood-brain barrier to brain tumors [241, 242]. According to Wu et al., PNPs enhance delivery efficiency and effectively inhibit drug-resistant tumor cells. Co-delivering anti-cancer agents by PNPs increases drug accumulation within tumors and improves therapeutic efficacy [243].

The synthetic 12-amino acid peptide GE11 (YHWYGYTPQNVI) has demonstrated efficacy against the epidermal growth factor receptor (EGFR) overexpression in cells. GE11 serves as a peptide ligand that selectively recognizes EGFR, finding utility in both diagnostic and therapeutic applications for EGFR-overexpressing cells. Colloidal systems decorated with GE11, proposed for drug delivery and diagnostics, or for anti-tumor drugs such as doxorubicin and camptothecine, offer advantages such as low peptide molecular weight, conjugate stability, and EGFR binding [244]. Various conjugates of GE11, including PEG, PLGA, and copolymers, have been proposed in the literature. However, a number of limitations exist. For instance, the binding density of GE11 on polymeric NP surfaces depends on the conjugation method and tends to be limited when applied to pre-formed NPs [245, 246].

Another peptide of interest is A6 (KPSSPPEE), derived from urokinase, which exhibits a strong affinity for CD44 [247]. A6 binding to CD44 inhibits the migration, invasion, and metastasis of tumor cells, while also modulating CD44-mediated cell signaling [248]. Rostami et al. proposed that functionalized polymeric NPs with the A6 peptide could provide highly effective cancer treatment [249]. IK1 (RPSFPPEE), a short peptide derived from the A6 sequence, has shown a strong affinity for CD44 in studies, making it a promising option for functionalizing NPs intended for vaccine delivery [250]. A6-functionalized nanocarriers have been successfully used to target multiple myeloma (MM) [251, 252]. Peptides such as KPQPRPLS or KATWLPPR, which bind to vascular endothelial growth factor receptors or neuropilin-1 receptors, facilitate endocytosis-mediated internalization of functionalized NPs and offer promising potential for engineering NPs for cancer targeting [223]. Given the significant expression of EGFR and CD44 in immune cells [253, 254], functionalizing vaccine carriers with these peptides can enhance the functionality of SVPs.

Another notable peptide is P5. In a study, the HER2-neu-derived P5 peptide (sequence: ELAAWCRWGFLLALLPPGIAG), when conjugated with liposome surfaces (Lip-P5), enhanced both prophylactic and therapeutic anti-tumor immunity. Following further validation, researchers concluded that Lip-P5-integrated with Pan HLA-DR-monophosphoryl lipid A (MPLA) could serve as a vaccine for $HER2^+$ BC treatment, able to induce cytotoxic T-lymphocyte (CTL) anti-tumor immune responses [255]. Overall, because of their tiny size and ease of production, peptides hold promise as candidates for functionalizing SVP platforms.

ABs

Surface modifiers of NPs can include ABs or their fragments that bind to the NPs through covalent bonding, adsorption, or using adapters [256]. When ABs are densely packed, spatial accessibility decreases due to steric hindrance between adjacent ABs. The method of functionalization dictates whether ABs are randomly immobilized on NPs or oriented in a specific manner [257]. Zumaya et al. demonstrated that functionalizing PLGA nanocarriers with anti-CD133 (prominin-1) monoclonal ABs enabled targeted delivery of superparamagnetic iron oxide NPs and oxaliplatin to colorectal tumors [258]. CD133, found on the surface of various cancers including brain, prostate, and CRC, serves as a cell surface marker [259, 260]. Hence, SVPs modified with anti-CD133 could potentially serve as platforms to elicit immune responses in the TME.

ABs can be used with various types of NPs. For example, the PD-1 AB blocks the PD-L1/PD-1 interaction between tumors and T cells, preserving the anti-tumor activity of

nanovaccine-induced T cells [261]. Lee et al. investigated attaching PD-L1 fragments onto PEG-*co*-PLGA polymers to enhance efficacy. Their research demonstrated that anti-PD-L1 NPs considerably elevated AB preservation in vivo without adverse side effects, suggesting potential for achieving tumor-specific delivery and enhancing immune activation through passive and active targeting [262]. Another promising platform for SVPs involves LNPs functionalized with ABs. Through streptavidin-biotin interactions, researchers have successfully conjugated CAB51 ABs targeting HER2 to cationic LNPs [263]. Additionally, cetuximab, a monoclonal AB targeting EGFR, is approved for the treatment of advanced CRC, NSCLC, and head and neck cancer. Cetuximab-functionalized nanostructured lipid carriers have been explored to mitigate dose-related adverse effects in targeting tumor tissues [264].

Polysaccharides

The widespread availability and biocompatibility of polysaccharides have made them highly utilized in biomedical applications [265]. Polysaccharides play an increasingly integral role in developing functional nanomedicines, serving as components to provide protection, enhance interaction with target tissues, or enable environment-responsive drug release [266]. Some polysaccharides are employed as ligands to increase nanomedicine absorption by receptor-mediated endocytosis. NPs' surfaces are frequently modified with natural polysaccharides such as chondroitin sulfate, heparin, chitosan, hyaluronic acid, and dextran [267].

Dextran, derived from glucose subunits and synthesized by the nonpathogenic leuconostoc mesenteroides bacterium, is notable for its anti-inflammatory and antithrombotic effects. Its functional hydroxyl groups enable easy conjugation with other substances [268]. Dextran-coated NPs have bioadhesive qualities and hinder circulatory opsonization. A specific receptor, known as the lectin receptor, serves as the primary mechanism for dextran uptake. Lectin receptors facilitate the internalization of dextran by cells and aid in its breakdown. Consequently, tumor cells or immune cells expressing these receptors can target dextran uptake due to their ability to recognize the component [269–271]. Hyaluronic acid is also a polysaccharide frequently used for NP functionalization and can be utilized in designing SVPs [272, 273].

Chitosan is another polymer used for functionalization, increasing surface rigidity and cellular uptake levels. NPs coated with chitosan have a greater likelihood of interacting with and being taken up by cell membranes, a crucial aspect when the enclosed drug targets intracellular structures [274]. For instance, the delivery of chemotherapeutics through chitosan-coated NPs represents a novel and efficient strategy for cancer therapy. Studies using methotrexate-loaded chitosan-coated bovine serum albumin NPs have demonstrated promising results in BC patients [275]. Furthermore, Baati et al. demonstrated that chitosan-coated silicon NPs exhibited optimal biodistribution profiles within TME and were sustainable, biodegradable, and eliminated, indicating their potential application in nano-oncology as tumor-targeting agents [276].

Aptamers

An aptamer is a single-stranded DNA or RNA molecule, generally falling between 20 to 80 nucleotides. Through hydrogen bonds, van der Waals forces, or electrostatic interactions, aptamers assume specific three-dimensional structures and exhibit highly selective binding to their target molecules [277]. Aptamers are typically produced using the systematic evolution of ligands by exponential enrichment from a large random sequence pool. Due to their advantageous characteristics, aptamers serve as ideal molecules for functionalizing NPs to deliver active ingredients to target sites [278]. Aptamers are easily recognized and bound to targets, non-immunogenic, facile to attach to conjugate NPs, maintain a small size post-coupling, and are relatively straightforward to manufacture and store. The attachment of aptamers to NPs can involve a linker molecule (bridge or spacer), either directly or indirectly, with connections being either covalent or non-covalent [279].

Kang et al. demonstrated the enhanced specificity and efficiency of aptamer-directed liposome delivery systems by conjugating liposomes with sgc8 aptamers, which deliver drug cargoes to target cells. This aptamer targets PTK7, an upregulated member of the receptor protein tyrosine kinase family found in various cancers, including hematological malignancies. Another study revealed that the combination of the sgc8 aptamer and NPs could specifically bind to tumoric cells [280, 281]. Furthermore, Zhu et al. proposed using metal nanomaterials for targeting BC cells. By employing the S2.2 aptamer as a surface functionalizing agent for Ag-Au nanostructures, they demonstrated that Apt-Ag-Au nanostructures could interact with BC cells overexpressing membrane MUC1 proteins and achieve photothermal therapy [282].

In a recent paper by Zheng et al., an aptamer, iDC and CD209, were utilized to target DCs. Their results confirmed that aptamer-functionalized nanovaccines have the ability to identify circulating classical DCs (cDCs), which are a subpopulation of DCs that could prime naïve T cells. With their excellent ability to target cDCs, iDC-functionalized nanovaccines induced potent anti-tumor immunity, effectively inhibiting tumor incidence and metastasis, thus providing a promising platform for cancer prevention [283].

Lipids

Lipid-coated polymeric NPs offer numerous advantages in drug delivery, including enhanced target specificity, prolonged circulation half-life, and reduced cytotoxicity [222]. While the targeted specificity of lipid-functionalized NPs remains relatively understudied, Cao et al. investigated the cytotoxicity of ZnO NPs. Their study explored methods to enhance the biocompatibility and biological stability of ZnO NPs with varied morphologies through preparation and surface functionalization. The results revealed distinct behaviors of pristine and lipid-coated ZnO nanocrystals of various morphologies in biological media, highlighting variations in their physical and chemical characteristics. This insight is invaluable for advancing multifunctional inorganic nanomaterials aimed at improving drug efficacy, minimizing cytotoxicity, and exploring novel applications [284]. Additionally, lipid-coated NPs have shown promise in developing supramolecular magnetogels for controlled drug release [285]. Given that lipids, such as MPLA, can serve as adjuvants in anti-cancer vaccines [286], their functionalization on NP surfaces holds potential for the design of SVPs.

4.3.2 | Functionalization of NPs with small molecules

Studies have demonstrated that coating NPs with small molecules such as carboxylates, phosphates, and sulfates can extend their circulation time in blood vessels and prevent premature removal from the body [287]. These substances also modify the reactivity of NP surfaces by covering specific particle areas. Furthermore, modifying NPs with small molecules facilitates the targeting of vaccines to specific immune system components and enhances the engagement of specific receptors, thereby amplifying the strength of the immunological reaction [288, 289]. For instance, molecules with multiple carboxyl groups, including carboxylates, have been extensively investigated as surface modifiers for various MNPs used in drug delivery and cancer therapeutics. The presence of multiple carboxyl groups allows these molecules to bind strongly to Fe_3O_4 and serve as anchors for conjugated cancer drugs [290].

Vitamins are attractive small molecules for modifying drug carrier platforms. One study discussed folate-conjugated Gold-NPs (Au-NPs) as both passive and active cancer targets. Folate-loaded Au-NPs are either taken up by endocytotic vesicles or released into the cytoplasm. Compared with ABs or other targeting ligands, folate-conjugated NPs have the advantage of transporting their targets into the lysosome for destruction [291]. Another vitamin used for NP functionalization is biotin (also known as vitamin B7, vitamin H, or coenzyme R) [292]. Research by Cheng et al. indicated that biotinylated chitosan NPs inhibit liver cancer cell proliferation in vitro and activate the immune system in vivo [293].

Mono- and oligosaccharides are other types of small molecules that can be used for SVPs functionalization. Researchers have bonded monosaccharides such as glucose, galactose, mannose, and thymidine to PEG and PLGA polymers [294]. This approach exploits the natural affinity of cell receptors for specific monosaccharides, enhancing the selectivity and efficiency of drug delivery. By conjugating these monosaccharides to the polymer backbone, the resulting drug delivery agents can potentially achieve improved cellular uptake and enhanced therapeutic efficacy. In the field of cancer vaccines, Sun et al. introduced mannose as a modifier for biodegradable NPs. They hypothesized that mannose- and bisphosphonate-modified calcium phosphate NPs would improve DNA vaccine targeting to APCs and enhance T cell responses. According to their findings, mannose-modified nano-vaccines demonstrated increased cellular uptake, enhanced antigen presentation, accelerated AB production, and stronger anti-tumor effects compared to non-modified vaccines. Therefore, incorporating mannose modification in DNA vaccines could offer significant benefits in treating infections and cancer [295]. Additionally, saccharides were successfully used for Au-NPs functionalization. Fallarini et al. studied the immunological effects of Au-NPs conjugated with small, non-immunogenic saccharides. They demonstrated that saccharide-functionalized Au-NPs induce immune responses, triggering a complex cascade of events that ultimately led to immunization. This approach underscores the potential of designing NP-based vaccines by leveraging complex features of saccharide-modified NPs [296].

5 | Optimizing SVPs with click chemistry

Following the exploration of therapeutic cancer vaccines as alternatives to traditional treatments [297, 298], it is essential to acknowledge the challenges that hinder their clinical efficacy [191]. These challenges include the immunosuppressive TME and the necessity for targeted delivery to APCs [299, 300]. Addressing these complexities requires innovative chemical strategies, with click chemistry (Table 3) emerging as a valuable tool for optimizing cancer vaccine delivery platforms through specific and rapid chemical reactions [60, 301]. For example, conjugating multiple antigens from different proteins onto virus-derived carriers using click chemistry with unnatural amino acids has shown promising results in treating infectious diseases and cancers [42, 302].

TABLE 3 Overview of various click chemistry reactions.

Reaction	Mechanism	Applications	Ref.
CuAAC	Involves the coupling of azide and alkyne groups in the presence of Cu(I) catalyst.	Conjugating biomolecules, such as antigens and carriers.	[303]
SPAAC	Utilizes a copper-free reaction relying on the inherent reactivity of strained cyclooctyne derivatives with azides.	Utilizing bioorthogonal click chemistry for in vivo studies.	[304]
Thiol-ene/yne click chemistry	Includes the addition of thiols to alkenes or alkynes to form thioether or thioester linkages.	Synthesizing and modifying biomolecules.	[305]
Inverse electron demand diels-alder (IEDDA)	Entails the cycloaddition of strained alkenes with electron-deficient dienophiles.	Conjugating biomolecules and employing bioorthogonal labeling.	[306]
Staudinger ligation	Involves the reaction between an azide and phosphine to form an amide bond.	Synthesis and modification of biomolecules.	[307]

Abbreviations: CuAAC, copper-catalyzed azide-alkyne cycloaddition; IEDDA, inverse electron demand diels-alder; SPAAC, strain-promoted azide-alkyne cycloaddition.

K. Barry Sharpless introduced "click chemistry" in 2001, a class of efficient, selective, and modular chemical reactions that occur under mild conditions without generating byproducts [308]. It enables the synthesis and modification of diverse molecular structures with high yields and biocompatibility [309]. Click chemistry is characterized by its selectivity and reliability, involving simple starting materials for covalent linkages such as copper-catalyzed azide-alkyne cycloaddition (CuAAC) [303], strain-promoted azide-alkyne cycloaddition (SPAAC) [310], and Staudinger ligation [304]. It has significantly contributed to vaccine development due to its modular nature, facilitating the easy conjugation of antigens, carriers, and adjuvants [311].

By employing click chemistry reactions, researchers have been able to attach specific targeting moieties to vaccines, enabling their preferential accumulation in lymph nodes [60]. Additionally, surface modification techniques, when combined with click chemistry, provide precise control over the functionalization of vaccine carriers and SVPs. Click chemistry enables selective and efficient attachment of ligands and functional groups to target sites, thereby improving stability, solubility, and immune recognition [312, 313]. Recent studies have explored metal-free bioorthogonal chemical reactions for personalized and targeted therapy, opening new possibilities to enhance the effectiveness of cancer vaccines [60, 314]. These reactions, particularly those used to modify dendrimer surfaces, show promise for advanced vaccine delivery strategies [315, 316]. Additionally, in the context of cancer [317], innovative chemical reaction-based approaches have demonstrated targeting of EGFR-overexpressing cancer cells. In the following sections, we delve into various types of click chemistry as versatile pathways for developing SVPs.

5.1 | CuAAC reaction

The CuAAC reaction is a method used to conjugate TSAs (azide-functionalized peptide) to carrier proteins (alkyne-functionalized protein), ensuring a controlled and defined vaccine structure [318]. This mechanism strengthens the body's immune defense to specifically target cancer cells. Traditional methods may lack specificity, leading to heterogeneous products. He et al. concentrated on recent developments in CuAAC-based carbohydrate click chemistry for therapeutic and diagnostic applications. This method has facilitated collaboration between chemists and practitioners in life sciences. Triazolyl carbohydrate derivatives were synthesized to evaluate their anti-cancer properties, especially against cancer cell lines. The study targeted carbonic anhydrase and synthesized triazolyl glycocoumarin derivatives, demonstrating anti-proliferative activities in BC cells. CuAAC was utilized to develop enzyme inhibitors with potential anti-cancer properties. The research also addressed protein tyrosine phosphatases (PTPs), crucial in cancer, by modifying glycosides to produce bis-triazolyl and mono-triazolyl PTPs inhibitors with inhibitory activities in the micromolar range. Overall, the study contributes to innovative approaches for cancer therapy and diagnosis [319].

Al-hujaj et al. conducted a study focusing on the significant annual mortality associated with breast and PCa. Given the ineffectiveness and side effects of current cancer drugs, the research aimed to develop a safer and more efficient alternative for long-term cancer treatment. A series of 1,2,3-triazole derivatives (T1, T2, and T3) were synthesized using a Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition process. The compounds were analyzed by Infrared,

Hydrogen-1 Nuclear Magnetic Resonance (^{1}H NMR), and electrospray ionization mass spectrometry methods. in vitro cytotoxicity assays showed considerable cytotoxic activity for most compounds, with T1 and T2 proving to be the most promising derivatives. In particular, the IC_{50} values for T1, T2, and T3 against the PCa (PC-3) cell lines exceeded those of the standard drug 5-FU, indicating the potential utility of these compounds as effective anti-cancer drugs [320].

One study presented a significant advancement in cancer treatment, demonstrating the use of Cu(I)-catalyzed click chemistry to trigger the aggregation of azide/alkyne-modified micelles, leading to enhanced accumulation of micelles in tumor tissues. This innovative approach addressed the challenge of insufficient drug concentration in tumor tissues and suboptimal treatment approaches, which contribute to tumor recurrence and metastasis. Furthermore, the combination of doxorubicin with the adjuvant MPLA induced immunogenic cell death, promoting DC maturity, antigen presentation, and the activation of potent effector T cells in vivo. The integration of anti-PD-L1 therapy further enhanced the anti-tumor and metastasis-suppressing effects while also providing long-term immunity through memory T cell responses, protecting against tumor recurrence. This study presented promising implications for the advancement of targeted cancer therapies through the use of click chemistry to induce NP accumulation in tumor tissues [321].

In a different study, Luo et al. proposed a novel approach for developing synthetic cancer vaccines by incorporating a macrophage-activating C-type lectin (Mincle) agonist as a multifunctional component. The study successfully designed and synthesized four conjugates using the Sialyl Thomsen-nouveau antigen, which demonstrated robust T cell-dependent immunity and self-adjuvanting capabilities. The use of click chemistry, specifically a triazolyl linker, facilitated the precise attachment of the Mincle agonist to the antigen, contributing to the overall success of the synthetic vaccine design. The study's findings underscored the potential of Mincle ligands as a platform for the development of novel vaccine carriers with self-adjuvanting properties, representing a significant advancement in cancer treatment strategies. The incorporation of click chemistry in the synthesis process further exemplified the innovative and sophisticated nature of these completely synthetic Mincle-dependent self-adjuvanting cancer vaccines [322].

5.2 | SPAAC reaction

The SPAAC reaction is a copper-free reaction used for biorthogonal labeling of viral proteins (azide-modified) with fluorophores (cyclooctyne-functionalized) to study viral particle interactions with immune cells. This technique is also employed to label vaccine components with imaging agents, enabling in vivo tracking of vaccine distribution and interactions [323]. The research conducted by Derks et al. explores the use of SPAAC as an adaptable conjugation method for attaching functional components to prostate-specific membrane antigen (PSMA). This technique shows significant potential for PSMA-targeted imaging and treatment in PCa. The team synthesized and characterized four dual-labeled PSMA ligands to demonstrate the concept of intraoperative radiodetection and fluorescence imaging for PCa. These ligands were produced via solid-phase chemistry and were linked using either SPAAC or traditional N-hydroxysuccinimide (NHS)-ester coupling methods. The effectiveness of tumor targeting was evaluated in BALB/c nude mice with subcutaneous (SC) LS174T-PSMA and LS174T wild-type tumors. SPAAC chemistry enhanced the lipophilicity of the ligands, leading to substantial and specific accumulation in SC LS174T-PSMA tumors up to 24 hours after injection. The newly developed SPAAC-based PSMA ligands demonstrated significant PSMA-specific tumor targeting, highlighting the advantages of click chemistry in creating PSMA ligands [324].

Stefanetti et al. conducted research on developing glycoconjugate vaccines to prevent nontyphoidal Salmonella infections. They synthesized the O-Antigen, a lipopolysaccharide with a single N-acetylgalactosamine residue linked to a serine or threonine residue of a protein or glycoprotein. Cross-reactive material 197 (CRM 197), a non-toxic mutated variant of the diphtheria toxin, was used as the carrier protein for the glycoconjugate vaccine. The Stefanetti group compared different chemical methods: thiol chemistry and two-click chemistry methods, including copper-free click reaction and copper-catalyzed click reaction. They determined that the click chemistry approaches demonstrated greater efficiency and yielded a site-selective glycoconjugate with a higher level of uniformity. In the copper-free click reaction, conjugate formation was 78% at a 1:1 alkyne-to-azide ratio compared to 40% in the copper-catalyzed click reaction at a 5:1 alkyne-to-azide ratio. Stefanetti study's outcomes emphasize that the production of site-selective glycoconjugate vaccines is achievable through the application of copper-free click chemistry with CRM 197 as the carrier protein. This particular approach was prioritized for further testing due to its heightened conjugation efficiency and its capacity to circumvent the use of toxic metals [325]. This investigation underscores the potential of glycoconjugate vaccine development, paving the way for innovative targeted immunotherapy approaches in cancer treatment.

Wang et al. introduced an innovative method for in vivo cancer targeting utilizing glycopolyester NPs (GP-NPs) for metabolic cell labeling, followed by click chemistry. Their work centered on synthesizing GP-NPs through azido-sugar-initiated ring-opening polymerization of O-carboxyanhydrides (OCAs) to achieve effective cancer targeting in vivo. The findings revealed that GP-NPs could successfully label LS174T colon cancer cells with azido groups in tumor-bearing mice, enhancing anti-cancer efficacy. The study suggested the use of azido-sugar-initiated polymerization of OCAs to develop sugar delivery systems that exhibit high stability and controlled release. It emphasized the increasing tumor-targeting effect of dibenzocyclooctyne (DBCO-cargo) over time in response to azido-modified tumor cells. The research illustrated how NP-mediated passive targeting, enabled by the EPR effect, combined with azido-sugar-mediated cancer cell labeling through efficient click chemistry. The study demonstrated the targeting of azido-sugars metabolically expressed by cancer cells, facilitated by covalent bond formation via efficient click chemistry, which minimizes immune responses and capitalizes on the higher density of cell-surface sugars compared to proteins [326].

In another study, Yoon et al. explored a novel approach to enhance tumor targeting efficiency through bioorthogonal click chemistry and metabolic engineering. The researchers introduced an artificial azide-reporter-targeting technique aimed at improving the tumor-targeting capabilities of NPs while addressing tumor heterogeneity. They successfully produced azide-containing chemical reporters on the surface glycans of various tumor cell lines, including lung cancer (A549), brain cancer (U87), and BC (BT-474, MDA-MB231, MCF-7), using metabolic engineering in vitro. This method enabled precise targeting of these unnatural glycans with bioorthogonal molecules, avoiding side reactions through bioorthogonal click reactions both in vitro and in vivo. The study compared the tumor-targeting efficiency of artificial azide reporter-targeting bicyclononyne-conjugated glycol chitosan NPs (BCN-CNPs) against integrin $\alpha v\beta 3$-targeted cyclic RGD-conjugated chitosan NPs (cRGD-CNPs). The findings revealed that the fluorescence intensity of azide reporter-targeted BCN-CNPs in tumor tissues was 1.6 times greater and showed a more uniform distribution compared to cRGD-CNPs. This technique has been previously applied in biological and biomedical research for the specific labeling of proteins and DNA, monitoring zebrafish growth, and NP delivery. The authors emphasized the potential of this artificial azide-reporter-targeting strategy to create more uniform tumor cells, ultimately enhancing the tumor-targeting efficiency of NPs [327].

Another study presented a novel approach for tumor treatment using a non-viral aptamer-T cell targeting strategy. This approach involved attaching tumor cell surface-specific single-stranded DNA aptamers to $CD3^+$ T cells through N-azidomannosamine sugar metabolic cell labeling and click chemistry. The findings revealed that the aptamer-T cells could specifically identify and attach to tumor cells, including SGC-7901 gastric cancer and CT26 colon carcinoma cells, both in vitro and in vivo in mice following adoptive transfer, resulting in significant reductions in tumor volume. The aptamer-T cells exhibited notable cytotoxic activities, characterized by elevated levels of perforin, granzyme B, CD107a, CD69, and Fas ligand (FasL). Remarkably, these aptamer-T cells demonstrated superior anti-tumor effects compared to anti- PD1 immune checkpoint monoclonal antibody treatment in mice, and their combination with anti- PD1 treatment produced synergistic anti-tumor effects. This study emphasized the potential of the adoptive non-viral aptamer-T cell strategy as a promising and effective approach for tumor-targeted immunotherapy. The integration of click chemistry into this aptamer-T cell targeting method marked a significant advancement, providing a safe, precise, and effective means for tumor treatment. This strategy facilitated the efficient labeling of live T cells with azides for subsequent conjugation with aptamers, thereby enhancing the safety and effectiveness of the proposed T cell engineering technique [328].

Koo et al. emphasized the promise of bioorthogonal copper-free click chemistry as an innovative in vivo targeting strategy for NPs. This method involved generating targetable glycans, specifically unnatural sialic acids with azide groups, on cancer cells through IT injection of the precursor N-azidoacetylmannosamine-tetraacylated (Ac4ManNAz). These azide groups facilitated enhanced NP accumulation at the target site via bioorthogonal copper-free click chemistry within living organisms. The authors highlighted the significance of metabolic glycoengineering, which entails introducing unnatural glycans onto cells by administering specific precursors that align with the cells' intrinsic metabolic pathways. The study also noted the benefits of employing NPs over small molecules in the context of bioorthogonal copper-free click chemistry. NPs exhibited longer circulation times and a multivalent effect, thereby increasing the likelihood of binding to unnatural glycans on target cells in vivo. This could improve the effectiveness of targeted drug delivery techniques. The findings revealed that the accumulation of DBCO-conjugated PEGylated liposomes increased significantly with higher concentrations of Ac4ManNAz treatment, demonstrating that the biodistribution of NPs can be modulated artificially using chemical precursors in a dose-dependent manner. Additionally, the technique proved effective for targeted intracellular drug delivery [59].

5.3 | Thiol-ene/yne click chemistry

Modification of a viral glycoprotein (thiol-modified) involves conjugating it to a polymeric carrier (ene-functionalized) to create a vaccine construct with improved stability and immunogenicity. Click chemistry enables the selective functionalization of vaccine components with various moieties. Thiol-ene/yne click chemistry, for instance, is employed to modify antigens or carriers by incorporating functionalities such as polymers for improved pharmacokinetics [329]. Lanz-Landázuri et al. created comb-like amphiphilic polymers by attaching long paraffinic chains to microbial poly(γ, dl-glutamic acid) and poly(β, l-malic acid) through a two-step method. The initial step involved allylating carboxylic side groups, followed by a UV-initiated thiol-ene/yne click reaction with 1-alkanethiols containing 8, 12, and 16 carbon atoms. The characterization of these polymers was performed using techniques such as ^{1}H NMR, gel permeation chromatography, and differential scanning calorimetry. The resulting grafted polymers are self-assembled into NPs with sizes ranging from 80 to 240 nm. When incubated in water under physiological conditions, the lateral ester linkages hydrolyzed, leading to the breakdown of the polyester main chain or polyamide. Model drugs, theophylline and carbamazepine, were successfully encapsulated within these systems, with carbamazepine demonstrating particularly superior performance. Notably, rapid drug release from the NPs was observed under physiological conditions [330].

5.4 | IEDDA reaction

The IEDDA method is used to conjugate cancer-associated peptides (tetrazine-modified) to carrier proteins (trans-cyclooctene-functionalized), enabling the creation of targeted immunotherapy vaccines. This efficient and selective method, utilizing click chemistry, enhances the development of peptide-based vaccines [331]. Zhao et al. identified a critical need for a visible DDS in precision medicine. Bioorthogonal prodrug activation techniques mediated by DDS have demonstrated significant advantages in mitigating adverse medication reactions and expanding therapeutic indices. Despite these benefits, events associated with bioorthogonal prodrug activation remain challenging to monitor. In this study, the researchers established a self-reporting bioorthogonal prodrug activation system that translates prodrug activation events into fluorescence emission. The bioorthogonal reaction mechanism of tetrazine served dual purposes as both a prodrug activator and a fluorescence quencher within supramolecular assemblies, responding to reactive oxygen species (ROS) cues. The ensuing IEDDA reaction led to the simultaneous release of fluorescence and active medications, establishing a linear connection. Selective formation of ROS-instructed supramolecular assemblies occurred in both tumor cells and cell spheroids, guided by their distinct cellular redox status. The brilliance of the fluorescence served as an indicator following prodrug therapy [332].

In another study, Brand et al. introduced a technique involving an irreversible inverse electron-demand Diels-Alder process to precisely attach liposomal radiopharmaceuticals to a CoCrMo alloy, making it suitable for use in arthroscopic stents. Inspired by recent advancements in targeted imaging using tetrazine-trans-cyclooctene click chemistry, the study details the fabrication of 89Zr-labeled trans-cyclooctene-functionalized liposomal NPs. These NPs were tested on a polydopamine-coated CoCrMo surface with a tetrazine tag. The study assessed the ability of 89Zr-TCO-liposomal NPs (89Zr-TCO-LNP) to immobilize on the tetrazine surface compared to control suspensions of non-TCO-functionalized 89Zr-liposomal NPs [333]. The findings suggest that NPs designed using this approach can be potent SVPs capable of targeting tumors and delivering cancer vaccines directly to them, thereby increasing their effectiveness and reducing side effects.

5.5 | Staudinger ligation reaction

Staudinger ligation is a method used in vaccine synthesis to enhance the immunogenicity of a vaccine by ligating a phosphine-modified adjuvant to an azide-functionalized protein antigen, a process achievable through click chemistry [334]. Joshi et al. discovered the pivotal role of the immune system in cancer onset and progression. Despite macrophages typically being associated with pro-inflammatory responses, their interactions with tumors and metastases can also facilitate pro-oncogenic activities. The lack of a reliable tracking method has impeded research on macrophages and their interactions within cancer microenvironments. The authors propose a cell-based approach utilizing fluorophores to chemically modify macrophage surfaces, enabling the analysis of interactions between immune cells and cancer cells. Two commonly employed techniques involving Staudinger ligation reactions and NHS-ester reactions were used to impact glycans and cell surface proteins, respectively. The study demonstrates that these modifications do not impede macrophage responses to chemoattractants, and monitoring interactions with cancer cells becomes more feasible [335].

Overall, click reactions are an important tool in the development of SVPs. They enable the customization

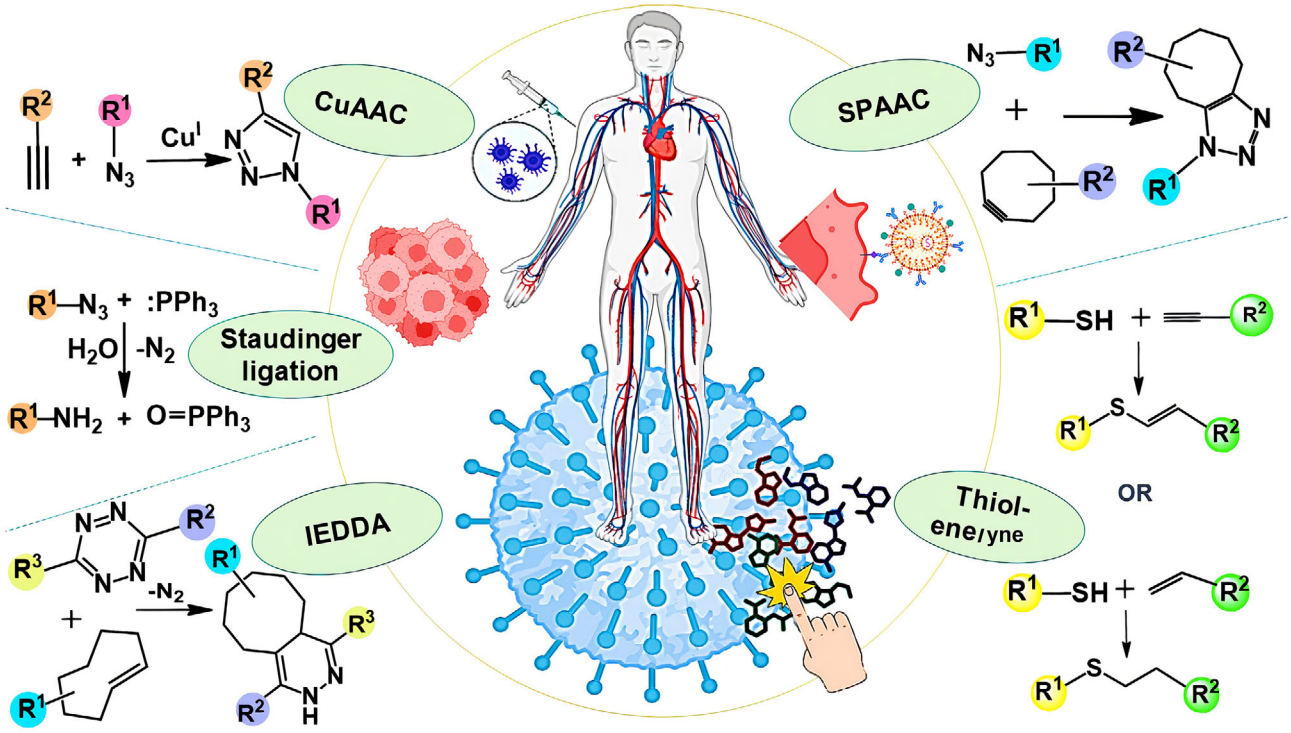

FIGURE 5 Click chemistry strategies for SVP assembly and functionalization. Illustration displaying various click chemistry strategies used in the assembly and functionalization of SVPs, showcasing their potential as targeted cancer therapeutic vaccines. These reactions facilitate precise, modular conjugation of antigens, carriers, and adjuvants, enhancing the stability, solubility, and immune recognition of vaccine platforms. Abbreviations: CuAAC, copper-catalyzed azide-alkyne cycloaddition; IEDDA, inverse electron demand diels-alder; SPAAC, strain-promoted azide-alkyne cycloaddition.

of vaccines to individual patient profiles or pathogenic strains. These reactions (Figure 5) preserve the integrity of the biological molecules, enhance the immune response, and potentially improve vaccine efficacy. They address challenges in vaccine development, such as biocompatibility, in vivo applicability, scalability for large-scale production, and the stability of vaccine constructs during storage and transportation [336–338]. Current research directions include exploring novel bioorthogonal click responses, integrating click chemistry with advanced imaging techniques, and conducting clinical translational studies [339]. Click chemistry has become a cornerstone in the toolbox of vaccine researchers, offering a transformative approach beyond traditional synthesis methods. Copper-free reactions, such as SPAAC, are being developed to address cytotoxicity concerns and limitations for in vivo applications [340]. Advanced variants and purification methods are being explored to achieve high specificity and selectivity in click reactions. Integration of click chemistry into different vaccine platforms can be challenging, but tailored strategies are essential for compatibility and efficient functionalization [341].

6 | Leveraging exosomes as versatile vehicles for SVPs

Exosomes are small extracellular vesicles, ranging in size from 30 to 150 nm, produced by nearly all cell types and found in various biological fluids. These vesicles carry biological cargoes such as lipids, proteins, and nucleic acids, playing a crucial role in intercellular communication and mediating physiological and pathological processes [342]. Due to their advantageous properties over most available delivery platforms, exosomes have emerged as an ideal delivery system, particularly in cancer immunotherapy [343].

Exosomes are mostly stable in body fluid, biocompatible, and exhibit minimal immunogenicity. They inherit biological cargoes from their parental cells, enhancing their capacity to activate immune responses by delivering and reprogramming recipient cells [344, 345]. Furthermore, exosomes possess intrinsic tropism at the cellular and tissue levels due to surface molecules, increasing their affinity and directionality towards specific targets [346, 347]. Besides their therapeutic applications, exosomes serve as ideal non-invasive diagnostic and prognostic biomarkers,

providing a molecular snapshot of their parent cells. These applications have been extensively explored in various cancers, including pancreatic cancer [38], CRC [348], BC [349], HCC [350], and NSCLC [351].

Notably, exosomes can be engineered to enhance cargo loading capacity, with click chemistry proving effective for improving targeting efficiency [352]. Their inherent properties allowed them, to serve as a versatile platform for delivering various nucleic acids, including DNA, mRNA, microRNA, siRNA, and proteins. For instance, bovine-milk-derived exosomes have been utilized to deliver an mRNA vaccine encoding the SARS-CoV-2 receptor-binding domain (RBD), effectively stimulating the production of neutralizing ABs against RBD in mice [353]. Furthermore, Sun's group developed an exosome-based multivalent vaccine against SARS-CoV-2. They engineered exosomes to express either the SARS-CoV-2 delta spike (Stealth X-Spike) or the more conserved nucleocapsid (Stealth X-Nucleocapsid) protein on their surface. A single dose of vaccine demonstrated significant immunization and elevated AB production in mouse and rabbit models [354].

In another study, Usman et al., successfully delivered Cas9 and gRNA mRNA targeting the oncogenic microRNA mir-125b-2 to the MOLM13 AML cell line using exosomes derived from red blood cells [355]. Additionally, Kim et al. utilized exosomes derived from OV to deliver CRISPR/Cas9 plasmids targeting poly(ADP-ribose) polymerase-1, resulting in a significant reduction in tumor volume in vivo [356]. Recently, Ruab et al. employed click chemistry to modify the surface of exosomes derived from M2 microglia, incorporating injured vascular targeting peptide (DA7R) and stem cell recruit factor 1 to enhance neural stem cell differentiation at the injury site. This approach led to a marked increase in neurogenesis and accumulation of exosomes at the ischemia site in an in vivo model [357]. Given their delivery capabilities, exosomes represent competitive delivery systems for a variety of diseases.

Exosomes, inherit their content and characteristics from their parent cells, functioning as a double-edged sword in cancer immunotherapy. Both tumor and immune-cell-derived exosomes play pivotal roles in this context. Immune cells such as DCs, macrophages, lymphocytes, and natural killer (NK) cells serve as the frontline defense against pathogens, eliminating them by activation of the innate immune response. Exosomes secreted by these immune cells significantly contribute to both innate and adaptive immune responses (Figure 6) [345]. DC-derived exosomes (DEXs), have been extensively studied and used as therapeutic vaccines, providing an effective alternative to direct tumor antigens. DEXs can directly activate T cells to target cancer cells by presenting MHC-peptide complexes and costimulatory molecules like CD80, CD86, and CD40 to T cell receptors. Alternatively, DEXs can activate other DCs by delivering MHC-peptide complexes, leading to widespread T cell activation [358, 359]. Recent studies highlighted the impact of DEXs expressing α-fetoprotein on the TME, resulting in a significant decrease in $CD25^{+}Foxp3^{+}$ regulatory T cells, IL-*10*, and TGF-β levels, while stimulating $CD8^{+}$ T cells [360].

In addition to DEXs, exosomes derived from NK cells inherit parental markers such as CD56, NK group 2 member D, Natural cytotoxicity receptors, killer proteins like FasL and perforin, as well as tumor suppressor microRNAs, enabling them to induce apoptosis and suppress the growth of tumor cells [343, 361]. Recent research has shown that NK-derived exosomes can induce apoptosis in the acute lymphoblastic leukemia NALM-18 cell line by delivering perforin and granzyme [362]. Furthermore, exosomes derived from macrophages exhibit significant anti-tumor activity by enhancing the cytotoxicity of T cells and NK cells. Notably, this activity is associated with exosomes derived from the M1 phenotype of macrophages [363, 364], whereas exosomes from the M2 phenotype carry high levels of pro-tumor microRNAs such as miR-21-5p and miR-155-5p [365]. A study has shown that M1 macrophage-derived exosomes can deliver substantial amounts of miR-let-7a-5p, activating apoptosis and autophagy signaling pathways in lung cancer cells [366]. Additionally, recent research demonstrates that M1 macrophage-derived exosomes suppress head and neck squamous cell carcinoma (HNSCC) by delivering long non-coding RNA (lncRNA) HOXA transcript at the distal tip [367].

Moreover, B cells and T cells are critical immune cells that produce exosomes containing valuable cargo inherited from their parental cells. B cell-derived exosomes, which include CD19, CD40, CD54, CD63, CD86, MHC-I, and MHC-II molecules as B cell markers and immunogenic molecules, stimulate the proliferation and activation of T cells [368]. T cell-derived exosomes express the T cell receptor, various adhesion molecules, and markers such as CD2, CD3, CD4, CD8, CD11c, CD25, CD69, LFA-1, CXCR4, FasL, and GITR [369]. Moreover, they also contain significant amounts of microRNAs that regulate recipient cells [370]. Exosomes produced by different phenotypes exert substantial regulatory effects on both immune and non-immune cells, demonstrating a potent capacity to target tumor cells [345]. However, the roles of exosomes derived from other immune cells, while crucial, fall outside the scope of this review.

Tumor-derived exosomes represent a significant aspect of cancer immunotherapy, acquiring diverse biological cargoes from their parent cancer cells. These cargoes can potentially facilitate tumor growth by delivering oncogenic

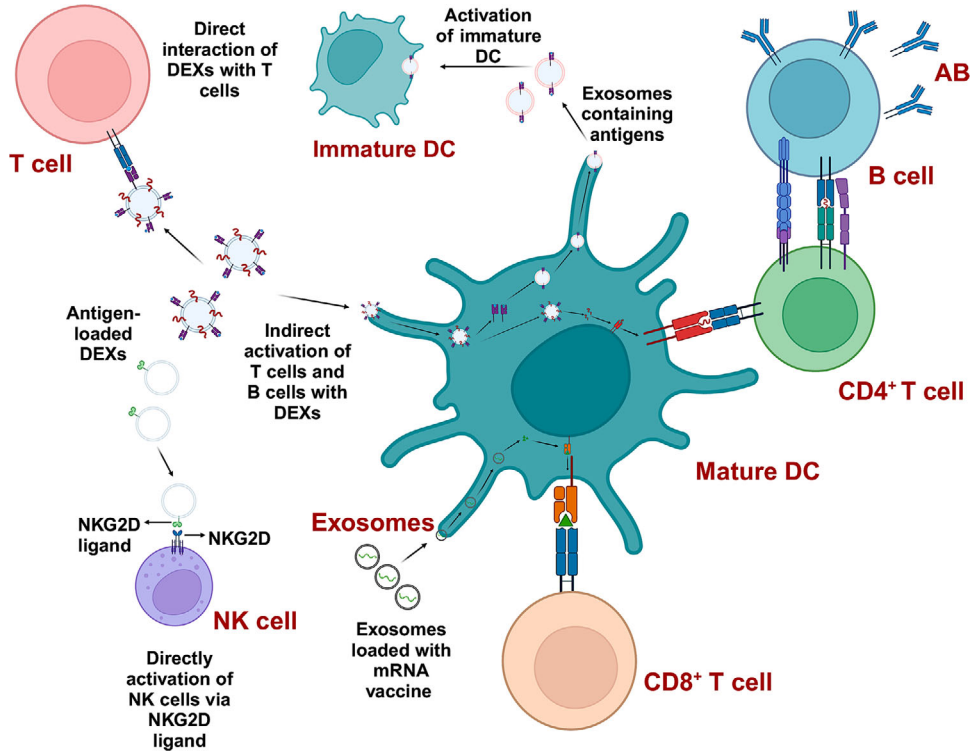

FIGURE 6 Exosomes as biocompatible carriers in cancer immunotherapy. Exosomes are biocompatible, low-toxicity carriers with significant therapeutic potential. They enable precise, targeted delivery of therapeutic agents while eliciting immune responses against cancer cells. Immune cell-derived exosomes, such as DEXs, can be engineered to activate T cells, B cells, and immature DCs, both via direct cell interactions and indirectly by delivering immune-stimulating cargoes like antigens and mRNA vaccines. Furthermore, exosomes can activate NK cells by delivering activating ligands such as NKG2D. Abbreviations: B cell, B lymphocyte; $CD4^+$ T cell, cluster of differentiation 4^+ T cell; $CD8^+$ T cell, cluster of differentiation 8^+ T cell; DC, dendritic cell; DEXs, dendritic cell-derived exosomes; NK cell, natural killer cell; NKG2D, natural killer group 2 member D; mRNA, messenger ribonucleic acid; T cell, T lymphocyte.

materials, reprogramming recipient cells, and influencing the TME [371, 372]. In addition, tumor-derived exosomes may exhibit abnormal surface glycoproteins that contribute to their ability to evade immune surveillance [373]. Importantly, these exosomes also contain some immunostimulatory molecules such as CD80, CD86, MHC complexes [374, 375], which theoretically could be utilized in vaccines, although studies have shown weak and insignificant immune responses [376, 377]. Recent approaches have aimed to enhance the vaccine potential of tumor-derived exosomes. For instance, one study demonstrated improved antigen processing and MHC-I loading in DCs after in vitro incubation with tumor-derived exosomes [378]. Another study highlighted increased proliferation and cytotoxicity of CTLs when loaded with exosome-derived HeLa cells [379]. Notably, due to their content and surface molecules, tumor-derived exosomes could serve as effective adjuvants for cancer vaccines. These findings underscore exosomes' potential as versatile and natural platforms for the development of SVPs.

7 | Conclusion and future perspectives

The escalating rates of cancer incidence and mortality underscore an urgent need for new treatment strategies. Among these, cancer vaccines offer a promising approach by stimulating robust immune responses against malignant cells while limiting unwanted effects. Various investigations have revealed the potential of cancer vaccines to induce potent and long-lasting anti-tumor immunity [380, 381]. However, despite their promise, the widespread adoption of cancer vaccines is hindered by challenges associated with their complex mechanisms of action and variability in patient responses [382, 383].

The effectiveness of cancer vaccines is significantly influenced by the route of administration. As shown in Table 1, the most common routes for cancer vaccines include IV, SC, intradermal (ID), IM, and IT. Each mode of administration affects the immune response differently. IV and IM injections are generally preferred in clinical trials of mRNA cancer vaccines. IM administration is simple, well-tolerated, and allows flexible dosing, with

minimized side effects at the injection site [384]. Additionally, research has shown that IV vaccine injections activate the systemic immune response, enhancing T cell activation and remodeling the TME, though challenges like rapid vaccine component degradation and serum protein aggregation remain [385]. IV peptide vaccines have been reported to activate more $CD8^+$ T cells compared to SC injections, leading to enhanced anti-tumor effects in mice [386]. Alternatively, the skin offers an ideal site for vaccination, given its high concentration of immune cells. ID injections effectively target local APCs, activating both humoral and cellular immunity [387]. In one study, a PCa vaccine was administered using both SC and ID routes in a murine model. The SC route activated both humoral and cell-mediated immunity. In contrast, the ID route primarily stimulated a humoral immune response with strong Th2 activation, which is associated with enhanced AB production, leading to tumor reduction [388]. Additionally, vaccines administered directly to tumor-draining lymph nodes stimulated nearby immune cells and triggered inflammation, which helped reduce the tumor burden and improve survival rates [389]. Interestingly, another study found that delivering DC vaccines via the skin (ID) elicited a stronger anti-cancer immune response compared to direct lymph node injections [390]. Ultimately, factors such as vaccine platform, composition, cancer type, and antigen choice are crucial in determining the optimal administration route to maximize vaccine efficacy [40].

Among different types of vaccine platforms, mRNA-based therapeutic cancer vaccines represent a significant advancement in cancer treatment and SVP design. Preliminary preclinical and early clinical trials have demonstrated the viability and efficacy of these vaccines in eliciting robust anti-tumor immune responses [384]. mRNA vaccines provide benefits such as rapid development and scalable manufacturing, which are essential for addressing the critical demand for effective cancer therapies [391, 392]. Additionally, innovative approaches like personalized neoantigen vaccines show promise in addressing antigenic heterogeneity and enhancing vaccine efficacy tailored to individual patients [393, 394].

One of the main challenges of mRNA-based vaccines is scalability. This limitation became evident during the COVID-19 pandemic, where the technology's capacity for rapid production was demonstrated. Manufacturing typically relies on in vitro transcription, which can be scaled up under good manufacturing practices to facilitate widespread distribution. Unlike traditional vaccines, mRNA production does not require cell cultures or extensive purification processes, allowing faster batch production. However, supply chain constraints and stringent quality control requirements pose significant challenges for scaling mRNA vaccine production from laboratory to commercial levels [395–398]. Additionally, mRNA vaccines face issues such as instability, susceptibility to enzymatic degradation, and limited cellular uptake, all of which reduce delivery efficiency and therapeutic potential. To overcome these barriers, various nanocarriers, including LNPs, polymeric NPs, and bio-nanocarriers, have been developed. These delivery systems protect mRNA from degradation, enhance cellular uptake, and improve pharmacokinetics, resulting in more effective antigen presentation and stronger immune responses. Recent advancements in NP design have improved the safety, tolerability, and delivery efficiency of these platforms. Nevertheless, challenges like immunogenicity, liver accumulation, and limited targeting beyond the liver remain for mRNA-based therapies [47, 399–401].

Incorporating nanocarriers and click chemistry reactions, offers solutions to current limitations. Nanocarriers enable precise vaccine delivery and controlled release, while click chemistry enhances vaccine stability and targeting efficiency. For example, click chemistry-based conjugation strategies provide precise control over vaccine design, allowing for the incorporation of multiple antigenic epitopes to enhance immune stimulation [402, 403]. Furthermore, the use of exosomes as versatile vehicles for cancer vaccine delivery presents both opportunities and challenges. While exosomes offer advantages such as stability and biocompatibility, concerns arise when they are derived from tumor cells [404].

Overall, the integration of advanced technologies, including mRNA-based vaccines, engineered carriers, and click chemistry reactions, brings hope to the battle against cancer. Even with challenges posed by the TME and vaccine scalability, advancements in targeted delivery systems show promise for enhancing cancer immunotherapy outcomes. This integration results in SVPs that interact precisely with immune cells, activating their responses against cancer cells while preventing adverse effects. Furthermore, SVPs can be optimized for antigen loading. Despite these benefits, continued research and innovation in SVP design are crucial to improving therapeutic outcomes and meeting the urgent demand for effective cancer treatments. With collective expertise and resources, we can initiate a new era of personalized and efficacious cancer immunotherapy, ultimately aiming toward the eradication of this devastating disease.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the results of this study are available within the article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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