



Mini Review

Recent Developments of Vaccines as a Precision Medicine Approach to Cancer Immunotherapy



Joseph F. Murphy*

ImmunePCS LLC, Boston, MA, USA

Received: April 11, 2024 | Revised: May 08, 2024 | Accepted: May 22, 2024 | Published online: June 25, 2024

Abstract

Precision medicine uses information about a person's genes, proteins, environment, lifestyle, and tumor characteristics to prevent, diagnose, or treat diseases such as cancer. Given recent advances in cancer immunotherapy, there is renewed interest in therapeutic cancer vaccines. Some therapeutic cancer vaccines use patient-specific tumor antigens to create individualized vaccines, whereas others target shared tumor-associated antigens. Although challenges remain, progress has been made in vaccine engineering, particularly with messenger RNA (mRNA)-based platforms. This mini-review focuses on recent developments in vaccine engineering, key therapeutic obstacles, and selected human clinical trials, with particular emphasis on personalized approaches.

Introduction

The field of precision medicine, also referred to as personalized or individualized medicine, is a burgeoning area of research and development, particularly in relation to immunotherapy.¹ Tailoring treatment to a specific patient, rather than using more conventional, broad-spectrum treatments, circumvents many of the side effects associated with traditional approaches. Cancer immunotherapy has emerged at the forefront of this treatment modality, especially with the advent of immune checkpoint inhibitors (ICIs), which have shown significant clinical benefits against several types of cancer.² These ICIs are monoclonal antibodies directed against immunosuppressive molecules, such as programmed cell death protein-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte antigen-4. Despite recent progress, challenges remain in antigen selection, tumor heterogeneity, immune suppression, manufacturing, and clinical validation. This mini-review summarizes recent developments in cancer vaccine engineering, key therapeutic obstacles, and selected recent clinical studies, with particular emphasis on mRNA-based approaches.

Precision medicine

Adoptive cell transfer therapy has made enormous progress in

cancer immunotherapy in recent years by marshaling and amplifying the body's immune system to fight cancer. Functional immune cells, specifically tumor-infiltrating lymphocytes (TILs), which can recognize tumor-derived peptides presented by human leukocyte antigen (HLA) molecules, are isolated from the patient's tumor, engineered or expanded *ex vivo*, and then readministered to the same patient.¹ This therapeutic modality can be divided into three subtypes: unmodified TILs, chimeric antigen receptor (CAR)-engineered T cells, and T cells with engineered T-cell receptors (TCRs).³

The most successful form of this treatment modality is CAR T cell therapy. To date, this modality has received six U.S. Food and Drug Administration (FDA) approvals for hematological malignancies.⁴ Although this autologous treatment modality has shown considerable success in blood cancers, disadvantages arise from difficulty penetrating solid tumors and factors such as excessive costs, toxic side effects, and lack of tumor-specific antigens. T cells expressing engineered TCRs represent another therapeutic alternative, as their target repertoire is not limited to membrane proteins. Moreover, intrinsic features such as high antigen sensitivity and near-physiological signaling can improve tumor cell detection and destruction with improved T cell persistence.⁵ However, engineered TCRs can show off-target cross-reactivity; in one clinical experience, an affinity-enhanced MAGE-A3 TCR cross-reacted with a titin-derived peptide expressed in cardiac muscle, causing fatal cardiotoxicity.⁶

Natural killer (NK) cell therapy is currently emerging as an attractive option, as it offers several advantages over CAR T cell therapies, including multiple mechanisms of action and reduced alloreactivity. CAR NK therapy also potentially offers an "off-the-shelf" allogeneic product, eliminating the need for a personalized, patient-specific product associated with current CAR T cell therapy.

Keywords: Vaccines; Immunotherapy; Messenger RNA; Checkpoint inhibitors; Chimeric antigen receptor; T cells; Natural killer cells.

*Correspondence to: Joseph F. Murphy, ImmunePCS LLC, Boston, MA 02169, USA. ORCID: <https://orcid.org/0000-0002-3988-5120>. Tel: +1-617-657-3320, E-mail: joseph.murphy@immunepcs.com

How to cite this article: Murphy JF. Recent Developments of Vaccines as a Precision Medicine Approach to Cancer Immunotherapy. *Cancer Screen Prev* 2024;3(2):111–115. doi: 10.14218/CSP.2024.00009.

pies.⁷ However, drawbacks of this treatment modality include low efficiency of CAR transduction, limited cell expansion, and lack of available targets.⁸

A recent development in this precision medicine approach demonstrated that antitumor T cells in the blood of patients with metastatic solid cancers can be identified and isolated using a newly identified signature. Although these cells are sparse, they can now be retrieved without surgery and used to develop personalized cancer immunotherapies.⁹ Researchers analyzed T cells using blood from patients with metastatic cancer with T cells from within the tumor, looking for identical receptors. Using single-cell transcriptomic profiling techniques, they identified unique molecular signatures for antitumor T cells in the blood in six of eight blood samples from patients with colorectal cancer, breast cancer, and melanoma. Moreover, the T cells from the blood were found to be less exhausted than the intra-tumor T cells. These cells can potentially be amplified *ex vivo* and re-infused into the same patient. Based on the antitumor results observed in both pre-clinical studies and current human clinical trials, this modality may contribute to future cancer treatment approaches.^{10,11}

Therapeutic vaccines

Vaccines are biological preparations that elicit an immune response and provide active acquired immunity against a particular infectious or malignant disease. Vaccine immunization is traditionally thought of as a means of preventing disease, and vaccines contain or encode antigens that prime the immune system to respond to a target pathogen or antigen. Examples of conventional vaccine platforms include:

Live or attenuated

A weakened form of the pathogen causing the disease elicits a strong and long-lasting immune response. One to two doses can confer lifetime protection against diseases such as measles, mumps, and rubella.

Inactivated

A non-live version of the disease-causing pathogen can induce protective immunity. This type is generally less immunogenic than a live attenuated vaccine and may require booster doses.

Toxoid

Utilizes the toxin created by the pathogen instead of the actual pathogen and is used to protect against diphtheria and tetanus. Vaccines can also be used therapeutically. Advances in design and development have renewed interest in therapeutic vaccination as a precision medicine strategy.¹ Therapeutic vaccines differ from preventive or prophylactic vaccines, such as measles and influenza, which protect against future disease, in that they prime a patient's immune system to combat an existing disease.¹¹

Therapeutic vaccination for cancer takes advantage of the fact that cancer cells possess distinguishing proteins, or antigens, which differ from normal cells. Although immune surveillance can recognize and eliminate abnormal cells, tumors can develop mechanisms to evade immune detection. For this reason, there is a current focus on vaccines not as a means of preventing cancer but treating it. Initially, research efforts concentrated on developing vaccines against shared proteins commonly expressed in certain cancers. However, the failure of this strategy in large clinical trials in the mid-2010s has shifted the focus toward personalized approaches.¹²

Personalized cancer vaccines are tailored specifically to individual patients. They work by:

- Inducing antigen-specific CD4+ and/or CD8+ T-cell responses against tumor-derived antigens;
- Promoting immune recognition and elimination of tumor cells presenting those antigens, with the potential to generate immunologic memory.

Cancer cells can generate mutated proteins that the immune system recognizes as foreign, prompting an immune response. Individualized vaccine approaches commonly focus on identifying tumor-specific neoantigens. Tumor tissue obtained at biopsy or surgery can be genetically analyzed to identify tumor-specific neoantigens and other candidate antigens.¹¹ Vaccines can then be designed to target selected antigens. Vaccine-induced T cells can recognize and destroy tumor cells presenting these antigens, with the potential to generate immunologic memory.¹⁴

Although enormous progress has been made in recent years with cancer vaccines, considerable hurdles remain. For example, cell-based vaccines are very labor-intensive, and the process of isolating and culturing patient-specific immune cells requires substantial resources and expertise, resulting in high production costs. Additionally, tumors can develop immune evasion mechanisms and create immunosuppressive microenvironments, which include barriers to immune infiltration by anti-cancer immune cells, selective recruitment of immunosuppressive cells, induction of T cell death, production of immunosuppressive enzymes and metabolites, and hypoxic conditions in tumors, all of which can hinder vaccine-induced anti-cancer immune responses.¹⁵ Moreover, because of high intratumoral and intertumoral heterogeneity, a vaccine targeting antigens from one tumor sample may not cover all tumor clones or metastatic sites.¹⁶

Vaccine development, from basic research to approval, typically takes about 5 to 10 years.¹⁷ Although a large number of vaccine studies are conducted at the preclinical stage, less than 10% of vaccines are approved. Four broad cancer vaccine platform types are summarized (Table 1).¹⁸ A major driver of recent vaccine development is the significant progress made with messenger RNA (mRNA) development.^{19,20} The relatively short time required to design and manufacture mRNA vaccines encoding selected antigens is a major advantage. mRNA platforms also offer flexibility for encoding multiple antigens and for rapid manufacturing.²¹ Moreover, mRNA platforms can support rapid and scalable manufacturing through *in vitro* transcription. mRNA cancer vaccines include both shared-antigen and individualized approaches and remain under active clinical investigation.

Although cancer vaccines have been researched for over 30 years, few have achieved major clinical success. Sipuleucel-T (Provenge®), an autologous cellular immunotherapy for metastatic castration-resistant prostate cancer, is the sole cancer vaccine approved for clinical use in the United States.^{22,23}

- Other FDA-approved cancer immunotherapies are sometimes discussed alongside therapeutic cancer vaccines, but their mechanisms and regulatory classifications differ:
- Bacillus Calmette-Guérin (BCG) is a live attenuated *Mycobacterium bovis* preparation used intravesically to treat certain bladder cancers;
- Nadofaragene firadenovec (Adstiladrin®) is a non-replicating adenoviral vector-based gene therapy approved for high-risk BCG-unresponsive non-muscle-invasive bladder cancer;
- T-VEC (Imlygic®) is an oncolytic viral therapy used to treat certain unresectable melanoma lesions.

This landscape has changed in recent years due to some of the

Table 1. Cancer vaccine types

Vaccine	Description
Cell-based	Generated normally from either complete cells or cell fragments, resulting in a wide range of tumor antigens, which induce a broad immune response. Examples include dendritic cells (DCs), which can be immunogenic but may be expensive and complex to produce.
Viral vector	Uses a modified version of a virus as a vector that leads to a strong immune response involving both B and T cells. Engineered oncolytic viruses act as vectors capable of presenting high quantities of tumor antigens, resulting in long-term memory, but are also complex to produce.
Peptide-based	Comprised of synthetic or biosynthetic peptides representing known or predicted tumor-antigen epitopes, these vaccines aim to elicit antigen-specific T-cell responses. Their immunogenicity may be limited by the small size of peptide epitopes and by major histocompatibility complex (MHC) polymorphisms.
Nucleic acid-based (deoxyribonucleic acid (DNA) or messenger RNA (mRNA))	Capable of encoding full-length tumor antigens, which allows APCs to present multiple antigens simultaneously, eliciting strong MHC I-mediated CD8 ⁺ T cell responses, resulting in both humoral and cellular immunity. To initiate transcription, DNA vaccines must enter the cell nucleus, whereas mRNA vaccines only require entry to the cytoplasm to allow antigen translation and expression. DNA vaccines carry the potential risk of inserting mutations into the genome, a risk not associated with mRNA vaccines.

APCs, antigen-presenting cells; DCs, dendritic cells; DNA, deoxyribonucleic acid; MHC, major histocompatibility complex; mRNA, messenger RNA.

aforementioned advances. Improvements in target identification, formulation, manufacturing and development, combination therapy regimens, and patient selection are showing promise. A 2022 landscape analysis identified approximately 360 active clinical trials of cancer vaccines.²³ For example, one study reported results from a clinical trial using the VB10.16 vaccine. VB10.16 is a therapeutic vaccine composed of three parts: the first encodes the E6/E7 fusion protein of human papillomavirus (HPV16 E6/7), which plays a key role in developing certain types of cancer; the second comprises a dimerization entity; and the third encodes a protein that specifically binds to antigen-presenting cells. The authors reported that this vaccine was well tolerated and showed promising evidence of efficacy and strong HPV16-specific T-cell responses in patients with high-grade cervical intraepithelial neoplasia.²⁴

Another study reported on TG4050, an individualized viral vector vaccine comprising a modified Vaccinia virus Ankara viral vector encoding tumor-specific neoantigens developed using advanced genetic engineering and artificial intelligence technologies. The authors reported that this personalized vaccine was safe, well-tolerated, and induced T cell responses in cold tumors from patients with head and neck carcinoma.²⁵

Early clinical trials of mRNA therapeutics include studies of paracrine vascular endothelial growth factor, mRNA for heart failure, and CRISPR-Cas9 mRNA for a congenital liver-specific storage disease.²⁶ Developing vaccines against cancer is more challenging than against infectious diseases due to the weak immune response and immunosuppressive effects within the tumor microenvironment.²⁷ However, progress is being made, and several studies are reporting positive results.

A randomized phase IIb study reported that the individualized neoantigen therapy mRNA-4157 (V940), when combined with pembrolizumab, improved recurrence-free survival compared with pembrolizumab alone in patients with resected high-risk melanoma.²⁸ Exploratory subgroup analyses suggested that the recurrence-free survival benefit was similar in tumor mutational burden-high and non-high groups. The individualized therapy encoded up to 34 patient-specific neoantigens selected from tumor sequencing data.

Another recently reported phase I clinical trial from Memorial Sloan Kettering Cancer Center used mRNA vaccines directed against the patient's tumor neo-antigens.²⁹ Tumors were surgically

removed from patients, and autogene cevumeran was developed to encode up to 20 patient-specific neoantigens. After surgery, treatment was administered sequentially: atezolizumab, autogene cevumeran, and then mFOLFIRINOX; 16 patients received atezolizumab and autogene cevumeran, and 15 of these 16 subsequently received mFOLFIRINOX. Eight of 16 vaccinated patients generated high-magnitude neoantigen-specific T-cell responses. At a median follow-up of 18 months, these vaccine responders had a longer median recurrence-free survival (not reached) than non-responders (13.4 months; $P = 0.003$). Given the small, non-randomized phase I study, these findings were hypothesis-generating rather than definitive evidence of clinical efficacy. A follow-up phase II trial (NCT05968326) has opened to build upon this approach to determine its effectiveness.

Preclinical work on STX-001, a locally administered lipid nanoparticle-formulated self-replicating mRNA encoding IL-12, reported systemic immune responses and antitumor activity in solid-tumor models.³⁰ In preclinical models, STX-001 induced immunogenic tumor cell death, promoted T-cell and NK-cell recruitment to the tumor microenvironment, and enhanced antitumor responses when combined with PD-1/PD-L1 checkpoint inhibitors. These findings support further clinical evaluation but do not establish clinical efficacy.

Future directions

mRNA vaccines are rapidly becoming established as a versatile technology for future applications, especially given recent advances. Directly targeting antigens to immune cells is being investigated as a strategy to improve vaccine potency. For example, dendritic cells are pivotal mediators of both B-cell and T cell immunity. Given their potency as antigen-presenting cells, they are currently the focus of mRNA-delivery systems targeting immune cells for the delivery of cell-specific antigens.³¹ Clinical studies suggest that personalized mRNA vaccination can act as an immune modulator and may complement ICIs.³²

An addition to the mRNA arsenal is self-amplifying RNA (saRNA). saRNA displays several structural similarities to conventional mRNA technology and may offer advantages such as prolonged antigen expression and lower dose requirements.³³ Clinical development of saRNA platforms is ongoing. Although no saRNA can-

cer vaccine had received FDA approval at the time of publication, the first self-amplifying mRNA vaccine was approved in Japan for COVID-19.³⁴

In addition to the advent of mRNA technologies, other technologies are also emerging that show promise as anti-cancer therapies. One such approach involves the administration of engineered inactivated tumor cells to elicit an immune response. In this preclinical study, the authors used CRISPR-Cas9 technology to engineer tumor cells to release interferon beta (IFN- β) and granulocyte-macrophage colony-stimulating factor in a glioblastoma humanized mouse model. The engineered therapeutic tumor cells not only targeted and eliminated the tumors but also improved survival and long-term immunity in primary, recurrent, and metastatic cancer models.³⁵

Another recent study published in *Cancer Discovery* reported an approach to identify proteins involved in both cancer cell metabolism and immune responses within tumors. The authors developed BipotentR, a computational tool designed to identify proteins that could disrupt cancer cell metabolism while promoting an immune response in the tumor microenvironment.³⁶ Results from both preclinical and clinical models that analyzed gene expression data revealed that BipotentR identified 38 cancer cell-specific immune-metabolic regulators, providing insights into patient outcomes post-immunotherapy. Moreover, artificial intelligence techniques used to assess the activity levels of these regulators within tumors revealed that estrogen-related receptor alpha was highly active in immunotherapy-resistant tumors across various cancer types.

Limitations

This narrative mini-review was not based on a systematic literature search and therefore may not capture all relevant studies. The field is evolving rapidly, and several examples discussed were early-phase clinical trials, conference abstracts, or preclinical reports; efficacy and regulatory status should therefore be interpreted cautiously.

Conclusions

Precision medicine has become an important framework in cancer therapy, including immunotherapy. Immune checkpoint blockade has improved outcomes for some patients, but additional treatment modalities are needed. mRNA-based cancer vaccines are under active clinical development, including individualized neoantigen approaches, but no mRNA cancer vaccine was FDA approved at the time of publication. Early-phase and phase II studies have shown immunogenicity and encouraging clinical signals in selected solid tumors, although larger randomized studies are required to establish efficacy. Advances in lipid nanoparticle delivery, antigen selection, manufacturing, and strategies to address tumor heterogeneity and immunosuppression may further strengthen this field.

Acknowledgments

The author is grateful to Tara Finn for careful reading of this manuscript.

Funding

None.

Conflict of interest

JFM is the Founder and President of ImmunePCS LLC. The author declares no other conflict of interests.

Author contributions

JFM is the sole author of the manuscript.

References

- [1] Murphy JF. Therapeutic Vaccination and Cancer Immunotherapy. *J Explor Res Pharmacol* 2024;9(1):25–29. doi:10.14218/JERP.2023.00049.
- [2] Bai R, Lv Z, Xu D, Cui J. Predictive biomarkers for cancer immunotherapy with immune checkpoint inhibitors. *Biomark Res* 2020;8:34. doi:10.1186/s40364-020-00209-0, PMID:32864131.
- [3] Zhao X, Pan X, Wang Y, Zhang Y. Targeting neoantigens for cancer immunotherapy. *Biomark Res* 2021;9(1):61. doi:10.1186/s40364-021-00315-7, PMID:34321091.
- [4] Pan K, Farrukh H, Chittepu VCSR, Xu H, Pan CX, Zhu Z. CAR race to cancer immunotherapy: from CAR T, CAR NK to CAR macrophage therapy. *J Exp Clin Cancer Res* 2022;41(1):119. doi:10.1186/s13046-022-02327-z, PMID:35361234.
- [5] Baulu E, Gardet C, Chuvin N, Depil S. TCR-engineered T cell therapy in solid tumors: State of the art and perspectives. *Sci Adv* 2023;9(7):eadf3700. doi:10.1126/sciadv.adf3700, PMID:36791198.
- [6] Liu Y, Yan X, Zhang F, Zhang X, Tang F, Han Z, *et al.* TCR-T Immunotherapy: The Challenges and Solutions. *Front Oncol* 2021;11:794183. doi:10.3389/fonc.2021.794183, PMID:35145905.
- [7] Murphy JF. Natural Killer Cells: Future Role for Cancer Immunotherapy. *Int J Pharma Bio Sci* 2022;2(6):116–117. doi:10.47191/ijpbms/v2-i6-01.
- [8] Kang S, Gao X, Zhang L, Yang E, Li Y, Yu L. The Advances and Challenges of NK Cell-Based Cancer Immunotherapy. *Curr Oncol* 2021;28(2):1077–1093. doi:10.3390/curroncol28020105, PMID:33652996.
- [9] Yossef R, Krishna S, Sindiri S, Lowery FJ, Copeland AR, Gartner JJ, *et al.* Phenotypic signatures of circulating neoantigen-reactive CD8(+) T cells in patients with metastatic cancers. *Cancer Cell* 2023;41(12):2154–2165.e5. doi:10.1016/j.ccell.2023.11.005, PMID:38039963.
- [10] Zhang B, Yang M, Zhang W, Liu N, Wang D, Jing L, *et al.* Chimeric antigen receptor-based natural killer cell immunotherapy in cancer: from bench to bedside. *Cell Death Dis* 2024;15(1):50. doi:10.1038/s41419-024-06438-7, PMID:38221520.
- [11] Leko V, Rosenberg SA. Identifying and Targeting Human Tumor Antigens for T Cell-Based Immunotherapy of Solid Tumors. *Cancer Cell* 2020;38(4):454–472. doi:10.1016/j.ccell.2020.07.013, PMID:32822573.
- [12] Tian Y, Hu D, Li Y, Yang L. Development of therapeutic vaccines for the treatment of diseases. *Mol Biomed* 2022;3(1):40. doi:10.1186/s43556-022-00098-9, PMID:36477638.
- [13] Drew L. Cancer-vaccine trials give reasons for optimism. *Nature* 2024;627(8005):S33. doi:10.1038/d41586-024-00840-z, PMID:38538945.
- [14] Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. *J Hematol Oncol* 2022;15(1):28. doi:10.1186/s13045-022-01247-x, PMID:35303904.
- [15] Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. *Adv Immunol* 2006;90:51–81. doi:10.1016/S0065-2776(06)90002-9, PMID:16730261.
- [16] Buonaguro L, Tagliamonte M. Selecting Target Antigens for Cancer Vaccine Development. *Vaccines (Basel)* 2020;8(4):615. doi:10.3390/vaccines8040615, PMID:33080888.
- [17] Okay S. Effect of coronavirus disease 2019 on the vaccine development paradigm. *Explor Immunol* 2023;3:433–441. doi:10.37349/ei.2023.00111.
- [18] Orenstein WA, Offit PA, Edwards KM, Plotkin SA. *Plotkin's Vaccines*, 8th ed. Amsterdam: Elsevier; 2022.

- [19] Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov* 2018;17(4):261–279. doi:10.1038/nrd.2017.243, PMID:29326426.
- [20] Miao L, Zhang Y, Huang L. mRNA vaccine for cancer immunotherapy. *Mol Cancer* 2021;20(1):41. doi:10.1186/s12943-021-01335-5, PMID:33632261.
- [21] Pan S, Fan R, Han B, Tong A, Guo G. The potential of mRNA vaccines in cancer nanomedicine and immunotherapy. *Trends Immunol* 2024;45(1):20–31. doi:10.1016/j.it.2023.11.003, PMID:38142147.
- [22] Memorial Sloan Kettering Cancer Center. Cancer Vaccines: The Types, How They Work, and Which Cancers They Treat. 2024. Available from: <https://www.mskcc.org/cancer-care/diagnosis-treatment/cancer-treatments/immunotherapy/cancer-vaccines>. Accessed May 2024.
- [23] Janes ME, Gottlieb AP, Park KS, Zhao Z, Mitragotri S. Cancer vaccines in the clinic. *Bioeng Transl Med* 2024;9(1):e10588. doi:10.1002/btm2.10588, PMID:38193112.
- [24] Hillemanns P, Denecke A, Woelber L, Böhmer G, Jentschke M, Schjetne KW, *et al.* A Therapeutic Antigen-Presenting Cell-Targeting DNA Vaccine VB10.16 in HPV16-Positive High-Grade Cervical Intraepithelial Neoplasia: Results from a Phase I/IIa Trial. *Clin Cancer Res* 2022;28(22):4885–4892. doi:10.1158/1078-0432.CCR-22-1927, PMID:36129459.
- [25] Ottensmeier CHH, DeLord JP, Lalanne A, Lantz O, Jamet C, Tavernaro A, *et al.* Safety and immunogenicity of TG4050: A personalized cancer vaccine in head and neck carcinoma. *J Clin Oncol* 2023;41(16_suppl):6082. doi:10.1200/JCO.2023.41.16_suppl.6082.
- [26] Rohner E, Yang R, Foo KS, Goedel A, Chien KR. Unlocking the promise of mRNA therapeutics. *Nat Biotechnol* 2022;40(11):1586–1600. doi:10.1038/s41587-022-01491-z, PMID:36329321.
- [27] Murphy JF. Angiogenesis and the Tumor Microenvironment. In: Rezaei N (ed). *Handbook of Cancer and Immunology*. Cham: Springer; 2022:1–17. doi:10.1007/978-3-030-80962-1_87-1.
- [28] Weber JS, Carlino MS, Khattak A, Meniawy T, Ansstas G, Taylor MH, *et al.* Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study. *Lancet* 2024;403(10427):632–644. doi:10.1016/S0140-6736(23)02268-7, PMID:38246194.
- [29] Rojas LA, Sethna Z, Soares KC, Olcese C, Pang N, Patterson E, *et al.* Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. *Nature* 2023;618(7963):144–150. doi:10.1038/s41586-023-06063-y, PMID:37165196.
- [30] Sowell RT, Khurana JS, Su Z, Zhao W, Shenoy GN, Dey M, *et al.* Abstract 2731: STX-001, a locally administered LNP-formulated self-replicating mRNA that encodes the therapeutic payload IL-12, induces deep systemic immune responses to solid tumors. *Cancer Res* 2023;83(7_Suppl):2731. doi:10.1158/1538-7445.AM2023-2731.
- [31] Clemente B, Denis M, Silveira CP, Schiavetti F, Brazzoli M, Stranges D. Straight to the point: targeted mRNA-delivery to immune cells for improved vaccine design. *Front Immunol* 2023;14:1294929. doi:10.3389/fimmu.2023.1294929, PMID:38090568.
- [32] Makker S, Galley C, Bennett CL. Cancer vaccines: from an immunology perspective. *Immunother Adv* 2024;4(1):ltad030. doi:10.1093/immadv/ltad030, PMID:38223410.
- [33] Papukashvili D, Rcheulishvili N, Liu C, Ji Y, He Y, Wang PG. Self-Amplifying RNA Approach for Protein Replacement Therapy. *Int J Mol Sci* 2022;23(21):12884. doi:10.3390/ijms232112884, PMID:36361673.
- [34] First self-amplifying mRNA vaccine approved. *Nat Biotechnol* 2024;42(1):4. doi:10.1038/s41587-023-02101-2, PMID:38233659.
- [35] Chen KS, Reinshagen C, Van Schaik TA, Rossignoli F, Borges P, Mendonca NC, *et al.* Bifunctional cancer cell-based vaccine concomitantly drives direct tumor killing and antitumor immunity. *Sci Transl Med* 2023;15(677):eabo4778. doi:10.1126/scitranslmed.abo4778, PMID:36599004.
- [36] Sahu A, Wang X, Munson P, Klomp JPG, Wang X, Gu SS, *et al.* Discovery of Targets for Immune-Metabolic Antitumor Drugs Identifies Estrogen-Related Receptor Alpha. *Cancer Discov* 2023;13(3):672–701. doi:10.1158/2159-8290.CD-22-0244, PMID:36745048.