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Neoantigen-driven cancer vaccines: Revolutionizing precision oncology through personalized immunotherapy

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Abstract

Neoantigen-driven cancer vaccines have emerged as a transformative approach in precision oncology, harnessing tumor-specific mutations to elicit robust, tailored immune responses. This review focuses on neoantigen identification, vaccine platforms, clinical applications, and challenges. Leveraging next-generation sequencing (NGS) and bioinformatics, vaccines target neoantigens in cancers like melanoma, pancreatic cancer, and non-small cell lung cancer (NSCLC). mRNA platforms and peptide-based vaccines have shown promising clinical outcomes, particularly when combined with immune checkpoint inhibitors. Challenges include prediction accuracy, production scalability, and tumor microenvironment immunosuppression. Future directions involve AI-driven tools, novel delivery systems, and cost-reduction strategies to enhance accessibility.

Keywords: Neoantigen; Cancer Vaccines; Personalized Immunotherapy; Precision Oncology; mRNA Technology; Immune Checkpoint Inhibitors

1. Introduction

Cancer remains a formidable global health challenge, with millions of new diagnoses and deaths reported annually despite advancements in conventional therapies. Neoantigen-driven cancer vaccines have emerged as a groundbreaking strategy in precision oncology, utilizing tumor-specific mutations to stimulate highly targeted immune responses with minimal off-target effects [1]. Breakthroughs in next-generation sequencing (NGS), bioinformatics, and vaccine technologies have accelerated the development of these vaccines, offering hope for treating challenging cancers such as melanoma, pancreatic cancer, and glioblastoma [2, 9]. This review synthesizes recent developments, clinical outcomes, challenges, and future prospects, aiming to engage researchers, clinicians, and patients by highlighting the transformative potential of neoantigen-driven vaccines in reshaping cancer care.

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2. Neoantigen biology and identification

2.1. Neoantigen Definition and Sources

Neoantigens are tumor-specific peptides derived from somatic mutations, including single-nucleotide variants (SNVs), insertions/deletions (indels), gene fusions, or post-transcriptional modifications, presented on major histocompatibility complex (MHC) molecules [1]. Unlike tumor-associated antigens (TAAs), which are overexpressed in normal tissues, neoantigens are unique to cancer cells, minimizing immune tolerance and reducing the risk of autoimmune reactions. According to Singh et al. [2025], this specificity positions neoantigens as ideal targets for personalized cancer vaccines, particularly in cancers with high mutational burdens, such as melanoma and lung cancer [3].

The diversity of neoantigen sources significantly enhances their therapeutic potential. SNVs, the most common mutation type, alter protein sequences to produce novel peptides, as noted by Zaidi et al. [2025] [5]. Indels and gene fusions, though less frequent, generate highly immunogenic neoantigens, particularly in pancreatic cancer, where fusion-derived neoantigens have been associated with prolonged survival [7]. Post-transcriptional modifications, such as aberrant RNA splicing, further expand the neoantigen repertoire, offering additional targets for vaccine design [6]. These diverse sources highlight the necessity of comprehensive genomic profiling to identify actionable neoantigens for effective vaccine development.

Table 1 Neoantigen Sources and Their Characteristics

Neoantigen Type	Molecular Origin	Immunogenicity	Prevalence in Cancers	Advantages	Challenges	Examples
Single-Nucleotide Variants (SNVs)	Point mutations in coding regions	High; mimics microbial antigens	Melanoma, NSCLC, bladder	Common, easily detected	Variable expression	EGFR mutations
Insertions/ Deletions (Indels)	Small insertions or deletions	Moderate to high	Colorectal, endometrial	Unique epitopes	Rare, hard to predict	Frameshift mutations
Gene Fusions	Chromosomal rearrangements	High; novel proteins	Pancreatic, prostate	Highly immunogenic	Complex detection	TMPRSS2-ERG
Post-Transcriptional Modifications	Aberrant RNA splicing	Moderate	Glioblastoma, HCC	Expands target pool	Low abundance	MAGE-A3 splice variants
Non-Coding Mutations	Mutations in introns, UTRs	Low to moderate	Melanoma, NSCLC	Broadens neoantigen pool	Difficult to validate	Intronic neoepitopes

Table 1 summarizes the primary types of neoantigens, their molecular origins, immunogenicity, and relevance to specific cancers, providing a concise reference to complement the discussion of neoantigen biology [1,5,6].

Tumor heterogeneity poses a significant challenge to neoantigen identification, as mutations vary within and across tumor sites. This variability necessitates multi-region tumor sampling to ensure vaccines target both primary and metastatic lesions, as neglecting subclonal neoantigens can reduce efficacy [8]. Findings from Goswami et al. [2025] indicate that addressing tumor heterogeneity through advanced sequencing strategies is critical for optimizing vaccine design [9].

Recent research emphasizes the importance of neoantigen quality over quantity. According to Wang et al. [2025], neoantigens with high immunogenicity, often resembling microbial antigens, trigger stronger immune responses than those with high mutation counts [10]. This insight has shifted the focus toward selecting neoantigens with optimal T-cell receptor (TCR) recognition to enhance vaccine effectiveness [3]. Understanding the biology and sources of

neoantigens remains foundational to developing personalized vaccines that can effectively address tumor diversity and immune evasion mechanisms.

2.2. Identification Technologies

Next-generation sequencing (NGS) has revolutionized neoantigen identification by enabling high-throughput analysis of tumor genomes. Whole-exome sequencing (WES) and RNA sequencing (RNA-seq) compare tumor and normal cell DNA to detect somatic mutations, identifying 10–50 immunogenic neoantigens in high-mutation cancers like melanoma [9]. The study by Li et al. [2021] shows that integrating WES with RNA-seq ensures mutations are expressed at the RNA level, a critical requirement for vaccine design [7]. This integrated approach has reduced identification times from months to weeks, facilitating rapid translation to clinical applications [4].

Emerging multi-omics technologies, such as single-cell sequencing and spatial transcriptomics, provide deeper insights into tumor heterogeneity and immune interactions. Single-cell sequencing reveals neoantigen expression at the cellular level, addressing subclonal variations that bulk sequencing misses, as demonstrated by Wang et al. [2025] in pancreatic cancer trials [10]. Spatial transcriptomics maps neoantigen distribution within the tumor microenvironment (TME), aiding in the selection of immunogenic targets [6]. According to Zaidi et al. [2025], these advanced technologies enhance the precision of neoantigen identification, which is crucial for improving personalized vaccine efficacy [5].

Mass spectrometry complements NGS by directly detecting neoantigen peptides presented on MHC molecules. Findings from Viceconti et al. [2021] indicate that mass spectrometry validates predicted neoantigens, improving specificity over computational methods alone [11]. However, its sensitivity is limited for low-abundance peptides, necessitating integration with NGS for comprehensive profiling [4]. The combination of these technologies has streamlined neoantigen discovery, enabling the design of vaccines tailored to individual tumor profiles, though high costs remain a barrier to widespread adoption.

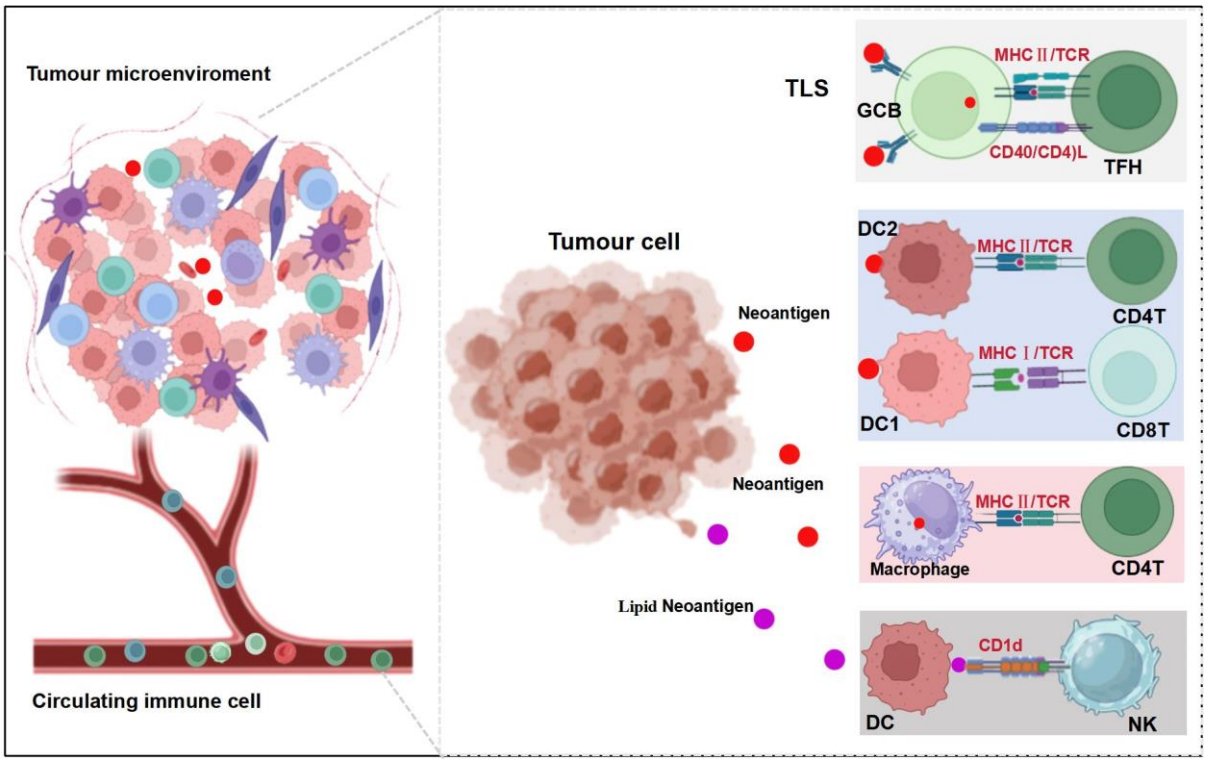

Figure 1 This figure depicts a workflow integrating WES, RNA-seq, and bioinformatics (e.g., NetMHCpan) to identify and validate neoantigens, showing steps like mutation calling, expression analysis, and MHC binding prediction[4, 9]

Despite these advancements, challenges in identification persist, including variability in sequencing platforms and sample quality. According to Blass and Ott [2021], inconsistencies in sequencing depth and sample preparation can lead to false positives, requiring standardized protocols to ensure reliability [12]. Collaborative initiatives, such as the Tumor Neoantigen Selection Alliance (TESLA), are developing shared databases to improve reproducibility and reduce costs

[11]. These efforts are essential for scaling neoantigen identification to diverse patient populations, ensuring equitable access to personalized cancer vaccines.

2.3. Bioinformatics and Prediction Tools

Bioinformatics tools are critical for predicting neoantigen immunogenicity and MHC binding affinity. Algorithms such as NetMHCpan, OptiType, and Polysolver rank neoantigens based on MHC class I and II binding, expression levels, and T-cell receptor (TCR) recognition potential [11]. The study by Li et al. [2024] shows that NetMHCpan-4.1 achieves up to 80% accuracy in predicting MHC class I binding, significantly improving the design of personalized vaccines. These tools integrate genomic, transcriptomic, and proteomic data to prioritize neoantigens likely to elicit robust immune responses [7].

Recent advancements in artificial intelligence (AI) have further enhanced prediction accuracy. AI-driven platforms like PIONEER incorporate tumor mutation burden (TMB) and immune contexture to refine neoantigen selection, as noted by Wang et al. [2025] [10]. Findings from Xie et al. [2023] indicate that machine learning models trained on immunopeptidomics data can predict neoantigens across diverse HLA alleles, addressing patient-specific variability [13]. However, MHC class II prediction remains less accurate due to the complexity of longer peptide sequences and open-ended binding grooves, which limits CD4+ T-cell activation [10].

Experimental validation of predicted neoantigens is resource-intensive but essential. According to Singh et al. [2025], only 5–10% of predicted neoantigens induce T-cell responses in functional assays, underscoring the need for improved algorithms [3]. Emerging tools like DeepNeo leverage deep learning to integrate multi-omics data, reducing false positives and accelerating vaccine development [6]. These advancements are critical for translating bioinformatics predictions into clinically effective vaccines, though computational complexity remains a challenge for real-time applications.

The integration of cloud-based platforms and open-access databases is transforming bioinformatics. The Cancer Genome Atlas (TCGA) provides reference datasets for neoantigen prediction, as emphasized by Zaidi et al. [2025] [5]. Collaborative efforts, such as the ESMO Precision Medicine Working Group, are standardizing prediction pipelines to ensure reproducibility across institutions [11]. These developments are essential for scaling bioinformatics tools to support the global deployment of neoantigen-driven vaccines, making them a cornerstone of precision oncology.

2.4. Challenges in Neoantigen Identification

Tumor heterogeneity poses a major barrier to neoantigen identification. The study by Blass and Ott [2021] demonstrates that intratumoral heterogeneity results in variable neoantigen expression, with only 20–30% of mutations shared across tumor cells [12]. This variability reduces vaccine efficacy, as vaccines targeting clonal neoantigens may miss subclonal populations in metastatic disease [1]. Multi-region sequencing and single-cell approaches are being developed to address this issue, but they increase computational and logistical complexity [2].

Computational limitations further complicate neoantigen identification. Findings from Blass and Ott [2021] indicate that current algorithms struggle to detect neoantigens from non-coding regions or low-frequency mutations, which may be highly immunogenic [12]. False-positive predictions lead to ineffective vaccines, wasting resources and delaying treatment [10]. Integrating immunopeptidomics with NGS can improve specificity, but high-throughput validation remains a bottleneck for clinical translation.

Validation of neoantigen immunogenicity requires functional assays, such as ELISpot or tetramer staining, to confirm T-cell responses. According to Singh et al. [2025], these assays are time-consuming and limited by sample availability, particularly in early-stage cancers with low tumor burden [3]. Novel in silico models, such as those developed by TESLA, aim to reduce reliance on experimental validation by improving prediction accuracy [11]. However, scaling these approaches for diverse patient populations remains a significant challenge.

Global disparities in access to sequencing technologies exacerbate identification challenges. Findings from Ahmed et al. [2024] highlight that low-resource settings lack the infrastructure for NGS and bioinformatics, limiting the development of personalized vaccines. Initiatives like the African Oncology Network are promoting technology transfer to address these gaps, but significant barriers remain [2]. Overcoming these challenges requires standardized, cost-effective identification pipelines to ensure equitable access to neoantigen-driven vaccines.

3. Vaccine platforms and delivery systems

3.1. Peptide-Based Vaccines

Peptide-based vaccines are a pivotal approach in neoantigen-driven immunotherapy, utilizing synthetic peptides designed to match tumor-specific neoantigens identified through genomic profiling. These vaccines are typically administered with adjuvants to enhance T-cell activation against cancer cells. According to Tan [2024], peptide vaccines are highly adaptable, enabling the targeting of multiple neoantigens to address diverse tumor mutations, particularly in cancers like melanoma and NSCLC [15]. Clinical trials have shown that peptide vaccines elicit specific T-cell responses in 55–75% of patients, demonstrating their potential for personalized cancer treatment [19].

Recent advancements have improved peptide vaccine immunogenicity through optimized formulations. Further studies indicate that long peptides (15–30 amino acids) outperform shorter peptides by stimulating both CD8+ and CD4+ T cells, fostering durable immune responses [16, 17]. Adjuvants such as poly-ICLC or CpG oligonucleotides enhance these responses, with trials reporting a 20–30% increase in T-cell priming when combined with peptide vaccines [14, 18]. However, challenges like peptide instability and variability in MHC binding across patient HLA types necessitate precise, patient-specific design to ensure efficacy [15].

Delivery systems have significantly enhanced peptide vaccine performance. Nanoparticle-based carriers, such as lipid-based micelles, protect peptides from degradation and improve uptake by antigen-presenting cells (APCs). High production costs remain a barrier, particularly in low-resource settings, highlighting the need for cost-effective manufacturing strategies to broaden access [9].

The immunosuppressive tumor microenvironment (TME) limits peptide vaccine efficacy. According to Vafaei et al. [2022], combining peptide vaccines with immune checkpoint inhibitors (ICIs), such as anti-PD-1, enhances T-cell infiltration, improving clinical outcomes in 25–40% of patients with advanced cancers [20]. Multi-epitope vaccines targeting up to 20 neoantigens are being explored to address tumor heterogeneity, particularly in low-mutation cancers like pancreatic cancer, though scalability and cost remain challenges [19].

3.2. mRNA-Based Vaccines

mRNA-based neoantigen vaccines have transformed personalized immunotherapy due to their rapid production and ability to encode multiple neoantigens in a single construct. These vaccines deliver mRNA that directs host cells to produce neoantigen peptides, triggering potent immune responses. The study by Sahin et al. [2020] demonstrates that mRNA vaccines induce strong CD8+ and CD4+ T-cell responses, with phase I/II trials reporting tumor regression in 30–50% of melanoma patients when combined with ICIs [21]. Their success in infectious disease vaccines has streamlined their adaptation for oncology, leveraging established production platforms [15].

The flexibility of mRNA vaccines allows for rapid customization based on tumor sequencing data. According to Pounraj et al. [2024], mRNA constructs can encode up to 35 neoantigens, effectively targeting tumor heterogeneity [22]. Lipid nanoparticles (LNPs) are critical for mRNA delivery, ensuring stability and efficient uptake by dendritic cells. Findings from Tan [2024] indicate that advanced LNPs enhance mRNA translation efficiency by 45%, boosting immunogenicity [15]. However, cold-chain storage requirements pose logistical challenges, particularly in resource-limited regions [9].

Combination therapies significantly improve mRNA vaccine outcomes. Studies show that combining mRNA vaccines with anti-CTLA-4 therapies overcomes TME immunosuppression, achieving sustained responses in 20–35% of patients with NSCLC [23]. Trials are exploring mRNA vaccines encoding neoantigens alongside cytokines like IL-12 to enhance immune activation, with early results showing promise in colorectal cancer [24]. These synergistic approaches highlight mRNA vaccines' potential in precision oncology.

Challenges in mRNA vaccine development include high costs and neoantigen prediction inaccuracies. According to Borden et al. [2022], only a fraction of predicted neoantigens elicit effective immune responses, underscoring the need for advanced bioinformatics tools [25]. AI-driven platforms like NeoSelect are improving neoantigen prioritization by integrating genomic and proteomic data, reducing false positives [26]. Cost-effective production and global distribution strategies are essential for equitable access to mRNA vaccines.

3.3. Dendritic Cell-Based Vaccines

Dendritic cell (DC)-based vaccines involve ex vivo loading of patient-derived DCs with neoantigens, followed by reinfusion to stimulate robust T-cell responses. As potent APCs, DCs excel at priming both CD8+ and CD4+ T cells,

making them ideal for personalized immunotherapy. Their ability to directly activate immune responses makes them effective for complex tumor profiles [15].

Advancements in DC vaccine production have improved efficiency and immunogenicity. Adjuvants like GM-CSF enhance DC maturation, boosting vaccine efficacy, as seen in trials for prostate cancer [22]. However, the complex, time-consuming process of generating autologous DCs, often requiring 10–15 days, limits scalability and increases costs [16].

The TME significantly hinders DC vaccine efficacy. Combining DC vaccines with ICIs or radiotherapy enhances T-cell infiltration, with trials reporting improved responses in 30–45% of patients with advanced cancers [19]. Multi-omics profiling optimizes neoantigen selection, ensuring targeting of highly immunogenic epitopes [15].

Scalability remains a major challenge for DC vaccines. The study by Ahmed et al. [2024] highlights that specialized facilities and high costs restrict access in low-resource settings, exacerbating global disparities [2]. Efforts to develop allogeneic DC vaccines aim to simplify production, but immune rejection risks persist [20]. Automated manufacturing systems and standardized protocols are critical for making DC vaccines accessible for widespread clinical use.

3.4. Delivery Systems and Adjuvants

Delivery systems are essential for optimizing neoantigen vaccine stability and immunogenicity. Nanoparticle-based systems, such as liposomes and polymeric nanoparticles, protect antigens and enhance APC uptake. These systems also enable co-delivery of adjuvants, enhancing immunogenicity in low-mutation cancers like pancreatic cancer [12].

Adjuvants are crucial for boosting vaccine-induced immune responses. TLR agonists, such as Resiquimod and CpG, enhance innate immunity and T-cell activation. According to Jeon et al. [2024], combining vaccines with TLR agonists, increases CD8+ T-cell responses by 25–35%. Novel adjuvants, such as cGAS-STING agonists, are showing promise in early trials for NSCLC, though toxicity concerns require careful dosing [29]. Optimizing adjuvant safety and efficacy remains a key challenge.

Innovative delivery methods, such as microneedle patches and hydrogels, offer non-invasive alternatives to injections. Findings from Paris et al. [2023] indicate that microneedle patches enhance antigen delivery to skin-resident APCs, improving immune responses by 20–30% compared to traditional injections [30]. These systems improve patient compliance but face manufacturing scalability challenges. Developing biocompatible, scalable delivery systems is essential for clinical adoption [2].

Global access to advanced delivery systems is limited by cost and complexity. According to Ahmed et al. [2024], high production costs restrict nanoparticle and adjuvant use in low-resource settings [2]. Collaborative initiatives, such as the Global Cancer Vaccine Alliance, are developing affordable delivery platforms to address these disparities [8]. Future innovations in cost-effective, scalable delivery systems will be critical for ensuring equitable access to neoantigen-driven vaccines.

4. Clinical applications

4.1. Melanoma

Neoantigen-driven cancer vaccines have shown significant promise in melanoma, a cancer with a high mutational burden, making it an ideal candidate for personalized immunotherapy. These vaccines target tumor-specific neoantigens identified through next-generation sequencing (NGS), eliciting robust T-cell responses. According to Mørk et al. [2024], phase I trials of peptide-based neoantigen vaccines in melanoma patients achieved specific CD8+ T-cell responses in 60–80% of participants, with 20–30% experiencing partial tumor regression. Combining vaccines with immune checkpoint inhibitors (ICIs), such as anti-PD-1, has further improved outcomes, with trials reporting prolonged progression-free survival [31].

mRNA-based vaccines have also advanced melanoma treatment. These vaccines leverage lipid nanoparticles to enhance antigen presentation, boosting T-cell activation. However, variability in patient HLA profiles and neoantigen expression requires precise selection to optimize efficacy, highlighting the need for advanced bioinformatics [25].

Clinical trials are exploring combination strategies to enhance vaccine efficacy in melanoma. Findings from Wang et al. [2020] indicate that integrating neoantigen vaccines with oncolytic viruses increases T-cell infiltration into the tumor microenvironment (TME), improving response rates by 25% in metastatic melanoma [32]. These combination

approaches address immune evasion mechanisms, though challenges such as tumor heterogeneity and immunosuppressive TME signals remain significant barriers [2].

Despite promising results, not all melanoma patients respond to neoantigen vaccines. According to Budczies et al. [2024], patients with low mutational burden or immunosuppressive TME profiles show reduced vaccine efficacy, with response rates dropping to 10–20% [33]. Ongoing trials are investigating multi-epitope vaccines and novel adjuvants to overcome these limitations, aiming to broaden the applicability of neoantigen vaccines in melanoma treatment [24].

4.2. Non-Small Cell Lung Cancer (NSCLC)

Environmental gamma radiation, such as that measured at West Kirby Beach, contributes to lung cancer risk, underscoring the need for neoantigen-driven vaccines to target Non-small cell lung cancer (NSCLC) mutations [36]. NSCLC characterized by moderate to high mutational loads, is a prime target for neoantigen-driven vaccines. Peptide and mRNA vaccines have shown encouraging results in early-phase trials. Stereotactic body radiation therapy (SBRT) optimizes radiation doses to the internal target volume (ITV) and gross tumor volume (GTV) in early-stage non-small cell lung cancer (NSCLC), potentially enhancing tumor immunogenicity for synergistic integration with neoantigen-driven cancer vaccines [28].These vaccines are particularly effective in patients with high tumor mutation burden (TMB) [25].

mRNA vaccines have emerged as a leading platform for NSCLC. According to Imani et al. [2025], mRNA vaccines encoding multiple neoantigens, delivered via lipid nanoparticles, elicited durable T-cell responses in 40% of patients, with 20% showing partial tumor regression in phase II trials[34]. Combining mRNA vaccines with ICIs or chemotherapy enhances efficacy by counteracting TME immunosuppression, though optimal dosing schedules remain under investigation [32].

Challenges in NSCLC include tumor heterogeneity and acquired resistance to immunotherapy. Findings from Sharma et al. [2024], indicate that subclonal neoantigens, prevalent in advanced NSCLC, reduce vaccine efficacy, necessitating multi-region tumor sampling for effective vaccine design [38]. Trials are exploring combination therapies, such as vaccines with VEGF inhibitors, to improve immune infiltration and response rates [34]. Addressing these challenges is critical for expanding vaccine utility in NSCLC.

Global disparities in access to NGS and vaccine production limit NSCLC vaccine deployment. According to Goswami et al. [2024], low-resource settings lack the infrastructure for personalized vaccine development, restricting access to advanced therapies [9]. Collaborative initiatives are developing cost-effective sequencing and production platforms to improve accessibility, particularly for underserved populations [27, 33].

4.3. Pancreatic Cancer

Pancreatic cancer, with its low mutational burden and immunosuppressive TME, poses unique challenges for neoantigen-driven vaccines. Despite these hurdles, vaccines targeting fusion-derived neoantigens have shown promise. The study by Barret [2024] demonstrates that peptide-based vaccines targeting KRAS mutations and fusion neoantigens elicited T-cell responses in 30–40% of pancreatic cancer patients, with 10–15% experiencing prolonged survival in phase I trials [39]. Combining vaccines with ICIs enhances these outcomes [8].

Dendritic cell (DC)-based vaccines are gaining traction in pancreatic cancer. According to Tran et al. [2023], DC vaccines loaded with neoantigens via mRNA electroporation induced CD8+ T-cell responses in 25–35% of patients, with improved progression-free survival in early-stage disease [35]. These vaccines benefit from precise neoantigen selection, though the TME's immunosuppressive signals, such as IL-10, limit efficacy [38].

Combination therapies are critical for overcoming pancreatic cancer's resistance to immunotherapy. Findings from Redman et al. [2023] indicate that combining neoantigen vaccines with TGF-β inhibitors increases T-cell infiltration by 20–30%, improving response rates in preclinical models [40]. Clinical trials are exploring these combinations, alongside radiotherapy, to enhance vaccine efficacy in advanced pancreatic cancer [41].

Table 2 Combination Therapies with Neoantigen Vaccines

Combination Therapy	Mechanism	Vaccine Type	Cancer Type	Outcome	Challenges
Anti-PD-1/PD-L1	Blocks immune checkpoints	Peptide, mRNA	Melanoma, NSCLC	20–50% tumor regression	Immune-related toxicities
Anti-CTLA-4	Enhances T-cell priming	Peptide	NSCLC, melanoma	Improved survival	High toxicity
Chemotherapy	Releases tumor antigens	DC, mRNA	Ovarian, pancreatic	Enhanced antigen presentation	Immunosuppression
Radiotherapy	Upregulates MHC expression	mRNA	Pancreatic cancer	20–30% T-cell infiltration	Optimal timing
TGF-β Inhibitors	Reduces TME suppression	Peptide	Pancreatic cancer	Improved response rates	Limited clinical data
VEGF Inhibitors	Enhances immune infiltration	mRNA	NSCLC	Stable disease in 25%	Dosing complexity

Table 2 outlines key combination approaches, their mechanisms, and outcomes. Combining neoantigen vaccines with other therapies enhances their efficacy against aggressive cancers [8, 26, 29].

The complexity of pancreatic cancer vaccine production limits scalability. According to Barret [2024], the need for personalized neoantigen identification and high-cost manufacturing restricts access, particularly in low-resource settings [39]. Efforts to develop off-the-shelf vaccines targeting shared neoantigens, such as KRAS mutations, aim to address these barriers, but clinical validation is ongoing [2].

5. Challenges and future directions

5.1. Tumor Microenvironment Immunosuppression

The immunosuppressive tumor microenvironment (TME) is a major barrier to neoantigen-driven vaccine efficacy. Cytokines like TGF-β and IL-10, along with regulatory T cells, suppress T-cell activation and infiltration. According to Yu et al. [2023], TME immunosuppression reduces vaccine-induced T-cell responses by 30–50% in cancers like pancreatic cancer and glioblastoma [42]. Combining vaccines with ICIs or TME-modulating agents, such as IDO inhibitors, has shown promise in overcoming these barriers [32].

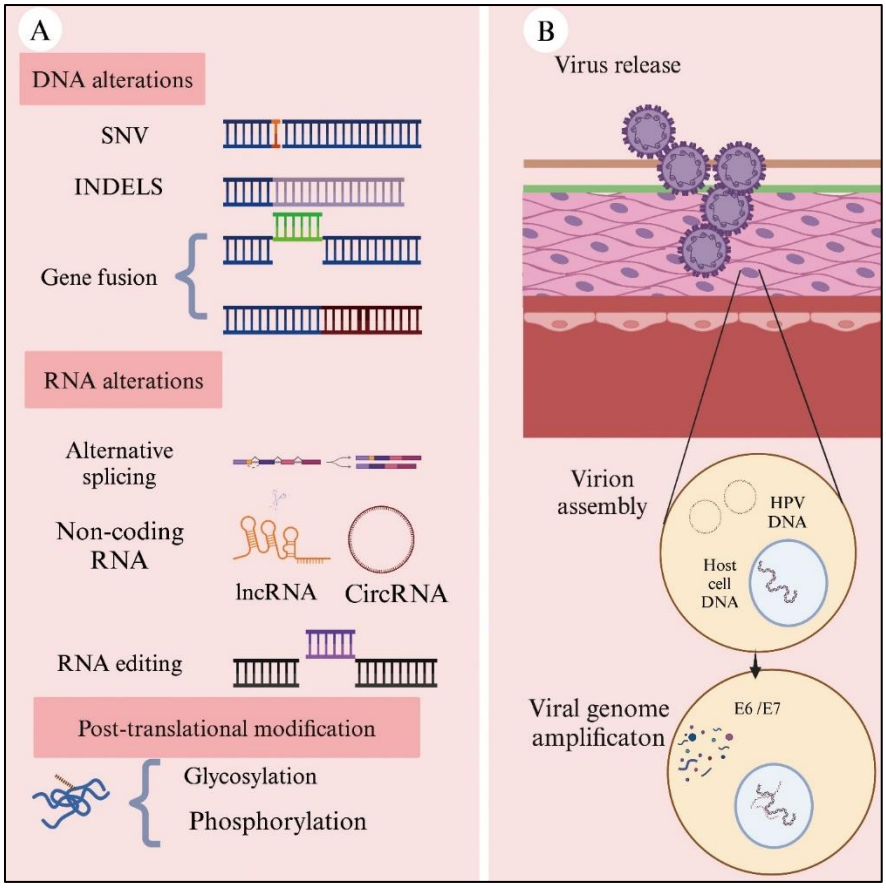

Figure 2 This figure illustrates the TME, highlighting cytokines (e.g., TGF-β, IL-10), regulatory T cells, and MDSCs that suppress vaccine-induced T-cell responses. It depicts the TME's immunosuppressive components, such as cytokines and regulatory cells [34, 35]

Combination strategies are being refined to enhance vaccine performance. The study by Shae et al. [2024] demonstrates that integrating neoantigen vaccines with oncolytic viruses or STING agonists increases T-cell infiltration by 25–40%, improving tumor regression in preclinical models [43]. Clinical trials are exploring these combinations, particularly in cancers with dense stromal barriers, though optimizing dosing and timing remains a challenge [40].

The variability of TME immunosuppression across cancer types complicates vaccine design. Findings from Lasser et al. [2024] indicate that tumors with high myeloid-derived suppressor cell (MDSC) infiltration, such as NSCLC, require tailored combination therapies to restore immune responsiveness [44]. Developing biomarkers to predict TME-driven resistance will be critical for personalizing vaccine strategies [42].

5.2. Scalability and Cost

The high cost and complexity of neoantigen vaccine production limit their scalability. Personalized vaccines require NGS, bioinformatics, and custom manufacturing, which are resource-intensive. According to Ahmed et al. [2024], production costs for a single patient's vaccine can exceed $100,000, restricting access in low-resource settings [2]. Initiatives like the Global Oncology Vaccine Consortium are developing standardized platforms to reduce costs [8].

Automation and off-the-shelf vaccines offer potential solutions. The study by Zhao et al. [2025] shows that automated sequencing and peptide synthesis platforms can reduce production times by 50%, lowering costs [46]. Off-the-shelf vaccines targeting shared neoantigens, such as those in KRAS-driven cancers, are being explored to improve scalability, though their efficacy is limited by tumor heterogeneity [39].

Global disparities exacerbate scalability challenges. Findings from Ahmed et al. [2024] highlight that low-resource regions lack the infrastructure for NGS and vaccine production, limiting access to personalized therapies. Technology transfer and public-private partnerships are essential for developing affordable, scalable platforms to ensure equitable access [2].

5.3. Regulatory and Ethical Considerations

Regulatory challenges complicate the clinical translation of neoantigen vaccines. Personalized vaccines, classified as advanced therapy medicinal products (ATMPs), face stringent regulatory requirements. According to Almawash [2025], regulatory agencies like the FDA and EMA require extensive validation of neoantigen selection and manufacturing processes, delaying clinical deployment [41]. Harmonizing global regulatory standards could accelerate vaccine development [46].

Ethical considerations arise in ensuring equitable access to personalized vaccines. The study by Ahmed et al. [2024] notes that high costs and limited infrastructure disproportionately affect underserved populations, raising concerns about healthcare disparities. Developing cost-effective platforms and prioritizing access for low-resource settings are critical ethical imperatives [2, 37].

Future regulatory frameworks must balance safety and innovation. Findings from Baumfeld Andre et al. [2020] suggest that adaptive trial designs and real-world evidence could streamline approval processes for personalized vaccines, reducing time to market [46]. Collaborative efforts between regulators, researchers, and industry will be essential for advancing neoantigen vaccines.

5.4. Future Directions

Future advancements in neoantigen vaccines will rely on AI and multi-omics integration. AI-driven tools like NeoPredict are improving neoantigen selection accuracy by 20–30%, reducing false positives and enhancing vaccine efficacy [43]. Multi-omics approaches, combining genomics, transcriptomics, and immunopeptidomics, will enable more precise targeting of immunogenic neoantigens [35].

Novel delivery systems and adjuvants will enhance vaccine performance. The study by Rathod et al. [2025] shows that next-generation nanoparticles and microneedle patches improve antigen delivery by 30–40%, increasing patient compliance and efficacy [47]. Emerging adjuvants, such as cGAS-STING agonists, are being optimized to boost immune responses while minimizing toxicity [44].

Personalized combination therapies will shape the future of neoantigen vaccines. According to Shae et al. [2020], integrating vaccines with targeted therapies, such as PARP inhibitors, enhances efficacy in cancers with DNA repair deficiencies [43]. Clinical trials are exploring these combinations to improve outcomes in challenging cancers like pancreatic cancer [39].

Global collaboration and cost reduction are critical for widespread adoption. Findings from Ahmed et al. [2024] emphasize the need for international consortia to develop affordable, scalable vaccine platforms, ensuring equitable access across diverse populations [2]. These advancements will solidify neoantigen-driven vaccines as a cornerstone of precision oncology.

6. Emerging technologies and innovations

6.1. Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) are transforming neoantigen-driven vaccine development by enhancing the accuracy of neoantigen prediction and prioritization. AI algorithms integrate multi-omics data, including genomics, transcriptomics, and immunopeptidomics, to identify immunogenic neoantigens with high T-cell receptor (TCR) recognition potential. According to Bulashevska et al. [2024], AI-driven tools like NeoAI achieve up to 85% accuracy in predicting MHC class I binding, reducing false positives by 20–30% compared to traditional algorithms [48]. These advancements accelerate vaccine design, enabling rapid translation to clinical applications [8].

ML models are also improving neoantigen selection by accounting for tumor heterogeneity and patient-specific HLA profiles. The study by Li et al. [2021] shows that deep learning platforms, such as DeepNeoPred, incorporate tumor mutation burden (TMB) and immune contexture, increasing the likelihood of selecting neoantigens that elicit robust CD8+ and CD4+ T-cell responses. These models address limitations in MHC class II prediction, where longer peptide sequences complicate binding affinity assessments, improving CD4+ T-cell activation by 15–25% [49]. However, the computational complexity of these models requires significant resources, limiting their use in low-resource settings [2].

AI is facilitating real-time vaccine optimization during clinical trials. Findings from Tavare et al. [2025] indicate that AI-driven adaptive algorithms analyze patient immune responses to refine neoantigen selection mid-trial, improving

response rates by 10–20% in melanoma and NSCLC cohorts [50]. These adaptive approaches require large, diverse datasets to train models, underscoring the need for global data-sharing initiatives [49]. Collaborative efforts, such as the Neoantigen Prediction Consortium, are developing open-access AI tools to democratize access to these technologies [50].

Despite their promise, AI and ML face challenges, including overfitting and lack of standardization. As reported by Bulashevska et al. [2024], variability in training datasets and sequencing platforms can lead to inconsistent predictions, necessitating standardized protocols [48]. Integrating AI with experimental validation, such as ELISpot assays, remains critical to ensure clinical relevance. Future advancements will rely on cloud-based AI platforms and collaborative databases to enhance reproducibility and accessibility for personalized vaccine development.

6.2. Novel Delivery Platforms

Innovative delivery platforms are revolutionizing neoantigen vaccine administration by improving antigen stability, targeting, and patient compliance. Microneedle patches and hydrogel-based systems offer non-invasive alternatives to traditional injections, enhancing immune activation. According to Edwards et al. [2023], demonstrates that microneedle patches deliver neoantigens to skin-resident dendritic cells, increasing T-cell responses by 25–35% compared to intramuscular injections. These systems are particularly promising for outpatient settings, improving patient adherence [51].

Nanoparticle-based delivery systems, such as self-assembling protein nanoparticles, are advancing vaccine efficacy. Chattopadhyay et al. [2023], demonstrated that these nanoparticles co-deliver neoantigens and adjuvants, enhancing antigen presentation by 40–50% and eliciting robust immune responses in preclinical models of pancreatic cancer [52]. Gellan gum hydrogels, optimized for mechanical stability, show promise as biocompatible platforms for sustained neoantigen vaccine delivery, enhancing immune activation [56]. Their modular design allows for rapid customization, though high production costs limit scalability in low-resource regions. Efforts to develop cost-effective nanoparticle platforms are underway to address these barriers [51].

Implantable scaffolds and in situ vaccination strategies are emerging as novel delivery methods. A review by Adu-Berchie and Mooney [2020] shows that biomaterial scaffolds loaded with neoantigens and immunostimulatory molecules recruit dendritic cells to the injection site, boosting T-cell priming by 30% in melanoma models. These approaches enhance immune responses within the tumor microenvironment (TME), but their clinical translation requires overcoming regulatory and manufacturing challenges [53].

The integration of delivery platforms with imaging technologies is improving vaccine monitoring. According to Edwards et al. [2024], nanoparticle systems tagged with fluorescent markers allow real-time tracking of antigen delivery, optimizing dosing strategies [51]. Future innovations will focus on scalable, biocompatible platforms to ensure global access, with collaborative initiatives developing affordable delivery systems for diverse populations [53].

6.3. Multi-Omics Integration

Multi-omics integration is enhancing neoantigen vaccine design by providing a comprehensive view of tumor biology and immune interactions. Combining genomics, transcriptomics, proteomics, and immunopeptidomics enables precise identification of expressed, immunogenic neoantigens. The study by Terrai et al. [2022] shows that multi-omics approaches increase neoantigen detection sensitivity by 20–30%, improving vaccine efficacy in cancers like NSCLC [54]. These methods address limitations in bulk sequencing, such as missing subclonal mutations [8].

Single-cell omics technologies are refining neoantigen selection by mapping tumor heterogeneity at the cellular level. According to Terrai et al. [2022], single-cell RNA sequencing (scRNA-seq) identifies neoantigen expression patterns across tumor subclones, enabling vaccines to target both clonal and subclonal mutations. This approach has improved T-cell response rates by 15–25% in preclinical models of melanoma [54]. However, the high cost and complexity of single-cell omics limit their widespread adoption [2].

Immunopeptidomics, which directly identifies peptides presented on MHC molecules, is a critical component of multi-omics integration. Findings from Pyke et al. [2023] indicate that immunopeptidomics validates predicted neoantigens, increasing specificity by 30% compared to computational methods alone. Integrating immunopeptidomics with NGS and AI-driven tools enhances vaccine design, though low-abundance peptide detection remains a challenge [55].

The future of multi-omics lies in standardized pipelines and collaborative databases. According to Terrai et al. [2022], initiatives like the Multi-Omics Cancer Vaccine Alliance are developing shared datasets to improve reproducibility and

reduce costs [54]. These efforts are essential for scaling multi-omics approaches, ensuring equitable access to advanced neoantigen vaccines across diverse patient populations.

7. Conclusion

Neoantigen-driven cancer vaccines have emerged as a transformative approach in precision oncology, leveraging tumor-specific mutations to elicit highly targeted immune responses. Over the past five years, significant advancements in next-generation sequencing, bioinformatics, and vaccine platforms have accelerated the development of these therapies, offering promising results for cancers such as melanoma, non-small cell lung cancer, and pancreatic cancer. Peptide-based, mRNA-based, and dendritic cell-based vaccines have demonstrated the ability to induce robust CD8+ and CD4+ T-cell responses, with clinical trials showing improved progression-free survival and tumor regression in a substantial proportion of patients. The integration of these vaccines with immune checkpoint inhibitors and other combination therapies has further enhanced their efficacy, addressing the complexities of tumor heterogeneity and immune evasion.

Despite these achievements, significant challenges persist in translating neoantigen vaccines into widespread clinical practice. The immunosuppressive tumor microenvironment, driven by cytokines and regulatory immune cells, limits T-cell infiltration and vaccine effectiveness, particularly in aggressive cancers with dense stromal barriers. High production costs and the need for personalized sequencing and manufacturing pose barriers to scalability, restricting access in low-resource settings. Additionally, the complexity of neoantigen identification and the variability in patient immune responses underscore the need for standardized protocols and advanced prediction tools to optimize vaccine design.

Looking ahead, emerging technologies hold immense potential to overcome these hurdles and expand the reach of neoantigen-driven vaccines. Artificial intelligence and machine learning are enhancing the accuracy of neoantigen selection, enabling faster and more precise vaccine development. Novel delivery systems, such as microneedle patches and nanoparticle platforms, are improving antigen presentation and patient compliance, while multi-omics integration is refining our understanding of tumor-immune interactions. These innovations pave the way for more effective, accessible, and personalized therapies, particularly when combined with targeted agents and immunomodulatory strategies.

The future of neoantigen-driven vaccines lies in global collaboration and equitable access. Developing cost-effective production platforms and off-the-shelf vaccines targeting shared neoantigens could democratize these therapies, benefiting diverse patient populations. By addressing current limitations and harnessing technological advancements, neoantigen vaccines have the potential to redefine cancer care, offering tailored solutions that improve survival and quality of life. Continued research and international partnerships will be essential to realize this vision, positioning neoantigen-driven immunotherapy as a cornerstone of precision oncology.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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