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REVIEW ARTICLE

Decoding the Neoantigen Landscape: Designing Precision Vaccines for Cancer Immunotherapy

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SUMMARY

Neoantigens have emerged as pivotal elements in modern cancer immunology, offering promising avenues for personalized immunotherapy. These tumour-specific peptides originate from somatic mutations, insertions, deletions, or alternative splicing events, distinguishing them from normal cellular proteins. Their absence in healthy tissues prevents immune tolerance, allowing selective recognition by T cells and reducing the risk of off-target toxicity. The generation of neoantigens involves genetic alterations that produce abnormal proteins, which are subsequently processed and displayed by major histocompatibility complex (MHC) molecules for immune detection. Advances in computational biology and multi-omics technologies have enhanced the precision of neoantigen prediction and selection for therapeutic applications. Clinically, a strong correlation exists between neoantigen load and responsiveness to immune checkpoint inhibitors, underscoring their prognostic and predictive potential. Personalized neoantigen-based vaccines, designed according to individual tumour mutation profiles, have shown safety and efficacy in early clinical trials. Collectively, neoantigens represent a transformative frontier in precision oncology, driving the development of tailored cancer immunotherapies.

Keywords: *Neoantigens, cancer immunology, tumour-specific peptides, major histocompatibility complex, cancer vaccines, precision oncology.*

Neoantijen Manzarasının Kodunu Çözmek: Kanser İmmünoterapisi için Hassas Aşıların Tasarlanması

ÖZ

Neoantijenler, modern kanser immünolojisinde temel unsurlar olarak ortaya çıkmış ve kişiselleştirilmiş immünoterapi için umut vadeden yollar sunmuştur. Bu tümöre özgü peptitler, somatik mutasyonlar, insersiyonlar, delesyonlar veya alternatif ekleme olaylarından kaynaklanır ve bu da onları normal hücresel proteinlerden ayırır. Sağlıklı dokularda bulunmamaları, bağışıklık toleransını önleyerek T hücreleri tarafından seçici olarak tanınmalarını ve hedef dışı toksisite riskini azaltmalarını sağlar. Neoantijenlerin oluşumu, anormal proteinler üreten genetik değişiklikleri içerir ve bu proteinler daha sonra bağışıklık tespiti için majör histokompatibilite kompleksi (MHC) molekülleri tarafından işlenip görüntülenir. Hesaplamalı biyoloji ve çoklu omik teknolojilerindeki gelişmeler, neoantijen tahmini ve terapötik uygulamalar için seçiminin hassasiyetini artırmıştır. Klinik olarak, neoantijen yükü ile bağışıklık kontrol noktası inhibitörlerine yanıt arasında güçlü bir korelasyon vardır ve bu da prognostik ve öngörücü potansiyellerini vurgular. Bireysel tümör mutasyon profillerine göre tasarlanan kişiselleştirilmiş neoantijen bazlı aşılar, erken klinik çalışmalarda güvenlik ve etkinlik göstermiştir. Neoantijenler topluca, hassas onkolojide dönüştürücü bir sınırı temsil ediyor ve kişiye özel kanser immünoterapilerinin geliştirilmesini sağlıyor.

Anahtar Kelimeler: *Neoantijenler, kanser immünolojisi, tümör spesifik peptitler, majör histokompatibilite kompleksi, kanser aşıları, hassas onkoloji.*

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INTRODUCTION

The concept of neoantigens has emerged as a cornerstone in modern cancer immunology, offering novel opportunities for precision immunotherapy. Neoantigens are tumour-specific peptides that arise from somatic mutations, insertions or deletions, alternative splicing events, or other genomic alterations that are absent in normal tissues (Chakraborty, Majumder, Bhattacharya, Chatterjee, & Lee, 2024; Jiang et al., 2019). Because they are not subject to central tolerance, neoantigens are recognized as foreign by the host immune system, making them particularly attractive targets for cancer vaccines and T cell–based therapies (Bobisse, Foukas, Coukos, & Harari, 2016; Peng et al., 2019). Their tumour-restricted expression offers an advantage over conventional tumour-associated antigens, which may also be present in healthy tissues and therefore have a greater possibility of unintended effects. Recent studies have highlighted that neoantigen-specific immune cells, including both $CD4^+$ (Cluster of Differentiation 4^+) and $CD8^+$ (Cluster of Differentiation 8^+) T cells, can be comprehensively characterized to understand vaccine-induced immune landscapes, providing insight into the mechanisms of antitumour immunity (Liu et al., 2025).

From a biological standpoint, the generation of neoantigens begins with DNA mutations or transcriptomic alterations in cancer cells that give rise to abnormal proteins. These proteins undergo intracellular processing and are presented on the cell surface by Major Histocompatibility Complex (MHC) molecules, enabling recognition by cytotoxic T lymphocytes (Chakraborty et al., 2024; Jiang et al., 2019). In addition to single-nucleotide variants, recent evidence highlights alternative splicing as a significant source of neoantigen diversity, broadening the range of targets that can be exploited therapeutically (Huang, Wen, Tuerhong, Yang, & Li, 2024). Although this molecular diversity expands therapeutic possibilities, it simultaneously makes precise neoantigen detection and selection more challenging. Computational strategies that incorporate multi-omics data, machine learning models, and *in silico* prediction pipelines are increasingly employed to improve neoantigen identification and prioritize candidates for vaccine development (Wang, Gu, Sun, & Huang, 2025).

The clinical relevance of neoantigens is increasingly evident. Multiple studies have shown a strong association between neoantigen load and responsiveness to immune checkpoint blockade therapies (Jiang et al., 2019). Patients with higher mutational burdens often demonstrate more robust immune responses, underscoring the predictive value of neoantigens as biomarkers. Beyond their prognostic role, neoantigens also provide the foundation for a new generation of personalized vaccines. By tailoring vaccine formulations to an individual's unique tumour mutation profile, clinicians aim to elicit potent, patient-specific immune responses with minimal off-target effects (Pang et al., 2023; Peng et al., 2019). Findings from early-stage clinical studies have supported the practicality, safety profile, and immune-stimulating potential of this strategy. Early-phase clinical trials have validated the feasibility and safety of this approach, fueling optimism that such strategies may become integral to cancer management in the near future (Ma, Pham, & Li, 2022).

Despite this progress, numerous challenges remain. The accurate identification of immunogenic neoantigens is technically demanding. Current prediction pipelines integrate next-generation sequencing, transcriptomic data, and computational modelling to prioritize candidate peptides (Huang et al., 2024). However, only a subset of predicted neoantigens elicit functional immune responses, highlighting the gap between computational prediction and biological validation. Moreover, tumour heterogeneity and immune escape mechanisms further complicate therapeutic application. For example, selective pressure from the immune system can lead to the loss of antigen presentation machinery or clonal evolution of tumour cells, diminishing the long-term efficacy

of neoantigen-directed therapies (Jiang et al., 2019; Zhang et al., 2025).

To address these barriers, recent research has expanded beyond single mutation–derived antigens. Studies focusing on splicing-derived neoantigens illustrate how noncanonical mechanisms of antigen generation may provide untapped therapeutic opportunities (Huang et al., 2024). Similarly, the integration of multi-omics data and artificial intelligence has improved prediction accuracy, while nanotechnology-based delivery systems are being explored to enhance vaccine immunogenicity (Chakraborty et al., 2024; Pang et al., 2023). Comprehensive mapping of neoantigen-reactive immune cells in patients has further provided insights into vaccine efficacy, T-cell repertoire, and potential combinatorial strategies with other immunotherapies (Liu et al., 2025). Taken together, these developments are strengthening the clinical translation prospects of neoantigen-directed immunotherapy.

Importantly, neoantigen research is closely aligned with the principles of precision medicine rather than functioning as an isolated domain. By integrating tumour genomic profiles with immune response data, neoantigen-based approaches support the development of highly individualized therapeutic strategies. Contemporary reviews consistently highlight this transition toward personalized oncology, describing neoantigens as a critical link between molecular tumour characterization and clinical immunotherapy (Chakraborty et al., 2024; Jiang et al., 2019; Pang et al., 2023; Zhang et al., 2021). In parallel, advances in supporting technologies—such as nanotechnology-based delivery systems and gene-modulating approaches—continue to strengthen the translational potential of precision immunotherapies (Sanap, 2024; 2025). Collectively, these developments expand the clinical scope of neoantigens, encompassing therapeutic vaccines, adoptive T-cell–based interventions, and their emerging role as predictive biomarkers of immunotherapy response (Ma et al., 2022).

Neoantigens thus represent a new frontier in tumour immunology and therapeutic development. Their tumour specificity, immunogenic potential, and emerging clinical evidence position them as powerful tools in the fight against cancer. While substantial challenges remain in prediction, validation, and clinical translation, ongoing technological and methodological advances continue to refine the field. The integration of neoantigens into cancer immunotherapy not only expands treatment options but also exemplifies the promise of personalized medicine (Chakraborty et al., 2024; Jiang et al., 2019; Ma et al., 2022; Pang et al., 2023; Xie et al., 2023; Mardis et al., 2019; Zhang et al., 2021; Zhang, Jia, Zhang, & Zhu, 2022).

Unlike prior reviews that primarily addressed selected dimensions of neoantigen research, this review provides an updated and integrative overview spanning neoantigen biology, identification strategies, vaccine technologies, translational challenges, clinical progress, and future opportunities in precision immuno-oncology.

HISTORICAL BACKGROUND OF NEOANTIGENS

The concept of tumour neoantigens emerged from early immunology and tumour-immunosurveillance theories and advanced rapidly with molecular and technological progress. Early experimental work in animal models showed that tumour rejection could be mediated by immune responses against antigens present only in tumours; these observations laid the conceptual groundwork for identifying mutation-derived, tumour-specific peptides as distinct immunologic targets (Jiang et al., 2019).

The conceptual turning point came with demonstration that somatic mutations can create novel amino-acid sequences that, when processed and presented by MHC, are recognized by cytotoxic T lymphocytes. In the pre-genomic era, such neoantigens were identified case-by-case using biochemical and

immunologic assays; with the arrival of next-generation sequencing (NGS) and tumour–normal exome comparison, it became feasible to comprehensively catalogue somatic mutations and nominate candidate neoepitopes at scale. Reviews document this shift from serendipitous discovery to systematic immunogenomic pipelines: tumour DNA → mutation calling → *in silico* peptide-MHC binding prediction → experimental validation. That pipeline transformed neoantigen science from an observational niche into a clinically relevant therapeutic field (Jiang et al., 2019; Pang et al., 2023).

As methods matured, the types of neoantigen sources recognized expanded. Initially attention focused on single-nucleotide variants producing missense mutations, but subsequent work showed insertions/deletions (indels), frameshifts, gene fusions, aberrant splicing, and even viral integration or reactivated endogenous retroviral elements can produce neoepitopes. Reviews emphasize that recognizing this broader biochemical landscape increased the pool of candidate targets and explained why some tumours with modest point-mutation burdens nonetheless present immunogenic neoantigens (Chen, Goedegebuure, & Gillanders, 2021; Han et al., 2020).

A parallel methodological advance was immunopeptidomics—mass spectrometric profiling of peptides actually bound to MHC molecules. Immunopeptidomics provided direct evidence of which predicted neoepitopes are truly presented on tumour cells, closing an important gap between prediction and presentation. Combining immunopeptidomics with NGS and improved binding predictors greatly improved prioritization of candidates for vaccine design or adoptive T-cell therapies (Bobisse et al., 2016; Pang et al., 2023).

Clinical translation accelerated in the 2010s, when early trials began reporting encouraging immunogenicity and preliminary therapeutic signals, particularly in combination settings. Reviews note that these trial results both validated the underlying biology and exposed implementation challenges—speed, cost, antigen selection accuracy, and tumour heterogeneity—that must be overcome to make neoantigen therapies widely practical (I. Chen et al., 2021; Jiang et al., 2019; Zhao, Pan, Wang, & Zhang, 2021).

This review was conducted through a comprehensive literature search using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. Relevant articles published between 2015 and 2025 were identified using keywords such as "neoantigen," "cancer vaccines," "tumour immunotherapy," "personalized oncology," and "immune checkpoint inhibitors." Priority was given to peer-reviewed original research articles, clinical trials, and recent review papers based on scientific relevance, quality, and contribution to the field.

Contemporary reviews highlight key challenges that shaped the field's evolution:

1. Many predicted binders are not immunogenic *in vivo*;
2. Tumour heterogeneity and subclonal mutations complicate targeting;
3. Immunosuppressive tumour microenvironments blunt responses; and,
4. Technical and computational bottlenecks remain for rapid, reproducible neoantigen prioritization. In response, the field has invested heavily in better prediction algorithms (including machine-learning/artificial Intelligence models), standardized immunopeptidomic workflows, and trial designs that combine neoantigen vaccines with immune-modulating agents—an evolution from discovery-focused biology to integrated translational pipelines (I. Chen et al., 2021; Pang et al., 2023; Xie et al., 2023).

In sum, neoantigen research progressed from early immunologic observations to a genomics-driven, proteomics-validated, clinically translatable discipline. The historical arc—observation → molecular identification → computational prediction → pro-

teomic validation → clinical testing—captures how technological advances have repeatedly reset what is possible, and current reviews agree that further improvements in prediction, validation, and combinatorial clinical strategies will determine whether neoantigen-directed therapies become broadly effective and accessible (I. Chen et al., 2021; Han et al., 2020; Jiang et al., 2019, Pang et al., 2023; Zhao et al., 2021).

IDENTIFICATION AND PREDICTION OF NEOANTIGENS

The discovery pipeline for tumour-specific neoantigens integrates sequencing, immunopeptidomics, computational modelling, and functional assays. These approaches collectively identify tumour-specific sequence changes, predict which peptides are processed and presented by HLA molecules, and validate which elicit T-cell responses (Chakraborty et al., 2024; Gopanenko, Kosobokova, & Kosorukov, 2020; Ho et al., 2023; Ketelaars et al., 2025; Li et al., 2023; Tian et al., 2025; Xie et al., 2023).

Neoantigen sources and biological context: Neoantigens originate from diverse events beyond single nucleotide variants (SNVs). These include short insertions/deletions (INDELs), frame shifts, gene fusions, alternative splicing, intron retentions, RNA editing, transcription/splicing errors, proteasome-mediated peptide splicing, and tumour-specific post-translational modifications (PTMs). Noncoding regions, such as intronic or intergenic sequences and noncoding RNAs, also yield tumour-restricted peptides. Viral sequences or V(D)J recombination may contribute to certain malignancies. Recent proteogenomics studies confirm that noncoding and spliced sources can contribute substantially to the neoantigen pool, making their inclusion essential (Chakraborty et al., 2024; Gopanenko et al., 2020; Ho et al., 2023).

Genomics and transcriptomics-mutation discovery: Whole-exome sequencing (WES) of paired tumour and normal DNA remains the primary method for identifying nonsynonymous somatic mutations, with whole-genome sequencing (WGS) expanding detection to structural variants and noncoding regions. RNA sequencing (RNA-seq) complements DNA data by confirming mutant allele expression, detecting allele-specific or alternative splicing events, and estimating transcript abundance. Full-length transcript sequencing helps reconstruct complex isoforms and fusion-derived epitopes. Running multiple variant callers and performing manual curation improves accuracy, while specialized callers target INDELs or gene fusions. Together, these methods generate a comprehensive set of candidate mutations (Gopanenko et al., 2020; Ho et al., 2023; Li et al., 2023).

HLA genotyping and antigen presentation: Accurate HLA (Human Leukocyte Antigen) typing is critical, as a patient's HLA repertoire defines which peptides can be presented. Tools applied to WES, WGS, or RNA-seq data infer class I and class II alleles, while allele-specific loss (HLA-LOH) should also be assessed, as it reduces presentation and promotes immune evasion. HLA information integrates with peptide prediction to ensure candidate epitopes are feasible within an individual's presentation context (Gopanenko et al., 2020; Ho et al., 2023).

***In silico* peptide prediction:** Candidate mutant peptides are processed through bioinformatic pipelines that simulate antigen processing (proteasomal cleavage, TAP transport) and HLA binding. Common predictors include NetMHCpan, NetCTL, and MHCflurry for class I, and NetMHCIIpan for class II epitopes, though MHC-II predictions are less precise due to variable peptide lengths and polymorphism. Models trained on MS-derived ligandome data, such as NetMHCpan's updated versions, improve accuracy by incorporating naturally presented peptide datasets. Deep learning frameworks, including DeepHLApan and EDGE, further enhance performance by integrating transcriptomic and proteomic features (Chakraborty et al., 2024; Gopanenko et al., 2020; Ho et al., 2023; Ketelaars et al., 2025).

Immunopeptidomics: direct peptide evidence: Mass spectrometry (MS) provides direct detection of peptides bound to HLA molecules, offering proteomic confirmation of candidate neoantigens. Immunoprecipitation (IP)-based workflows isolate MHC–peptide complexes, while mild acid elution (MAE) recovers surface peptides but risks contamination. MS can identify peptides from canonical variants, splice events, or PTMs that escape genomic analysis. Database searches against reference proteomes or custom variant databases, supplemented with de novo sequencing, enhance discovery. Typical peptide lengths (8–12 amino acids, particularly 9-mers) correspond to HLA-I restrictions. Integration with predictors such as NetMHCpan narrows candidate lists for functional assays. Despite being resource-intensive, immunopeptidomics remains the gold standard for validating presentation (Gopanenko et al., 2020; Ho et al., 2023; Li et al., 2023; Tian et al., 2025).

Structure-based and physicochemical methods: Binding affinity alone does not ensure TCR (T-cell Receptor) recognition. Structure-based approaches model pMHC complexes and TCR:pMHC interactions through flexible docking, molecular dynamics, or energy-based scoring. These capture conformational and physicochemical features absent in sequence-based predictors. Immunogenic peptides often display hydrophobic or aromatic residues at TCR-contacting positions, and models now incorporate such features into immunogenicity scoring. Combining structure-aware modelling with binding prediction improves prioritization of epitopes likely to trigger T-cell responses (Gopanenko et al., 2020; Li et al., 2023).

Prioritization and scoring strategies: Given the abundance of predicted candidates, filtering is essential. Criteria include predicted binding affinity, mutant vs. wild-type differential binding, expression levels, allele frequency, peptide processing likelihood, presence in MS datasets, and physicochemical features linked to TCR interaction. Two approaches are common: stepwise filtering with hard cutoffs and integrated scoring systems that weight multiple factors. Machine-learning frameworks trained on peptidome and expression data reduce false positives compared to affinity-only models (Chakraborty et al., 2024; Gopanenko et al., 2020; Ho et al., 2023).

Functional validation: Computational predictions must be experimentally confirmed, as only a subset of predicted peptides are immunogenic. Validation assays include ELISPOT (Enzyme-Linked Immunospot Assay) for cytokine release, pMHC multimer staining, DNA barcode–based tetramer assays, and supported lipid bilayer (SLB) assays visualizing T-cell activation. High-parameter flow cytometry enables multiplex detection of CD^{8+} responses. Screening tumour-infiltrating lymphocytes (TILs) or peripheral blood mononuclear cells (PBMCs) often reveals low but detectable frequencies of neoantigen-specific T cells. Functional validation is therefore indispensable in defining clinically relevant targets (Gopanenko et al., 2020; Ho et al., 2023; Tian et al., 2025).

Databases and computational ecosystem: Numerous databases and pipelines support neoantigen discovery. General repositories such as IEDB (Immune Epitope Database and Analysis Resource) and specialized ones like TANTIGEN, TSNAdb, NeoPeptide, and dbPepNeo consolidate experimentally validated epitopes. Tools such as pVAC-Seq, TSNAD, LENS, and NeoSV automate variant annotation, peptide generation, and prioritization across mutation types. Mass-spectrometry–derived datasets provide training material for newer predictors like MSIntrinsic and EDGE, improving positive predictive value and benchmarking accuracy. Ensemble use of multiple tools and reference datasets is recommended to minimize biases from any single pipeline (Chakraborty et al., 2024; Gopanenko et al., 2020).

Current limitations include false positives in computational prediction, incomplete MS coverage leading to false negatives, limited accuracy of MHC-II prediction, tumour heterogeneity, and immune escape via

HLA loss. Advances in multi-omic integration, machine learning trained on naturally presented ligandomes, and scalable T-cell assays are steadily improving prediction pipelines. Ultimately, combining genomics, transcriptomics, proteomics, structure-based modelling, and experimental validation offers the most reliable route to selecting neoantigens for personalized cancer vaccines (Chakraborty et al., 2024; Gopanenko et al., 2020; Ho et al., 2023; Tian et al., 2025).

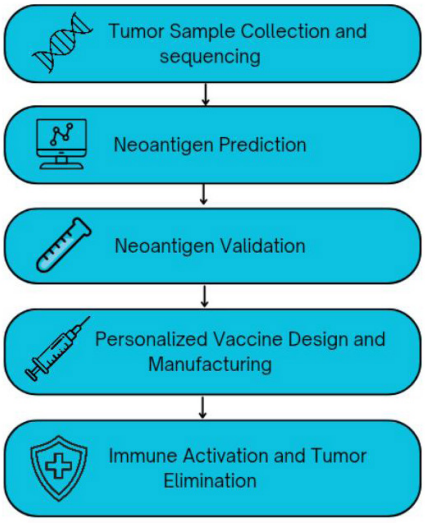

Figure 1. Workflow of personalized neoantigen vaccine development

PLATFORMS

Synthetic long peptides (SLPS) based platforms for neoantigen vaccines

Synthetic long peptide (SLP) vaccines are an established platform in neoantigen-based cancer immunotherapy. Unlike short peptide vaccines, which often induce limited CD^{8+} T-cell activity, SLPs—typically comprising 20–35 amino acids—are designed to engage both CD^{4+} and $CD8^{+}$ T cells. While CD^{8+} cells directly kill tumour cells, the involvement of CD4+ cells will support and sustain CD^{8+} T-cell activation. SLPs do so by ensuring antigen processing and presentation through MHC class I and class II pathways (Chen, Yang, Wang, & Liu, 2020). This dual activation enhances antigen-specific immune coordination and generates a stronger, more durable antitumour response.

In the SLP platform, the process begins with the identification of tumour-specific mutations using next-generation sequencing of patient tumour and normal tissue. Bioinformatics tools are then used to predict mutated peptide fragments (neoepitopes) based on peptide–MHC binding affinity and expression levels. Selected sequences are synthesized chemically under Good Manufacturing Practice (GMP) conditions to form long peptides that encompass the identified neoantigens. This coordinated antigen presentation supports balanced helper and cytotoxic T-cell responses while reducing immune tolerance (X. Chen et al., 2020).

Preclinical studies and clinical investigations have validated the immunogenicity and safety of this approach. It has been emphasized that SLP-based vaccines not only elicit potent cytotoxic and helper T-cell responses but also facilitate epitope spreading, where secondary immune responses are generated against additional tumour antigens not included in the initial vaccine design (Tian et al., 2025). This phenomenon broadens the immune repertoire and contributes to long-term tumour control. Peptides as versatile regulators in cancer immunotherapy have been shown to play a key role in modulating immune responses, enhancing the potential of SLPs in personalized therapy (Lei, Liu, Bai, Zheng, & Wang, 2025).

A key strength of the SLP platform lies in its flexibility and compatibility with various adjuvant systems. Poly-ICLC (a synthetic double-stranded RNA analogue) and GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor) are among the most frequently used adjuvants to boost dendritic cell activation and enhance antigen presentation efficiency (Cai et al., 2021). The formulation and delivery method can be tailored to the patient, often involving multiple peptide pools administered through subcutaneous or intradermal injections at defined intervals. These prime–boost vaccination schedules help sustain immune memory and reinforce T-cell activation.

Clinically, personalized SLP-based neoantigen vaccines have demonstrated encouraging outcomes across multiple tumour types. In hepatocellular carcinoma patients with vascular invasion, a personalized neoantigen SLP vaccine prevented postoperative recurrence and maintained a favourable safety profile (Cai et al., 2021). Similarly, in patients with advanced pancreatic cancer who were refractory to standard therapies, an SLP vaccine elicited measurable $CD4^+$ and CD^{8+} memory T-cell responses, accompanied by improved immune infiltration at tumour sites and acceptable tolerability (Chen, Z. et al., 2021). These findings underline the clinical feasibility and therapeutic potential of SLPs even in cancers traditionally considered immunologically "cold." Development and clinical applications of therapeutic cancer vaccines with individualized and shared neoantigens have highlighted the potential of combining SLPs with other immunotherapies to maximize clinical benefit (Hao, Long, Yang, Deng, & Ding, 2024).

The platform supports rapid tumour-tailored vaccine design and can be integrated with other immunotherapies such as immune checkpoint inhibitors to enhance therapeutic outcomes. Furthermore, the safety, reproducibility, and modularity of peptide synthesis make SLPs a scalable option for personalized vaccine development. These features support sustained antitumour immunity and make SLPs attractive candidates for combination strategies and future personalized cancer immunotherapy SLP platforms exemplify a rational and personalized approach to cancer immunotherapy (Cai et al., 2021; X. Chen et al., 2020; Z. Chen et al., 2021; Hao et al., 2024; Lei et al., 2025; Supabphol, Li, Goedegebuure, & Gillanders, 2021).

RNA-based platforms for neoantigen vaccines

RNA-based vaccine platforms have emerged as transformative tools in personalized cancer immunotherapy. Their ability to encode multiple tumour-specific neoantigens allows robust and adaptable immune activation against diverse malignancies. Neoantigens, arising from tumour-specific genetic alterations such as nonsynonymous mutations, insertions or deletions, and fusion transcripts, are absent in normal tissues and thus serve as highly specific vaccine targets (Guasp, Reiche, Sethna, & Balachandran, 2024). The synthetic flexibility of RNA platforms enables patient-tailored vaccine development guided by sequencing and HLA profiling.

Design and optimization of RNA constructs

Therapeutic RNA has been extensively engineered to improve stability, translation, and immunogenic control. *In vitro*–transcribed (IVT) mRNA is the most established format, incorporating optimized 5′ and 3′ untranslated regions (UTRs), cap structures, and poly(A) tails to enhance half-life and protein production (Esprit et al., 2020; Guasp et al., 2024). Chemical modifications, particularly pseudouridine and N1-methyl-pseudouridine, reduce innate immune sensing while improving translation (Esprit et al., 2020). Codon optimization and G–C enrichment enhance expression, while inclusion of trafficking sequences directs antigen presentation through both MHC-I and MHC-II pathways (Guasp et al., 2024).

To avoid interferon-mediated translational inhibition, dsRNA contaminants produced during transcription are eliminated by purification methods such as high-performance liquid chromatography (Guasp et al., 2024; Nguyen et al., 2025). These refinements yield consistent and scalable manufacturing compatible with good manufacturing practices, positioning mRNA as a cornerstone for personalized cancer vaccines (Esprit et al., 2020).

Delivery systems and immune activation

Efficient delivery of mRNA to APCs is central to vaccine success. Two main strategies are used: *ex vivo* dendritic cell (DC) electroporation and *in vivo* administration of formulated RNA (Esprit et al., 2020; Guasp et al., 2024). While DC-based vaccines allow controlled antigen loading, direct *in vivo* delivery through nanocarriers offers simplicity and reproducibility.

Lipid nanoparticles (LNPs) have become the leading delivery vehicle due to their ability to protect RNA from enzymatic degradation, facilitate endosomal escape, and enable cytosolic translation. Typically composed of ionizable lipids, cholesterol, helper lipids, and PEG-lipids, LNPs ensure RNA stability and controlled biodistribution (Guasp et al., 2024; Nguyen et al., 2025). In preclinical models, mRNA–LNP vaccines induced strong antigen-specific $CD8^+$ and $CD4^+$ T-cell responses and achieved complete tumour regression (Nagaoka et al., 2025; Nguyen et al., 2025). LNPs can also stimulate innate immune pathways such as STING and inflammasome signaling, further enhancing immunogenicity (Guasp et al., 2024).

Hybrid lipopolyplex (LPP) formulations combine the transfection efficiency of lipids with the long-term stability of polymers. LPP-mRNA vaccines encoding multiple neoantigens generate potent cytotoxic T-cell responses and durable memory, supporting both therapeutic and prophylactic potential (Fan et al., 2024). These findings underscore that efficient delivery is critical for eliciting robust neoantigen-specific immunity.

Emerging RNA modalities

Beyond IVT mRNA, newer RNA formats enhance stability and translational control. Chemically synthesized minimal mRNA (CmRNA) eliminates cap and poly(A) requirements, relying instead on internal ribosome entry sites for cap-independent translation (Imani, Tagit, & Pichon, 2024). This design ensures efficient protein synthesis even under stress conditions and enables precise chemical tuning of immune activation (Imani et al., 2024).

Circular RNA (circRNA) represents another promising platform. Its covalently closed structure confers exceptional resistance to exonuclease degradation and allows prolonged antigen expression (Wang et al., 2024). Modified circRNAs containing internal ribosome entry sites or m6A motifs can efficiently translate encoded peptides, eliciting strong antigen-specific T-cell responses and long-lived immune memory. Preclinical studies in hepatocellular carcinoma models confirmed that circRNA vaccines maintain protein expression and act as self-adjuvanting systems with notable antitumour efficacy (Wang et al., 2024).

Self-amplifying and replicon RNA systems

Self-replicating RNA (saRNA) and replicon constructs further extend RNA vaccine potency by encoding viral replicase machinery that amplifies antigen expression intracellularly. These systems produce prolonged antigen presentation from small doses, generating robust $CD4^+$ and $CD8^+$ T-cell responses (Maine et al., 2020). Incorporation of regulatory motifs, such as downstream loops from alphaviruses, prevents translational shutdown during antiviral signaling, ensuring sustained protein synthesis (Maine et al., 2020). When combined with immune checkpoint inhibitors, such as PD-1 blockade, replicon RNA vaccines enhance polyfunctional T-cell infiltration and improve tumour control (Maine et al., 2020).

Therapeutic synergies and clinical prospects

RNA vaccine platforms exhibit strong synergy with other cancer therapies. Combination with radiation therapy enhances tumour infiltration by immune cells and downregulates inhibitory receptor expression within the tumour microenvironment (Salomon et al., 2023). Co-administration with cytokine-encoding replicons, such as IL-12, increases T-cell clonality and epitope spreading, promoting durable tumour regression (Salomon et al., 2023).

Clinically, RNA-based neoantigen vaccines are advancing rapidly. Personalized mRNA vaccines such as BioNTech's *autogene cevumeran* (BNT122) have demonstrated safety and early clinical efficacy in solid tumours, including melanoma and pancreatic cancer (Wang et al., 2024). The ability to rapidly synthesize RNA constructs based on each patient's mutational landscape, combined with progress in lipid nanocarriers and computational neoantigen prediction, positions RNA-based vaccines as a central strategy in next-generation cancer immunotherapy.

Dendritic cells - based platforms for neoantigen vaccines

Dendritic cell (DC)-based vaccine systems, which use the specialized antigen-presenting abilities of DCs to trigger strong neoantigen-specific immune responses, have become advanced instruments in tailored cancer immunotherapy. By digesting tumour-derived neoantigens and delivering them to T cells to start focused antitumour responses, DCs serve as expert antigen-presenting cells that connect innate and adaptive immunity. Neoantigens are highly specific vaccination targets with a low risk of autoimmunity since they are produced by tumour-specific somatic mutations, such as nonsynonymous mutations, insertions, deletions, and fusion transcripts, and are not present in normal tissues (Ding et al., 2021; Li, Abudureheman, & Xu, 2025; Tang, Zhang, Zhang, & Yang, 2021).

Design and optimization of DC-based vaccines

Ex vivo culture, neoantigen loading, maturation, and reinfusion are the steps in the manufacturing process that follow the isolation of patient-derived DC precursors from peripheral blood mononuclear cells. Cytokine cocktails, usually comprising GM-CSF and IL-4, are used to develop monocytes or CD34+ hematopoietic progenitors into immature DCs. Through phagocytosis, macropinocytosis, and receptor-mediated endocytosis, these immature DCs demonstrate a significant capability for capturing antigens (Gu, Zhao, & Song, 2020; Tang et al., 2021).

Peptide-based pulsing using synthetic neoantigen peptides made for MHC class I (8–11 amino acids) or class II (13–25 amino acids) presentation is one method of neoantigen loading. The benefits of long peptides include the ability to activate CD^{4+} and CD^{8+} T cells via direct presentation as well as cross-presentation pathways. Other methods for endogenous protein synthesis include mRNA transfection and tumour lysate pulsing (Liang et al., 2024; Morisaki et al., 2023; Morisaki et al., 2024; Xiong et al., 2022).

The effectiveness of the vaccination depends on DC maturation through pathogen-associated molecular patterns like lipopolysaccharide, poly(I:C), or cytokine mixtures after antigen loading. Mature DCs release immunostimulatory cytokines including IL-12 and upregulate costimulatory molecules (CD80, CD86, and CD40), which polarize T cell responses toward the protective Th1 phenotype (Gu, Zhao, & Song, 2020; Tang et al., 2021).

Neoantigen identification and selection

Successful DC vaccine development requires robust neoantigen identification pipelines integrating genomic, transcriptomic, and immunoinformatic approaches. The process begins with whole-exome sequencing of matched tumour and normal tissue, followed by RNA sequencing to confirm transcript expression. HLA typing enables prediction of peptide-HLA binding affinity using algorithms such as NetMHCpan or deep learning-based tools like DeepHLApan (Chang & Wu, 2025; Ding et al., 2021; Kumari et al., 2024; Morisaki et al., 2024; Wu et al., 2019).

DeepHLApan considers both HLA-peptide binding probability and immunogenicity, improving prediction precision by 20.5-55.4% compared to binding-only models. Recent insights reveal that neoantigen architecture—defined by concurrent expression patterns and clonality—critically determines immunogenicity. Tumours with clonal neoantigen expression enable synergistic T cell responses, while heterogeneous expression creates immunodominance hierarchies that suppress responses to subclonal neoantigens (Wu et al., 2019).

Delivery systems and immune activation

DC vaccines are administered via subcutaneous, intradermal, or intranodal routes, with doses ranging from 1×10^6 to 1×10^7 mature DCs per injection. Upon administration, DCs migrate to lymph nodes where they present neoantigens to naïve T cells, initiating clonal expansion of neoantigen-specific CD4+ helper and CD8+ cytotoxic T lymphocytes (Li et al., 2025; Tang et al., 2021; Wu, Li, Yang, & Xu, 2023; Y. Zhang et al., 2024).

An additional amplification mechanism involves DC-derived exosomes carrying functional MHC-peptide complexes that can be taken up by circulating monocytes, transforming them into functional antigen-presenting cells. This creates a cascade effect, systemically amplifying neoantigen-specific immune responses beyond the directly administered DCs (Morisaki et al., 2025).

Clinical progress and therapeutic efficacy

Multiple clinical trials have demonstrated safety, feasibility, and immunogenicity across diverse malignancies. In lung cancer, Neo-DCVac achieved a 25% objective response rate and 75% disease control rate, with patients who had progressed on immune checkpoint inhibitors responding favorably when combined with anti-PD-1 therapy. Hepatocellular carcinoma trials showed 83% oneyear recurrence-free survival with Neo-DCVac-02. Glioblastoma studies demonstrated 87.5% progression-free survival for 5.4-27.3 months, with median 15-fold increases in neoantigen-specific cytotoxic T cells (Ding et al., 2021; Wu et al., 2023; Y. Zhang et al., 2024).

Common observations include excellent safety profiles with predominantly grade 1 adverse events, consistent induction of neoantigen-specific T cell responses, enhanced efficacy when combined with immune checkpoint inhibitors, and feasible manufacturing within 8-12 weeks from tumour sequencing (Ding et al., 2021; Papakonstantinou et al., 2025; Wu et al., 2023).

DNA-based platforms for neoantigen vaccines

Since the 1990s, DNA vaccines have been known to generate potent immune responses. They remain a major research focus and have advanced into clinical trials for both infectious diseases and cancer (X. Zhang et al., 2024). Cancer neoantigens are tumour-specific mutation-derived epitopes presented on MHCs, making them ideal immunotherapy targets due to their absence in normal tissues and high immunogenicity (Duperret et al., 2019). Plasmid DNA vaccines have been considered a promising strategy for personalized cancer immunotherapy, owing to their straightforward production and cost-effectiveness. The risk of integration into the host genome is minimal and is even lower than the rate of spontaneous mutations. Effective antigen expression, processing, and presentation are essential for the efficacy of DNA vaccines. In a murine melanoma model, Tondini et al. (2019) investigated an enhanced polyepitope DNA vaccine and demonstrated its ability to induce T cell responses. Additionally, combining the DNA vaccine with anti-PD-1 therapy resulted in suppressed tumour progression (Liu et al., 2022; Tondini et al., 2019).

Neoantigen vaccines based on SLP, RNA, or DC platforms successfully generate neoantigen-specific T cells and are linked to positive clinical results. Simultaneously targeting multiple neoantigens is crucial for enhancing antitumour immunity and preventing immune escape. Nonetheless, producing these vaccines under GMP guidelines remains a process that is both lengthy and costly. In contrast, the recombinant DNA vaccine platform offers a significant advantage through the relative simplicity and scalability of plasmid DNA production. This makes it a highly appealing option for the clinical development of polyepitope neoantigen cancer vaccines (Li et al., 2021).

Engineered DNA vaccines incorporating multi-epitope neoantigen strings effectively generate polyfunctional CD8+ T-cell responses. When neoantigens are selected for high MHCI binding affinity, these vaccines frequently induce T cells capable of simultaneous cytokine production (IFNγ, TNFα, IL2) and expression of cytolytic markers like CD107a (Liang & Zhao, 2021).

This platform is capable of delivering multiple antigens, is highly adaptable for engineering, and features a straightforward, scalable manufacturing process ideal for personalized vaccines (Chakraborty et al., 2024). Neoantigen DNA vaccines are safe, feasible, and capable of inducing neoantigen-specific immune responses (X. Zhang et al., 2024).

A key limitation of early DNA vaccine platforms has been their limited success in human trials, with efficacy often dependent on advanced delivery methods like electroporation. It is also noted that, while minimal, there exists a theoretical risk of genomic integration (Chakraborty et al., 2024). Traditional plasmid DNA vaccines face limitations like gene silencing and nuclease degradation. Innovative, cell-free alternatives such as linear DNA amplicons, dbDNA, and bacterial backbone-free vectors like minicircles address these issues by enhancing persistence and expression (Viborg, Kleine-Kohlbrecher, & Rønø, 2024).

Nanomaterials and nanoparticles platforms for neoantigens in cancer immunotherapy

Nanomaterials and nanoparticles have emerged as transformative tools in cancer immunotherapy, particularly for neoantigen delivery and vaccine development. Due to their nanoscale dimensions, tuneable surface properties, and high loading capacity, these systems enable efficient delivery of therapeutic molecules, adjuvants, and tumour antigens to immune cells. They enhance antigen stability, cellular uptake, and immune activation, offering a promising approach to overcome the limitations of conventional cancer vaccines (Liang & Zhao, 2021; Peng et al., 2019; Wu, B. et al., 2024).

Nanomaterials platform in cancer immunotherapy

Nanomaterials function as both delivery systems and immunomodulators. Their structural diversity, encompassing lipid nanoparticles, polymeric nanocarriers, metal-based nanostructures, and protein assemblies—allows precise control over antigen release kinetics and immune cell targeting. These systems protect neoantigens from enzymatic degradation and promote uptake by antigen-presenting cells (APCs), particularly dendritic cells (DCs) (Baljon et al., 2024; Peng et al., 2019; Yu et al., 2020). The resulting activation of $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ helper T cells leads to strong anti-tumour immune responses and long-term immune memory (Liang & Zhao, 2021; B. Wu et al., 2024).

Beyond delivery, nanomaterials can actively modulate the tumour microenvironment by inducing immunogenic cell death, enhancing antigen presentation, and overcoming immune suppression. Their flexibility allows the co-delivery of adjuvants, checkpoint inhibitors, and cytokines, providing synergistic activation of the innate and adaptive immune systems (Baljon et al., 2024; Zheng et al., 2024). Bibliometric studies also indicate rapid global growth in this field, highlighting trends toward biocompatible, biodegradable, and stimuli-responsive nanomaterials (B. Wu et al., 2024).

Lipid and protein nanoparticle platforms for neoantigens

Lipid nanoparticles (LNPs) are among the most advanced nanocarriers for cancer immunotherapy. Their biocompatibility and ability to encapsulate nucleic acids, peptides, or proteins make them ideal for neoantigen delivery (Luo, Wang, Lia, & Nel, 2025; Yu et al., 2020). LNPs can be engineered for lymph node targeting, where immune activation primarily occurs. Such systems enhance DC maturation, antigen cross-presentation, and systemic anti-tumour immune responses.

Another notable class is protein-based nanoparticles, such as ferritin nanocages, which self-assemble into uniform architectures capable of displaying or encapsulating neoantigens (Zheng et al., 2024). These nanostructures effectively stimulate cell-mediated immunity, inhibiting both tumour growth and metastasis. Recombinant ferritin-based vaccines have demonstrated enhanced antigen stability, efficient trafficking to lymphoid organs, and strong activation of T-cell responses.

In addition, mRNA-loaded lipid nanoparticles have gained attention as vehicles for in situ antigen expression. By delivering tumour-specific mRNA directly to APCs, they induce de novo synthesis of neoantigens, promoting potent and durable immune activation. When combined with chemotherapeutic nanocarriers such as silicasomes, these formulations

significantly enhance the cancer immunity cycle, particularly in aggressive cancers like pancreatic carcinoma (Luo et al., 2025).

Nanovaccines and polymeric nanoparticles for immune activation

Nanovaccines co-delivering peptide neoantigens and immune agonists have shown remarkable success. Platforms integrating STING and TLR4 agonists achieve a balanced activation of innate and adaptive immunity, promoting cytokine release, T-cell proliferation, and long-term immune memory (Baljon et al., 2024). These multifunctional systems offer precise control over antigen dose and temporal release.

Polymeric nanoparticles, particularly poly(lactic-co-glycolic acid) (PLGA) carriers, are widely used for controlled and sustained antigen delivery. PLGA nanoparticles co-encapsulating NY-ESO-1 peptides and immunostimulants have induced strong $CD8^+$ and $CD4^+$ T-cell as well as B-cell responses (Dolen et al., 2021). Their biodegradability and low toxicity make them suitable for clinical translation.

An innovative approach involves cancer cell membrane-coated nanoparticles, which utilize the membranes of tumour cells to camouflage synthetic cores. This biomimetic surface enables presentation of multiple tumour-associated antigens, facilitating natural recognition by dendritic cells and eliciting robust anti-tumour immunity (Huang et al., 2023). When loaded with therapeutic agents such as gambogic acid, these particles further combine cytotoxic and immunogenic effects.

Research trends and future directions

The integration of nanotechnology with immunology is paving the way toward personalized nanovaccines and precision immunotherapy. Nanomaterials are being optimized for targeted antigen delivery, co-stimulation of immune pathways, and real-time monitoring of immune responses (Gu et al., 2020; Li et al., 2025; Morisaki et al., 2024). Emerging trends include smart nanoplatforms that respond to tumour-specific cues such as pH or redox gradients, releasing their payload selectively within the tumour microenvironment. Although the potential is vast, challenges remain in large-scale production, long-term stability, biosafety, and regulatory approval. Continued interdisciplinary research is required to translate these promising nanoplatforms from preclinical models to clinical applications. Overall, nanomaterial-based neoantigen systems represent a frontier in cancer immunotherapy, offering innovative strategies to achieve durable tumour regression and immunological memory (Liang & Zhao, 2021; Peng et al., 2019; B. Wu et al., 2024).

To facilitate comparison among the major neoantigen vaccine platforms, Table 1 summarizes their mechanisms, advantages, limitations, representative clinical applications.

Table 1. Comparison of major neoantigen vaccine platforms

Platform	Mechanism	Advantages	Limitations	Representative Clinical Applications	References
Synthetic Long Peptide (SLP)	Long peptides are processed by APCs and presented through MHC-I and MHC-II pathways to activate T cells.	Strong cellular immunity, safe, induces immune memory	HLA restriction, individualized manufacturing	Melanoma, pancreatic cancer, hepatocellular carcinoma	Cai et al., 2021; X. Chen et al., 2020; Z. Chen et al., 2021; Hao et al., 2024
mRNA Vaccine	Encodes patient-specific neoantigens that are translated in host cells.	Rapid design, multi-epitope delivery, potent $CD4^+$ and $CD8^+$ T-cell responses	Cold-chain storage, delivery challenges	Melanoma, pancreatic cancer, solid tumours	Esprit et al., 2020; Guasp et al., 2024; Nguyen et al., 2025
Dendritic Cell Vaccine	Patient-derived dendritic cells loaded with neoantigens stimulate tumour-specific T cells.	Highly efficient antigen presentation, personalized	Expensive, labor-intensive	Lung cancer, glioblastoma, hepatocellular carcinoma	Ding et al., 2021; Tang et al., 2021; Wu et al., 2023
DNA Vaccine	Plasmid DNA encoding neoantigens is delivered into host cells.	Stable, economical, scalable	Lower immunogenicity, electroporation required	Melanoma, early clinical trials	Duperret et al., 2019; Liu et al., 2022; X. Zhang et al., 2024
Nanoparticle-based Vaccine	Nanocarriers deliver neoantigens and adjuvants to antigen-presenting cells.	Protects antigen, targeted delivery, enhanced immune response	Complex manufacturing, regulatory challenges	Preclinical and emerging clinical studies	Baljon et al., 2024; Liang & Zhao, 2021; Peng et al., 2019; B. Wu et al., 2024

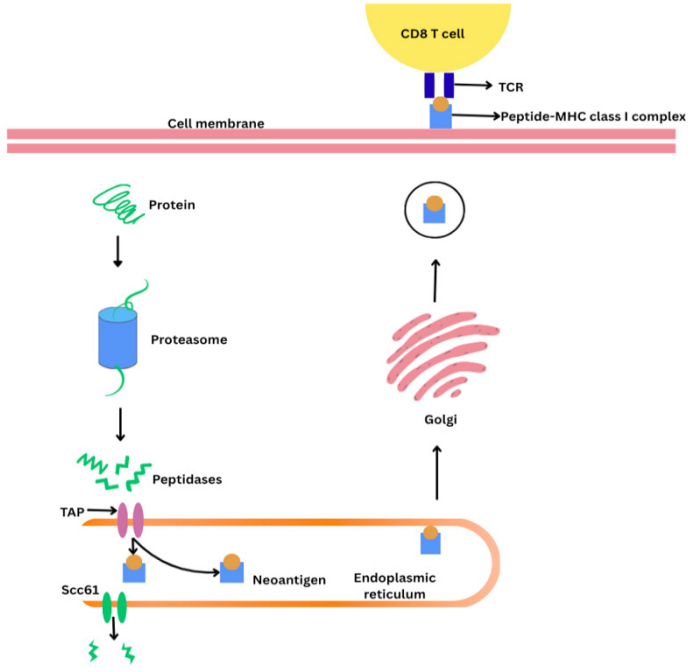

Figure 2. Schematic representation of the mechanism of action of neoantigen-based cancer vaccines. Prepared by the authors based on information adapted from cited literature

MECHANISM OF ACTION OF NEOANTIGEN

1. **T- Cell activation:** As shown in figure 2, $CD8^+$ and $CD4^+$ T cells are activated, multiply, and turn into $PD\text{-}1^+$ effector and memory T cells that can enter tumours (Lang, Schrörs, Löwer, Türeci, & Sahin, 2022).
2. **Recognition and attack:** Inside the tumour, these activated T cells recognize neoantigens on tumour cells and antigen-presenting cells (APCs), which helps control the tumour (Lang et al., 2022).
3. **T Cell teamwork:** $CD8^+$ T cells directly kill cancer cells, while $CD4^+$ T cells help by changing the tumour environment (Lang et al., 2022).
4. **Amplifying the response:** When T cells recognize their target, they release IFN-γ. This signal increases the display of neoantigens on tumour cells and APCs, making the tumour more visible to the immune system (Lang et al., 2022).
5. **Self-Perpetuating Cycle:** Killing tumour cells releases more tumour antigens. This «antigen spreading» further stimulates and expands more memory T cells, creating a repeating immune cycle (Lang et al., 2022).
6. **Core trigger:** Cytotoxic T lymphocytes (CTLs) are crucial because they are activated by recognizing neoantigen peptides bound to MHC class I molecules on tumour cells (Lv et al., 2025).
7. **Initial requirement:** For this to start, neoantigens must first be processed and displayed by MHC molecules so they can be recognized by T cell receptors (TCRs) (Shang et al., 2022).
8. **Key amplification loop:** The recognition of antigens by T cells itself causes tumour cells and APCs to display even more neoantigens, strengthening the immune response (Shang et al., 2022).
9. **The goal of therapy:** The main aim of neoantigen-targeting therapies (like vaccines) is to start or boost this entire tumour-specific T-cell response (Lang et al., 2022; Lv et al., 2025).

COMPARATIVE FEATURES OF NEOANTIGEN-BASED VACCINES AND CONVENTIONAL CANCER IMMUNOTHERAPIES

Table 2. Comparative features of neoantigen-based vaccines and conventional cancer immunotherapies. Compiled by the authors based on published studies

Aspect	Conventional cancer immunotherapies	Neoantigen-Based Vaccines	Key Difference
Target Antigens	Shared tumour-associated antigens (TAAs)	Patient-specific mutation-derived neoantigens	Neoantigens provide improved tumour specificity (Ho et al., 2023; Li et al., 2024).
Personalization	Non-personalized, for broad patient groups	Highly personalized for individual patients	Supports precision medicine strategies (Aljabali, Hamzat, Alqudah, & Alzoubi, 2025; Khan et al., 2021; D. Wu et al., 2024; Zhang et al., 2025).
Immunogenicity	Moderate to low due to immune tolerance	High, elicits strong CD8+ T cell responses	Enhanced T-cell activation may occur (Braun et al., 2025; Ho et al., 2023; Naffaa, Al-Ewaidat, Gogia, & Begiashvili, 2025).
Mechanism	Target shared proteins or antigens expressed on tumour	Target neoepitopes specific to tumour mutations	More focused anti-tumour immunity (Aljabali et al., 2025; Li et al., 2021).
Clinical Efficacy	Mixed, often limited clinical benefit	Promising efficacy has been observed in trials involving melanoma, lung cancer, and colorectal cancer.	Encouraging responses reported in melanoma and solid tumours (Braun et al., 2025; Naffaa et al., 2025).
Safety Profile	Possible off-target effects and autoimmunity	Generally well-tolerated with fewer adverse effects	Lower risk to healthy tissues (Braun et al., 2025; Fan et al., 2023).
Manufacturing & Scalability	Off-the-shelf, large-scale manufacturing possible	Complex, customized manufacturing per patient	More complex production workflow (Aljabali et al., 2025; Zhang et al., 2025)
Cost and Time	Lower production cost, rapid availability	Higher cost and longer production timelines	Personalization increases expense and timelines (Biswas, Chakrabarti, Padul, Jones, & Ashili, 2023).
Regulatory Status	Multiple approved vaccines for clinical use	Mostly in clinical trial phases	Regulatory pathways are still evolving (Naffaa et al., 2025).
Advantages	Established safety profile, easier logistics	Personalized, higher immunogenicity, targeted therapy	May improve precision oncology outcomes (Liu et al., 2023).

CLINICAL PROGRESS OF NEOANTIGEN-BASED CANCER VACCINES

Neoantigen-based cancer vaccines have progressed from theoretical immunogenomics to clinically validated immunotherapies. Their development reflects steady refinement from early feasibility studies to advanced programs integrating artificial intelligence, bioinformatics, and optimized delivery technologies.

The first clinical evidence came from high-risk melanoma patients vaccinated with long synthetic peptides targeting up to twenty patient-specific neoantigens formulated with the TLR3 agonist poly-ICLC. This phase I trial demonstrated strong CD^{4+} and CD^{8+} T-cell activation against endogenously processed neoantigens and cytolytic activity against autologous tumour cells, confirming both safety and functionality of individualized vaccines (Ott et al., 2017). This success established the basis for precision immunization targeting unique tumour mutations.

Subsequent progress has centered on improving vaccine design and delivery. Biomaterial-assisted platforms now enable co-delivery of multiple neoantigens and adjuvants to antigen-presenting cells, promoting balanced MHC I/II presentation and potent T-cell responses. Synthetic antigen-presenting constructs and modular biomaterials enhance intracellular processing and reproducibility while simplifying manufacturing (Guo, Lei, & Tang, 2018). These strategies represent a shift from simple peptide emulsions toward intelligent carriers capable of fine immunomodulation. Advances in formulation have also made personalized production clinically viable. FRAME-001, developed for advanced non-small cell lung cancer, exemplifies this transition. Using tumour genomic and transcriptomic data, individualized peptides were synthesized through a high-throughput platform and formulated with Montanide ISA 51 VG under good manufacturing practice conditions. The stable emulsions met all purity standards for over thirty weeks, proving the feasibility of GMP-compliant, patient-specific vaccines (Oosting et al., 2022).

The global clinical landscape has expanded rapidly, with over 160 registered trials, most in early phases and dominated by peptide, protein, dendritic-cell, and nucleic-acid vaccines. Combination regimens (particularly with checkpoint inhibitors) are most common because vaccines broaden T-cell repertoires that respond better to PD-1 or PD-L1 blockade (Yu, He, Li, & Wu, 2022). BioNTech's autogene cevumeran, an mRNA-based vaccine in pancreatic ductal adenocarcinoma, improved recurrence-free survival when paired with PD-L1 inhibitors, while Moderna's mRNA-4157 plus pembrolizumab reduced distant metastasis risk by 65 % in high-risk melanoma, prompting phase III evaluation (Li et al., 2021; Yu et al., 2022). These findings illustrate the synergy between neoantigen vaccines and immune checkpoint therapy. Clinical translation has extended beyond melanoma and lung cancer. In gynecologic oncology, the long-peptide vaccine NeoVax formulated with poly-ICLC is under evaluation for ovarian cancer with nivolumab after durable T-cell responses were achieved in melanoma (Tang, Cai, Diao, Guo, & Yang, 2022). In follicular lymphoma, exome and transcriptome profiling revealed that even tumours with modest mutation loads harbor multiple immunogenic neoantigens, validating personalized polyvalent vaccine design. Nearly all patients possessed at least one high-quality neoantigen candidate, confirming feasibility in hematologic malignancies (Ramirez et al., 2024). These findings emphasize the adaptability of the approach across tumour types when antigen prediction is optimized.

Computational and AI-based platforms have transformed neoantigen identification and prioritization. Machine-learning models trained on MHC-bound peptide datasets, complemented by mass-spectrometry profiling, improve prediction of binding affinity and peptide cleavage patterns. Transformer-based frameworks such as TransPHLA outperform traditional tools by rapidly ranking neoantigen candidates for inclusion in vaccines (Kumar, Dixit, Srinivasan, & Vincent, 2024). Integrating whole-ex-

ome data with AI pipelines now allows personalized vaccine design within hours instead of weeks, which accelerates clinical translation (Magoola & Niazi, 2025). Simultaneously, CRISPR-driven genome editing enhances immune programming and vaccine optimization. Coupling CRISPR with RNA platforms enables real-time modification of mRNA constructs (adjusting codon usage and secondary structure to strengthen immunogenicity) and allows engineering of immune cells with improved antigen recognition (Magoola & Niazi, 2025). These advances illustrate a data-driven paradigm where computational modelling and gene editing converge to refine therapeutic precision dynamically.

Despite the technical sophistication of these systems, economic and translational considerations remain central. Personalized production entails high cost and regulatory complexity, yet the field continues to attract significant investment. Since 2013, equity funding in neoantigen vaccine developers has surpassed USD 12 billion, dominated by RNA-based platforms. Strategic alliances between major pharmaceutical companies, such as Moderna–Merck and Genentech–vaccibody, reflect growing confidence in the long-term clinical and commercial potential of this modality (Li et al., 2021).

Overall, the evolution of neoantigen-based cancer vaccines demonstrates cohesive advancement from conceptual feasibility to broad clinical testing. Early melanoma trials proved immunogenicity, while innovations in delivery, formulation, and computation have expanded applicability across solid and hematologic malignancies. The integration of AI, CRISPR, and precision manufacturing continues to accelerate development; this positions neoantigen vaccines as a cornerstone of next-generation personalized immunotherapy. As large-scale trials mature, these vaccines are expected to deliver durable and patient-specific immune control, marking a pivotal step in the transformation of cancer treatment.

Table 3 summarizes representative clinical trials evaluating personalized neoantigen vaccines across different cancer types, highlighting their vaccine platforms, clinical phases, major findings.

Table 3. Representative clinical trials of personalized neoantigen-based cancer vaccines

Clinical Trial / Vaccine	Cancer Type	Vaccine Platform	Phase	Key Findings	References
NeoVax	High-risk melanoma	Synthetic long peptide	Phase I	Induced robust $CD4^+$ and $CD8^+$ T-cell responses with durable immune memory.	Ott et al., 2017
FRAME-001	Advanced non-small cell lung cancer	Personalized peptide vaccine.	Phase I	Demonstrated feasibility and safety of individualized vaccine manufacturing.	Oosting et al., 2022
Autogene Cevumeran (BNT122)	Pancreatic ductal adenocarcinoma	mRNA vaccine	Phase I	Showed encouraging immune responses and delayed disease recurrence	Li et al., 2021; Yu et al., 2022
mRNA-4157 + Pembrolizumab	High-risk melanoma	mRNA vaccine	Phase II	Improved recurrence-free survival and reduced distant metastasis.	Li et al., 2021; Yu et al., 2022
NeoVax + Nivolumab	Ovarian cancer	Long peptide vaccine	Early clinical evaluation	Produced durable neoantigen-specific immune responses.	Tang et al., 2022
Personalized Dendritic Cell Vaccine	Advanced lung cancer	Dendritic cell vaccine	Phase I	Demonstrated safety and induction of tumour-specific T-cell immunity	Ding et al., 2021

CHALLENGES AND LIMITATIONS OF NEOANTIGENS

Neoantigen-based cancer immunotherapy offers a promising approach for tailored treatment; nonetheless, it has numerous substantial obstacles and limitations:

1. **Tumour heterogeneity**: Varying expression of neoantigens due to tumour cell population heterogeneity makes it difficult to target all malignant cells. Temporal and spatial heterogeneity necessitates frequent approach adjustments and monitoring (Castro, Zanetti, & Carter, 2021; Singh et al., 2025; Sun et al., 2025).
2. **Limited neoantigen prediction accuracy**: Due to algorithmic and technical limitations, these bioinformatic techniques can produce false positives or negatives, which lowers the effectiveness of vaccine development. Reliability is further impacted by sequencing limitations and issues with tumour sample quality (Ahmed, Mazhar, & Shabbir, 2024; Aljabali et al., 2025; Lybaert et al., 2023; Pu, Peddle, Zhu, Tejpar, & Verbandt, 2024; Zhang et al., 2020).
3. **Tumour immune evasion**: Tumours may lose or downregulate relevant MHC molecules, or they may establish immune-suppressive processes such as upregulating checkpoints (PD-1/PD-L1), which significantly reduces the immune response's ability to defend against neoantigen vaccines (Borden, Buetow, Wilson, & Hastings, 2022; Chen, Fang, Chen, & Chen, 2021; Wang, Yu, & Zhang, 2022).
4. **Manufacturing & Scalability Barriers**: Neoantigen vaccines require individualized production due to their highly personalized nature, which requires significant time, facilities, and financial resources, hence impeding rapid roll-out and conventional clinical practice (Katsikis, Ishii, & Schliehe, 2024; Liu et al., 2022; Zhang et al., 2020).
5. **Dynamic tumour evolution**: Under treatment pressure, the cancer mutational environment may change, leading to the loss or modification of previously identified neoantigens, reducing the long-term effect and requiring re-sequencing and vaccine redesign (Ahmed et al., 2024; Aljabali et al., 2025; Singh et al., 2025).
6. **Safety & autoimmunity risks**: Normal (self) proteins are cross-reactive with others, which can cause autoimmune toxicity, including systemic inflammatory reactions and off-target tissue damage (Singh et al., 2025).
7. **Suboptimal immune activation**: Many patients have weak or nonexistent T cell responses to expected neoantigens, either because of insufficient immunogenicity or because of escape mechanisms built into the tumour microenvironment (Aljabali et al., 2025; Sonar, Singh, Mandadi, & Sharma, 2025).
8. **Problems with sample and data quality**: Clinical samples, especially FFPE tissue, have a tendency to limit sequence quality, which affects the finding of neoantigens and reduces pipeline prediction success rates overall (Lybaert et al., 2023; Pu et al., 2024).
9. **Input data from multi-focal/metastatic disease**: Incomplete targeting may arise from single-site biopsy dependence, which may overlook spatially-distributed neoantigen patterns, especially in metastatic or multi-focal disease (Liu et al., 2022).
10. **Need for combination treatments**: To increase success, neoantigen methods often require supplementation with adoptive T-cell treatments, cytokines, or checkpoint inhibitors. This complicates clinical regimen planning and increases the possibility of side effects (Chen et al., 2019; Reynolds, Tran, Jain, & Narendran, 2022; Sonar et al., 2025).

REGULATORY ASPECTS

Neoantigens are unique mutations found on tumour cells but not normal cells. Advances in sequencing and bioinformatics have improved their identification. Vaccines targeting these neoantigens can safely trigger a patient-specific immune attack against the tumour, leading to personalized treatment. Various vaccine types have shown promising results in trials, improving survival and quality of life. Because neo-

antigen vaccines are individualized products, regulatory evaluation is more complex than for conventional off-the-shelf vaccines. Each patient-specific batch requires standardized manufacturing workflows, rapid release testing, and strict chain-of-identity systems to ensure the correct product reaches the intended patient. Quality control must verify sequencing accuracy, sterility, purity, potency, and batch consistency under Good Manufacturing Practice (GMP) conditions. In addition, clinical development pathways are complicated by small patient cohorts, variable production timelines, and personalized dosing approaches, which may delay regulatory approval and increase costs (Peng et al., 2019; Y. Zhang et al., 2024; Zhu & Liu, 2021). However, their efficacy is challenged by the immune escape mechanisms of tumour cells (Peng et al., 2019). Personalized neoantigen-based vaccines and ACT approaches have shown encouraging antitumour results. Decreased production turnaround time, reduced manufacturing cost, better detection of immunogenic neoantigens, improved computational algorithms, and effective treatment biomarkers are expected to add to the feasibility, affordability, and momentum of neoantigen targeting therapies (Zhu & Liu, 2021). The primary objectives of this clinical study are safety and immunogenic potential of neoantigen vaccines in patients with cancer. The study was designed to assess tolerability, monitor immune responses to the encoded neoantigens, and explore their potential impact on recurrence-free survival compared with standard clinical outcomes (Y. Zhang et al., 2024). Clinical trials show neoantigen vaccines are a precise and safe cancer treatment. Advances in sequencing and machine learning have improved neoantigen identification, enabling the development of various vaccine types. These trials are exploring combinations with conventional therapies to improve efficacy. Innovative strategies, like activating T-cells outside the body, are also being used to overcome tumour immunosuppression (Duperret et al., 2019). Genocea Biosciences's GEN-009 vaccine trial (NCT03633110) is one of the few Phase 1/2a clinical trials that have shown promising efficacy among the current neoantigen personalization therapies with an estimated completion date of December 2022 (Zhang et al., 2021). The recent development of platforms that screen a patient's PBMCs against neoantigen libraries offers a promising approach for directly identifying CD^{4+} and CD^{8+} T-cell antigens, with successful applications in both infectious disease and oncology (Morisaki et al., 2025; Papakonstantinou et al., 2025). Despite this potential, the utility of these biological assays is currently constrained by their high cost, technical complexity, and a limited ability to detect subdominant or cryptic neoantigens—those that fail to elicit a natural immune response but may still be effectively targeted by vaccination (Li, Goedegebuure, & Gillanders, 2017).

CONCLUSION

Based on the comprehensive review, it is concluded that neoantigens constitute a pivotal advancement in the domain of cancer immunotherapy, embodying the principles of precision oncology. Their fundamental distinction—arising from tumour-specific mutations—confers a high degree of immunogenic specificity and a reduced potential for on-target, off-tumour toxicity. Substantial progress has been achieved in the methodologies for neoantigen identification, leveraging next-generation sequencing, bioinformatic prediction algorithms, and immunopeptidomics. Concurrently, a diverse array of vaccine platforms, including synthetic peptides, nucleic acids, and dendritic cell-based systems, has demonstrated the feasibility of eliciting robust, patient-specific T-cell responses.

Clinical investigations increasingly validate the therapeutic potential of neoantigen-targeting strategies, with evidence indicating synergistic efficacy when combined with immune checkpoint blockade. Notwithstanding this promising trajectory, significant challenges persist. These encompass intratumoural heterogeneity, mechanisms of immune escape, the technical and economic complexities of personalized manufacturing, and the imperative for

enhanced predictive accuracy. Future progress is contingent upon continued innovation in computational biology, multi-omics integration, and scalable production processes. Ultimately, neoantigen-based interventions represent a paradigm shift toward individualized cancer treatment, holding considerable promise for improving clinical outcomes and solidifying its position as a cornerstone of modern immuno-oncology.

This review further distinguishes by integrating current evidence on neoantigen biology, identification strategies, therapeutic platforms, translational barriers, and future clinical opportunities into a single critical perspective.

AUTHOR CONTRIBUTION STATEMENT

Concept (D.S.; S.Y.; N.K.; P.M.; J.P.; D.A.), Supervision (D.S.), Literature Search (S.Y.; N.K.; P.M.; J.P.; D.A.), Writing (S.Y.; N.K.; P.M.; J.P.; D.A.), Critical Reviews (D.S.)

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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