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Therapeutic Vaccines in Non-Small Cell Lung Cancer: Immunologic Mechanisms, Therapeutic Platforms, and Barriers to Efficacy

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Abstract

Therapeutic vaccines for non-small cell lung cancer (NSCLC) aim to improve treatment outcomes for a disease with high global incidence, mortality, and recurrence risk despite receiving standard multimodal therapy. This field focuses on the use of cancer antigens as vaccine targets in the context of immunology, influenced by immunovigilance, immunoreduction, and the tumor microenvironment, which suppresses the immune system. Mechanistic requirements for effective vaccination include selecting cancer antigens that are highly and homogeneously expressed, functionally linked to oncogenic pathways, and efficiently presented via MHC molecules to coordinate T cell responses. Peptide-based, dendritic cell-based, nucleic acid-based, and microbial vector-based vaccine platforms demonstrate safety and induction of antigen-specific cellular immunity responses. However, survival remains moderate and inconsistent, particularly in advanced-stage patients. Future progress will depend on rigorous, mechanism-based design that integrates data-driven antigen and epitope selection with tailored platform and route selection to shape the desired immune response, while also facilitating personalized and optimized vaccination strategies.

1. Introduction

Lung cancer represents a major public health concern, as it remains one of the most prevalent and lethal malignancies worldwide [1–3]. In 2022, approximately 2.4 million new cases and 1.8 million mortalities were reported globally, with 82% of newly diagnosed cases resulting in death [1, 4–6]. These epidemiological profiles underscore the limited ability of current therapies to achieve durable disease control, particularly in settings with a lower human development index (HDI) where access to early detection and advanced therapies is restricted [6]. Collectively, these outcomes reflect the inability to establish sustained tumor-specific immune control. Therefore, driving the need for treatment strategies that can induce durable anti-tumor immunity [7–9].

Histologically, lung cancer is classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all cases. Subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [10]. Management of NSCLC is multimodal and stage-dependent, incorporating surgery and radiotherapy in early stages, whereas advanced stages rely on systemic therapies such as chemotherapy, targeted therapy, and immunotherapy [11, 12]. However, high recurrence rates,

systemic toxicity, and drug resistance limit the long-term effectiveness of conventional treatments [13].

Immune checkpoint inhibitors (ICIs), a type of immunotherapy, have transformed the treatment landscape and become the gold standard of care in advanced NSCLC, particularly drugs targeting the PD-1/PD-L1 pathway [14, 15]. Despite this, they generally elicit durable immune responses in only a minority of patients. Consistent with this limitation, a retrospective study of ICI monotherapy in common oncogene-driven NSCLC reports low and heterogeneous ORR ranging from 3-28% [16]. Moreover, long-term clinical benefits are constrained by the frequent occurrence of primary and acquired resistance [17]. Resistance by tumor-intrinsic mechanisms arises from alterations within tumor cells that impair DNA damage responses, signaling pathways, and immune recognition. In contrast, tumor-extrinsic mechanisms originate outside the tumor cell and are shaped by immune cells and non-immunological components within the tumor microenvironment [17–19]. Additionally, the clinical activity of ICIs relies on predictive biomarkers such as PD-L1 expression and tumor mutational burden (TMB) [20]. In which, dependence of inhibitory checkpoints releases rather than new anti-tumor immunity generation limits effectiveness in immunologically" cold" tumors lacking robust antigen presentation and immune infiltration [21, 22]. These challenges underscore the need for strategies that actively prime, generate immune memory, and facilitate durable tumor-specific immune response in NSCLC.

Therapeutic cancer vaccines, a form of active immunotherapy, offer promising strategies to address these unmet needs [16]. Unlike preventive vaccines, which are administered to reduce the risk of disease, therapeutic vaccines are designed to eliminate existing cancer cells by establishing immune memory to provide robust protection against recurrence and to facilitate vaccine-induced tumor cell death in cancer patients [23]. To date, no therapeutic cancer vaccines have received global regulatory approval for NSCLC [24]. CIMAvax-EGF remains the most clinically advanced candidate, having been approved in several Latin American regions with reports of improvements in median overall survival and progression-free survival [24]. However, a large-scale analysis of NSCLC vaccine clinical trials shows that most candidates are still in the early stages of development, with only a small fraction reaching phase III. Although the field remains largely exploratory, a meta-analysis of 11 randomized controlled trials (RCTs) showed significantly prolonged survival with a good safety profile in advanced NSCLC patients treated with therapeutic vaccines [25]. This analysis suggests that therapeutic vaccines have potential as an effective post-first-line therapy or as first-line maintenance therapy, with greater benefits seen in squamous cell carcinoma [25, 26].

Although previous reviews have largely focused on cataloging vaccine platforms or summarizing clinical trial results, this review critically analyzes how immunological mechanisms and clinical implementation strategies shaped therapeutic effectiveness. The present review encompasses several major therapeutic cancer vaccine platforms and their immunological underpinnings for NSCLC. Its scope is limited to vaccine-based strategies and excludes prophylactic vaccines, adoptive cell therapies including CAR-T and TCR-T approaches, or other non-vaccine immunotherapies. By integrating mechanistic insights with clinical evidence, this review aims to identify key lessons from past clinical experience and provide insights for the rational design of future therapeutic cancer vaccines for NSCLC.

2. Materials and Methods

2.1. Immunological landscape of NSCLC

Cancer immunology describes immune system recognition, restraint, and control of malignant cells during tumor development. In the earliest stages, the development of cancer is repressed by a process called immunosurveillance, in which innate and adaptive immune cells continuously patrol tissues to detect and eliminate cells undergoing cancer transformation before they develop into clinically apparent tumors [27, 28]. In this context, innate immune cells such as natural killer (NK) cells, macrophages, and dendritic cells respond to stress signals and modifications in self-recognition, whereas CD8+ lymphocytes, CD4+ lymphocytes, and B cells elicit more targeted responses against cancer antigens [27, 28].

The mechanism of immunosurveillance is not infallible; cancer undergoes immunoediting that organizes the dynamic process into three interconnected phases referred to as the three Es model of immunity-cancer coevolution: elimination, equilibrium, and escape (Figure 1) [29–31]. During the elimination phase, immune effector mechanisms efficiently identify and eliminate large numbers of lesions formed by cancer cells, thereby expanding immunosurveillance into an antitumor response to maintain early lesions in a subclinical state [31–34]. The system switches to the equilibrium phase when some fraction of transformed cells survives. This phase describes a prolonged period in which antitumor immune responses inhibit tumor proliferation without achieving full eradication. Immune cells selectively target and eliminate tumors with high immunogenicity, while

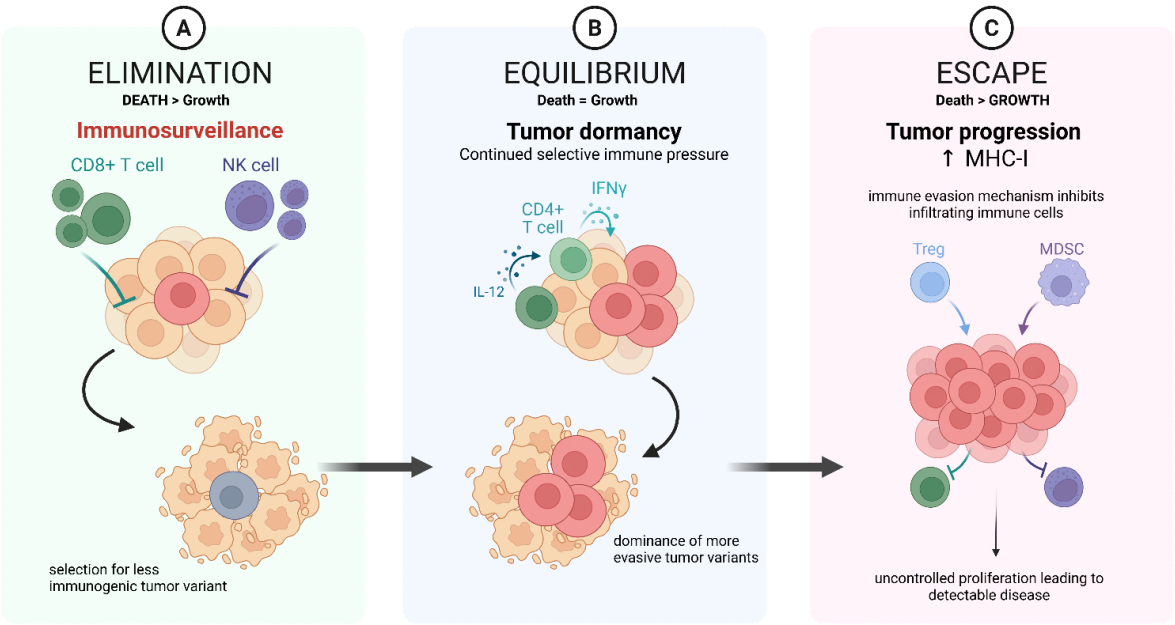

Figure 1. Cancer immunoediting phases. Adapted from Kostecki et al. [30] and visualizes using Biorender.

cells that express fewer antigens, present antigens poorly, or are more resistant to immune attack are more likely to survive. Over time, sustained selection determines which variants persist, resulting in increasing tumor populations capable of evading the immune system [31–34]. Progression to the escape phase marks the dominance of immune-resistant cancer cells and the failure of effective immune regulation. Tumor cells can create an immunosuppressive microenvironment by downregulating antigen-presenting pathways, upregulating inhibitory ligands, secreting immunosuppressive cytokines, abnormally expanding myeloid-derived suppressor cells (MDSC) and tumor-associated macrophages (TAM). This condition results in functional exhaustion of NK cells and impaired antibody- and complement-mediated mechanisms, thereby enabling tumor growth, invasion, and metastasis [31–34].

Although the principles of immunosurveillance and immunoediting apply broadly to various types of cancer, NSCLC exhibits unique immunological characteristics. NSCLC falls into the category of the most mutagenic solid tumors, particularly in smoking-related diseases, resulting in higher tumor mutation burden and increased neoantigen generation compared to non-smokers [35, 36]. High TMB levels in NSCLC are associated with higher CD8+ infiltration, PD-L1 expression, and better outcomes with PD-1/PD-L1 blockade [37]. However, high heterogeneity contributes to divergent responses to immunotherapy and immune evasion [38].

In addition, distinct immune landscapes are present across histological subtypes. Squamous cell carcinoma is generally characterized by higher immune infiltration and inflammatory signals, while adenocarcinoma more frequently exhibits an immune-evasive phenotype [39]. These features of NSCLC highlight the importance of tailoring vaccination strategies to tumor subtypes, mutation background, and immune context.

2.2. Cancer Antigens in NSCLC

2.2.1. Tumor-Associated Antigen (TAA) in NSCLC

Cancer antigens are classified into two distinct groups based on their intrinsic characteristics and expression patterns: tumor-associated antigens and tumor-specific antigens [40]. Tumor-associated antigen (TAA) is an overexpressed or abnormally expressed endogenous protein in neoplastic cells compared to normal tissue. Notable examples of TAA include MUC1, WT1, survivin, and NY-ESO-1 [41–43]. A substantial subset of TAA, typically restricted to immune-privileged germline tissues but abnormally expressed in certain cases of NSCLC, has been identified as a cancer-testis antigen (CTA). TAA, including CTA, has been widely used in peptide vaccines and can be encoded in nucleic acid or viral vectors to increase epitope coverage [41–43].

Despite promising immunogenicity in preclinical models, TAA-based vaccines generally fail to produce sustained clinical benefits in NSCLC [25, 44]. This discrepancy results from TAA's nature as a self-protein, making TAA susceptible to central and peripheral immune tolerance, where T cell populations may be removed from the immune repertoire [45]. Additionally, antigenic loss and tumor heterogeneity allow outgrowth of antigen-negative clones despite measurable T-cell responses [44]. Notably,

heightened immune pressure against TAA increases the risk of off-tumor toxicity, as vaccine-induced T cells cannot fully distinguish between tumor cells and healthy tissues with low antigen expression [46]. Altogether, these factors help explain why TAA-based vaccines show limited efficacy in clinical trials despite strong immunogenicity in experimental settings.

2.2.2. Tumor-Specific Antigen (TSA) in NSCLC

Tumor-specific antigen (TSA), in contrast to TAA, are peptides generated as a result of tumor-specific genetic alterations, namely, nonsynonymous mutations, insertions, deletions, or gene fusions that are not naturally present in healthy tissues [41, 47]. The capacity of mutations to generate tumor-specific antigens (TSAs) depends on several key factors. First, the mutated sequence must be successfully translated into a functional protein. Second, the resulting mutant protein must be effectively processed into peptides that can be presented. Third, the mutated peptide must bind with sufficient affinity to the major histocompatibility complex (MHC) molecule. Finally, the peptide–MHC complex must exhibit adequate affinity for recognition by the T cell receptor [48]. This encompasses TSA generated from passenger mutations and oncogenic driver mutations, such as EGFR and KRAS mutant proteins [49]. Oncogenic driver mutations arise from functionally vital mutations that are highly attractive for immunotherapy. TSA is recognized as foreign by the immune system and bypasses central tolerance, greatly reducing the risk of autoimmunity [41, 47]. TSA can be used as a public or personalized vaccine, with peptide-, nucleic acid-, or dendritic-based platforms as ideal platforms [50].

However, targeting oncogenic driver-derived TSA does not completely prevent immune escape. Although these mutations are important for cancer survival, cancer cells can evade immune pressure by impairing antigen processing, downregulating HLA expression, and expanding subclones with low epitope expression [51, 52]. Moreover, activation of an alternative signaling pathway may maintain tumor growth without eliminating the targeted mutation [53]. These adaptive responses indicate that functional importance alone is not sufficient for long-term immune control [51].

2.3. Tumor Microenvironment-Mediated Barriers to Vaccine Efficacy in NSCLC

Despite the identification of highly immunogenic tumor antigens, the immune response induced by NSCLC vaccines is often limited by the immunosuppressive tumor microenvironment (TME). In NSCLC, regulatory T cells (Treg), MDSCs, and TAMs are key immunosuppressive cells of the NSCLC TME. These cells inhibit the expansion of CD8+, suppressing cytokine production and dampening antigen presentation [39]. Moreover, TAMs further increase immunosuppression by releasing inhibitory cytokines and competing with T cells for essential metabolic resources [54]. Beyond immune regulation, hypoxia, nutrient deprivation, and abnormal tumor vascularization limit immune cell infiltration and function. These synergistic interactions reinforce immunosuppression; such constraint underscores the need for context-aware vaccination strategies [39, 55].

2.4. Immunologic and Computational Requirements for Rational Vaccine Design in NSCLC

2.4.1. Tumor Specificity and Tumor Restriction

Tumor specificity is described as the exclusive expression of antigens on tumor cells that are absent in healthy tissues. On the other hand, tumor-restricted antigen expression is mainly observed in the tumor environment and is minimal in healthy tissues. Both concepts are crucial for vaccine safety, reducing off-tumor toxicity and minimizing autoimmunity by targeting tumor-specific or highly restricted antigens. Absent or low expression in healthy tissues ensures safety, and high expression in tumor cells indicates broad immune targeting, which is essential for the formulation of effective and safe cancer vaccines [45, 56].

2.4.2. Expression Level and Homogeneity

Immune recognition is strengthened by increased expression levels, with a large number of antigens displayed on the tumor surface via MHC I molecules. This antigen display facilitates the identification of CD8+ cells and antibodies, as well as the elimination of cancer cells [57, 58]. A homogenous antigen expression, in which most tumor cells display the same antigen, is more likely to induce an effective and coordinated response against most tumor cells. Conversely, heterogeneous expression, characterized by varying levels of antigen across tumor cells or lesions, allows some tumor cells to evade immunosurveillance, leading to immune evasion and treatment resistance [59].

2.4.3. Functional Relevance

Antigens that are functionally relevant in NSCLC are derived from oncogenic drivers or pathways essential for cancer survival and proliferation. The likelihood of immune invasion is greatly reduced by strategically targeting these antigens, as cancer cells cannot easily downregulate crucial growth proteins withoutcompromising the overall survival. Examples such as alpha-enolase (ENO1) facilitate self-renewal through the AMPK/mTOR signaling pathway, as well as MET, HER2,

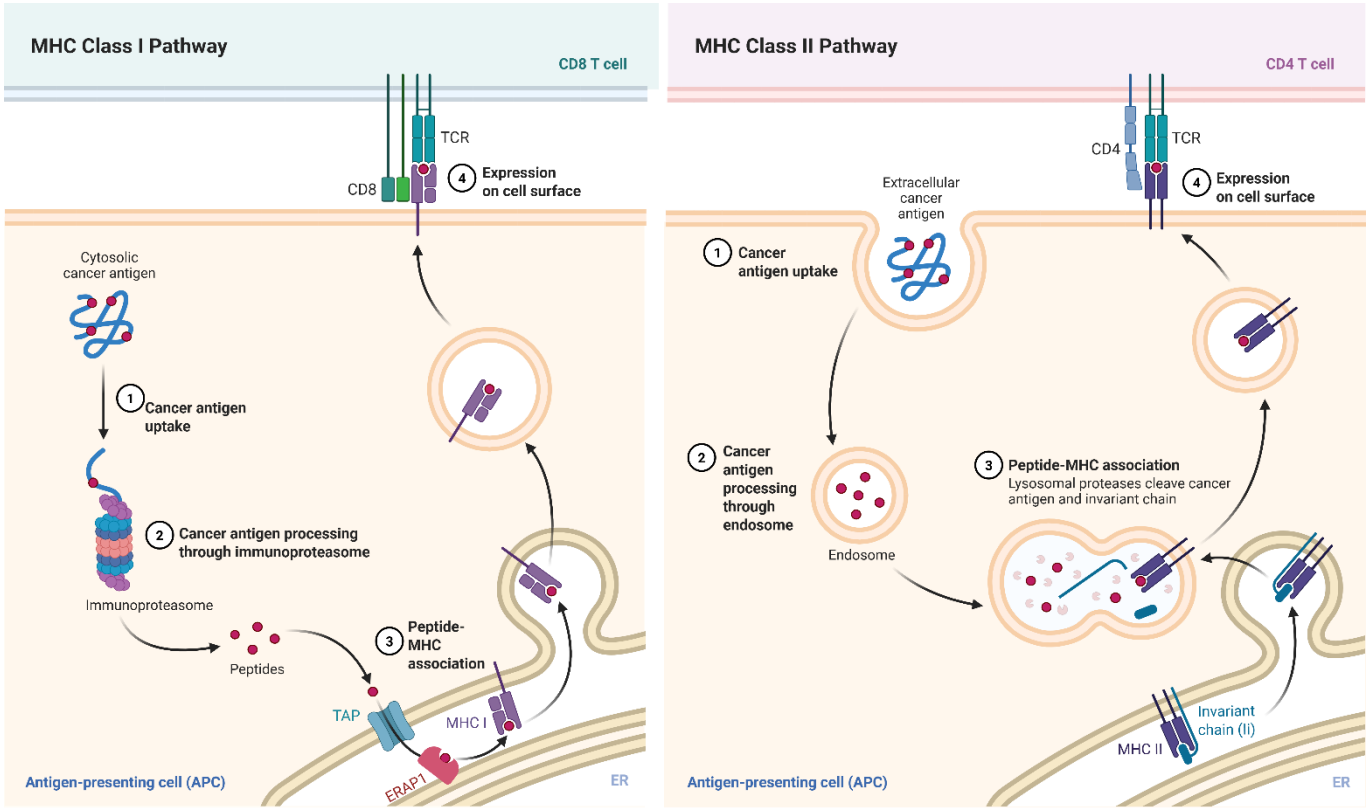

Figure 2. Antigen processing and presentation in cancer. Adapted from Lau et al. [60] and visualized using Biorender.

and MDM2, which are vital for tumor progression. EGFR and KRAS driver-mutation-associated antigens promote tumor proliferation and survival and are functionally relevant as targets. Immunotherapy targeting these antigens limits cancer cells' ability to evade through antigen loss, thereby improving treatment persistence [60–63].

2.4.4. MHC Class I and II Presentation

Antigen presentation via class I and class II MHC plays a key role in how therapeutic vaccines for NSCLC interact with T lymphocytes (Figure 2). Presentation in the MHC class I pathway is primarily responsible for the processing of intracellular antigens. Intracellular antigens undergo degradation into peptide fragments by the immunoproteasome in the cytosolic compartment. Then, transported to the endoplasmic reticulum (ER) via the transporter associated with antigen processing (TAP) and further cleaved by endoplasmic reticulum aminopeptidase 1 (ERAP1) to achieve the required length before being assembled into MHC class I molecules. Afterward, it is translocated to the cell membrane for CD8+ recognition. This pathway facilitates the direct recognition and elimination of tumor cells by CD8+ T cells [60].

In contrast, the MHC class II antigen presentation pathway is responsible for presenting exogenous antigens, in which antigen-presenting cells (APC) internalize and process extracellular antigens in the endolysosomal compartment. The generated peptide fragments undergo degradation of invariant chain (Ii) and CLIP fragments from the peptide binding cleft before being loaded onto MHC class II molecules. The resulting peptide-MHC class II complex is then translocated to the cell surface, where interaction with CD4+ occurs. Thereby, providing cytokines and co-stimulatory signals necessary to maintain and enhance CD8+ and B cell responses. Overall, efficient antigen processing and presentation via MHC class I and II pathways ensure that NSCLC vaccines can trigger a coordinated cellular immune response necessary for effective cancer elimination [60].

2.4.5. Building a Therapeutic Cancer Vaccine

Effective cancer immunization depends on four interrelated components: cancer antigens, formulation, adjuvant, and delivery mechanism (Figure 3). All of these components significantly influence the effectiveness of NSCLC vaccines. Cancer antigens include TAA and TSA, with a growing preference for TSA due to its origin from tumor-specific mutations, recognition as non-self, and independence from central tolerance mechanisms. These antigens can be delivered as whole-tumor or cell-based formulations, which risk diluting critical epitopes among many self-proteins [56]. On the other hand,

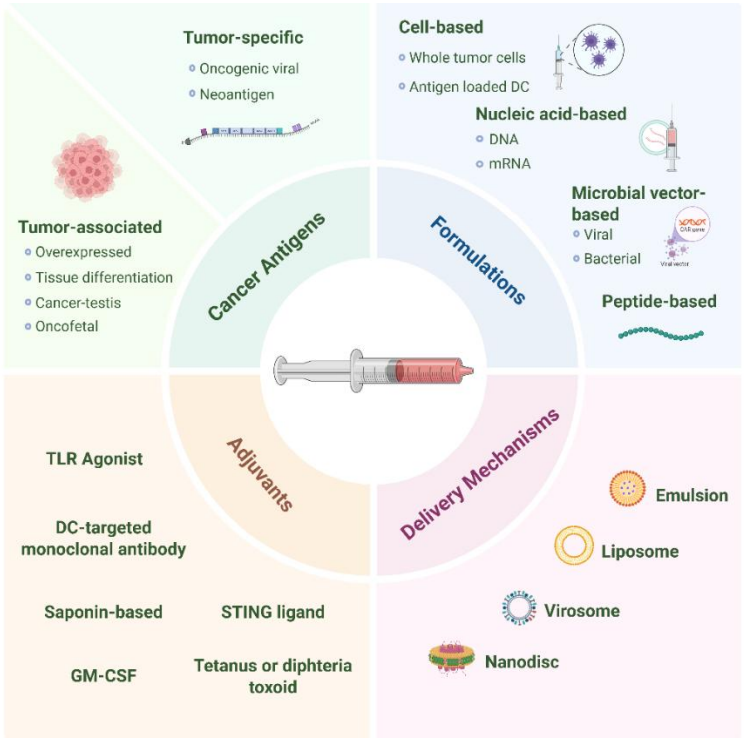

Figure 3. Components of a vaccine. Adapted from Hu et al. [56] and visualized using Biorender.

more precisely defined protein, peptide, or nucleic acid constructs coordinate the immune response to target immunogenic epitopes. Given that antigens alone rarely breach tolerance, the addition of adjuvants is crucial for facilitating dendritic cell activation and T cell maturation [36]. Meanwhile, delivery systems such as water-in-oil emulsions (e.g., Montanide), liposomes, virosomes, and nanodiscs protect the antigenic load, enhance uptake and processing by APC, and enhance T cell responses [56].

2.4.6. Computational Considerations in Designing NSCLC Therapeutic Vaccines

The rational selection of antigens for NSCLC therapeutic vaccine depends on clear immunological and computational criteria. For successful T cell recognition, MHC-binding affinity predictions are often used as thresholds for epitope prioritization. MHC class I and II binding thresholds are commonly defined using percentile rank and binding affinity (IC_{50}). Across therapeutic cancer vaccine studies, predicted MHC binding threshold of IC_{50} < 50 nM or percentile rank <0.5% is commonly adopted, as strong binders are commonly adopted [64]. Modern pipelines rely on NetMHCpan/NetMHCiipan, MHCflurry, MixMHCpred, pVACtools, and other related tools as core components of epitope prediction and prioritization [64–66]. Collectively, these quantitative parameters enable antigen selection beyond qualitative reasoning and lead to reproducible, clinically applicable vaccine designs [67].

3. Peptide Vaccines in NSCLC

3.1. Mechanistic Basis and Design Principles

Peptide-based vaccines targeting NSCLC are designed to deliver antigens to the immune system that effectively activate T lymphocytes. Short peptides (8-11 amino acids) can bind directly to MHC class I molecules on the surface of APC, which triggers a CD8+ response. Short peptides are easy to synthesize, cost-effective, but may not fully activate T cells due to presentation by non-professional APC. In addition, the human leukocyte antigen (HLA) type that the peptide binds to is limited, which restricts its use in specific populations. In contrast, a synthetic long peptide vaccine (SLP) of 11-30 amino acids requires processing by specialized APC. It can be presented on MHC class I and II molecules, thereby enabling more coordinated CD8+ and CD4+ responses and promoting epitope spreading [68].

3.1.2. Antigen-Presenting Cells, Cross-Presentation, and Adjuvants

In bioinformatics, the functions of APCs and cross-presentation mechanisms are inferred indirectly from in silico simulations of antigen processing and MHC loading, rather than from direct empirical experiments. The epitope prediction framework generally combines proteasomal cleavage algorithms, MHC class I and II binding, and TAP transport to estimate the efficiency of vaccine candidates. These computational models are crucial for predicting which peptides are likely to be

involved in cross-presentation pathways to elicit robust CD8+ response against cancer antigens [69, 70].

3.1.3. Epitope-HLA Considerations in NSCLC

Epitope-HLA interactions in NSCLC primarily focus on predicting epitopes that will be presented in genetically heterogeneous populations. Here, multiepitope vaccine formulations are constructed by selecting peptides predicted to bind to multiple common HLA alleles. These include binding of class I epitopes to various HLA-A or HLA-B molecules and class II epitopes to various HLA-DR, HLA-DP, or HLA-DQ molecules. In silico assessments of HLA coverage, epitope redundancy, and potential overlap with self-peptides ensure optimal population coverage and mitigate the risk of inadequate epitope presentation [71].

3.2. Clinical Studies of Peptide-Based Vaccines in NSCLC

Peptide vaccines are currently being explored as a therapeutic option in NSCLC and have shown promising safety and immunogenicity in early clinical trials. GV1001, a peptide-derived hTERT with strong binding to MHC class II, demonstrates safety and immunogenic capability in a phase I/II study. Recently, the personalized neoantigen vaccine OSE2101 has attracted attention for its ability to elicit a stronger immune response and improve survival compared with chemotherapy in certain advanced NSCLC patients. These highlight the clinical potential of peptide-based vaccines designed for NSCLC [25].

4. Dendritic Cell (DC) Vaccines

4.1. Mechanism of DC Vaccines

Dendritic cell (DC)-based vaccines are personalized immunotherapy approaches that harness the unique ability of dendritic cells to present antigens and activate tumor-specific T cells. Ex vivo culture is the conventional method for inducing dendritic cells from monocytes in the patient's peripheral blood, then loading them with cancer antigens such as whole tumor lysates, specific peptides, mRNA, or apoptotic bodies [72]. Maturation of this platform is achieved using cytokines or pathogen-related stimuli before reinfusion. After administration, mature DCs migrate to regional lymph nodes to present antigens via MHC molecules to naive CD8+ and CD4+ T cells, which triggers clonal expansion and differentiation into effector cells [73].

4.2. Clinical Studies of NSCLC DC Vaccines

Clinically, DC vaccines for NSCLC have been shown to be safe and capable of eliciting tumor-specific T cell responses. However, varying DC quality plays a role in the rarity of marked tumor regression [51]. DCVAC/LuCa was evaluated in a phase II trial in advanced NSCLC, showing a favorable safety profile and improved overall survival as a combination therapy to chemotherapy [74]. Additionally, WT1 peptide DC vaccines have also demonstrated immunogenicity and prolonged progression-free survival in small NSCLC cohorts [75].

5. Nucleic Acid (DNA and mRNA) Vaccines in NSCLC

5.1. Mechanism of DNA/mRNA Vaccines

Nucleic acid-based vaccines for NSCLC use DNA or mRNA constructs to trigger in vivo expression of tumor antigens by delivering genetic instructions that encode tumor antigens, which are then processed and presented on MHC class I and II. This antigen presentation enables the activation of CD8+ and CD4+ T cells. Its plasmids also act as intrinsic adjuvants by activating innate sensors, such as TLRs and cGAS-STING, to promote inflammatory cytokine production and dendritic cell maturation. This platform is designed to balance increased reactivity or reduced antigen expression due to excessive detection [25, 76–78].

DNA and mRNA vaccines differ fundamentally in delivery, intracellular trafficking, and expression kinetics. DNA vaccines are typically delivered via electroporation, which permits nuclear entry for transcription [79]. Whereas mRNA vaccines rely on lipid nanoparticle (LNP) for cellular uptake and endosomal escape, they also function directly in the cytoplasm [80]. Additionally, mRNA vaccines are usually formulated with nucleoside-modified mRNA to enhance translational efficiency and protein expression, as well as to reduce innate immune overactivation [81].

5.2. Clinical Studies of Nucleic Acid-Based Vaccine in NSCLC

The majority of early clinical trials are mRNA vaccines, reflecting their favorable safety profile and efficient antigen expression. One of the earliest mRNA vaccine candidates, CV9201, encoded five shared TAAs, including NY-ESO-1, MAGE-1, MAGE-C2, survivin, and 5T4. In a phase I/IIa trial conducted in 46 patients with advanced NSCLC, CV9201 showed good safety and induced antigen-specific T cell responses in a substantial proportion of patients [82]. Formulation expansion was done by incorporating additional antigens, including MUC1, in the CV90202 vaccine. It was evaluated in combination with radiotherapy and an immune checkpoint inhibitor, with demonstrated broad immune activation and manageable toxicity. However, durable clinical benefit remained confined to selected patient subsets [83]. Moreover, personalized neoantigen has emerged as a strategy to overcome immune tolerance associated with shared TSA. Vaccine encoding patient-specific neoantigens, such as

mRNA-4157/V940, has demonstrated encouraging survival benefits in melanoma as a combination therapy and is currently under evaluation for NSCLC [84].

6. Microbial Vector Vaccines

6.1. Mechanism of Microbial Vector-Based Vaccines and Their Clinical Studies in NSCLC

Microbial vector-based vaccines targeting NSCLC employ genetically modified viruses or bacteria as delivery vehicles to facilitate in vivo expression of tumor-related antigens by introducing them into host cells. These vectors trigger innate immune response via pathogen-associated molecular patterns (PAMPs), thereby inducing dendritic cell maturation, type I interferon signaling, and effective antigen processing [85]. Consequently, vector-encoded tumor antigens are presented via MHC class I and II pathways, fostering $CD8^+$ T cell and $CD4^+$ T cell responses. Microbial vector vaccines facilitate prolonged in vivo antigen expression and robust immune priming, eliminating the requirement for exogenous adjuvants [85].

6.2. Clinical Studies of Microbial Vector-Based Vaccine in NSCLC

The poxvirus-based vaccine TG4010 (MVA-MUC1-IL-2) is the most clinically studied microbial vector in NSCLC, encoding the TAA MUC1 and interleukin-2 to stimulate immune responses. Early-phase trials combining TG4010 showed an acceptable safety profile and induction of MUC1-specific $CD8^+$ T cell responses, but clinical benefits were modest and limited to certain patient subsets [86, 87]. Other viral vector platforms, including adenovirus, have entered early clinical trials but have not advanced to late-phase trials, reflecting challenges in efficacy and translation [25, 87]. Viral vectors are effective at inducing $CD8^+$ T cell responses but are limited by pre-existing antiviral immunity, which reduces transgene expression and complicates repeated dosing [86, 87]. In contrast, bacterial vectors such as Listeria monocytogenes and Salmonella species elicit strong innate immune stimulation and preferentially target APC [88]. However, their clinical development has been constrained by safety concerns about the risk of systemic inflammation in immunocompromised patients [89].

7. Limitations and Future Directions

7.1. Limitations of Therapeutic Vaccines in NSCLC

Therapeutic vaccines for NSCLC face several intrinsic limitations that impact their biological promise. Patients administered with NSCLC vaccines often have undergone intensive treatment where antigen exposure, prior therapy, and systemic inflammation associated with cancer compromise immune systems. In this context, vaccines must elicit renewed T cell responses in immunosuppressive environments. Additional barriers include immune tolerance to tumor antigens similar to self-antigens, significant antigen heterogeneity within tumors, low intrinsic immunogenicity, and challenges in practical vaccine delivery with marked significance for platforms that rely on strong in vivo infection of APC [90].

7.2. Future Directions for Therapeutic Vaccines in NSCLC

Future directions must address the challenges mentioned, including the need for an extensive selection of antigens, a vaccine platform, and routes of administration to elicit the desired innate and adaptive immune responses. This strategic integration can remodel TME, promote T cell migration and retention, or alleviate immune checkpoint-mediated exhaustion. Simultaneously, the integration of high-resolution immune monitoring techniques will be crucial in correlating specific design attributes and combinations with in situ immune changes and clinical outcomes. This, in turn, facilitates mechanism-based optimization of NSCLC vaccine therapy rather than relying on trial-and-error methods [90].

4. Conclusions

Therapeutic cancer vaccines for NSCLC have been examined in this review to explain how various platforms, such as peptide-based vaccines, dendritic cell-based vaccines, nucleic acid-based vaccines, and microbial vector-based vaccines, aim to elicit effective antitumor immunity and to identify their clinical efficacy limitations. Through various studies, NSCLC has been identified as an immunologically complex cancer, in which TAA and TSA present diverse yet heterogeneous target landscapes. Simultaneously, factors such as immunoediting, impaired antigen presentation, and immunosuppressive TME hinder vaccine-mediated responses.

Important clinical observations indicate that most NSCLC vaccine platforms are safe and can elicit antigen-specific cellular immune responses. However, moderate and inconsistent survival benefits are provided by these interventions, particularly in patients who have undergone extensive prior treatment and are in advanced stages of disease. Major barriers include tolerance to self-like antigens, antigen heterogeneity, low immunogenicity, and complex manufacturing and suboptimal in vivo delivery for nucleic acid-based vaccines.

The existing literature emphasizes that future progress will depend on the development of more rigorous and mechanism-based vaccine design protocols. This

includes data-driven antigen and epitope selection, prioritizing clonally expressed and functionally relevant antigens, platforms that optimally facilitate the desired innate and adaptive immune responses, and strategic combinations to enhance T cell maturation and effector function. In conclusion, therapeutic cancer vaccines for NSCLC show significant biological potential but remain underdeveloped clinically. Realizing this potential requires a comprehensive approach that integrates advances in antigen discovery, platform engineering, TME modification, and biomarker-driven clinical development.

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