

The Potential of Molecular Vaccines in the Prevention of Breast Cancer

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Abstract: Breast cancer is the most common malignant tumour among women worldwide and poses a serious threat to public health; the development of highly effective and safe preventive measures is key to reducing its disease burden. As a highly promising immunopreventive strategy, the potential of molecular vaccines in breast cancer prevention has attracted considerable attention. This paper adopts an 'Immunological Basis -- Platform Technology -- Prevention Strategy' framework to systematically reviews the immunological theoretical basis of molecular vaccines in breast cancer prevention, the technical characteristics and preclinical evidence of the three mainstream vaccine platforms (nucleic acid vaccines, peptide vaccines and cell-based vaccines), as well as the latest advances in immunological intervention strategies for ductal carcinoma in situ (DCIS). It comprehensively explores the feasibility of applying molecular vaccines to breast cancer prevention, providing theoretical references and insights for subsequent related research and clinical translation.

Keywords: Breast Cancer; Molecular Vaccines; Genetic Vaccine; Peptide Vaccine.

1. Introduction

Breast cancer is the most common malignant tumour among women worldwide; it is estimated that there are approximately 2.3 million new cases and nearly 700,000 deaths annually. Although advances in early screening and systematic treatment have significantly improved patient prognosis, the incidence of breast cancer continues to rise, making the development and optimisation of prevention strategies crucial for controlling the burden of the disease[1]. Currently, primary prevention of breast cancer relies primarily on two approaches: chemoprevention—represented by selective oestrogen receptor modulators and aromatase inhibitors, which reduce the risk of hormone receptor-positive breast cancer by blocking the oestrogen signalling pathway; and prophylactic surgery—including bilateral mastectomy and oophorectomy with salpingectomy, primarily indicated for carriers of high-risk gene mutations such as BRCA1/2. However, chemoprevention faces challenges such as low adherence and side effects including thromboembolism and endometrial cancer, whilst prophylactic surgery is irreversible and has a significant impact on quality of life; neither approach is well-suited to meeting the prevention needs of the general population on a large scale[2].

Molecular vaccines offer a novel approach to breast cancer prevention. Unlike traditional passive prevention strategies, vaccine-based prevention aims to utilise the immune system's active surveillance and memory functions to identify and eliminate abnormal cells at the precancerous stage, thereby achieving 'immune interception'[3]. In recent years, with the identification of key antigens such as HER2 and α -lactalbumin, breakthroughs in novel delivery systems, and an in-depth analysis of the immune microenvironment of ductal carcinoma in situ (DCIS), the scientific basis for the use of molecular vaccines in breast cancer prevention has gradually matured. As a precursor to invasive breast cancer, approximately half of DCIS cases may progress to invasive cancer if left untreated; therefore, 'immune interception' at

the DCIS stage to prevent its progression to invasive cancer represents an important direction in breast cancer prevention research[2].

This paper systematically evaluates the applicability and clinical translation potential of molecular vaccines in breast cancer prevention, following the sequence of 'immunological basis—platform technology—prevention strategies'. It does so by examining three dimensions—the feasibility of immunological mechanisms, the maturity of technological platforms, and clinical application scenarios—using chemoprevention and prophylactic surgery as control baselines.

2. Immunological Basis and Key Challenges of Molecular Vaccines for Breast Cancer Prevention

The immunological basis for the use of molecular vaccines in breast cancer prevention rests on two core theories: firstly, the theory of tumour immune surveillance, whereby a healthy immune system is capable of recognising and eliminating newly emerging tumour cells; and secondly, the abnormal expression of tumour-associated antigens (TAAs) during the precancerous stage. However, in the process of translating theory into clinical practice, the triple barriers of immune tolerance, antigenic heterogeneity and immunological ageing present biological challenges that must be overcome.

2.1. Tumour Immune Surveillance and Immune Editing in Breast Cancer Development

The theory of tumour immune surveillance posits that the adaptive immune system continuously recognises and eliminates immunogenic transformed cells during the early stages of tumour development. However, tumour cells gradually acquire immune resistance through the three stages of immune editing—elimination, equilibrium and escape[4]. In the development of breast cancer, this process of immune editing correlates closely with the histological

progression of breast ductal epithelium from normal to atypical hyperplasia, and subsequently to ductal carcinoma in situ (DCIS) and invasive carcinoma.

Studies have shown that the DCIS stage corresponds to the equilibrium phase of immune editing: the density and functional status of tumour-infiltrating lymphocytes (TILs) in DCIS reflect both the residual capacity of the host's anti-tumour immunity and predict the risk of progression. A systematic analysis of the DCIS immune microenvironment has revealed that high-density CD8⁺ TILs are associated with a lower risk of recurrence, whilst the upregulation of the immune checkpoint molecule PD-L1 in some DCIS cases suggests the early initiation of immune evasion[5]. These immunological characteristics establish DCIS as an ideal window for preventive vaccine intervention—the immune system has not yet completely lost its ability to recognise tumour antigens, but there are already signs of a weakened immune response that can be enhanced by vaccination[2].

2.2. Antigen Selection for Preventive Vaccines: from TAA to 'Retired' Tissue Proteins

Antigen selection strategies for preventive vaccines have evolved from traditional tumour-associated antigens to 'retired' tissue-specific proteins. Traditional TAAs include HER2, MUC1, Mammaglobin-A and hTERT, among others; these proteins are abnormally overexpressed or undergo post-translational modifications in breast cancer cells, constituting 'non-self' signals recognisable by the immune system. In breast cancer, abnormal glycosylation of MUC1 exposes peptide epitopes that are normally masked, making it a preferred target for polypeptide vaccine design; Studies have confirmed that conjugating MUC1 glycopeptides to a tetanus toxoid carrier can induce strong humoral and cellular immune responses in mouse models and significantly inhibit breast tumour growth[6].

In recent years, the newly proposed concept of 'retired tissue-specific proteins' has opened up new avenues for antigen selection in preventive vaccines. Taking α -lactalbumin as an example, this protein is expressed only in mammary tissue during lactation; in postmenopausal women who have completed lactation, α -lactalbumin is no longer expressed in normal tissue but can be reactivated in breast cancer cells. This indicates that vaccines targeting α -lactalbumin are associated with minimal toxicity toward normal tissues, significantly widening the safety window for preventive vaccines in healthy populations[7]. The core concept of this strategy lies in restricting the immune attack to 'retired' self-proteins that are expressed only in the tumour state, thereby circumventing the autoimmune risks faced by traditional TAA vaccines.

2.3. Immune Tolerance, Heterogeneity and Immunological Ageing: Biological Barriers to Preventive Vaccines

Despite a solid theoretical foundation in immunology, the translation of preventive vaccines from the laboratory to clinical practice faces three biological barriers. Firstly, there is central and peripheral immune tolerance—tumour-associated antigens (TAAs) are essentially self-proteins; the negative selection of autoreactive T cells in the thymus and the immunosuppressive effects of peripheral regulatory T cells (Tregs) jointly maintain a state of immune tolerance towards TAAs, making it difficult for vaccines to induce an effective anti-tumour immune response[8].

Secondly, there is tumour antigenic heterogeneity. Breast cancer exhibits significant antigenic heterogeneity both in terms of molecular subtypes and between individuals; a single-antigen vaccine is unlikely to cover all breast cancer subtypes.

Thirdly, there is immunological ageing, which is particularly important for breast cancer prevention strategies targeting middle-aged and elderly women. Studies have shown that with advancing age, the antigen-presenting capacity of dendritic cells (DCs) declines, the naive T-cell pool shrinks, and T-cell receptor diversity decreases; these changes collectively result in the intensity of the immune response induced by vaccines in elderly high-risk populations being significantly lower than in younger individuals[9]. Furthermore, the chronic, low-grade inflammatory microenvironment in breast tissue may further attenuate vaccine efficacy by promoting the recruitment of immunosuppressive cells.

3. Technical Characteristics and Research Progress of the Three Major Molecular Vaccine Platforms

Molecular vaccines, as an emerging preventive and therapeutic strategy, aim to combat breast cancer cells by activating the body's immune system. Currently, molecular vaccines for breast cancer are primarily categorised into three mainstream platforms: nucleic acid vaccines, peptide vaccines and cell-based vaccines. Each platform possesses unique characteristics, mechanisms of action and current research status.

3.1. Nucleic Acid Vaccines

DNA vaccines deliver genes encoding tumour antigens to host cells via plasmid vectors, utilising the host cell's transcription and translation mechanisms to express antigenic proteins, which subsequently activate CD8⁺ and CD4⁺ T-cell immune responses via the MHC-I and MHC-II pathways, respectively. DNA vaccines have demonstrated a favourable safety profile and broad-spectrum immune activation capacity in breast cancer models; however, the low transfection efficiency and insufficient immunogenicity of naked DNA remain the primary bottlenecks limiting their clinical translation[10]. Physical delivery techniques such as electroporation and gene guns can improve the transfection efficiency and immunogenicity of DNA vaccines to some extent, but they increase the complexity of clinical procedures.

The successful validation of mRNA vaccines during the COVID-19 pandemic has greatly advanced their prospects for application in cancer prevention. Compared with DNA vaccines, mRNA vaccines do not need to enter the cell nucleus but are translated directly in the cytoplasm, thereby eliminating the theoretical risk of genomic integration, whilst offering higher transfection efficiency and faster antigen expression kinetics. The maturation of the lipid nanoparticle (LNP) delivery system represents a key technological breakthrough enabling mRNA vaccines to progress from concept to clinical application; For targets such as HER2 and MUC1, mRNA vaccines have already induced antibody titres and T-cell responses superior to those of DNA vaccines in mouse models[11]. However, the long-term safety of mRNA vaccines—particularly the chronic toxicity of LNPs and the immunogenicity of repeated dosing—still requires further validation in preventive clinical trials involving healthy

populations.

For both DNA and mRNA platforms, the selection of target antigens and the optimisation of immunogenicity remain key factors determining the success of preventive nucleic acid vaccines[4]. In a preventive context, vaccines need to induce not only therapeutic immune responses against established tumours, but also a persistent immune surveillance capability that can be activated at the earliest stages of precancerous lesions.

3.2. Peptide Vaccines: Precision Targeting and Immunogenicity-Enhancing Strategies

Peptide vaccines based on chemically synthesized tumor antigen peptide fragments have unique advantages such as extremely high safety, standardized production, favorable consistency between batches and no need for cold-chain transportation, making them theoretically the most suitable vaccine platform for large-scale prophylactic vaccination of healthy populations. However, peptide vaccines display weak immunogenicity when used alone, and immunogenicity-enhancing strategies are therefore required. Three mainstream strategies are currently available: first, conjugation with Toll-like receptor (TLR) agonists; second, multi-epitope tandem design, in which multiple T-cell and B-cell epitopes are concatenated into a single peptide fragment to expand the coverage of immune responses; third, delivery via nanoparticle carriers, where liposomes, polymeric nanoparticles or virus-like particles (VLPs) are adopted for multivalent display to mimic repetitive antigen arrays of pathogens and enhance B-cell receptor cross-linking as well as antibody responses.

It is worth noting that the safety advantages of polypeptide vaccines confer them a unique position in the prevention of breast cancer in healthy populations; however, their clinical value depends on the success of immunogenicity-enhancing strategies. For instance, the combined use of the Azurin and Mammaglobin-A genes resulted in a dual effect of immune system activation and suppression of tumour progression in a BALB/c mouse model, suggesting that a multi-antigen combination strategy may represent a viable approach for the prevention of breast cancer using peptide vaccines[12]. Furthermore, the combination of nanodrug delivery systems with peptide vaccines is emerging as a cutting-edge strategy to overcome inherent limitations such as low immunogenicity and short in vivo half-lives[13].

3.3. Cellular Vaccines: DC Vaccines and Personalised Immune Activation

DC vaccines are a representative example of cellular vaccine platforms. Their core principle involves isolating monocytes or DC precursor cells from a patient's peripheral blood, loading them with tumour antigens in vitro, and then reinfusing them into the patient to utilise the unique ability of DCs as professional antigen-presenting cells to activate the patient's own T-cell immune response. This personalised immune activation strategy has already accumulated preliminary clinical evidence in the treatment of breast cancer.

Autologous DC vaccines loaded with breast cancer cell lysates can polarise a Th1-type immune response in patients and exhibit significant cytotoxic activity against patient-derived breast cancer cells, providing an immunological basis for the expansion of DC vaccines into preventive applications [14]. DC vaccines have demonstrated the ability to induce specific immune responses in various breast cancer subtypes,

including HER2-positive and triple-negative types, whilst exhibiting good safety profiles[15]. The application of DC vaccines for immune interception at the precancerous stage—particularly in DCIS—is a direction worthy of focused exploration[16].

However, the expansion of DC vaccines into preventive settings faces three substantial obstacles: firstly, standardisation of preparation—the preparation of autologous DC vaccines involves multiple stages, including cell isolation, in vitro culture, antigen loading and quality control, making it difficult to ensure consistency between batches; secondly, cost-effectiveness—the high cost of personalised preparation makes it difficult to roll out on a large scale among the healthy population; thirdly, the assessment of preventive efficacy—evaluating the vaccine's preventive effect in healthy populations requires large-scale, long-term randomised controlled trials, the design and implementation of which face dual ethical and statistical challenges[17].

4. DCIS Immunological Interception: From Intervention in Precancerous Lesions to Comparison of Preventive Strategies

DCIS is a clonal proliferation of ductal epithelial cells in the breast that has not breached the basement membrane; it accounts for approximately 20 per cent of newly diagnosed breast cancers. DCIS is not a fatal disease in itself, but some patients may progress to invasive ductal carcinoma. The immune microenvironment of DCIS is in a transitional phase between immune surveillance and immune evasion, providing an ideal intervention window for the 'immune interception' strategy of molecular vaccines[18].

4.1. The DCIS Immune Microenvironment: The Biological Basis for the Transition from Immune Surveillance to Vaccine Intervention

The immune microenvironment of DCIS exhibits transitional characteristics: on the one hand, the infiltration density and subtype composition of TILs in DCIS differ significantly from those in invasive breast cancer. The density of CD8⁺TILs is significantly higher in high-grade DCIS than in low-grade DCIS, whilst the proportion of FOXP3⁺Tregs increases with rising DCIS grade, suggesting that an immunosuppressive microenvironment is gradually established during DCIS progression[5].

On the other hand, the expression patterns of immune checkpoint molecules provide important guidance regarding the timing of vaccine intervention. The expression rate of PD-L1 in basal-like DCIS is significantly higher than in luminal-type DCIS, and it correlates positively with TIL density, suggesting that PD-L1 upregulation may represent an adaptive escape mechanism adopted by tumour cells under immune pressure. Studies analysing the antigen profiles of DCIS and invasive breast cancer have identified a set of candidate antigens that are highly expressed and immunogenic as early as the DCIS stage; these antigens span multiple breast cancer subtypes, providing an experimental basis for antigen selection in DCIS vaccines[19].

These characteristics of the DCIS immune microenvironment suggest that immune interception at the DCIS stage offers a dual advantage: the immune system

retains its ability to recognise and respond to tumour antigens, whilst tumour cells have not yet established fully developed immune evasion mechanisms. This makes it more likely that the vaccine-induced immune enhancement will eliminate abnormal cells before DCIS progresses to invasive cancer.

4.2. Clinical Trials of DCIS Vaccines: Early Evidence for Immune Interception Strategies

Current clinical trials of vaccines for DCIS are primarily focused on HER2 peptide-based vaccines. Vaccines based on HER2-derived peptides such as E75 and AE37 have been the subject of several clinical trials in DCIS patients; preliminary results indicate that these vaccines can induce HER2-specific CD8⁺T-cell responses, with a reduction in DCIS histological grade observed in some patients. HER2 peptide vaccines have demonstrated good safety profiles in DCIS patients, with key immunological endpoints (such as delayed-type hypersensitivity reactions and antigen-specific T-cell proliferation) meeting pre-specified criteria; however, the increase in the rate of pathological complete remission has not yet reached statistical significance[20].

A key challenge facing clinical trials of DCIS vaccines is the lack of validated surrogate endpoints[2]. In therapeutic vaccine trials, objective response rates and progression-free survival are well-established endpoints; however, in a preventive setting, progression from DCIS to invasive cancer typically takes several years, and trials using the incidence of invasive cancer as the primary endpoint require extremely large sample sizes and very long follow-up periods. Therefore, the development of reliable immunological surrogate endpoints is a crucial prerequisite for accelerating the clinical translation of DCIS vaccines.

4.3. Immunological Interception, Chemoprevention and Preventive Surgery: A Three-Dimensional Comparative Analysis

A systematic comparison of molecular vaccine-mediated immune interception with existing breast cancer prevention strategies is a crucial step in assessing its clinical feasibility. The following section provides a cross-comparison of the three strategies across five dimensions: target population, protective efficacy, side effect profile, acceptability and cost-effectiveness.

effectiveness.

In terms of target population, chemoprevention is primarily aimed at high-risk women with a Gail model score of ≥ 1.66 per cent, whilst prophylactic surgery is limited to carriers of confirmed pathogenic mutations such as BRCA1/2. The potential target population for immunological interception using molecular vaccines includes DCIS patients and high-risk individuals who have not yet undergone prophylactic intervention; however, its precise indications remain to be defined by clinical trials. In terms of protective efficacy, tamoxifen in chemoprevention reduces the risk of hormone receptor-positive breast cancer by 30%–65%, whilst bilateral mastectomy as part of prophylactic surgery reduces the risk of breast cancer by over 90% in BRCA mutation carriers[21]. However, the protective efficacy of molecular vaccines remains unknown due to a lack of data from large-scale randomised controlled trials (RCT). In terms of the spectrum of side effects, chemoprevention is associated with systemic side effects such as thromboembolism, endometrial cancer and hot flushes; preventive surgery leads to irreversible changes in body image and surgical complications; and preliminary safety data for molecular vaccines indicate that their side effects are primarily injection-site reactions and flu-like symptoms, suggesting that they are theoretically safer than the former two options. In terms of acceptability, although there is clear evidence-based medical evidence that tamoxifen and aromatase inhibitors reduce the risk of hormone receptor-positive breast cancer, the proportion of eligible high-risk women who actually undergo chemoprevention is less than 20 per cent, primarily due to concerns about side effects and insufficient risk awareness[22]. With regard to preventive surgery, only approximately 30–50 per cent of BRCA mutation carriers opt for prophylactic mastectomy, and this uptake rate is influenced by various factors such as cultural background, age and reproductive plans[23]. Molecular vaccines, due to their non-invasive nature, are theoretically more acceptable; however, this hypothesis still requires validation through empirical research. In terms of cost-effectiveness, chemoprevention has been demonstrated to be cost-effective in high-risk populations; preventive surgery is cost-effective only for BRCA mutation carriers; whilst the cost-effectiveness of molecular vaccines remains to be supported by clinical trial data.

Table 1. A Five-Dimensional Comparison Table of Three Prevention Strategies

strategy	Immunological Interception	Chemoprevention	Preventive Surgery
target population	DCIS patients and high-risk individuals who have not yet undergone prophylactic intervention (its precise indications remain to be defined by clinical trials)	high-risk women with a Gail model score of ≥ 1.66 per cent	carriers of confirmed pathogenic mutations such as BRCA1/2
protective efficacy	Lack of large-scale RCT data renders its protective efficacy undetermined.	Tamoxifen reduces the risk of hormone receptor-positive breast cancer by 30%–65%.	Bilateral mastectomy reduces breast cancer risk by over 90% in BRCA mutation carriers. [21]
side effect profile	Preliminary safety profiles reveal the main adverse events are injection site reactions and influenza-like symptoms.	systemic adverse events such as thromboembolism, endometrial cancer and hot flushes.	irreversible body image alterations and surgical complications.
acceptability	Its non-invasive feature theoretically leads to higher acceptability. (his hypothesis still requires verification via empirical studies.)	Fewer than 20% of eligible high-risk women receive chemoprevention in practice.	Approximately 30%–50% of BRCA mutation carriers opt for prophylactic mastectomy.
cost-effectiveness	Cost-effectiveness evaluation awaits supporting clinical trial data.	Cost-effectiveness has been demonstrated in high-risk groups.	Cost-effectiveness is limited exclusively to BRCA mutation carriers.

Taking the above analysis into account, immunological interception via molecular vaccines offers theoretical

advantages in terms of non-invasiveness and target specificity; however, in terms of protective efficacy and long-term safety, it falls far short of the evidence-based standards established for chemoprevention and prophylactic surgery. Current research gaps are concentrated in three areas: the lack of large-scale clinical trials for preventive vaccines, insufficient data on the long-term persistence of immune protection, and the unclear definition of the population that would benefit from vaccine prevention. The three strategies exhibit a complementary distribution in terms of target population, risk-benefit ratio and acceptability—molecular vaccines may bridge the gap between the poor adherence associated with chemoprevention and the high invasiveness of preventive surgery, and are particularly suitable for moderate-risk individuals with a history of DCIS who refuse chemoprevention or preventive surgery.

5. Conclusion and Outlook

Molecular vaccines for breast cancer prevention are transitioning from theoretical validation to clinical translation. From an immunological perspective, the theory of tumour immune surveillance and the abnormal expression of precancerous antigens provide a clear scientific basis for preventive vaccines; however, the triple biological barriers of immune tolerance, antigenic heterogeneity and immunological ageing must be overcome through the synergistic combination of multi-antigen immunisation strategies and interventions targeting immunological ageing. In terms of technological platforms, mRNA vaccines lead in terms of delivery efficiency and immunogenicity, building on the technical advancements from COVID-19 vaccines; peptide vaccines hold a unique position in the prevention of healthy populations due to their safety advantages; whilst the personalised immune activation strategies of DC vaccines are suitable for the precision prevention of high-risk populations.

Immune interception of DCIS represents the preventive scenario currently closest to clinical translation—the immune microenvironment of DCIS is in a transitional phase between immune surveillance and immune evasion, providing an ideal biological window for vaccine intervention. However, although Phase I/II clinical trials of HER2 peptide vaccines in DCIS patients have preliminarily demonstrated safety and immunogenicity, there remains a significant gap before large-scale clinical application.

The most pressing research gaps in this field currently include: firstly, the need to design and initiate multicentre, randomised, controlled Phase III clinical trials targeting high-risk healthy individuals and DCIS patients, with the incidence of invasive cancer as the primary endpoint, whilst establishing a reliable system of immunological surrogate endpoints; secondly, the need to conduct long-term follow-up studies to assess the durability of vaccine-induced immune protection and to clarify the timing and strategies for booster immunisation; third, there is a need to establish breast cancer risk stratification models based on multi-omics data to precisely identify target populations likely to benefit from vaccine prophylaxis. In the future, key directions for advancing this field will include improvements in the technical maturity of mRNA and peptide vaccine platforms; the design of multi-antigen combination vaccines; strategies to reverse immunological ageing in conjunction with prophylactic vaccines; and optimised combination strategies integrating vaccine prophylaxis with chemoprevention and

preventive surgery.

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