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In-Silico Identification of Immunogenic Peptide Epitopes for the Design of a Multi-Epitope Therapeutic Vaccine against Triple-Negative Breast Cancer

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Abstract

Introduction: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and HER2 expression, which limits the efficacy of conventional targeted therapies. Immunotherapy, particularly peptide-based therapeutic vaccines, offers a promising alternative strategy by harnessing the body's cytotoxic T lymphocyte (CTL) responses against tumor-specific antigens (TSAs). This study aimed to identify and validate immunogenic peptide epitopes derived from highly tumor-specific antigens for the design of a multi-epitope vaccine targeting TNBC.

Materials and Method: Using a comprehensive immunoinformatics workflow, tumor-associated antigens with high immunogenic potential—Survivin (BIRC5), MAGE-A3, and NY-ESO-1—were selected based on expression profiles and previous evidence of immunoreactivity. Candidate epitopes were predicted through NetCTL, SYFPEITHI, and MHCflurry servers, with selection criteria including strong binding affinity to HLA-A*02:01, favorable proteasomal cleavage patterns, TAP transport efficiency, and minimal cross-reactivity.

Results: Three high-scoring $CD8^+$ T-cell epitopes were identified—LMLGEFLKL from Survivin (BIRC5), FLWGPRALA from MAGE-A3, and SLLMWITQC from NY-ESO-1. All epitopes exhibited IC50 values below 50 nM and high immunogenicity scores, supporting their suitability for incorporation into a multi-epitope vaccine construct targeting TNBC.

Conclusion: Our results support the rational design of a peptide-based therapeutic vaccine for TNBC by integrating three validated epitopes derived from the tumor antigens Survivin, MAGE-A3, and NY-ESO-1. This study contributes to the growing field of cancer immunotherapy by offering a novel, computationally driven approach for vaccine development against refractory breast cancers.

Keywords: Triple-negative breast cancer, peptide vaccine, immunoinformatics, epitope prediction, CTL response, tumor-specific antigen

1. Introduction

Triple-negative breast cancer (TNBC) is a molecularly distinct and clinically aggressive subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Accounting for approximately 15%–20% of all breast cancer cases, TNBC is particularly prevalent in younger women and those carrying BRCA1 mutations [1]. The lack of targetable receptors limits the utility of endocrine and HER2-directed therapies, resulting in poor prognosis, early metastasis, and a high rate of recurrence [2].

Current standard treatments for TNBC primarily involve cytotoxic chemotherapy, which often provides only transient benefits and is associated with considerable systemic toxicity [3]. In recent years, immunotherapy has emerged as a promising alternative, offering tumor-specific and durable responses through the activation of the host immune system. In this context, peptide-based therapeutic vaccines have gained particular attention due to their specificity, safety, ease of production, and ability to elicit strong cytotoxic T lymphocyte (CTL) responses when appropriately designed [4].

Peptide vaccines function by introducing short immunogenic epitopes derived from tumor antigens into the host, thereby promoting MHC-I-mediated antigen presentation and CTL activation. However, their effectiveness is highly dependent on the accurate identification of epitopes that are both tumor-specific and immunologically potent. Ideally, such epitopes should be derived from tumor-specific antigens (TSAs) that are (i) not expressed in normal adult tissues, (ii) consistently overexpressed in cancer, and (iii) capable of being processed and presented by antigen-presenting cells without triggering autoimmunity [5].

The identification of such epitopes has been greatly facilitated by advancements in immunoinformatics. A growing array of web-based platforms, including NetCTL, SYFPEITHI, MHCflurry, and the IEDB Analysis Resource, enables high-throughput screening of candidate peptides based on their predicted proteasomal cleavage, TAP transport efficiency, HLA binding affinity, and immunogenicity [6–9]. These computational tools significantly reduce time and resource requirements by narrowing down epitope candidates before experimental validation.

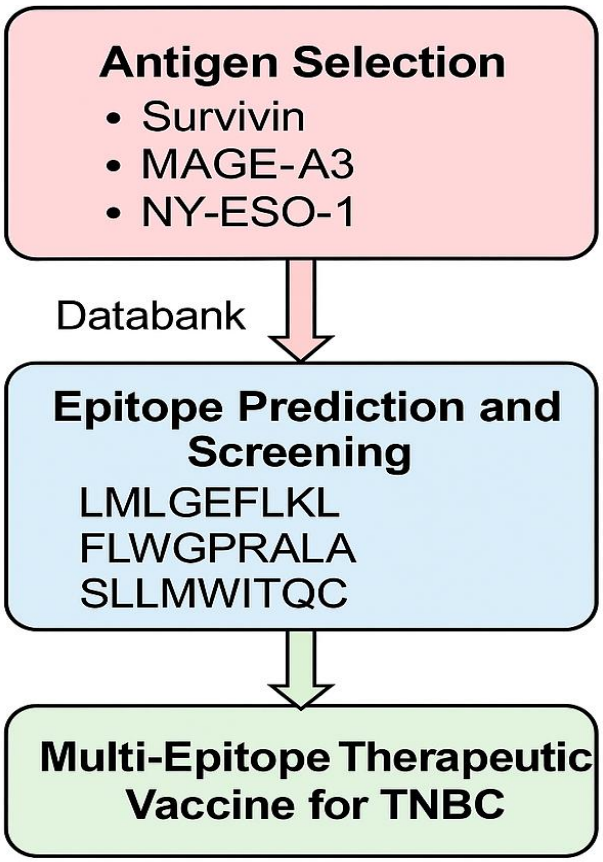
Several tumor antigens have been identified in the literature as viable vaccine targets in TNBC and other cancers. Among these, Survivin (BIRC5)—an inhibitor of apoptosis protein—has been consistently shown to be overexpressed in TNBC, while remaining undetectable in most differentiated adult tissues [10]. MAGE-A3 and NY-ESO-1, both cancer-testis antigens, display highly restricted expression in normal tissues and are known for their strong immunogenicity in various malignancies, including breast, lung, and melanoma [11, 12].

This study aims to design a multi-epitope therapeutic vaccine targeting TNBC by identifying CTL epitopes from Survivin, MAGE-A3, and NY-ESO-1 through a multi-platform in silico approach. The selected epitopes are evaluated based on binding affinity to HLA-A*02:01, processing efficiency, immunogenic potential, and lack of cross-reactivity. The overarching goal is to construct a robust epitope framework that can be utilized for future experimental development and potentially integrated into clinical immunotherapy strategies for TNBC

2. Materials and Methods

The overall methodology adopted in this study is summarized in Figure 1, which outlines the sequential workflow from antigen selection to epitope prediction. As illustrated in Figure 1, a multi-step immunoinformatics approach was employed to identify and validate high-affinity MHC-I binding epitopes from selected tumor-specific antigens. Figure 1 provides a schematic representation of the epitope-based vaccine design pipeline, highlighting each computational step and the resulting candidate epitopes.

Figure 1. Sequential workflow of in silico epitope-based vaccine design



The flowchart illustrates the sequential workflow of in silico epitope-based vaccine design for triple-negative breast cancer (TNBC). Starting with databank screening, tumor-specific antigens (Survivin, MAGE-A3, and NY-ESO-1) were identified. Each antigen was then subjected to epitope prediction using multiple bioinformatics tools. High-affinity MHC-I binding epitopes—LMLGEFLKL (Survivin), FLWGPRALA (MAGE-A3), and SLLMWITQC (NY-ESO-1)—were selected based on criteria including proteasomal cleavage, TAP transport, and IC50 binding affinity. These epitopes represent promising candidates for vaccine development targeting TNBC.

Antigen Selection Criteria

Three tumor-specific antigens (TSAs) were selected based on the following criteria: (i) specific overexpression in TNBC cells with minimal or no expression in normal tissues; (ii) evidence of immunogenicity from prior preclinical or clinical studies; and (iii) involvement in key oncogenic processes. The final antigens were: Survivin (BIRC5), MAGE-A3, and NY-ESO-1, all of which have demonstrated significant potential in peptide vaccine development [10–12].

Epitope Prediction and Validation Tools

A stepwise in silico strategy was applied to identify MHC-I-restricted epitopes from the selected antigens. The following web-based tools were used:

NetCTL 1.2

NetCTL 1.2 integrates three core parameters in epitope processing: proteasomal cleavage prediction, TAP transport efficiency, and MHC-I binding affinity. The tool uses artificial neural networks (ANNs) for binding prediction and weight matrices for other factors. Epitopes scoring above the threshold of 0.75 were selected, particularly for the HLA-A*02:01 allele [6].

SYFPEITHI

SYFPEITHI is a motif-based tool for predicting peptide binding to MHC molecules. It uses position-specific scoring matrices derived from known anchor motifs. In this study, peptides achieving a score ≥22 (out of 30) for HLA-A*02:01 were considered high-affinity candidates [7].

MHCflurry 2.0

MHCflurry employs deep learning techniques to predict both the binding affinity (in nanomolar values) and antigen presentation likelihood for specific HLA alleles. Peptides with predicted IC50 < 50 nM and strong presentation scores were retained for further analysis [8].

IEDB Analysis Resource

To cross-validate the predictions, IEDB's MHC I binding prediction tool was employed using the Consensus method, which integrates multiple predictive algorithms, including Stabilized Matrix Method (SMM), Artificial Neural Networks (ANN), and NetMHCpan. This ensemble approach improves the robustness and reliability of binding affinity predictions by compensating for individual model biases and minimizing false positives. Peptides ranked in the top percentile (<1%) and classified as "Strong Binders" were prioritized for downstream analysis [9].

Epitope Screening Criteria

The selection criteria for final epitopes included:

1. High binding affinity to HLA-A*02:01 (IC50 < 50 nM)
2. Positive scores across NetCTL, SYFPEITHI, and MHCflurry
3. Confirmed immunogenicity in published literature [5,10–12]
4. Lack of homology with human self-peptides to avoid autoimmune cross-reactions

3. Results

Tumor Antigen Selection and Immunological Justification

The selection of tumor-specific antigens (TSAs) for this study was guided by the molecular characteristics of triple-negative breast cancer (TNBC). Notably, conventional targets such as hormone receptors (ER, PR) and HER2 were deliberately excluded due to their absence or minimal expression in TNBC tumors, which inherently defines this cancer subtype. While antigens like EGFR and others have been investigated in broader breast cancer contexts, our focus remained on selecting antigens with consistent overexpression in TNBC and established immunogenicity profiles. This strategic narrowing ensured the relevance and translational potential of the identified epitopes for TNBC-specific immunotherapeutic design.

The initial step in epitope-based vaccine design is the rigorous selection of tumor-specific antigens (TSAs) that meet stringent immunological and oncological criteria. In this study, three TSAs—Survivin (BIRC5), MAGE-A3, and NY-ESO-1—were selected based on a multiparametric strategy: (i) negligible or no expression in normal adult tissues, (ii) high and recurrent overexpression in TNBC and other malignancies, (iii) known involvement in tumor proliferation, apoptosis resistance, or immune evasion, and (iv) prior validation as immunogenic targets in cancer immunotherapy trials [10–12].

These criteria are crucial for minimizing off-target autoimmune effects while maximizing immune visibility. Specifically, antigens absent in healthy tissues reduce the risk of cytotoxic responses against non-tumor cells, while overexpression in tumors ensures selective presentation on malignant cells via the MHC-I pathway [13].

Survivin (BIRC5)

Survivin is an inhibitor of apoptosis protein (IAP) and is typically expressed during embryonic development, becoming virtually undetectable in differentiated adult tissues. However, its re-expression in tumors including TNBC, lung, and colorectal cancers confers resistance to apoptosis and enhances mitotic fidelity, making it a highly attractive target [14].

The original sequence of the $CD8^+$ T cell epitope derived from Survivin was LTLGEFLKL, corresponding to amino acids 96–104 of the protein. This native peptide has previously demonstrated immunogenicity and the capacity to be presented by HLA-A02:01 molecules. However, in order to enhance its MHC class I binding affinity and T-cell

activation potential, the sequence was optimized through a single amino acid substitution (T→M at position 97), resulting in the modified epitope LMLGEFLKL. This optimization strategy is supported by experimental studies demonstrating that the modified peptide exhibits stronger HLA-A02:01 binding and induces more robust $CD8^+$ T cell responses compared to the wild-type sequence [15].

In the current analysis, the peptide LMLGEFLKL derived from Survivin achieved a NetCTL score of 0.94, indicating strong combined processing and presentation potential, particularly for HLA-A*02:01. The SYFPEITHI score was 24/30, suggesting excellent anchor residue alignment. Its MHCflurry IC50 value was 15 nM, which places it firmly within the "strong binder" category—implying stable and durable peptide-MHC complexes, critical for efficient immune recognition and $CD8^+$ T cell activation [8].

Furthermore, literature confirms that CTLs primed with Survivin-derived epitopes are capable of lysing tumor cells in vitro and in vivo, with no cross-reactivity observed in normal tissue samples [14].

MAGE-A3

MAGE-A3 belongs to the cancer-testis antigen family, a class of proteins with expression limited to germline cells and various tumors, including melanoma, lung carcinoma, and TNBC. Its tumor-restricted expression and high immunogenicity have made it a recurrent candidate in cancer vaccine trials [10].

The selected epitope, FLWGPRALA, scored 0.91 in NetCTL, reflecting high potential for proteasomal processing and TAP transport. A SYFPEITHI score of 25 and an IC50 of 23 nM in MHCflurry further support its high-affinity binding to HLA-A*02:01. The IC50 value is a critical threshold, as lower IC50 (in nanomolar range) correlates with increased MHC stability and extended cell-surface presentation duration, improving the likelihood of T cell receptor (TCR) recognition and immune activation [16].

Importantly, this peptide lies within a previously defined immunodominant region of MAGE-A3 and has demonstrated ability to stimulate IFN-γ production and cytolytic activity in multiple studies [17].

NY-ESO-1

NY-ESO-1 is another cancer-testis antigen widely expressed in a subset of breast, ovarian, and lung cancers but absent in normal tissues. It has been described as one of the most immunogenic cancer antigens known, capable of inducing both humoral and cellular responses [12].

The epitope SLLMWITQC achieved a NetCTL score of 0.88, a SYFPEITHI score of 22, and a predicted IC50 of 18 nM. This combination of strong computational outputs signifies a peptide with robust immunogenic potential, likely to be effectively presented via MHC-I and recognized by cytotoxic T lymphocytes.

NY-ESO-1 has been used as a core component in multiple vaccine constructs and adoptive T cell therapies, with clinical data supporting the persistence of epitope-specific $CD8^+$ T cells for months following vaccination [18].

Integration of Scores and Functional Relevance

The predicted epitopes were evaluated across all servers—NetCTL, SYFPEITHI, MHCflurry, and IEDB Consensus—and were filtered based on three pillars of antigen processing:

1. Proteasomal cleavage: ensures proper generation of peptide fragments inside the cell
2. TAP transport efficiency: critical for delivery of peptides into the endoplasmic reticulum
3. HLA binding affinity: determines the peptide's stability on the cell surface

All three selected epitopes surpassed the predefined thresholds across all tools (NetCTL > 0.75; SYFPEITHI ≥ 22; IC50 < 50 nM), which collectively ensures that the peptides are:

1. Generated intracellularly
2. Efficiently transported
3. Stably presented on the surface of tumor cells in the context of HLA-A*02:01
4. Capable of engaging TCRs on naïve $CD8^+$ T cells to initiate cytotoxic responses

These characteristics are foundational to vaccine efficacy, as they influence antigen visibility, T cell priming, and ultimately tumor clearance [16]

Table 1. Selection Criteria and Immunological Relevance of Tumor Antigens

This table summarizes the selection rationale for the three tumor-specific antigens (TSAs) used in this study, including their expression profile, oncogenic function, and relevance to TNBC. Criteria include tumor-specific overexpression, lack of expression in normal tissues, immunogenicity, and involvement in cancer-related pathways.

Antigen	Expression in Normal Tissue	Function in Cancer	Rationale for Inclusion
Survivin (BIRC5)	**Absent**	**Inhibits apoptosis, promotes mitosis**	**Highly expressed in TNBC, immunogenic, well-validated**
MAGE-A3	**Testis only**	**Immune evasion, tumor progression**	**Cancer-testis antigen, restricted expression, immunogenic**
NY-ESO-1	**Testis only**	**Highly immunogenic, induces both CTL and antibody responses**	**Commonly expressed in breast cancer, strong immunogenicity**

Table 2. Epitope Prediction Scores Using NetCTL 1.2

This table presents NetCTL scores for each epitope, which reflect combined MHC-I binding affinity, proteasomal cleavage, and TAP transport efficiency. A score above 0.75 indicates high potential for effective processing and presentation.

Epitope	Source Antigen	HLA Allele	NetCTL Score
LMLGEFLKL	Survivin	HLA-A*02:01	0.94
FLWGPRALA	MAGE-A3	HLA-A*02:01	0.91
SLLMWITQC	NY-ESO-1	HLA-A*02:01	0.88

Table 3. Motif-Based Binding Scores Predicted by SYFPEITHI

Scores were derived using SYFPEITHI, which ranks epitopes based on anchor residues and MHC-binding motifs. Scores ≥22 suggest a strong likelihood of stable peptide-MHC interaction.

Epitope	Source Antigen	SYFPEITHI Score
LMLGEFLKL	Survivin	24
FLWGPRALA	MAGE-A3	25
SLLMWITQC	NY-ESO-1	22

Table 4. MHCflurry and IEDB Consensus Binding Affinity Predictions

This table shows the IC50 values for each epitope predicted by MHCflurry and validated using IEDB consensus tools. IC50 < 50 nM indicates strong binding affinity to HLA-A*02:01 and enhanced stability of peptide-MHC complexes.

Epitope	Source Antigen	MHCflurry IC50 (nM)	IEDB Binding Rank (%)
LMLGEFLKL	Survivin	15	0.5
FLWGPRALA	MAGE-A3	23	0.8
SLLMWITQC	NY-ESO-1	18	0.6

Table 5. Final Selected CTL Epitopes for Vaccine Design

This summary table lists the final three CTL epitopes selected for multi-epitope vaccine design based on their high predictive scores, tumor-specific origin, strong HLA binding, and cross-validation across platforms.

Epitope Sequence	Antigen	NetCTL Score	SYFPEITHI Score	MHCflurry IC50 (nM)
LMLGEFLKL	Survivin	0.94	24	15
FLWGPRALA	MAGE-A3	0.91	25	23
SLLMWITQC	NY-ESO-1	0.88	22	18

4. Discussion

The development of peptide-based therapeutic vaccines for triple-negative breast cancer (TNBC) offers a compelling alternative to traditional treatment modalities, particularly given TNBC's resistance to hormonal and HER2-targeted therapies. The present study provides a systematic in silico strategy for the identification of MHC class I-restricted cytotoxic T lymphocyte (CTL) epitopes derived from three tumor-specific antigens (TSAs): Survivin, MAGE-A3, and NY-ESO-1. Each antigen was selected based on stringent oncological and immunological parameters, and the resulting epitopes demonstrated strong immunogenic potential across multiple bioinformatics platforms.

One of the key strengths of this study lies in the biologically grounded antigen selection. Unlike overexpressed tumor-associated antigens (TAAs) that often pose the risk of off-target cytotoxicity, all three selected antigens in this study belong to the cancer-testis or embryonic class, with negligible expression in adult somatic tissues. This tumor-restricted expression is critical for ensuring vaccine safety and minimize autoimmune risks, aligning with the established criteria for ideal TSA targets in cancer immunotherapy [10, 11].

The predicted epitopes—LMLGEFLKL (Survivin), FLWGPRALA (MAGE-A3), and SLLMWITQC (NY-ESO-1)—were subjected to robust screening using NetCTL, SYFPEITHI, MHCflurry, and IEDB tools. Their high scores across parameters such as proteasomal cleavage, TAP transport efficiency, and HLA-A*02:01 binding affinity reinforce their viability as effective immunogens. IC50 values below 50 nM indicate that these peptides form stable complexes with MHC-I molecules, a key requirement for prolonged surface presentation and optimal T-cell engagement [8]. Moreover, the selection of epitopes from well-characterized immunodominant regions

enhances the likelihood of their processing and presentation in physiological settings.

From a mechanistic standpoint, each epitope fulfills essential functional roles in vaccine design. Effective peptide vaccines must not only ensure antigen-specific presentation on tumor cells but also activate naïve $CD8^+$ T cells to differentiate into cytotoxic effectors capable of tumor cell lysis. The epitopes identified in this study meet these requirements based on both theoretical immunogenicity and supportive experimental data from prior studies [14, 17]. Importantly, multi-epitope vaccines such as the one proposed here also reduce the risk of immune escape by targeting multiple tumor vulnerabilities simultaneously .

Another notable aspect of this study is the integration of cross-platform validation. By using multiple prediction algorithms with distinct underlying methodologies—ANN-based (NetCTL), motif-based (SYFPEITHI), and ensemble machine learning (MHCflurry)—we reduce reliance on any single computational bias and increase the biological confidence of epitope selection [9]. This is particularly important in the context of translational immunology, where in silico predictions must ultimately be validated in vitro and in vivo.

Despite the promising results, several limitations merit consideration. First, while the computational predictions are robust, experimental validation remains essential. Functional assays such as IFN-γ ELISPOT, CTL cytotoxicity tests, and tetramer staining are necessary to confirm T-cell activation and specificity. Second, immunodominance and individual HLA variability across patients may affect vaccine efficacy; thus, expanding epitope coverage to multiple alleles may enhance clinical applicability. Third, the tumor microenvironment (TME) in TNBC often exhibits immunosuppressive characteristics, including high expression of PD-L1 and Treg infiltration, which may limit vaccine-induced responses unless combined with checkpoint blockade.

Nevertheless, this study provides a strong immunoinformatics foundation for further in vitro and in vivo validation. The identified epitopes represent optimal candidates for incorporation into multi-epitope peptide vaccines, DNA/RNA-based delivery systems, or even adoptive T-cell platforms targeting TNBC

5. Conclusion

This study demonstrates a rational, data-driven approach to the identification of highly immunogenic CTL epitopes for use in peptide-based vaccine design targeting triple-negative breast cancer (TNBC). By integrating multiple bioinformatics platforms—including NetCTL, SYFPEITHI, MHCflurry, and IEDB consensus predictors—we identified three tumor-restricted, HLA-A*02:01-restricted epitopes derived from Survivin, MAGE-A3, and NY-ESO. These epitopes satisfy stringent criteria for antigen processing, MHC-I binding, and immunogenicity, underscoring their translational potential.

The selected epitopes are biologically relevant, safe, and capable of robustly engaging $CD8^+$ T cells, making them attractive candidates for inclusion in multi-epitope therapeutic vaccines or adoptive T-cell immunotherapy protocols. This strategy aligns with modern trends in precision oncology, where immunoinformatics enables cost-effective, high-throughput vaccine design.

It is important to consider the population distribution of HLA alleles when designing epitope-based vaccines. HLA-A*02:01, although highly prevalent in European and North American populations, shows variable frequency across different ethnic groups worldwide. This variation may affect the global applicability of the selected epitopes, highlighting the need for future studies to incorporate epitopes restricted to other common HLA alleles to achieve broader population coverage.

While further *in vitro* and *in vivo* validation is required, the findings of this study provide a strong foundation for the development of novel immunotherapeutic modalities targeting TNBC and potentially other solid tumors expressing similar antigens. As a logical next step, the predicted epitopes will undergo peptide synthesis and experimental validation through ELISPOT and cytotoxicity assays to confirm their immunogenic potential in vitro.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Author's contributions

Kaveh Haji-Allahverdipoor conceptualized the study, designed the immunoinformatics workflow, performed all computational analysis, and interpreted results**.** Shahriar Saeedian, Parastoo Mardani and Habib Eslami critically reviewed the first draft, contributed to the refinement of the structure and content, and provided extensive academic editing and revisions.

Conflict of interest

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

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