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Nano-liposomal Vaccine Delivery Systems for Enhancing Cell-Mediated Immunity against *Staphylococcus aureus*: Current Progress, Preclinical Advances, and Future Perspectives

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Abstract

S. aureus is one of the most clinically important bacterial pathogens due to its ability to survive in host immune systems, cause persistent infection and easily acquire antimicrobial resistance. The spread of methicillin-resistant Staphylococcus aureus (MRSA) worldwide has underscored the critical need for MRSA vaccines with sustained protection that surpasses the action of existing antibiotics. Although much research has been conducted over the years, previous vaccine candidates have shown limited clinical success, mostly due to the failure to generate strong enough cell-mediated immunity for bacterial clearance. With the advancement of nanotechnology, Nanoliposomes have emerged as one of the most promising systems for vaccine delivery due to their superior biocompatibility, high antigen loading capacity, controlled release characteristics and their ability to improve the antigen presentation by the professional antigen presenting cells. Optimised physicochemical properties, such as particle size, lipid composition, surface charge, membrane stability and incorporation of adjuvants, enable nanoliposomal vaccines to effectively activate innate and adaptive immune responses and generate a balanced activation of Th1 and Th17 lymphocytes, which is critical for protective immunity against S. aureus. The present review gives a detailed and critical description of what is known about the host immune responses to staphylococci with special focus on the mechanisms involved in cellular immunity and antigen presentation. In addition, the structural properties, physicochemical properties, immunomodulatory mechanisms, formulation strategies, and considerations of nanoliposomal vaccine delivery systems are discussed. Representative preclinical studies are comparatively analyzed to understand the key formulation parameters that shape vaccine efficacy and current formulation challenges for vaccine manufacturing, stability, safety and clinical translation are critically examined. Other innovative technologies, such as multifunctional Nanoliposomes, nucleic acid (mRNA) vaccines, targeted delivery systems, systems immunology, and artificial intelligence in vaccine design are also mentioned as potential pathways for next-generation antibacterial vaccines. Covering topics such as Staphylococcus aureus, Methicillin-resistant Staphylococcus aureus (MRSA), Nanoliposomes, Vaccine delivery systems, Cell-mediated immunity, Th1 and Th17 responses, Nano vaccines, Antigen presentation.

Keywords

Staphylococcus aureus;
Nanoliposomes;
Vaccine Delivery Systems;
Cell-Mediated Immunity;
Th1/Th17 Immune Responses.

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1. Introduction

Staphylococcus aureus is a bacterium that can cause a variety of infections in the skin and soft tissues as well as invasive infections including septic arthritis, osteomyelitis, pneumonia, infective endocarditis, septic[emergence] and bacteremia. The bacterium is able to survive in both community and hospital settings and has a large arsenal of virulence factors that allow it to evade host immune responses and persist in the host. [1]. The appearance and worldwide transmission of multidrug resistant strains, especially methicillin-resistant S. aureus (MRSA), have added to the difficulties of disease management, as they have reduced therapeutic choice and increased the morbidity, mortality, and economic burden of healthcare-associated infections. Therefore, S. aureus has been identified as one of the most threatening bacterial pathogens that need to be targeted for the development of effective preventive measures, other than routine antibiotic use. [2]

Antimicrobials are still the mainstay of S. aureus infection management, but antimicrobial resistance has been a constant emerging threat, and the persistence of infection has been further complicated by the ability of S. aureus to survive in biofilms, grow within cells, and cause recurrent infections [3]. The emergence of resistant clones, such as MRSA and strains with reduced susceptibility to the last-line antibiotics has highlighted the need for alternative means of prevention. [4]. Vaccination, unlike antibiotic treatment, could offer permanent protection by inducing immunological memory and decreasing the occurrence of a disease and transmission of the bacteria. However, despite decades of intensive research, a vaccine to protect against S. aureus has been a scientific challenge due to its complexity to evade the host immune response, antigenic diversity, and ability to disrupt innate and adaptive immune responses. These challenges have led researchers to explore novel vaccine formulations and novel vaccine delivery systems for achieving strong and long-lasting protective immunity. [6]

Coordinated innate and adaptive immune responses are required for protective immunity to Staphylococcus aureus. Humoral immunity is involved in bacterial neutralization and opsonization; however, new data suggests that antibody-mediated protection is not enough to prevent invasive infection with S. aureus. Rather, the cell-mediated immune response is very important, which includes antigen presenting cells, $CD4^+$ T lymphocytes, macrophages, and neutrophils. In particular, T helper 1 (Th1) and T helper 17 (Th17) responses are crucial in bacterial clearance, producing interferon-gamma (IFN-γ), interleukin-17 (IL-17) and other pro-inflammatory cytokines that facilitate recruitment, activation and intracellular killing of bacteria by phagocytes. As a result, the research of vaccines has become more focused on the ability to elicit not just antibody responses but also cell-mediated responses to provide better long-term protection from systemic and recurrent S. aureus infections. [9]

With the latest developments in nanotechnology, new vaccines delivery system platforms have emerged that can circumvent many of the disadvantages of traditional vaccines. Nanoparticle-based delivery systems can also increase the stability of the antigens, help ensure the safety of antigen components in the vaccine, increase antigen uptake by antigen-presenting cells, and provide control over the release of the antigen, which can result in more sustained and robust immune response. [10]. Moreover, Nano-carriers can be fabricated to specifically interact with specific immune cells, to enhance lymphatic drainage and to serve as antigen carriers and immunostimulatory adjuvants at the same time. Nanoliposomes have proved a very promising system to deliver vaccine because of their excellent biocompatibility, biodegradability, low toxicity, and remarkable versatility in encapsulating hydrophilic or hydrophobic antigens among the various Nanotechnology based vaccine delivery system [11].

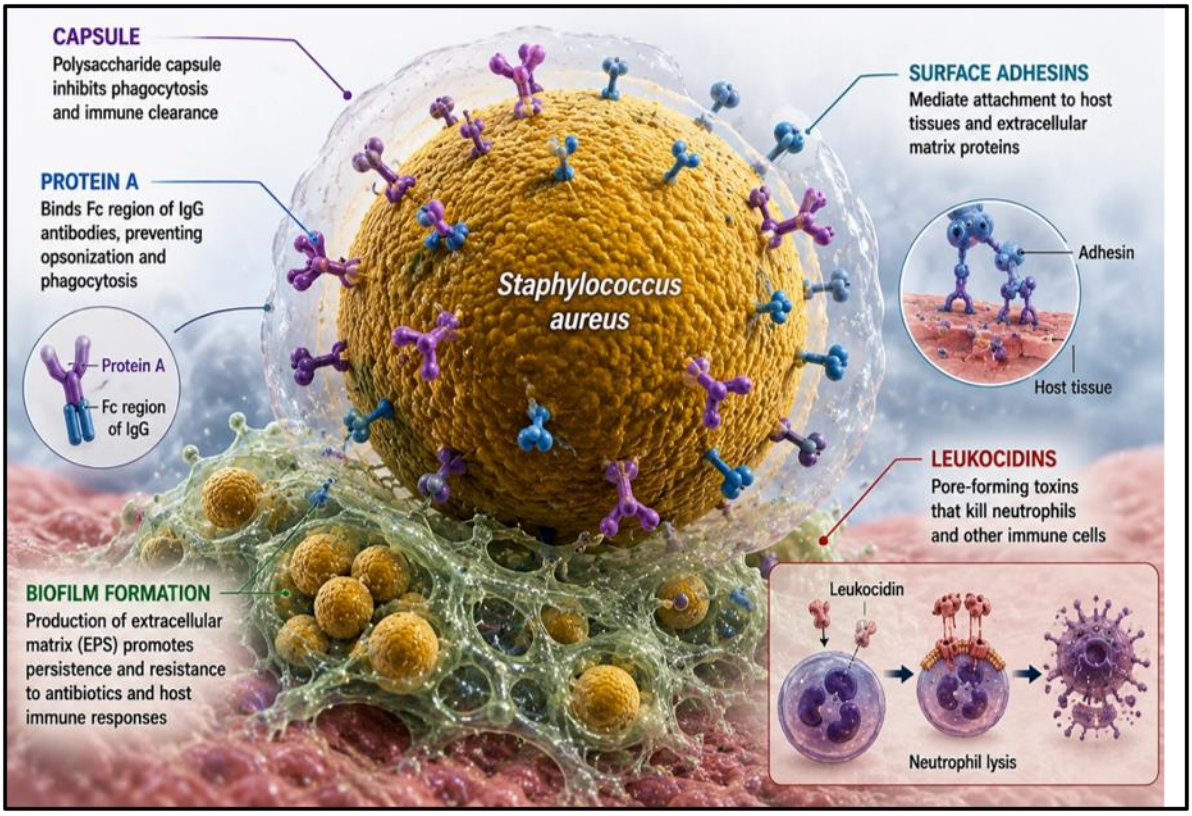


Figure 1. Structural features and major virulence factors of Staphylococcus aureus, including the capsule, protein A, surface adhesions, biofilm formation, and leukocidins.

A. The host immune response to Staphylococcus aureus. The host immune response to Staphylococcus aureus.

2.1 Innate Immune Response

S. aureus is a ubiquitous opportunistic pathogen which, upon encountering the host's innate immune system, does so right after breaching physical barriers like the skin or mucosal surfaces. Pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors and scavenger receptors present on macrophages, dendritic cells, neutrophils and epithelial cells mediate recognition of S. aureus. They detect conserved pathogen-associated molecular patterns (PAMPs) such as peptidoglycan, lipoteichoic acid, bacterial lipoproteins, cell wall components and launch intracellular signaling pathways that trigger the host inflammatory response. [12] .Once activated, innate immune cells quickly begin to secrete pro-inflammatory cytokines and chemotactic cytokines (TNF-α, IL-1β, IL-6, CXCL1, CXCL8) that quickly attract neutrophils and monocytes to the site of infection. Neutrophils phagocytose bacteria, produce reactive oxygen species (ROS), and express antimicrobial peptides, and make neutrophil extracellular traps (NETs). At the same time, macrophages play a role in the clearance of bacteria by engulfing them, releasing cytokines and serving as an antigen presentation system, thus connecting innate and adaptive immunity. [13]

Critical Analysis: Early S. aureus infections are controlled by activation of innate immunity, but the virulence factors of S. aureus (protein A, capsular polysaccharides, leukocidins, biofilm formation) mean that innate immunity alone is not usually sufficient to eliminate the infection. Therefore, subsequent activation of antigen-specific adaptive cellular immunity is needed for protection. [14]

2.2 Adaptive Immune Response

The adaptive immune system is crucial in establishing long-lasting immunity and orchestrating the clearance of innate-immune-resistant bacteria. Dendritic cells (DCs) present processed antigens on dendritic cells (MHC) molecules which activate naïve lymphocytes in secondary lymphoid organs. The main players of protective immunity in $CD4^+$ T-cell subsets are Th1 cells and Th17 cells. Th1 cells produce IFN-γ that activates macrophages and also helps them kill bacteria inside their cells, while Th17 produce IL-17 and IL-22 that recruit neutrophils and induce production of antimicrobial peptides. Though B lymphocytes and antibody production play a role in opsonization and toxin neutralization, antibody-mediated immunity has so far failed to completely protect in clinical trials. Critical Analysis: Lack of activation of cell-mediated immunity in previous candidates was the main reason for the failure of these products as vaccines. Vaccine platforms need to focus on dendritic cell maturation and induction of Th1/Th17 polarization as well as humoral responses [16].

3. Nanoliposomes as Vaccine Delivery Platforms

3.1 Structural Characteristics and Physicochemical Properties

Nanoliposomes are spherical vesicles with a nanoscale size which are formed by phospholipid bilayers enclosing an aqueous core. They have an amphiphilic structure: hydrophilic antigen can be placed in the center and hydrophobic compound can be encapsulated in the lipid bilayer. Particle Size: Diameters of 50-200nm allow good drainage into the lymphatics and uptake by dendritic cells. Surface Charge (Zeta Potential): Positively charged (cationic) liposomes are good at internalizing into cells in an electrostatic way. Lipid Composition & Rigidity: Incorporation of cholesterol decreases membrane permeability which results in prevention of early antigen leakage. [17]

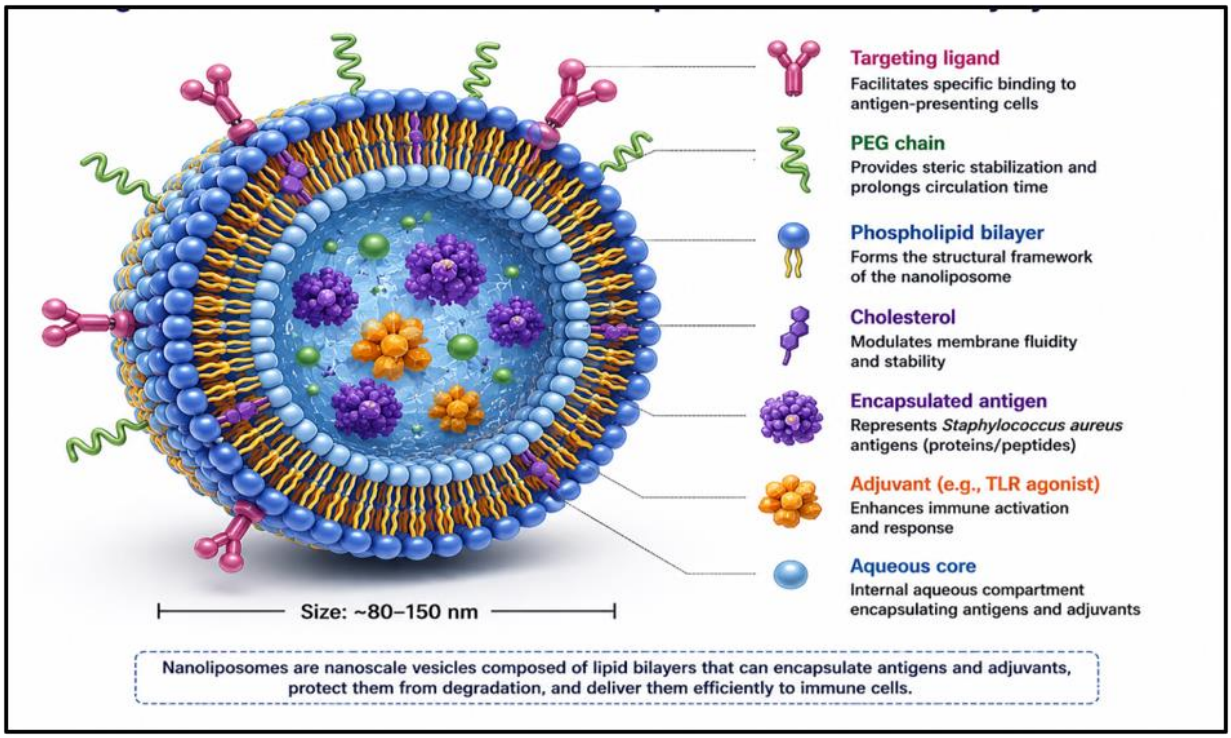


Figure 2. Schematic representation of a nanoliposomal vaccine delivery system showing the phospholipid bilayer, encapsulated antigen, adjuvant, cholesterol, PEG chains, and targeting ligands.

3.2 Interaction with Antigen-Presenting Cells (APCs)

Nanoliposomes interact with dendritic cells (DCs) and macrophages through multiple endocytic pathways. Following internalization Encapsulated antigens processed via the endosomal–lysosomal pathway are presented on **MHC class II** molecules to activate $CD4^+$ helper T cells. Certain formulations promote endosomal escape, enabling antigen cross-presentation via **MHC class I** molecules to stimulate $CD8^+$ cytotoxic T lymphocytes also Nanoliposomes induce functional DC maturation, upregulating co-stimulatory markers (CD80, CD86, CD40) and promoting IL-12 and IL-23 secretion. [18-19]

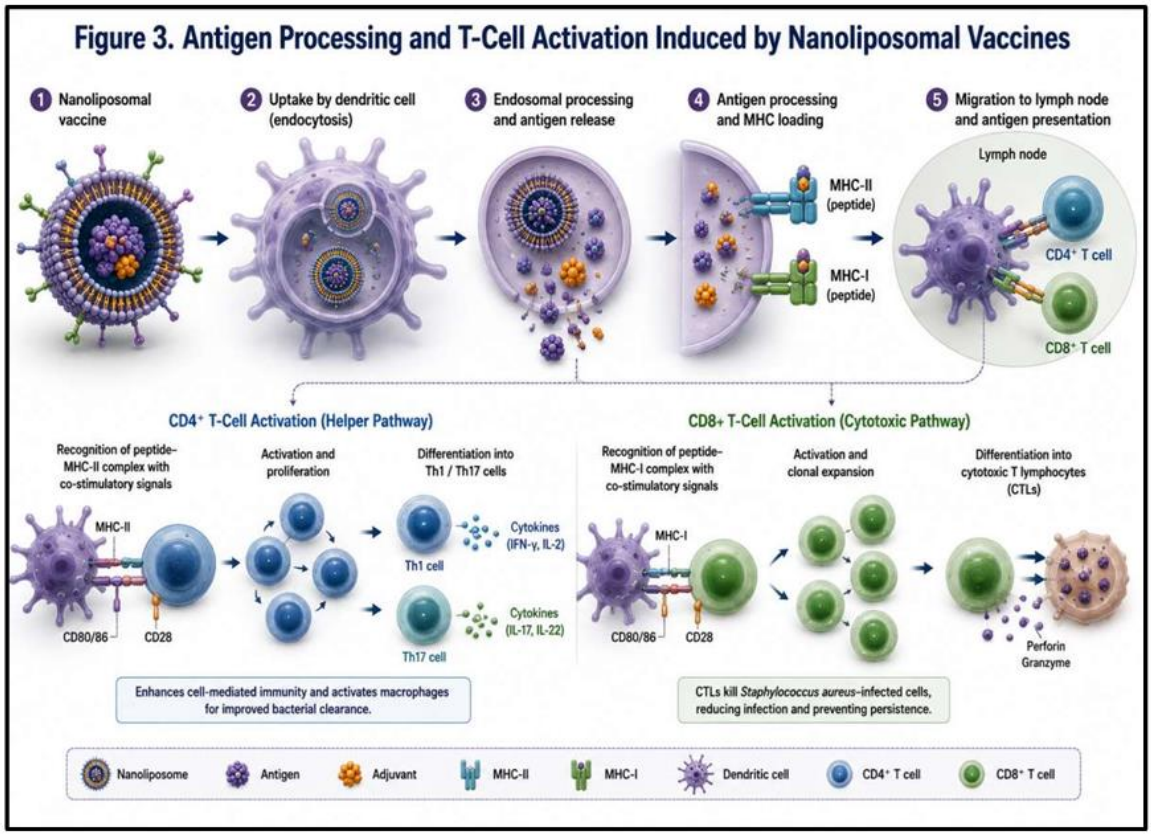


Figure 3. Uptake of nanoliposomal vaccines by dendritic cells, antigen processing, MHC-mediated presentation, and activation of $CD4^+$ and $CD8^+$ T cells.

3.3 Immunomodulatory Mechanisms

Nanoliposomes function as active immunomodulators. Encapsulating Toll-like receptor (TLR) agonists—such as monophosphoryl lipid A (MPLA) or CpG oligodeoxynucleotides (CpG-ODN)—within liposomes creates synergistic immune activation. This promotes polarization toward protective Th1 (IFN-γ) and Th17 (IL-17) phenotypes while generating long-lived memory T lymphocytes. [20]

3.3 Design Considerations for Optimizing Nanoliposomal Vaccines

Optimizing nanoliposomal performance requires balancing multiple interdependent variables: **Size Optimization:** Balancing rapid lymphatic transit (<200 nm) with local depot effects for sustained release. **Membrane Fluidity:** Utilizing saturated lipids (e.g., DPPC) with cholesterol for maximum physiological stability. **Surface Functionalization:** Conjugating targeting ligands (e.g., mannose or antibodies) to selectively direct vesicles to APC receptors. [21]

4. Comparison between Delivery Platforms

To highlight the unique benefits of Nanoliposomes, Table 1 compares conventional formulations, Nanoliposomes, and alternative polymeric Nano carriers.

Table 1: Comparative Evaluation of Vaccine Platforms Against *Staphylococcus aureus*

Feature / Parameter	**Conventional Vaccines**	**Nanoliposomal Vaccines**	**Polymeric Nanoparticles (PLGA)**
Antigen Stability	Low; vulnerable to enzymatic degradation	**High**; lipid bilayer protects antigen	High; matrix entrapment
APC Targeting & Uptake	Low / Passive diffusion	**Enhanced**; membrane fusion & endocytosis	Moderate; surface modification required
Antigen Presentation	MHC-II predominant	**Dual MHC-I and MHC-II** (Cross-presentation)	MHC-II predominant (MHC-I variable)
Th1 / Th17 Activation	Minimal to moderate	**Robust Th1 (IFN-γ) and Th17 (IL-17)**	Moderate Th1 / Variable Th17
Adjuvant Co-delivery	Administered as separate mixtures	**Synchronized co-encapsulation**	Co-encapsulation possible
Controlled Release	Minimal / Rapid clearance	**Tunable / Sustained release profile**	Sustained (burst release risk)
Biocompatibility & Safety	Established; limited cellular efficacy	**Excellent biocompatibility & low toxicity**	Biodegradable (acidic degradation products)

5. Preclinical Applications of Nanoliposomal Vaccines Against *S. aureus*

5.1 Overview of Preclinical Evaluation

Preclinical studies evaluate candidate vaccines across several critical parameters: antigen-specific IgG titers, T-cell proliferation, cytokine secretion profiles (IFN-γ, IL-17, IL-2), bacterial clearance from systemic organs (kidneys, spleen, lungs), and survival rates following MRSA challenge. [22]

5.2 Comparative Analysis of Preclinical Studies

A systematic assessment of preclinical literature reveals that multi-component antigen selection combined with adjuvant cationic Nanoliposomes consistently yields superior survival outcomes compared to single soluble antigens. [23]

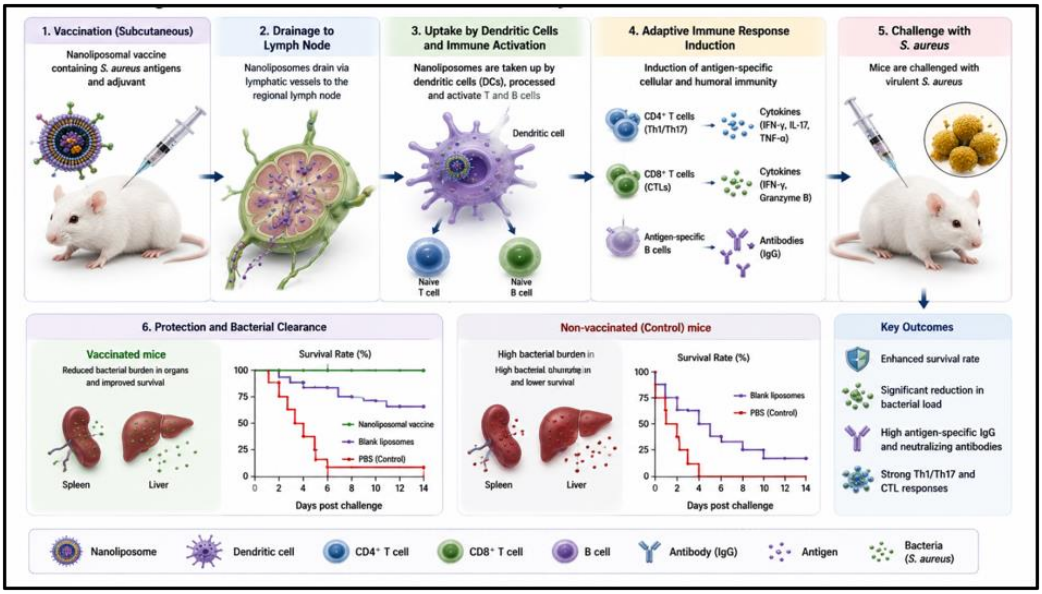


Figure 4. Illustration of the preclinical evaluation of nanoliposomal vaccines in a murine model, including vaccination, lymph node targeting, immune activation, and protection against Staphylococcus aureus

Table 2: Representative Preclinical Studies of Nanoliposomal Vaccines Against *S. aureus*

Liposome Composition & Properties		Adjuvant Included	Animal Model & Route	Key Immunological Outcomes	Protective Efficacy
Biofilm Matrix Proteins (BMPs)	Phospholipids + Cholesterol (100–180 nm, Neutral/Slightly Anionic)	Encapsulated BMP matrix components	Albino Rats (Subcutaneous)	Elevated serum CXCL5, increased leukocyte counts, neutrophil recruitment, lymphocyte activation.	Enhanced protection against biofilm-associated infection vs. soluble antigen.
Recombinant Clumping Factor A (rClfA)	Cationic Lipid Bilayer (DPPC/Chol/DOTAP) (120 nm, Positive charge)	CpG-ODN (TLR9 agonist)	Murine MRSA model (Intramuscular)	Strong Th1/Th17 polarization, elevated IFN-γ and IL-17 production, balanced IgG1/IgG2a titers.	Significant reduction in bacterial load in kidneys and spleen; improved survival.
Multicomponent Virulence Factors (Hla, FhuD2, Csa1A)	Sterically stabilized Nanoliposomes (PEGylated lipid formulation)	MPLA (TLR4 agonist)	Murine Systemic Bacteremia Model	Multi-epitope T-cell recognition, high memory T-cell generation, broad antibody	Broad protection across genetically diverse

Liposome Composition & Properties		Adjuvant Included	Animal Model & Route	Key Immunological Outcomes	Protective Efficacy
				neutralization.	MRSA clinical isolates.

6. Current Challenges and Translational Limitations

Despite encouraging preclinical performance, several major hurdles impede clinical translation:

1. **Physicochemical Instability:** Susceptibility to lipid oxidation, hydrolysis, aggregation, and premature antigen leakage during storage.
2. **Manufacturing & Scalability:** Maintaining consistent particle size distribution, encapsulation efficiency, and batch-to-batch reproducibility under Good Manufacturing Practice (GMP) conditions.
3. **Safety & Reactogenicity:** Excessive positive charge in cationic liposomes or aggressive adjuvant combinations may trigger systemic reactogenicity or local toxicity.
4. **Pathogen Complexity:** *S. aureus* exhibits extensive antigenic diversity and functional redundancy, necessitating multivalent antigen formulations. [24-27]

7. Future Directions and Emerging Technologies

The future of *S. aureus* nanoliposomal vaccines lies at the intersection of nanotechnology, computational biology, and molecular immunology:

- **mRNA-Nanoliposomal Platforms:** Leveraging lipid nanoparticles and Nanoliposomes to deliver mRNA encoding conserved staphylococcal toxins or surface proteins, facilitating endogenous antigen expression and powerful cellular immunity.
- **AI and Immunoinformatic:** Utilizing machine learning to predict conserved immunogenic epitopes, optimizing multivalent formulations before synthesis.
- **Active APC Targeting:** Functionalizing Nanoliposomes with mannose or DEC-205 ligands for targeted receptor-mediated endocytosis by dendritic cells. [28-30]

8. Conclusion

Conventional vaccine approaches relying solely on antibody induction have repeatedly failed to protect against invasive *Staphylococcus aureus* infections. Protective immunity requires the simultaneous activation of humoral and cell-mediated pathways, particularly Th1 and Th17 responses. Nanoliposomes represent an exceptionally versatile delivery platform capable of protecting antigens, facilitating dual MHC-I/MHC-II presentation, and orchestrating targeted immune responses. Overcoming current stability and manufacturing challenges through interdisciplinary innovation will be essential to translate these promising Nano vaccines from preclinical models into successful clinical therapies against multidrug-resistant *S. aureus*.

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