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mRNA-Based Vaccine Platforms Targeting *Plasmodium falciparum* Circumsporozoite Protein: A Comprehensive Review

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ABSTRACT

Malaria remains a major global health burden, with *Plasmodium falciparum* responsible for the majority of severe disease and mortality, particularly in sub-Saharan Africa, as consistently reported by the World Health Organization. Although recent vaccine approvals marked significant progress, currently deployed protein-based platforms such as RTS, S/AS01 and R21/Matrix-M demonstrated only moderate and waning efficacy, underscoring the need for innovative strategies. The purpose of this review is to critically evaluate mRNA-based vaccine platforms targeting the circumsporozoite protein of *P. falciparum*, examining their molecular design, immunological performance, translational potential, and current limitations. This article was developed through a comprehensive narrative synthesis of contemporary literature in molecular vaccinology, malaria immunology, and nucleic acid delivery technologies. Accumulating evidence indicated that mRNA platforms offered rapid antigen engineering, potent humoral and cellular immune induction, and flexible manufacturing scalability, with promising preclinical immunogenicity against circumsporozoite protein epitopes. Lipid nanoparticle delivery systems enhanced antigen expression and promoted balanced adaptive immune responses. Nevertheless, challenges remained regarding durability of protection, cold chain logistics, antigenic diversity, and implementation in endemic regions. mRNA-based circumsporozoite protein vaccines represented a transformative frontier in malaria prevention, warranting intensified translational research and strategic global investment.

Keywords: mRNA vaccines, Circumsporozoite protein, *Plasmodium falciparum*, Malaria immunology, Lipid nanoparticles.

INTRODUCTION

Malaria continues to exert profound clinical and socioeconomic consequences across tropical and subtropical regions [1, 2]. Among the five species infecting humans, *Plasmodium falciparum* accounts for the most severe manifestations, including cerebral malaria, severe anemia, and multi organ failure [3, 4]. Despite decades of vector control initiatives, chemoprophylaxis, and therapeutic interventions, durable vaccine mediated protection has remained elusive. The World Health Organization has endorsed protein based vaccines such as RTS,S/AS01 and more recently R21/Matrix-M; however, both demonstrate moderate efficacy that declines over time, necessitating booster administration and raising questions regarding long term population level impact.

The circumsporozoite protein, a dominant surface antigen expressed during the sporozoite stage, has been a central target in pre erythrocytic vaccine design. [5] Antibodies directed against this protein can neutralize sporozoites before hepatocyte invasion, thereby interrupting the infection cycle at its earliest stage. Nevertheless, conventional recombinant protein platforms have faced challenges related to antigen presentation, immune durability, and manufacturing complexity [6]. The rapid advancement of messenger RNA vaccine technologies, demonstrated at global scale by companies such as Moderna and Pfizer, has transformed modern vaccinology. These platforms allow rapid antigen design, scalable production, and potent induction of both humoral and cellular immunity. This review

examines the biological relevance of circumsporozoite protein, the molecular architecture of mRNA vaccine platforms, emerging preclinical and clinical evidence, comparative advantages and challenges, and future translational directions. The purpose is to provide an integrated and critical synthesis of current knowledge to guide next-generation malaria vaccine development.

Biological and Immunological Significance of Circumsporozoite Protein

The circumsporozoite protein is the predominant surface antigen of *P. falciparum* sporozoites and plays a pivotal role in parasite motility, salivary gland invasion in mosquitoes, and hepatocyte infection in humans [7]. Structurally, it consists of a central repetitive region composed primarily of NANP motifs, flanked by conserved N-terminal and C-terminal domains. These structural features confer both functional and immunological relevance.

The central repeat region is highly immunogenic and constitutes the primary target of neutralizing antibodies. Antibodies directed against NANP repeats can immobilize sporozoites within the dermis and bloodstream, preventing their migration to the liver [8]. The C-terminal domain contains thrombospondin-type repeat motifs that facilitate hepatocyte binding through interactions with heparan sulfate proteoglycans.

Protective immunity against malaria involves a complex interplay between humoral and cellular responses. High titers of anti-circumsporozoite antibodies correlate with reduced infection risk, while CD4 T helper cells support antibody maturation and isotype switching. CD8 cytotoxic T lymphocytes targeting infected hepatocytes contribute to elimination of intracellular parasites during the liver stage [9]. Targeting the pre-erythrocytic phase offers a strategic advantage because parasite numbers are relatively low before hepatic replication. Interruption at this stage prevents symptomatic blood stage infection and transmission. However, antigenic polymorphism within the circumsporozoite protein and immune evasion mechanisms pose significant obstacles.

A comprehensive understanding of circumsporozoite protein structure, epitope distribution, and immune correlates of protection is therefore essential for rational vaccine design, particularly when leveraging flexible platforms such as mRNA technology.

Molecular Architecture of mRNA Vaccine Platforms

Messenger RNA vaccines operate by delivering synthetic transcripts encoding a target antigen into host cells, where endogenous translational machinery produces the antigenic protein [10]. Two principal formats exist: conventional non-replicating mRNA and self-amplifying mRNA derived from alphavirus backbones. The latter contains replicase sequences that enable intracellular RNA amplification, potentially enhancing antigen expression at lower doses.

Optimization strategies are critical to maximize stability and translational efficiency. Nucleoside modifications, including incorporation of pseudouridine analogues, reduce innate immune sensing through toll like receptors and enhance ribosomal engagement [11]. Codon optimization improves translational kinetics without altering protein sequence, while optimized untranslated regions increase transcript stability.

Lipid nanoparticle delivery systems protect mRNA from enzymatic degradation and facilitate cellular uptake [12]. These nanoparticles typically consist of ionizable lipids, phospholipids, cholesterol, and polyethylene glycol conjugated lipids [13]. Following endocytosis, endosomal acidification triggers ionizable lipid protonation, destabilizing the membrane and releasing mRNA into the cytoplasm. Antigen expression within host cells promotes both major histocompatibility complex class I and class II presentation pathways. Endogenously synthesized circumsporozoite protein fragments are presented to CD8 T cells [14], while extracellular release and uptake by antigen-presenting cells stimulate CD4 T cell responses and antibody production.

The modular nature of mRNA platforms enables rapid redesign to incorporate multiple epitopes, modified antigen sequences, or consensus constructs addressing polymorphic variation. This adaptability represents a critical advantage in combating genetically diverse pathogens such as *P. falciparum.*

Preclinical and Clinical Evidence for mRNA CSP Vaccines

Preclinical investigations have demonstrated promising immunogenicity of mRNA vaccines encoding circumsporozoite protein in murine and non human primate models [15]. Studies report robust induction of NANP specific antibody titers and enhanced germinal center responses compared with some recombinant protein formulations. Neutralization assays reveal functional inhibition of sporozoite invasion into hepatocyte cultures.

In addition to humoral responses, mRNA platforms elicit measurable CD4 and CD8 T cell activation, characterized by interferon gamma production and cytotoxic activity against infected hepatocytes [16]. Such balanced immune responses are particularly valuable in malaria, where sterilizing immunity likely requires both antibody-mediated neutralization and cellular effector mechanisms. Comparative analyses suggest that mRNA vaccines may achieve higher peak antibody titers and broader epitope recognition than traditional subunit vaccines. However, durability of immunity remains under investigation, as long-term protection data are limited.

Early-phase clinical evaluation of mRNA malaria vaccines is emerging, with preliminary safety profiles indicating acceptable reactogenicity similar to other mRNA platforms [17]. Immunogenicity outcomes demonstrate dose-dependent antibody responses, though correlates of protection in humans remain to be fully defined. Despite encouraging findings, challenges persist in translating preclinical success into durable field efficacy. Differences in transmission intensity, host genetics, and parasite diversity complicate extrapolation from controlled models to

endemic settings. Rigorous clinical trials in malaria-exposed populations will be essential to establish real-world effectiveness.

Advantages and Challenges of mRNA Platforms in Malaria Vaccine Development

mRNA vaccine platforms offer several compelling advantages for malaria control. Rapid design and synthesis enable swift iteration in response to emerging data on antigen structure or polymorphism. Manufacturing processes are cell free and scalable, facilitating global production without reliance on complex recombinant protein purification systems [18].

The capacity to encode multiple antigens within a single construct supports multivalent vaccine strategies targeting distinct parasite stages [19]. Furthermore, endogenous antigen expression promotes balanced activation of humoral and cellular immunity, potentially surpassing the predominantly antibody focused responses elicited by some protein vaccines.

Nevertheless, logistical challenges remain. mRNA vaccines often require stringent cold chain conditions to preserve stability, posing obstacles in resource limited regions where malaria burden is highest. Advances in thermostable formulations are therefore imperative. Durability of protection represents another concern. While high antibody titers can be achieved, sustained immunity without frequent boosters remains uncertain. Cost considerations, infrastructure requirements, and community acceptance must also be addressed.

Antigenic diversity within circumsporozoite protein may limit cross strain protection [20]. Rational design incorporating conserved epitopes or consensus sequences may mitigate this issue, yet requires continued surveillance of parasite genetic variation. While mRNA platforms represent a transformative opportunity, strategic planning is necessary to ensure equitable and effective deployment.

Future Directions and Translational Perspectives

Future development of mRNA-based circumsporozoite vaccines should prioritize multistage constructs combining pre-erythrocytic and blood stage antigens to enhance protective breadth. Self-amplifying mRNA formats may reduce dosage requirements, improving cost-effectiveness and accessibility [21, 22]. Systems biology approaches integrating transcriptomics, proteomics, and immune profiling can elucidate correlates of protection and inform rational booster strategies. Personalized immunogen design guided by regional parasite genomics may further optimize efficacy.

Innovations in lipid nanoparticle chemistry aimed at improving thermostability and reducing reactogenicity will facilitate implementation in endemic settings. Collaborative partnerships among academic institutions, biotechnology firms, and global health organizations are essential for advancing clinical trials.

Integration of mRNA vaccines into existing malaria control programs requires alignment with vector management strategies and chemoprophylaxis policies [23]. Regulatory frameworks must balance rigorous safety evaluation with expedited pathways for diseases of high global burden. Ultimately, sustained investment in translational research and infrastructure will determine whether mRNA technology can achieve durable, large-scale impact against *P. falciparum* malaria.

CONCLUSION

The circumsporozoite protein remains a rational and strategically advantageous target for malaria vaccine development due to its critical role in sporozoite infectivity and its capacity to elicit protective humoral and cellular immune responses. While currently approved protein-based vaccines represent important milestones, their moderate efficacy and waning immunity highlight the need for next-generation platforms. Messenger RNA vaccine technologies offer unprecedented flexibility in antigen design, rapid scalability, and the ability to induce balanced adaptive immunity through endogenous antigen expression. Preclinical data demonstrate robust immunogenicity of mRNA circumsporozoite constructs, and early clinical findings suggest acceptable safety profiles. Nevertheless, challenges related to durability of protection, cold chain logistics, antigenic diversity, and equitable global distribution must be addressed. Continued refinement of lipid nanoparticle delivery systems, multivalent antigen engineering, and rigorous field evaluation in endemic populations will be central to realizing the promise of this platform. Large-scale, multicenter clinical trials in malaria-endemic regions should be prioritized to rigorously evaluate the long-term efficacy, durability, and implementation feasibility of mRNA-based circumsporozoite protein vaccines.

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