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COMMENTARY

Transdermal immunization of *P. falciparum* surface antigen (MSP-1_{19}) via elastic liposomes confers robust immunogenicity

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ABSTRACT

As transdermal immunization results in poor immunogenicity, which is attributed to poor permeability of antigens through the skin, we believed ultradeformable lipid vesicles (elastic liposome) might address the challenges encountered during transdermal immunization. The elastic liposome, versatile carrier, proves better vehicle for transcutaneous delivery of protein, peptide and nucleic acid antigens. Our recently published article[1] is suggestive of improved immunogenicity of carboxyl-terminal 19 kDa fragment of merozoite surface protein-1 (PfMSP-119) of *Plasmodium falciparum* when administered subcutaneously via elastic liposomes (Fig. 1).

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As is evident from the work done by malaria vaccinologists, erythrocytic merozoite invasion process is one of the most promising targets for the development of vaccine against malaria.[2,3] Merozoite surface protein-1 (MSP-1), a polypeptide of 190–230 kDa, present on the surface of all known *Plasmodium* spp., is a leading malaria vaccine candidate antigen.[4] At the time of rupturing the schizont, MSP-1 undergoes proteolytic cleavage to produce at least 4 fragments of variable molecular weights (83, 28–30, 38–45 and 42 kDa).[5] Further, during merozoite invasion, the carboxy terminal, cysteine rich, 42 kDa (MSP-1_{42}) is further processed (secondary processing of MSP-1 during the successful invasion of RBCs) to yield a 19-kDa fragment (MSP-1_{19}) that remains associated with merozoites.[6,7] The potential of MSP-1_{19} and MSP-1_{42} in terms of immunogenicity has already been explored and documented against the asexual stage of malaria parasite.[8,9] The scarcity of B and T cell dominant epitopes present on merozoite surface protein vaccine forced us to think and to come up with some innovative strategy to achieving humoral and cell-mediated immune (CMI) response elicited by topically applied PfMSP-1_{19}-loaded elastic liposomes. We discovered that effective immunoadjuvant property of this elastic liposomes justifies its potential for the delivery of soluble malaria antigen to achieving robust and heightened immunogenicity. This novel carrier shows its value to explore the feasibility of developing asexual blood stage malaria vaccine.

The effective vaccination against infectious diseases is one of the major achievements of the modern preventive medicine.[10] Vaccination stimulates specific immune response, and induces long-lasting immunologic memory to protect against subsequent infections.[11] Most of the available vaccines are of intramuscular administration, which could be painful and their proper administration requires aseptic technique, skilled and trained personnel. The suboptimal presentation of antigen to antigen presenting cells due to the absence of co-stimulatory molecules on myocytes leading to poor immunogenicity of surface antigen (MSP-1_{19}). Our findings[1] has shown that transdermal delivery of PfMSP-1_{19} through elastic liposomes has been accomplished as one of the promising alternative approaches to invasive routes of administration. Moreover, transdermal immunization has proven advantageous over parenteral routes in avoiding systemic adverse effects, maintaining uniform blood levels and increased patient compliance. We believe non-invasive topical immunization via skin may allow vaccination by individuals without needing medically trained personnel and makes wide spread vaccination cost effective and feasible.

Transcutaneous immunization (TCI) is an innovative technique, having both practical and immunological merits requiring simple introduction of antigens to host using a topical application to the intact skin.[12] Transcutaneous immunization is crucially important and is of interest because of ease of administration, and capability in eliciting robust immune responses when compared with conventional and invasive needle injections administered in equivalent doses.[13] The epidermal antigen presenting cells (LCs) and migratory T-lymphocytes, collectively termed as skin-associated lymphoid tissue (SALT), and constituting skin-immune system, are crucial players in eliciting cell-mediated and humoral immune responses.[14] Transcutaneous immunization activates potent antigen-presenting cells (LCs) by the adjuvants, and LCs

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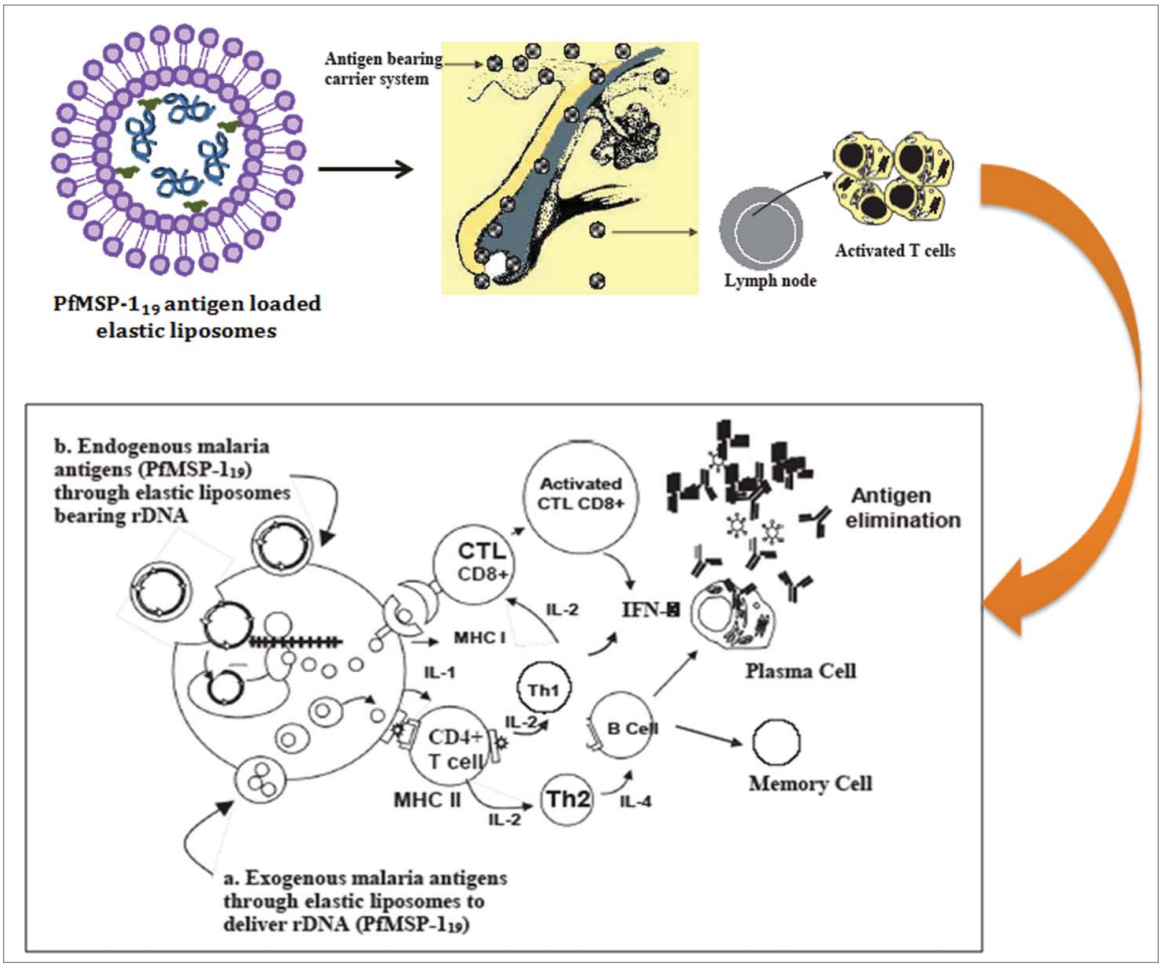

Figure 1. Schematic showing the proposed concepts of anti-malarial vaccine based on elastic liposome mediated delivery of PfMSP-1_{19}

rapidly migrate from epidermis to draining lymph nodes, carrying antigen(s) to induce robust systemic and cellular immune responses.[15–19]

There has been advancing interest in the development of novel lipid-based vesicular approaches for effective transcutaneous immunization. The very recent development in vesicle designing for transcutaneous bioactive(s) delivery is the use of elastic liposomes that differ from conventional liposomes and niosomes by the virtue of their characteristic fluid membrane and high elasticity[20] of elastic liposomes.

We took advantage of this delivery vehicle to achieving significantly high immune response of asexual blood stage antigen of *Plasmodium falciparum*, PfMSP-1_{19} (Fig. 1). In addition, we have reportedly shown to have achieved an adjuvant effect when immunized via transcutaneous route to induce immune responses at both systemic and mucosal sites. The immune responses mediated by MSP-1_{19} are largely antibody-dependent on high antibody titers essentially required to confer protection[21,22] against asexual blood stage *P. falciparum* infection. We, based on our finding,[1,23] claim that elastic liposome-mediated topical delivery of well-characterized *P. falciparum* antigen (PfMSP-1_{19}) to achieving significantly higher, and perdurable humoral (specific IgG antibodies and isotypes, IgG 1 & IgG3) as well as cell-mediated immune response (IFNg). Our recent investigation suggests better efficacy of elastic liposomes in delivering PfMSP-119 in order to evoke immune responses against asexual blood stage *falciparum* malaria protection (Fig. 1). Malaria antigen-loaded elastic liposomes following transdermal route has proven better vehicle than conventional liposomes when delivered via intramuscular route. The better immune responses mounted by the elastic liposomes loaded malaria antigen is due to preservation of immunogenicity of less number of B and T cell dominant epitope available on widely used surface antigen (MSP-1) of *P. falciparum*.

Concluding remark

In addition to the effective transdermal delivery of PfMSP-1_{19}, elastic liposomes formulation reported might also prove to be a valuable carrier towards pathological tissues such as cancer, inflammation and infection sites, and ischemic areas where delivery of antigen has always been a problem compared to normal tissues. Moreover, the enhanced immunogenicity and protective efficacy of PfMSP-1_{19} when used as vaccine formulation upon being delivered via elastic liposomes is one of the glaring advantages of this carrier. The novel and ultradeformable carriers (elastic liposomes) overcome the skin permeability barrier and deliver antigenic payload to immunologically active cells of skin and draining lymph nodes. Elastic liposomes through their enhanced elasticity, better antigen presentation,

controlled antigen release, immunoadjuvant properties and greater entrapment efficiency could be further explored as an effective tool for transdermal vaccination. Although non-invasive administration of elastic liposomes offering needle-free vaccine delivery, giving rise to higher antibody titer, and strong cellular responses for clearing asexual blood stage infections of *P. falciparum*, further studies with elastic liposome and more *Plasmodium* antigens might enhance the vaccine development effort against malaria.

Disclosure of potential conflict of interest

The authors have declared that no competing interest exists.

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