Development of a Malaria Transmission Blocking Nanoparticle Vaccine

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ABSTRACT

We have developed a potent transmission-blocking malaria vaccine via the encapsulation of recombinant Pf525 antigen into Selecta’s biodegradable, synthetic vaccine particle platform (SVP™) and combining it with nanoparticle formulations containing TLR7/8 or TLR9 agonists. Pf525 is a sexual stage antigen of Plasmodium falciparum expressed on the surface of its zygote and ookinete forms. It has been long known that antibodies to Pf525 can block the development of P. falciparum oocysts in mosquito midgut, thus Pf525 has been extensively studied as a candidate antigen for transmission-blocking vaccines. Several formulations of SVP[Pf525] nanoparticles were co-administered as a candidate antigen for transmission-blocking vaccines.

Transmission Blocking Approach vs. Traditional Infection Preventing Vaccine

- Target sporozoite
- Anti- CSPAb
- CTL against CSP
- Prevent infection
- Eliminate infected hepatocytes
Sporozoite surface proteins, poorly immunogenic, multiple vaccine failures

- Target gametocyte or ookinetes
- Anti-Pf525 Ab
- Prevent transmission
Gametocyte surface proteins immunogenic ‘Altruistic’ vaccine

Figure 1. The concept of transmission blocking malaria vaccine

SVP: Application of a Modular Vaccine Platform for Induction of Long-term Humoral Immunity

- T cell antigen e.g.
  - Disease-specific peptide epitopes
  - Protein antigens

- Adjuvant e.g.
  - TLR7/8 Agonist
  - TLR9 Agonist

Targeted Synthetic Vaccine Particles (SVP)[Pf525]

Targeted Synthetic Adjuvant Particles (TSAP)
2 adjuvant encapsulating formations
tSVP[R848]
tSVP[CpG]

Figure 2. SVP technology for malaria vaccine

Induction of Antibodies to Pf525 by Several SVP[Pf525] Formulations

Figure 3. BALB/c mice were injected s.c. 3 times with 3-week intervals (d0, 21, 42) with either SVP or free Pf525 (with or w/o alum) and their serum assayed for Pf525 antibodies and also tested in standard membrane feeding assay (SMFA). A – Pf525 ELISA (d54), B – SMFA (d54)

SVP Vaccination Results in Significant Pf525 Dose Sparring

Figure 5. BALB/c mice were injected s.c. 2 or 3 times with 3-week intervals (d0, 21, 42) with either SVP (0.002-1 μg of Pf525) or 8 μg of free Pf525 with alum and their serum assayed for Pf525 antibodies at d33 (A) or d54 (B).

Strong Inhibition of Oocyst Formation by Serum from SVP-immunized Mice

Dose-dependent Induction of Antibodies to Pf525 by SVP Vaccination Using R848 and CpG Adjuvants

Figure 4. BALB/c mice were injected s.c. 3 times with 3-week intervals (d0, 21, 42) with either SVP or free Pf525 with alum and their serum assayed for Pf525 antibodies and tested in SMFA at d54. A – Pf525 ELISA (d54), B – SMFA (d54)

Figure 6. BALB/c mice were immunized with SVP on d0 and 21 and their serum assayed for Pf525 antibodies, tested for Ab avidity and in SMFA (d33). Results for different SVP[R848] (A) and SVP[CpG] (B) formulations shown

CONCLUSIONS

- SVP[Pf525] nanoparticles have been formulated and tested for antibody induction in vivo
- Co-administration of SVP[Pf525] with SVP[CpG] or SVP[R848] resulted in robust antibody titers over a wide range of SVP-encapsulated Pf525 doses
- SVP containing 2 ng of Pf525 resulted in titers comparable to that obtained with 8 μg of Pf525 in alum (4000-fold dose sparing)
- Serum from SVP-immunized mice showed 97-99% inhibition in oocyst formation in standard membrane feeding assay (SMFA)
- SVP[Pf525] co-administered with novel SVP[CpG] or SVP[R848] formulations showed 100% oocyst inhibition in SMFA, which correlated either with elevated antibody titers or antibody avidity