Spotlights on new publications

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New vaccine candidates III

Malaria

Compilation No. (1)

In a previous "Spotlights of new publications, PUJ 2023; 16(1):88-90", the subunit vaccine RTS,S/AS01 (RTS,S) that specifically targets *P. falciparum* circumsporozoite protein was discussed. It was the first malaria vaccine recommended by the WHO for administration to children living in countries with moderate to high malaria transmission. Unfortunately, its short duration of protection was its only drawback in the majority of the conducted clinical trials. The present compilation represents a collaborative work of scientists from Portugal, Malaysia, and Netherlands who searched for an alternative approach using the whole-sporozoite (WSpz) immunization strategy to deliver specific *Plasmodium* antigens. Previous reports showed several experimental studies that utilized three formulations: 1) radiation-attenuated sporozoites (RAS); 2) chemoprophylactic sporozoites (CPS), in which the parasitic stages were eliminated by a schizonticidal drug in the first round of intraerythrocytic schizogony; and 3) newly generated genetically attenuated (GAs) WSpz in which hepatic development is arrested at either an early (EA-GA) or at a late (LA-GA) stage. Since none of these studies covered a comparative analysis between these formulations, **Diana Moita** and her colleagues conducted the present compilation in a rodent model.

Results revealed that EA-GA failed to exhibit complete protection against challenge infection at any immunization dosage. However, it exhibited the highest peak of protection at the highest immunization dose, that markedly decreased thereafter. On the other hand, RAS, CPS, and LA-GA showed comparable, and dosage-dependent protection. Accordingly, the investigators hypothesized that high EA-GA dose enhanced hepatocytic apoptosis that potentially compromised WSpz ability for hepatocytes invasion, in the subsequent booster dose, eliciting the highest peak of protective immune responses. Immunological analyses revealed that effector $CD8^+$ T cells elicited by EA-GA showed limited developmental plasticity, i.e., with a potential negative impact on memory cells functions and, thus, on the host protective immunity. Additionally, another explanation for EA-GA reduced protection level was suggested in a previous study that attributed this result to a phenomenon of high-dose tolerance/suppression of T cells that might lead to reduced proliferation of T-cell receptors. Based on the results of the present compilation, the investigators concluded the non-practical use of EA-GA in further prioritization, and recommended future studies using other formulation for the best optimization. Compiled from **"The effect of dosage on the protective efficacy of whole-sporozoite formulations for immunization against malaria." NPJ Vaccines 2023 Nov 24; 8(1):182.**

Compilation No. (2)

Several issues encouraged the investigators to conduct the present compilation. First, prevalence of *P. vivax* clinical cases, missed asymptomatic cases, and hepatic latent relapses that may lead to more morbidity and mortality rates especially in developing countries. Second, Duffy-negative individuals in sub-Saharan Africa are not protected from erythrocytic invasion, as previously reported. Third, the majority of control strategies were focused on *falciparum* malaria, while the impact for *P. vivax* was much less pronounced. Lastly, there were increased reports of high transmission rates of *P. vivax* infections in endemic areas. Therefore, **Watson *et al*.** aimed to address the urgent requirement for additional control strategies against *P. vivax* infections.

In *P. vivax*, erythrocytic stages are initiated by invasion of reticulocytes and immature RBCs using the endogenous Duffy binding protein (*Pv*DBP) to attack Duffy antigen receptor for chemokines (DARC). Among the structural regions of *Pv*DBP/DARC interaction, cysteine-rich region II (*Pv*DBPII) gained much attention because it has three subdomains (SDs), and SD2 possesses the highest binding motif. Previous studies demonstrated that murine monoclonal antibodies against *Pv*DBPII failed to inhibit reticulocytes invasion *in vitro* because they recognized SD3 that does not contain the highest binding motif. However, reduced risk of infection was recorded in human cases from whom *Pv*DBPII-specific memory B cells were isolated to generate human monoclonal antibodies (humAbs).

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Besides, previous studies conducted using clinical *P. vivax* isolates from Cambodia and Brazil, demonstrated humAbs ability to induce a short-term *ex vivo* growth inhibition up to 80% at 100 µg/ml. Accordingly, the present compilation hypothesized that *Pv*DBP is a potential therapeutic target and protective vaccine candidate against *P. vivax* infections.

To achieve their objective, the study investigated the functional activity of humAbs obtained from nine naturally infected (NI) patients and three vaccinated (NV) healthy individuals in cultured *P. knowlesi* genetically modified, i.e., replacement of *Pk*DBP with *Pv*DBP. Utilizing *in vivo* growth assay, the investigators assessed the invasion inhibition activity of humAbs. Additionally, to evaluate antagonistic or synergistic effects, six pairwise combinations (NI/NV) were tested. Results revealed 70-100% inhibition of RBCs invasion (IC_{50} values ranged from 51 to 338, and 33 to 99 µg/ml for NI, and NV humAbs, respectively). None of these combinations showed synergistic activity; instead, they exhibited antagonistic effects at higher concentrations. Only one combination (099100/094083) exhibited relatively strong inhibition at concentrations between 10 and 100 µg/ml. Based on the obtained results, the study concluded that little outcome can be achieved in future clinical trials using humAbs combinations. However, the investigators claimed that mutant *P. knowlesi* were easily cultured for investigation of the inhibitory activity of individual or combined humAbs. Compiled from **"Human monoclonal antibodies inhibit invasion of transgenic *Plasmodium knowlesi* expressing *Plasmodium vivax* Duffy binding protein." Malar J 2023 Dec 4; 22(1):369.**