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LONG TERM IMMUNE RESPONSES INDUCED AGAINST *PLASMODIUM VIVAX* CSP AND MSP-1 CHIMERIC VACCINE CANDIDATES DELIVERED BY NOVEL ADENOVIRAL VECTORS

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Protection against malaria based on pre-erythrocytic and erythrocytic antigens depends on IFN- γ production by CD4 and CD8 T cells. Adenoviral vectors have been used to induce robust cellular immune responses in recent malaria vaccine clinical trials and reports indicate that adenoviruses are capable of long periods of transgene expression, a desirable for malaria vaccines since immune responses lasting several transmission cycles are necessary to exert a substantial effect on disease incidence. To test the durability of the immune responses induced by adenoviral vectors encoding a multistage *Plasmodium vivax* chimeric protein vaccine including promiscuous T cell and B cell epitopes from the circumsporozoite protein (CSP) and merozoite surface protein-1 (MSP-1), we primed BALB/c mice with one of two different recombinant adenoviral vectors and assessed their immune responses and ability to induce memory T cells by boosting the mice one year post priming. We found that mice immunized with the recombinant proteins or one of the two protein-encoding adenoviral vectors - Simian Adenovirus 36 (SAd36) or a recombinant human adenovirus 5 modified to contain the fiber-knob region of adenovirus serotype 3 (Ad5/3) - displayed no significant decrease in antibody titers against the CSP and MSP-1 protein chimeras when antibody titers were compared between day 20 and 1 year post priming. We subsequently boosted mice with the heterologous adenoviral vector 1 year post priming, followed by two protein boosts 20 and 40 days later. We found that in comparison to mice receiving only protein immunizations, both heterologous adenoviral regimens induced CD4 and CD8 T cells capable of producing higher levels of IFN- γ , IL-2, and TNF- α upon *ex vivo* stimulation with the MSP-1 or CSP chimeric recombinant proteins or peptide pools representing T or B cell epitopes derived from these chimeric proteins. Taken together, the data demonstrate that our novel multistage malaria vaccine is able to induce long lasting humoral and cellular immune responses able to recognize two different *Plasmodium* antigens when delivered by a regimen that includes adenoviral vectors.

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A HYBRID *PLASMODIUM VIVAX* BLOOD STAGE-TRANSMISSION BLOCKING VACCINE CANDIDATE ELICITS ROBUST CELLULAR IMMUNE RESPONSES AND LONG-LIVED FUNCTIONAL ANTIBODIES

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Malaria control efforts focused on the use of vector based interventions have resulted in a significant reduction of *Plasmodium falciparum* cases. Unfortunately, the unique biological features of *P. vivax* make vector control interventions ineffective against this parasite. Transmission Blocking Vaccines (TBVs) are considered the best alternative for achieving malaria control as antibodies induced by TBVs taken up by the mosquito during the blood meal interrupt parasite development. However, a major concern for post-fertilization TBVs is a short lived antibody response as the human host is not exposed to these mosquito stage antigens, needed to induce a natural boosting effect. A transmission blocking formulation could also result in low compliance since it would not be protective against the disease. To address these problems, we designed a multistage chimeric

vaccine denominated *P. vivax* erythrocytic stage-transmission blocking chimera (PvES-TBC). This vaccine candidate includes 5 promiscuous T helper cell epitopes derived from the erythrocytic antigen MSP-1 which were genetically linked to the MSP-1 19kDa fragment and to the transmission blocking antigen Pvs25. PvES-TBC was tested in comparative experiments with Pvs25 in mice. PvES-TBC induced a strong cellular and humoral immunity able to recognize both MSP-1 and Pvs25. Additionally, when compared to Pvs25, PvES-TBC elicited a more robust antibody response as determined by a significantly higher avidity and a bias toward IgG2a production. This response was determined to last for a period longer than 2 years after the final boosting in mice immunized with PvES-TBC, an effect not observed in the Pvs25 group. The long lasting response was related to a significantly higher proportion of long lived plasma cells in mice immunized with PvES-TBC. When the transmission blocking ability of antibodies was tested by membrane feeding assays using wild *P. vivax* isolates, the antibodies produced in response to PvES-TBC were able to block 90% of mosquito infections. These characteristics make PvES-TBC a promising transmission blocking vaccine candidate that warrants clinical development.

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SAFETY AND IMMUNOGENICITY OF THE NOVEL *PLASMODIUM FALCIPARUM* BLOOD-STAGE VACCINE CHAD63-MVA RH5 IN A PHASE IA CLINICAL TRIAL

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The development of an effective malaria vaccine remains a vital goal if eradication is likely to be achieved. Candidate antigens for blood-stage *Plasmodium falciparum* vaccines have been hampered with issues of polymorphism and the need to induce extremely high antibody concentrations for these vaccines to be effective. The reticulocyte-binding protein homologue 5 (RH5) is the most promising blood-stage *P. falciparum* candidate antigen to date. It is essential for parasite survival and erythrocyte invasion and, unlike other blood-stage antigens (e.g. AMA1 and MSP1) RH5 does not appear to come under significant immune pressure in endemic settings, and there is limited polymorphism. Vaccination with an RH5-based vaccine confers protection against malaria challenge in non-human primates and the antibodies induced by vaccination are able to cross-inhibit *in vitro* all *P. falciparum* isolates tested to date. We report on a first-in-human Phase Ia clinical trial (NCT02181088) of an RH5-based vaccine delivered using the viral vectors chimpanzee adenovirus serotype 63 (ChAd63) and modified vaccinia virus Ankara (MVA) in a heterologous prime-boost strategy. The trial was conducted in Oxford and Southampton, United Kingdom and recruited twenty-four healthy, malaria-naïve volunteers aged 18-50. The first four volunteers (Group 1) received a lead-in dose (5 x 10⁹ viral particles, vp) of the ChAd63 RH5 vaccine alone before dose escalation to the full dose (5 x 10¹⁰ vp) in Group 2. The first four volunteers in Group 2 received ChAd63 alone, and the final sixteen were boosted with MVA RH5 eight weeks after ChAd63 RH5 at doses of 1 – 2 x 10⁸ plaque-forming units, pfu. Data on all adverse events were recorded for 28 days after each vaccination and serious adverse event (SAE) data were collected for the duration of the study. This is the first RH5-based vaccine to be tested in humans. The vaccines were well tolerated, with no safety concerns and there were no SAEs. T cell and serum antibody responses were assessed by *ex-vivo* interferon- γ ELISpot, ELISA and *in vitro* growth inhibition activity (GIA) assays. The vaccines were immunogenic and these data will be presented.