Fusion molecules containing properly folded 6C were affinity purified using a rat monoclonal antibody. A preclinical study screening of a series of adjuvant formulations (stable emulsions, liposomes, and alum) containing the immune modulators GLA, SLA, and/or QS21 plus GMZ2.6C was performed in C57BL/6 mice to identify a vaccine suitable for further human clinical studies. Those adjuvant formulations containing the synthetic TLR4 agonists GLA or SLA elicited the highest parasite-specific IFA titers, the greatest IFN-γ responses in CD4+ TH1 cells, and the highest percentage of multi-functional CD4+ T cells expressing IFN-γ and TNF in response to GMZ2.6C. GMZ2.6C combined with GLA or SLA formulated with QS21 provided the strongest TB activity four weeks following the last immunization. Furthermore, SMFA activity correlated strongly with the titer of antibodies recognizing sexual-stage parasites as measured in a gametocyte-extract ELISA. Vaccines combining GMZ2.6C with an adjuvant formulated with a synthetic TLR4 agonist show considerable promise, and scale-up manufacturing of the components is underway.

982

A FRAMEWORK FOR EVALUATING DIFFERENT MALARIA TRANSMISSION BLOCKING VACCINES

Anais Bompard[1], Dari F. Da[2], Sanna Rijpma[3], Serge Yerbanga[2], Thierry Lefevre[4], Sumi Biswas[5], Teun Bousema[3], Anna Cohuet[4], Thomas Churcher[1]

[1]Imperial College, London, United Kingdom, [2]IRSS/IRD, Bobo-Dioulasso, Burkina Faso, [3]Radboud University, Nijmegen, Netherlands, [4]MIVEGEC Université Montpellier, CNRS-Institut de Recherche pour le Developpement, Montpellier, France, [5]The Jenner Institute, University of Oxford, Oxford, United Kingdom

Transmission blocking vaccines (TBVs) against malaria are intended to induce immunity against the stages of the parasites which infect mosquitoes. Used within a community they protect the immediate neighbourhood of vaccinated individuals and could be a key tool for malaria elimination. Various TBV candidates are currently under evaluation. Their efficacy at reducing the number of infectious mosquitoes is dependent both on the level of parasite exposure (measured as the mean oocyst number in the control group, which may vary widely between locations) and on antibody titre (which decays with time between vaccination campaigns). This makes it important to understand the shape of the 3D relationship between efficacy, exposure and titre for each TBV candidate in order to compare them and predict their long term effectiveness in the field using early clinical trial data. Here we present a new mathematical framework for understanding this 3D relationship which takes into account the high variability generated by the membrane feeding assay. A variety of different functional forms are fit to the direct and standard membrane feeding assay data simultaneously for each TBV candidate, in order to generate smooth curves that allow the different candidates (with different titres) to be directly compared. Efficacy estimates from 4 different monoclonal antibodies (Pfs230, Pfs25, Pfs 48/45.1 and Pfs 48/45.5) are generated that allow their respective strengths and weakness in different conditions of malaria exposure and antibody titre to be identified. For example results indicate that pfs230 causes transmission blockade at a lower IgG titre than pfs25 and is more sensitive to changes in parasite exposure. This framework procures a comprehensive, easily accessible method of evaluating TBV candidates and can be combined with Phase II clinical trial data to predict their public health benefit in different field settings.

983

TRANSMISSION BLOCKING ACTIVITY OF ANTIBODIES TO *PLASMODIUM FALCIPARUM* GLURP-PF10C CHIMERIC PROTEIN FORMULATED IN DIFFERENT ADJUVANTS

Will Roeffen[1], Michael Theisen[2], Marga van de Vegte-Bolmer[1], Theo Arens[1], Gorm Anderson[3], Michael Christiansen[3], Sanjay Singh[4], Rajesh Kumar Singh[4], Robert Sauerwein[1]

[1]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands, [2]Statens Serum Institut, Copenhagen, Denmark, [3]University of Copenhagen, Copenhagen, Denmark, [4]Gennova, Pune, India

Plasmodium falciparum (Pf) is transmitted to a human host by bites of infected Anopheles mosquitoes after completion of parasite reproduction and sporogony. Clinical development of vaccines against transmission stages is critical for effective control and eradication of malaria. We generated a chimeric protein composed of ***Pf***-sub-unit fragments Glutamate-rich Protein (R0) fused in frame to a correctly folded fragment of ***Pf***s48/45 (10C). R0-10C was expressed as a recombinant protein in ***Lactococcus lactis*** and purified by affinity-chromatography. The soluble protein generated strong transmission blocking antibodies in rodents as determined in the Standard Membrane Feeding Assay (SMFA). Potency of different adjuvant/R0.10C combinations was tested in mice and rats using Freund's adjuvant, aluminium hydroxide (Alum), Alum with addition of GLA (TLR4-agonists), Stable Emulsion (SE)/GLA and AbISCO-100. All formulations produced high antibody titres recognizing the native Pfs48/45 protein in macrogametes/zygotes. Interestingly, Alum adjuvated combinations were the more potent inducers of transmission blocking antibodies. Moreover, SMFA activity correlated strongly with the titer of antibodies recognizing the native antigen as measured in a gametocyte-extract ELISA. The combined data provide a strong basis for entering the next phase of clinical grade R0-10C production and testing.

984

SCREENING FOR HIGHLY IMMUNOGENIC REGION OF PYGM75, A NOVEL TRANSMISSION-BLOCKING VACCINE CANDIDATE

Mayumi Tachibana, Motomi Torii, Moe Sudo, Takafumi Tsuboi, Tomoko Ishino

Ehime University, Matsuyama, Japan

Malaria transmission-blocking vaccines (TBVs) are intended to induce antibodies that inhibit parasite mating or further development inside mosquito midgut. Thus, TBV-immunized individuals cannot transmit malaria to mosquito vector, which could be one of good strategies to eradicate malaria. The number of candidate antigens for TBV is limited, and up to now, one leading vaccine-candidate, Pfs25, expressing on the ookinete surface is under phase I clinical trial. Thus, we urgently need to discover more vaccine targets. Previously, we reported that a novel male specific protein named PyGM75, is localized to the surface of microgametes in ***Plasmodium*** yoelii and that anti-PyGM75 antibodies had strong transmission-blocking activity. Since genomic database demonstrates that orthologue genes for PyGM75 are existed in human malaria parasites, ***Plasmodium falciparum*** and ***P. vivax***, this could be a promising candidate for TBV development. In this study, our aim is to determine which region of PyGM75 contains suitable epitopes for effective transmission-blocking antibodies. We produced 5 truncated PyGM75 recombinant proteins, excluding transmembrane domain in C-terminal, using wheat-germ cell-free expression system, and designated them as regions I, II, III, IV and V. Region-specific antibodies were collected by affinity purification from anti PyGM75full rabbit serum. Then the transmission-blocking efficiency of purified region-specific antibodies was examined by the membrane-feeding assay. As a result, specific antibodies against region V significantly reduced the numbers of oocysts on the mosquito midgut as efficiently as PyGM75full antibodies. These data suggested that the major epitopes for transmission-blocking antibodies