WORLD HEART FEDERATION

WORLD CONGRESS ON RHEUMATIC HEART DISEASE

2-4 November 2023 • Abu Dhabi

Submission Id: 330

Title: A M-PROTEIN BASED SUPER IMMUNOGEN PROVIDES LONG-TERM IMMUNOGENICITY AND PROTECTION AGAINST GROUP A STREPTOCOCCUS (STREPA) UPPER RESPIRATORY TRACT INFECTIONS

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Background & Aims: The primary contributor to group A streptococcus (StrepA; Streptococcus pyogenes) disease burden is rheumatic heart disease (RHD), which accounts for at least 15.6 million cases, resulting in 282, 000 new cases and 233, 000 deaths annually. A vaccine is urgently needed to combat RHD. Peptides hold significant potential as prophylactic and protective agents against a diverse range of infectious diseases. Their molecular compactness facilitates the design of multicomponent vaccines, allowing the strategic incorporation of epitopes from diverse target antigens.

Methods: Through a series of systematic amino-acid substitutions within the minimal M-protein epitope p145, we pinpointed a super immunogen, denoted as p*17. Peptide p*17 was conjugated to diphtheria toxoid (DT) or a non-toxic form of DT, CRM197 and combined with K4S2 (minimal epitope from the neutrophil anti-chemotaxis factor, SpyCEP) also conjugated to DT/CRM197.

Results: Mice vaccinated intramuscularly with the combination vaccine (p*17/K4S2) formulated in aluminium hydroxide were protected against upper respiratory tract (URT) challenge with covR/S mutant (MT) StrepA, 5448AP. Enduring Antibody (IgG) levels in the sera and saliva remained high up to 10 months post last-vaccine boost. Likewise, protection was observed for up to one-year post last vaccine boost. The vaccine lost its efficacy when tested in mice that lack mature B-cells (MuMT), indicating that antibodies play a major role in vaccine immunogenicity and efficacy. Furthermore, passively transferred purified IgG protected SCID mice against invasive challenge and mice were also protected following URT challenge with pre-opsonised StrepA. In a whole-cell ELISA, we also showed that vaccine-induced serum IgG recognises and binds to StrepA strains with multiple emm types.

Conclusions: Overall, we have identified a super immunogen that marks a significant advance towards the development of vaccine to combat RHD. The vaccine is currently undergoing a phase 1 clinical trial.