Cell-Mediated Immune Responses Elicited in Volunteers Immunized with the Novel Live Oral *Salmonella Enterica* Serovar Paratyphi A Vaccine Strain CVD1902

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Background: A candidate live oral attenuated *S*. Paratyphi A (PA) vaccine strain (CVD1902) harboring mutations in *guaBA* and *clpX* gene was developed to combat paratyphoid A fever. In this study, we evaluated whether immunization with CVD1902 elicits PA-specific T-cell mediated immune (CMI) and B memory responses in humans.

Methods: Peripheral blood mononuclear cells (PBMC) were obtained before and 28 days after immunization from two cohorts of volunteers who participated in a Phase-1 clinical trial. Each cohort consisted of 6 vaccinees (Cohorts 4 and 5 receiving a single oral dose with 10e9 and 10e10 CFU of CVD1902. respectively) and 2 Placebo controls (Saline only). Cytokines in culture supernatants (IFN-γ, RANTES, TNF-α, IL-10, and IL-23P40) were measured following in vitro stimulation with PA particles or PA flagella. We also evaluated the induction of B memory (B_M) cells against PA-LPS, using a standard B_M protocol, in 11 vaccinees and 4 placebo controls (cohorts 4 and 5).

Results: Significant post-vaccination increases (> 2 fold from pre-vaccination levels) for at least one of the cytokines evaluated was observed in 5 of 6 (83%) vaccinees, while 4 (67%) of them showed increases in two or more cytokines. None of the 2 placebo controls (0%) showed cytokine responses. Post-vaccination increases in PA-LPS-specific IgG and IgA B_M (>15 spot forming cells/10e6 expanded PBMC above pre-vaccination levels) were observed in 7 of 11 (64%) and 6 of 11 (55%) vaccinees, respectively, but not in placebo controls (0 of 4).

Conclusions: Previous extensive studies with live oral typhoid vaccine (Ty21a) and volunteers challenged with wild-type *S.* Typhi suggested that CMI responses may play a critical role in protection against typhoid fever. The data showing similar T and B cell-mediated PA specific-CMI responses elicited by CVD1902 in humans suggests that this might be an effective vaccine against paratyphoid A fever.