Abstract

Title of Thesis: "Immunogenicity and efficacy studies of typhoidal Salmonella immunogen in animal models"

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The severe intestinal disease typhoid, along with the growing paratyphoid fever, has a high rate of morbidity and mortality globally. There are licensed typhoid vaccines on the market, but there isn't one as of yet for paratyphoid. In the current work, we used a bacterial ghost platform to create a bivalent vaccination against *Salmonella* Typhi and *Salmonella* Paratyphi A. Bacterial ghost cells (BGs) are cell membranes generated from bacteria that are devoid of cytoplasm and yet maintain their whole cellular shape, including all surface characteristics. Moreover, the intrinsic adjuvant qualities of BGs stimulate a stronger humoral and cellular immunological response to the target antigen. *Salmonella* Typhi and *Salmonella* Paratyphi A ghost cells were prepared using sodium hydroxide. Electron microscopy was used to characterize the bacterial ghost cells. BALB/c mice were immunized intraperitoneally with the bivalent typhoidal bacterial ghost cells on the 0^{th}, 14^{th}, and 28^{th} day of the immunization schedule. An investigation of the hematopathology of adult mice during the immunization period revealed that the immunogen was safe and had no negative effects on the animals' health. Significant amount of increased, serum and secretory antibody titers against the outer membrane protein, lipopolysaccharide, whole cell lysate of both bacteria and Vi-polysaccharides of *Salmonella* Typhi were detected after complete immunization. In comparison to non-immunized control mice, bivalent typhoidal ghost cell-immunized animals exhibited improved survival, reduced bacterial colonization in systemic organs, and less inflammation and/or tissue degradation in histopathological investigation. Serum antibodies from animals that have received vaccinations have superior killing capabilities against *Salmonella* Typhi and *Salmonella* Paratyphi A, and they can dramatically reduce bacterial motility and mucus penetration ability. Significant passive protection was also seen when immunized animals' lymphocytes and serum antibodies were adopted and transferred to naïve animals following bacterial infection. Result from the ex-vivo studies revealed that, splenic cell of immunized animals showed an increase in $CD4^+$, $CD8a^+$, and $CD19^+$ cell populations. We also observed a dominant IgG2a antibody response over IgG1 in serum of immunized animals. On the other hand, there is a strong Th1-Th17 response in immunized mice was obtained from dendritic cell and splenic cell restimulation, and co-culture study. For the long-term memory response following vaccination, we have evaluated T cell memory response. Significant induction of T effector memory response suggested that the proposed vaccine was effective over the long run. Overall, Bivalent Typhoidal Bacterial Ghost cells (BTBGs) are safe and augmented protective humoral and mucosal antibody response, induces cellular immunine response as well as stimulate memory responses. The newly formulated bacterial ghost cell-based vaccine is protective against both *Salmonella* Typhi and *Salmonella* Paratyphi A infections as well. This vaccine formulation acts as bivalent vaccine candidate and can be used to prevent typhoidal and paratyphoidal infectons near future.

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