## ABSTRACT

**Title: Studies on host protective response to *Salmonella* infection**

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Typhoid and paratyphoid fevers, collectively known as enteric fever are caused by *Salmonella enterica* serovar Typhi (*S.* Typhi) and *S. enterica* serovar Paratyphi A and B (*S.* Paratyphi), and remain major threats to public health in the developing world. Although improved food and water hygiene with proper sanitation is the key to the permanent solution of this problem, vaccination of the high-risk population would result in immediate reduction of morbidity and mortality. Commercially available, injectable typhoid vaccines are modestly effective and work through the induction of systemic Vi antibody response, whereas the efficacy of the licensed oral vaccine is compromised owing to oral tolerance. These vaccines are ineffective against Vi negative salmonella strains. Additionally, no commercial vaccines against paratyphoid fever exist to-date. A broad-spectrum vaccine that is safe to use at all age groups, and can provide long term protection against both these serovars is urgently required. A major bottleneck in developing a broad-spectrum vaccine is the limited knowledge on the correlates of vaccine-induced protection against enteric fever. Despite serum antibody titres being widely used for this purpose, they are often poorly correlated with the secretory antibodies in the intestine and the cell mediated immune response, both of which are required for long term protection against typhoid fever.

The studies undertaken for my PhD thesis has several components. Firstly, I established an iron overloaded murine model to study the pathogenesis of *S.* Paratyphi A infection. Second, A chimeric antigenic formulation, called rCTB-T2544 was developed by conjugating a somatic antigen, rT2544 of *S.* Typhi and *S.* Paratyphi A and the B subunit of the cholera toxin (CTB) from *Vibrio cholerae*. Intranasal immunization with rCTB-T2544 evoked strong and sustained systemic and intestinal mucosal immunity and conferred with the protection against *S.* Typhi and *S.* Paratyphi A infection in iron overloaded mice model. Thirdly, another mucosal adjuvant FliC was co-administered systemically with rT2544 that showed considerable protection with a smaller dose of the individual components and provided with a platform for designing a multivalent vaccine against enteric diseases in the future. Both the vaccine formulations substantiated the potentiality of the mucosal antibodies to inhibit bacterial motility and bacterial attachment to the host epithelial cells by *in vitro* studies. The role of follicular helper T cells, gut homing lymphocytes, cytotoxic T lymphocytes in the circulation was underappreciated prior to this study. The current study focused on the contribution of mucosal antibodies in the intestine and cell mediated immune response that might significantly contribute to the overall vaccine outcome. A prime-boost regimen with intranasal followed by systemic immunization may be ideal for typhoid and paratyphoid vaccination and demands further elucidation. This study has special implications for India to reduce the burden of both acute enteric fever cases and the asymptomatic carrier stage, the latter being the reservoir of infection and responsible for future development of gall bladder adenocarcinoma.


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