A novel candidate vaccine against typhoid and paratyphoid fever

Global burden of typhoid and paratyphoid fever

- >12-33 million cases with ~ 216,000 - 600,000 deaths per year globally
- Incidence in India 102-2219 per 100,000 populations
- Typhoid-causing bacteria (*Salmonella* Typhi) is responsible for nearly 50% of all blood-culture positive infections in Nepal and also the predominant cause of neonatal ICU infection
- Typhoid may cause life-threatening complications like intestinal perforation and encephalopathy if not treated properly
- A chronic carrier state of *Salmonella* Typhi infection (no manifestation of acute typhoid fever) may lead to gall bladder cancer

The Lancet Global Health, 2014

Why we need a new vaccine for typhoid and paratyphoid fever

- **Diagnostic problems**
  - A positive blood culture is confirmatory, but the yield is low
  - Widal test and Typhidot are widely used , but unreliable for diagnostic purposes
- **Therapeutic problems – multidrug resistance**
  - High incidence of resistance to penicillins and co-trimoxazole
  - Variable resistance to chloramphenicol and fluoroquinolones
  - A fluoroquinolone-resistant strain (H58 haplotype) has recently spread across 74 countries from several continents
  - Resistance to 3rd generation cephalosporins (Extensively drug resistant or XDR strain) has been reported from Pakistan

Why we need a new vaccine for typhoid and paratyphoid fever

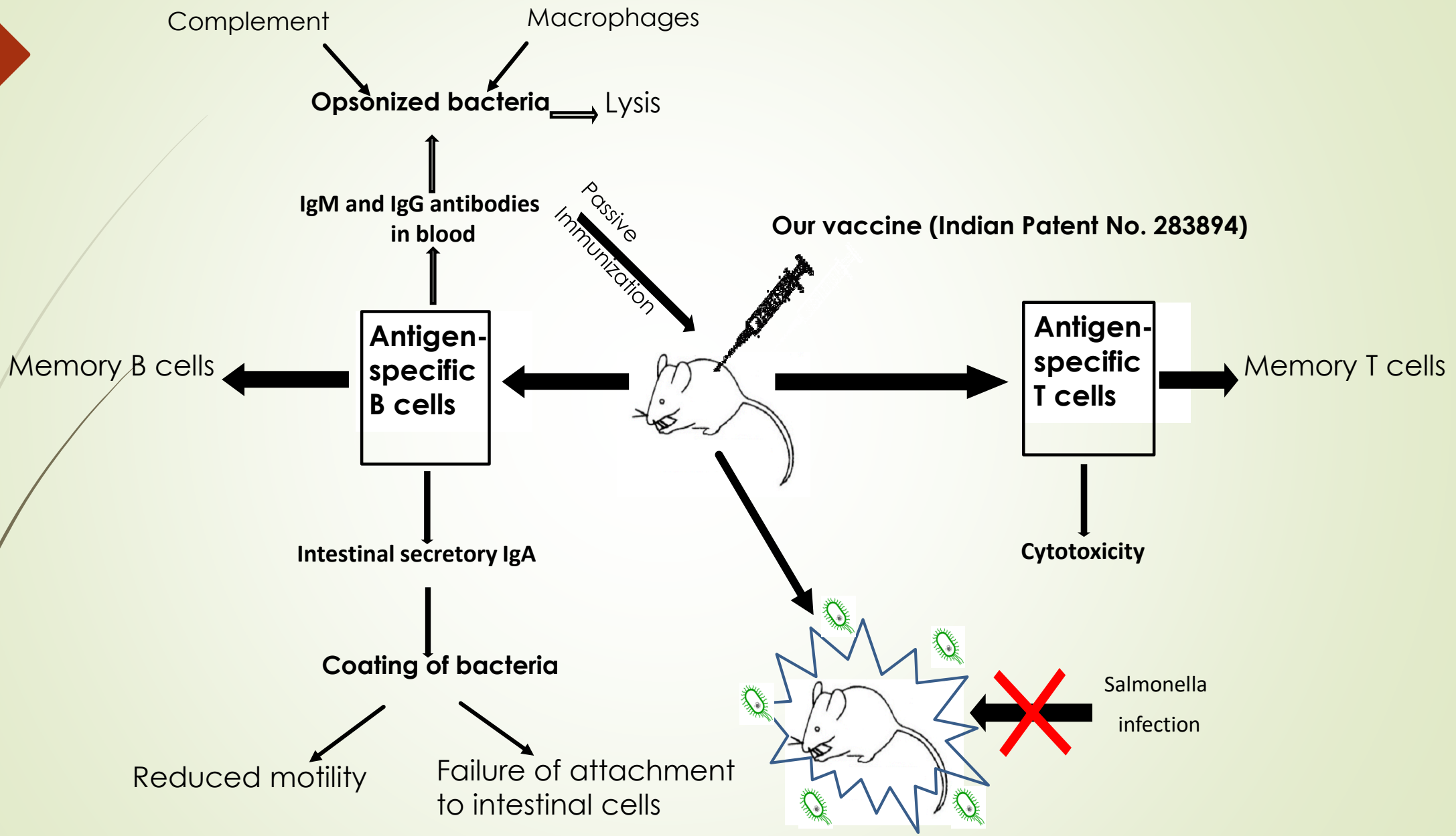
- **Vaccine-related problems**
  - Currently available vaccines have modest efficacy with 85% protection at the end of 1 year and 50% after 2 yrs (Fraser et al, 2007)
  - However, they are ineffective against the bacteria that lack polysaccharide capsule
  - No safe and effective vaccine is widely available for smaller children

What is our novel vaccine and how does it work

- Our vaccine contains an outer membrane protein of *Salmonella* Typhi/Paratyphi that aids in attachment to the human intestinal cells. The protein is conserved across the circulating clinical strains of the bacteria.
- When injected subcutaneously into the mouse, the vaccine induces
  - strong IgM and IgG antibody response in the blood that coats the bacteria, facilitating its removal by the body's immune system.
  - Antibody secreting plasma cells and memory B-cells which are specific for the vaccine antigen in the spleen, mesenteric lymph nodes and intestine
  - Secreted antibodies in the stool which inhibits bacterial motility and blocks attachment to the intestinal cells
  - Finally, a strong T-cell response (both effector and memory T cells) which are important not only for immediate, but also for long-term protection against Typhoid and paratyphoid fever

What is our novel vaccine and how does it work

- The mice immunized with the vaccine were protected against challenges with *Salmonella* Typhi and Paratyphi infections. Also, transfer of the sera from the immunized mice protected previously unimmunized animals against the infection.
- Most importantly, people suffering from acute typhoid fever developed vaccine antigen-specific and protective IgG antibodies in their blood.


Complement
Macrophages
Opsonized bacteria
Lysis
IgM and IgG antibodies in blood
Passive Immunization
Our vaccine (Indian Patent No. 283894)
Antigen-specific B cells
Memory B cells
Antigen-specific T cells
Memory T cells
Intestinal secretory IgA
Cytotoxicity
Coating of bacteria
Reduced motility
Failure of attachment to intestinal cells
Salmonella infection

How is our candidate vaccine different from the existing ones

Criteria	Our vaccine (T2544 vaccine)	Vi-TT vaccine	Vi-polysaccharide vaccine	Live vaccine (Ty21a)
Input material	Protein	Protein-polysaccharide conjugate	Polysaccharide	Whole bacterial cell
Cold chain requirement	May be required	Required	Required	Required
Safety	High (expected)	High	High	Not recommended under 6 yrs of age
Immunogenicity	Antibodies and cell-mediated immunity	Antibodies and cell mediated immunity	Antibodies	Antibodies and cell mediated immunity
Intestinal immunity	Yes	No	No	Yes
Long term efficacy	Yes (in animal studies)	Yes (limited report)	Poor	Poor
Efficacy against intracellular bacteria	Yes	Not known	No	Yes

How is our candidate vaccine different from the existing ones

Criteria	Our vaccine (T2544 vaccine)	Vi-TT vaccine	Vi-polysaccharide vaccine	Live vaccine (Ty21a)
Protection against Salmonella Paratyphi	**Yes**	**No**	**No**	**Cross protection reported**
Interference with other vaccine-induced immunity	Not expected	May be (immunity against tetanus)	No	No
Mass vaccination	May be effective	May become ineffective in the future (Vi-negative Typhi and Paratyphi strains may replace Vi-positive strains)	May become ineffective in the future (Vi-negative Typhi and Paratyphi strains may replace Vi-positive strains)	May be effective
Production cost	Low	High	high	High
Scalability	High	Less	Less	Less