



Enterotoxin Vaccines: The Bitoun Lab

Diarrheal disease is a major cause of morbidity and mortality in the developing world. Enterotoxic *E. coli* (ETEC) are a major contributor to this human health burden. *E. coli* can cause disease through two toxic proteins – the heat stable (ST) and heat labile (LT) enterotoxins. The lab of **Jacob Bitoun** is focused on developing a vaccine against the ST protein, with the goal of reducing the incidence of ST-mediated diarrheal disease.

Heat Stable *E. coli* Toxin

The Heat Stable *E. coli* toxin (ST) is the smaller of the two *E. coli* diarrhea-causing toxins. At only 18-19 amino acids long, it is technically challenging to work with. However, recent studies demonstrate that ST is the more important enterotoxin from a human disease standpoint, as ETEC that express only the heat labile toxin (LT) cause minor diarrheal disease. ST also suppresses the natural adjuvant characteristics of the LT. This leads to recurrent infection, with similar ETEC strains and long-term morbidity, as children with chronic diarrheal disease are malnourished. This can cause developmental delays intellectually and physically, a phenomenon known as stunting. This can exacerbate economic problems in areas of the developing world where diarrheal disease is endemic and common in children less than five years old. Thus, development of a viable vaccine that is protective against the effects of the ST is a high world health priority.

Vaccine Development

There is currently no murine model for ETEC-mediated diarrheal disease, since ETEC is only a pathogen of piglets and humans. Murine studies are good tools to evaluate toxicity but ETEC vaccine studies rely on controlled human infection models. The Bitoun lab is also working with enteroids, mini-organs generated from the intestinal stem cells (including crypt cells) of mice and humans and grown in culture.

Vaccine Development (cont.)

Resembling an “inside-out” small intestine, the lab is able to use this system to tease apart the precise effects of ST on specific cell types in the intestinal tract. Specifically, the Bitoun lab wants to fully clarify what benefit ST provides to the E. coli expressing it, and how these actions lead to pathogenesis. With this information in hand, they will work to develop an effective murine vaccine model. Towards this goal, they have shown that ST can bind zinc. The WHO recommends zinc supplementation at diarrheal disease onset.

Additionally, ST is able to downregulate the activity of TH17 cells, a vital component of the mucosal immune response to bacterial infection. Leveraging Dr. Bitoun’s training as a biochemist with the strength of Tulane’s varied Infectious Disease research programs, the lab is well-equipped to develop a vaccine approach to curbing diarrheal disease based on an in-depth understanding of ST.

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