Abstract

“Progress and challenge in developing vaccines against enterotoxigenic *Escherichia coli* (ETEC)”

Enterotoxigenic *Escherichia coli* (ETEC) continue to be a top cause of moderate-to-severe diarrhea in children less than five years in developing countries and the most common cause of diarrhea in children and adults traveling from developed countries to developing countries and regions. ETEC strains are also the predominant cause of neonatal diarrhea and post-weaning diarrhea in livestock animals. Currently, there is no licensed vaccine against children’s diarrhea, travelers’ diarrhea, or animal post-weaning diarrhea. ETEC strains produce over 23 immunologically different adhesins and two distinct enterotoxins (heat-labile toxin, LT, and heat-stable toxin, STa). LT and STa are potent toxins; moreover, the 19-amino acid STa is poorly immunogenic. An effective ETEC vaccine would need to carry multiple adhesin antigens to induce broad anti-adhesin immunity, preferably small intestinal mucosal immunity, against the heterogeneous adhesins. This vaccine also has to carry safe toxin antigens to induce antitoxin antibodies neutralizing LT and STa toxins. The efficacy of such a vaccine would need to be assessed by suitable animal challenge models in prior to human subject studies. Progress has been made to overcome these challenges. We have developed the MEFA (multiepitope fusion antigen) based structural vaccine technology and integrated the most important and virulent ETEC adhesin antigens into a backbone carrier for a single MEFA protein to induce broad antibodies against all target adhesins. We also generated toxoids as safe antigens and toxoid fusions to enhance anti-STa immunogenicity, and have identified toxoid fusion 3xSTaN12S-mnLT the leading antigen to induce protective antibodies against both toxins.
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Abstract (cont’d)

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Moreover, we demonstrated that CFA MEFA (CFA/I/II/IV) either co-administered with toxoid fusion 3xST\textsubscript{AN12S}-mnLT or further genetically fused to the toxoid fusion for a CFA-toxoid MEFA (CFA-3xST\textsubscript{AN12S}-mnLT) induced protective antibodies against the seven most important adhesins (CFA/I, CS1-CS6) and both toxins. In addition, a pig challenge model has been developed to unambiguously measure the protective efficacy of antitoxin antibodies against ETEC diarrhea, and a pig-and-rabbit dual-challenge model to evaluate ETEC vaccine efficacy. This structure-defined MEFA technology perhaps can be applied in general for multivalent vaccine development against other diseases.

Bio-Summary

Dr. Weiping Zhang is a Professor in the Diagnostic Medicine/Pathobiology Department at Kansas State University College of Veterinary Medicine. He received his BS and MS training in China, and PhD at Iowa State University in 1996. His research mainly focuses on pathobiology of enterotoxigenic Escherichia coli (ETEC) in diarrheal disease and vaccine development against diarrhea caused by ETEC and other enteric pathogens for livestock animals and humans. His research program is supported by NIH, EVI/PATH/Bill and Melinda Gates Foundation, USDA and National Pork Board.