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IDENTIFICATION AND CHARACTERIZATION OF HUMAN MONOCLONAL ANTIBODIES FOR IMMUNOPROPHYLAXIS AGAINST ENTEROTOXIGENIC ESCHERICHIA COLI

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Background. Enterotoxigenic *Escherichia coli* (ETEC) infections are the major cause of diarrheal morbidity among children living in developing countries. ETEC mediates small intestine adherence through bacterial adhesion followed by production of enterotoxins that induce diarrhea. Currently there is no vaccine available for ETEC. One of the most predominant adhesin of pathogenic ETEC strains is colonization factor antigen I (CFA/I). The CFA/I adhesion tip, CfaE, is required for ETEC binding to human intestinal cells and colonization. Human antibodies against CfaE have potential to block colonization of ETEC and serve as a potent immunoprophylactic against ETEC-related diarrhea.

Methods. A panel of human IgG1 monoclonal antibodies (HuMAbs) were generated against CfaE. The antibodies were tested *in vitro* for blockage of bacterial adhesion to intestinal cells and *in vivo* for inhibition of bacterial colonization in the ileum. Antibody epitope analysis were performed using BioLuminate software (Schrodinger, Inc.), followed by mutagenesis of the predicted residues located in the antibody/CfaE interface and *in-vitro* binding assays.

Results. The lead IgG1 anti-CfaE HuMAbs blocked 50% of adhesion of ETEC bacterial cells to human intestinal cells at concentrations ranging from 0.3 to 1.3 ug/ml. *In vivo* studies revealed 2 to 4 log decrease in colony forming units in the small intestine when the bacteria were pre-incubated with anti-CfaE MAbs as compared to an irrelevant isotype control. *In silico* epitope analysis revealed critical residues involved in the MAbs interaction with CfaE. Two of the leads HuMAbs recognize epitopes sequence conserved across other 6 major adhesins.

Conclusions. We have identified a panel of fully human IgG1 monoclonal antibodies against CfaE protein of ETEC. These antibodies are capable of blocking *in vitro* and *in vivo* ETEC adhesion to intestinal cells at low concentrations. Two lead antibodies recognizing sequence conserved epitopes have the potential for cross-protection against multiple ETEC strains.

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