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Identification and Characterization of Human Monoclonal Antibodies for Immunoprophylaxis against Enterotoxigenic Escherichia coli

Serena Giuntini  
*University of Massachusetts Medical School*

Matteo Stoppato  
*University of Massachusetts Medical School*

Monir Ejemel  
*University of Massachusetts Medical School*

*See next page for additional authors*

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Serena Giuntini, Matteo Stoppato, Monir Ejemel, Danielle Wisheart, Mark S. Klempner, and Yan Wang

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

Serena Giuntini, Matteo Stoppato, Maja Sedic, Monir Ejemel, Danielle Wisheart, Mark S. Klempner, Yang Wang
MassBiologics of UMMS, Boston, MA

Background. Enterotoxigenic Escherichia coli (ETEC) infections are the major cause of diarrhea 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.

Contact:
Serena Giuntini
MassBiologics of UMMS
Serena.giuntini@umassmed.edu