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## AIEC Engagement of CEACAM6: Defining the Link to Crohn's Disease

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### RELEVANCE TO IBD:

Although the cause(s) of Crohn's disease and ulcerative colitis is (are) not known, current evidence supports an interaction between luminal bacteria and host innate and adaptive immune responses in a genetically susceptible host, which ultimately leads to recurrent episodes of acute and chronic mucosal inflammation. Through research activities aimed at defining the mechanisms of inflammatory injury in the gut, it is now evident that both loss of epithelial barrier function and mucosal integrity, with increases in permeability to macromolecules, and participation of the intestinal microflora are essential features of chronic inflammatory bowel diseases (IBD).

Consequently, an improved understanding of the complex nature of the interactions between luminal bacteria and host epithelial and immune cells is required to shed light on both the cause and triggers of mucosal inflammation in IBD. In this way, novel and rational strategies can be developed for ultimate use in the management - both for treatment and prevention - of humans afflicted with IBD.

In the search to understand the microbial link to Crohn's disease, the importance of a particular lineage of *E. coli* has recently emerged: the ileal mucosa of Crohn's disease patients is colonized by 'adherent and invasive *Escherichia coli*' (AIEC). While non-pathogenic *E. coli* remain in the lumen of the gut, AIEC, instead, penetrate into the intestinal epithelium. This invasive phenotype could, undoubtedly, contribute to the hyper-inflammatory response observed in IBD.

This application was prompted by a recent report that AIEC attach to ileal mucosa via the carcinoembryonic antigen-related cellular adhesion molecule 6 (CEACAM6), the significance of which was highlighted by its review in the New England Journal of Medicine (2007;357(7):708-10). Considering that CEACAM6 is not expressed by rodents, it has been impossible to define the contribution of AIEC binding to this receptor *in vivo*. The studies outlined herein take advantage of novel transgenic mouse lines expressing a human complement of CEACAM receptors to elucidate the role of CEACAM6 binding in AIEC colonization and disease in the intestinal tract. The proposed work will be complemented with *in vitro* studies aimed at defining cellular responses to AIEC binding to CEACAM6.

The 'CEACAM-humanized' mice employed herein represent the first opportunity to establish an *in vivo* model of AIEC infection and disease. Moreover, our combined experience in the cellular, molecular, and immunologic aspects of CEACAM receptor biology (Gray-Owen) and gastrointestinal infections and disease (Sherman) provide us with established tools and the relevant expertise required to delineate this important host-pathogen interface. By defining the interactions of adherent and invasive *E. coli* with host cells and tissues, we will advance knowledge in this emerging field. Our work has the potential to provide a new model of IBD and to reveal new strategies to treat and, ultimately, cure IBD.