TARGETING THE GUANYLATE CYCLASE C RECEPTOR WITH AN AGONIST PEPTIDE FROM ENTEROTOXIGENIC *Y. ENTEROCOLITICA*

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Heat-stable enterotoxin peptides (ST's) are expressed by enterotoxigenic strains of bacteria in order to co-opt an endogenous ligand-receptor system that regulates fluid homeostasis within the gut. Bacteria such as *E. coli, V. Cholerae, and Y. enterocolitica* have evolved ST's which mimic native guanylin/uroguanylin peptides by activating guanylate cyclase C (GC-C), yet possess increased resistance to heat/enzymatic degradation as well as superagonist activity by virtue of a third disulfide bond. We have previously utilized ST peptides derived from an *E. coli* isolate, as well as analogs of the endogenous peptide hormone uroguanylin, as imaging and therapeutic agents for GC-C-expressing colorectal cancers. In this work, we have compared the ability of these peptides to target GC-C and engender production of cGMP with that of an ST analog derived from *Yersinia enterocolitica*. Previous results had suggested that the *Y. enterocolitica* sequence may elicit higher cyclase activity than other peptides in this class. We have generated the peptide GENDWDWCCELCCNPACFGC both with and without an N-terminal DOTA chelating moiety and characterized its receptor binding affinity and ability to stimulate cGMP production in comparison to other peptides in this class. Our findings indicate that the *Yersinia* peptide possesses receptor binding affinity and cyclase stimulating activity intermediate between known *E. coli* ST analogs and human uroguanylin. However, *in vivo* biodistribution results obtained using the ^{64}Cu-labeled DOTA-peptide demonstrated normal tissue distributions substantially different from *E. coli*-derived peptides, and more akin to those obtained with radiolabeled uroguanylin peptides.