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Targeting human colorectal cancer cells using radiolabeled *E. coli* heat-stable enterotoxin analogs

The guanylate cyclase C (GC-C) receptor protein is normally expressed at high levels on the luminal surface of the gastrointestinal epithelium. Binding of the endogenous peptides guanylin and uroguanylin to GC-C initiates a signaling cascade, leading to phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR). Phosphorylation of CFTR opens the channel, resulting in net flow of water and Cl^- ions into the intestinal lumen. Perhaps via gene transfer from vertebrate hosts, enteropathogenic strains of *E. coli* have evolved a homologous peptide, the *E. coli* heat-stable enterotoxin (ST_h), which has the highest affinity for the GC-C receptor of any known ligand. Expression of GC-C persists in mucosal cells that have undergone malignant transformation, providing a specific marker for human colorectal cancer. Presentation of the GC-C receptor on the surface of colorectal cancer cells therefore provides a specific target for binding of radiolabeled heat-stable enterotoxin analogs. The goal of the work presented here is to develop analogs of the ST_h with N-terminal pendant chelating moieties that can deliver imaging and therapeutic radionuclides to primary and metastatic colon cancer tissues. Data will be presented relating to a modified ST_h analog. This analog has been synthesized and labeled with nonradioactive indium and the radioisotope ^{111}In. The analog was evaluated for receptor binding affinity *in vitro*, as well as for *in vivo* pharmacokinetic characteristics in SCID mice with human colon cancer xenografts. Receptor binding affinity was in the nanomolar range for both labeled and unlabeled peptides, and *in vivo* results demonstrated localization of radiolabel within the tumor mass.