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Synthesis and Characterization of a ^{68}Ga/NIR Labeled Peptide for Somatostatin Receptor Targeting

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BACKGROUND: Growing clinical evidence has shown that intraoperative imaging with fluorescent contrast agents can improve tumor identification and demonstrates the emerging role of fluorescence-guided surgery in cancer. To facilitate characterization, fluorescent probes have been dual-labeled with a radionuclide to enable cross-validation with nuclear imaging. A clinical radiotracer would serve as an ideal model for dual labeling since it could provide a benchmark to support translation. Here, we synthesized a dual-labeled octreotide analog using a multimodality chelator (MMC) that minimizes the effects of dye labeling, and evaluated agent properties in somatostatin receptor-2 (SSTR2) expressing cells and xenografts.

METHODS: MMC synthesis was performed by selectively attaching azide and acetate pendant arms to a DOTA analog. Tyr3-octreotide (TOC) was conjugated to the MMC on solid-phase and the conjugate was labeled with IRDye800 to produce MMC-TOC(IR800). ^{68}Ga labeling was performed using eluate fractionation and two cation exchange methods. Stability was examined in mouse serum. In vitro studies were carried out in SSTR2-expressing human colorectal carcinoma cells (HCT116(SSTR2)) and compared to ^{68}Ga-DOTA-TOC. PET/CT and near-infrared fluorescence (NIRF) imaging was conducted in HCT116(SSTR2) xenografts and compared to ^{68}Ga-DOTA-TOC.

RESULTS: MMC-TOC was synthesized on solid-phase and dual labeling was confirmed by HPLC. ^{68}Ga labeling was optimized for buffer concentration and reaction time, and produced comparable radiochemical yields (86.7-89.4%). No breakdown products were found following serum incubation. ^{68}Ga-MMC(IR800)-TOC uptake was 17.7±1.6% in HCT116(SSTR2) cells and reduced to 4.1±1.8% in the presence of a 10-fold excess of octreotide. Uptake in parental HCT116 cells was 1.9±0.9%. The findings were in agreement with ^{68}Ga-DOTA-TOC and indicate receptor-mediated uptake of the dual-labeled agent. PET/CT showed ^{68}Ga-MMC(IR800)-TOC localization in tumors with a tumor-to-muscle ratio of 3.4 (n=3), and correlated with NIRF images.

CONCLUSION: The MMC scaffold is effective for developing a dual-labeled octreotide analog that retains receptor-binding properties and permits multimodal imaging.