Fluorescent Peptide Conjugates for Intraoperative Imaging

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Surgical resection is the main treatment for pancreatic neuroendocrine tumors (pNETs) and can be curative if tumors are completely removed [(1)]. However, the small size of these tumors, presence of multifocal lesions, and frequent lymph node metastases complicate intraoperative localization and margin detection. Positive margins range from 10-30% in pNETs and are strongly associated with increased risk of death. Alternatively, extended pancreatectomy may have unnecessarily wide surgical margins that can cause pancreatic insufficiency in up to 40% of patients and impair quality of life [(2-4)]. Organ-sparing R0 resections could reduce incidences of tumor recurrence and postoperative pancreatic insufficiency but require clear tumor visualization, particularly during minimally invasive surgery where tactile feedback is absent. Since current imaging modalities cannot provide tumor-specific localization in the operating room, more effective imaging approaches are critically needed.

Fluorescence-guided surgery (FGS) is an intraoperative imaging modality that is typically performed in the near-infrared fluorescence (NIRF) spectral range, where the combination of low tissue autofluorescence and high depth penetration can increase detection sensitivity [(5)]. Given the near-universal expression of somatostatin receptor subtype 2 (SSTR2) in well-differentiated NETs, we converted the clinically approved SSTR2-targeted radiotracer ^{68}Ga-DOTA-TOC into a fluorescent analog, referred to as MMC(IR800)-TOC [(6)]. MMC (multimodality chelator) is a cyclen analog that permits bioorthogonal dye conjugation and allowed

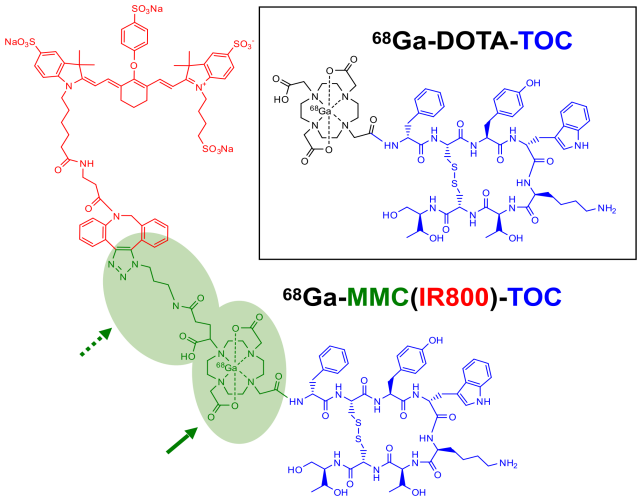

Fig. 1. Chemical structure of ^{68}Ga-MMC(IR800)-TOC showing a similar footprint to ^{68}Ga-DOTA-TOC. MMC

us to utilize quantitative radioactive techniques to demonstrate selective binding in SSTR2 expressing cells and *in vitro* and in animal models. Tumor targeting was further demonstrated by *ex vivo* staining of human pNET biospecimens, suggesting high potential for clinical translation [(7)].

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