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Dual labeling as a tool for cross-validating the imaging properties of a hybrid somatostatin analog

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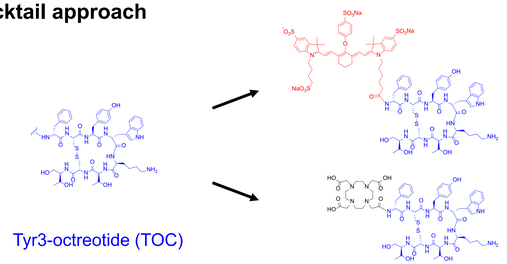
Background

Surgery is the primary treatment option for most solid tumors and can be curative if all cancer cells are removed. For several types of neuroendocrine tumors (NETs), surgery is indicated not only for localized lesions but also for metastatic disease to control excessive hormone production. Clinical evidence has shown that fluorescent agents can improve intraoperative detection of tumors compared to visual observation. An ideal approach for developing an intraoperative imaging agent for NETs would be to build upon the clinically established imaging utility of radiolabeled peptides that target somatostatin receptor-2 (SSTR2) overexpression. Using a customized multimodality chelator (MMC), we introduced a fluorescent label onto the radiolabeled somatostatin analog, ^{68}Ga-DOTA-TOC, and produced the bioactive dual-labeled analog, ^{68}Ga-MMC(IR800)-TOC. Here, we examined the tumor-targeting properties and pharmacokinetics of the dual-labeled analog in tumor xenografts and showed the impact of dual labeling on tracer characterization.

Rationale for dual labeling

Cocktail approach



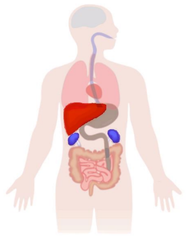
IR800-TOC

MW	2086
Log P	n/a

DOTA-TOC

MW	1421
Log P	-2.9

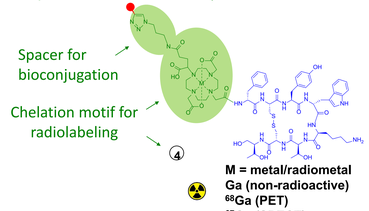
Differences in pharmacokinetic disposition



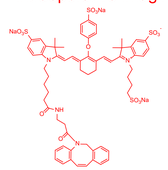
Dual labeling

M-MMC(IR800)-TOC

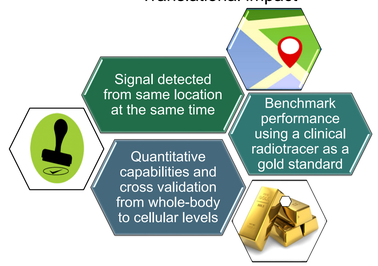
1. **MMC** ("Radioactive linker" for quantitative assessment)
2. **TOC** (Targeting moiety)
3. **IR800-DBCO** (Near-infrared reporter for intraoperative imaging)



M = metal/radiometal
Ga (non-radioactive)
^{68}Ga (PET)
^{67}Ga (SPECT)



Translational impact



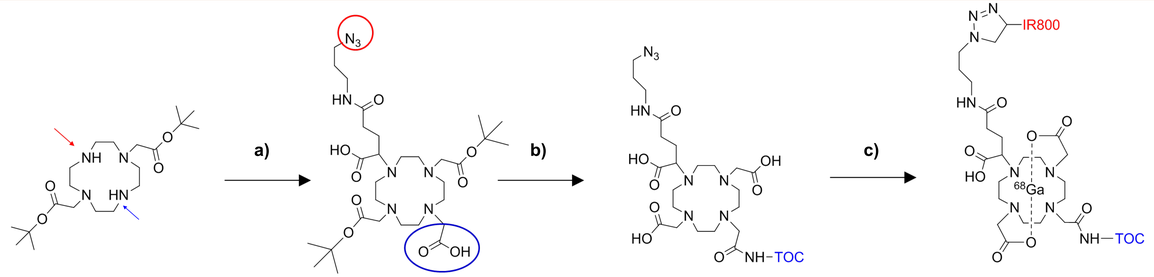
Conclusions

The MMC scaffold is effective for developing a dual-labeled octreotide analog. Maximizing the distance between the dye and pharmacophore allowed retention of *in vivo* receptor-binding properties. For the fluorescent DOTA-TOC analog, a delayed optical imaging time point (24 h) provides an optimal tumor-to-tissue contrast.

References

1. Advances in the Development of Multimodal Imaging Agents for Nuclear/ Near-infrared Fluorescence Imaging, Ghosh, S. C. and **Azhdarinia, A.**. Curr Med Chem. 2015.
2. A Modular Dual Labeling Scaffold That Retains Agonistic Properties for Somatostatin Receptor Targeting, Ghosh, S. C., et al. JNM. 2017.
3. Synthesis of a Fluorescently Labeled 68Ga-DOTA-TOC Analog for Somatostatin Receptor Targeting, Ghosh, S. C., et al. ACS Med Chem Lett. 2017.

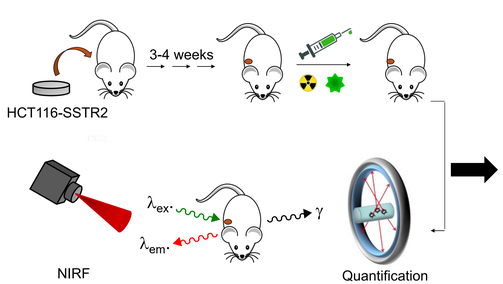
Synthesis of a dual-labeled TOC analog

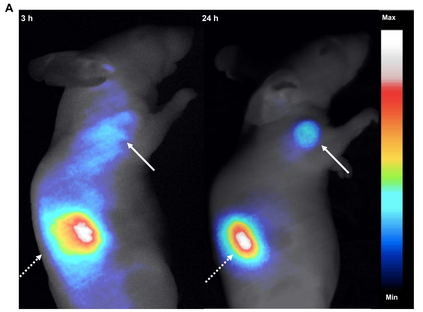


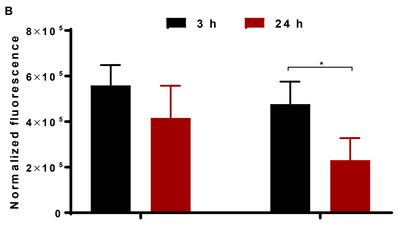
MMC-TOC — ^{68}Ga/Ga-MMC(IR800)-TOC

a) site-specific conjugation of azido and acetate pendant arms onto a cyclen analog; **b)** conjugation of TOC to MMC-intermediate on solid-phase to afford MMC-TOC; **c)** IR800 conjugation in solution phase and ^{68}Ga/Ga labeling (acetone method) to yield the final product.

In vivo imaging in SSTR2-expressing xenografts and quantitative biodistribution

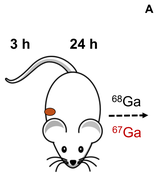


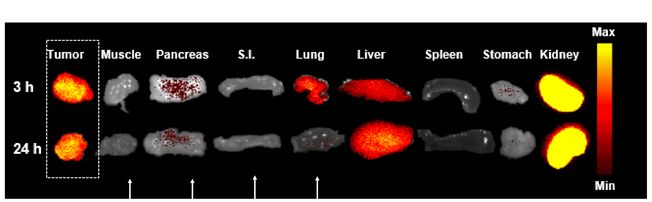


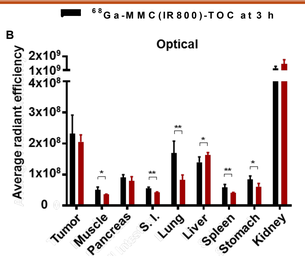


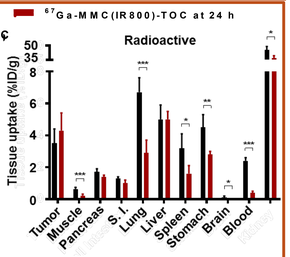
Determination of optimal imaging time point and *ex vivo* quantitative analysis and nuclear/NIRF contrast determination. (A) Representative NIRF images of Ga-MMC(IR800)-TOC were acquired in HCT116-SSTR2 xenografts at early and delayed time points using a custom EMCCD fluorescence imaging system. Solid arrows indicate tumor, dashed arrows indicate kidney. **(B)** tissue fluorescence by analysis of EMCCD imaging. * P< 0.005. Data are presented as mean ± standard deviation (n=5).

SSTR2-mediated tumor-targeting









Quantitative biodistribution assessment by dual labeling. (A) *Ex vivo* optical images (IVIS) of organs resected from HCT116-SSTR2 xenografts injected with ^{68}Ga-MMC(IR800)-TOC or ^{67}Ga-MMC(IR800)-TOC. Determination of **(B)** tissue fluorescence by analysis of IVIS imaging at major sites of NET incidence (pancreas, small intestine, lung) and clearance organs (kidney, liver). Corresponding determination of **(C)** radioactive uptake by gamma counting. * P< 0.05, ** P< 0.01, ***P< 0.001. Data are presented as mean ± standard deviation (n=5). S.I., small intestine.

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