Tracking Tumor Response to Chemotherapy Using a Multimodal Imaging Probe

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Background

We have recently developed a multi-modal imaging probe (CLIO-EPPT) targeting the underglycosylated mucin-1 tumor-specific antigen (uMUC-1), which is one of the early hallmarks of tumorogenesis in a wide variety of tumors. Our tumor-selective multimodal imaging probe consists of crosslinked superparamagnetic iron oxide nanoparticles (CLIO) for MR imaging, modified with Cy5.5 dye (for optical near-infrared imaging, NIRF), and has peptides (EPPT), specifically recognizing uMUC-1, attached to the nanoparticle's dextran coat (1).

Previously we demonstrated the suitability of CLIO-EPPT as a multimodal imaging probe in *subcutaneous* tumor models. This study describes the application of CLIO-EPPT for tumor detection in an *orthotopic* mouse model of human pancreatic adenocarcinoma. In addition, we employed CLIO-EPPT in order to track tumor outcome in response to chemotherapy using the same model. With this series of studies, we have established the utility of CLIO-EPPT for tumor detection and monitoring in a clinically relevant scenario.

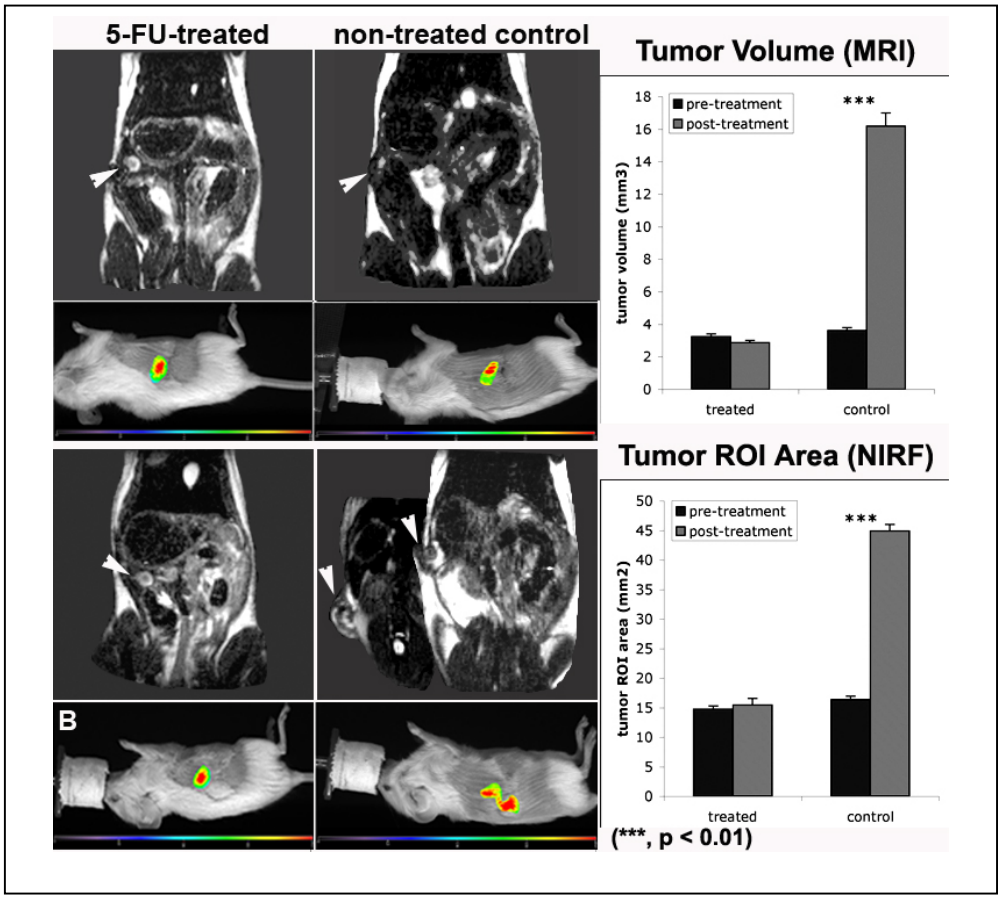
Materials and Methods

Imaging: *In vivo* MR imaging was performed on NOD.SCID mice bearing orthotopically-injected uMUC-1-positive CAPAN-2 pancreatic adenocarcinoma tumors before and 24 hours after i.v. injection of CLIO-EPPT. For T2 map construction, imaging parameters were as follows: TR/TE = 3000/8, 16, 24, 32, 40, 48, 56, 64. FOV = 40x40mm, matrix size 128x 128, slice thickness = 0.5mm. NIRF imaging on the same animals was performed immediately after each MRI session. Probe accumulation in orthotopically-growing tumors was confirmed by *ex vivo* imaging and immunohistochemistry.

Treatment: The treatment protocol involved i.p. injection of 30mg/kg of the pyrimidine analogue 5-fluorouracil (5-FU) once daily for five days beginning 14 d following tumor implantation. 5-FU is a clinically approved therapeutic agent for pancreatic cancer, which exerts its antitumor effects by inhibiting DNA/RNA synthesis.

Results

In order to establish probe accumulation, we constructed pre- and post-contrast T2 maps of tumor-bearing animals. Analysis of T2 maps revealed a 47% average T2 reduction in orthotopically growing pancreatic adenocarcinomas following CLIO-EPPT administration ($p \leq 0.01$). The specific accumulation of CLIO-EPPT in these tumors and the integrity of CLIO-EPPT after persistence in the circulation were confirmed by NIRF imaging and correlative dual channel fluorescence microscopy of tumor sections



In a treatment model of pancreatic cancer, the tumor-specific accumulation of CLIO-EPPT allowed the tracking of differential tumor growth in animals injected with 5-FU vs. non-treated controls. Whereas in treated animals, tumor volume as estimated by MRI remained stable during the course of therapy, in non-treated controls, there was an over four-fold increase in tumor volume by 21 d post-implantation. Tumor localization, distribution, and growth over time, as determined by *in vivo* NIRF imaging demonstrated remarkable agreement with MRI, thus establishing the feasibility of utilizing the NIRF modality carried by CLIO-EPPT for continuous tumor monitoring and collection of detailed time-course data regarding therapeutic response (See figure).

Summary

This study demonstrates the feasibility of using a multimodal targeted imaging probe, CLIO-EPPT, to specifically identify orthotopically implanted uMUC-1-expressing pancreatic adenocarcinomas as well as to track tumor response to therapy in a comprehensive and efficient way. Considering the high cost associated with the development and testing of new cancer therapeutics and the corresponding interest in accurate, non-invasive assessment of their effectiveness, we believe that CLIO-EPPT represents a valuable research tool with considerable relevance to clinical development.

References

Moore A, Medarova Z, Potthast A, Dai G. In vivo targeting of underglycosylated MUC-1 tumor antigen using a multimodal imaging probe. Cancer Res 2004; 64:1821-1827.