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Targeted, multi-modality PET-CT and optical imaging platform for visualizing biological function

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Hybrid PET-optical imaging using targeted probes

Nahrendorf M, Keliher E, Marinelli B, et al. (Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School) PNAS 2010;107:7910–15.

Summary

In this paper, Nahrendorf et al. demonstrate a multi-modality imaging platform that combines the use of nuclear (positron emission tomography, PET), anatomic (computed tomography, CT), and optical (fluorescence-mediated tomography, FMT). The performance of this integrated imaging system was demonstrated with detection and localization of implanted colon cancer lesions in a mouse model. This study was performed using an imaging probe based on a dextran-coated (cross-linked iron oxide, CLIO) nanoparticle that accumulates preferentially in macrophages. These nanoparticles are dual-labeled with either fluorine-18 (^{18}F) or copper-64 (^{64}Cu), short half-life positron emitting radioisotopes, and with a far red fluorescent dye (VT680). First, linearity and the minimum detection thresholds of PET (Siemens Inveon) and optical (VisEn Medical FMT-2500) imaging over a range of concentrations for the imaging agents, ^{18}F -CLIO-VT680 and ^{64}Cu -CLIO-VT680, were evaluated using a phantom that consisted of serial dilutions of the probes in agar. Image z-stacks were collected and volume rendered to produce 3-dimensional images, and excellent correlation ($r^2 > 0.99$) between the PET and optical signals was found. The PET and optical images were then converted into a standard (DICOM) format, and 3-dimensional surface rendered reconstructions of the PET and optical images were co-registered using imaging landmarks and fiducial markers. Congruence between these images in the xy-plane was demonstrated and quantified with a cross-correlation function (CCF) based on Pearson's coefficient. A maximum correlation coefficient of the 2-dimensional signal of 0.85 was found.

The *in vivo* performance of this imaging platform was demonstrated by imaging the distribution of the ^{64}Cu -CLIO-VT680 probe in a BALB/c mouse model using an autologous CT26 colon cancer implanted subcutaneously in the mouse flank. The mice were injected with the dual-labeled probe, and then studied with PET-CT and optical imaging 24 hours later. The tumors were clearly seen in the flank of the mice on both imaging modalities. After image co-registration, the fluorescence concentrations were shown to correlate with PET activity. In addition, co-localization of the PET and optical signals in the xy-plane was

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demonstrated *in vivo*. The functional capability of this approach was then further demonstrated by visualizing multiple molecular markers *in vivo* simultaneously. Tumor-bearing mice were injected intravenously with 3 optical probes: 1) an RGD (arginine–glycine–aspartic acid) peptide that binds to $\alpha_v\beta_3$ integrin (excitation 635 nm); 2) a nanoparticle, described above, that targets tumor associated macrophages (excitation 680 nm); and 3) a cathepsin that is sensitive to over expressed proteases (excitation 750 nm). The tumor from the 3 spectrally resolved datasets collected from separate optical channels was co-localized with the PET-CT images. However, on higher magnification, each imaging agent was found to have a unique distribution within the immediate vicinity of the tumor. The integrin signal was found to be highest at the margins and the cathepsin and macrophage activity was greater within the bulk lesion. These findings were validated on excised tumor *in vitro* with microscopy and autoradiography.

Comment

The multi-modality platform demonstrated in this paper illustrates an exciting new direction for molecular imaging that has potential to be translated for future use in the clinic. This integrated approach provides a robust strategy for not only identifying the location of neoplastic lesions *in vivo* but also for determining the functionality of the diseased tissue. Here, the spatial distribution of the tissue's biological behavior, including macrophage migration, cathepsin activity, and integrin expression, is revealed simultaneously in 3-dimensions in a mouse model of colon cancer. Co-registration of these functional images with CT is performed to provide useful anatomical landmarks for orientation purposes. Visualizing biological phenomena using more than one distinct imaging modality, such as PET and optical imaging, allows for the strength of each approach to contribute synergistically to the final interpretation of the image in a way that far surpasses the capability of each individual technique alone. PET is a highly sensitive method that is well-suited for localizing lesions on whole body imaging but has limitations in resolution, whereas optical imaging is a spectrally flexible mode that provides multi-channel capabilities but has limitations in sensitivity. Thus, the integration of these two approaches represents a powerful combination that can also be used to perform cross-validation of the individual results.

By providing comprehensive spatial information about multiple forms of biological function registered anatomically in real time, this enabling technology represents a significantly leap forward in the emerging field of molecular imaging. A key to future growth in this direction lies in the development of novel probes that have selective uptake in diseased tissues and a sufficiently long half-life and safe toxicity profile for *in vivo* use [1,2]. Moreover, the emergence of new optical imaging modalities based on flexible optical fibers, such as confocal and two-photon [3], allows for these integrated strategies to be used in hollow organs, such as the colon, esophagus, and stomach. These innovations in imaging promise to accelerate progress in molecular medicine by providing a means to answer important scientific and clinical questions related to personalized medicine, including: 1) what targets are prominently expressed in individual tumors; 2) how fast are drugs accumulating in these lesions; 3) how rapidly are therapeutic agents being metabolized; 4) what are the differences in biological pathways between diseased and normal tissue; and 5) how are these signaling pathways regulated. Moreover, the ability to accurately and quickly co-register these large, diverse imaging data sets will become important. The future development of targeted, multi-modality imaging platform for visualizing biological function promises to revolutionize molecular medicine and has important implications for guiding therapy in the individual patient.

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