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PET/Fluorescence Imaging: An Opportunity to Integrate Diagnosis with Surgery

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Over the last a few decades, the field of imaging science witnessed exponential growth on many imaging techniques including Computed Tomography (CT), Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), bioluminescence, fluorescence, and Magnetic Resonance Imaging (MRI) [1,2]. With the ability to image specific biological pathways at the molecular and cellular level *in vivo* [3], molecular imaging techniques are widely used in diagnostic and therapeutic field. It also successfully accelerates the drug discovery and development process, especially for personalized medicine development. Generally, each molecular imaging technique has its own advantages and limitations in spatial and temporal resolution, depth penetration, sensitivity and cost [4]. It is possible that synergistic effect could be obtained by the fusion of two or more *in vivo* imaging techniques [5-7]. In particular, PET is a powerful imaging technique closely related to clinical translation in oncology. PET could provide critical *in vivo* information on the distribution of radio labeled biomolecules, which would help a noninvasive cancer diagnosis [8-10]. In contrast, fluorescence imaging has been demonstrated to be a superior method for intra operative tumor detection [11-14]. In clinical practice, tumors were more efficiently detected using the tumor-specific intra operative fluorescence imaging than with the conventional visual inspection. Since both PET and optical imaging have unique features for clinical applications, PET/fluorescence dual modality imaging might greatly benefit the patients because the lesion could be located using noninvasive PET scans (diagnosis), and the optical motif would allow surgeons to identify the PET-detected lesions or smaller metastasis in intra operative image-guided surgery (therapy). Clearly, general methods are greatly needed for simple and efficient construction of PET/fluorescence dual modality probes.

PET/fluorescence probes could be efficiently constructed by using nanoparticle as the general platform [15-19]. For example, Quantum Dots (QDs) demonstrated great potential for *in vivo* optical imaging applications. Both radioactive tag and targeting ligand could be introduced to the surface of this nanomaterial for targeted PET/fluorescence imaging (Figure 1A). Large targeting ligands (such as antibody or proteins) themselves could also serve as the carrier for imaging tags [20-24]. After chemical modification, fluorescence and radioactive motifs could be introduced separately to these molecules. Several reports have demonstrated the feasibility of this approach (Figure 1B). Recently, hetero functionalized sarcophagine cage has been developed for PET/fluorescence imaging (Figure 1C) [25]. This hetero functionalized ligand could be considered as a cross-linking agent that could also be labeled with ^{64}Cu. The ligand was consecutively functionalized with RGD2 peptide and Cy5.5 dye in good yields and then efficiently labeled with ^{64}Cu under mild condition. The favorable ^{64}Cu-labeling property of cage-like sarcophagine, plus the hetero functional groups on each side, made this BaAn(Boc)Sar chelator very attractive for dual-modality imaging probe construction. In a proof of principle study, the constructed PET/optical tumor-targeting probe not only allows direct comparison between PET and fluorescence imaging, but also integrates the noninvasive PET imaging with image-guided surgery.

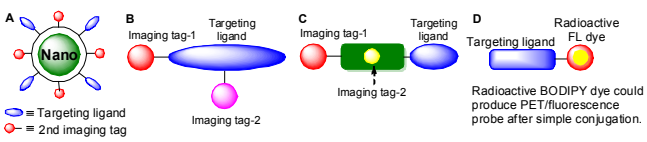

Figure 1: Synthesizing PET/fluorescence probes through (A) nanoparticle based approach; (B) antibody/protein/peptides based approach; (C) cross-linking agent that could also be radiolabeled; (D) radioactive fluorescence dyes.

Traditionally, the synthesis of PET/fluorescence dual modality agents has been achieved by introducing a fluorophore and a radiolabeled component as two separate entities [26,27]. Recently, significant amount of effort has been devoted to the synthesis of radioactive fluorescent dyes which could allow simple and efficient synthesis of [^{18}F]-PET/fluorescence dual modality agents (Figure 1D). In 2011, Li et al. demonstrated that boron-based [^{18}F]-fluoride captors could be hybridized with fluorophores and targeting agents for the PET/fluorescence dual modality imaging of sentinel lymph nodes in animal models [28]. Purser et al. pioneered in the design and synthesis of PET/optical probe using BODIPY dyes [29]. BODIPY dyes constitute a class of fluorophores that have been widely used for the fluorescent labeling of biomolecules [30-32]. Such dyes feature high stability, high quantum yields and an emission range that can be tuned into the near infrared [33,34]. BODIPY dyes also typically possess a boron-bound fluorine atom which could provide a site for the incorporation of a [^{18}F]-fluorine atom, a radionuclide of choice for positron emission tomography (PET) [30-32]. In the original study, radiosynthesis of ^{18}F-BODIPY dyes can be carried in the matter of minutes in aqueous solutions using the target [^{18}O]-water/[^{18}F]-fluoride solution. After the B-OH bond in a BODIPY dye was activated by trimethylsilyl trifluoromethanesulfonate (TMSOTf), a no-carrier added method was also reported using azeotropically dried tetrabutylammonium ^{18}F-fluoride (^{18}F-TBAF) [29]. The integrity of ^{18}F-BODIPY in PBS buffer (pH 7.5) was tested after incubation at room temperature up to 6 hours and >95% purity was obtained. This experiment clearly demonstrated that the product was resistant to hydrolysis at physiological pH. In the following *in vivo* study performed in mouse, the activity was accumulated primarily in the liver, kidneys, and gallbladder 2 hours post injection. No observable bone uptake up to 4 hours post injection indicated that the hydrolytic release of free

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^{18}F-fluoride from ^{18}F-BODIPY was negligible on the time scale of the ^{18}F-nuclear decay. In the *ex vivo* study, the fluorescence signals and PET signals of the major organs correlated very well, which validated the dual modality potential of the probe. This new approach, which was further validated and extended recently [35,36], is attractive because the positron emitting and fluorescence properties of the imaging agent are confined to the same molecular compartment.

In summary, both PET and fluorescence imaging have unique features for clinical applications. A system that integrates these two imaging modalities could greatly benefit patient management, for example by providing complimentary diagnosis information during surgery in a non-invasive manner. With recent advancements in PET/fluorescence probe synthesis, PET/fluorescence imaging would significantly advance the diagnosis and surgery of various cancers, and the research results could be translated into first-in human trials quickly.

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