Review Article

Functional endoscopy techniques for tracking stem cell fate

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Abstract: Tracking and monitoring implanted stem cells are essential to maximize benefits and to minimize the side effects of stem cell therapy for personalized or "precision" medicine. Previously, we proposed a comprehensive biological Global Positioning System (bGPS) to track and monitor stem cells *in vivo*. Magnetic resonance imaging (MRI), positron emission tomography (PET), bioluminescent imaging, fluorescence imaging, and single-photon emission computerized tomography (SPECT) have been utilized to track labeled or genetically-modified cells *in vivo* in rats and humans. A large amount of research has been dedicated to the design of reporter genes and molecular probes for imaging and the visualization of the biodistribution of the implanted cells in high resolution. On the other hand, optical-based functional imaging, such as photoacoustic imaging (PAI), optical coherence tomography (OCT), and multiphoton microscopy (MPM), has been implemented into small endoscopes to image cells inside the body. The optical fiber allows miniaturization of the imaging probe while maintaining high resolution due to light-based imaging. Upon summarizing the recent progress in the design and application of functional endoscopy techniques for stem cell monitoring, we offer perspectives for the future development of endoscopic molecular imaging tools for *in vivo* tracking of spatiotemporal changes in subclonal evolution at the single cell level.

Keywords: Endoscopy; stem cell research; cell tracking; biological GPS

Submitted Oct 19, 2018. Accepted for publication Feb 22, 2019.
doi: 10.21037/qims.2019.02.12
View this article at: http://dx.doi.org/10.21037/qims.2019.02.12

Introduction

Stem cell therapies (SCT) hold great potential for treating various human diseases and regenerating tissues; however, the heterogeneity and plasticity of stem cells render such SCT either beneficial (cell engraftment, differentiation, integration) or detrimental (e.g., the death of transplanted stem cells and subsequent inflammation and cancerous changes), depending upon the residual microenvironment (host inflammatory responses) at the recipient site (1). Such detrimental effects include the use of stem cell derivatives [e.g., conditioned medium (CM) and microvesicles (MVs)] to regenerate lung tissues on the release of TGF-β and IL-6 (2).

To address these issues, we described a comprehensive biological Global Positioning System (bGPS) to track transplanted stem cells (3) with eight desired elements for tracking and monitoring the implanted stem cells to ensure successful SCT: these include (I) sensitivity for single cell detection, (II) real-time positioning, (III) an inducible system, (IV) retractable, (V) targeted and durable, (VI) monitoring cell fate, (VII) compliant with the FDA GMP guidelines for clinical applications, and (VIII) quantification capacity (refer to *Table 1*) (3). Thus far, none of the existing imaging modalities meets all of these criteria (5); however, all currently available platforms appear to be complementary, conjuring up hope for integration. The measurable fabric

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Table 1 Comparison of different whole-body imaging modalities and endoscopic imaging modalities for cell tracking. Specifications of whole-body imaging modalities are cited from previous literature (4)

Imaging modality	Spatial resolution	Acquisition time	Labeling strategy	Advantages	Disadvantages
Bioluminescence imaging (BLI)	5–20 mm	Seconds	Reporter gene	Cheap, simple, high throughput	Small animals only, low resolution, only 2D images
Fluorescence tomography (FMT)	2–3 mm	Seconds to minutes	Reporter gene, fluorescence dye	Cheap, simple	Low resolution, cells need to be close to surface
Ultrasound (US)	150 μm–2 mm	Seconds to minutes	Reporter gene, antibody with microbubble	Cheap, relatively simple	Limited 3D capabilities, low signal to noise ratio
Single photon emission computed tomography (SPECT)	1–2 mm; 8–12 mm	Minutes	Reporter gene, incubation with radiotracer	3D imaging	Anatomic reference required, radioactive tracer required
Positron emission tomography (PET)	~1 mm; 4–6 mm	Seconds to minutes	Reporter gene, incubation with radiotracer	3D imaging	Anatomic reference required, radioactive tracer required
Magnetic resonance tomography (MRI)	25–500 μm; 0.5–5 mm	Minutes to hours	Internalization or surface labeling with nanoparticles or specific ions	3D imaging, good soft tissue contrast, no radiation, high resolution	Very expensive, complicated
Computed tomography (CT)	<50 μm; <1 mm	Seconds to minutes	Internalization or surface labeling with nanoparticles	3D imaging, relatively cheap, high resolution	Use ionizing radiation
Fluorescence endomicroscopy (FE)	1–20 μm	Seconds to minutes	Reporter gene, endogenous and exogenous fluorophore	Cheap, simple	Penetration depth limited to ~250 μm from probe
Multiphoton endoscopy (MPE)	1–3 μm	Seconds to minutes	Reporter gene, endogenous and exogenous fluorophore	Higher sensitivity, penetration depth than FE	Often requires bulky pulsed laser
Photoacoustic endoscopy (PAE)	~100 μm	Seconds to minutes	Internalization or surface labeling with nanoparticles	Deeper penetration than FE and MPE, 3D imaging	Lower spatial resolution than the optical imaging

matrix of such integration has yet to be fully elucidated and developed.

Tracking of implanted cells can be generally performed by (I) labeling cells using passive or active transport or (II) integrating a specific reporter gene to the targeted cells. The signal from the cells are then observed with magnetic resonance imaging (MRI), bioluminescence imaging (BLI), fluorescence imaging (FLI), positron emission tomography (PET), or single photon emission computed tomography (SPECT). The advantages and disadvantages of each imaging system are summarized in *Table 1*, as detailed in other reviews (4). However, none of the modalities can provide comprehensive and detailed visualization of the implanted stem cells to meet those eight criteria (3). As endoscopy can access internal organs (gastrointestinal tract, vaginal tract, and airway) and can treat and monitor the tissue simultaneously, we will discuss the clinical impact of endoscopic-based imaging techniques, focusing on the tools and methods that have been developed and tested in recent years. For each endoscopic imaging technique, we will summarize the currently used (I) cell labeling methods, (II) imaging probes, and (III) advantages and disadvantages.

Fluorescence endomicroscopy (FE)

FE or confocal laser endomicroscopy (CLE) is a new imaging tool that allows minimally-invasive, real-time *in vivo* imaging with sub-cellular spatial resolution (6). It combines the advantages of the confocal microscope to image biological tissue with high spatial resolution and the endoscope to reach tissues intravitally. FE has been applied in colon cancer detection (7) and the longitudinal study of

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live cells (8).

In stem cell research, FE has been used to study stem cell niches (9), homing and engraftment (10,11), and to investigate the safety of the implanted stem cells (12). Some studies showed the potential application of FE in monitoring stem cells during organ repair such as lung (13). Perez *et al.* labeled mesenchymal stem cells (MSCs) with fluorescence dye (Vybrant DiD Cell-Labeling Solution) which were injected into damaged lung tissue. Then, FE was used to monitor and quantify those cells over several days in live rats. This report was the first demonstration of stem cell tracking using FE in live animals (13).

Cell labeling

The cell labeling method for FE is similar to standard fluorescence imaging. Labeling can be performed through endogenous fluorophores, exogenous fluorescence dyes, and genetic modification. A cellular auto-fluorescence signal can be utilized to distinguish cellular morphological changes without exogenous contrast agents. Lin *et al.* demonstrated the FE system could detect a tissue auto-fluorescence signal from *ex vivo* human esophageal tissue by UV excitation (266 and 325 nm) (14). Membrane dyes, such as DiD and topical methylene blue, have been used to stain cells for endomicroscopy imaging (13,15,16). In other cases, MSCs are engineered to co-express the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) and enhanced green fluorescent protein (EGFP) to track the integrity of the implanted stem cells in the tumor (17).

Endoscopic probe

Most FE utilizes a fiber-bundle to image the tissue. Currently, there are two products on the market: FIVE1 from Optician and Cellvizio from Mauna Kea Technologies. Cellvizio uses two lasers (488 and 660 nm) and two channels to detect fluorescence signals from two spectral regions. The probe diameter is 2.6 mm, and the field of view is around 240 μm. The image acquisition speed is 12 frames/sec. This system is much faster than MRI and CT. Recently, a side-view endomicroscope has also been developed and tested, as shown in *Figure 1A* and *B* (8).

Advantages and limitations

Fiber-probe FE has a higher spatial resolution, sensitivity, and is cheaper compared to MRI, ultrasound, and CT imaging techniques. The lateral resolution of FE depends on the type of fiber bundle and the lens which is typically 2.5–5 μm (18). The sensitivity of FE to detect the reporter is high (10^{-9}–10^{-11} M) compared to MRI (10^{-3}–10^{-5} M) (19,20). While MRI and CT require bulky and costly equipment, FE can be performed through the working channel of a conventional endoscope and serve as a point-of-care imaging tool. The manufacturing cost is also much less than MRI, CT, and PET. Additionally, FE can access the targeted tissue intravitally through flexible optical fibers. Therefore, the imaging depth of FE is not limited to the surface of the tissue, which is the case of the whole-body fluorescence imaging system (21). However, if the size of the fiber-bundle is equal to or bigger than the anatomical cavities, such as terminal bronchioles and the internal tracts of small animals, noninvasive imaging through FE may be challenging. For example, one of the smallest commercially available fiber-based FE probe is Cellvizio, and the probe size is about 0.6 mm (6). However, the airway structure of the rat can be smaller than 0.4 mm. It is possible to intentionally puncture the biological tissue through the FE probe to image the targeted region, but this procedure is invasive and can be very hazardous in small animals such as a rat.

Multiphoton endoscopy

Multiphoton microscopy (MPM) is a powerful imaging technique that provides functional histopathological information of biological tissue with sub-cellular resolution, minimum photothermal damage, and less tissue scattering (22,23). Due to the nonlinear two-photon effect of near-infrared light, two-photon microscopy can image deeper tissue with less photo-damage compared to the fluorescence microscope, which makes it ideal for *in vivo* applications (24). Similar to the previously introduced FE technologies, multiphoton endoscopic imaging allows *in vivo* and *in situ* visualization of the histopathological process and can be used to monitor stem cell behavior. In stem cell research, MPM has been used to investigate *in vivo* MSC homing and evaluate cellular response (25,26). Rompolas *et al.* tracked the hair-follicle stem cells and progeny using a transgenic mouse. The fluorescence signal from epithelial nuclei was visualized using an MPM by inducing expression of a fusion protein of histone H2B with a green fluorescent protein (GFP) by the keratin 14 promoter (K14H2BGFP). Then the stem cells and their progeny were identified based on their unique morphological features (26). However, few

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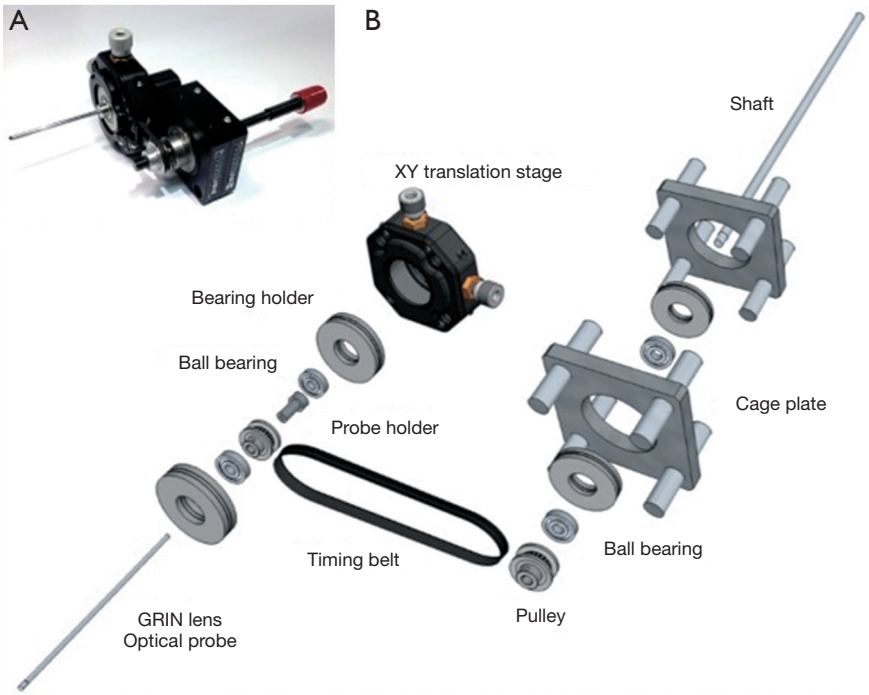

Figure 1 Schematics of a fluorescence endomicroscope (FE). (A) An FE based on the Gradient-index (GRIN) lens. This endoscope was developed for colorectal imaging (8). (B) Mechanical design of the GRIN lens-based FE probe. A custom-built 360-degree rotation mount combined with the side-view endomicroscope can provide a large scanning area within the colon.

studies of stem cell tracking using multiphoton endoscopy have been reported as of February 2019.

Cell labeling

Similar to fluorescence microscopy, the targeted cells can be visualized through staining using exogenous contrast agents, such as Au nanoparticles (AuNPs) (27-30), EGFP (31), and Quantum dots (QDs) (32). Also, taking advantage of two-photon effects, endogenous fluorophores, such as reduced nicotinamide adenine dinucleotide (NADH) and oxidized flavin adenine (FAD), can be targeted for label-free cell imaging (33-35). Second harmonic generation (SHG) is another label-free imaging technique based on the non-linear effect of light which is often used to visualize the collagen architecture within the tissue (36,37). Also, a genetic marker, such as GFP, can be used to identify the transplanted stem cells (38).

Endoscopic probe

Combining the custom double-clad fiber (DCF) and achromatic miniature objective, Liang *et al.* developed a miniature flexible fiber-based endoscopic probe for two-photon imaging (39). The custom DCF is made of a silica single-mode core, and it suppresses in-fiber nonlinear luminescence. The outer diameter of the probe is around 2.1 mm (*Figure 2A*). Alternatively, the microelectromechanical system (MEMS) scanner-based multiphoton endoscopy has been developed by several groups (36,37,40). The advantage of MEMS is a large scanning angle compared to PZT-based fiber scanning with less off-axis aberration. Liu *et al.* demonstrated SHG endoscopy using a rotational MEMS motor and a custom-built 1-micrometer ultrashort-pulse fiber laser (*Figure 2B*) (37). A 360-degree wide-field view of an SHG signal was acquired using a rotational scanning probe. Duan *et al.* achieved a lateral resolution of 2 μm, large FOV of 300×300 μm^2 and fast image acquisition speed of 5 frames/sec with a 3.4 mm outer diameter (OD) probe (*Figure 2C,D*) (40).

Advantages and limitations

Similar to FE, multiphoton endoscopic imaging can

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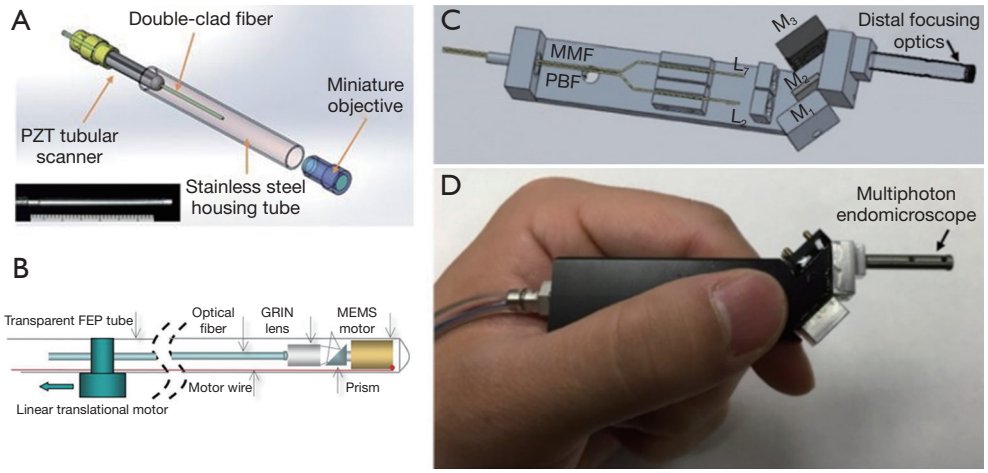

Figure 2 Different types of a multiphoton endomicroscope for two-photon imaging and second harmonic generation (SHG). (A) Two-photon endoscope based on a double-clad fiber. The scanning of the probe is provided by a PZT tube. A custom-made double-clad fiber significantly reduces the in-fiber fluorescence noise signal (39). (B) Schematic of the micromotor-based two-photon endoscope. The rotational scanning provides a wide field of view compared to the forwarding scanning-type probe (37). (C) Schematic of multiphoton endomicroscopy based on a 2D Micro-Electro-Mechanical Systems (MEMS) scanning mirror. A diachroic mirror (M2) selectively passes the excitation beam and reflects the fluorescence light (40). (D) Picture of 2D MEMS scanning multiphoton endomicroscope (40).

visualize *in vivo* tissue with subcellular resolution, high-sensitivity, and high acquisition speed close to real time. Also, two-photon excitation of near-infrared lowers the risk of photo-damage making it ideal for *in vivo* inspection and tracking of stem cells without damaging them. The limitation of two-photon microscopy is that it requires a bulky and expensive high-speed pulsed laser.

Photoacoustic endoscope (PAE)

PA imaging is a new imaging modality based on the photoacoustic effect in which the absorbed energy from the laser is transformed into kinetic energy through thermal expansion of the sample and detected by an ultrasound transducer. It combines the advantages of optical imaging to obtain high resolution, molecular sensitivity, and spectroscopic information and ultrasound imaging to acquire tomographic information of deep tissue.

Stem cells typically do not have optical contrast by themselves. However, numerous studies have used various contrast agents to monitor and track stem cells *in vivo*. Metal nanoparticles, such as gold, seem to be the most popular choice of contrast agents for PA imaging due to their high absorption coefficient and tunable optical properties (41). Recently, Kim *et al.* implanted stem cells labeled with Prussian blue nanoparticles (PBNPs) into a nude mouse. The labeled stem cells show a strong photoacoustic signal when imaged at 730 nm and were monitored for up to 14 days *in vivo* (42).

Cell labeling

Gold nanoparticles in the form of spheres (43), rods (44), and star shapes (45) have been commonly used to track stem cells *in vivo*. Nam *et al.* showed the longitudinal monitoring of stem cell behaviors up to one week using gold nanosphere labeled MSCs captured in the PEGylated fibrin gel injected into the limb of a Lewis rat (43). Jokerst *et al.* showed the increased uptake of gold nanorods by 5-fold into the MSCs by coating with silica. Increased signal-to-noise ratio allowed visualization of up to 100,000 cells. No cytotoxicity or changes in cell proliferation were observed (44). Due to the high energy absorption of gold, it can act as a photothermal therapy agent as well as a contrast agent. Liang *et al.* conjugated gold nanostars with CD44v6 monoclonal antibodies to target gastric cancer stem cells (GCSCs) for PA imaging and photothermal therapy. CD44v6-Gold nanostars actively targeted the GCSCs up to 4 h post-injection (45).

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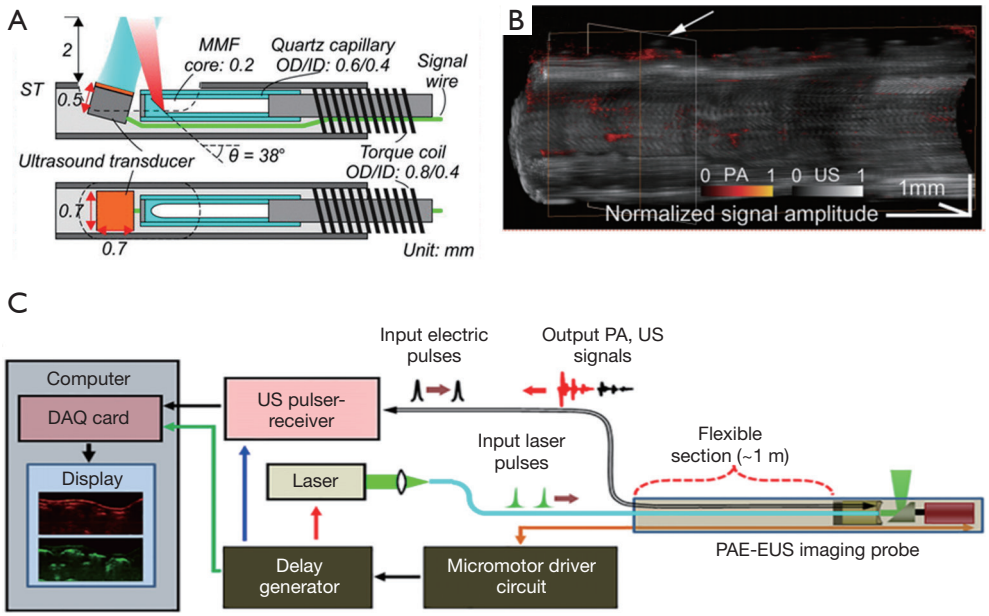

Figure 3 Different types of a photoacoustic (PA) endoscope. (A) Side view and top view of a catheter-based PA probe. The ultrasound transducer is placed next to the multi-mode fiber (MMF) to achieve optical/acoustic beam overlap (46). (B) PA signal from an *ex vivo* rabbit coronary artery acquired using the catheter-based PA probe. The white arrow indicates the PA signal from lipid deposition (46). (C) System diagram of micromotor-based PA probe. Reproduced from (47), with the permission of AIP Publishing.

Endoscopic probe

The photoacoustic endoscope (PAE) integrates a light-emitting optical fiber, ultrasound receiver, and circumferential scanning mechanism. Flexible shaft-based proximal rotation is a commonly used scanning mechanism in the PAE (*Figure 3A,B*) (48-50). This scanning mechanism does not have a mechanical scanning device at the distal portion of the probe, and thus, the probe can be miniaturized. However, the downside of this rotation scheme is the non-uniform distortion (NURD) and the slow speed of the rotation. Another type of PAE uses a micromotor for the circumferential scanning at the distal end of the imaging probe (*Figure 3C*). The ring ultrasound transducer and the optical fiber are co-aligned with each other (47,51). Recently, an all-optical photoacoustic probe has been developed based on the Fabry-Perot (FP) sensor (*Figure 4A,B*) (50). Since the optical ultrasound sensor can be much smaller than the electrical ultrasound transducer, the PAE can be miniaturized using an all-optical design.

Advantages and limitations

The advantage of the PAE is the penetration depth. It can image deeper than fluorescence endoscopy, two-photon (2P) endoscopy, and optical coherence tomography (OCT). Also, compared to ultrasound which only provides structural information, the PAE can give information on optical contrast and thermoelastic contrast with a higher spatial resolution (51). However, the limitation is the large size of the imaging probe since it has to fit both the ultrasound transducer and optical fiber. For an application such as intravascular imaging, the probe size has to be no more than 1 mm.

Multimodality endoscopic imaging

Since each imaging technology has unique advantages and disadvantages, researchers have developed reporters, genes, and probes that can be imaged with multiple imaging modalities (52,53). Multimodality imaging can minimize the drawbacks of using each imaging tool alone, increase the signal specificity and sensitivity, and gain a complete picture of stem cell behavior (52). Nam *et al.* combined ultrasound (US) and photoacoustic tomography (PAT) to monitor stem cell behaviors *in vivo* longitudinally (43). The mesenchymal stem cells (MSCs) labeled with gold nanotracers (AuNTs) were injected in the lower limb of a Lewis rat and imaged

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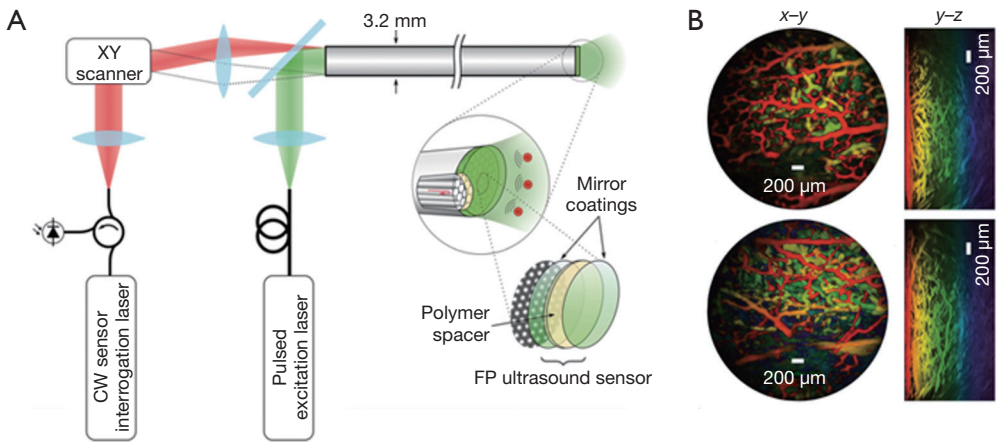

Figure 4 All-optical PA endoscope. (A) Schematic of the forward-viewing PA endoscopic system based on a Fabry-Perot ultrasound sensor. The imaging probe is made of a 3.2-mm-diameter fiber bundle to get a wide field-of-view. (B) Three-dimensional PA tomographic image of an avian embryonic vasculature obtained using the all-optical PA endoscopic probe. Vasculatures at different depths are color-coded (50).

with US/PAT for up to 10 days. Taking advantage of the high spatial resolution and molecular-specific contrast of PAT and deep penetration depth of the US, this study demonstrated the feasibility and benefits of using multimodal imaging for stem cell imaging.

Cell labeling

In one study by Wang *et al.*, polyethylene glycol (PEG) functionalized single-walled carbon nanotubes (PEG-SWNT) were used to label human MSCs for *in vivo* Raman/MRI/PA triple-modal imaging (54). SWNTs have strong inherent resonance Raman scattering that provides ultrasensitive Raman imaging (55). They also have a strong optical absorption coefficient that allows deep tissue imaging through photoacoustic imaging (56). The metallic nanoparticles can be conjugated with carbon nanotubes to serve as the T2-contrast for MRI (54). In another study, Zhang *et al.* demonstrated two-photon/photoacoustic dual-modality imaging using MSCs labeled with gold nanocages (57).

Endoscopic probe

While few studies have shown stem cell tracking using multimodality endoscopic probes, a lot of literature has reported multimodality endoscopic imaging probes with different resolutions and sensitivities. A miniature endoscopic probe that integrates OCT, US, and PAI has been developed and demonstrated for imaging of human arteries and ovarian tissue (*Figure 5A,B*) (58,60). Similar to the PA endoscopic probe, an optical fiber and ultrasound transducer are placed at the distal end of the endoscope. OCT allows the visualization of tissue structure 2 mm below the surface and PAI gives molecular contrast and blood vessel information. US provides information on deeper tissue structure than OCT. In a recent study, Li *et al.* showed an OCT/FI endoscope for imaging the gastrointestinal tract (*Figure 5C,D*) (59). FI provided molecular contrast with sub-cellular resolution. This probe also used a Micro-Electro-Mechanical Systems (MEMS) micromotor for scanning OCT and the FI beam. These imaging platforms are complementary to magnetic resonance imaging (MRI) which assessed the structural integrity of adipose-derived mesenchymal stem cell (MSC)-based tissue engineering for arthroscopic rotator cuff repair with the 28 months of follow-up (61), offering a new landscape for stem cell therapy.

Advantages and limitations

The advantages of multimodality imaging are that it can provide comprehensive information on implanted stem cells and the microenvironment. By combining a high-resolution imaging modality, such as fluorescence imaging, multi-photon microscopy (MPM), and Raman imaging, with techniques that allow large-area scannings, such as OCT, MRI, PAI, and US, we can track the stem cells at different scales. On the other hand, combining multiple imaging modalities can increase the cost, complexity, and the size of

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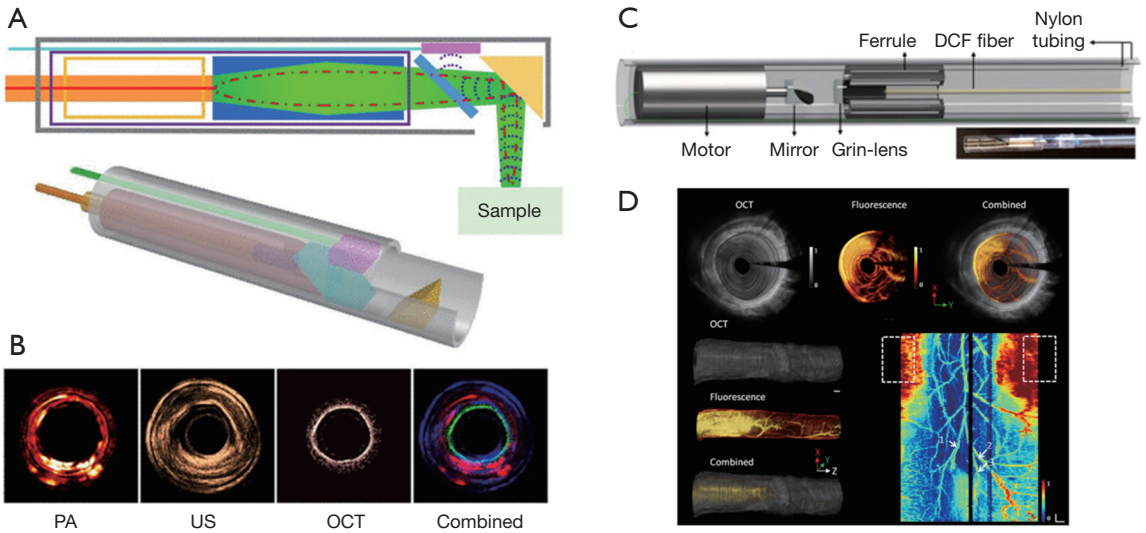

Figure 5 Different types of multimodality endoscopy. (A) OCT/US/PA trimodality probe. Scanning is provided by rotating the entire probe with an external rotational motor. (B) PA/US/OCT images of a human artery. Images of photoacoustic (PA) image provides molecular contrast. Ultrasound (US) image provides morphological information with considerable penetration depth. Optical coherence tomography (OCT) offers morphological information with high spatial resolution. Reprinted with permission from (58) ©2016 American Chemical Society. (C) OCT/fluorescence imaging (FI) endoscopic probe based on a micromotor. (D) OCT and FI of an *in vivo* rat colon. ICG was injected as a contrast agent to visualize blood vessels (59).

the endoscopic probe.

Conclusions

Stem cell therapy is a rapidly growing field in medical research as well as in the clinic, demanding effective imaging to track down the fate of implanted stem cells. Many molecular imaging techniques can be translated into an endoscope to provide high-resolution longitudinal monitoring of implanted stem cells. Fluorescence/confocal endomicroscopy and MPM endoscopy have a high potential to monitor stem cells *in vivo* with cellular resolution using endogenous fluorophores, exogenous fluorophores, or genetically-modified cells. Photoacoustic endoscopy is the new imaging modality that can image much deeper into the tissue and provide a molecular contrast using a contrast agent such as gold nanoparticles.

Although endoscopic imaging has its limitations, such as a small field of view and shallow imaging depth, compared to CT, MRI, and US imaging, we believe specific stem cell therapies will significantly benefit from functional endoscopic imaging. For example, adult tracheobronchial stem cells have recently been demonstrated to be an effective therapeutic option to cure airway disease, repair damaged airway tissue, and replace malfunctioning cells (62). Functional endoscopy allows tracking and monitoring of those implanted stem cells *in situ* with cellular resolution. Also, most of the endoscopic imaging probe can be combined with a conventional bronchoscope to provide multimodal imaging. Traditional cell tracking techniques, such as MRI and CT, will likely be combined with cellular-resolution endoscopic imaging in the future to monitor the fate of implanted stem cells effectively. The ultimate goal of relevant stem cell therapy imaging lies in the spatiotemporal determination of the ideal "therapeutic window" (63) for tracking subclonal evolution at the single cell level (64) in prevention and a "wait-and-watch" approach by continuous biomarker profiling of diseases during an entire lifetime (65).

Acknowledgements

Funding: This work was supported by the National Institutes of Health under grant P41-EB015890 and in part by the CHOC Children's Foundation, CHOC-UCI Joint Research Awards (2014, 2015, 2016).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Miao Y, Chen Z, Li SC. Functional endoscopy techniques for tracking stem cell fate. Quant Imaging Med Surg 2019;9(3):510-520. doi: 10.21037/qims.2019.02.12

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