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Endomicroscopy Technologies and Biomedical Applications

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Recent years have witnessed rapid developments of high-resolution optical imaging technologies, including (but not limited to) confocal, multispectral, optical coherence tomography, multiphoton fluorescence, second harmonic generation, Raman and/or coherent anti-Stokes Raman spectroscopy, and stimulated Raman scattering microscopy. The high-resolution, noninvasive (or minimally invasive), and real-time imaging capability make these technologies well positioned for performing "optical biopsy" *in situ* and in real time, with a resolution approaching or at that of standard histology. Clinical translation of these technologies, particularly for assessing internal organs, requires miniature probes for delivery, scanning, and collection of the probing/imaging beams. Endomicroscopy is emerging as a field to fulfil this need and represents tremendous potential for improving the current diagnostic yields. Advances in fiber optics, micro-optics, miniature light sources, sensitive detectors, and MEMS technologies have yielded extremely compact, highly flexible systems which easily interface with current endoscopes. Endomicroscopy can be combined with other "red-flagging" clinical diagnostic instruments to enable surveillance over a large area and confirm optimal sites for biopsy in a small area during a procedure.

In this special section, we are pleased to present seven papers with representative approaches in the area of endomicroscopy technologies. Among these papers, four are focused on technology development, two demonstrate *in vivo* applications on animal models, and one illustrates the clinical translation potential by endoscopic imaging of human subjects.

Several advances in optical technologies permit novel instrument design. A miniature objective lens is a critical building block in the construction of endomicroscopes. These lenses focus and collect the imaging beam to and from the sample. Optimal lens performance requires minimization of various aberrations. In this special section, the paper by Murray and Levene demonstrates a rigid two-photon fluorescence endomicroscope for *in vivo* deep brain tissue imaging based on a singlet GRIN lens. A simple yet effective method was proposed and demonstrated for correcting the spherical aberration associated with the GRIN rod lens. On a related topic, a paper by Hagen and Tkaczyk reports a novel miniature lens called a foveated lens, which is suitable for endomicroscopy. The unique feature of the miniature foveated lens is its fairly large field of view (FOV) with a high resolution in the central region and a relatively low resolution around the outer FOV. An endomicroscope designed with such a miniature lens can potentially be used for both area surveillance and biopsy guidance with the same instrument.

Beam scanning is another key consideration in an endomicroscope. The paper by Liang et al. systematically studies the beam illumination uniformity and the associated potential photodamage in a flexible, fiber-optic, scanning two-photon fluorescence endomicroscope under two commonly used scanning patterns, i.e., the spiral and the Lissajous scanning pattern. It was shown that illumination uniformity could have significant impact on light intensity sensitive time-course studies. The paper by Ford et al. reports an innovative optical sectioning method employed on a fiber bundle–based endomicroscope without the need for mechanical beam scanning. The central stage of the method is the control of illumination (uniform versus structured illumination) and insightful image analyses termed as HiLo imaging.

In addition to technology developments, we are pleased to see three papers in this special section that showcase the translation potential of the endomicroscopy technologies. The paper by Belanger et al. describes a multimodal endomicroscope that is capable of simultaneous CARS and two-photon fluorescence imaging at video rate and with high resolution. The paper demonstrates that this device could effectively assess spinal cord anatomy by imaging the myelin sheath (through CARS) and glial cells and axons (through two-photon fluorescence). The paper by Miller et al. demonstrates a scanning fiber-optic endoscope capable of simultaneous imaging of three fluorescent probes in different spectral bands. The flexible scanning endoscope offers a large view angle and has a footprint small enough for directly accessing a mouse colon. Along with molecular probes, *in vivo* imaging of mouse colonic dysplasia was demonstrated with the device. The last paper in this special section by Piyawattanametha et al. demonstrates clinical translation of their recently developed dual-axis confocal endomicroscope for human colon imaging. The flexible endomicroscope was delivered to the colon through the instrument channel of a therapeutic endoscope. With the help of topically applied near-infrared dye (ICG, FDA approved for human use), normal colonic mucosa microstructures at cellular or even subcellular level could be obtained *in vivo* and in real time.

Endomicroscopy is a rapidly developing field. The papers in this special section provide a small sample of the field. There are many design and engineering challenges associated with endomicroscopy technologies. The papers in this special section represent significant advances in technology development; however, challenges remain. Broad implementation of endomicroscopy in clinical practice could have a significant impact on the practice of medicine. The ability to conduct surveillance and direct optical biopsy at the same time may lead to a paradigm shift, resulting in fewer biopsies with greater accuracy. We hope these papers will be of interest to many researchers in the biophotonics community, particularly those who have been working in the area of endomicroscopy. We also hope this special section will inspire more interest from a broader community to join the effort for developing and translating emerging endomicroscopy technologies.

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Special Section Guest Editors