A handheld optical-sectioning microscope for cancer detection and surgical guidance

C. Yin1, A.K. Glaser1, Y. Chen1, L. Wei1, S. Abeytunge2, G. Peterson3, C. Glazowski2, N. Sanai4, M.J. Mandella3, M. Rajadhyaksha2 & J.T.C. Liu1

1 University of Washington, Department of Mechanical Engineering, Seattle, WA 98195, USA; 2 Memorial Sloan-Kettering Cancer Center, Dermatology Services, Department of Medicine, New York, NY 10010, USA; 3 Stanford University School of Medicine, Department of Pediatrics, Stanford, CA 94305, USA; 4 Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, Phoenix, AZ 85013, USA

Clinical needs

Early detection of oral cancers

- Existing screening tools have high sensitivity but poor specificity (many false positives).
- Gold standard diagnosis requires physical biopsy of suspicious lesions (many of which are benign), which is slow, expensive, and invasive.
- Real-time non-invasive “optical biopsy” or “point-of-care pathology” would help to examine suspicious lesions for early detection.

High-resolution image-guided resection of brain tumors

- Current imaging modalities (MRI, CT, and wide-field fluorescence) often lack the resolution, sensitivity, and contrast to accurately delineate tumor margins, especially for diffuse gliomas.
- 5-ALA-induced PpIX fluorescence is often undetectable in low grade gliomas via wide-field fluorescence imaging (see panel 9).
- High-resolution fluorescence microscopy has the resolution and sensitivity to quantify sparse PpIX expression in low-grade gliomas and guide tumor removal.

Handheld line-scanned (LS) dual-axis confocal (DAC) microscope

The dual-axis advantage

- Single-axis confocal
  - High-NA focusing – short working distance
  - More background noise from scattered light
- Dual-axis confocal
  - Low-NA focusing – long working distance
  - Less noise from scattered light

The line-scan advantage

- Point-scanned DAC
  - High contrast and imaging depth
  - Slow pixel-by-pixel scanning is required to construct an image, which leads to motion artifacts.
- Line-scanned DAC
  - High contrast at shallow depths only
  - Fast line-by-line scanning to minimize motion artifacts during handheld use.

ZEMAX ray-tracing simulations

- Illumination path
- Illumination spot diagrams
- Collection path
- Detector spot diagrams

Images of fluoresceintly labeled fresh tissues

- Mouse tongue stained with methylene blue (depth ~50 μm)
- Mouse kidney stained with methylene blue (depth ~100 μm)
- Mouse ear vasculature imaged at 16 frames/sec and color coded for imaging depth

Clinical: 5-ALA-induced PpIX for low-grade glioma resection

Why high-resolution microscopy?

Fact: Wide-field fluorescence image-guided surgery with 5-ALA-induced PpIX has improved outcomes for patients with high-grade gliomas. (Stummer et al., Lancet Oncology, 2008)

Shortcomings: 1) Image intensity is subjective, especially at the diffuse margins. 2) Poor sensitivity to detect sparse tumor cell populations (e.g., diffuse margins & low-grade gliomas)

Solution: Intraoperative confocal microscopy has the resolution/sensitivity to detect sparse and disseminated fluorescence from tumor cells. [Sanai et al., J. Neurosurg. 2011, Liu, Meza, & Sanai, Neurosurgery 2014]

Preliminary data: microscopic analysis of PpIX expression in the human brain

Acknowledgement of funding: NIH / NIBIB R00 EB008557 (Liu), NIH / NIDCR R01 DE023497 (Liu), NIH / NCI R01 CA175391 (Liu)