

# Multimodal imaging microscope for intraoperative detection of breast tumor positive margins

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# Outline

- Background & Introduction
  - Breast cancer incidence and state of the art
- Description of the Instrument and Methods
- Brief Results
  - Contrast agent and image analysis
- Conclusion
- Future Work

# Background

- According to the American Cancer Society, over 200,000 cases of breast cancer are diagnosed annually and over 150,000 of the patients diagnosed with early stage breast cancer choose to undergo Breast Conserving Surgery (BCS) [1].
- Unfortunately, intraoperative assessment of breast cancer margins using current strategies is inadequate, and thus rarely performed.
- Positive margins rate requiring a second operative procedure remains high, at about 20-40% nationwide [2].

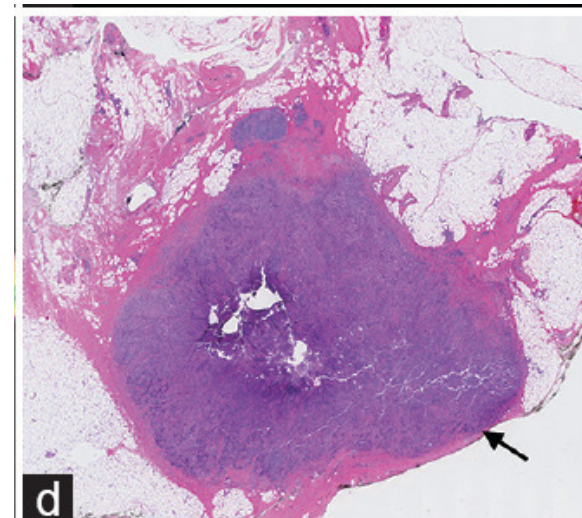
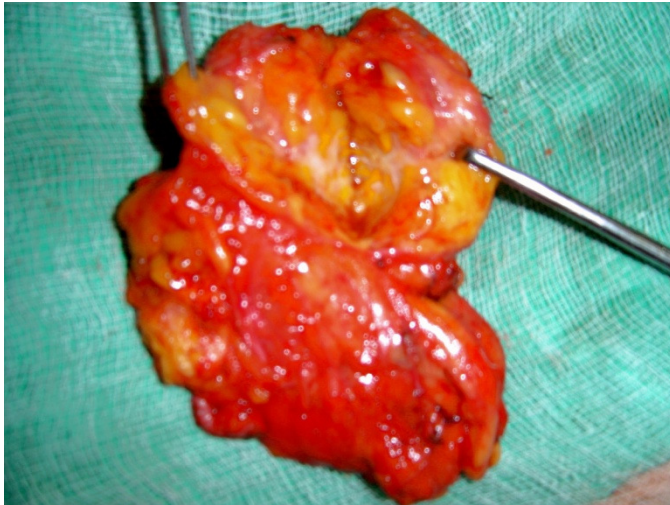
**Reliable assessment of margins and selective resection of positive margins could significantly reduce cancer recurrence and the need for repeated surgery.**

[1] American Cancer Society (ACS). Cancer Facts and Figures 2012. Atlanta, GA: American Cancer Society, Inc. 2012.

[2] Meric F, et al.. *Cancer* (2003) 97

# What is a safe surgical margin?

- The consensus among most of the surgeons and radiation oncologists is that there should be no tumor left within at least 1-2 mm distance from the surface of the surgical specimen [1].

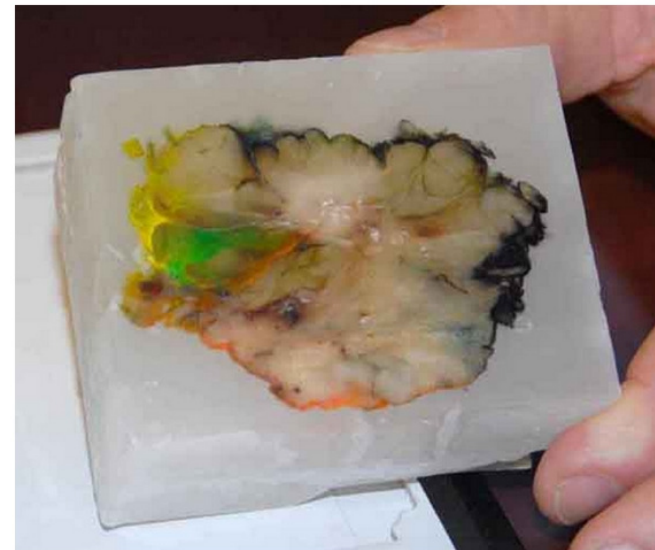


Source: Wikimedia Commons

[1] Azu M, et al., Ann Surg Oncol (2010)

# Current Approaches

- Current techniques for intraoperative pathologic assessment of surgical margins involve touch prep and frozen section analysis
- Touch prep analysis has a poor sensitivity and specificity, and therefore is not often used
- Frozen section analysis- is very difficult: breast specimens have a high percentage of fat tissue-very difficult to freeze and cut in thin slices for histopathological analysis during the surgery
- Surgical specimens are sent to the pathology lab, fixed, sectioned, stained, and read for results days later, after the patient has gone home
- Published reports indicate a 20-70% rate of positive margins left after surgery [1]
- If positive margins are found, surgery is repeated

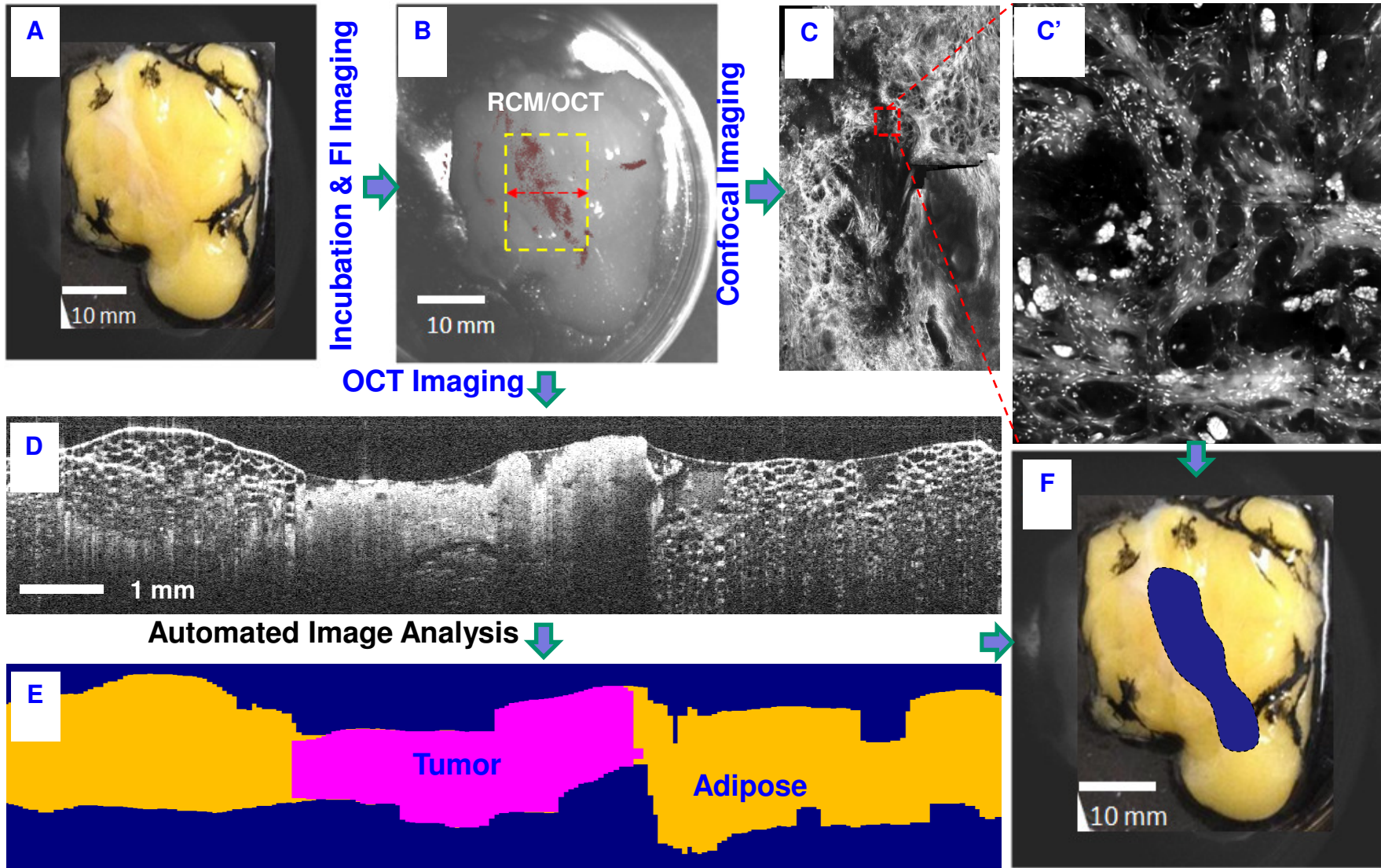


[1]. Jacobs L. Ann Surg Oncol. (2008)

- **Surgical bed analysis**
  - NIR Fluorescence imaging: Frangiony's group at. BID [1] - sensitivity/specificity issues
  - Cancer targeting contrast agent imaging: U. of Washington, Dartmouth, etc.- Long road to get FDA approval
- **Surgical specimen analysis**
  - Micro CT- limited resolution, low sensitivity/specificity
  - High resolution optical imaging (FCM, OCT, FFOCT, 2PM, etc.) – time consuming – not very suitable for real-time feedback
  - Fluorescence guided multimodal imaging – fast, reduced rates of FPs/FNs -

[1]. Vahrmeijer AL, et al., *Nat Rev Clin Oncol.* (2013)

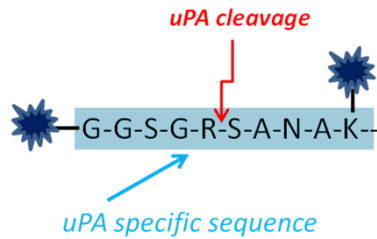
# Proposed Approach



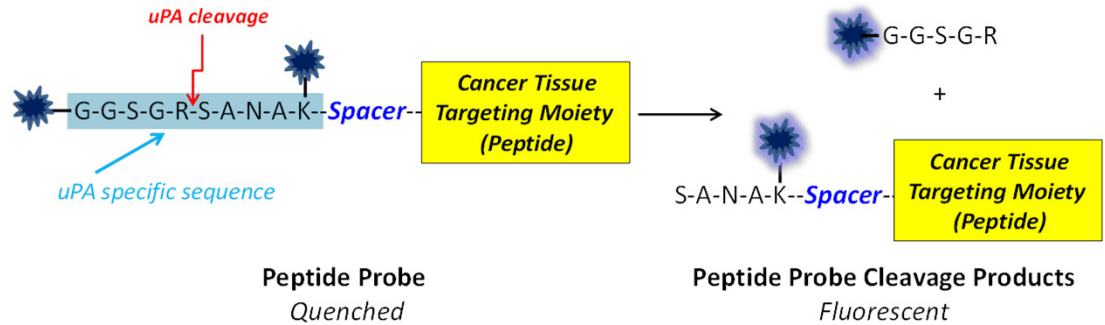
# Contrast Agent Requirements

- High sensitivity – minimal false negatives
- Short incubation time for activation – not extend the duration of the procedure with more than few minutes
- No impact on histological analysis – histology will still be the ultimate test

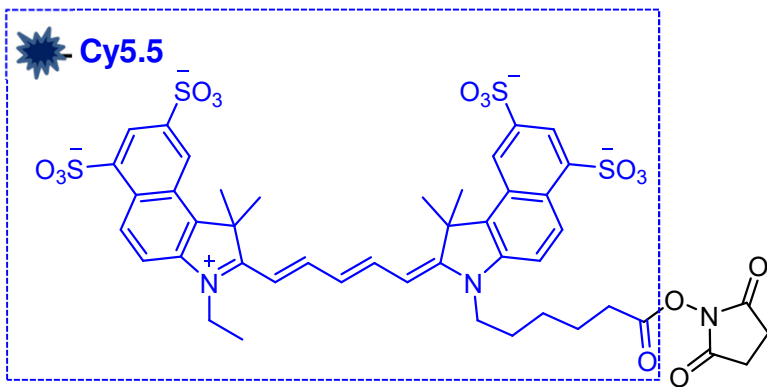
## Phase I Agent



## Phase II Agent



**Near IR Agent –  $\lambda_{max}$  675 nm (abs.)**



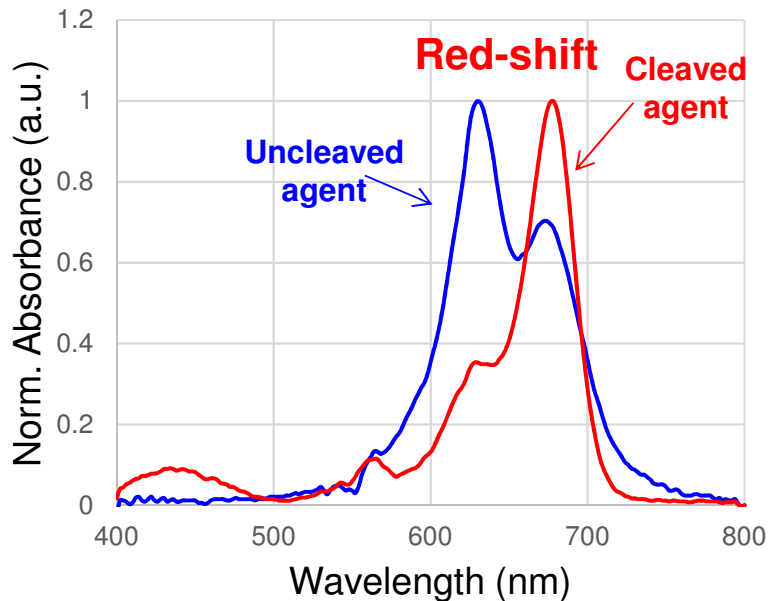
**Similar kinetics of enzyme activation  
(minimal effect of the tissue target moiety)**



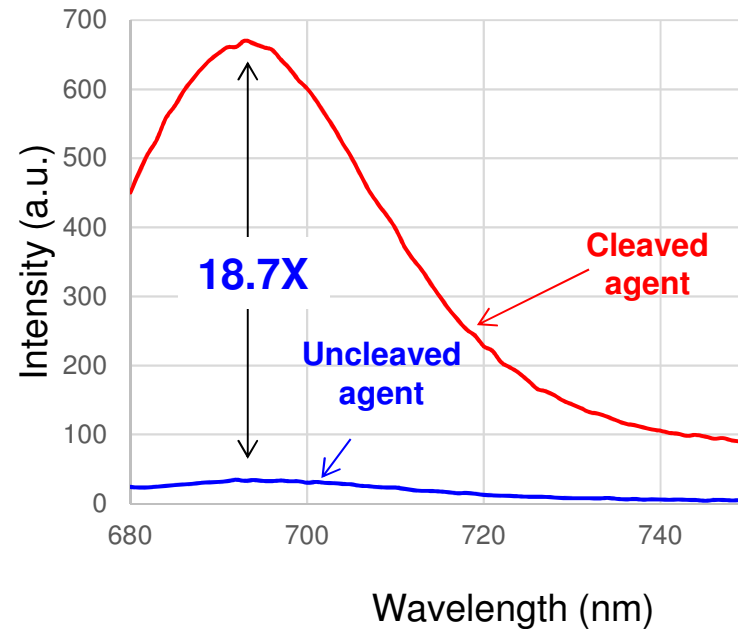
# Contrast Agent Characterization

- Absorption and Emission spectra obtained in 10X PBS Buffer
- Red-shift in UV spectrum maximum upon cleavage (635 nm → 675 nm)
- 18.7X increase in fluorescence upon full cleavage (690 nm max)

Absorption Spectra



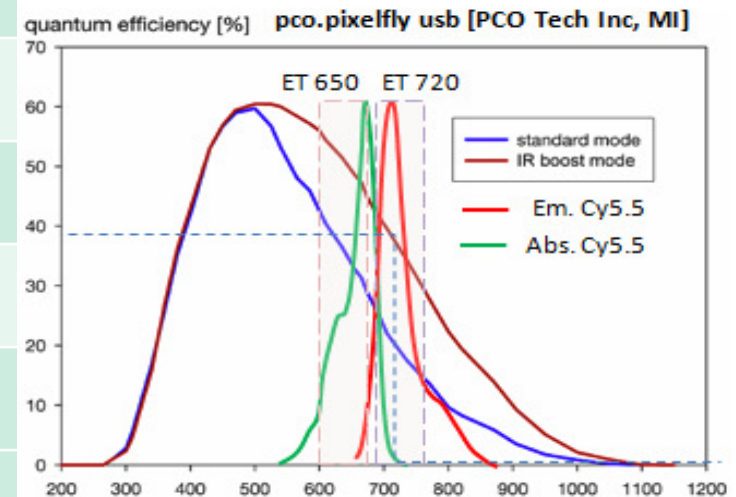
Emission Spectra (ex: 675 nm)



# Goals and Design Parameters of the System

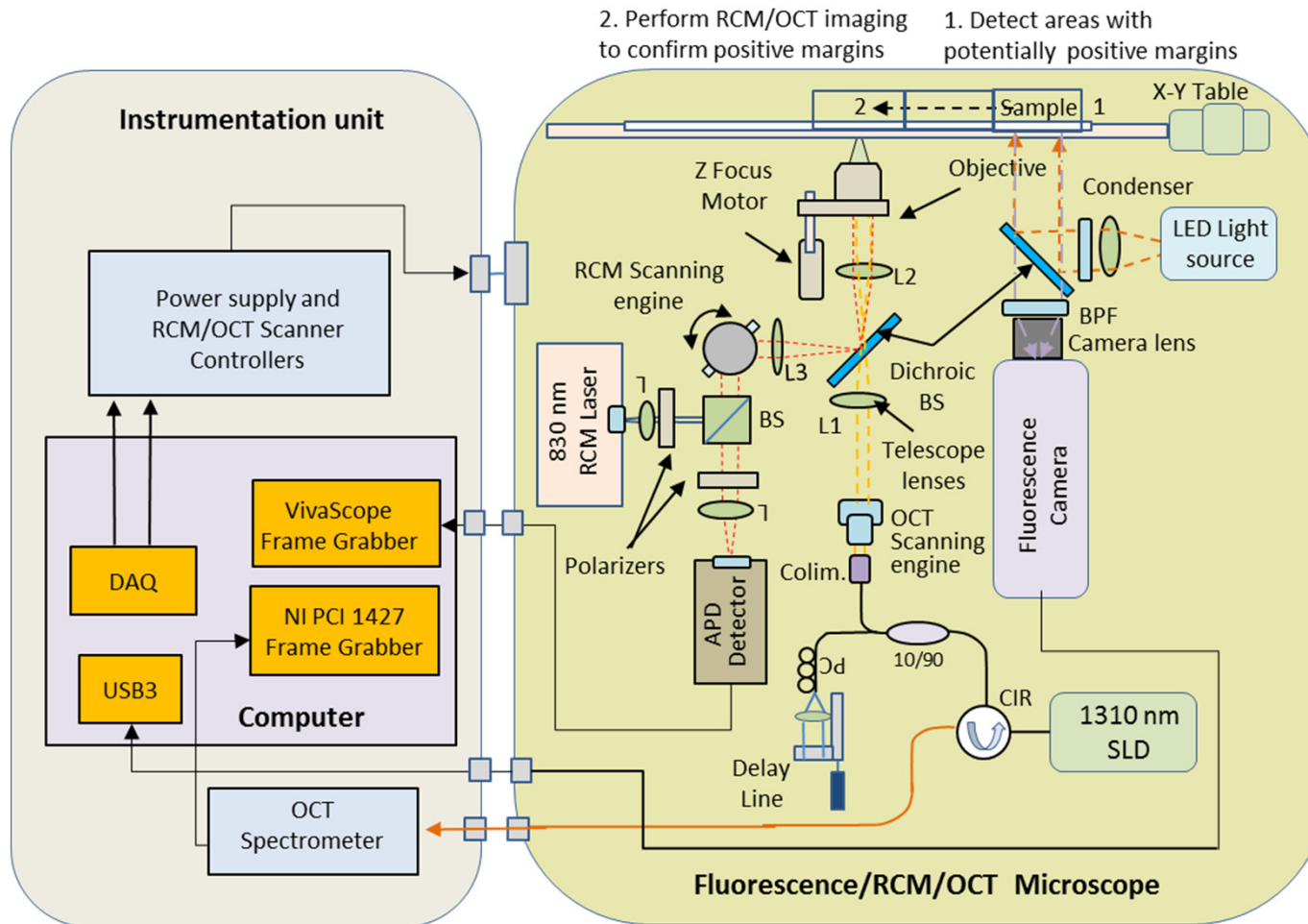
- Demonstrate an inverted combined fluorescence imaging-microscopy instrument which can be used in the surgical suite.

Design Parameters	RCM	OCT	FL
Wavelength	830 nm	1310 nm	675nm Ex/700 nm Em
Imaging speed	>10fps	>50fps	20 fps
Imaging range-axial	0.25 mm	2 mm	N/A
Axial resolution	2 $\mu$ m	7 $\mu$ m	N/A
Lateral resolution	1 $\mu$ m	10 $\mu$ m	100 $\mu$ m
Field of view	600 $\mu$ m	2 mm	25 mm



- Demonstrate 90% specificity in determining positive margins in a study at MDACC – over 50 specimens.

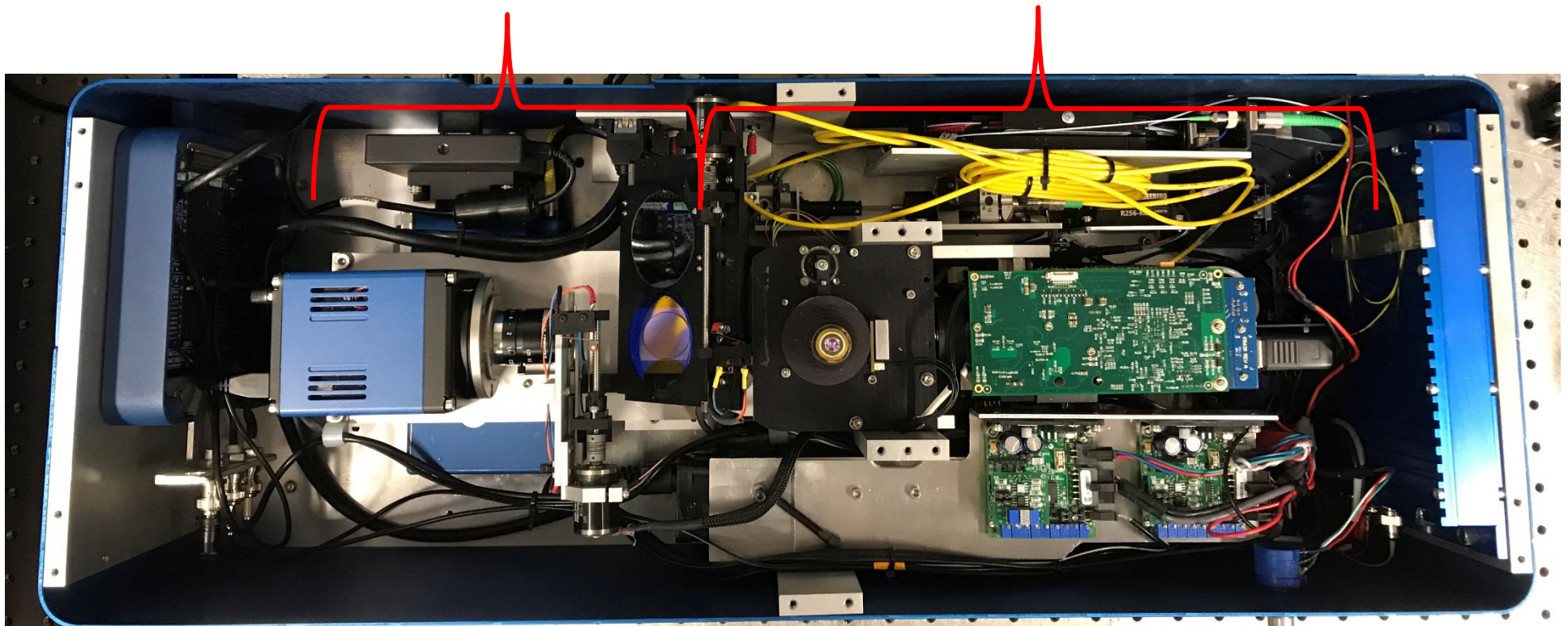
# Instrument Schematic



# Instrument Overview

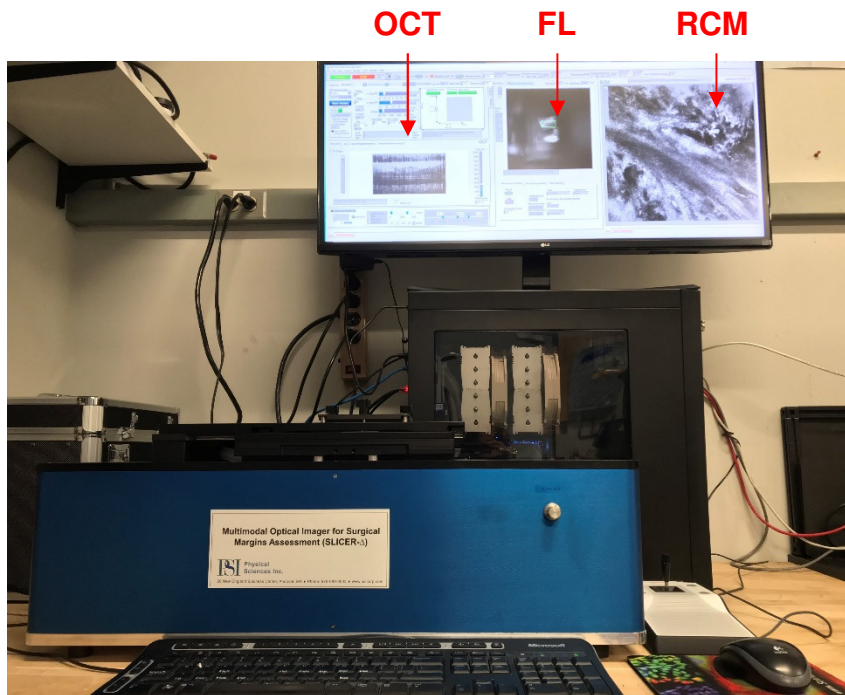
Fluorescence Module

RCM – OCT Modules



# Instrument Overview

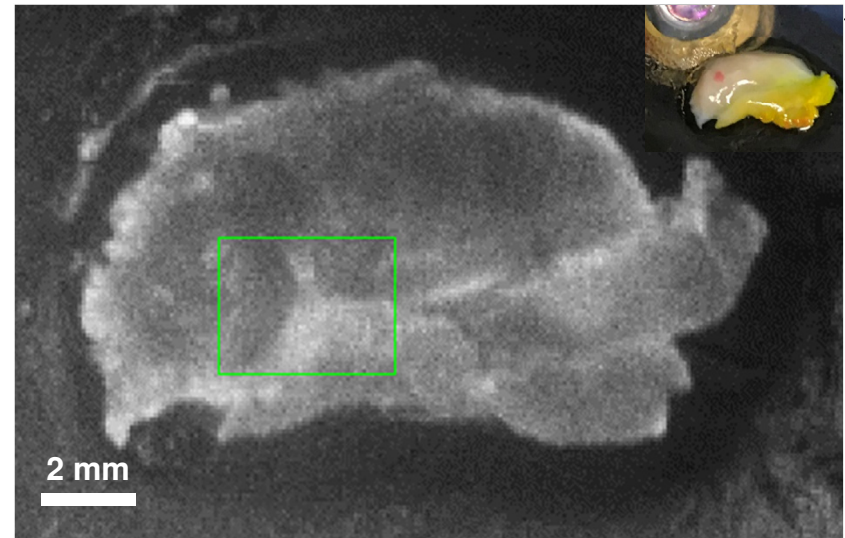
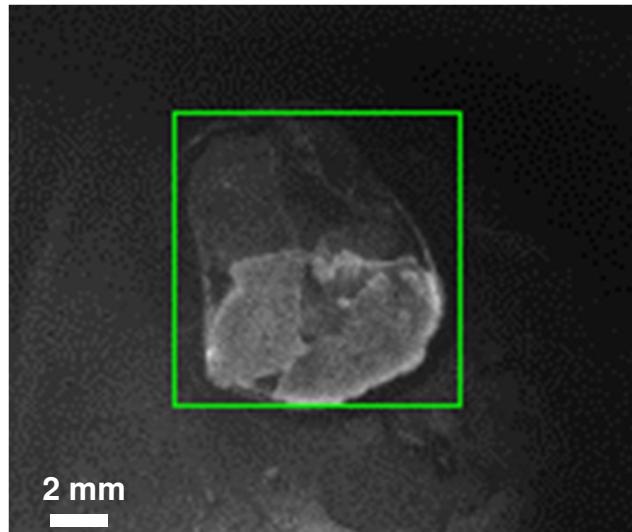
## Side view + LabVIEW software



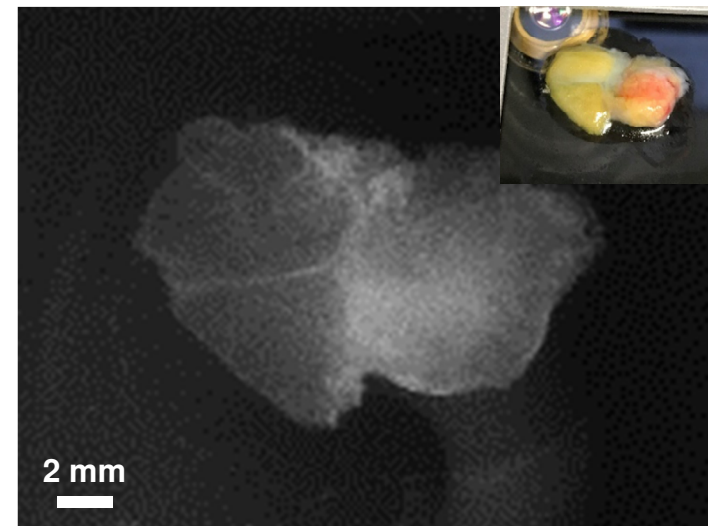
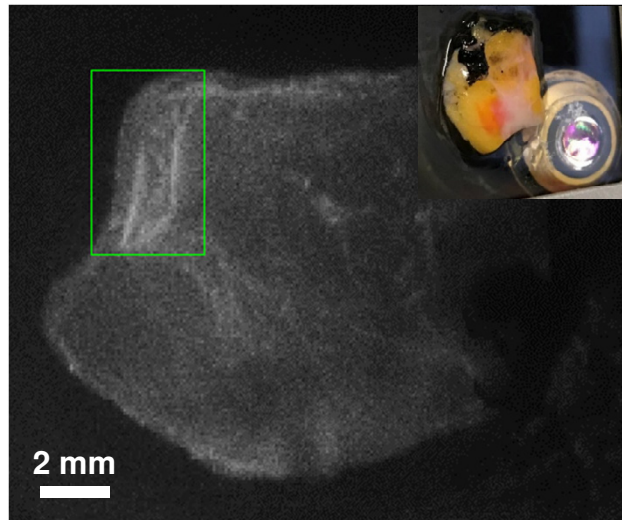
## View from above



# Contrast Agent: Clear Boundaries



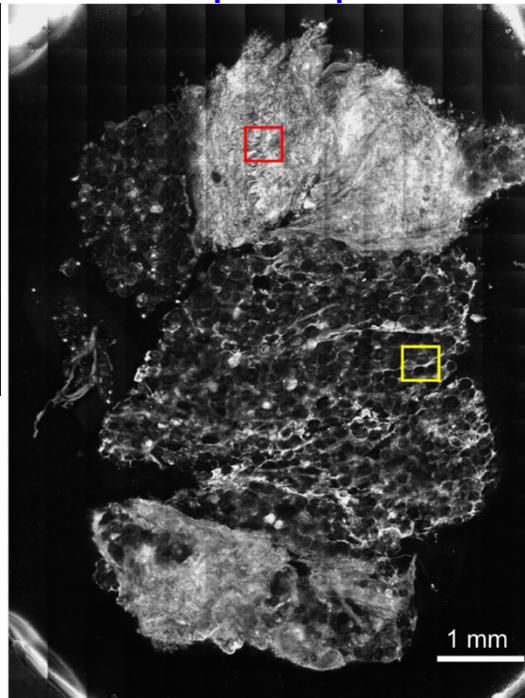
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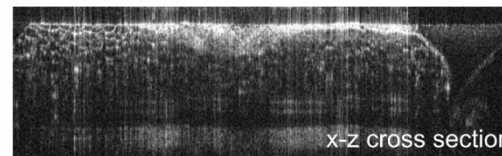
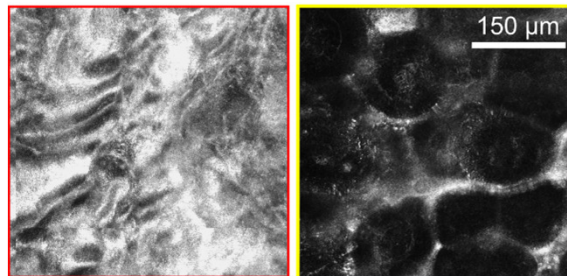
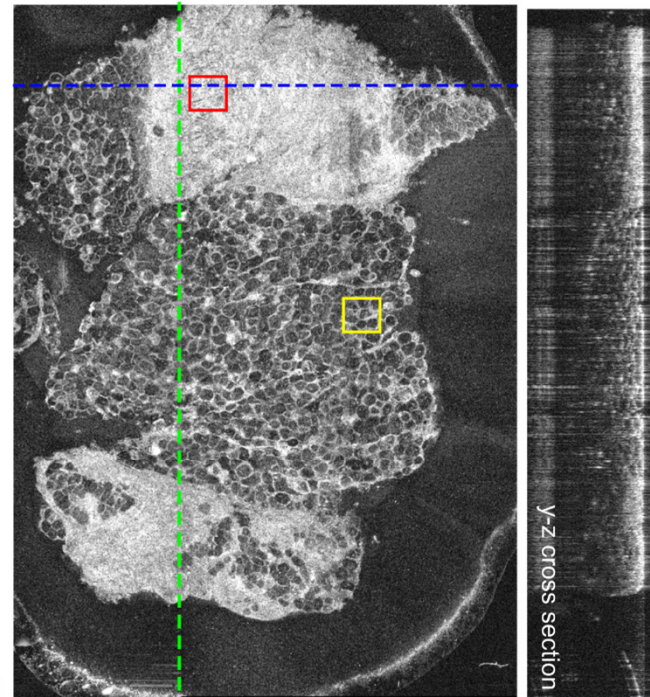
# RCM-OCT: Registering



Depth ~ 50 $\mu$ m

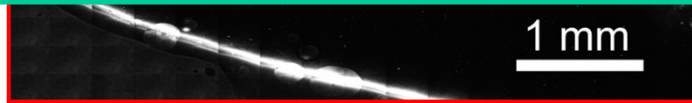
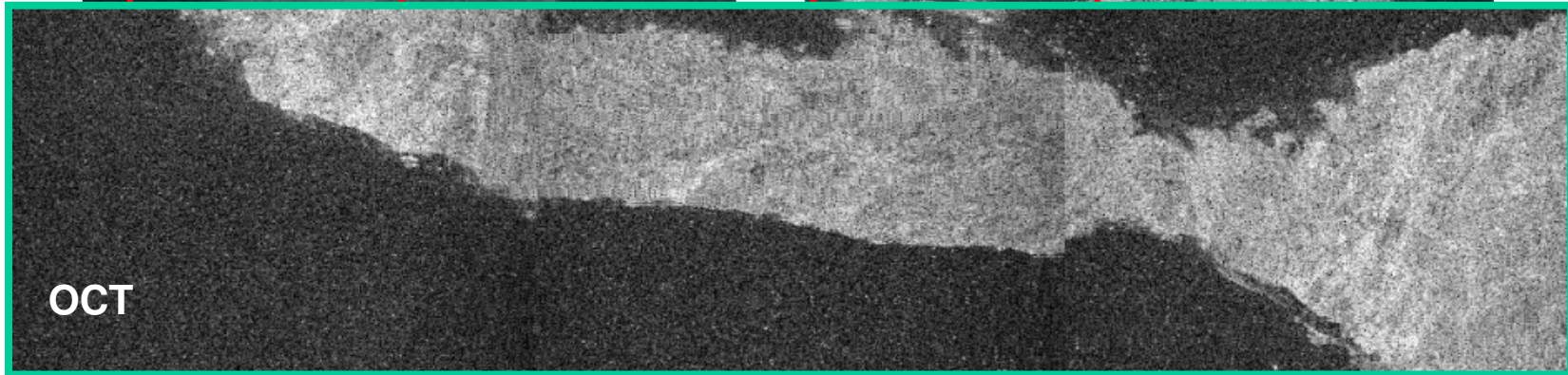
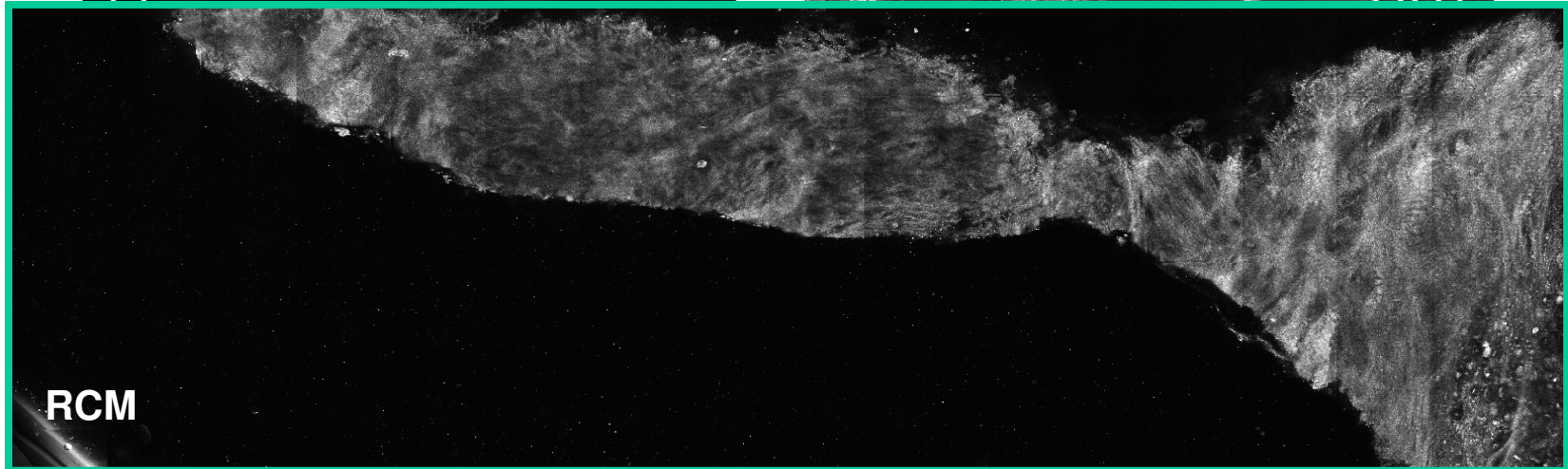


Depth ~ 45 $\mu$ m



- — — x-z cross section position
- — — y-z cross section position

# Trimodal

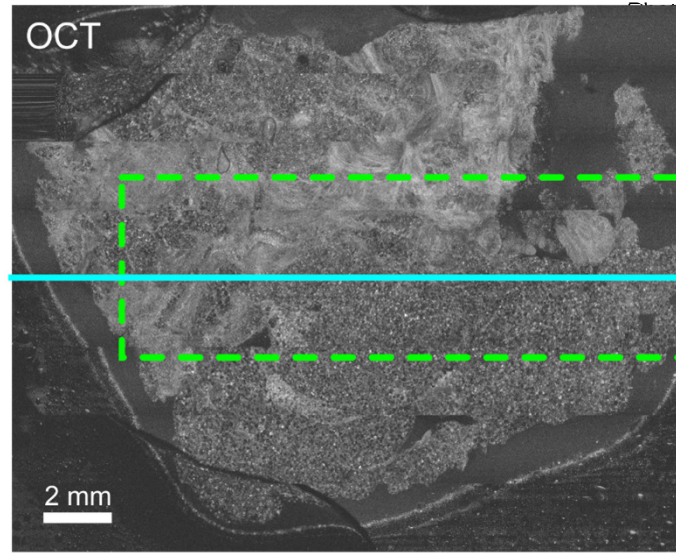
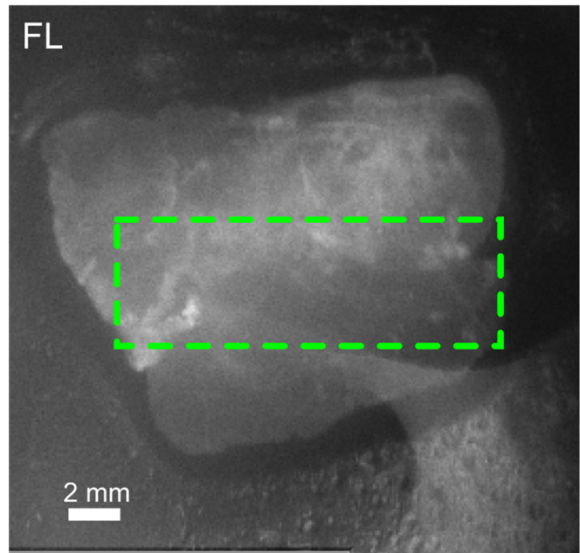
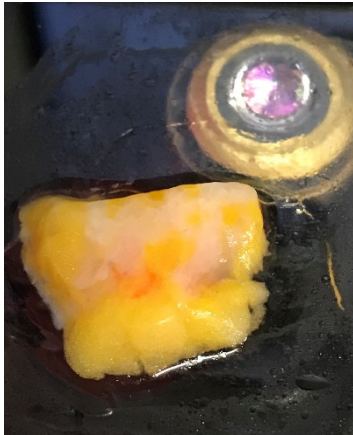


Depth ~ 50 $\mu$ m

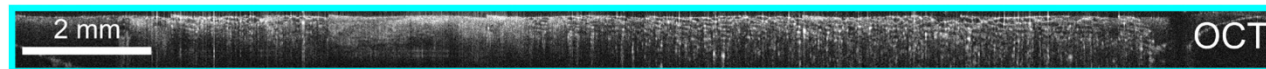
Background • Instrument & Methods • Results • Conclusion & Future Work



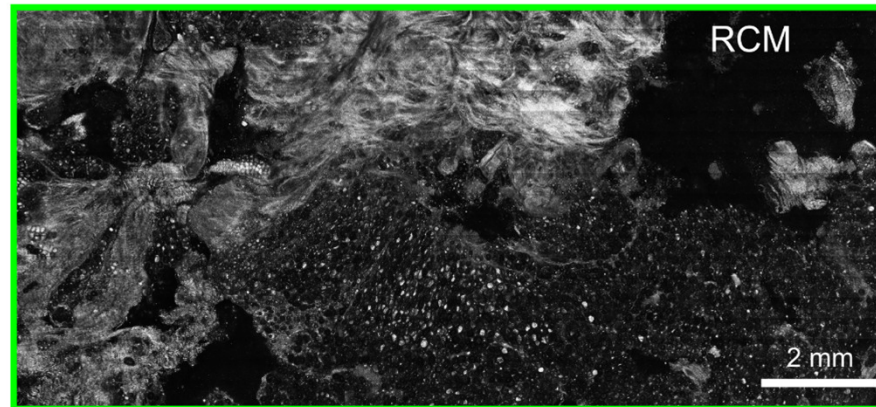
# Investigating Boundaries: ROI Registering



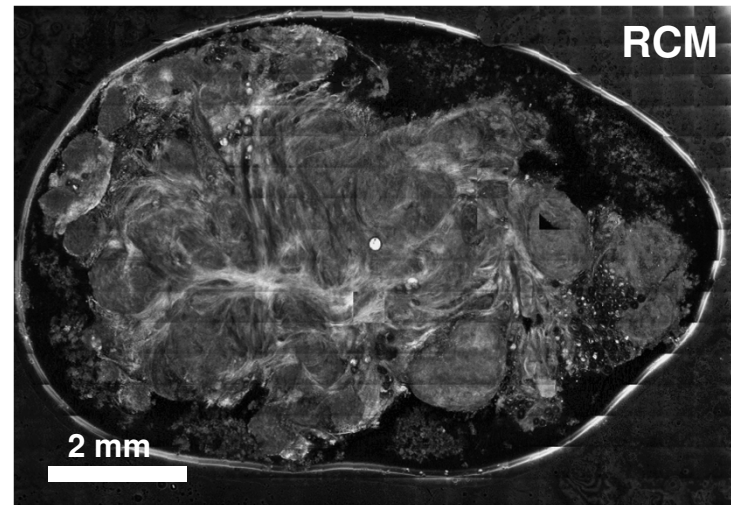
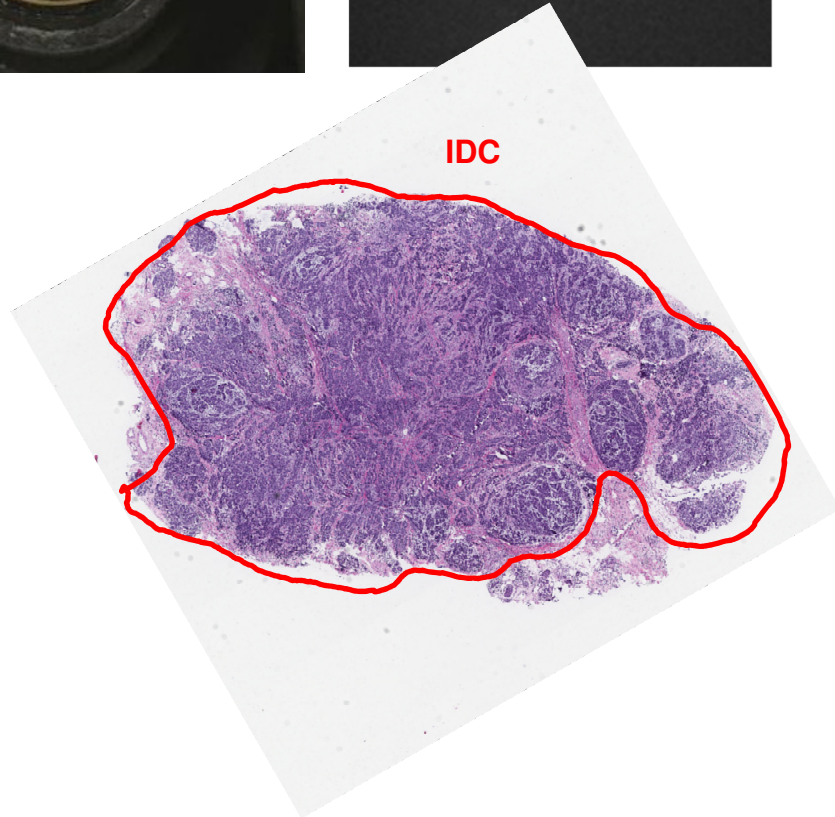
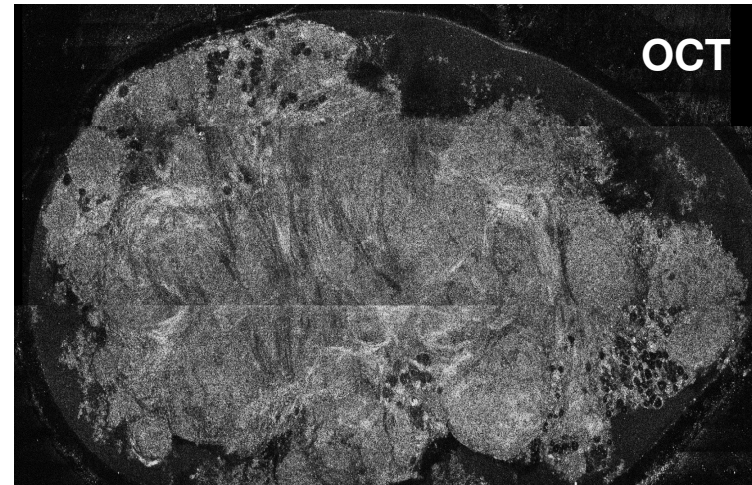
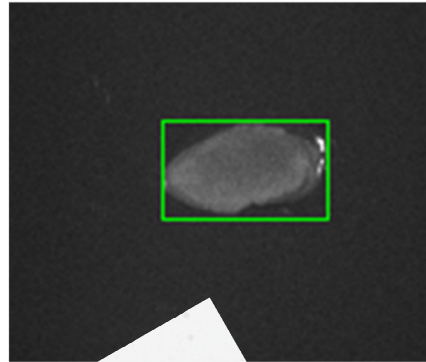
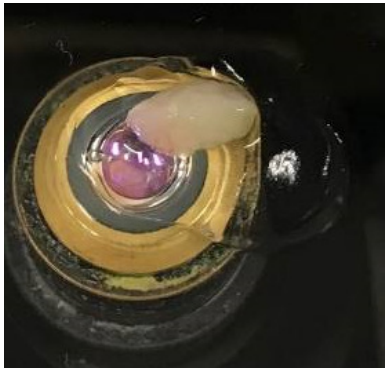
Depth ~ 100  $\mu$ m



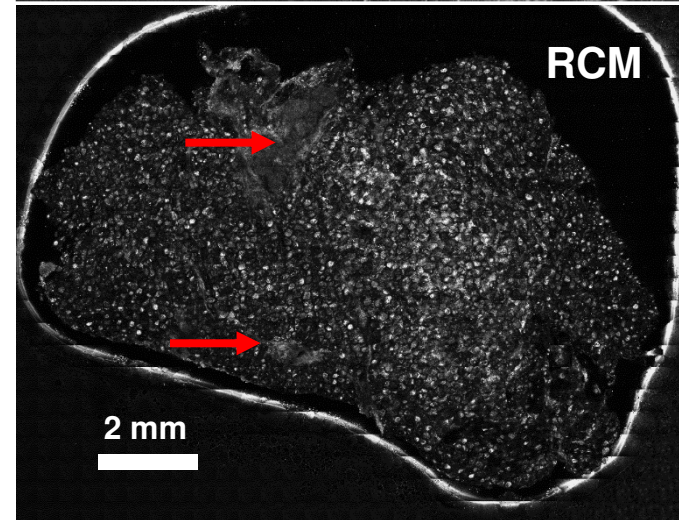
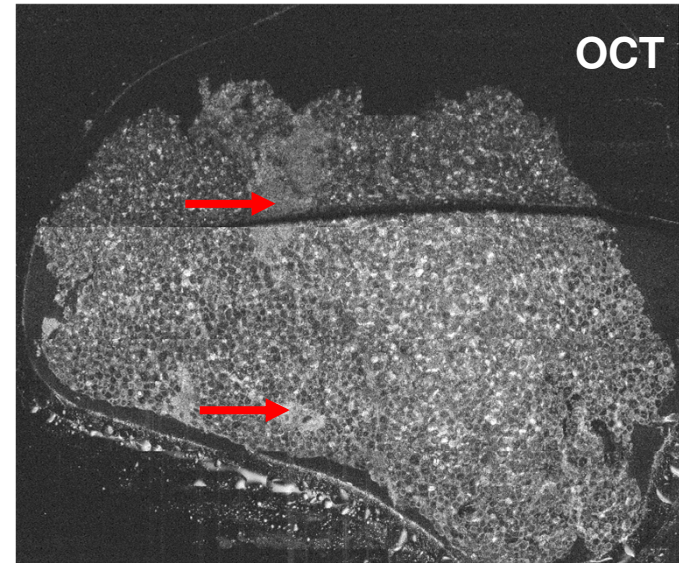
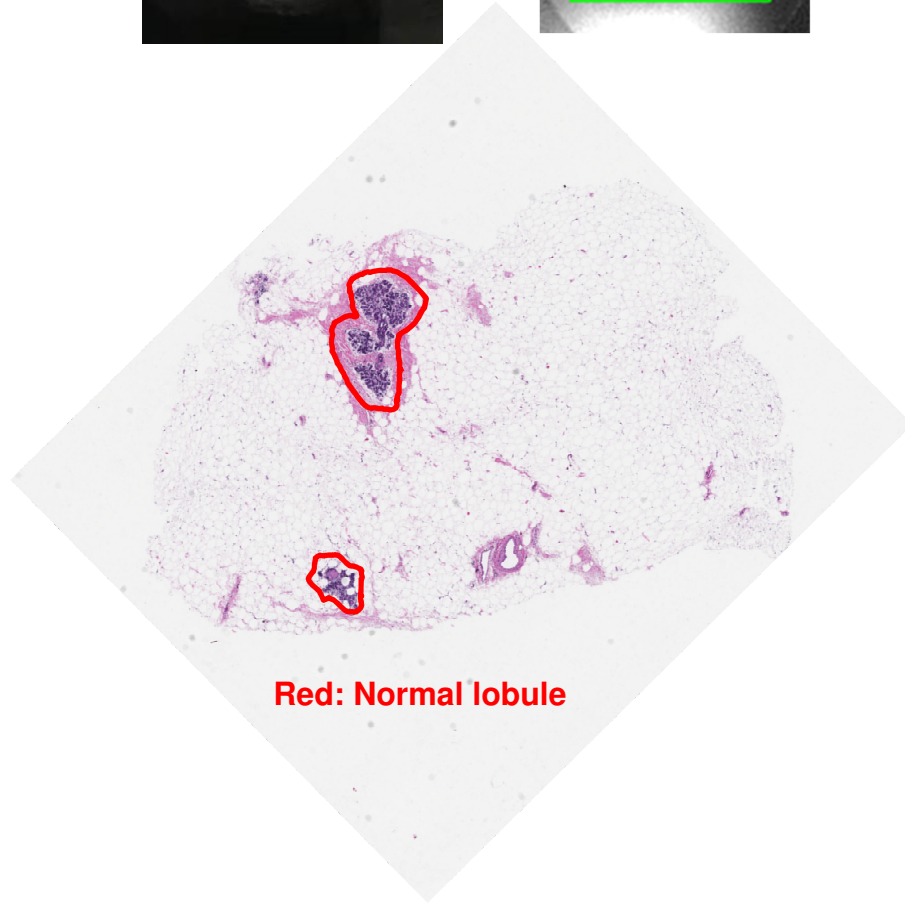
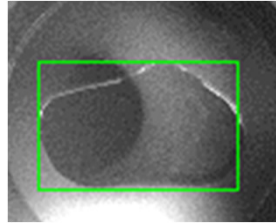
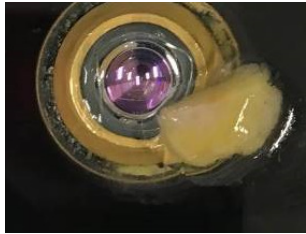
Depth ~ 50  $\mu$ m



# Histological Comparisons



# Histological Comparisons



# Conclusions

- **Highly specific and reactive contrast agent**
  - Very stable, low staining concentration [200nM]
- **Enhanced contrast fluorescence imaging was very useful in highlighting suspicious cancer presence - reduces the amount of time needed for analyzing the specimen with higher resolution microscopy, which can be applied only on the highlighted areas**
- **Histological comparison = proper algorithmic training based off ground truth**
  - Measures of specificity and sensitivity can be computed

## Future Work

- **Validate image quality and predictive capability against histological ground-truth**
- **RCM acquisition speed improvements**
- **Data saving speed and handling improvements**
  - Adding flexibility (these files can quickly become prohibitively large)

# Acknowledgements

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