Ultra-sensitive Raman microscopy and endoscopy tools for pre- and intraoperative imaging

EPIC Meeting at NKI December 2019

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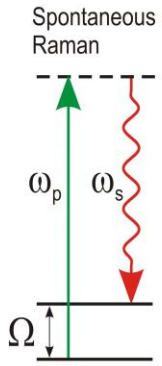
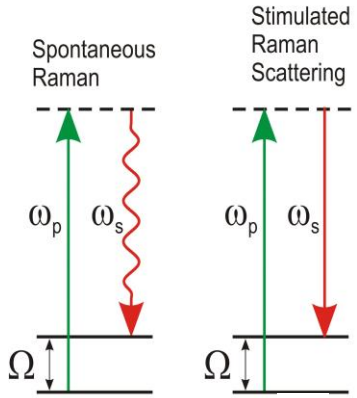
Raman Spectroscopy

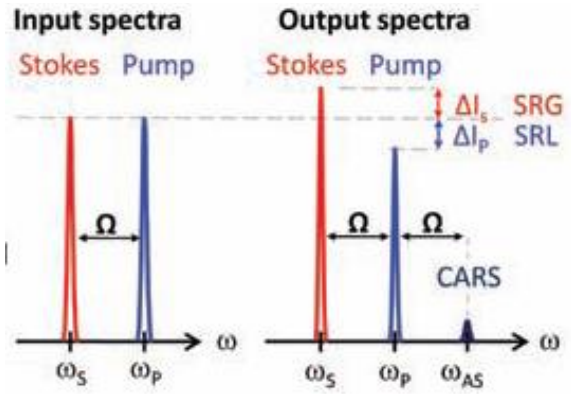
- Chemical information is derived by probing vibrational states of molecules
- Finds wide applications, e.g. in material science
- Downside: rather small cross section => low intensities and sensitivity



Stimulated Raman Spectroscopy/Microscopy

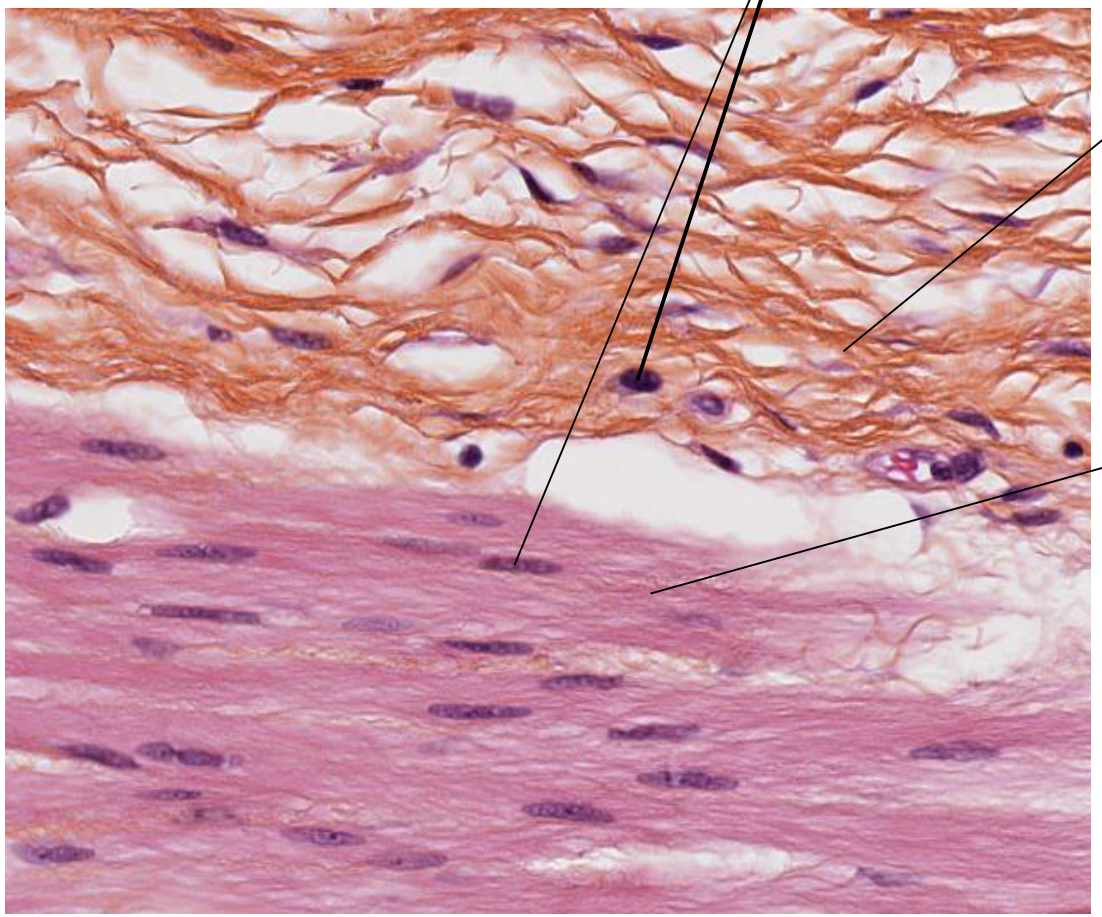
- Significant (x 10^6) increase in sensitivity by using two laser beams
- Stimulated Raman Spectroscopy
- Vibrational excitation is drastically amplified when energy difference between Pump and Stokes matches the vibration of chemical bond of interest (e.g. CH_2)
- Images can be generated by scanning the lasers beams in a scanning microscope and detecting intensity changes at each pixel





How can Stimulated Raman Micrsoscopy be used in Histology?

Histology: H&E staining



Hematein for **nuclei**

Saffron for **collagen** and **conjonctive tissue**

Eosin for **cytoplasm** and **muscular fibers**

Histology: H&E staining

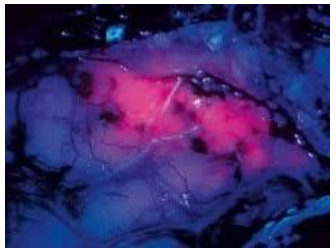
- Well established procedure
- Cutting – Fixing – Staining – Slicing
- Time consuming
- Could it be improved?

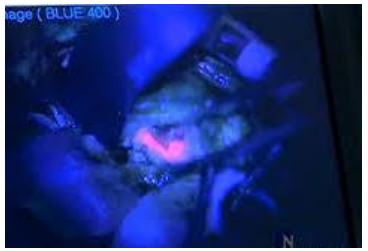
Requirement from the medical doctors - **Neurology**

- Intra-operative imaging of tumour tissue

  'Cutting' has functional consequences

- Not necessarily H&E (Haematoxylin and Eosin) staining (5ALA)

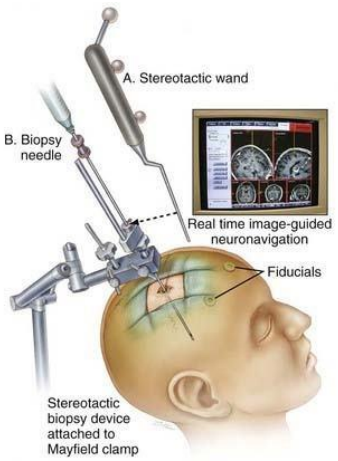


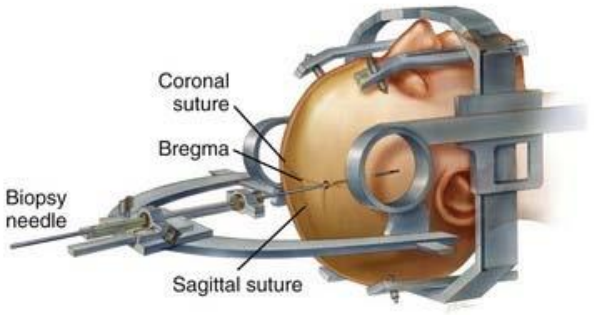


- Intra-operative means imaging **before** removing, ideally in a flexible probe

Requirement from the medical doctors - **Neurology**

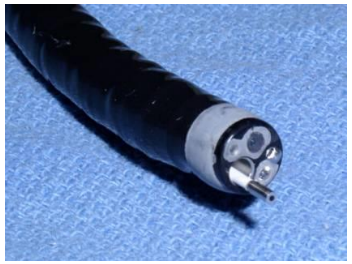
- **BUT** a first step providing ex vivo H&E diagnostic is valuable
- Also neurobiologist say that the immediate diagnostic after brain biopsy is valuable





Requirement from the medical doctors – **Gastric System**

- Although gastric system removal is less critical than brain there are situations where instant histology would save lives
  - The detection of peritoneal metastasis during a gastric surgery
  - The clear identification of low and high grade epithelial dysplasia taking place at the gastroesophageal junction
- Flexible CRS probes can be inserted into the user port of commercial endoscopes



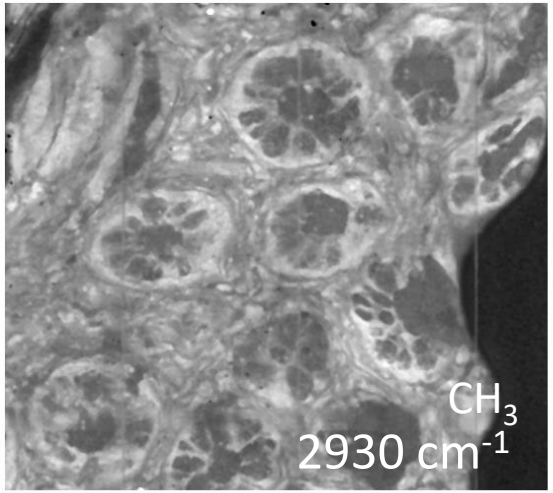
Goal

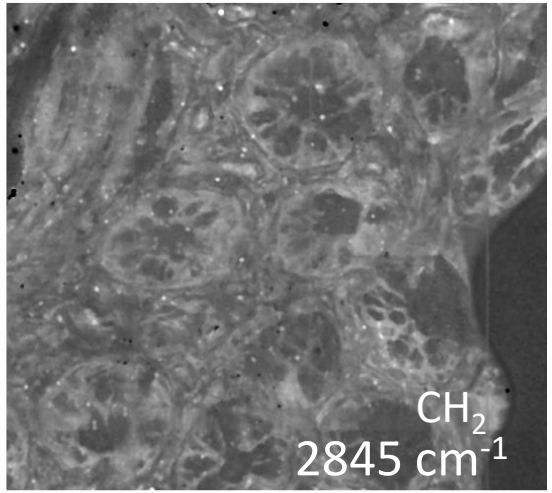
Is it possible to do:

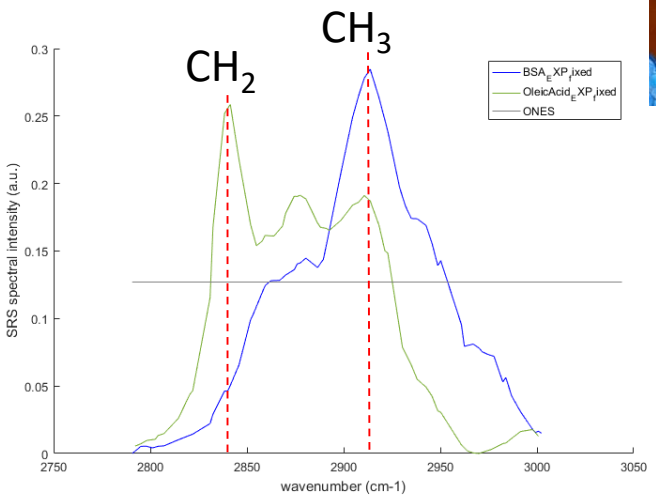
- Label free histology with H&E quality?
- Instantaneous to be compatible with in vivo sample?
- Perform label free histology in an endoscope to access deep tissue and intra-operative diagnostic?

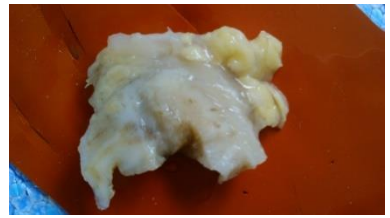
Stimulated Raman Histology (SRS)

Orringer et al., **Nat. Biomed. Eng. 1**, 0027 (2017) – SRH in the brain
B. Sarri et al, **Scientific Reports 9**, 10052 (2019) – SRH in the gastric system



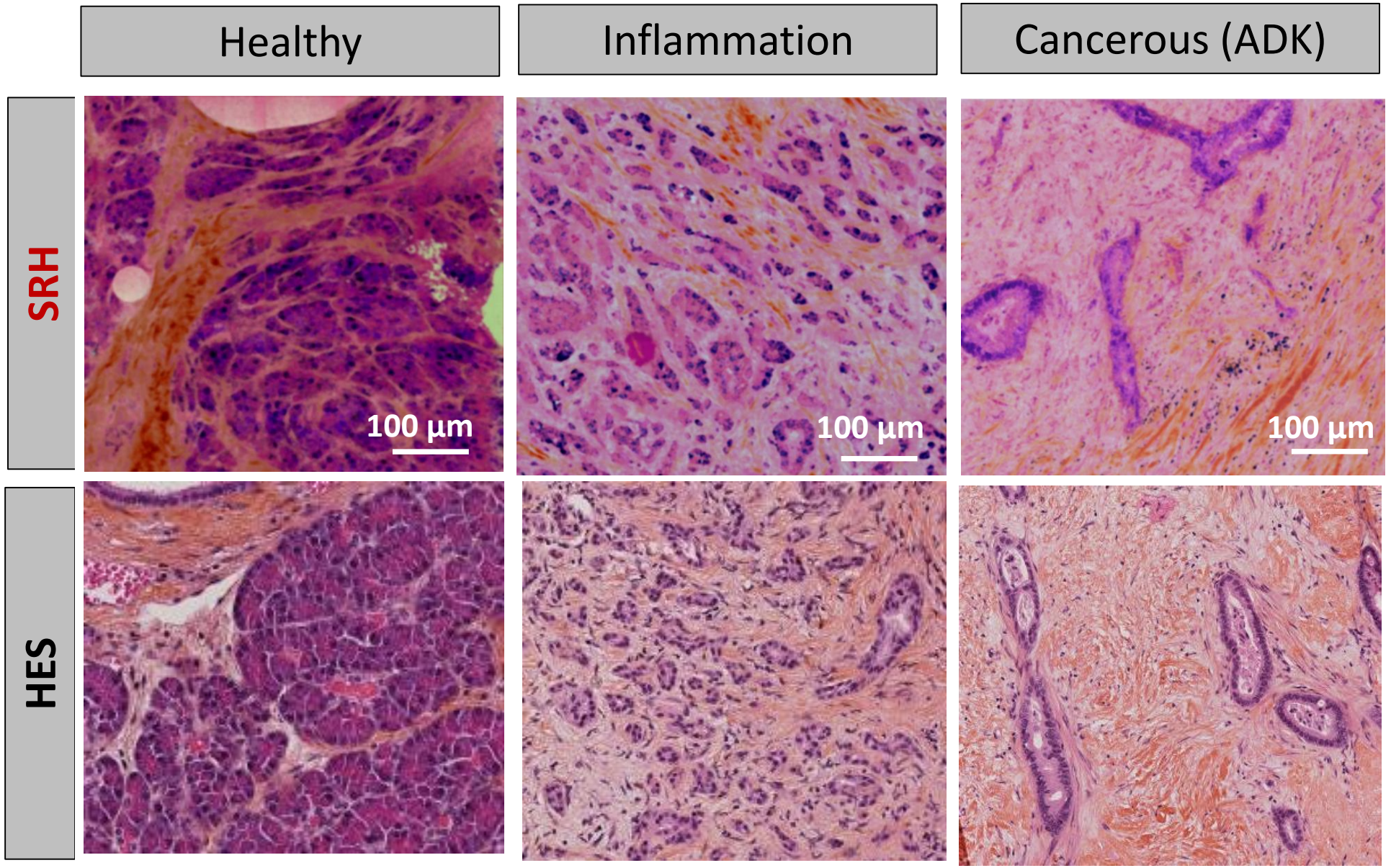






Fresh tissue

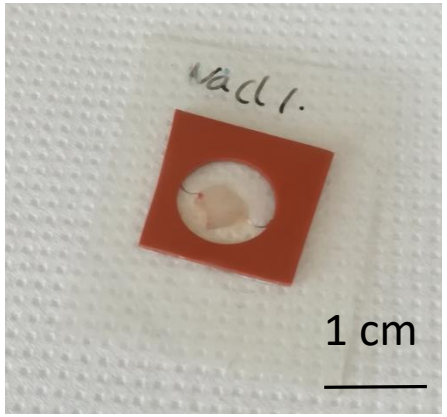
Diagnostic: SRH versus H&E : Colon Pancreas



B. Sarri at al., "Fast stimulated Raman imaging for intraoperative gastro-intestinal cancer detection," Scientific Reports 9, 10052 (2019)

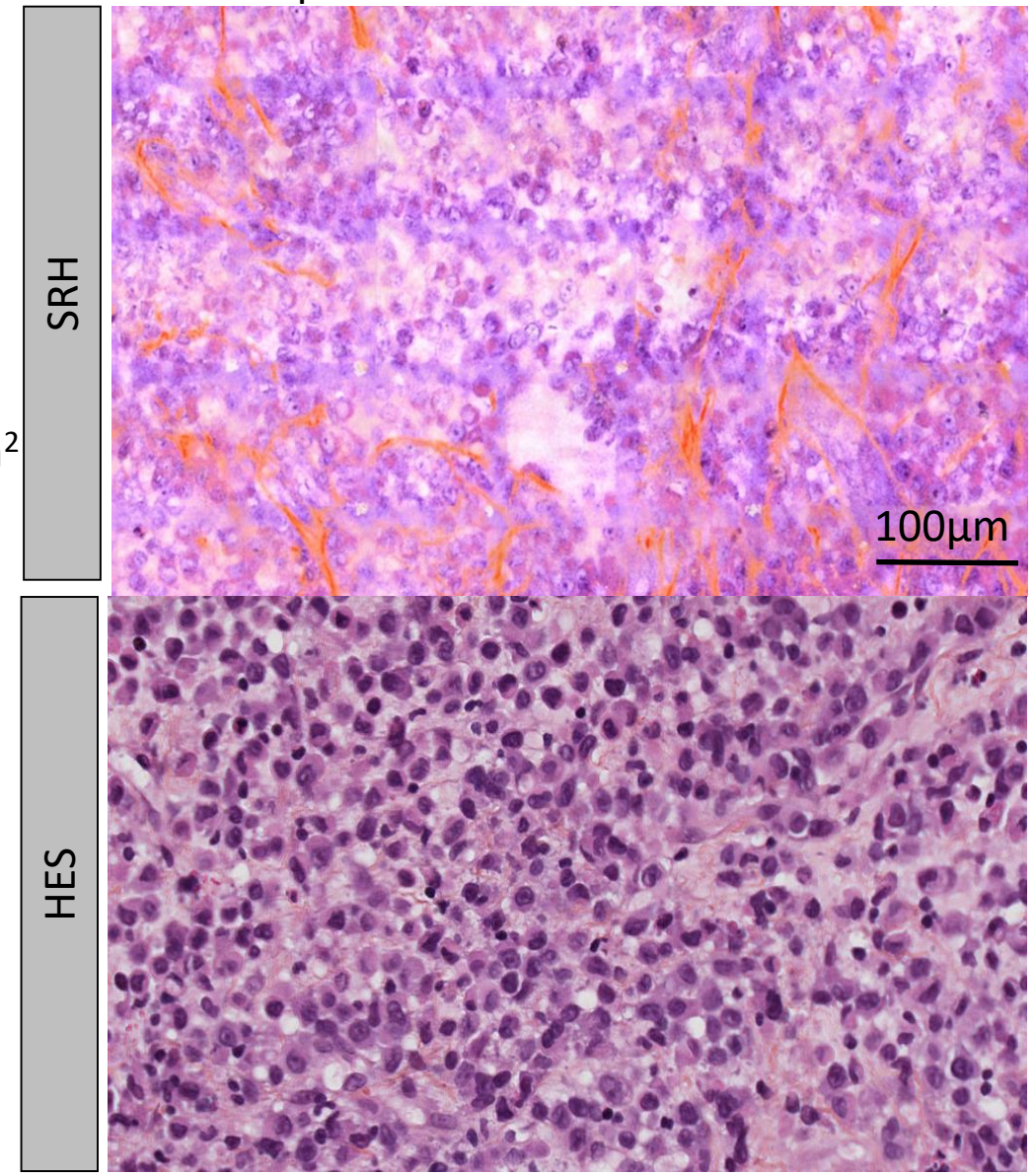
SRH Intraoperative context

Imaging speed: 10 min/mm^2



Fresh samples

Acquisition time: 20 minutes



B. Sarri et al, "Stimulated Raman histology: one to one comparison with standard hematoxylin and eosin staining," Biomed. Opt. Express 10, 5378-5384 (2019).

Conclusion

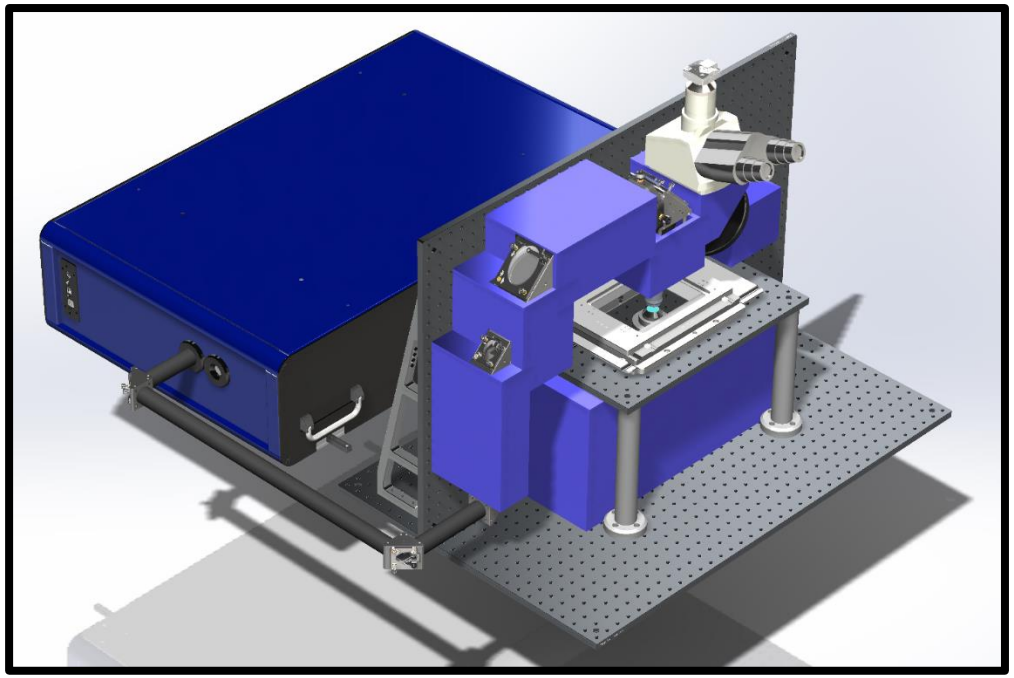
- Stimulated Raman Histology (SRH) can provide almost equal information as H&E-staining
- Information is available much faster => important especially during operation
- SRH can provide additional information due to improved z-resolution; less distortions from cutting
- SRH can be applied to various types of human tissue
- Compatible with general workflow in operatory room
- Further clinical studies necessary to show benefit of technology

Outlook: Coherent Raman imaging system

- **Stimulated Raman histology**
- Coherent Raman imaging (CARS)
- 2-photon imaging
- Second harmonic imaging

- User friendly interface

- Millimeter field of view
- Sub-micron resolution
- 3D imaging capability
- 1mm^2 image in <60s



Available in 2020!

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