College of Optical Sciences
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Compact Ultrafast Fiber Lasers for Biomedical Imaging

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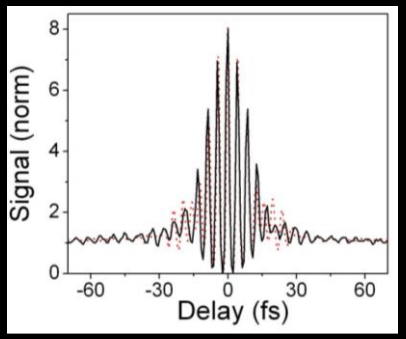
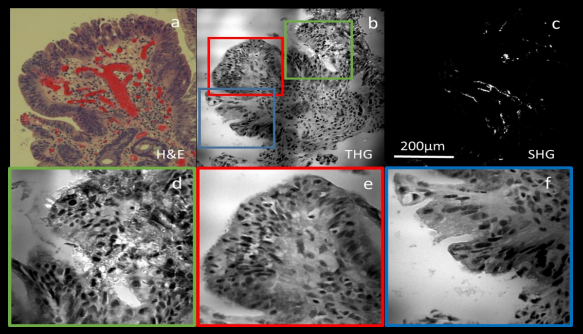
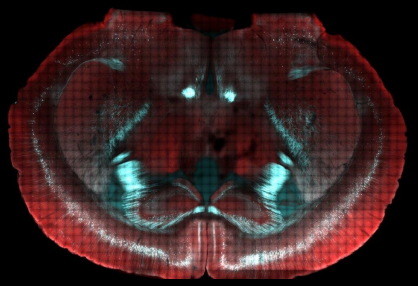
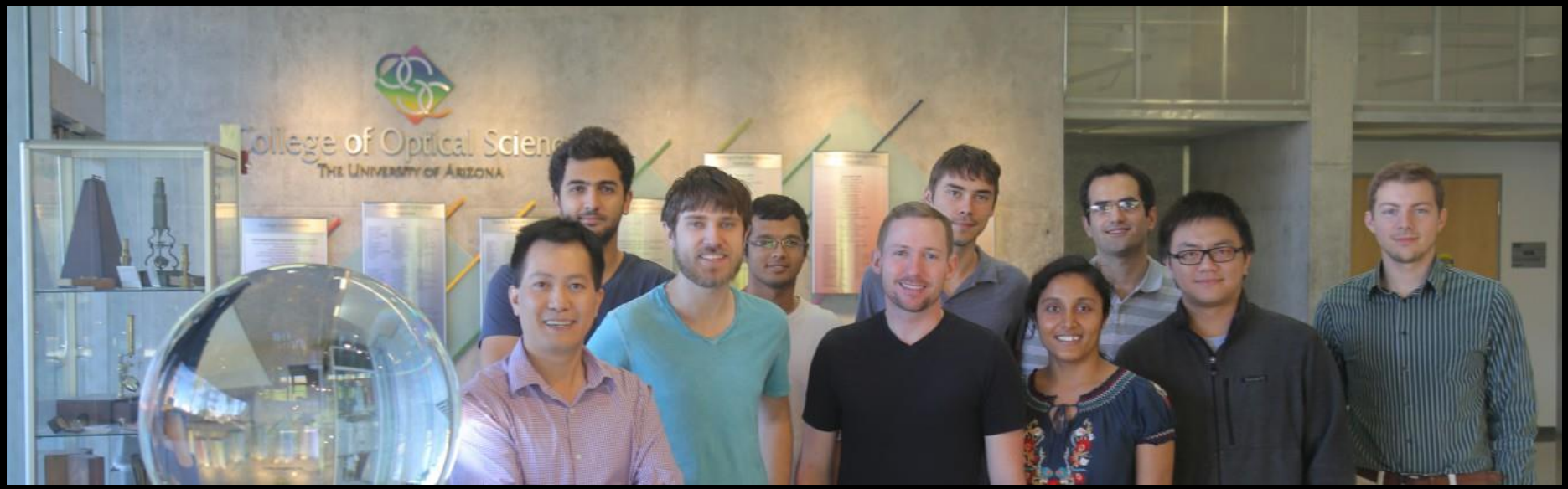






Our research group



Left to right: Khanh, Soroush, Alex, Raj, Josh, Dmitriy, Roopa, Babak, Neil, Dawson

R. Norwood, N. Peyghambarian, J. Barton, B. Banerjee, T. Matsunaga.
Barrett cancer imaging grant
Canon USA Inc.
AFRL
State of Arizona TRIF funding

Research directions

1. **Fundamental research:** To discover new physics and optical effects
2. **Laser development:**

   - Compact fiber laser sources: 1 μm, 1.55 μm, 2 μm and beyond

     - **<u>Ultrashort optical pulse generation</u>**
     - High power nanosecond fiber sources
     - Low noise single frequency lasers

3. **Applications:**

   - Frequency comb, precision measurements
   - **<u>Nonlinear optical imaging</u>**
   - Nonlinear spectroscopy, all-optical switching
   - THz generation, low noise microwave
   - Ultrafast laser material processing

Motivation

1fs = 10^{-15} s; 1fs to 1s is what 1s is to about 32 million years

- ✓ Interesting physics
- ✓ Many important applications

- Material processing
- Nonlinear microscopy
- Ultrafast spectroscopy
- Frequency combs and related
- Frequency conversion

Ahmed H. Zewail

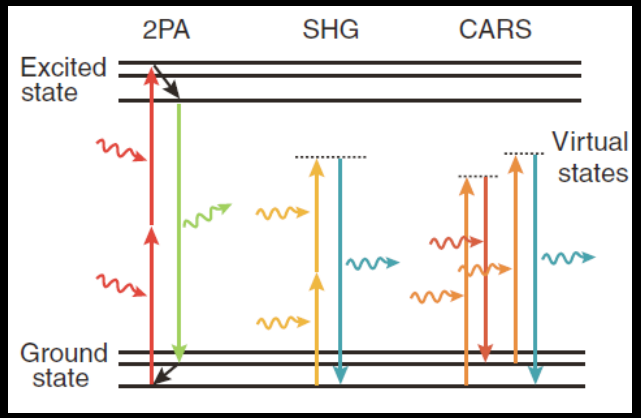
"for his studies of the transition states of chemical reactions using femtosecond spectroscopy".

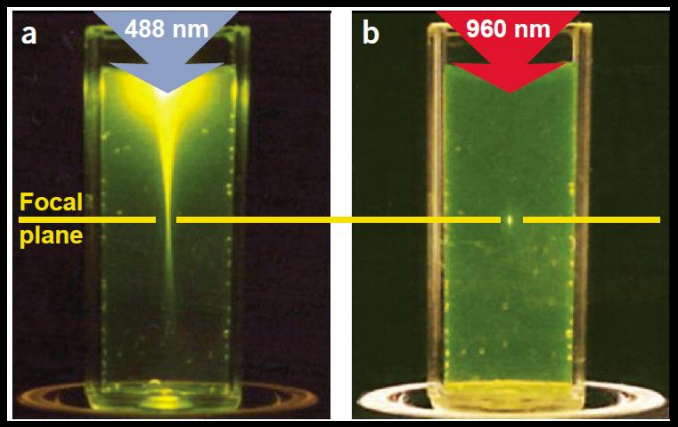
John L. Hall

Theodor W. Hänsch

"for their contributions to the development of laser-based precision spectroscopy, including the optical frequency comb technique".

Nonlinear optical imaging





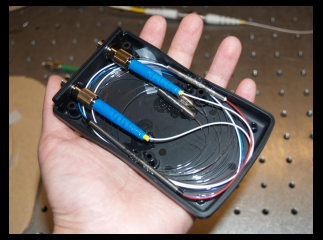
W. Zipfel *et al.*, nature 2003

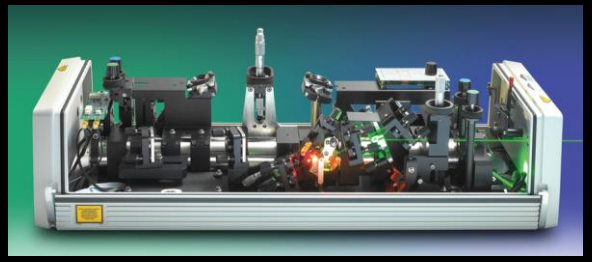
- 3D sectioning
- Non-invasive
- High resolution
- Chemical sensitivity (CARS)

The main bottleneck to make multiphoton microscopy widespread is the cost, size and complexity of the setup

Our research

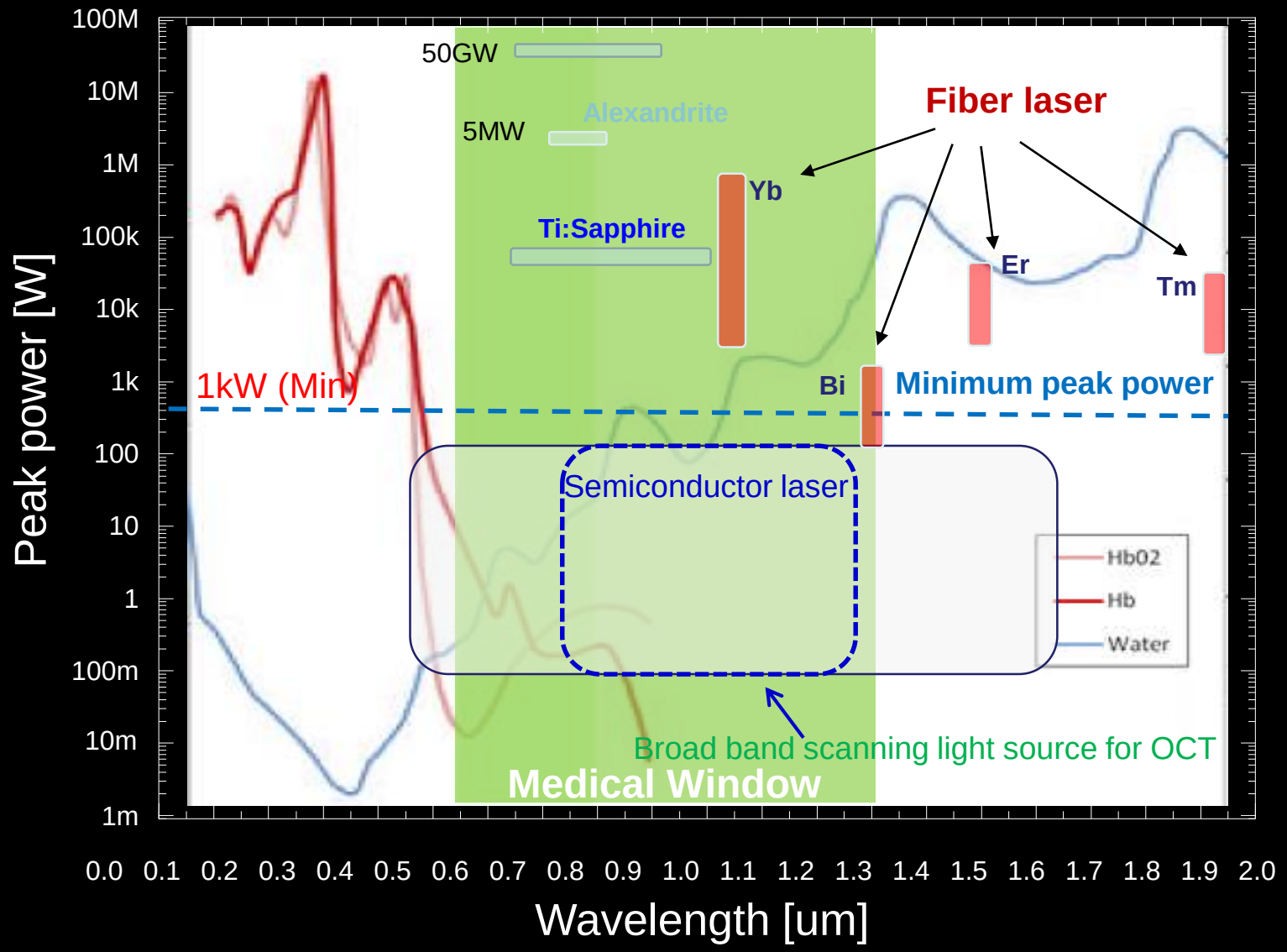
- New fiber laser sources for multiphoton imaging
  - ✓ compact, low cost, easy to use
  - ✓ excellent performance
  - ✓ meet requirements of most applications
- Explore new excitation wavelengths
- Multi-modal label-free imaging
- Clinical translation
- Other uses of multiphoton imaging



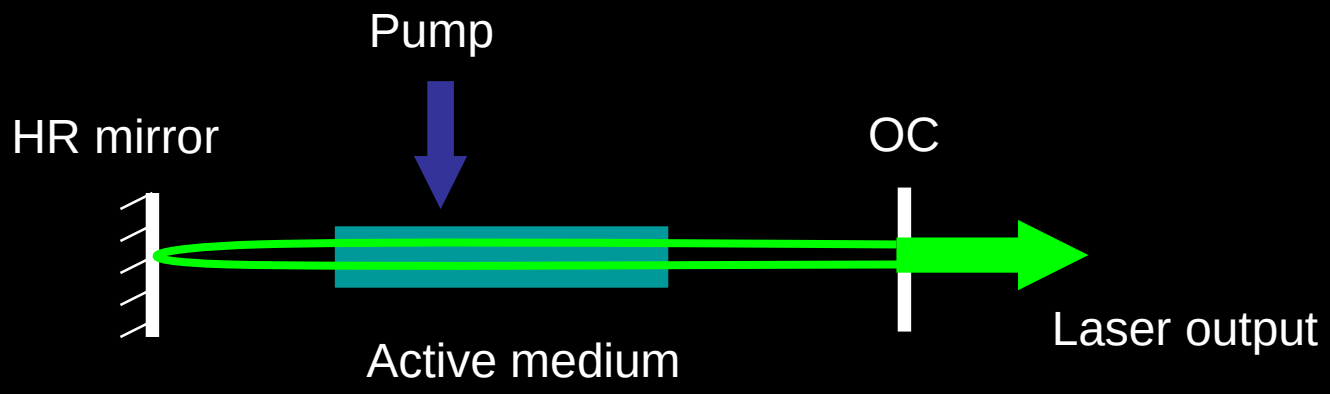


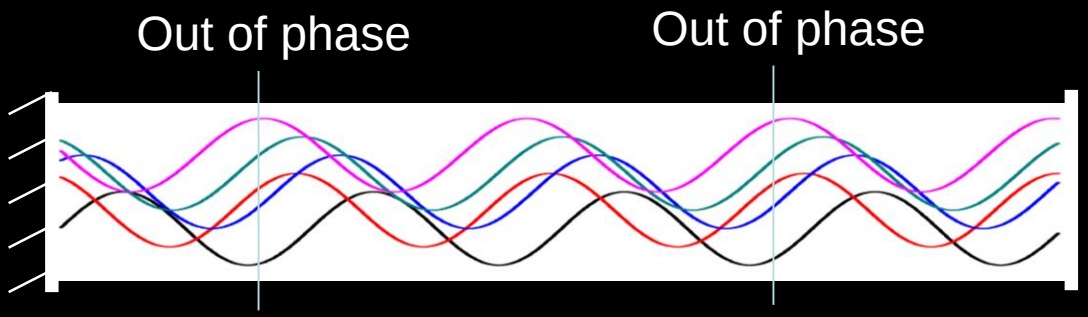
Courtesy of Spectra Physics

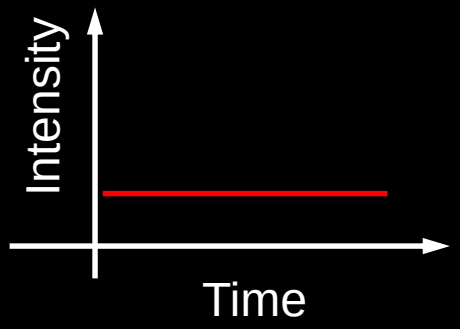
Laser source for nonlinear imaging



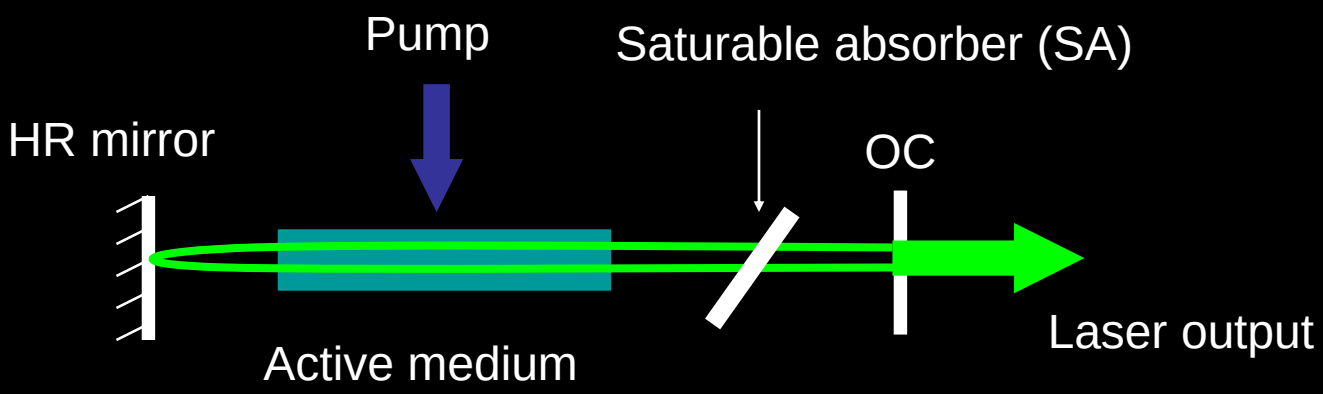
How does the laser work?

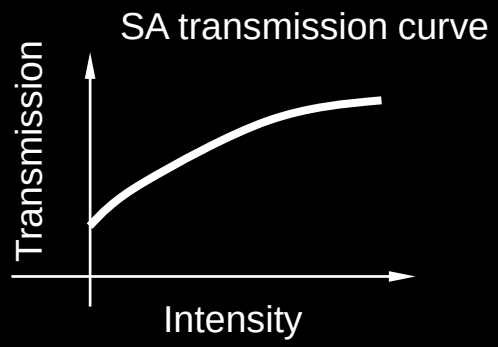


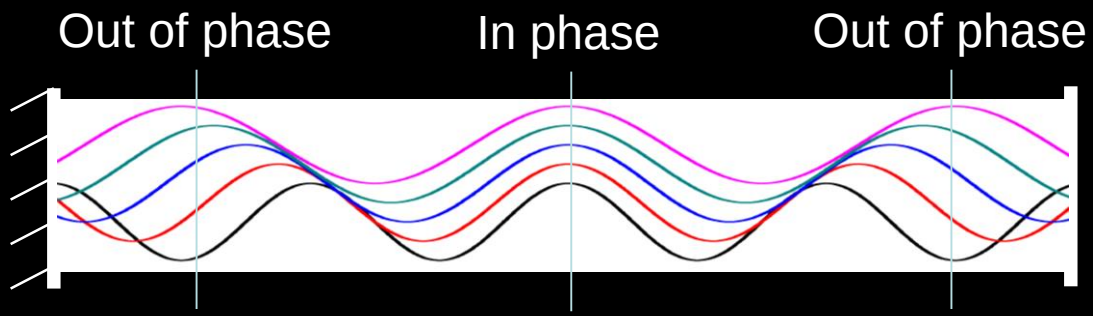


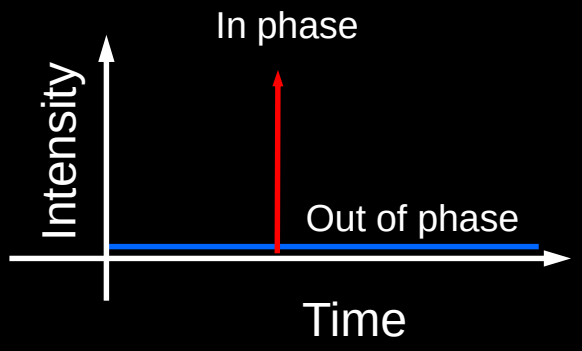


Mode-locking



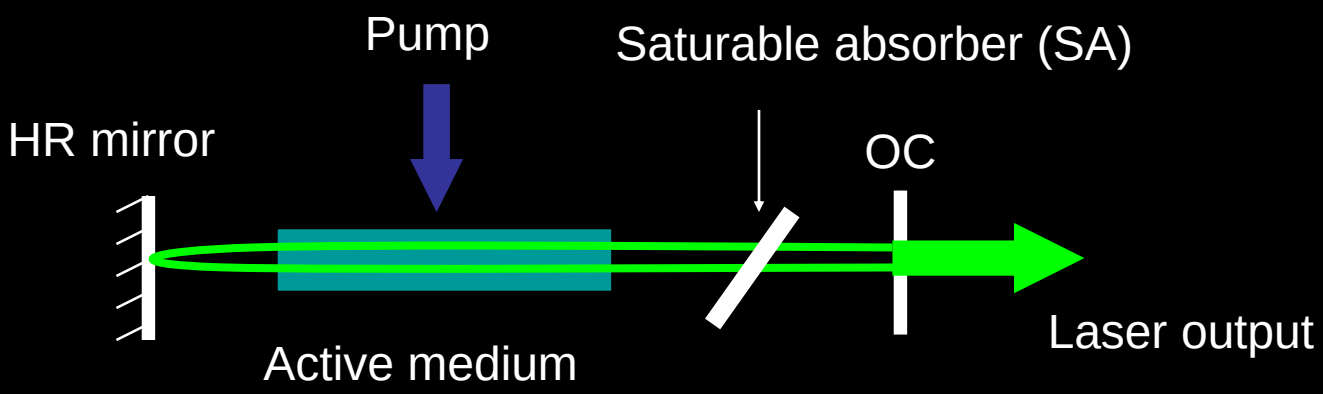


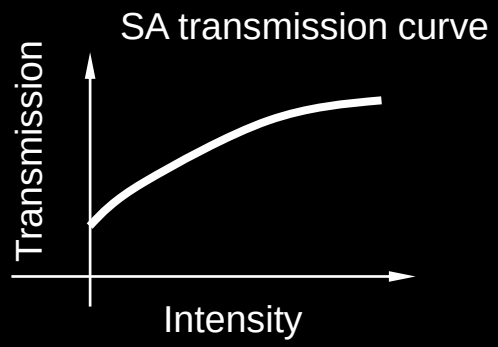


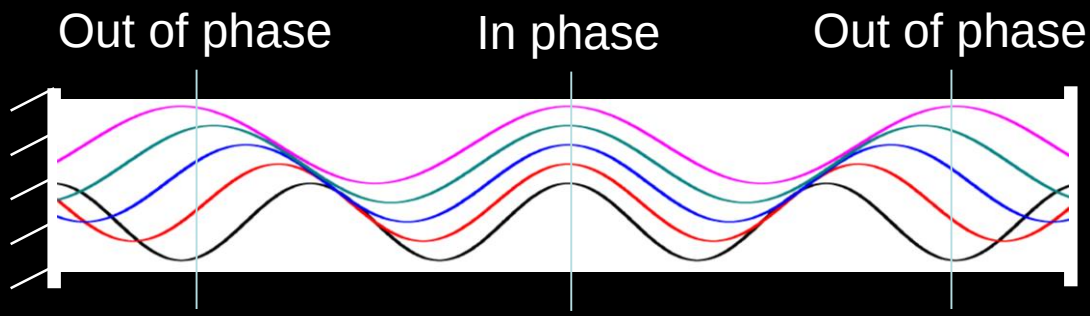


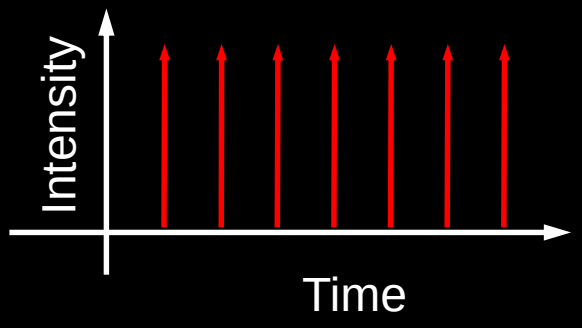
The laser peak power is increased by 10^5-10^6 times!

Mode-locking









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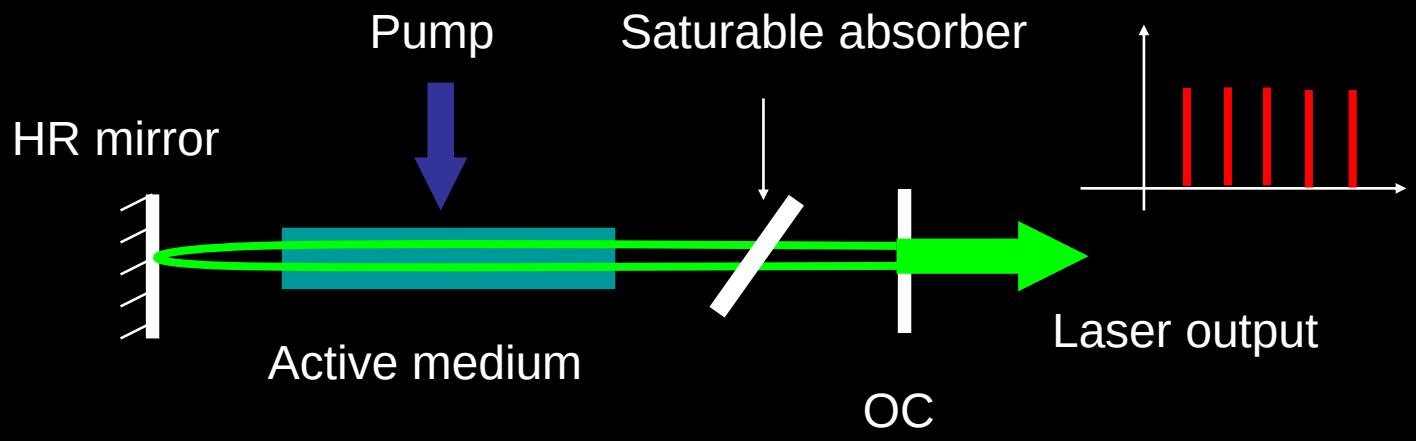
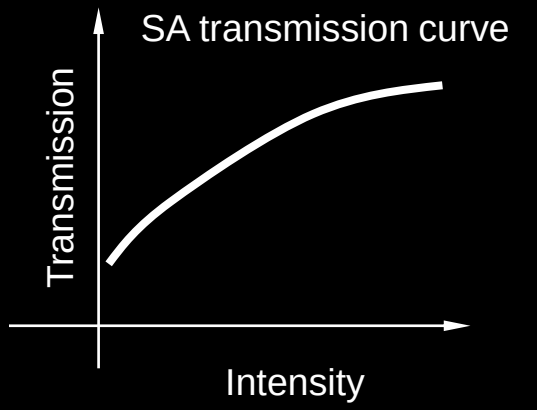
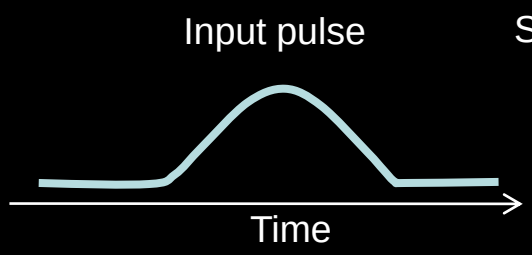
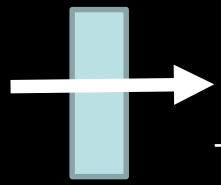
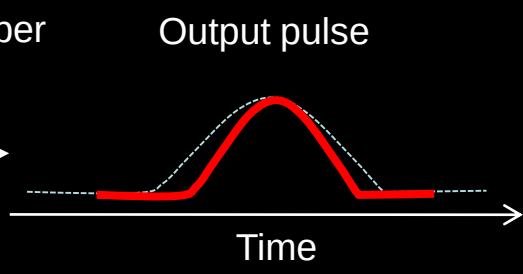




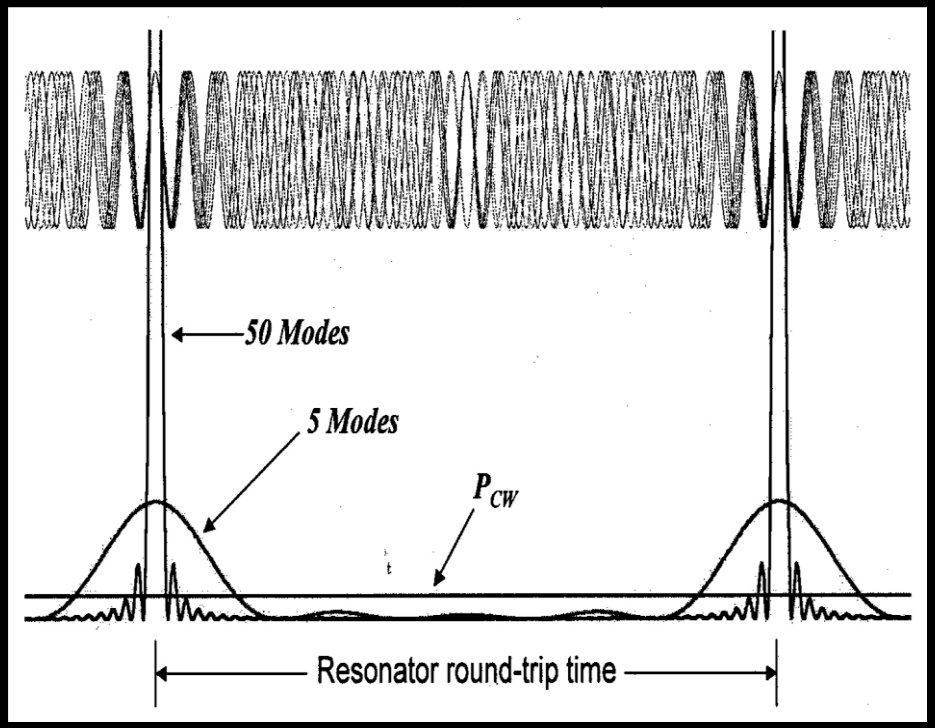




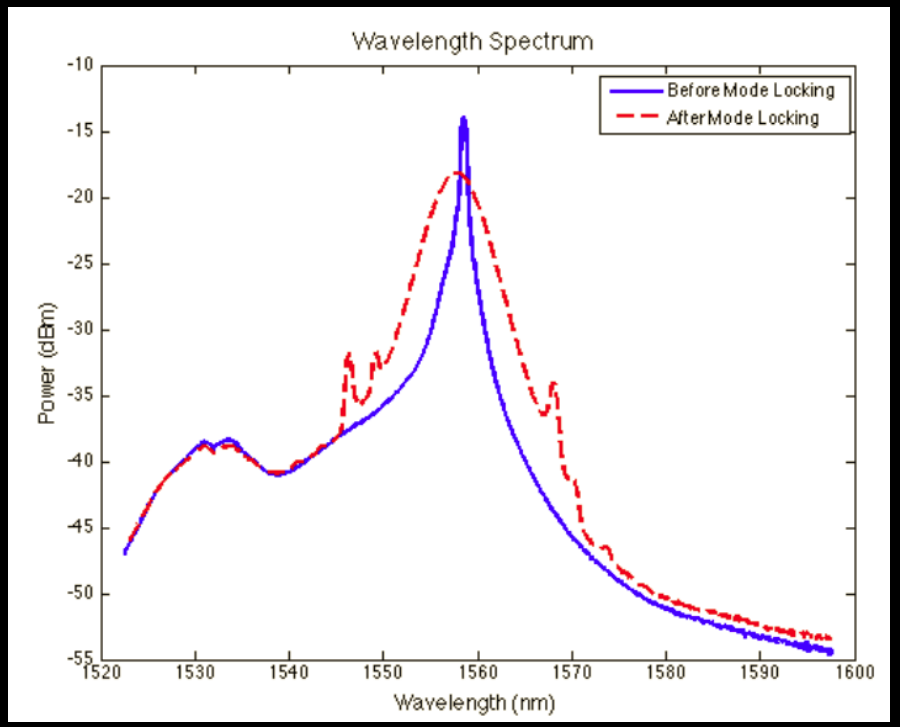


The wings see more loss

Mode-locking



Credit: H. Hause



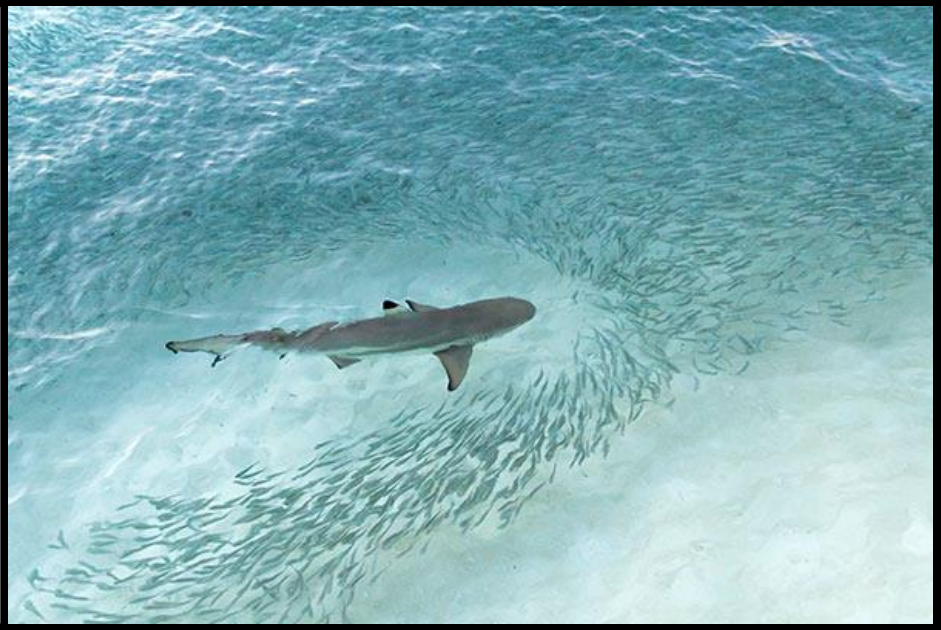
Credit: Oscar Herrera

There are more oscillating modes in a mode-locked laser compared with a CW laser

Collective behavior in nature

coolantarctica.com

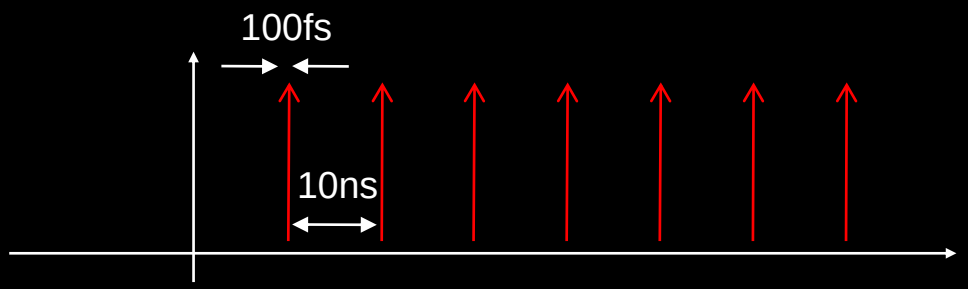
Group of penguins



School of fish

Interesting facts about mode-locked lasers

Mode-locked lasers do not “work” 99.9999% of the time!



Mode-locked lasers generate the highest peak power among lasers

Mode-locked lasers provide one of the shortest events in nature

Mode-locked lasers are one of the best frequency rulers

Mode-locked lasers have the lowest timing jitter compared with most elec. devices

Laser source for nonlinear imaging

Desirable laser parameters	
Wavelength	600-1300nm, 1700nm
Pulse duration	<100fs, picosecond for Raman imaging
Spectral bandwidth	Tens of nanometers, <1nm for Raman imaging
Pulse energy	>1nJ (limited by sample damage)
Average power on sample	<100mW
Repetition rate	1-100MHz

Laser source for nonlinear imaging

Femtosecond Ti:sapphire laser

700-1000nm

Crystal-based OPO

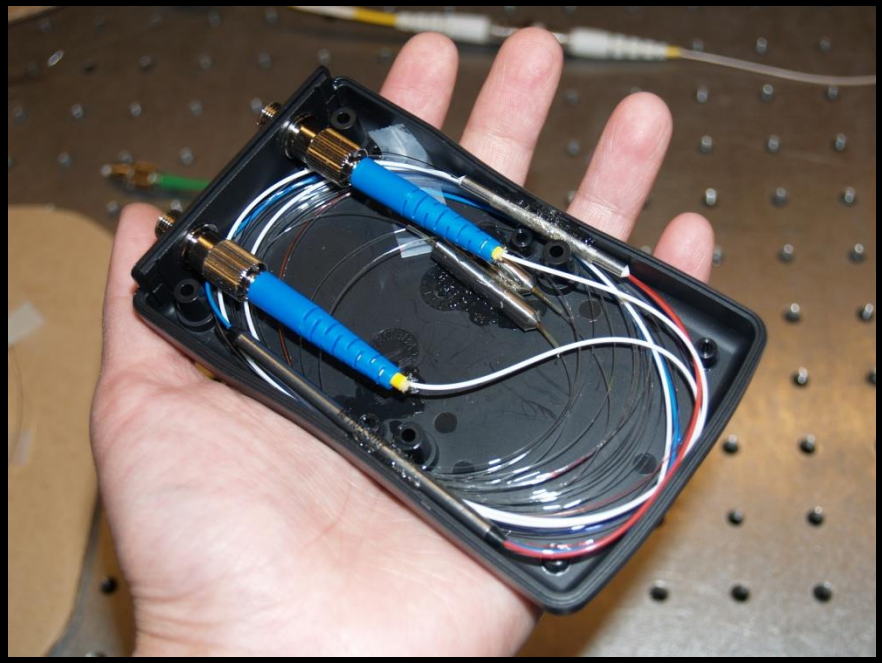
>1000nm

- Expensive
- Bulky
- Maintenance

→ Difficult to move out of research lab

Fiber laser platform

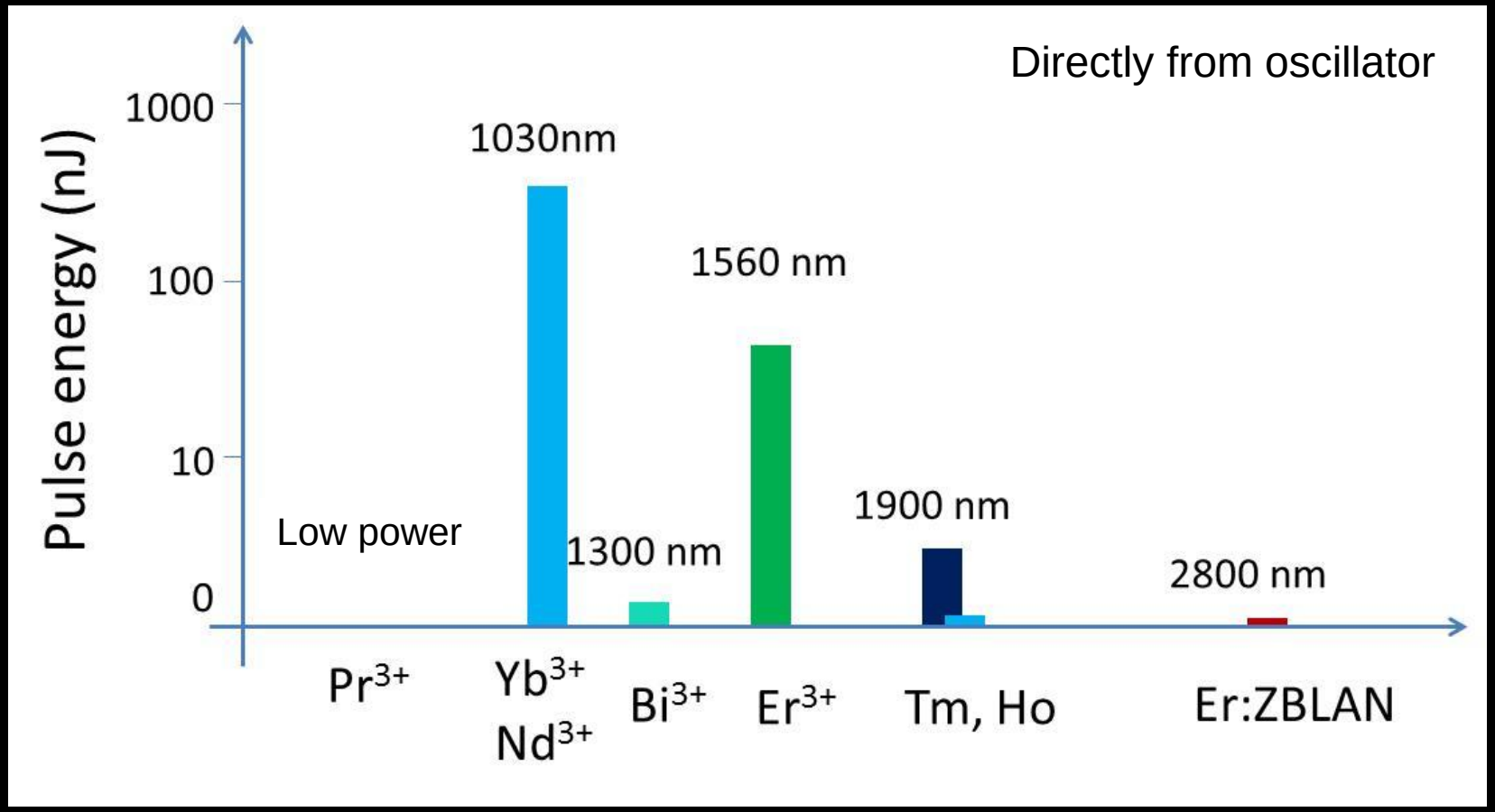
- High efficiency
- Compact
- Alignment free
- Reliable
- Low cost



Challenges:
High power
Mode-locking

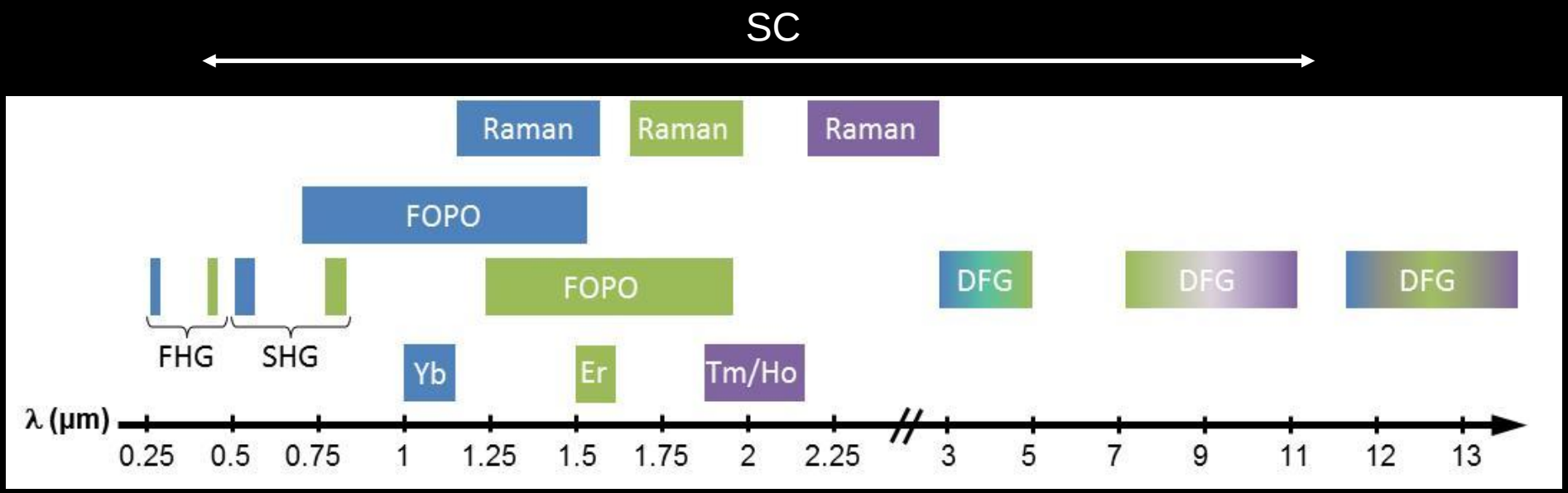
Solution:
New pulse shaping mechanism
New class of saturable absorber

Ultrafast fiber laser landscape



There are still a lot of wavelength gaps!

There are solutions

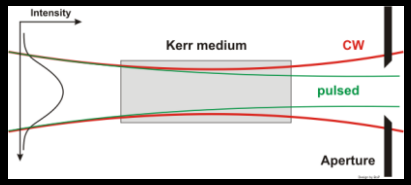


SC – supercontinuum generation
SHG – second harmonic generation
FHG – fourth harmonic generation
FOPO – fiber optical parametric oscillator
DFG – difference frequency generation
Raman – Soliton Raman self-frequency shift

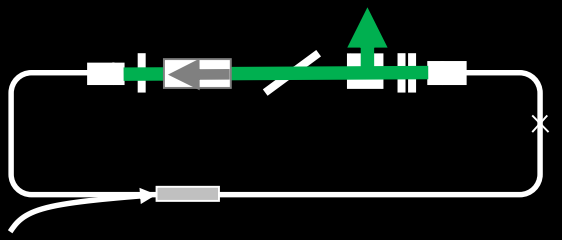
We need a compact mode-locked laser to do all of these cool stuffs!

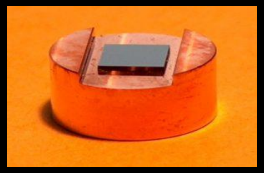
What is the best approach for mode-locking?

- Kerr lens (does not work for fiber, yet)
- Nonlinear Polarization Evolution (NPE)
- SESAM
- Carbon nanotubes (CNT) and graphene

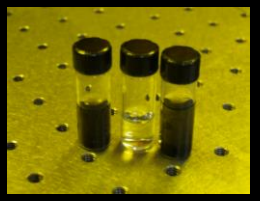


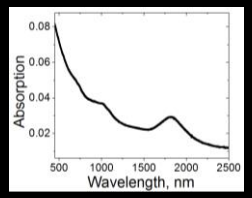
(Wikipedia)



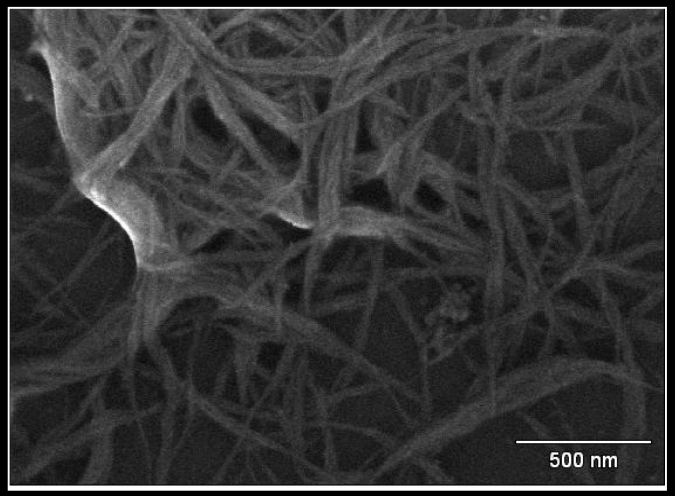


(Batop)

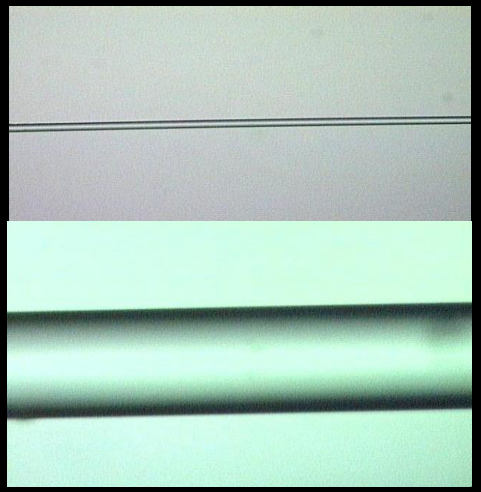




CNT mode-locked fiber laser



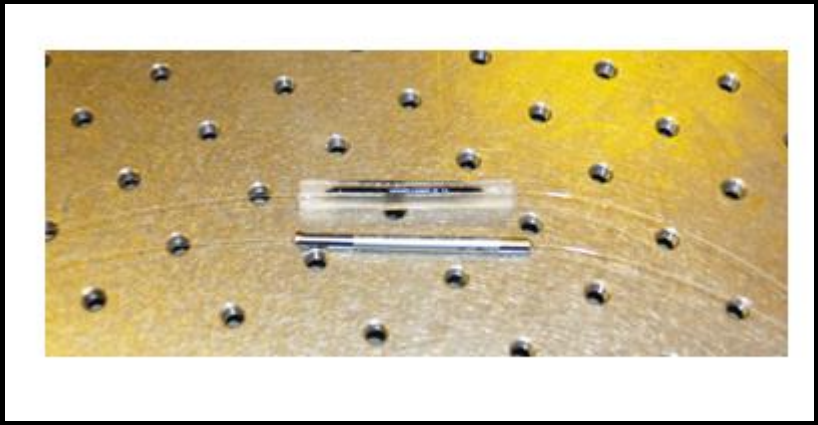
SEM image of carbon nanotube bundles



Fiber taper (top) and standard fiber (bottom)

First battery operated femtosecond fiber laser in the market

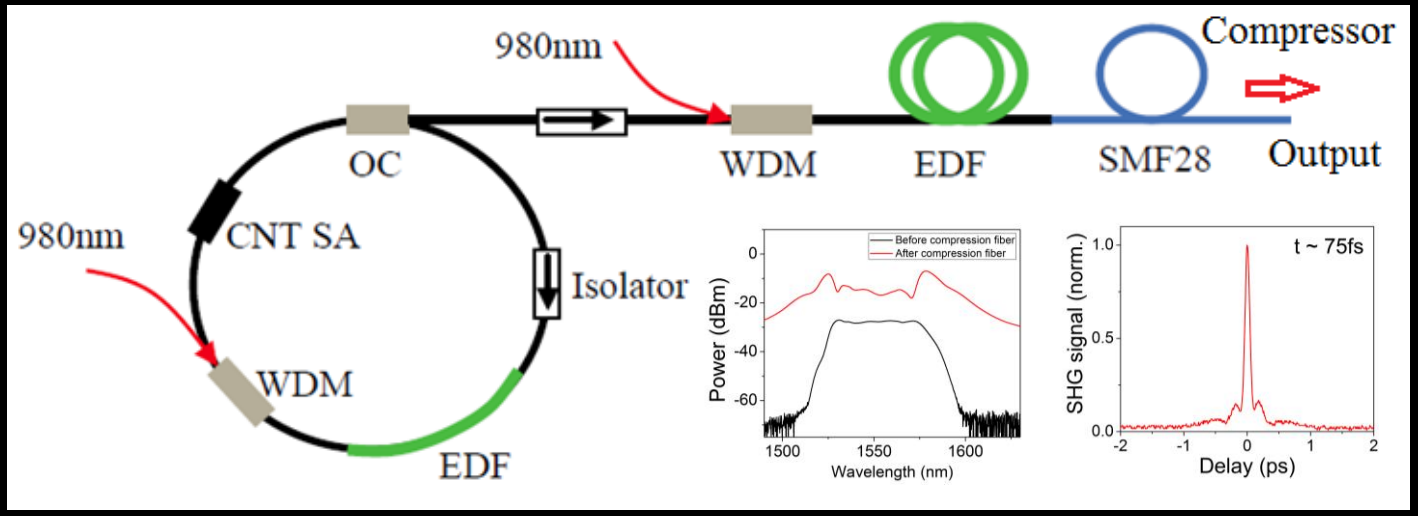
Fiber taper-based CNT SA



- Fiber format
- High damage threshold
- Long term reliability (>5000hours)
- Low cost

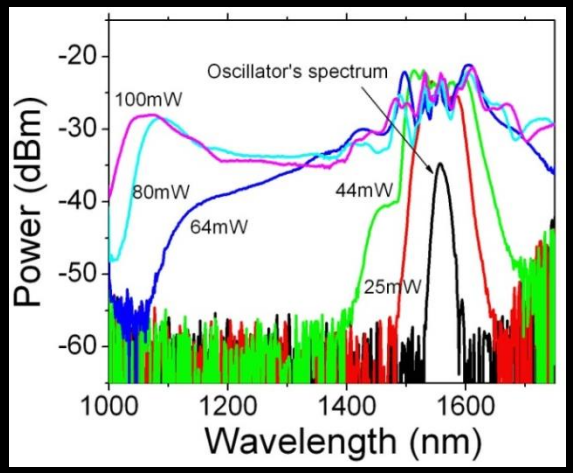
K. Kieu, OL 2007

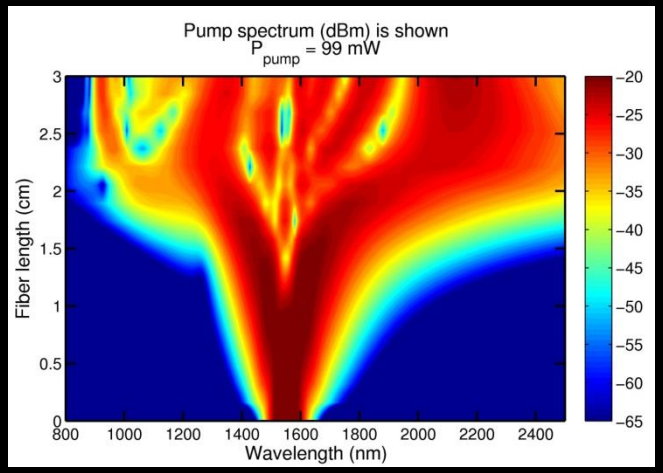
CNT mode-locked fiber laser

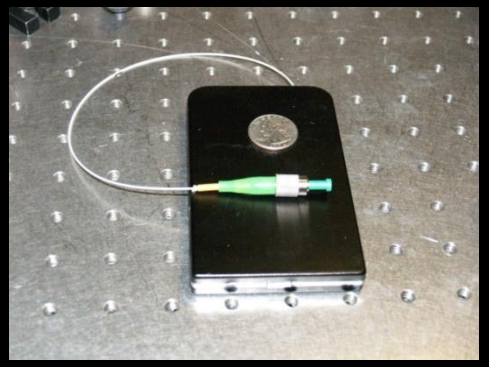


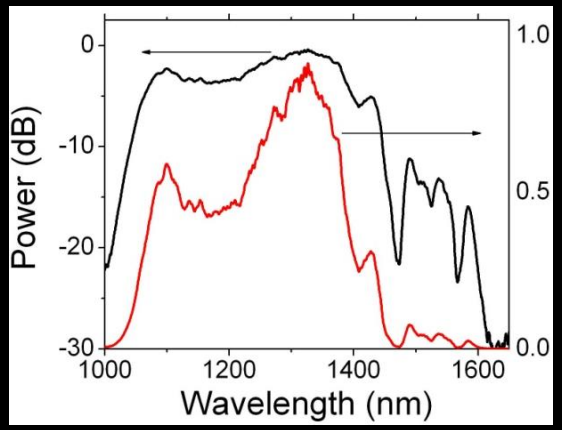
- All-fiber design
- Fiber delivery
- ~100mW average power
- <100fs, >10kW, 10-200MHz
- Wavelengths: 1550nm, 1030nm, 1700nm
- Battery operation possible
- ~$10k

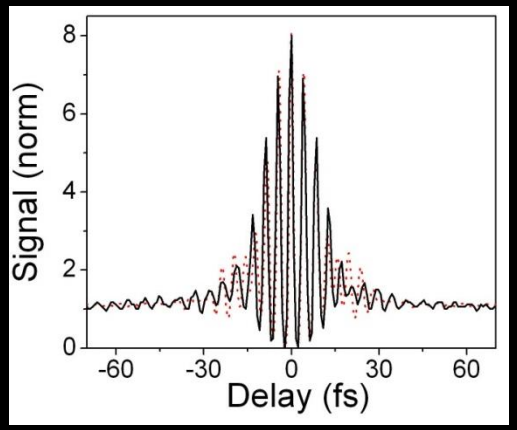
Supercontinuum generation

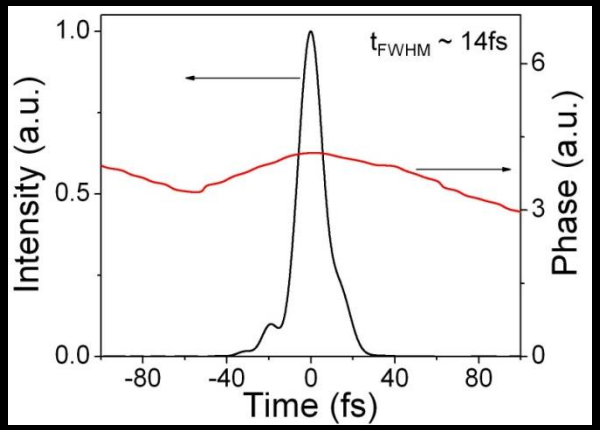








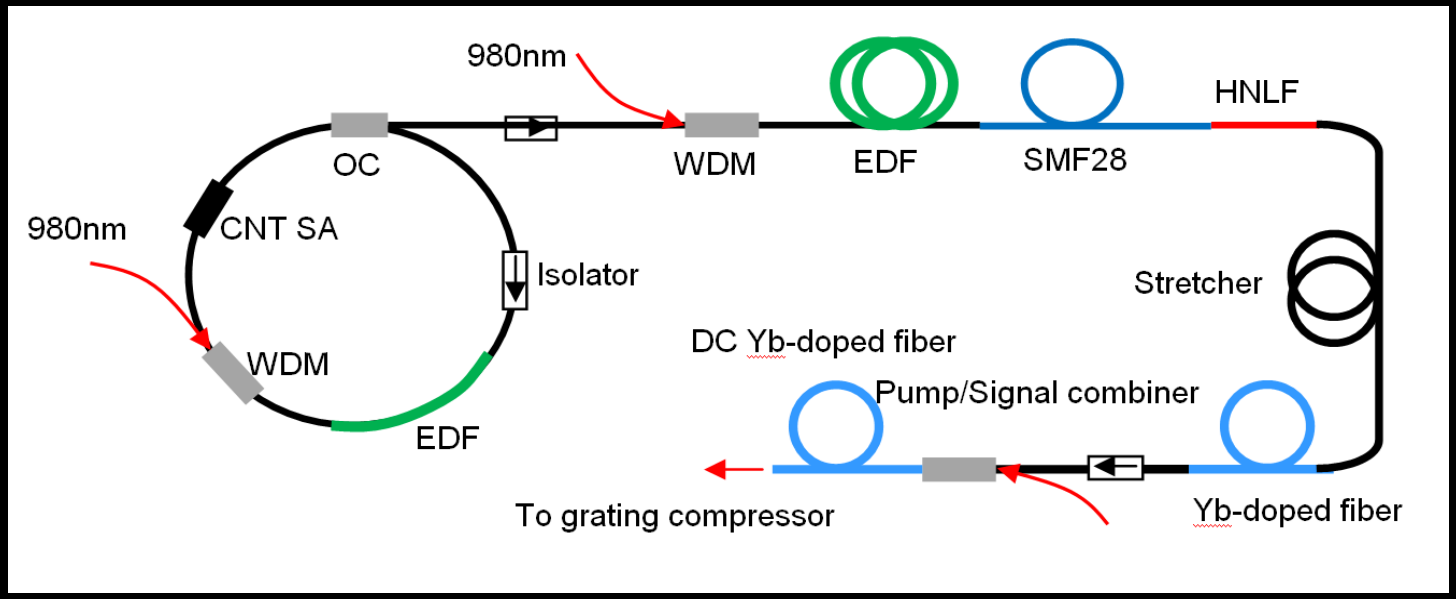




Handheld few-cycle fiber laser system for nonlinear spectroscopy, frequency comb, and OCT imaging

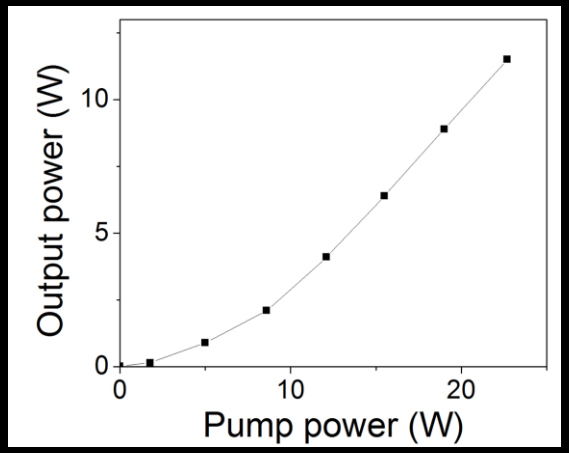
K. Kieu, PTL 2010

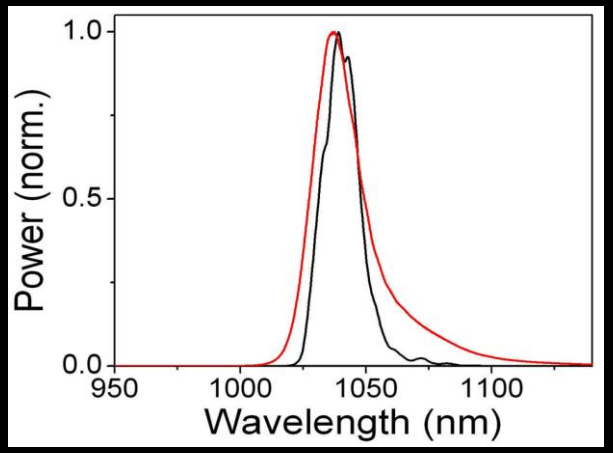
High power femtosecond laser at ~1μm

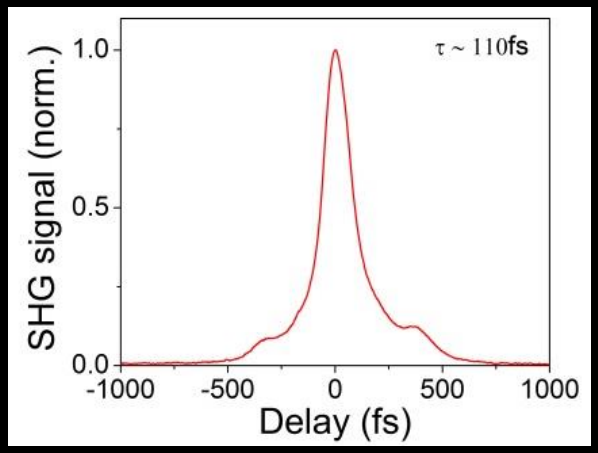


180x180x60mm

Fiber delivery





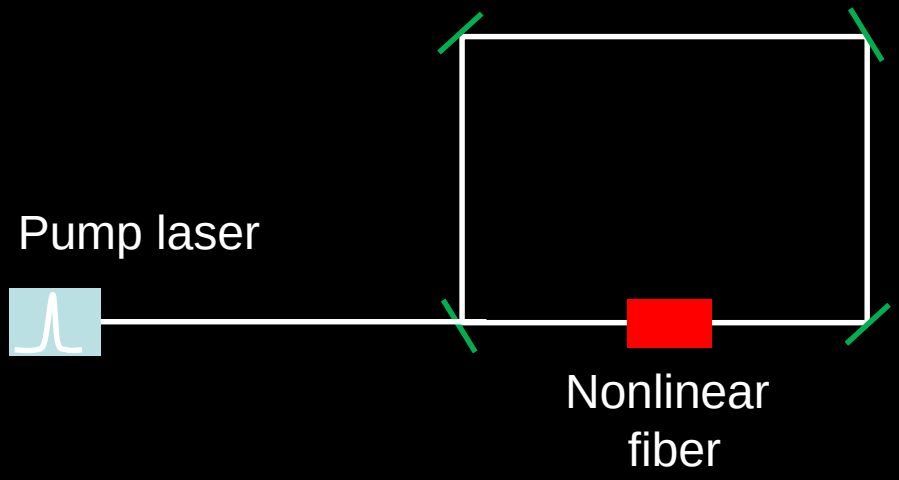


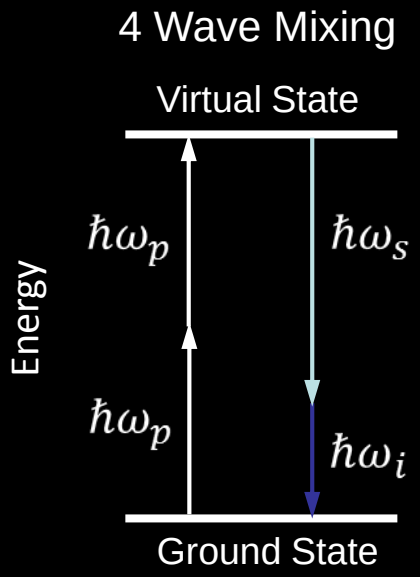
Kieu *et. al*, Opt. Expr. (2010)

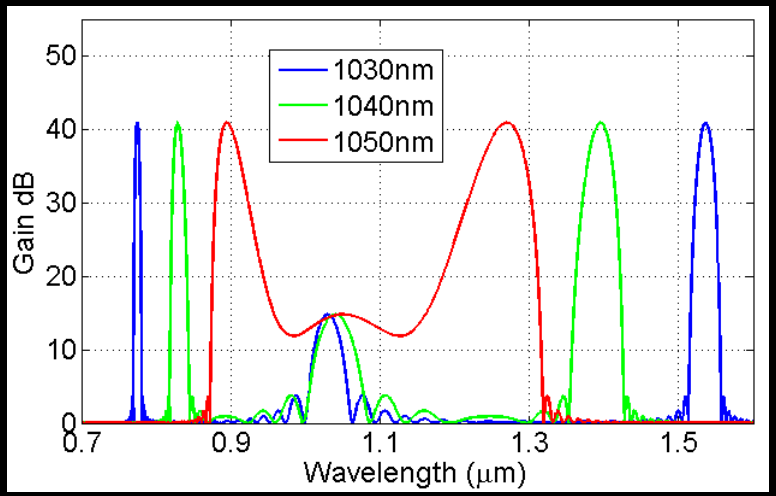
Fiber-based optical parametric oscillator

Requirements:

- Phase matching
- Tunable pump
- Synchronization

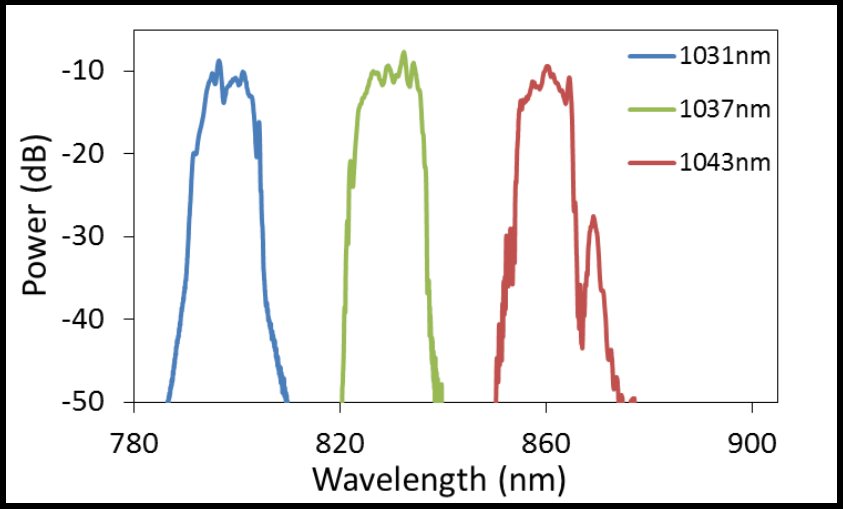


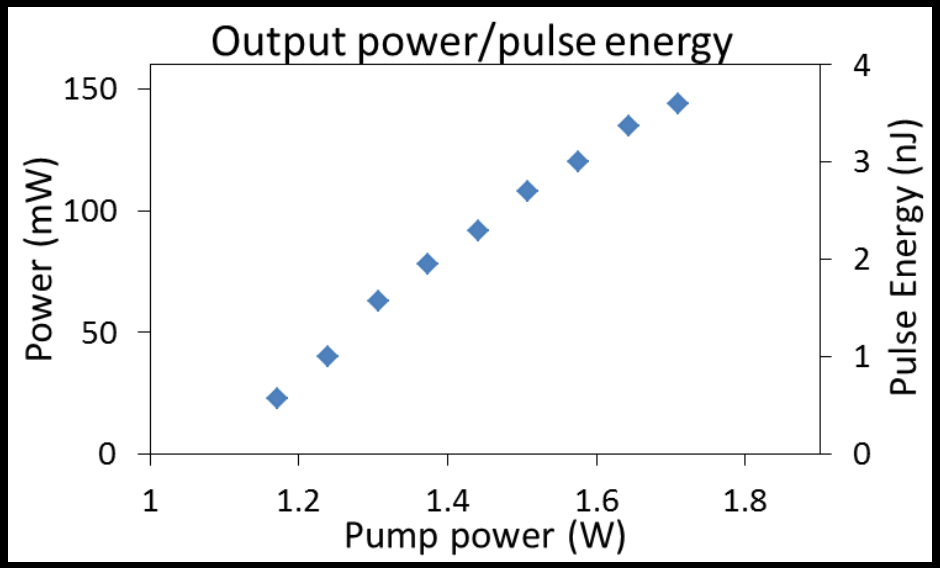


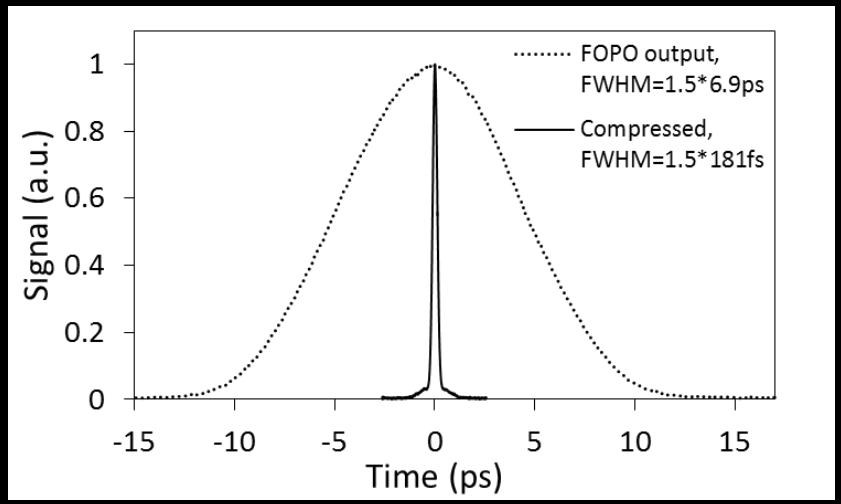


Fiber-based optical parametric oscillator

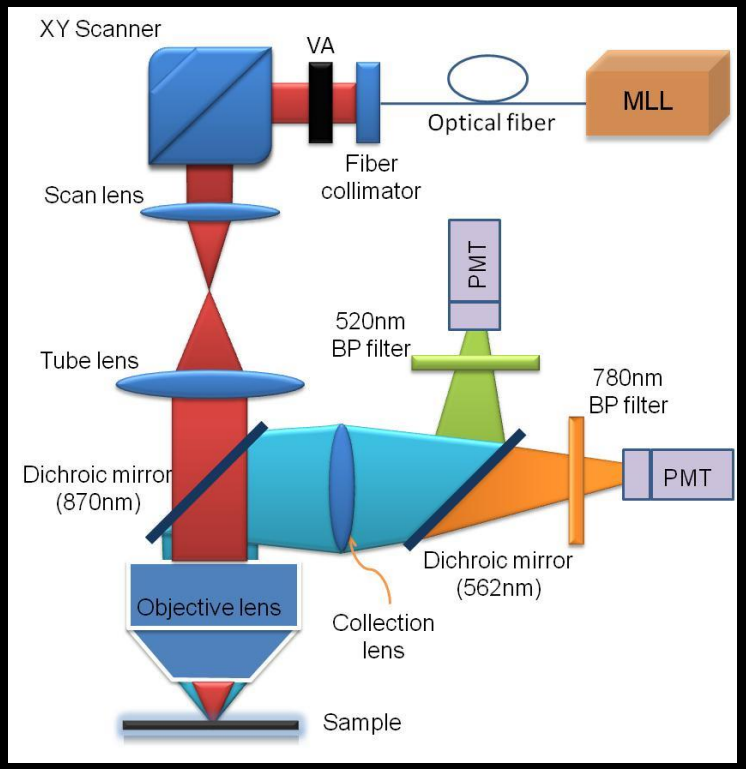
	Ti:Sapphire	FOPO
Pulse Energy	10nJ	3.9nJ
Tunability	700-1000nm	765-950nm 1200-1500nm
Pulse duration	<100fs	181fs



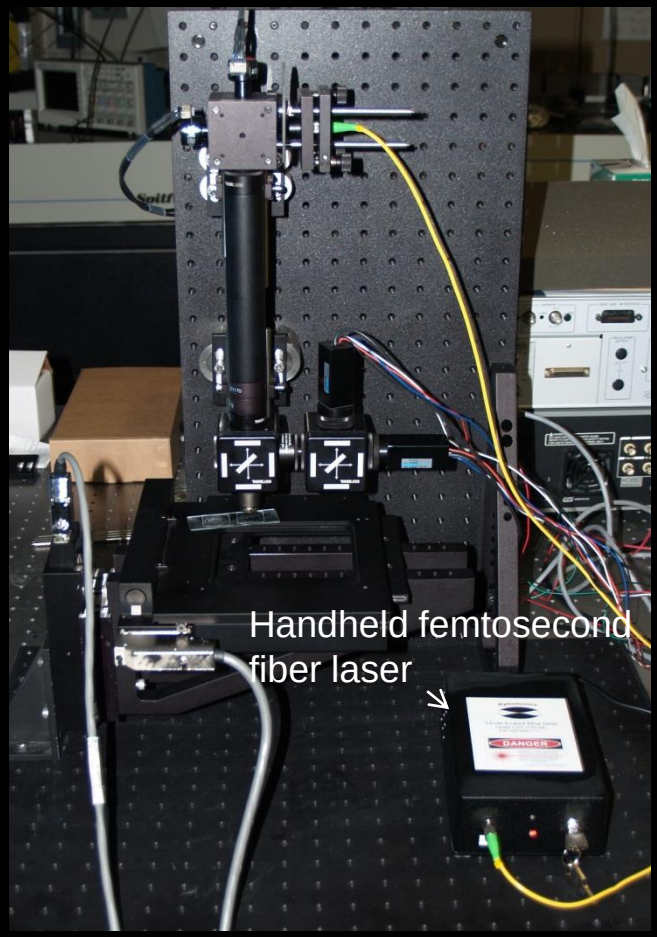




How about multiphoton imaging?



We develop compact fiber-based femtosecond lasers and construct specially designed multiphoton microscope. The overall cost and size of the whole system will be an order of magnitude lower than currently available commercially, while still providing the best image quality.



Home-built multiphoton microscope

K. Kieu *et. al.* BME 2013

There is a lot of fun when there is a microscope

First microscope

Onion has layers!

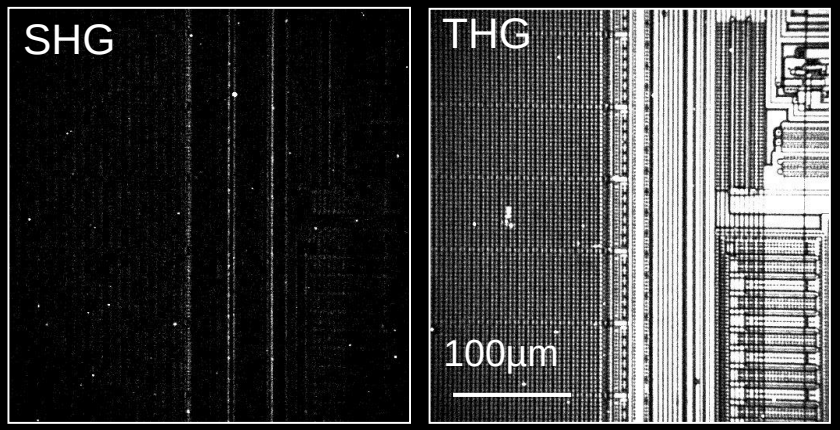
I see cells!

Bacteria!
Viruses !

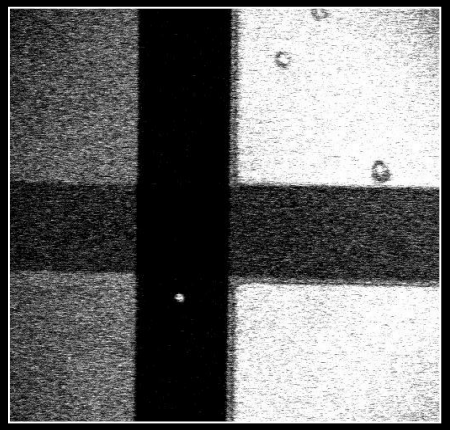
There is also a **nonlinear** microscopic world!

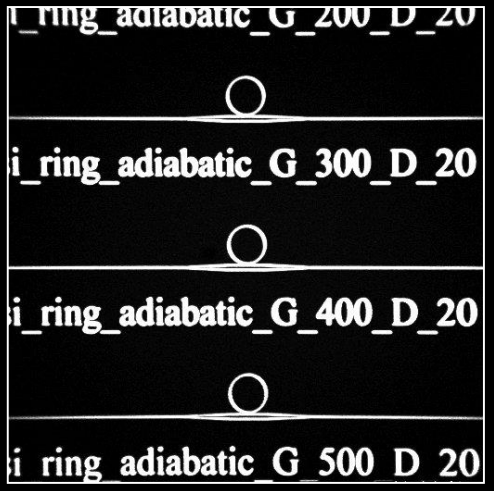
Multiphoton Material Characterization

Microprocessor chip

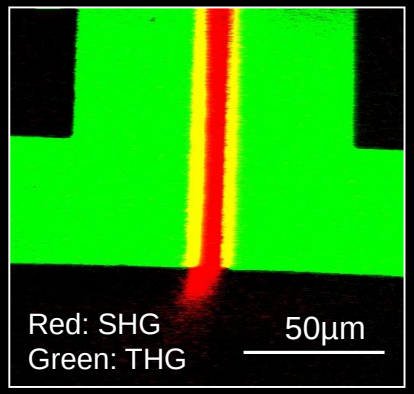


LC display:
'On' state has more THG

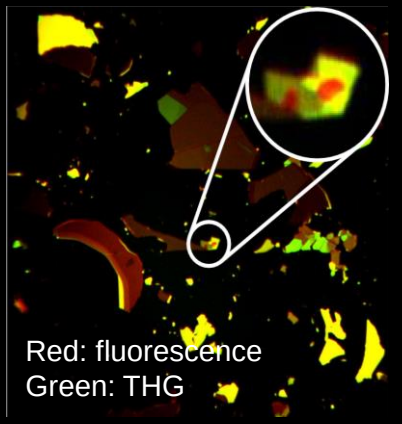




Silicon photonic chip (THG)

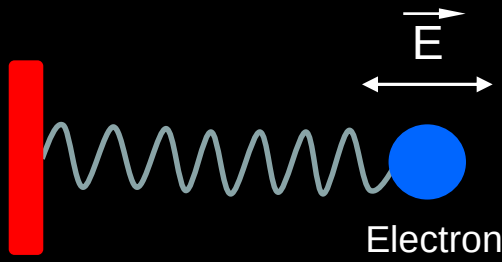


Polymer modulator



Graphene flakes

Nonlinear Optics-Is it safe?



$$P = \chi^{(1)}E + \chi^{(2)}E^2 + \chi^{(3)}E^3 + \dots$$

$\chi^{(2)}$, $\chi^{(3)}$… are very small

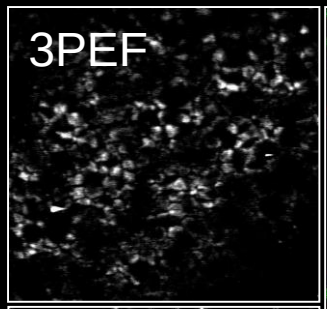
Credit: Alex Erstad

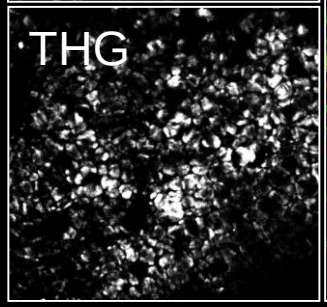
Linear Optics

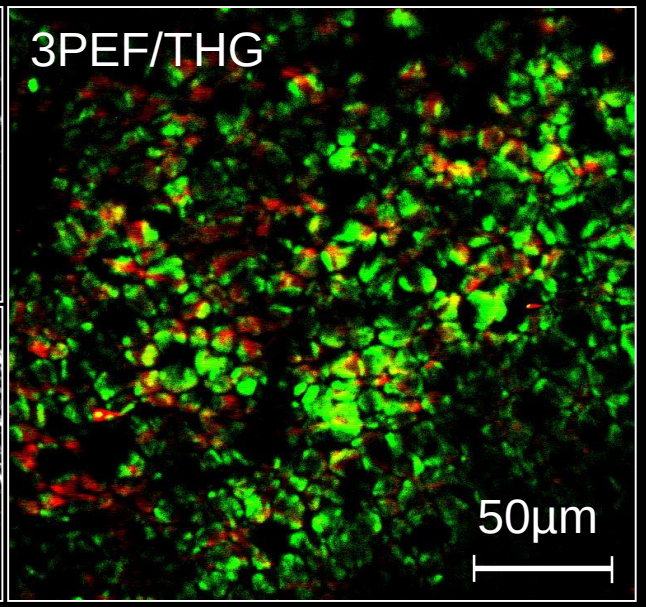
Nonlinear Optics

Extreme Nonlinear Optics

‘Laser guy learning biology’







Sample: Fresh leaf

Green: THG (520nm)

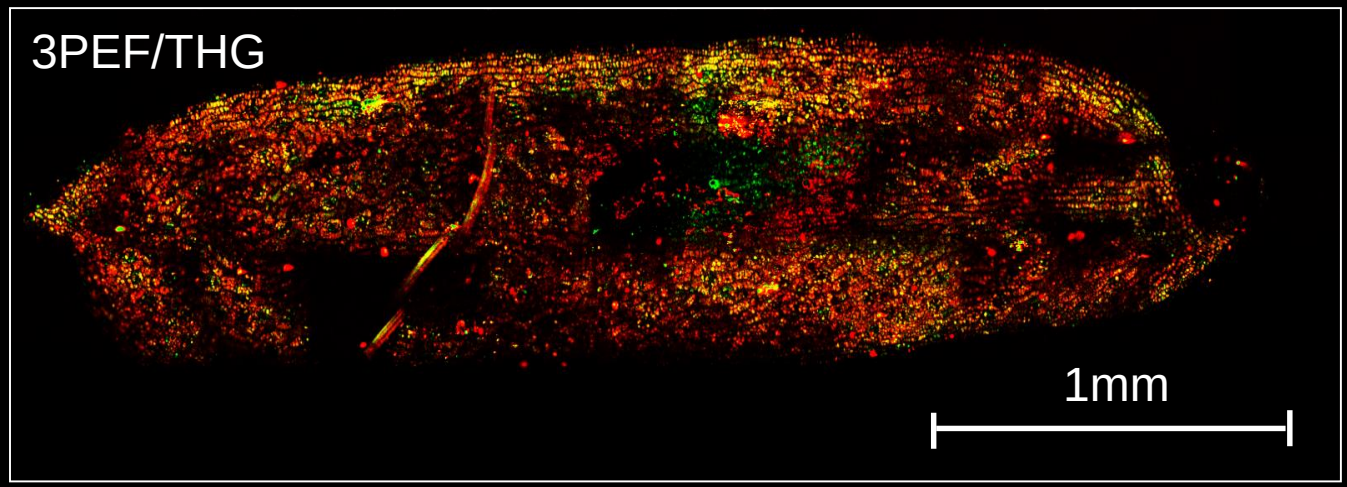
Red: 3PEF (650-750nm)

Excitation: 1560nm

0.3frame/s

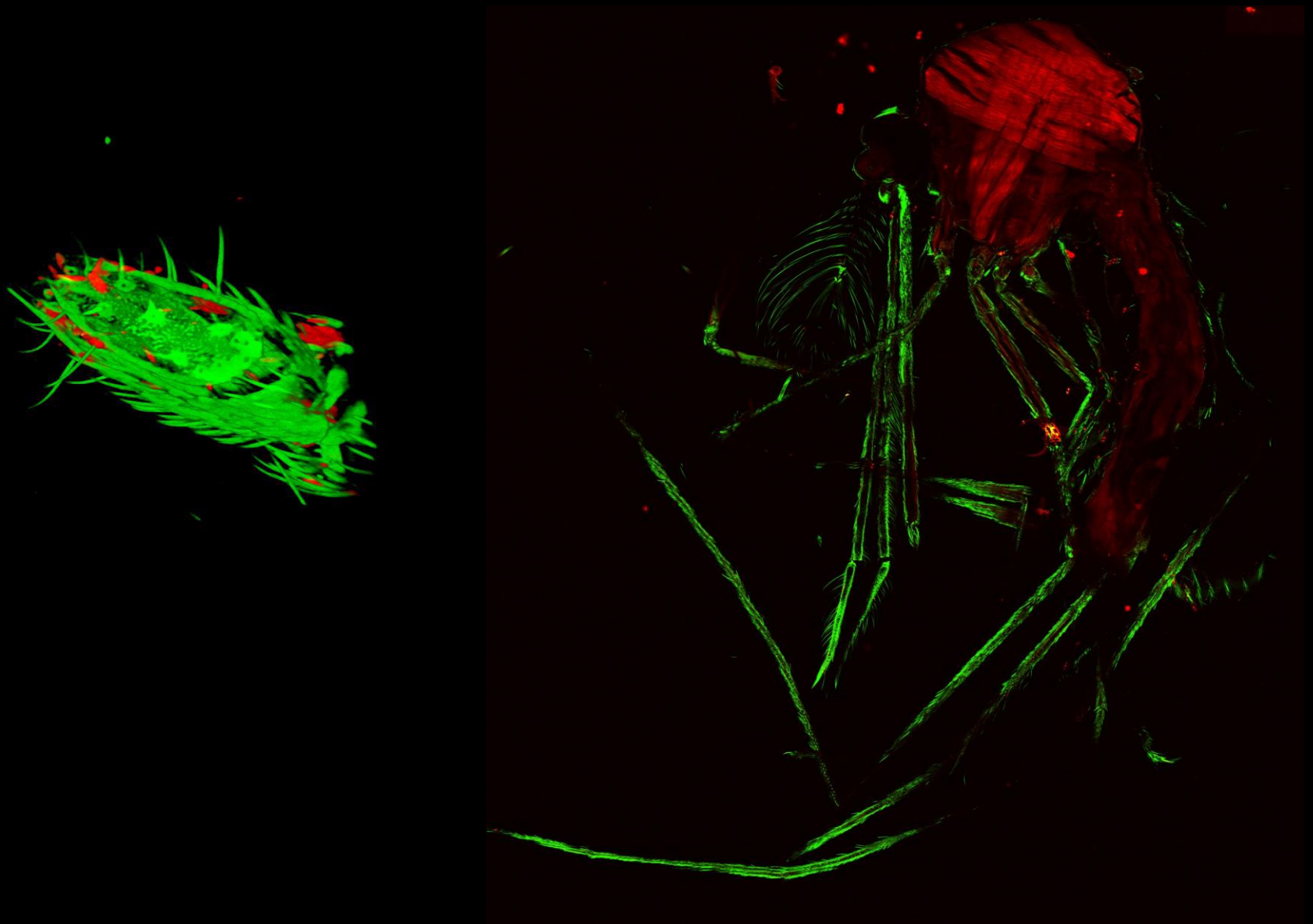
Laser power: 30mW

Aspheric lens 0.5NA



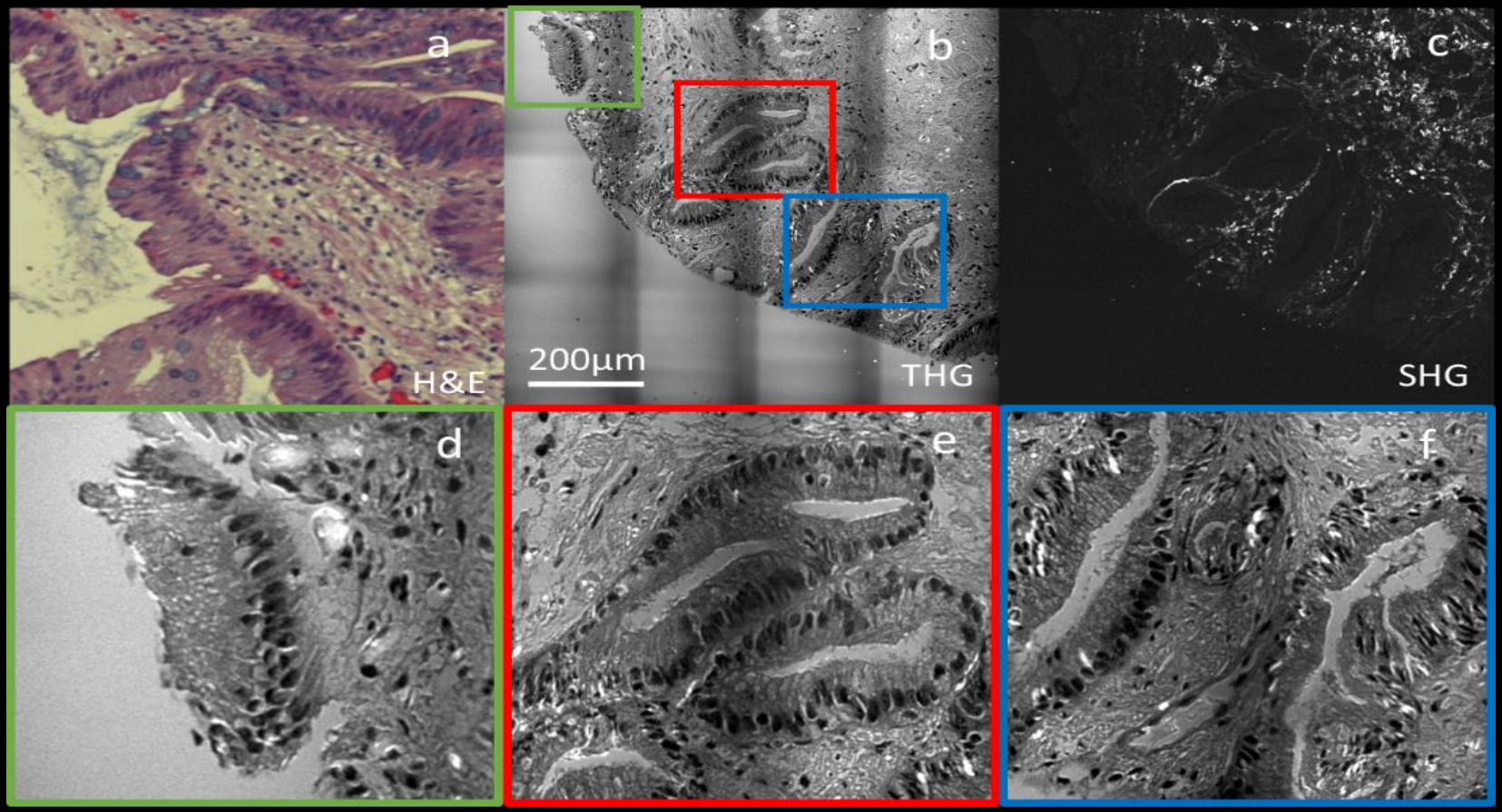
K. Kieu *et. al.* BME 2013

Whole body 3D imaging of small insects



Barretts' Cancer Imaging

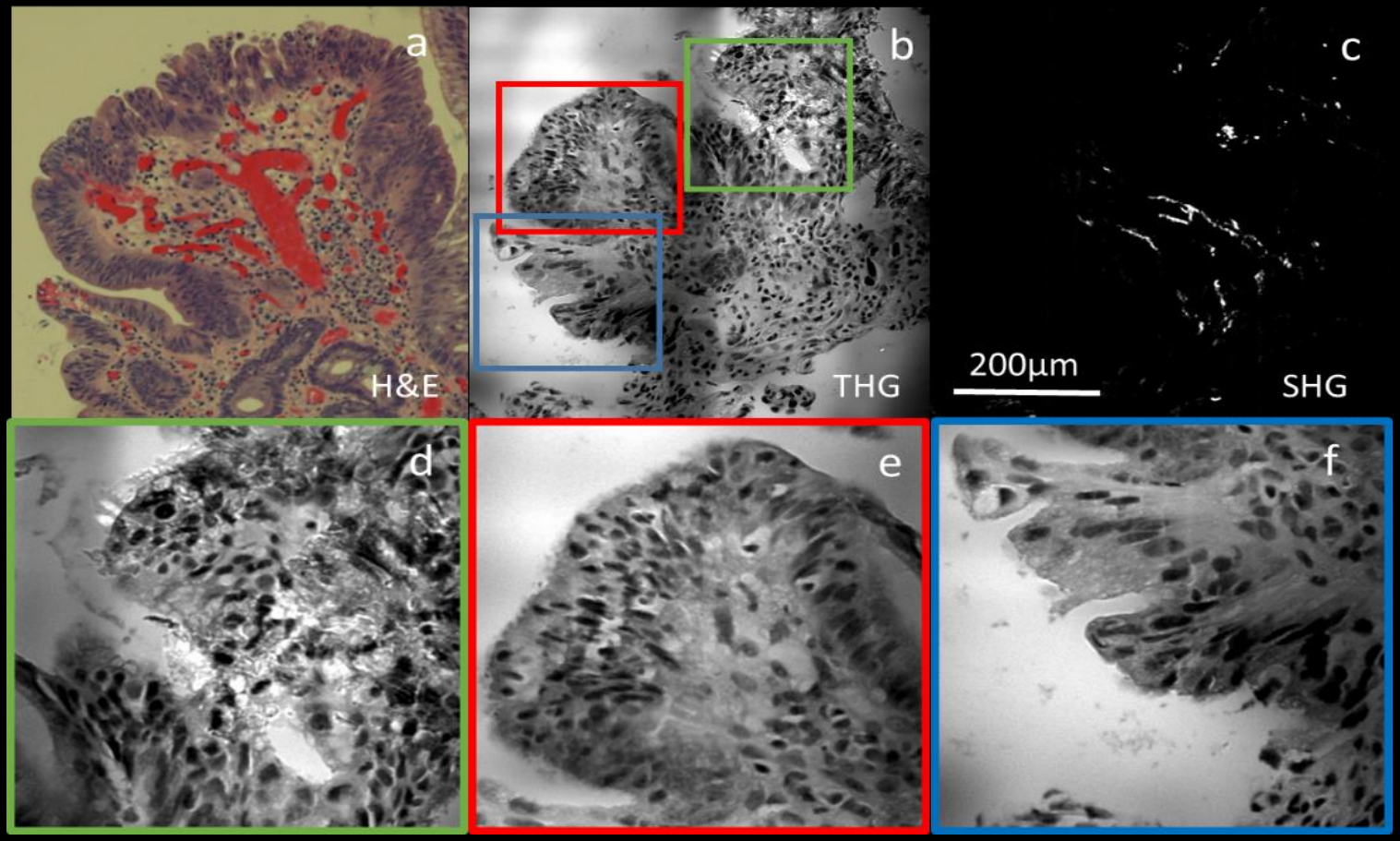
(Collaboration with Dr. B. Banerjee)



Comparison between multi-photon microscopy and conventional light microscopy of BE tissue with negative for dysplasia. (a) H&E conventional light microscopy image. (b, c) High resolution THG and SHG signals from a section residing 4µm below the section in (a). (d-f) magnified regions in (b). THG signal has a clear correlation to the H&E light-microscope image. The architectural structure of nuclei indicates that the tissue has no dysplastic feature.

Barretts' Cancer Imaging

(Collaboration with Dr. B. Banerjee)



MPM and conventional light microscopy images of High-grade dysplastic tissue.
(a) Conventional light microscopy image of the tissue after labeling with H&E.
(b, c) High resolution THG and SHG from MPM system. (d-f) magnified regions in (b).
The dense distribution of cell nuclei are indicators of high-grade dysplasia. The SHG image also shows significant change in the morphology of the collagen network.

Brain Imaging

(Collaboration with C. Barns, S. Cohen, A. Koshy, L. Madhavan)

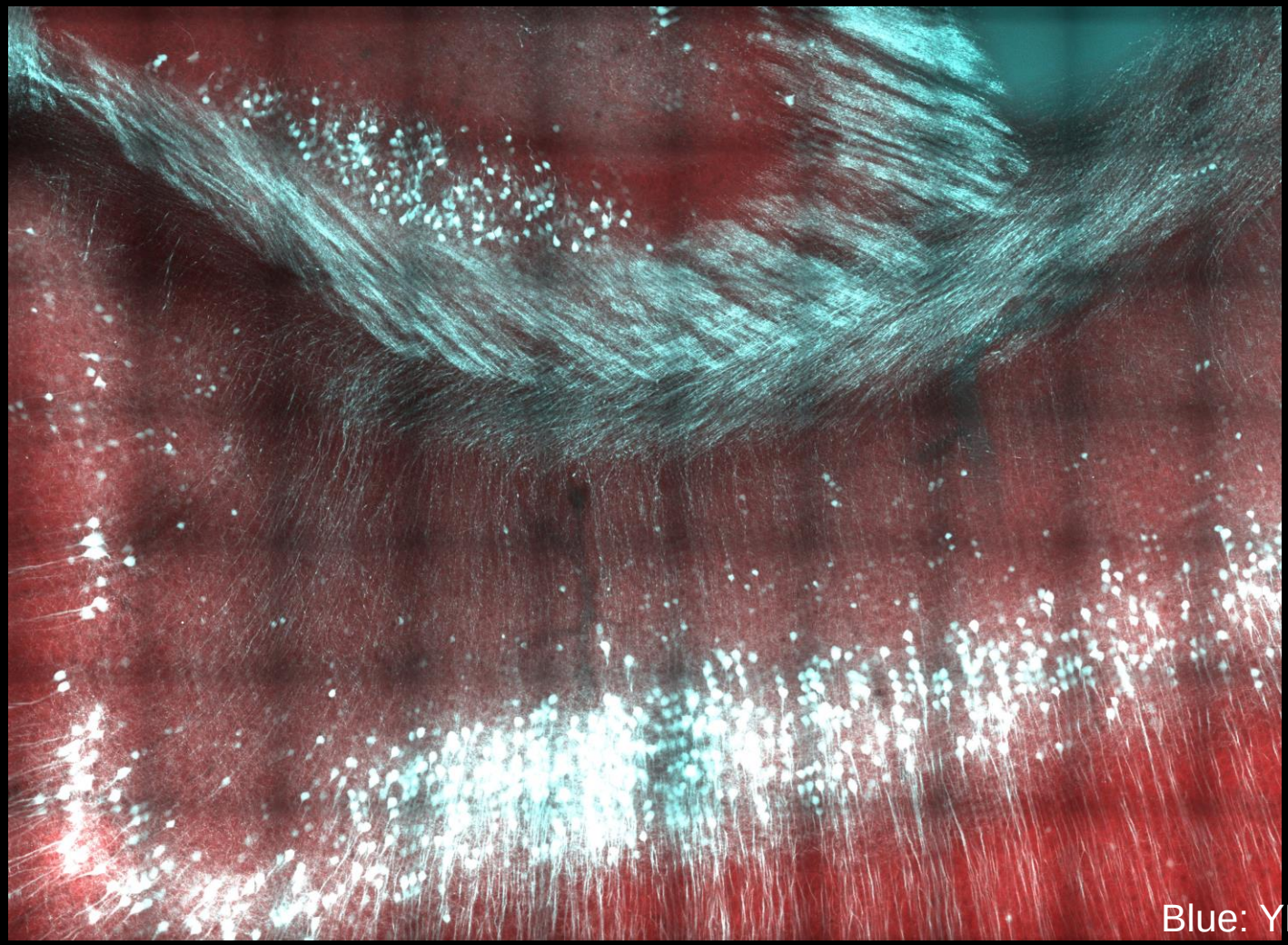
- Label-free identification of cell type
- Match behaviors to corresponding cells
- Stem cell imaging
- Parasite tracking
- Rapid whole brain imaging
- and more…

Brain Imaging

(Collaboration with C. Barns, S. Cohen, A. Koshy, L. Madhavan)

Brain Imaging

(Collaboration with C. Barns, S. Cohen, A. Koshy, L. Madhavan)

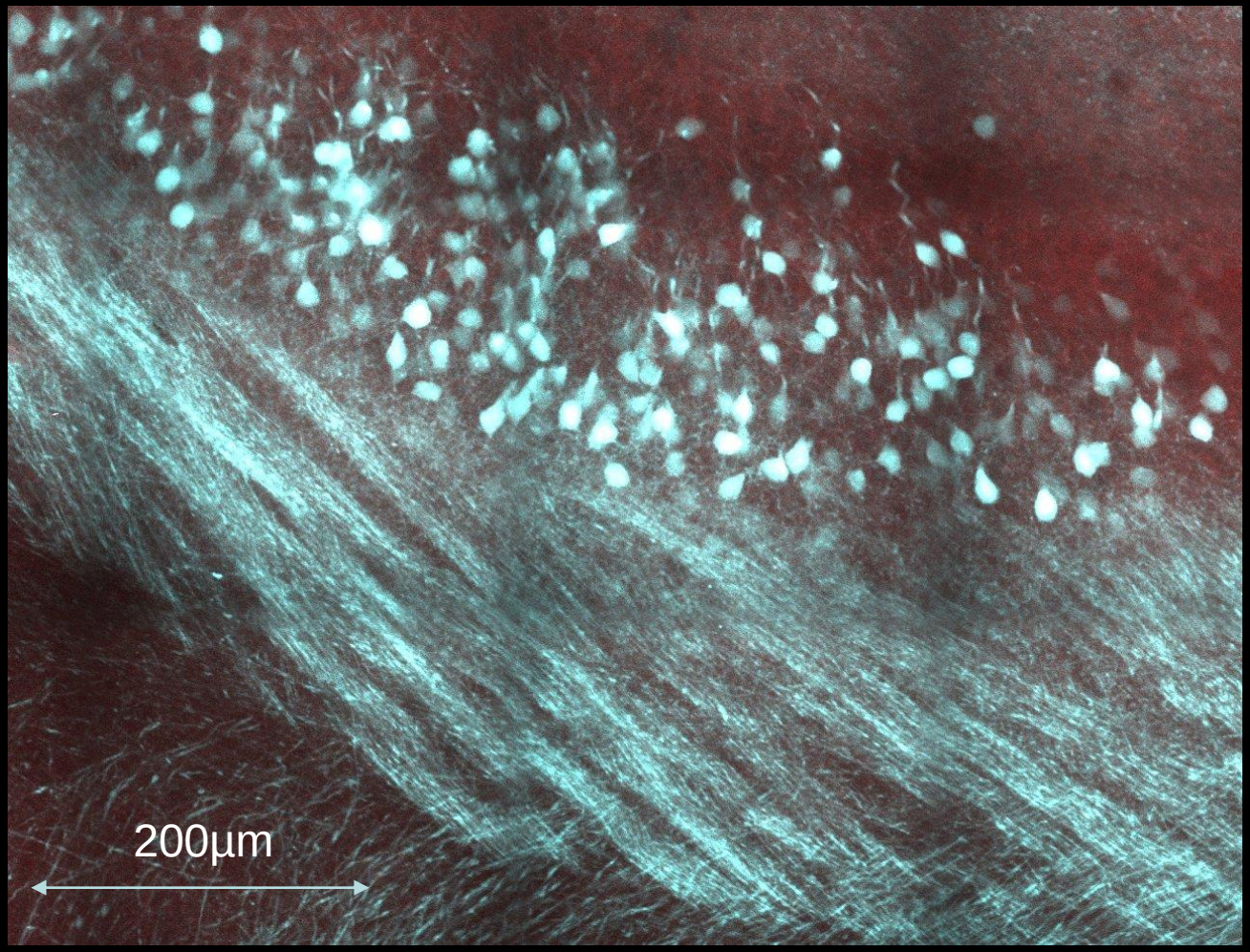


500µm

Blue: YFP
Red: Endogenous
1µm laser excitation

Brain Imaging

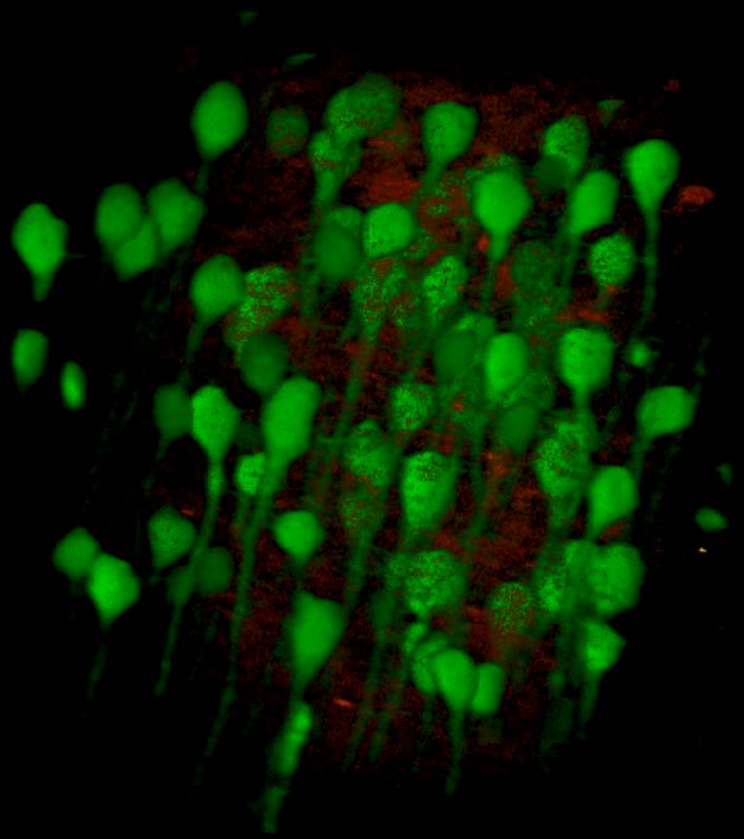
(Collaboration with C. Barns, S. Cohen, A. Koshy, L. Madhavan)



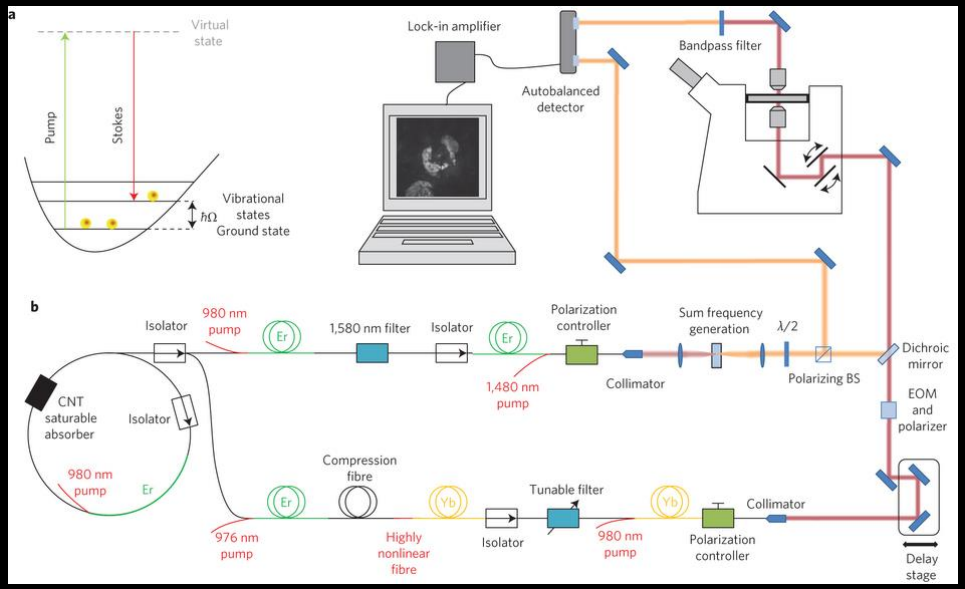
Blue: YFP
Red: Endogenous
1µm laser excitation

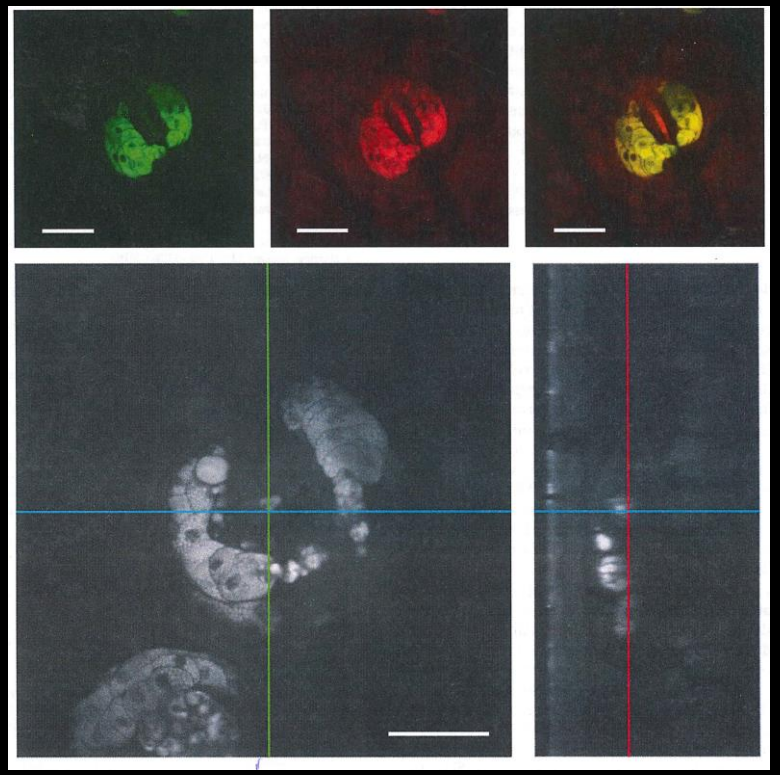
Brain Imaging

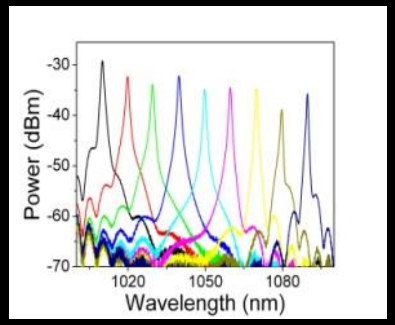
(Collaboration with C. Barns, S. Cohen, A. Koshy, L. Madhavan)

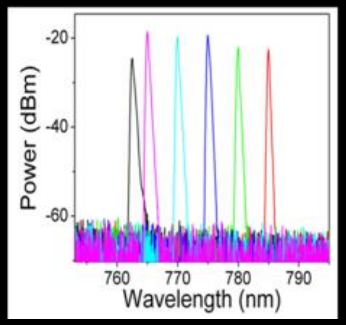


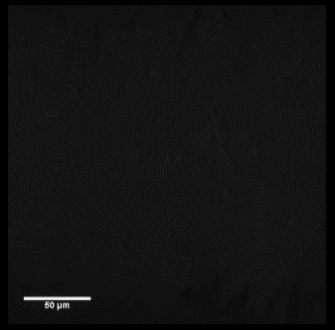
Widely tunable fiber lasers-SRS

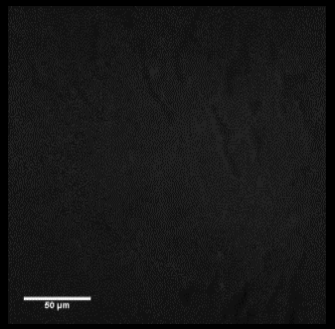








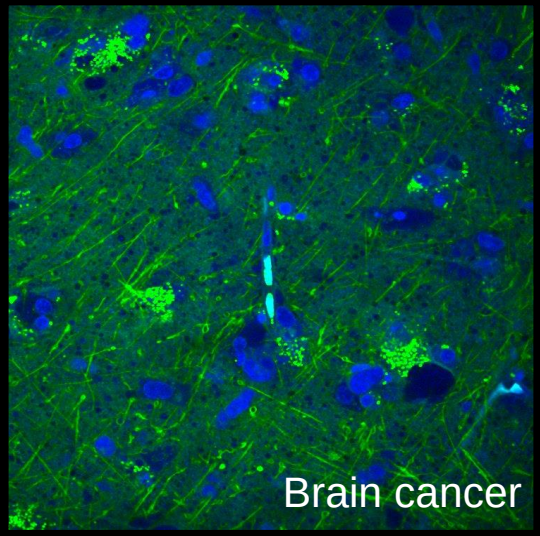


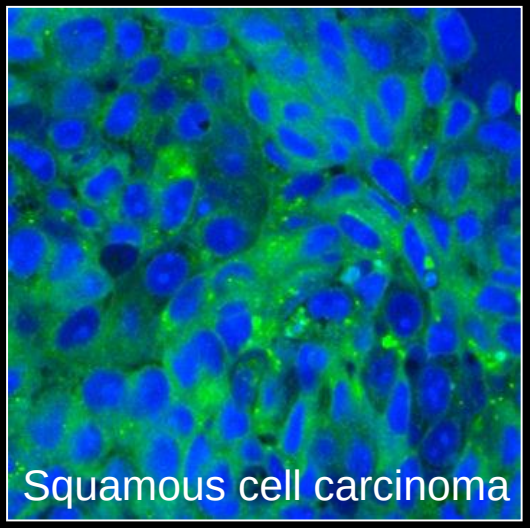


Nature Photonics 2014

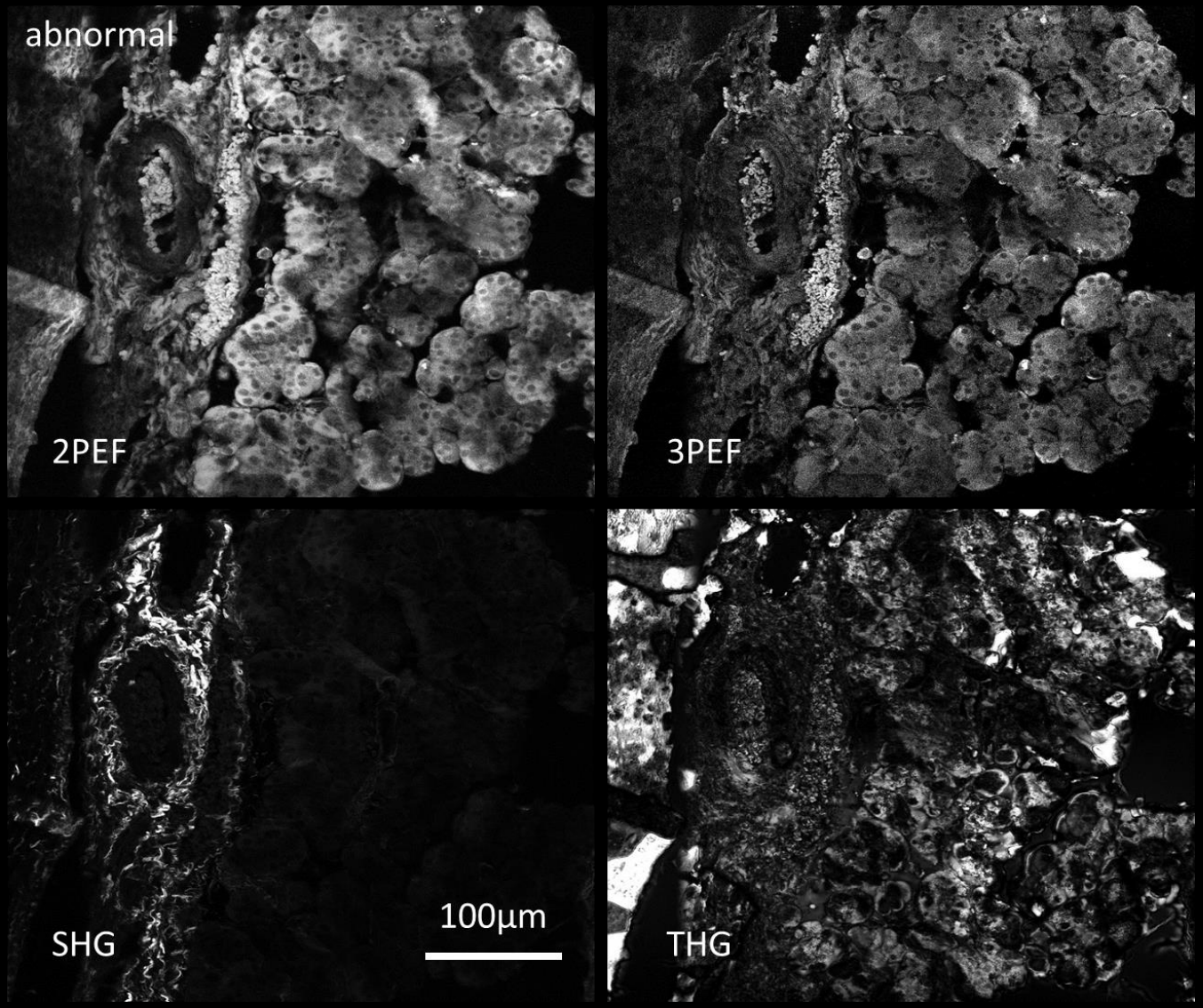
Widely tunable fiber lasers

Complete SRS microscope commercialized by Invenio

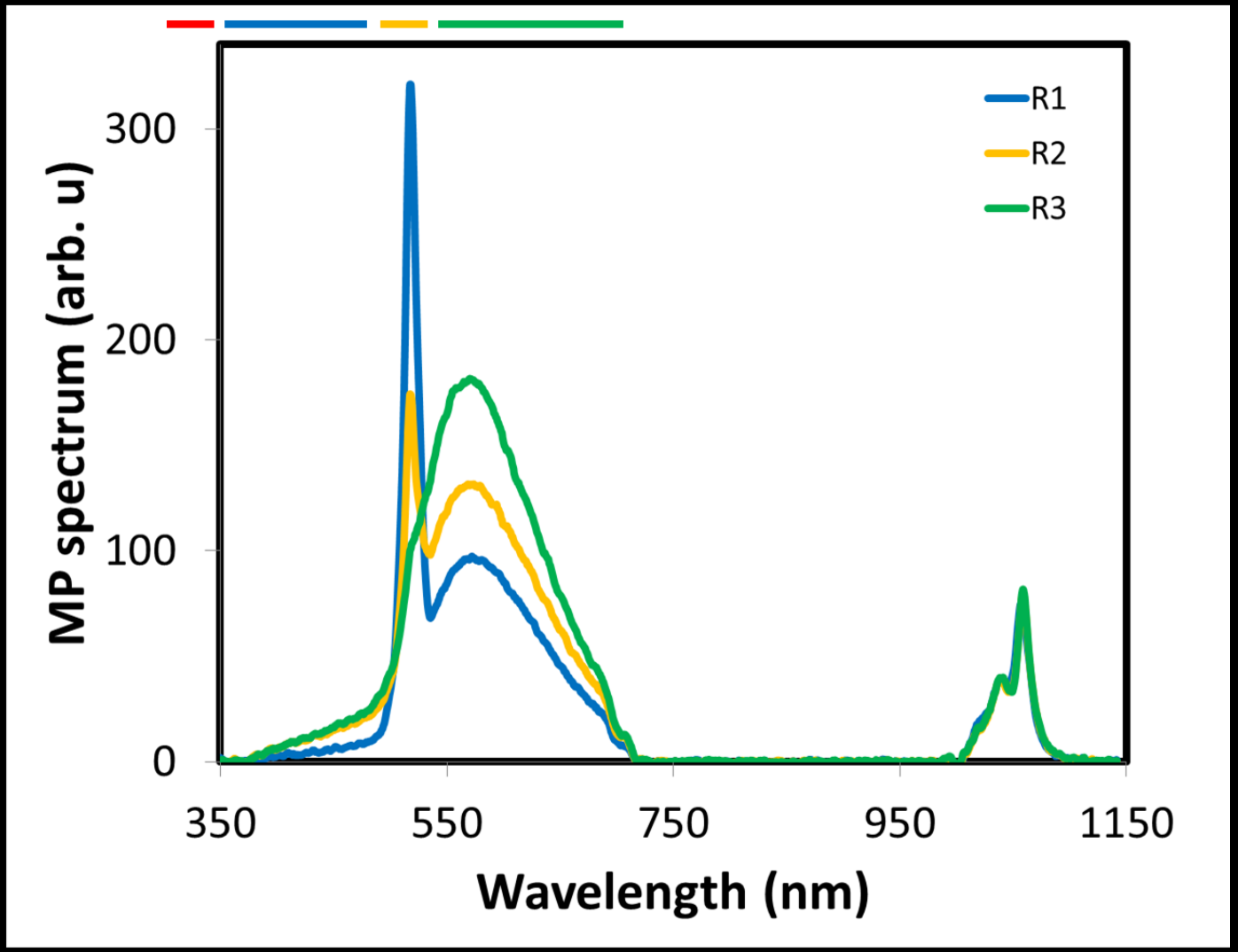




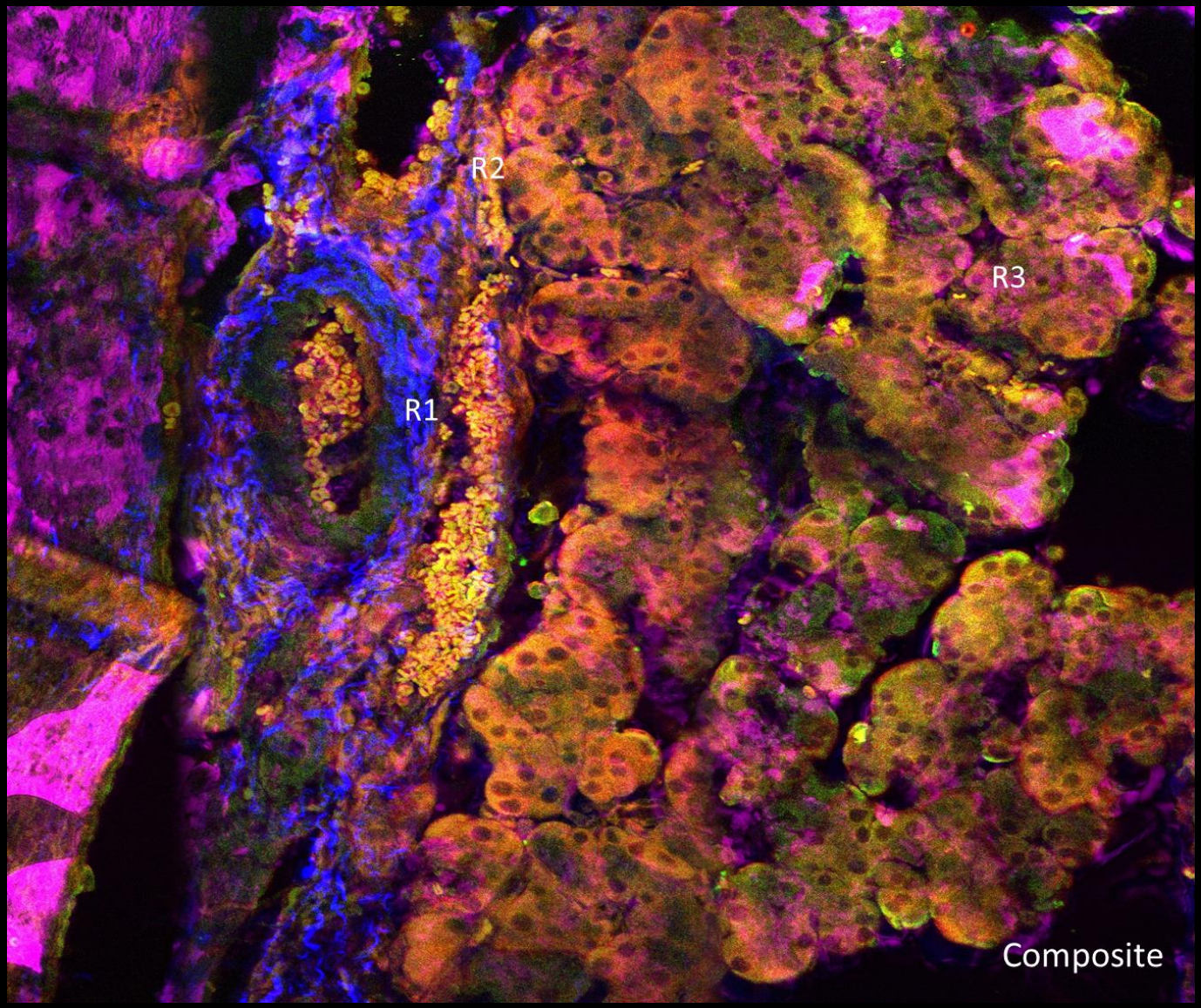
Latest result: pancreas imaging



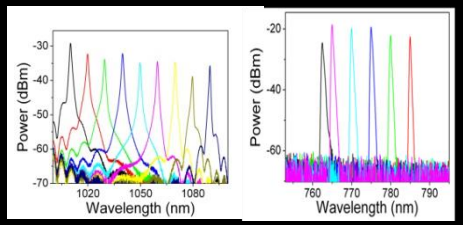
Latest result: pancreas imaging

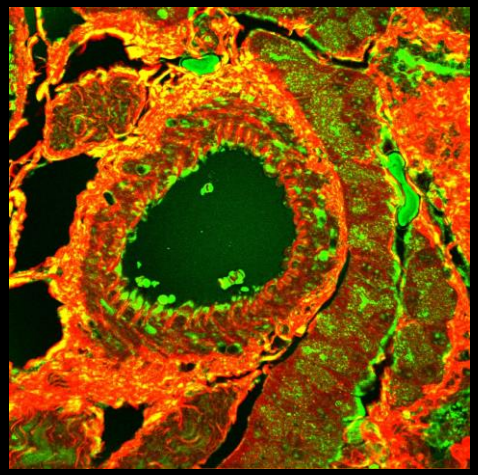


Latest result: pancreas imaging

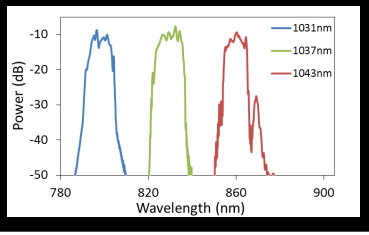


Universal fiber laser platform



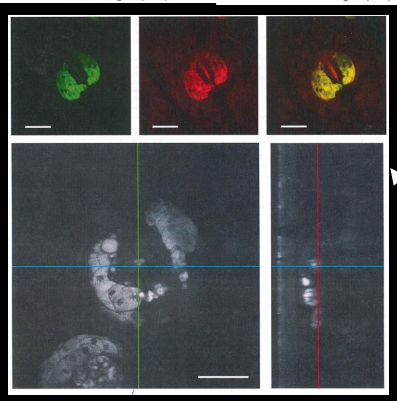


SHG/THG image of a pancreatic tissue



FOPO

Yb fiber source
1030nm, ~100fs, > 100mW



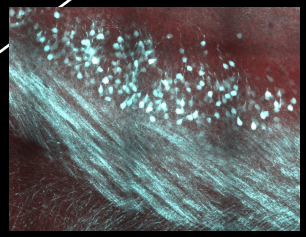
SRS imaging
Nature Photonics 2014

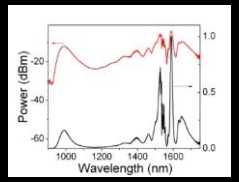
SHG and THG imaging

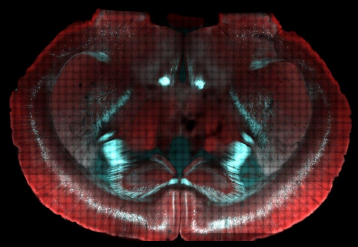
Supercontinuum
1000nm-2200nm, 100mW
Demonstrated OCT with 2μm resolution in air

Amp. and launched into HNLF
J. Biomed. Opt.(2011)

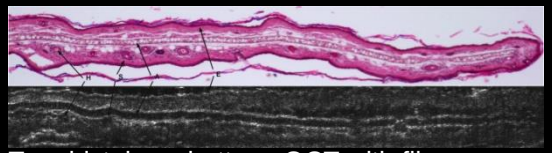
SC in HNLF, amplification in Yb fiber







2-photon imaging of whole mouse brain



Top: histology; bottom: OCT with fiber source

CNT ML Er fiber laser

K. Kieu et. al. Opt. Lett. **32**, 2242-2244 (2007)

Thank you for your attention!