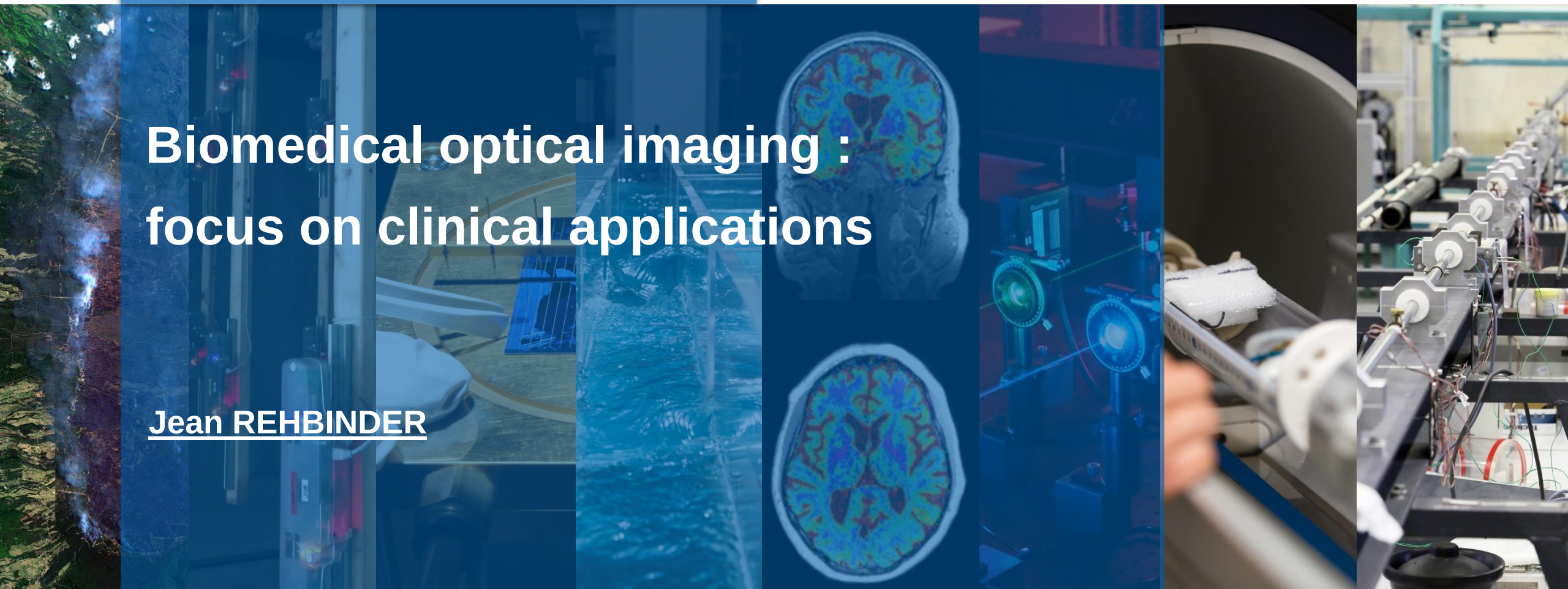
Laboratoire des sciences de l'ingénieur, de l'informatique et de l'imagerie



# Biomedical optical imaging : focus on clinical applications

Jean REHBINDER

https://www.ihu-strasbourg.eu/rendez-vous-de-scanner-et-dirm/

https://en.wikipedia.org/wiki/Radiology#/media/File:Radiologist_interpreting_MRI.jpg


**MRI**


**Ultrasound**


**X-ray**

**CT-scanner**

3D imaging of whole organs/ whole body
Mainly anatomical information,
sometimes functional (+ contrast agents)

# Optics in medicine = low-tech?


https://stock.adobe.com/fr

https://ophtalmo91.fr/examen-ophtalmologique/

Will light bring about the next revolution in medical imaging?

Photo by Chris Galbraith on Unsplash

I. Some physics

II. Conventional optics and fluorescence

III. Optical Coherence Tomography (OCT)

IV. Non-Linear Microscopy (NLOM)

V. Polarimetry

VI. Summary

VII. Closing remarks

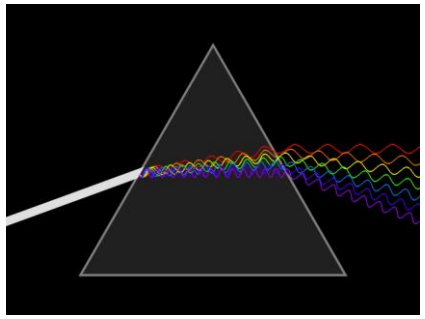
# Properties of light

Direction of propagation:

→ Geometrical optics
(lenses, microscope objectives, endoscopes …)

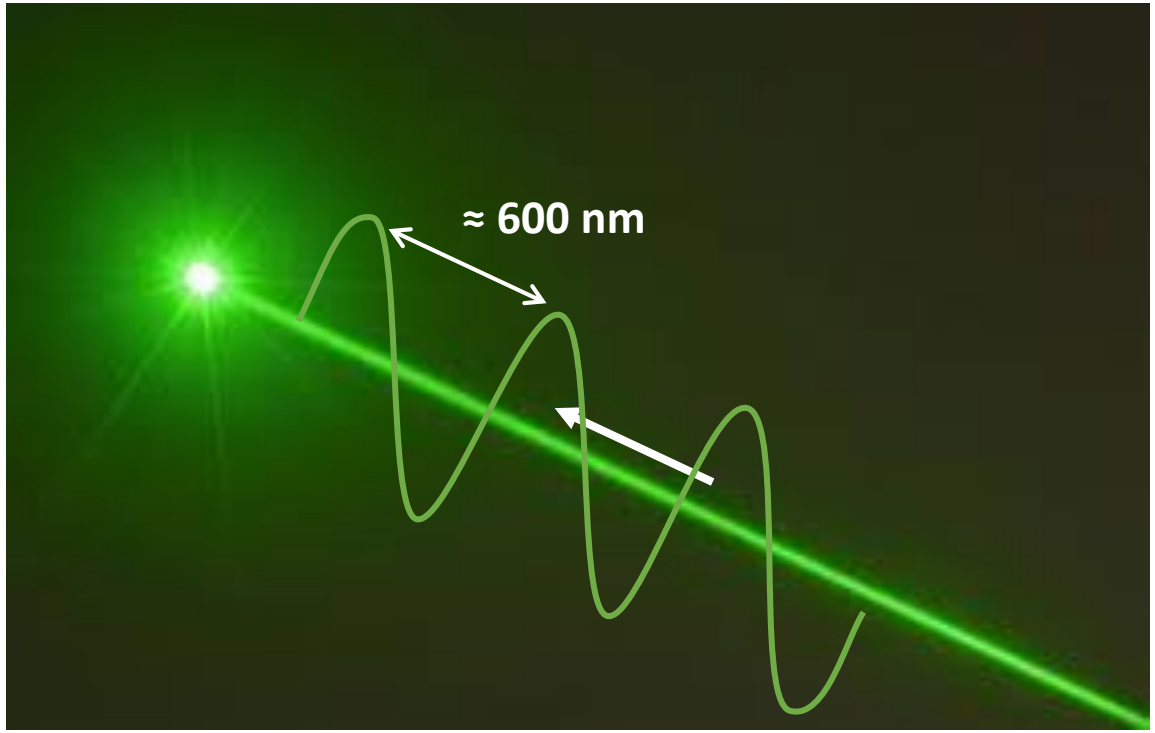
Wavelength (color):

→ Spectroscopy



Polarisation

→ Polarimetry




https://en.wikipedia.org/wiki/Wavelength#/media/File:Light_dispersion_conceptual_waves.gif

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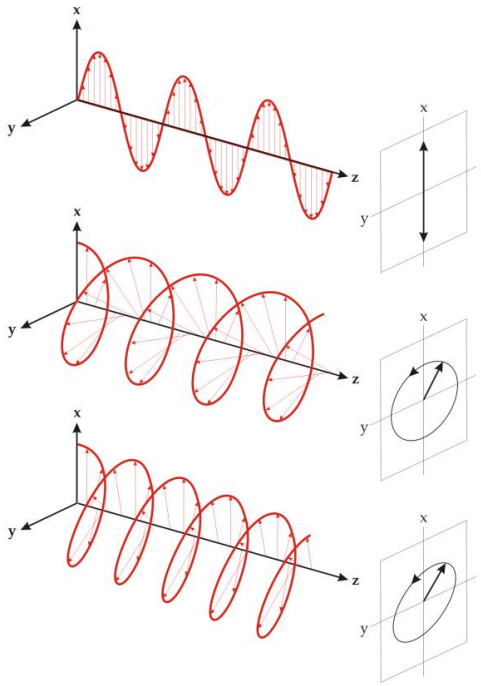
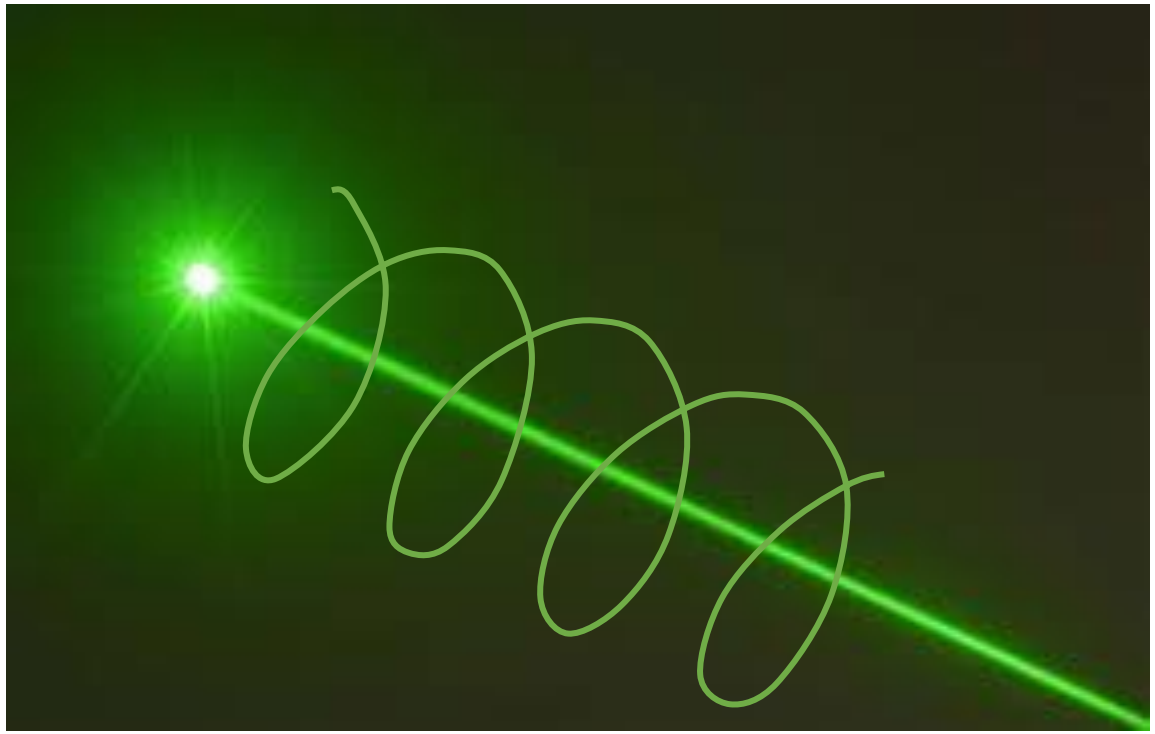
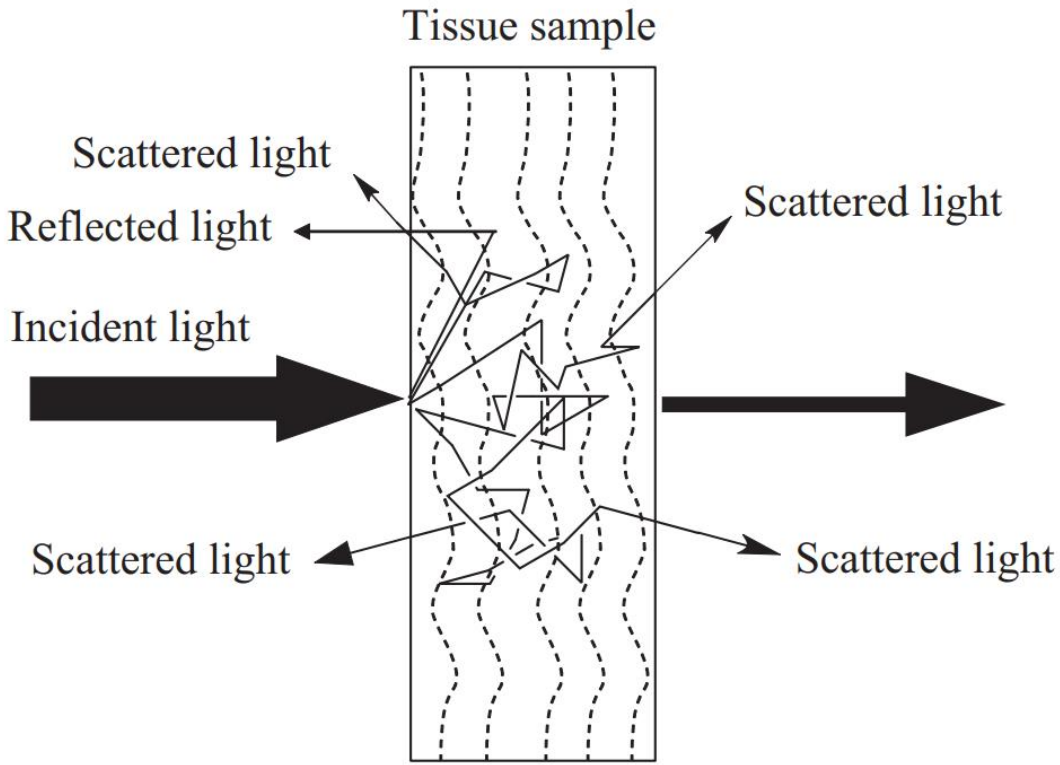
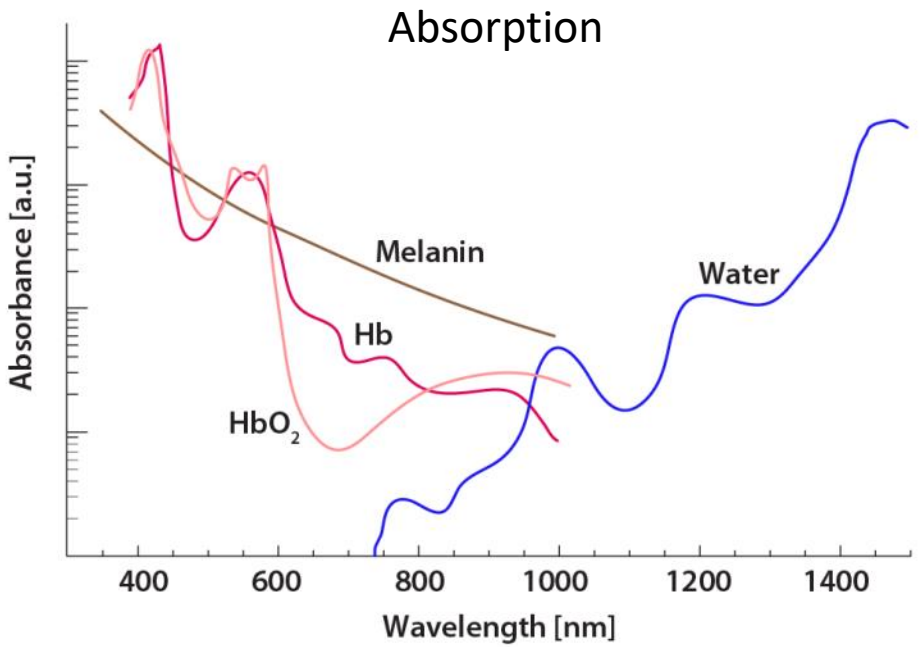


https://en.wikipedia.org/wiki/Wavelength#/media/File:Light_dispersion_conceptual_waves.gif

# Interaction of light with tissue




In biological tissues, scattering dominates over absorption

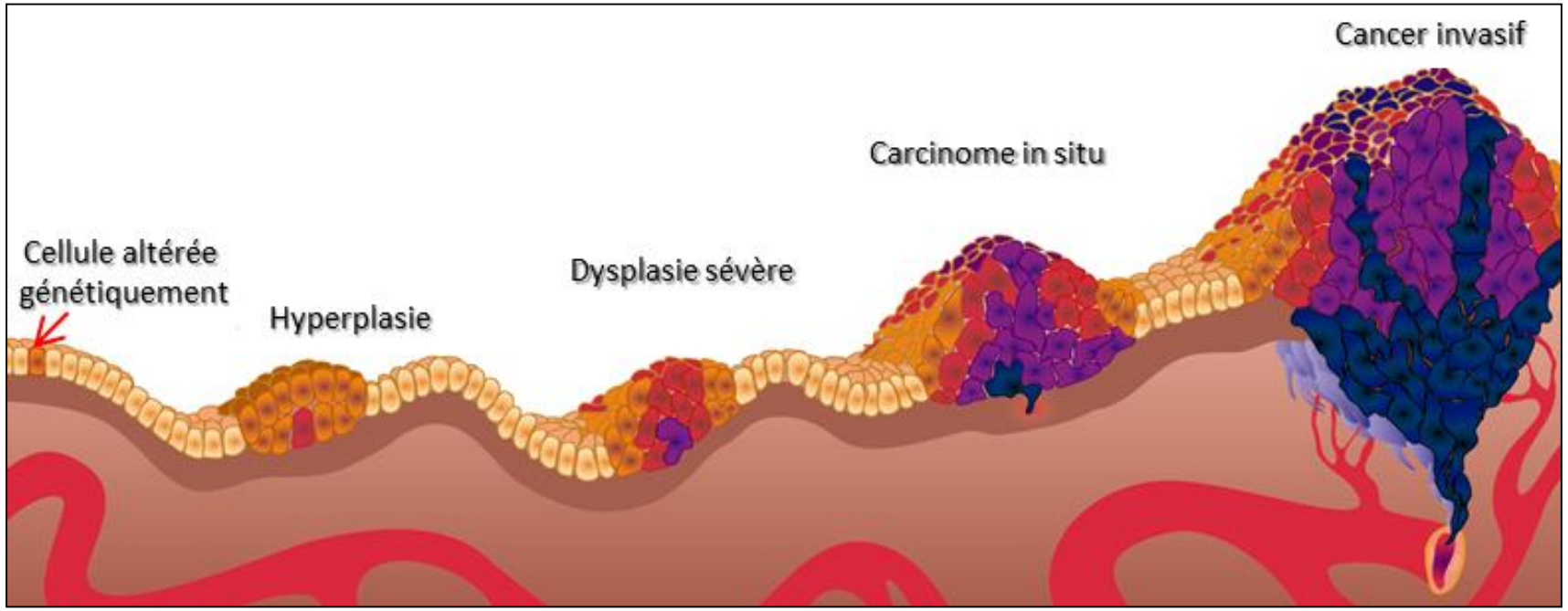
Deng, Wei, et al. "Optogenetics, the intersection between physics and neuroscience: light stimulation of neurons in physiological conditions." *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* 307.11 (2014): R1292-R1302.

# Penetration depth

Imaging typically limited to ≈ 1 mm depth
Scattering rapidly “blurs” the contrasts

# « Optical biopsy »

90% of cancers start from epithelia



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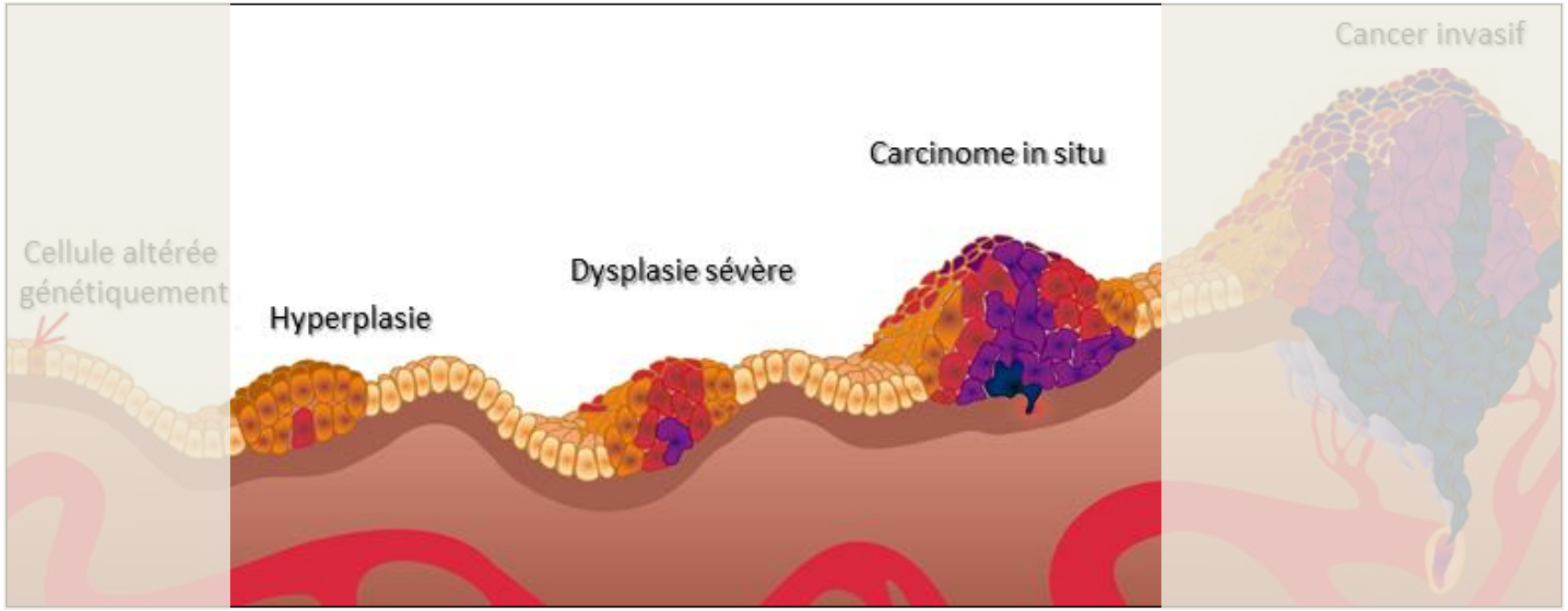
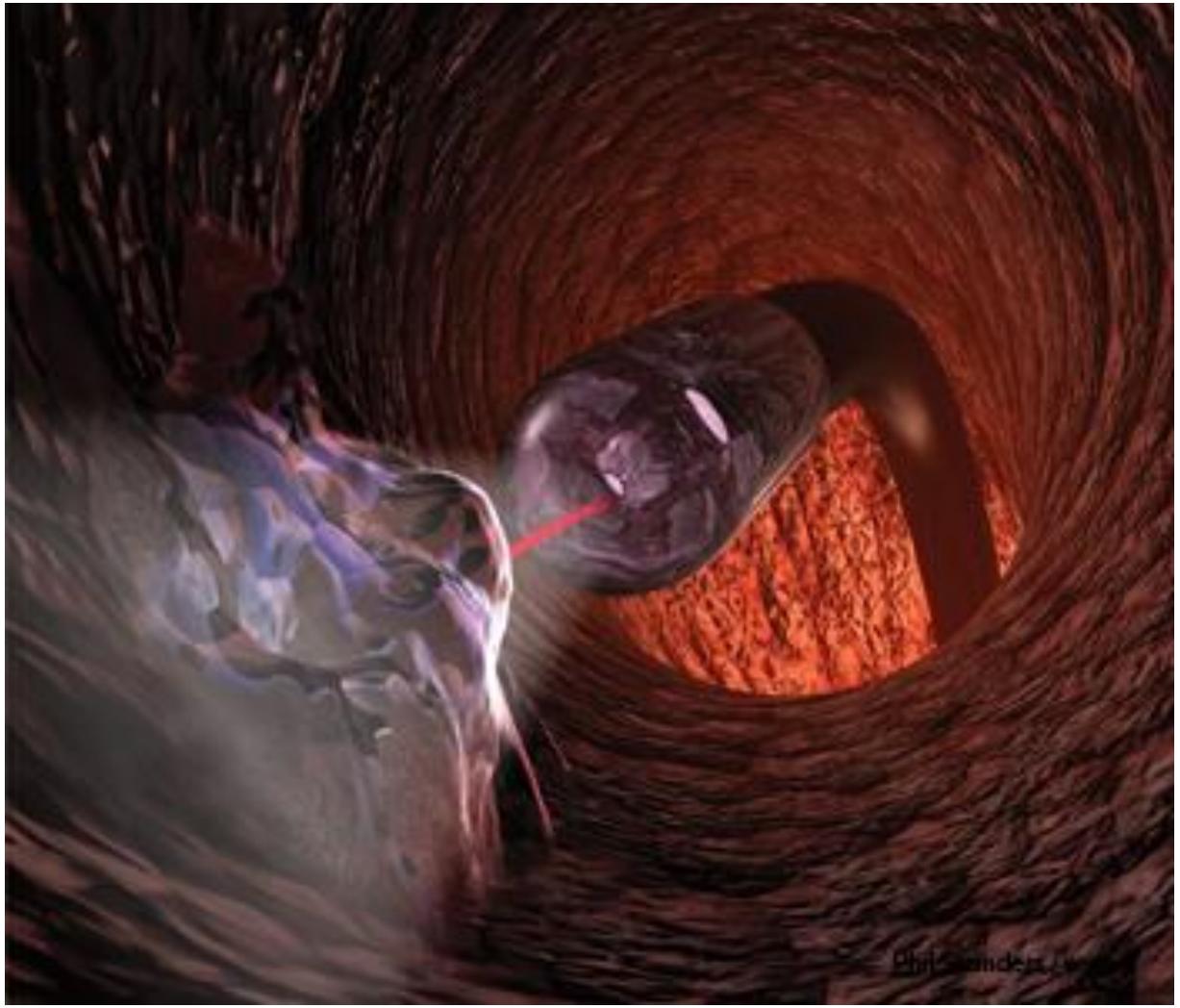
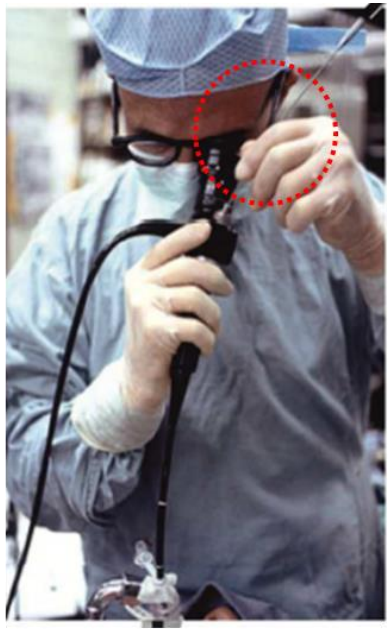
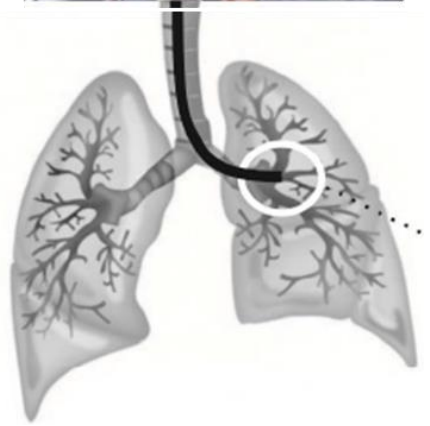


I. Some physics
II. Conventional optics and fluorescence
    I. Principle
    II. Instruments
    III. Clinical applications
    IV. Example : a (French) research group or start-up
III. Optical Coherence Tomography (OCT)
IV. Non-Linear Microscopy (NLOM)
V. Polarimetry
VI. Summary
VII. Closing remarks

# Endoscopy : bring light to the tissue

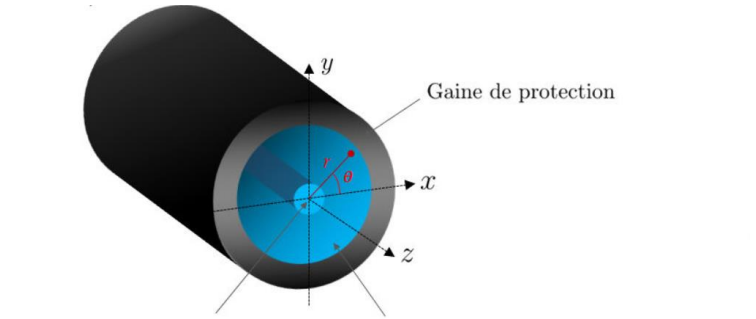


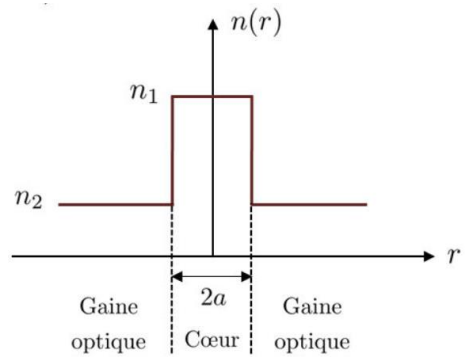


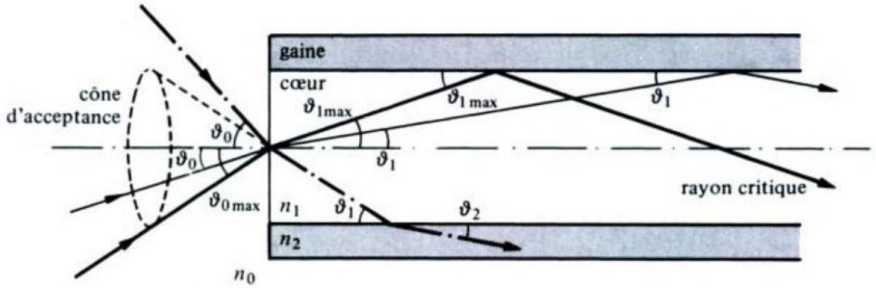


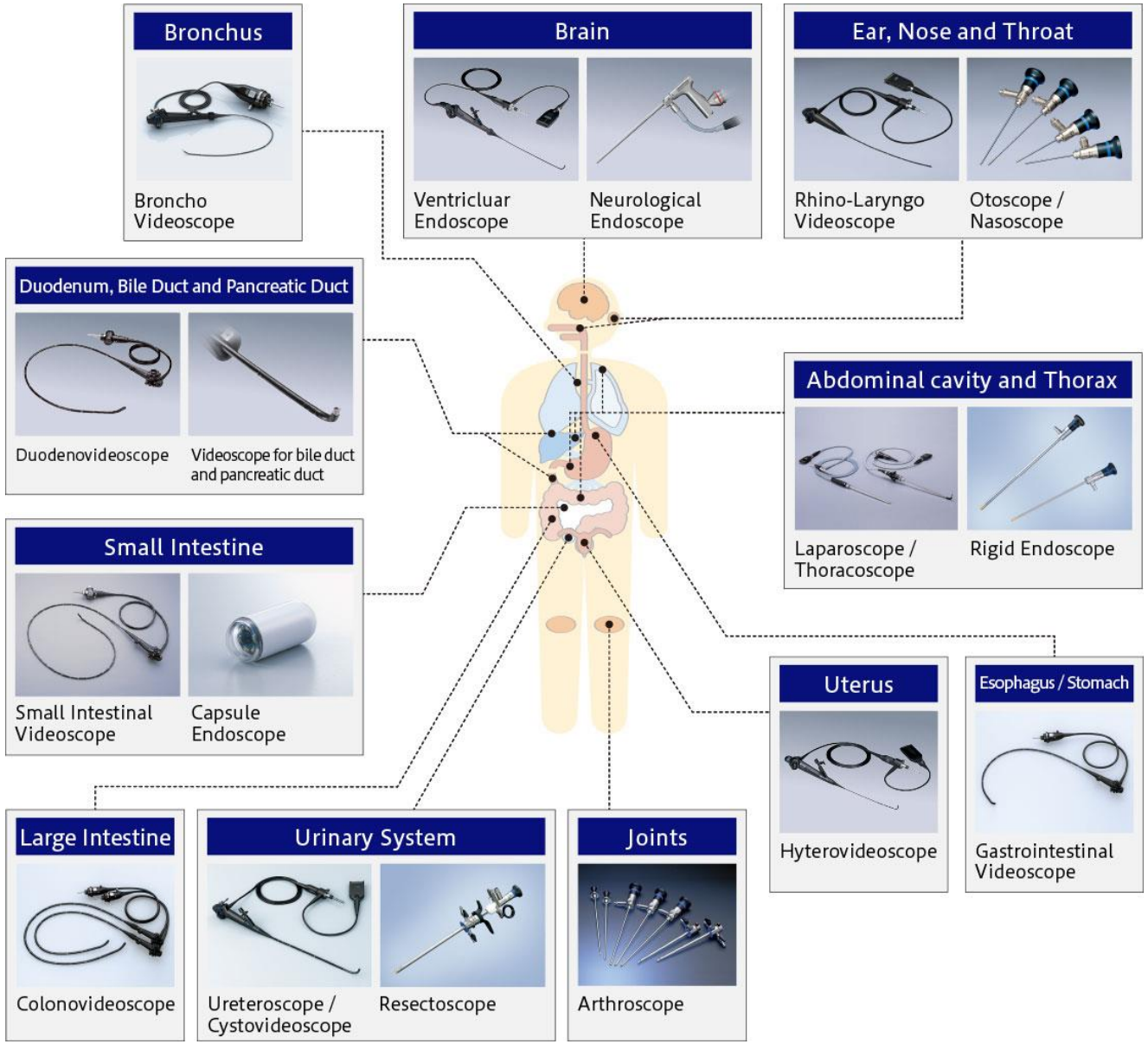
"Polarimetric Imaging for Cancer Diagnosis and Staging," Optics & Photonics News 23(10), 26-33 (2012)

# Endoscopes



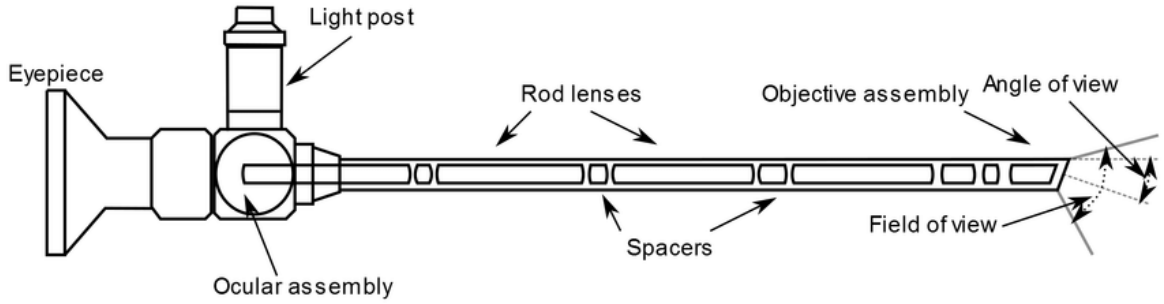



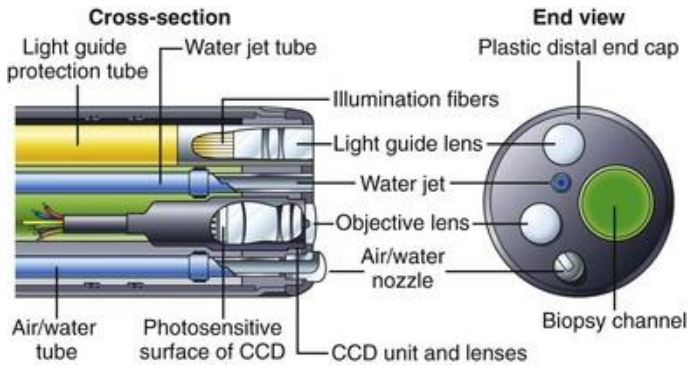




phD Thesis Jérémy Vizet

https://www.olympus-global.com/csr/social/medical/tec/lineup.html?page=csr

# Rigid endoscopes : minimally invasive surgery



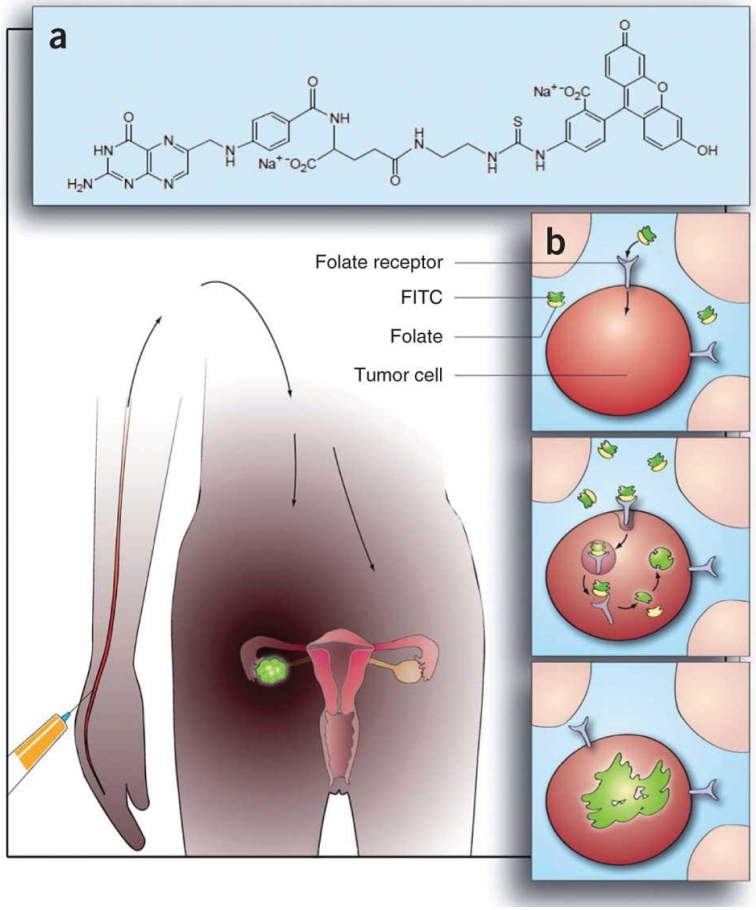



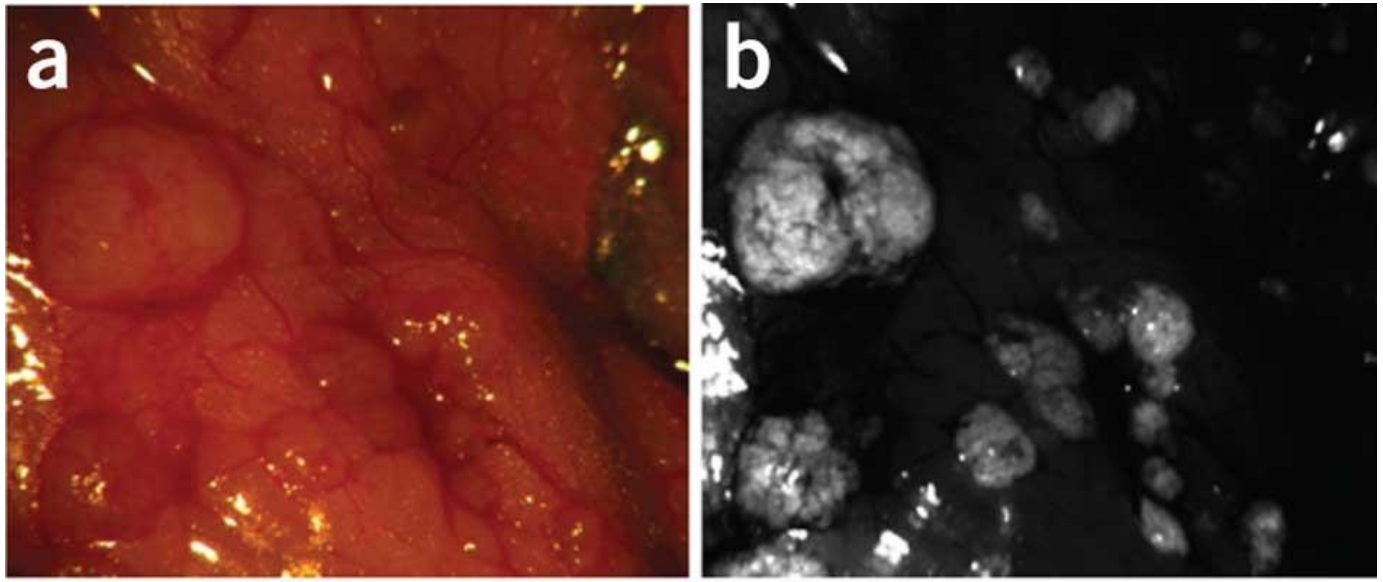

Wientjes, Rens, et al. "Automated objective routine examination of optical quality of rigid endoscopes in a clinical setting." *Plos one* 8.3 (2013): e59579.

https://clinicalgate.com/how-endoscopes-work/

Ponsky, T. A., & Ponsky, J. L. (2009). Advances in minimally invasive surgery. *Gastroenterology*, *136*(4), 1171-1173.

# Fluorescence

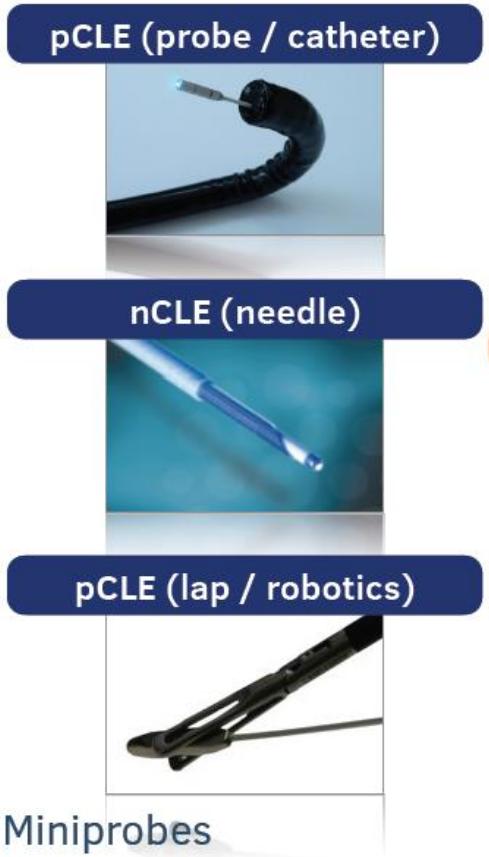


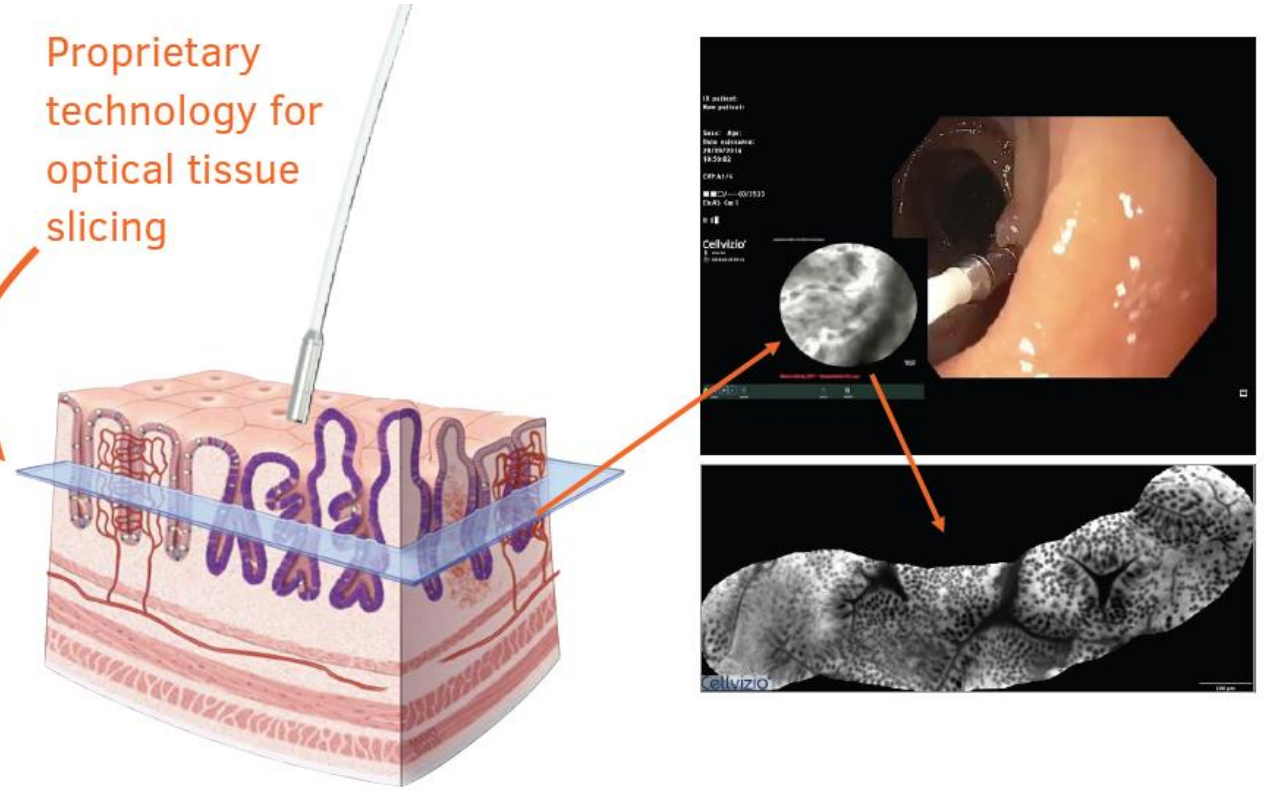

van Dam, G., Themelis, G., Crane, L. *et al.* Intraoperative tumor-specific fluorescence imaging in ovarian cancer by folate receptor-α targeting: first in-human results. *Nat Med* **17**, 1315–1319 (2011).

# Mauna Kea Technologies


Clinical Cellvizio® Platform




Miniprobes for various access methods (0.8 to 2.5 mm)




Breakthrough Confocal Laser Endomicroscopic scanning through 30,000 custom optical fibers produces 12 microscopic optical sections per second during standard endoscopy procedures

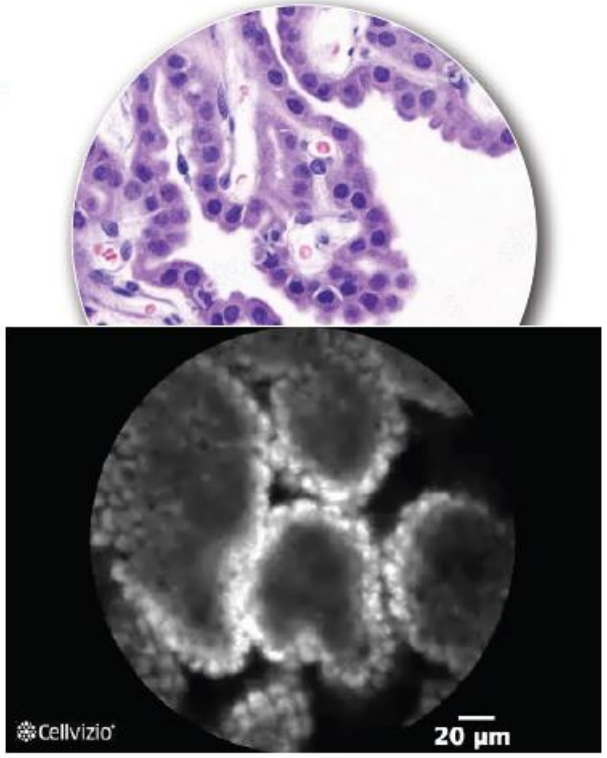


Mauna Kea Technologies

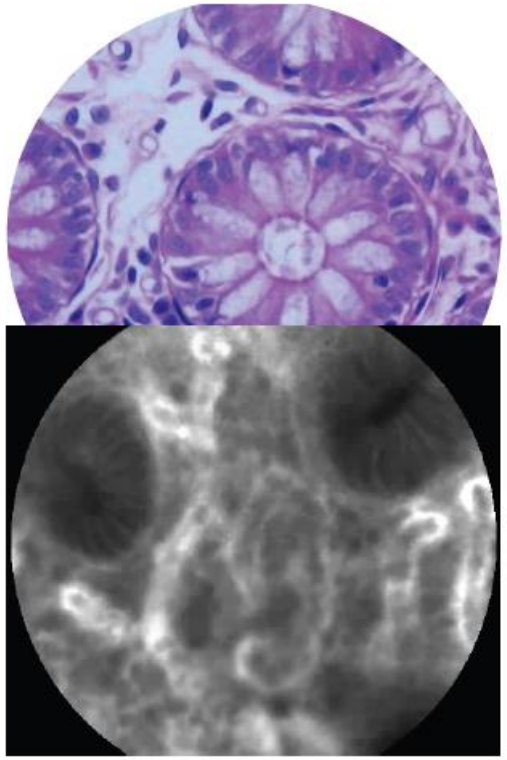
# Real-time *in-vivo* microscopy

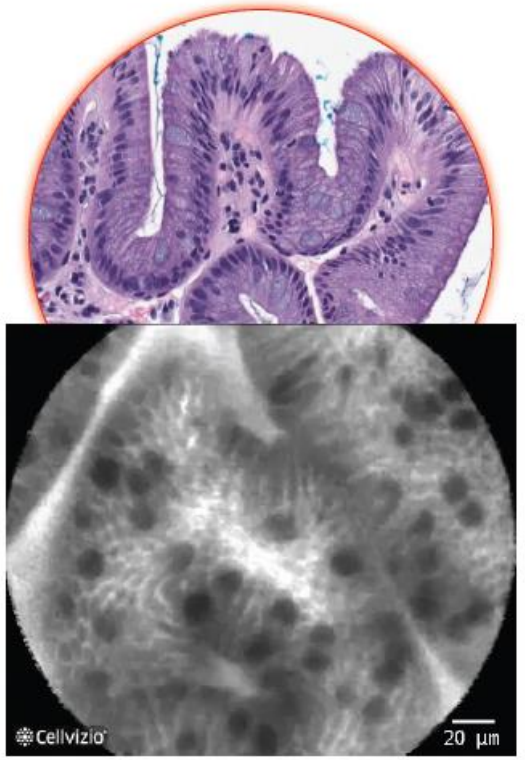
**From H&E histology…**
one image - static view

**…to Cellvizio®**
720 live microscopic images per minute - functional view



Brain

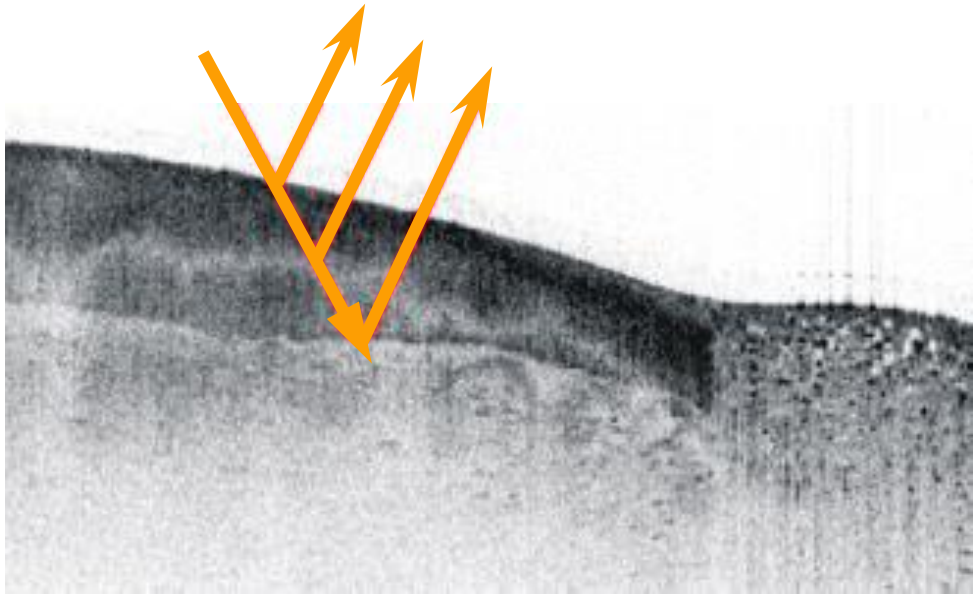

Colon



Esophagus

# Optical Coherence Tomography (OCT)

Similar principle to ultrasonnography ⋯ but with light!



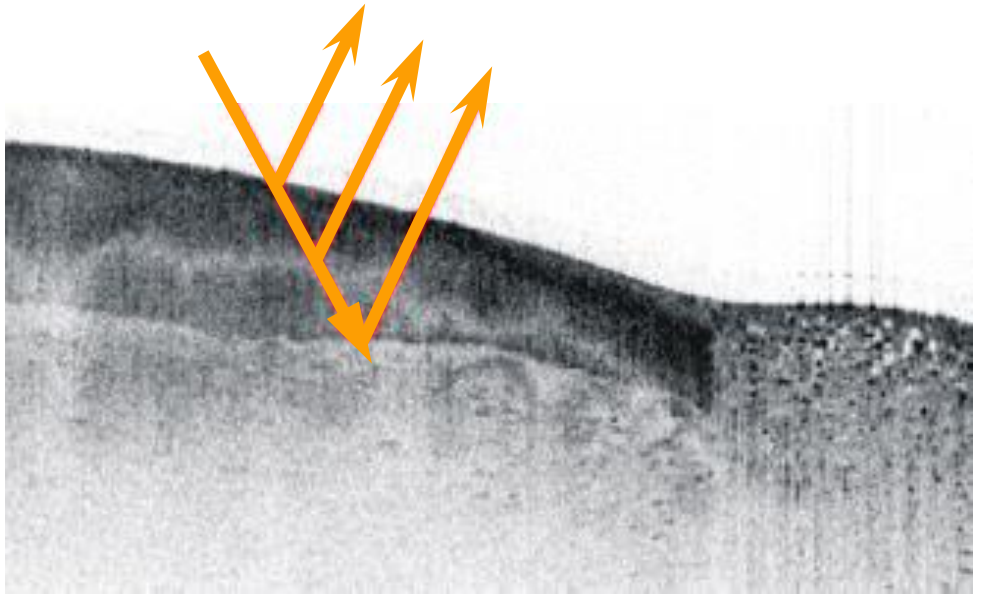
Ultrasound: 1-20 MHz – 1540 m/s
→echo detected with electronic transducers

Visible light: 375-750 THz – $3.10^8$ m/s !

*J. Fujimoto and al., Science **254**, 1178 (1991)*

# Optical Coherence Tomography (OCT)

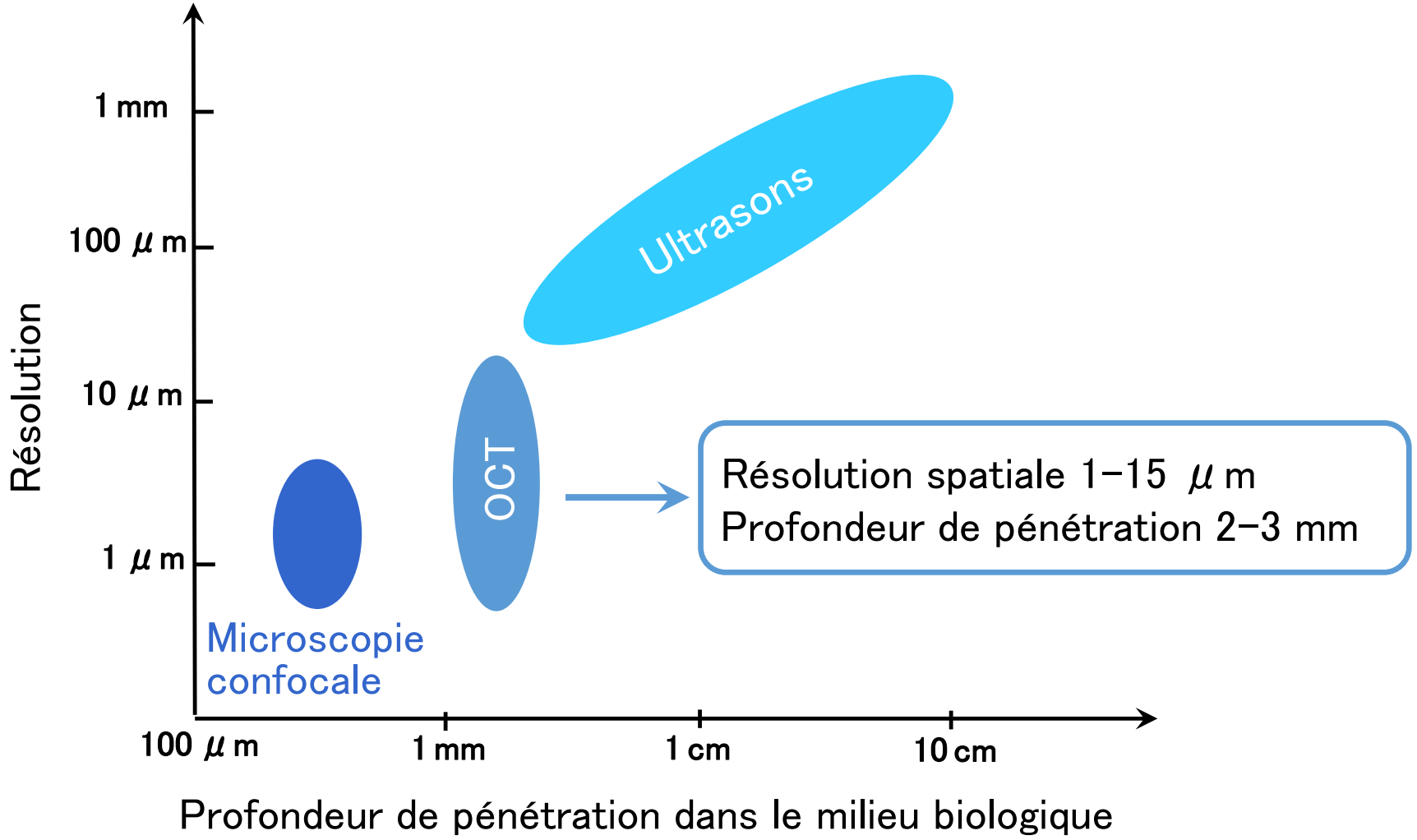
Similar principle to ultrasonnography ··· but with light!



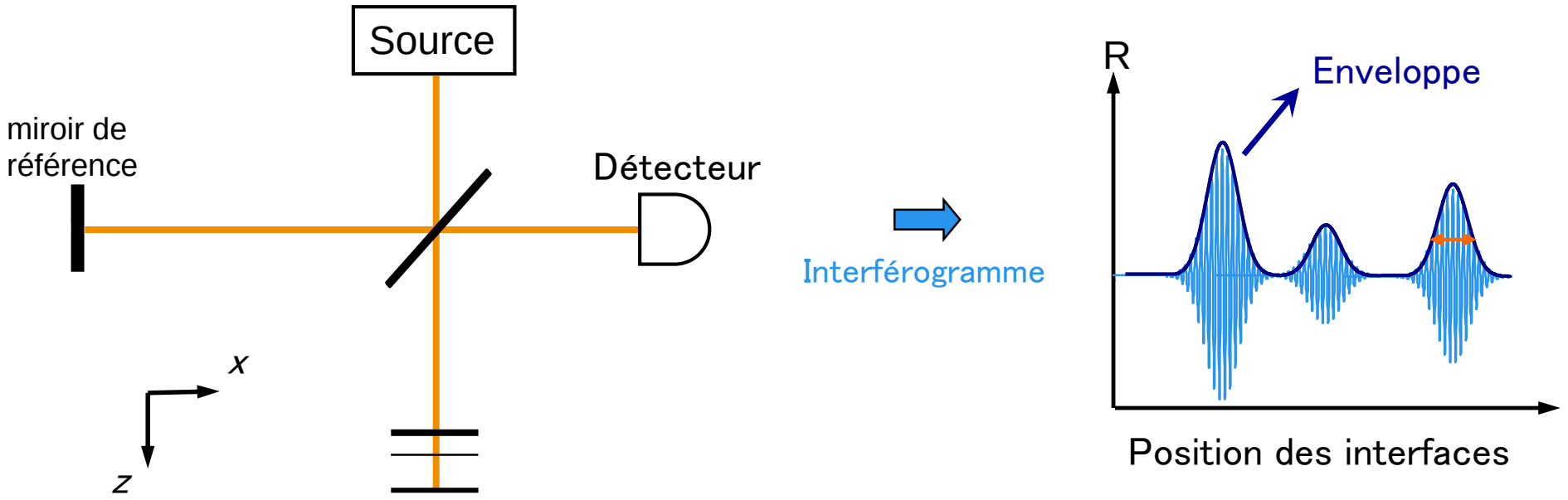
Principle: **interferometric measurement of the amplitude and travel time of light backscattered by the biological medium**

*J. Fujimoto and al., Science **254**, 1178 (1991)*

# OCT : unique properties

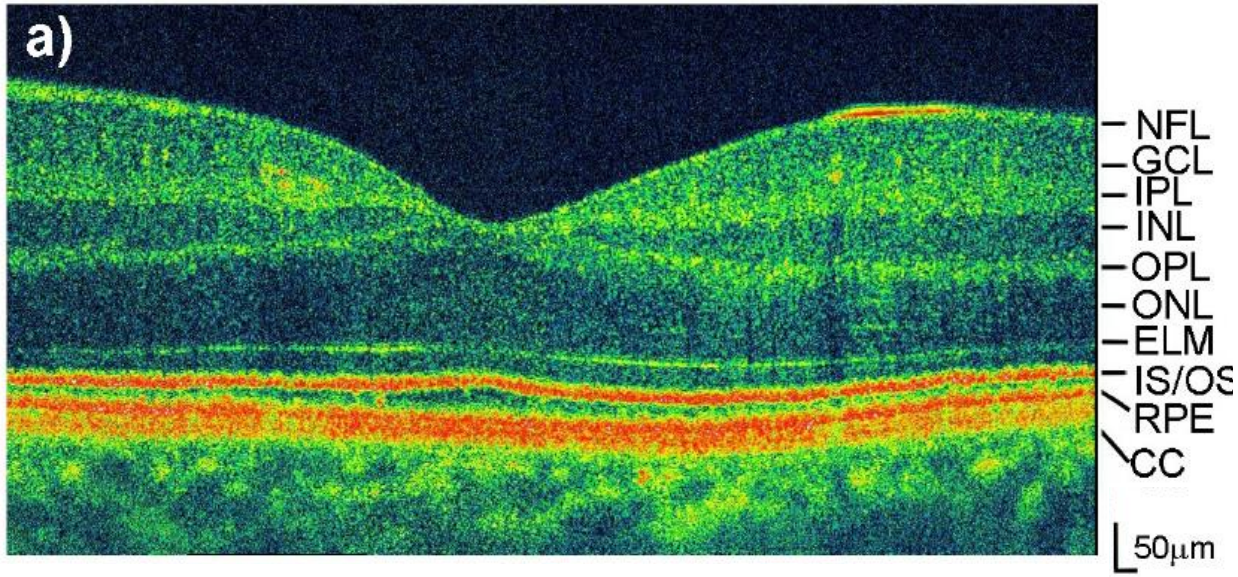


# OCT : working principle




- distribution des structures selon *z* obtenue par balayage de la différence de marche
- distribution des structures selon *x* et *y* obtenue par balayage 2D du faisceau

# Success story : OCT for ophtalmology

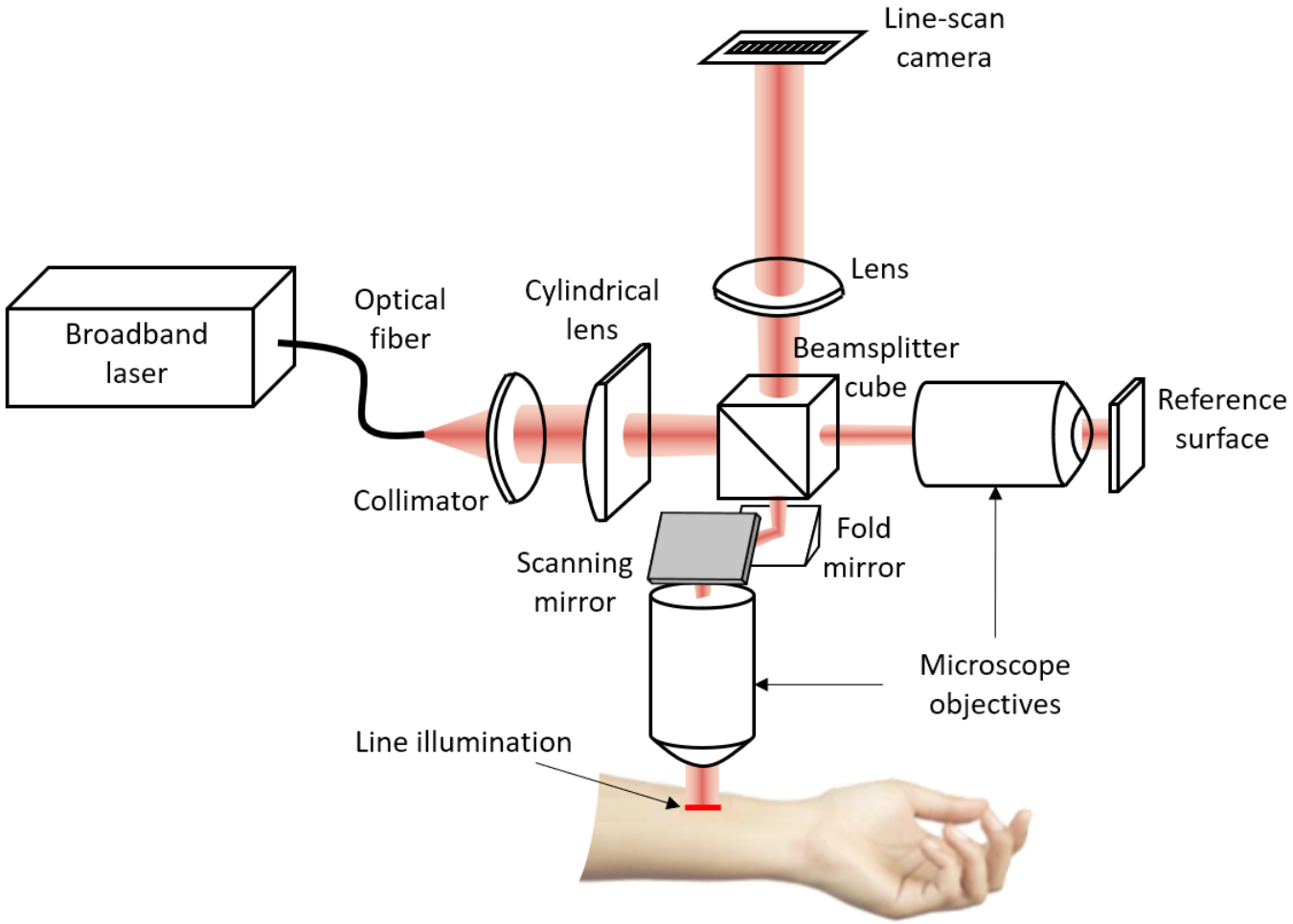






Wojtkowski, M., Srinivasan, V. J., Ko, T. H., Fujimoto, J. G., Kowalczyk, A., & Duker, J. S. (2004). Ultrahigh-resolution, high-speed, Fourier domain optical coherence tomography and methods for dispersion compensation. *Optics express*, *12*(11), 2404-2422.

# Damae Medical

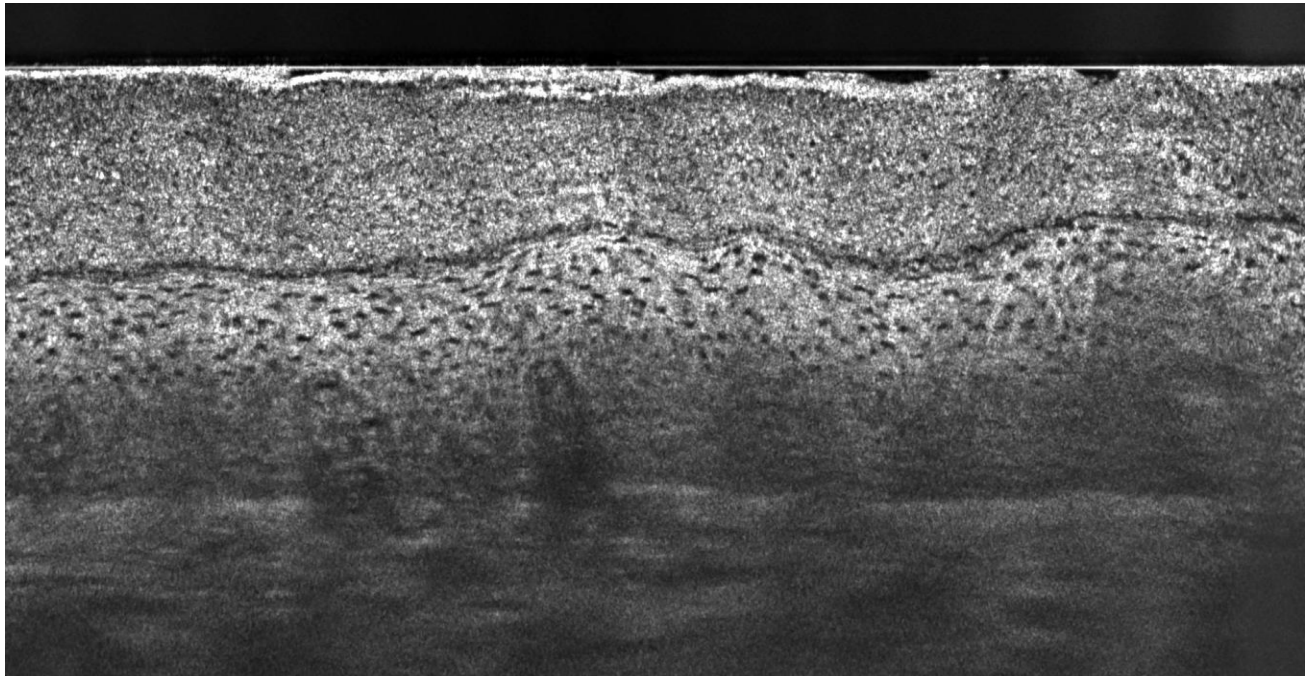
Line-Field Confocal Optical Coherence Tomography



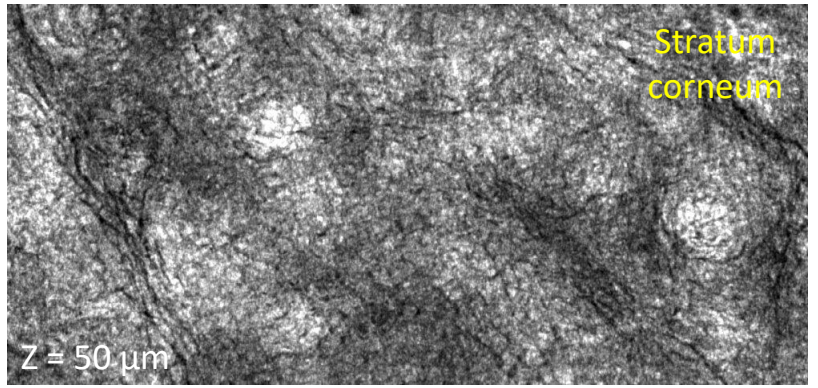

Technology invented by Pr. Arnaud Dubois
(CNRS, IOGS, UPSaclay)
Fully transfered to DAMAE Medical

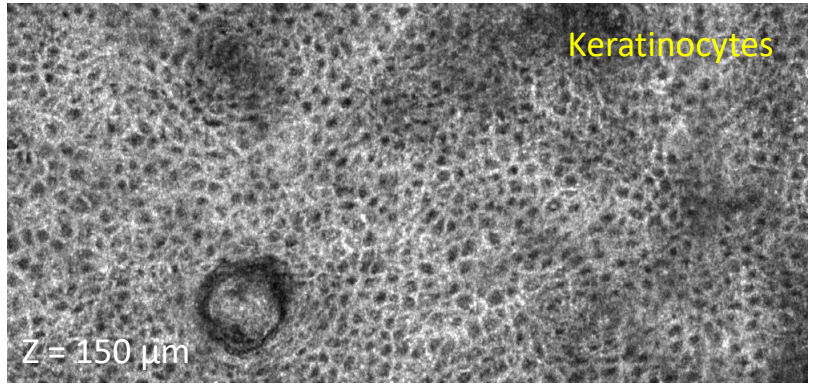
*Courtesy A. Dubois, IOGS & DAMAE Medical*

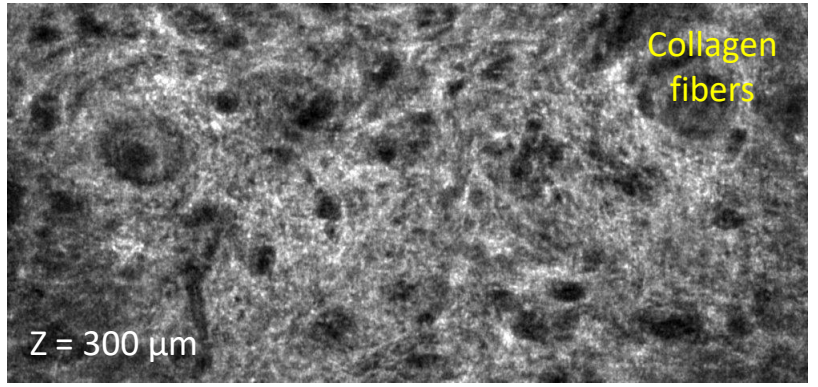
# Healthy skin



Horizontal sections



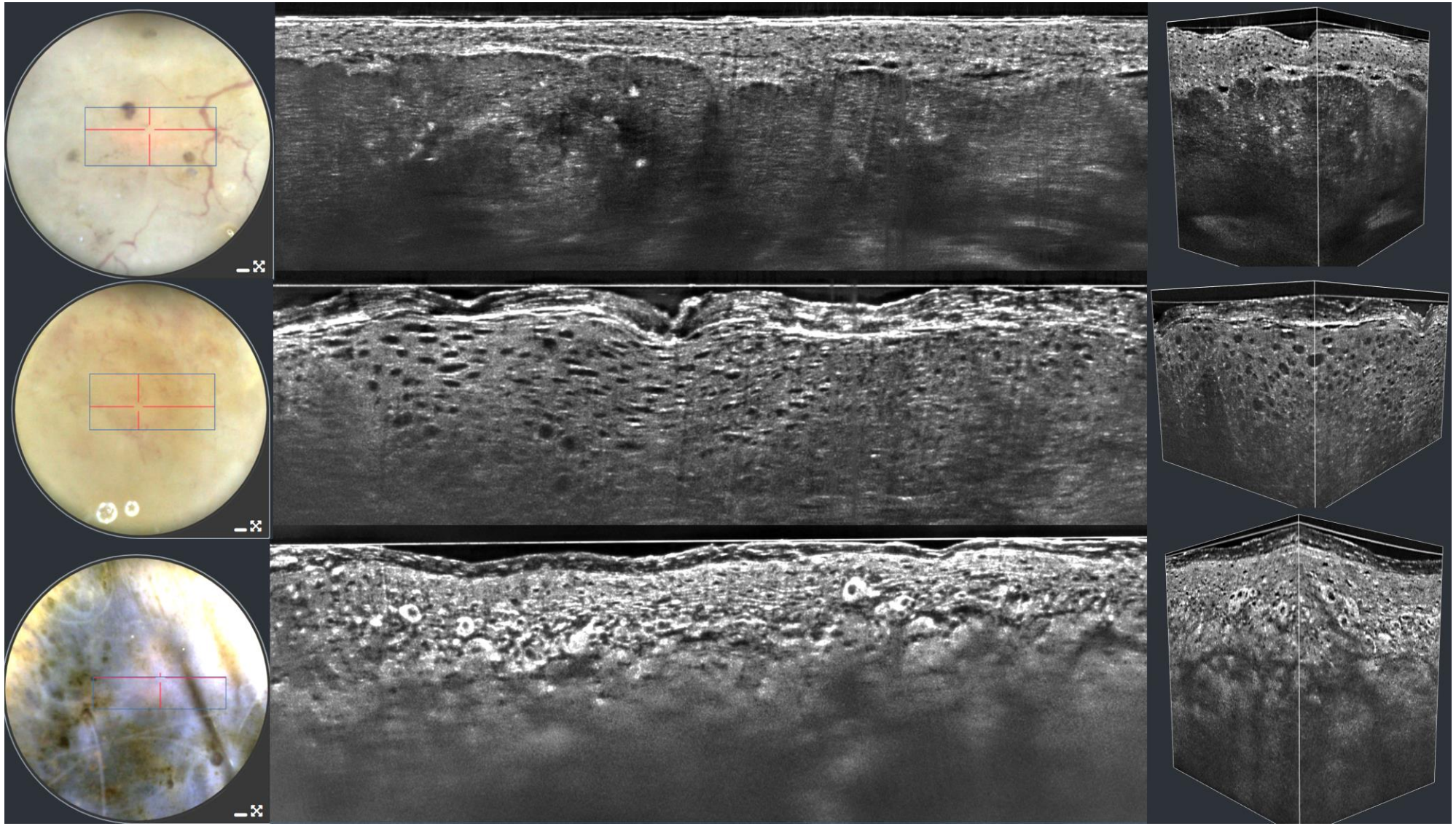

*Courtesy A. Dubois, IOGS & DAMAE Medical*

deepLive
by DAMAE MEDICAL

- **Cellular resolution** (~ 1 µm, isotropic)
- **Live vertical imaging mode** (1.2 mm x 0.4 mm, 8 fps)
- **Live horizontal imaging mode** (1.2 mm x 0.5 mm, 8 fps)
- **3D imaging mode** (1.2 mm x 0.5 mm x 0.5 mm, 30 s)

**+ video-dermoscopy (resolution: 5 µm ; field of view: 2.5 mm)**

*Courtesy A. Dubois, IOGS & DAMAE Medical*



**Basal Cell Carcinoma**

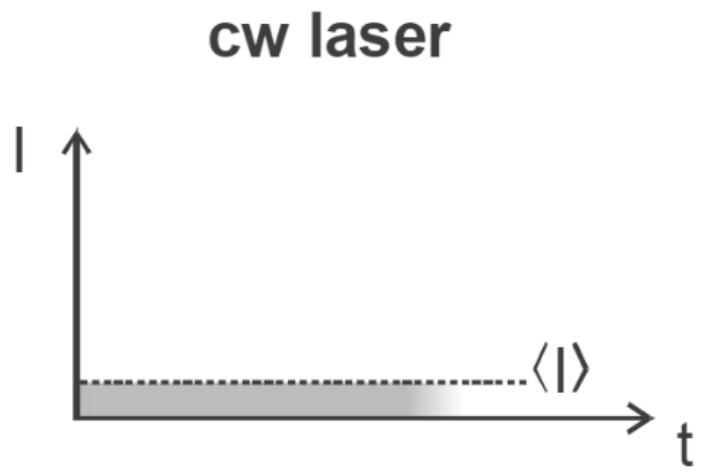
**Squamous cell carcinoma**

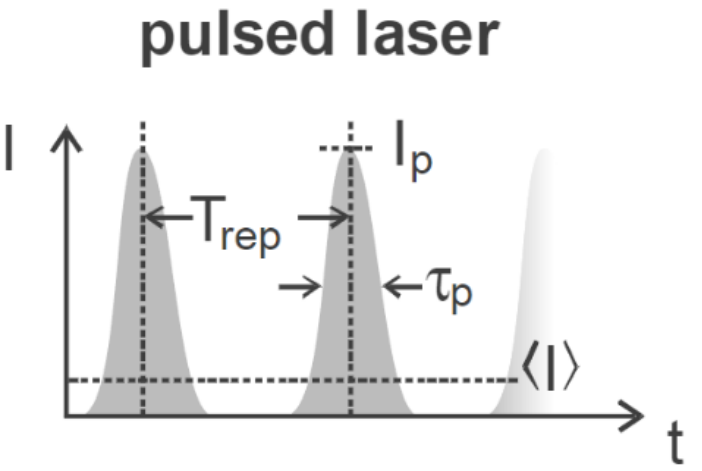
**Melanoma**

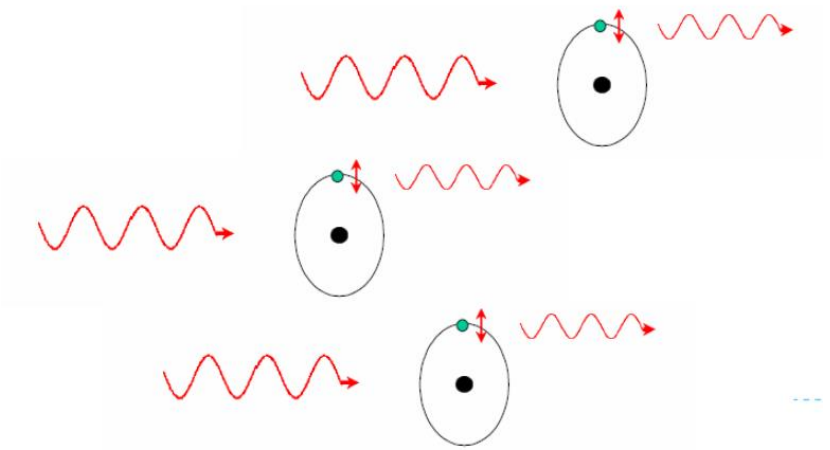
*Video-dermoscopy* *Vertical section* *3D*

*Courtesy A. Dubois, IOGS & DAMAE Medical*

# Non-Linear Optical Microscopy



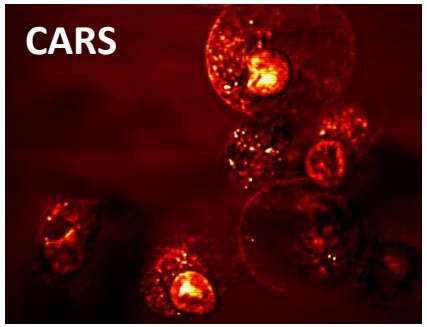
Linear Effects :
- Absorption
- Scattering

Signal ∝ I

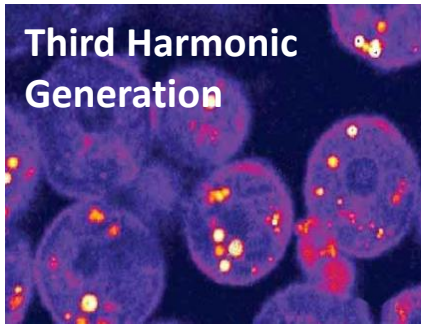
$$\vec{P}(t) = \varepsilon_0(\chi^{(1)}\vec{E} + \chi^{(2)}\vec{E}\vec{E} + \chi^{(3)}\vec{E}\vec{E}\vec{E} + \dots)$$

→ Non-Linear Effects :
Signal ∝ $I^{(n)}$

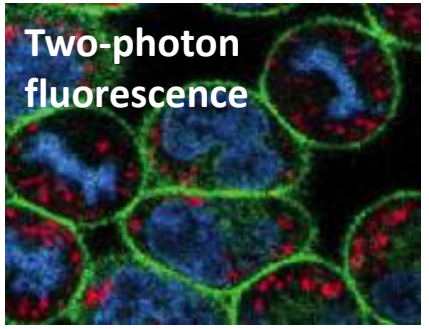
# Non-linear optical effects



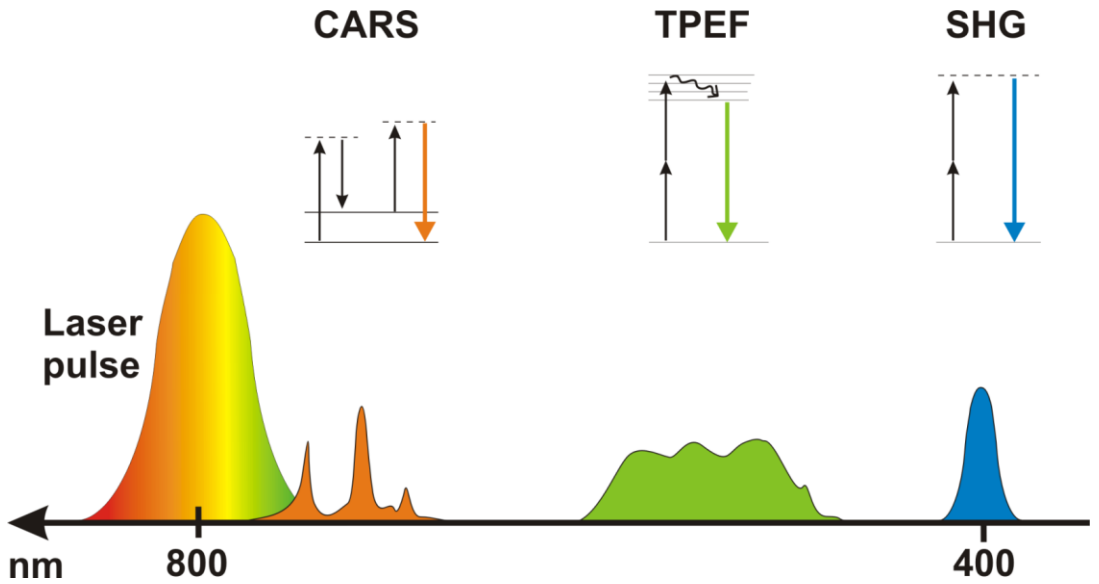

Cheng et al., *Biophys. J.* **83**, 502 (2002).



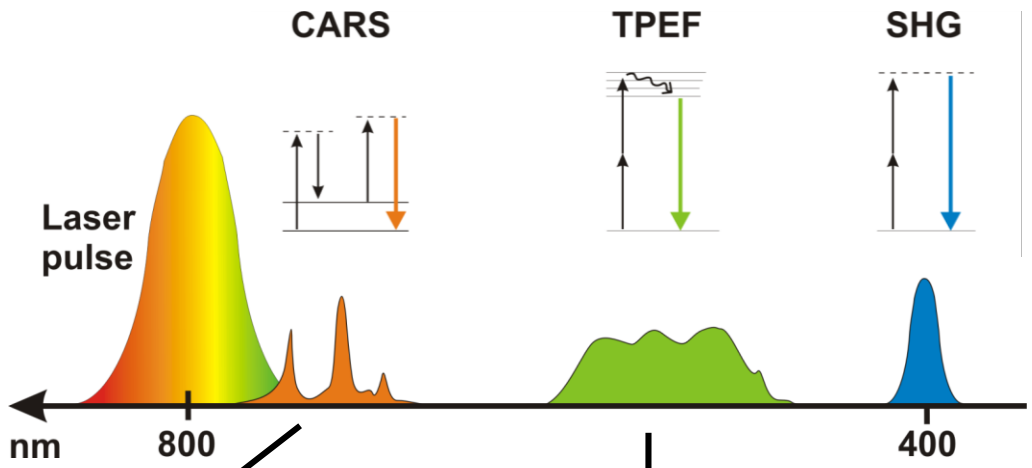

Débarre et al., *Nature Methods* **3**, 47 (2006).




Zipfel et al., *Nature Biotech.* **21**, 1369 (2003).



# Chemical & microstructural sensitivity




**CARS**

- coherent

---

- molecular Levels
  - vibrational
  - rotational
- "all" molecules

**TPEF**

- incoherent, spontaneous

---

- endogenous fluorophores
  - NAD(P)H, melanin, Elastin, tryptophan,…
- fluorescence markers
  - QDs, proteins (GFP),…

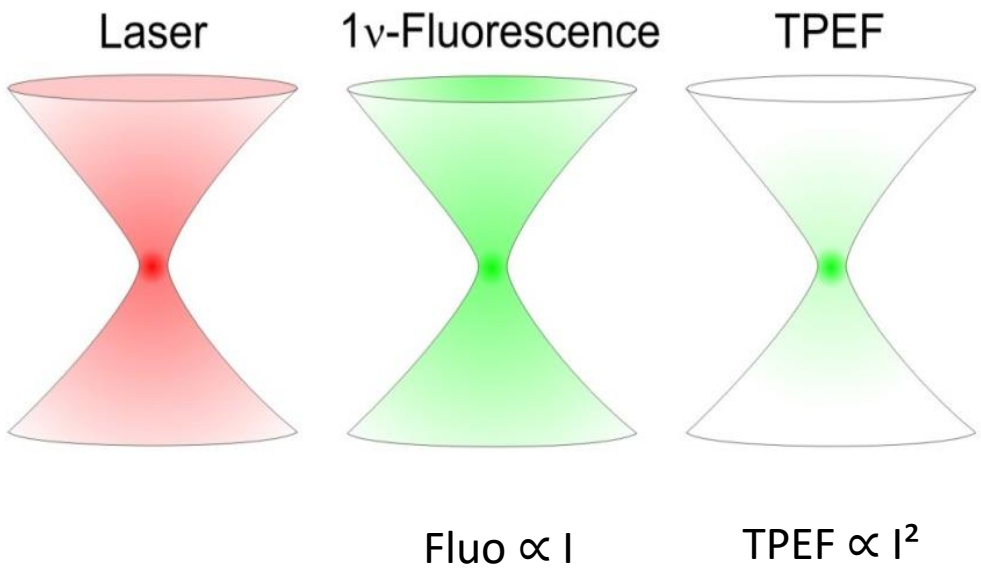
**SHG**

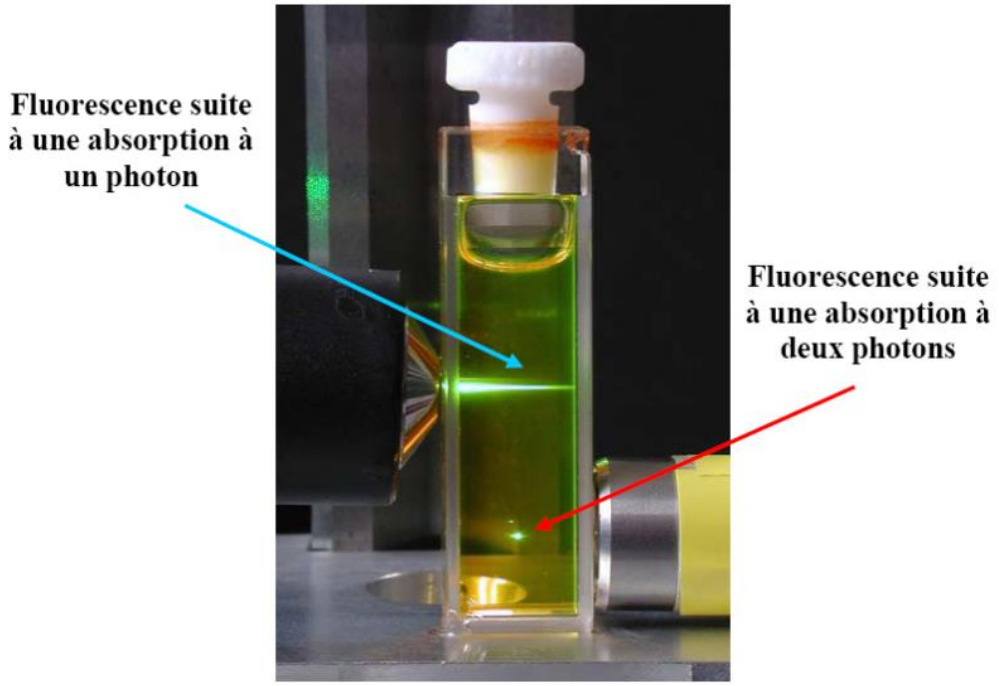
- coherent

---

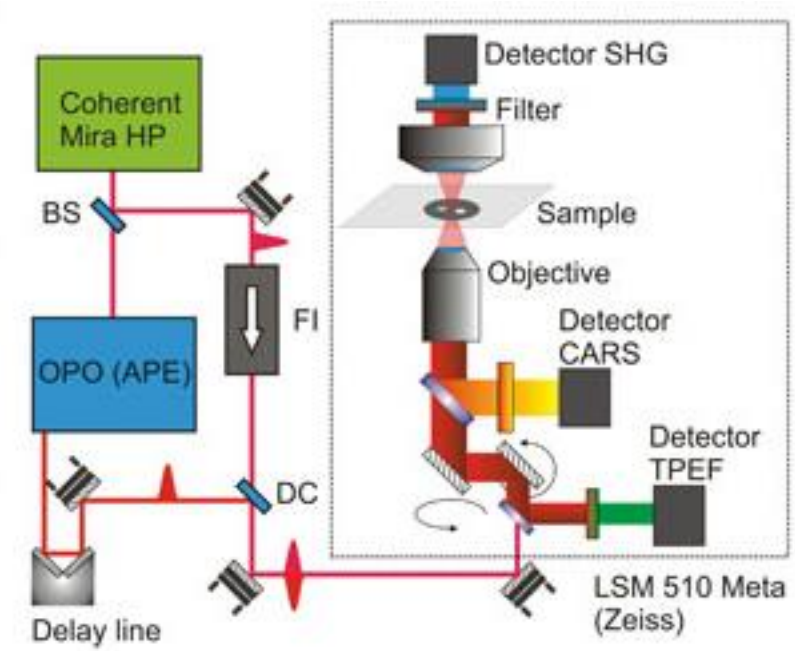
- virtual levels
  - always at $2\omega$
- noncentrosym. Media
- structures mol. & interfaces

# Inherent 3D capability



# NLOM setup




Challenging technique :

- ps- or fs-lasers
- precise optical alignement
- Rapid scanning
- Filters and detectors

Coherent.com

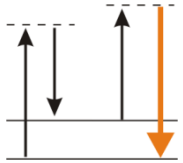
Popp, J., Dietzek, B., Meyer, T. (2012). Multimodal Nonlinear Microscopy: Histopathology of Brain Tumors *Wiley Analytical Science*

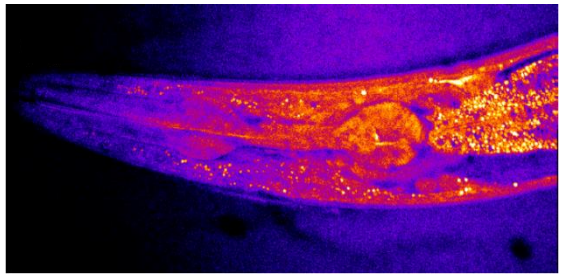
# LOB – Ecole polytechnique

**Biological processes at the sub-cellular level revealed through non-linear microscopy**

**C. elegans worm**

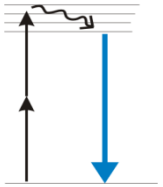
CARS

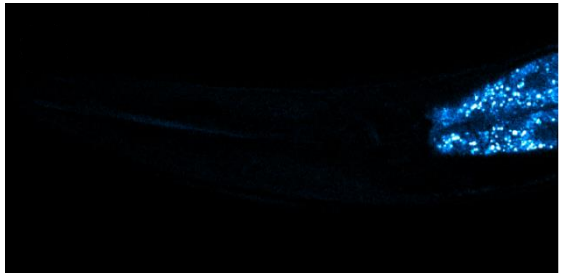




epithelial lipids

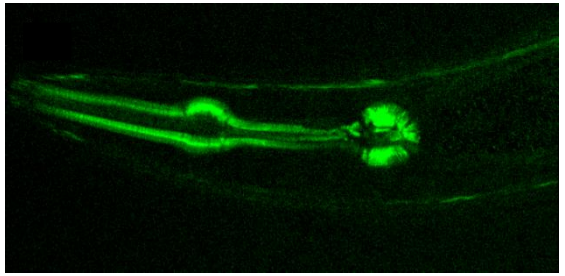
TPEF





fluorescent vesicles

SHG

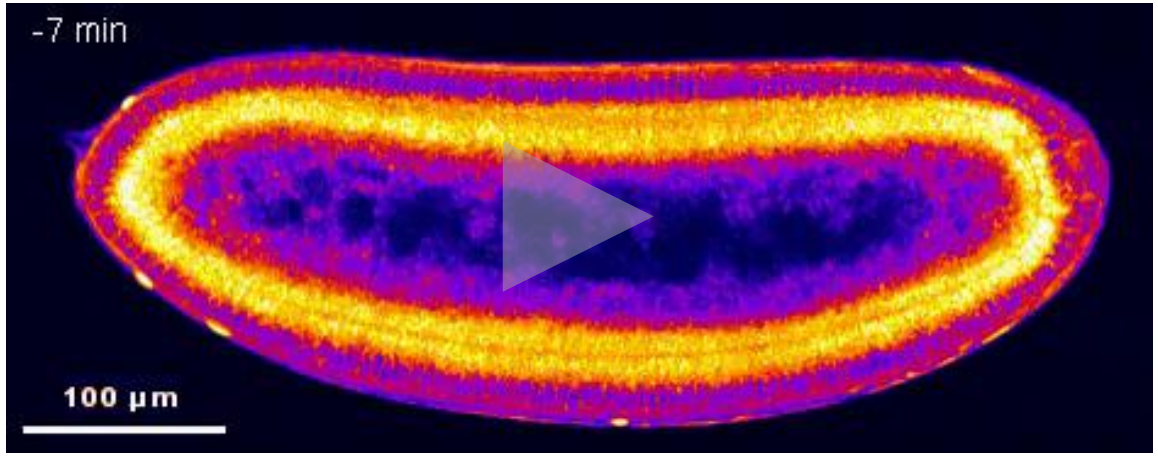


muscles

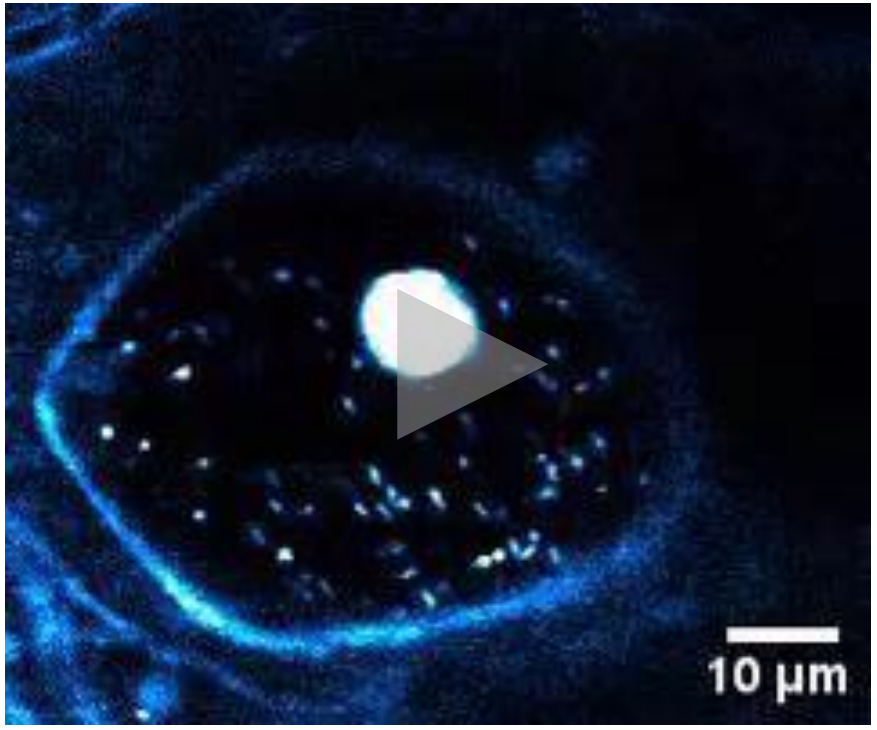
Mahou et al., Biomed. Opt. Exp. **2**, 2837 (2011).

# LOB – Ecole polytechnique

**Biological processes at the sub-cellular level revealed through non-linear microscopy**



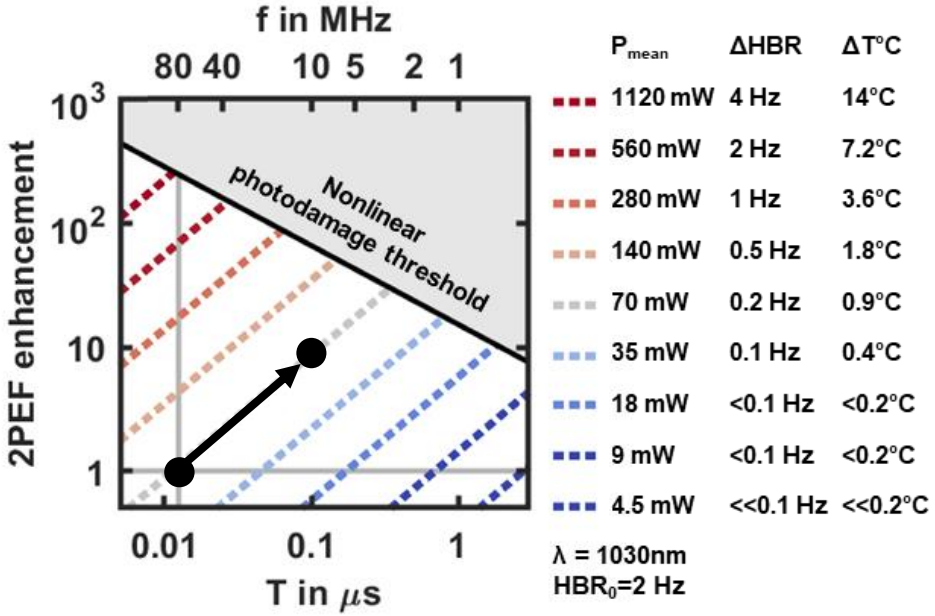

Supatto, Willy, et al. "In vivo modulation of morphogenetic movements in Drosophila embryos with femtosecond laser pulses." *Proceedings of the National Academy of Sciences* 102.4 (2005): 1047-1052.




THG imaging of flowing endogenous microparticles in the otolith cavity of a zebrafish. Excitation power: 100-150 mW. Axial resolution: 2µm. Time per pixel: 10 µs. Time between images: 620 ms. Typical signal level (particles): 30-80 photons

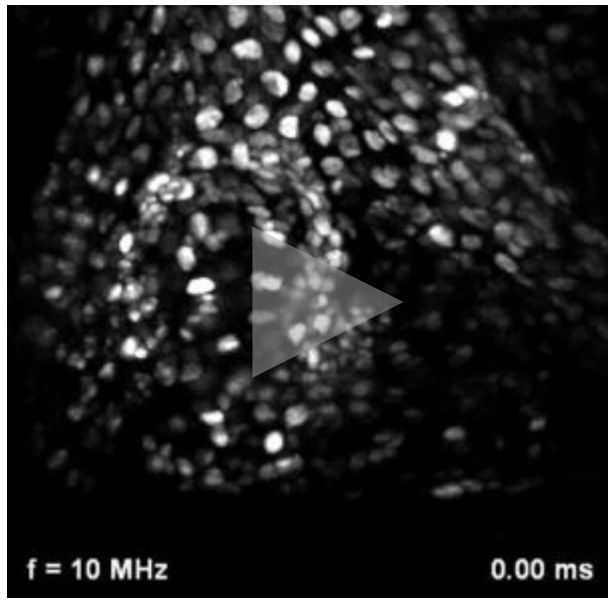
Joséphine Morizet, Guillaume Ducourthial, Willy Supatto, Arthur Boutillon, Renaud Legouis, Marie-Claire Schanne-Klein, Chiara Stringari, and Emmanuel Beaurepaire, "High-speed polarization-resolved third-harmonic microscopy," Optica 6, 385-388 (2019)

# Photodamage mitigation




| $P_{mean}$ | ΔHBR | ΔT°C |
|---|---|---|
| 1120 mW | 4 Hz | 14°C |
| 560 mW | 2 Hz | 7.2°C |
| 280 mW | 1 Hz | 3.6°C |
| 140 mW | 0.5 Hz | 1.8°C |
| 70 mW | 0.2 Hz | 0.9°C |
| 35 mW | 0.1 Hz | 0.4°C |
| 18 mW | <0.1 Hz | <0.2°C |
| 9 mW | <0.1 Hz | <0.2°C |
| 4.5 mW | <<0.1 Hz | <<0.2°C |

2PEF signal enhancement $= T\,{P_{mean}}^2 / T_0\,{P_0}^2$
$T_0 = 1/80MHz$ and $P_0 = 70mW$
On this graph: $n_D$-order Damage threshold $\sim T^{2/n_D-1}$




Zebrafish beating heart | mCherry | λ=1030nm
@**170 fps /** 40MHz pixel rate
**8x 2PEF signal enhancement**
FOV 200 x 200 µm

**Strategy**
**Decrease f=1/T to ~10 MHz at constant $P_{mean}$**
► 8x 2PEF enhancement
► ΔT°C < 1°C
► Still far from nonlinear photodamage
Best compromise!

*Courtesy V. Maioli*

Maioli et al, Biomedical Optics Express 2020

# My journey with polarimetry

1. PostDoc project 2013-2017

**Team of Angelo Pierangelo**

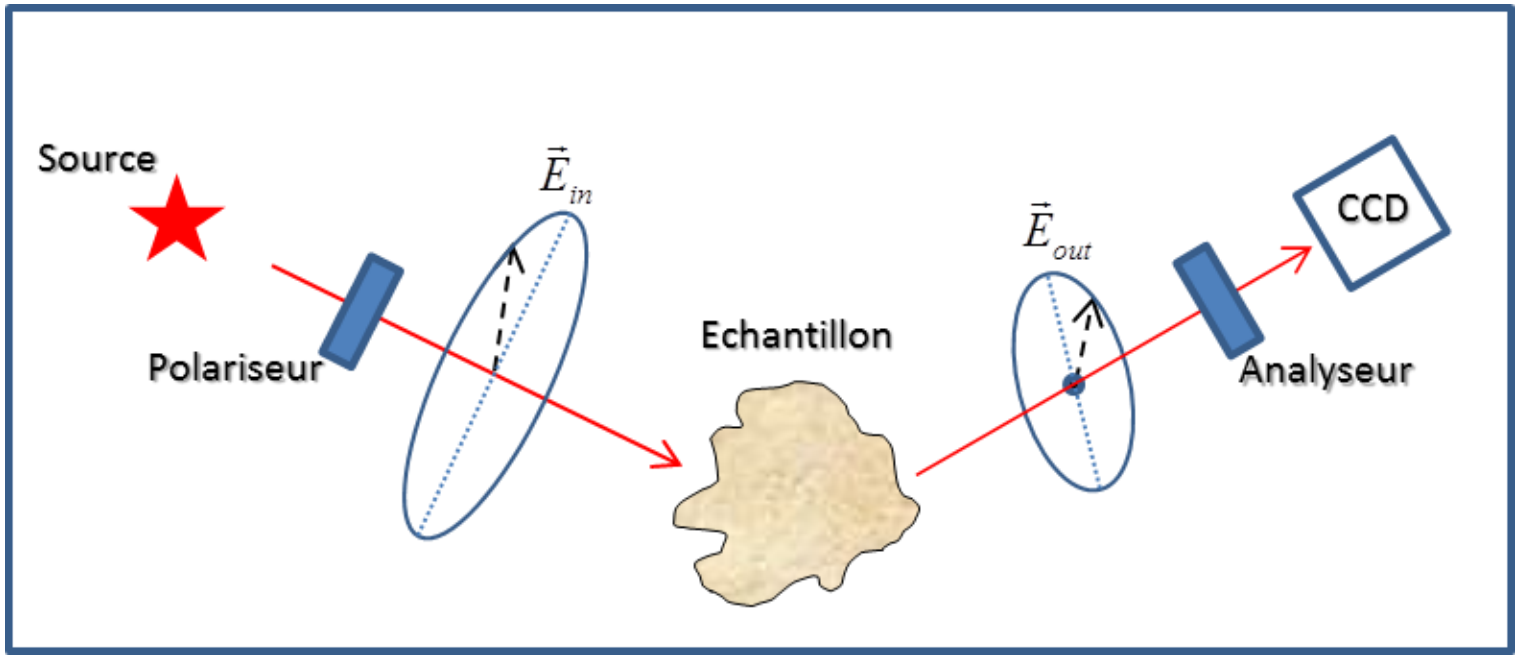
- Early detection of cervical cancer
- Diagnosis of risk of premature delivery

2. PostDoc and current position 2018-now

**Team of Jihad Zallat**

- Optical biopsy for skin cancer
- Valorisation through the Poladerme start-up

# Polarimetry



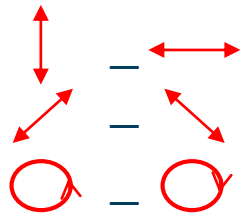

Caractérisation complète de la réponse polarimétrique : la Matrice de Mueller

$$\boldsymbol{S_{out}} = \boldsymbol{M} \times \boxed{\boldsymbol{S_{in}}}$$

$\in \mathbb{M}_{4,4}$

$$\mathbf{S} = \begin{bmatrix} S_0 \\ S_1 \\ S_2 \\ S_3 \end{bmatrix} = \begin{bmatrix} I \\ I_x - I_y \\ I_{+45°} - I_{-45}{}^{\circ} \\ I_L - I_R \end{bmatrix}$$

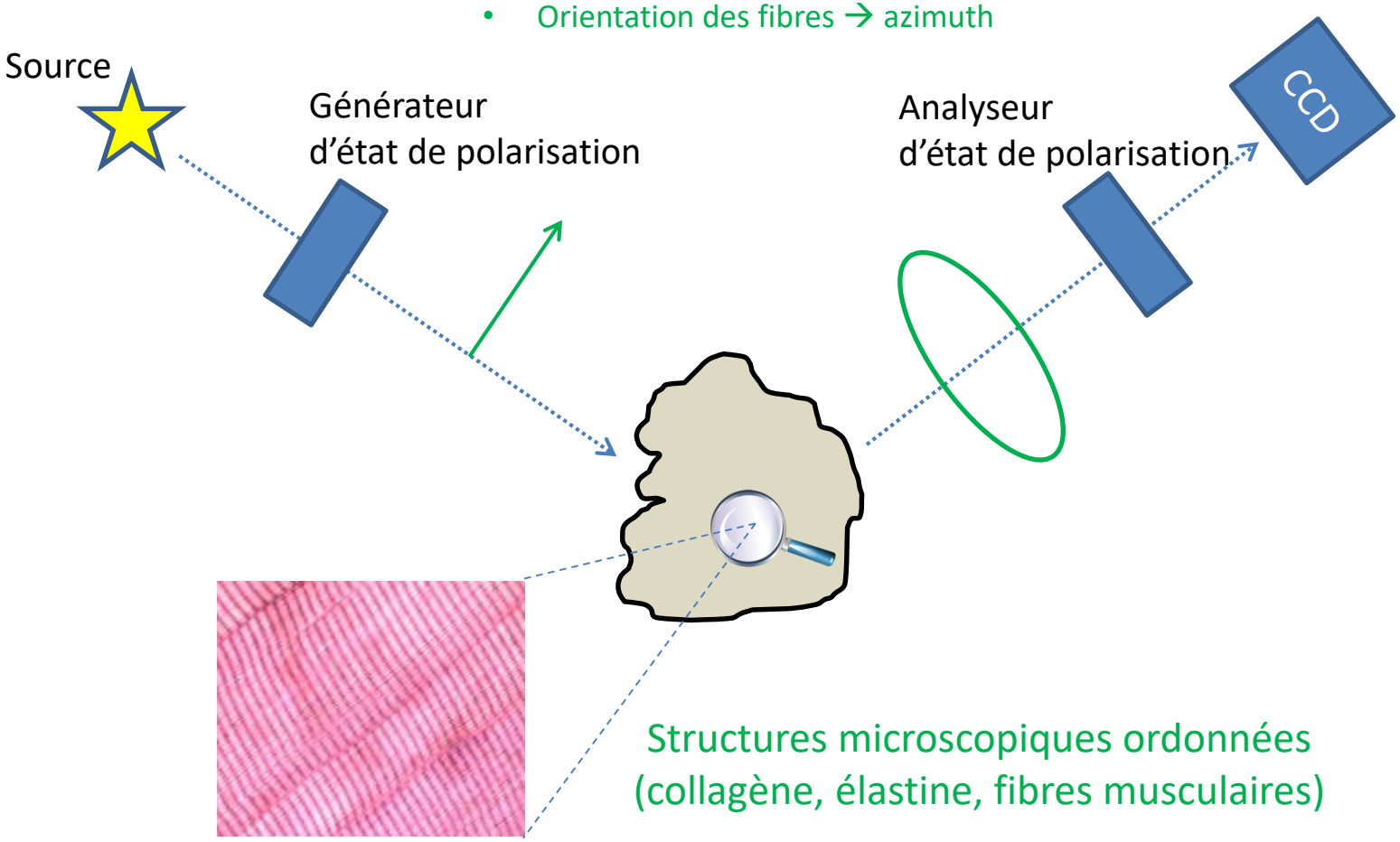
mesures d'**intensité**



# Polarimetric properties of tissues

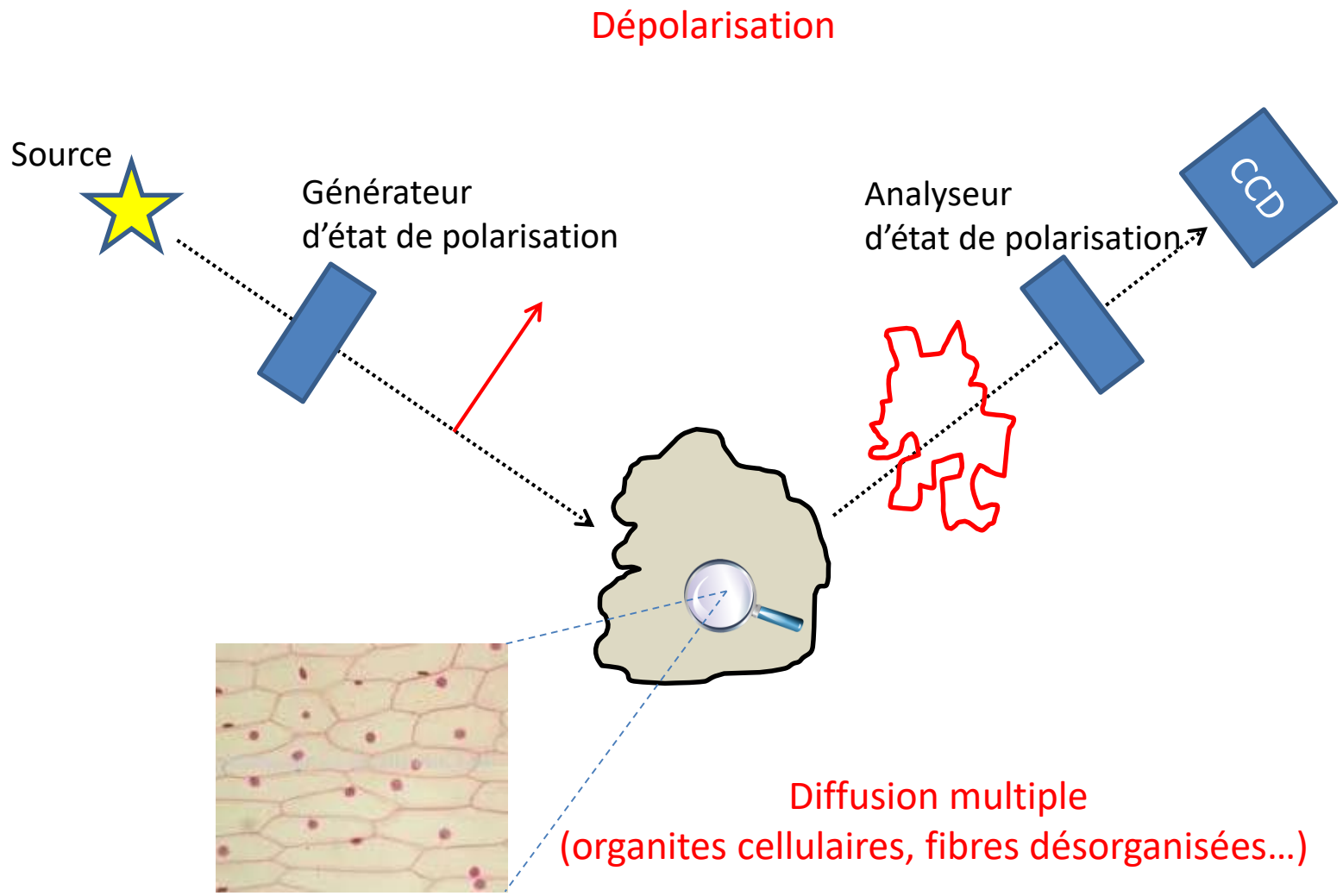
**Biréfringence**

- Densité des fibres → retardance
- Orientation des fibres → azimuth

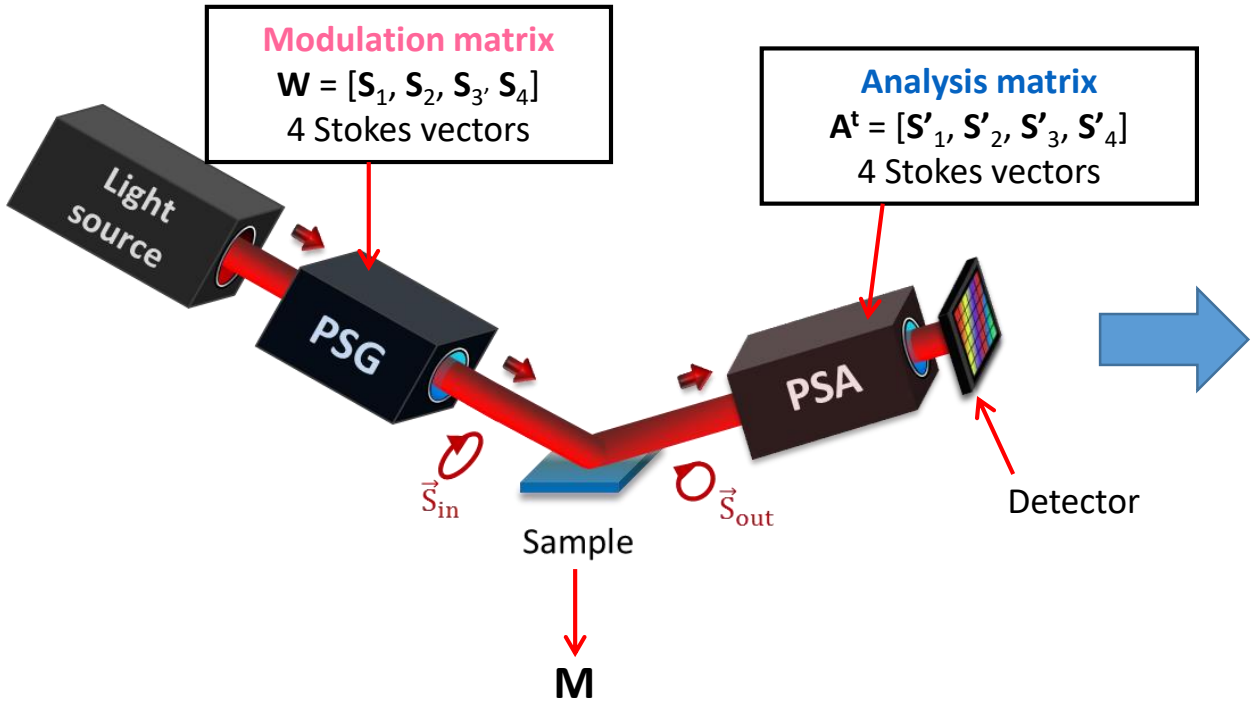



Structures microscopiques ordonnées
(collagène, élastine, fibres musculaires)

# Polarimetric properties of tissues



# Measurement of the Mueller matrix




**B** → Measured intensity matrix
(16 elements)

**B = A M W**

**M = $A^{-1}$ B $W^{-1}$**

**A** et **W** are obtained by calibration

**Eigenvalues Calibration Method (ECM)**

- Uses well-known polarization optical elements (polarizers, waveplates, etc.)
- No a priori modelling of the instrument needed

# Advantages of Mueller polarimetric imaging

- Wide field (~ 5x5 $cm^2$)
- Fast acquisition speed (0.25~1s)
- It explores both optical anisotropy (retardance) and scattering (depolarization) properties at the same time
- Scattering properties from deep depth (~1 cm, 650nm)[7]
- Bio-safe (visible light)

7. V. V Tuchin, “Light scattering study of tissues”. *Physics-Uspekhi* **40**, 495 (1997).

# Preterm birth: birth before 37 amenorrhea weeks

- Preterm birth was responsible for **~1 million perinatal deaths** in 2015[1]

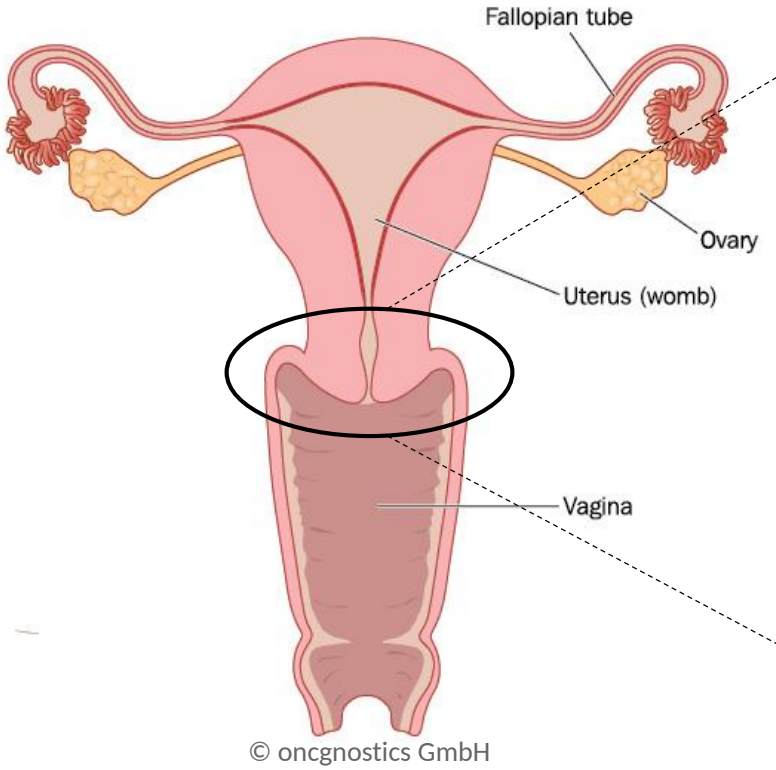
- **Current diagnostics**: measurements of cervical length shortening
  - 1~2 echographies per week[2]
  - Low diagnostic performance of the current method: ~50% women hospitalized for threatened preterm birth have actual preterm birth[3]

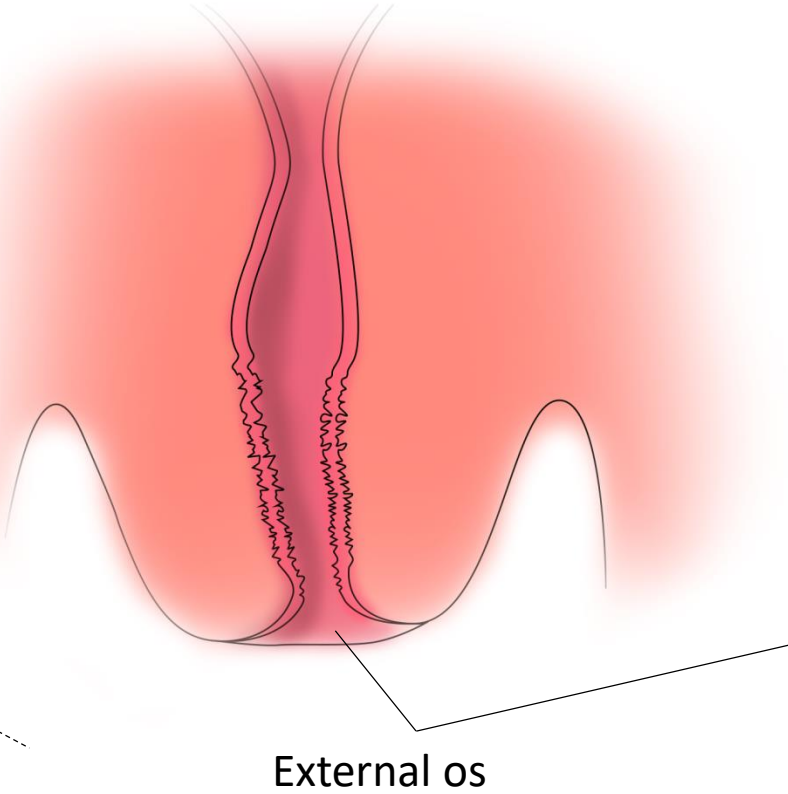
- **The goal**: development of a new diagnostic tool to improve the diagnosis of preterm birth


1. Liu, L., et al., Lancet **388**(10063), 3027–3035 (2016).
2. Lim, K., et al., J. Obstet. Gynaecol. Canada **40**(2), e151–e164 (2018).
3. McPheeters, M. L., et al., Am. J. Obstet. Gynecol. **192**(4), 1325–1329, Mosby Inc. (2005).

# The cervix: the orifice of the uterus

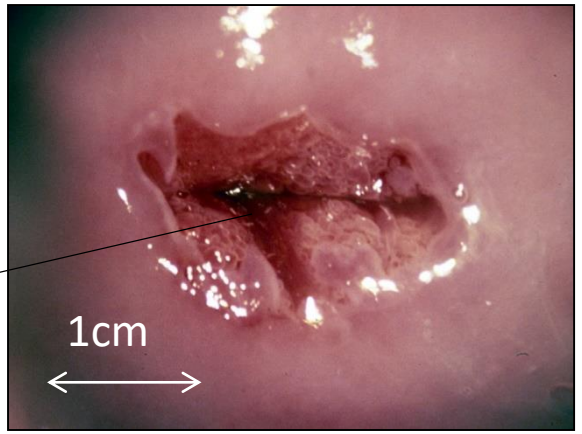
It mechanically keeps the fetus in the uterus



External os

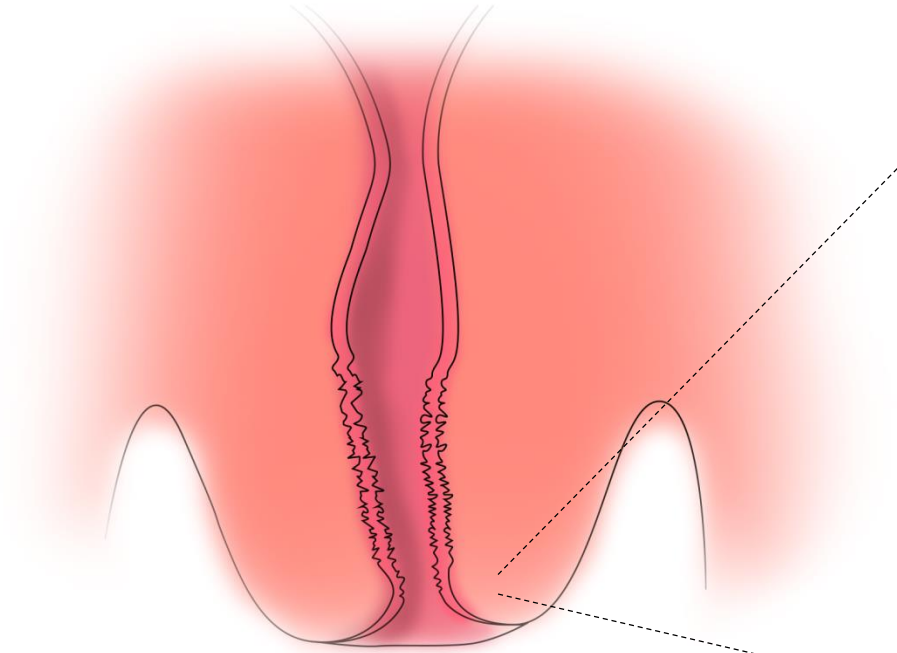
Cervix – frontal view



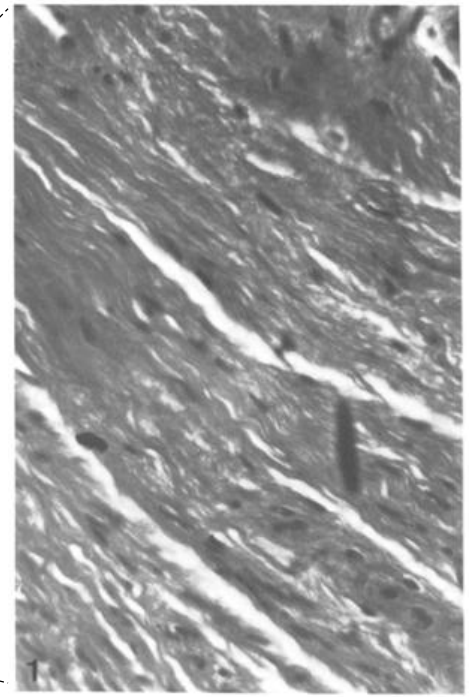

*Work lead by A. Pierangelo*

# The cervix: the orifice of the uterus

It mechanically keeps the fetus in the uterus



P. W. Theobald (1982)



Collagen plays an important role in mechanical poeprties of tissues

Collagenous connective tissue

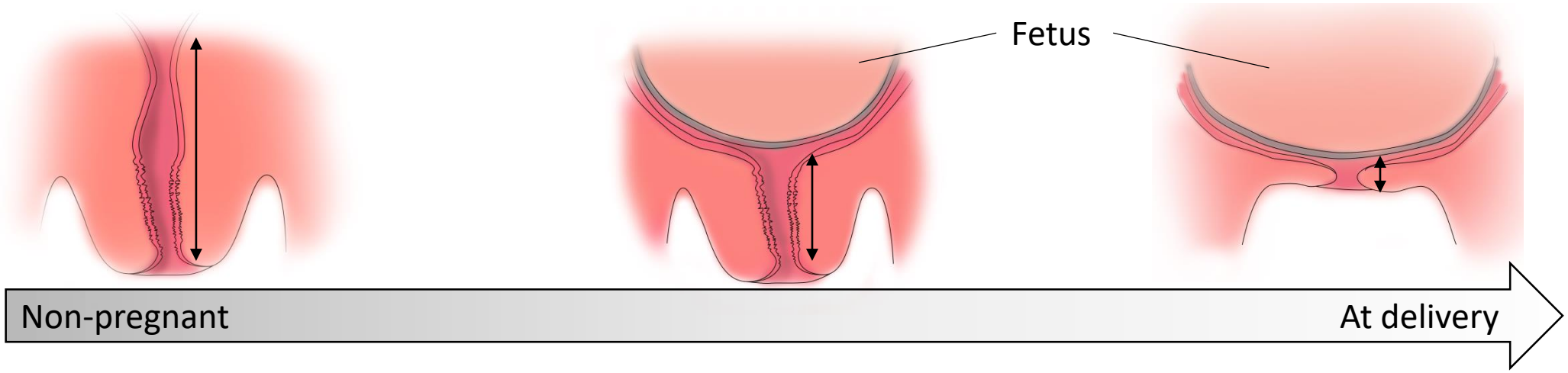
80% – Collagen
(70% type I, 30% type II collagen)

*Work lead by A. Pierangelo*

Created with BioRender.com

# Changes of the cervix during pregnancy

Macroscopic changes



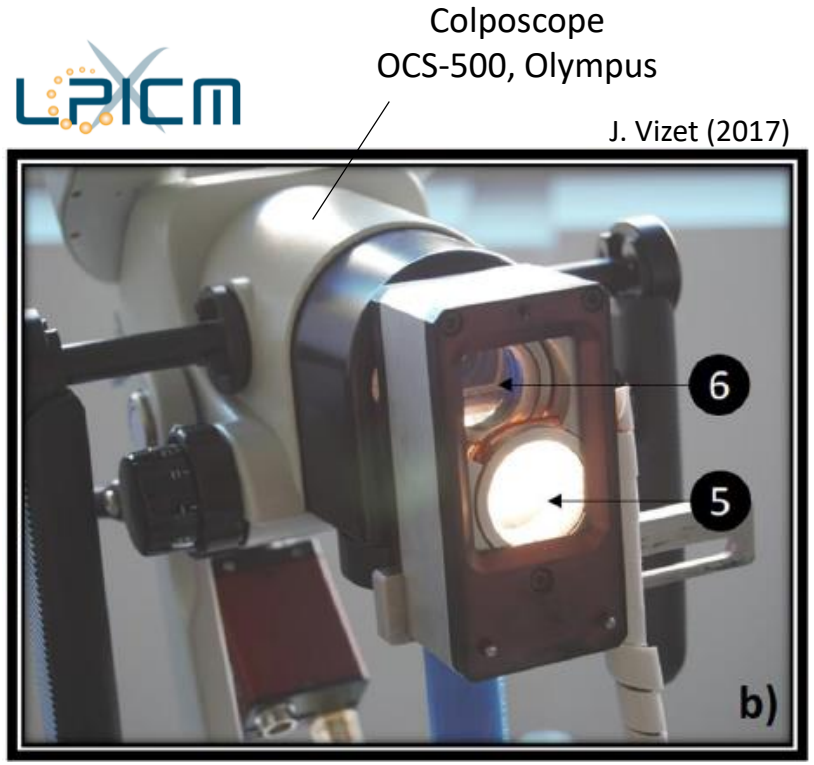

Microscopic changes

| | Not pregnant | At delivery |
|---|---|---|
| Hydration[4] ↑ | 75% | 81% |
| Collagen density[5] ↓ | | |
| Collagen solubility[4] ↑ | 32~40% | 80% |
| Stiffness[6] ↓ | 320±120 mbar | 53±26 mbar |


4. Myers, K., et al., Eur. J. Obstet. Gynecol. Reprod. Biol. **144**, S82–S89 (2009).
5. Akins, M., et al., J. Biomed. Opt. **15**(2), 026020 (2010).
6. Badir, S., et al., Prenat. Diagn. **33**(8), 737–741 (2013)

# The Mueller polarimetric colposcope (MPC)

The PSG and PSA are grafted on a colposcope




The Mueller polarimetric colposocpe
(5-PSG, 6-PSA)

**Specifications of imaging system**

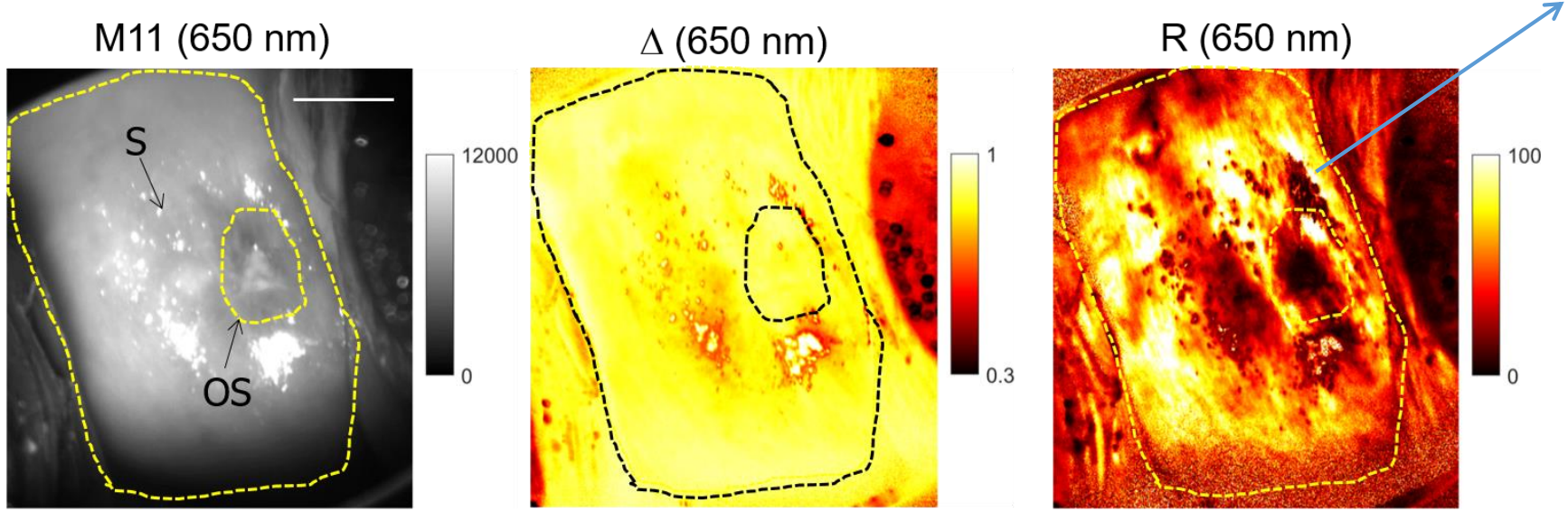
- Resolution: 800 X 600 pixels
- Field of view: 4X3 $cm^2$
- Wavelength: 650nm (FWHM: 40nm)
- FPS: 24 frames/s
- Light source: 300W Xenon

**Data collection**: 24 individual pregnant women

- A single examination for each patient
- Gestational age: 20-39 weeks
- Age: 16 – 41
- Primigravida: 12
- Multigravida: 12
- All timely delivered
- At the Brugmann university hospital in Brussels

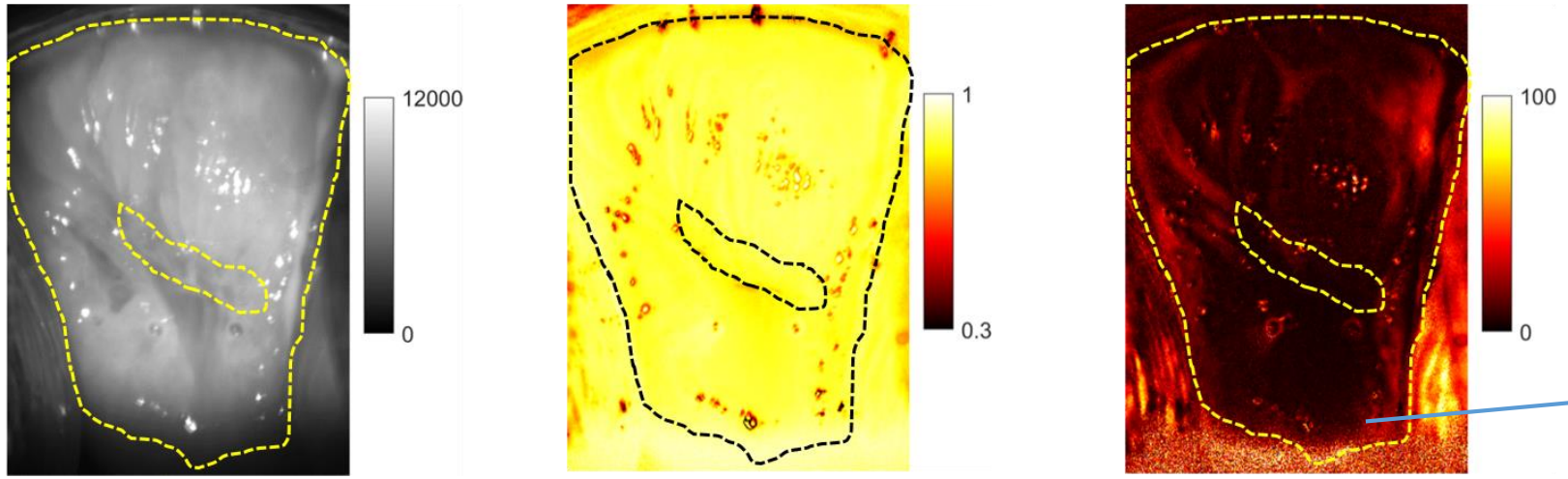
*Work lead by A. Pierangelo*

# Polarimetric contrasts for 2 patients




Squamous epithelium

Patient 1
29 weeks of amenorrhea and 3 days




Patient 2
28 weeks of amenorrhea and 5 days

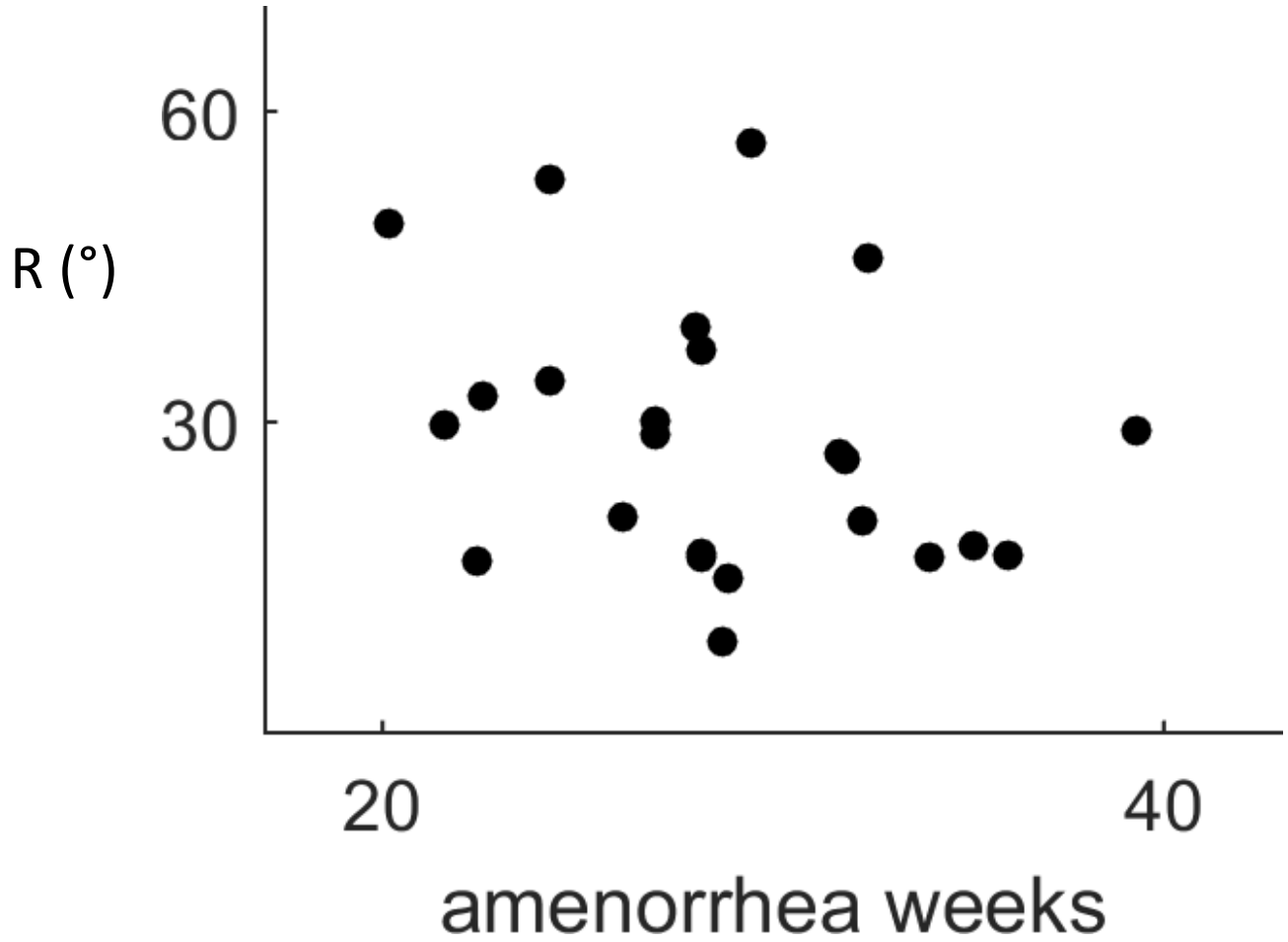
Glandular epithelium

*Work lead by A. Pierangelo*

Rehbinder, J., Vizet, J., Park, J. *et al.* Depolarization imaging for fast and non-invasive monitoring of cervical microstructure remodeling in vivo during pregnancy. *Sci Rep* **12**, 12321 (2022).

# Standardization of the term birth

Retardance does not correlate with gestational age



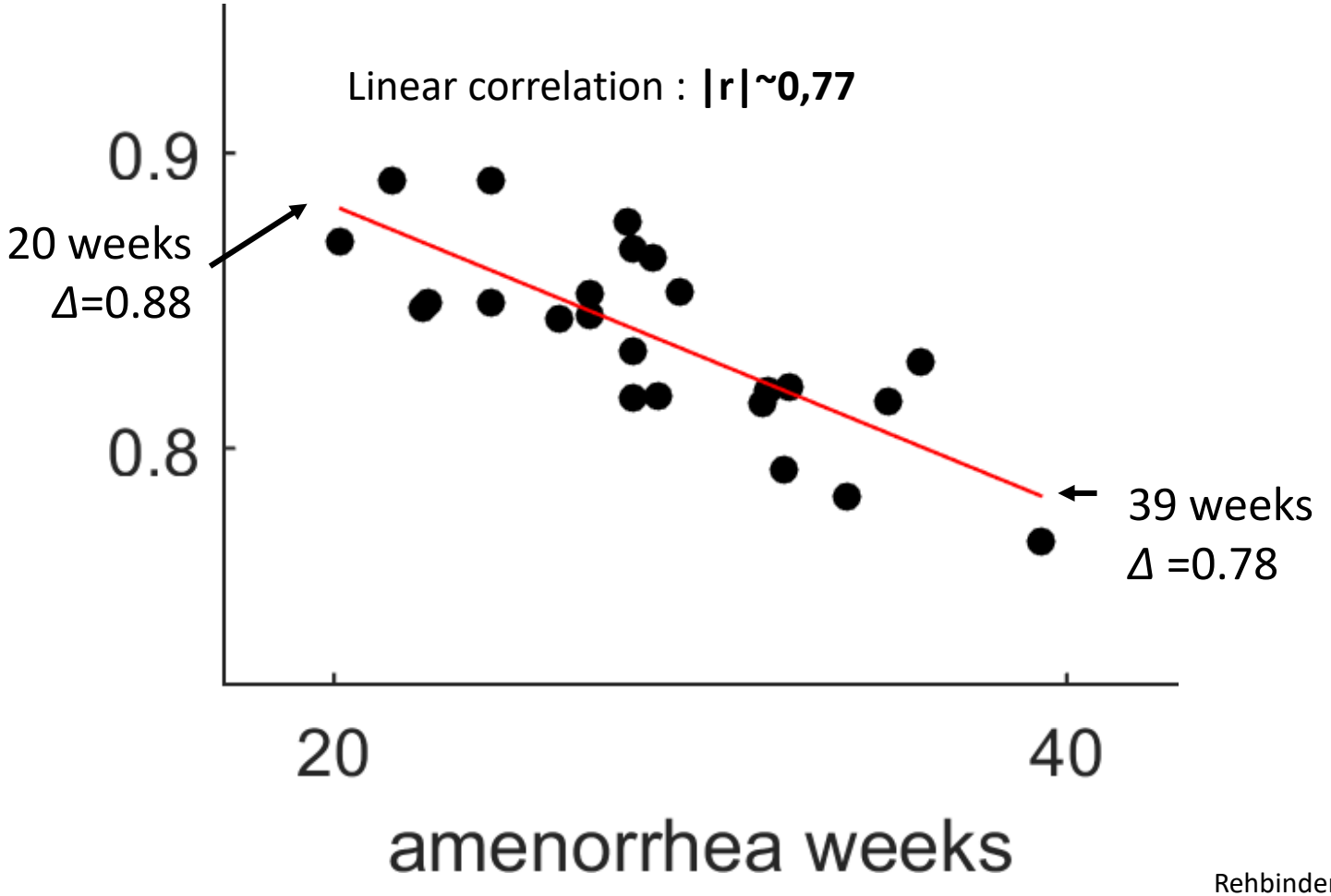

- Sensitive to the type of epithelium
- Probes only the surface

*Work lead by A. Pierangelo*

Rehbinder, J., Vizet, J., Park, J. *et al.* Depolarization imaging for fast and non-invasive monitoring of cervical microstructure remodeling in vivo during pregnancy. *Sci Rep* **12**, 12321 (2022).

# Standardization of the term birth

The cervix is losing depolarizing ability over the pregnancy



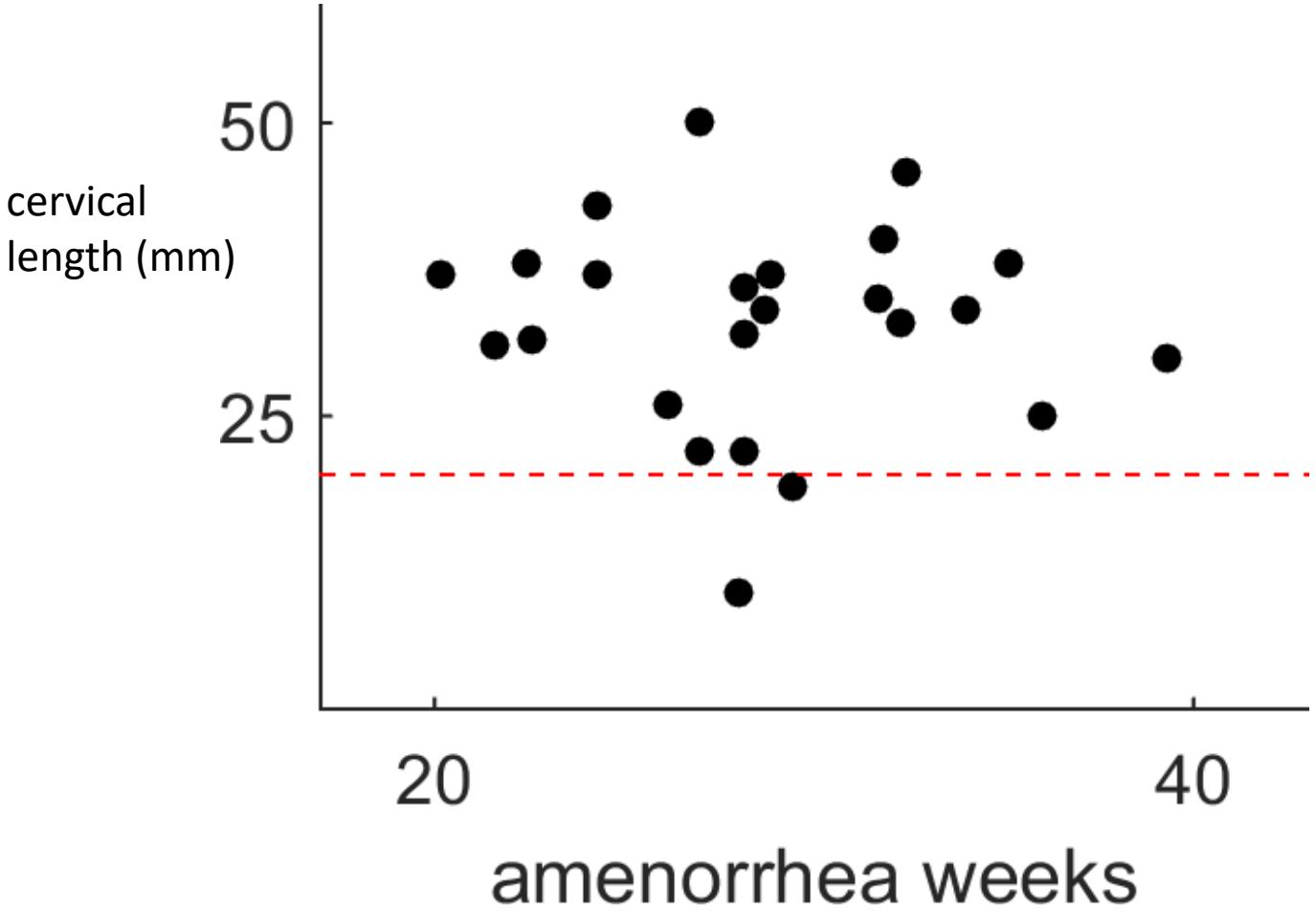

- Increased hydration[1] (particle density ↓)
- Decreased collagen density[2]
- Probes the volume scattering properties (less sensitive to the surface structure)

*Work lead by A. Pierangelo*

Rehbinder, J., Vizet, J., Park, J. *et al.* Depolarization imaging for fast and non-invasive monitoring of cervical microstructure remodeling in vivo during pregnancy. *Sci Rep* **12**, 12321 (2022).

# Standardization of the term birth

We have observed no trend in cervical length measurements




- Patients below the threshold for risk of preterm birth did delivered at term

*Work lead by A. Pierangelo*

Rehbinder, J., Vizet, J., Park, J. *et al.* Depolarization imaging for fast and non-invasive monitoring of cervical microstructure remodeling in vivo during pregnancy. *Sci Rep* **12**, 12321 (2022).

# Conclusion preterm birth

- The **depolarization** of the cervical tissue is decreasing during pregnancy.
- It reflects the cervical maturation during pregnancy.
- The depolarization parameter at **650 nm** is promising to define a standardization curve on a cohort of patient to follow the steady progression of pregnancy.
- A clinical study of 2 groups (normal vs preterm) is being carried out to figure out the longitudinal changes on 650 patients.

ANR Digit MC-PB

Clinical study *in vivo* on 650 patients (2000 Colposcopies)
Started december 2020 (Duration 36 mois)

*Work lead by A. Pierangelo*

# Polarimetry at ICube (Strasbourg)

**1**

- Polarization imaging at LSIIT in 1997
- Construction of several instruments
- Medical applications: data processing, collaboration with LPICM, ANR

**2**

- Patent for ultra-stable modulators
- POLARIS project (SATT)
- SATT : Transfer (IHU, Aesculap, Sakura, Storz, ...)

**3**

- SATT maturation support (Dermapol project)
- Clinical trial
- ARCHOS and creation of POLADERME in October 2021
- Filing of a new patent for the POLADERME solution
- POLADERM is owned by MDV and listed on the stock exchange on 10/02/2022

*Courtesy J. Zallat*

# Polarimetry at ICube (Strasbourg)

Evolution of the prototypes

**POLARIS**

**Dermapol**

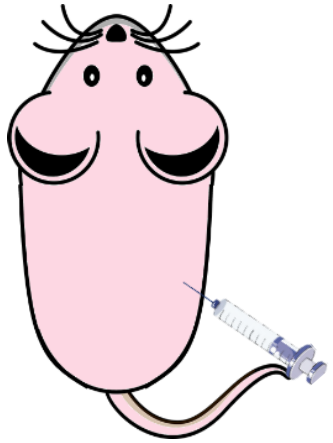
**Dermatoscope connecté (startup Poladerme)**

# Polarimetry at ICube (Strasbourg)

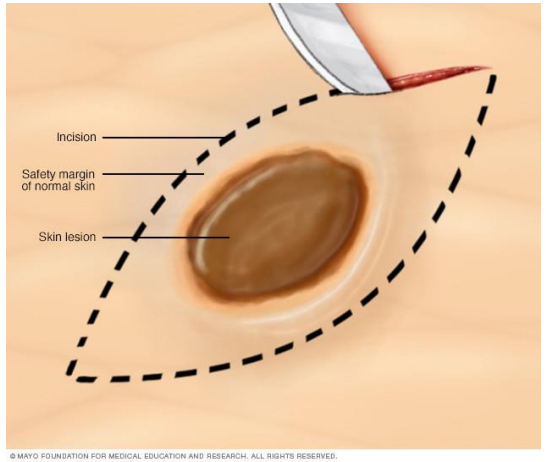
| POLARIS | Dermapol | Dermatoscope connecté |
|---|---|---|
| **Preuve de concept** | **Etude sur le petit animal et étude clinique** | **Industrialisation** |
| • ~1 m x 1 m<br>• ~50-100 k€<br>• Statique | • ~50 cm x 10 cm<br>• ~20-25 k€<br>• Transportable | • ~10 cm x 5 cm<br>• <100 €<br>• Connecté |
| • Image de Mueller complète<br>• Caméra scientifique<br>• Mesures ex-vivo | • Image de Mueller complète<br>• Caméra scientifique<br>• Mesures ex-vivo et in-vivo | • Etats de polarisation discrets + stéréo-photométrie + stéreo-vision<br>• 5 caméras smartphone<br>• Machine learning, IA |

# Dermapol

- **Non-invasive**
- **Sensitive to the organisation of the tissue**
- **Label-free**
- **Quick measurement**



evolution of grafted tumors in mice with and without treatment



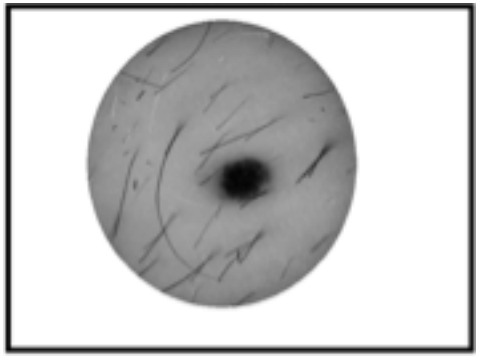

Clinical trial at Hôpital Civil of Strasbourg

Acquisition on all types of skin lesions, before biospy

# Polarimetric signatures for skin lesions

Visuel standard

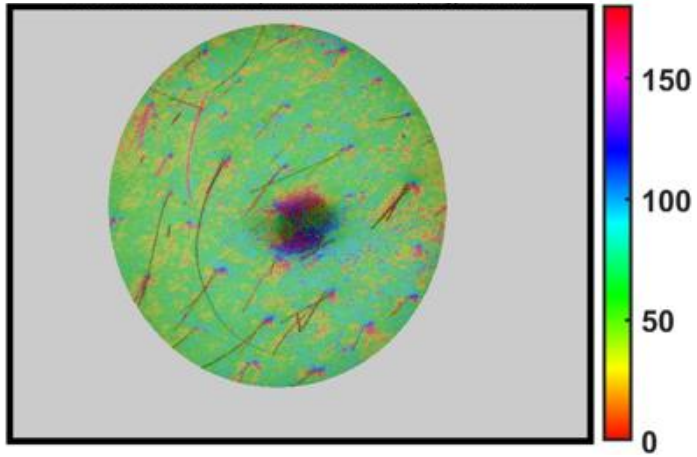
Intensité



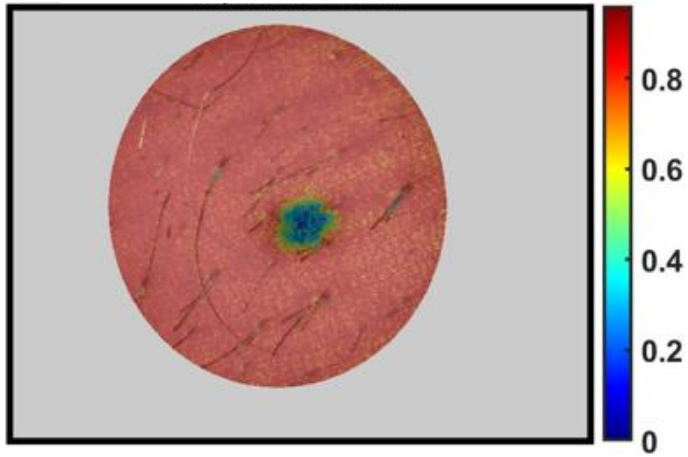
Naevus

**POLADERME**

Orientation de l'axe rapide du retardeur (deg) – 680 nm




Dépolarisation – 680 nm

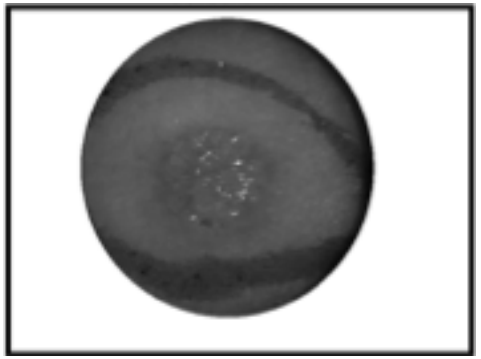



*Courtesy J. Zallat*

# Polarimetric signatures for skin lesions

Visuel standard

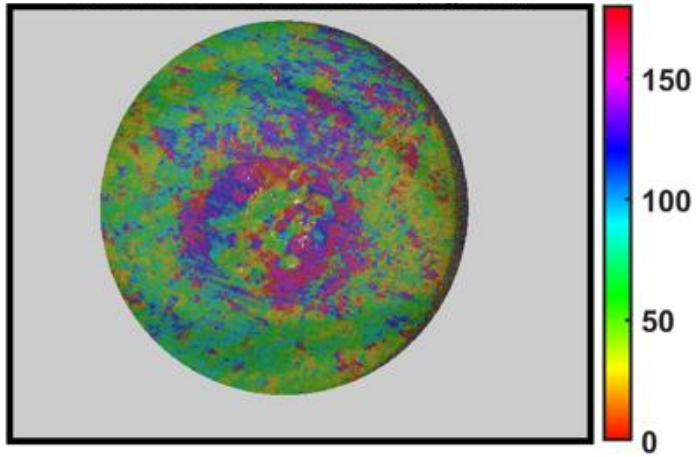
Intensité



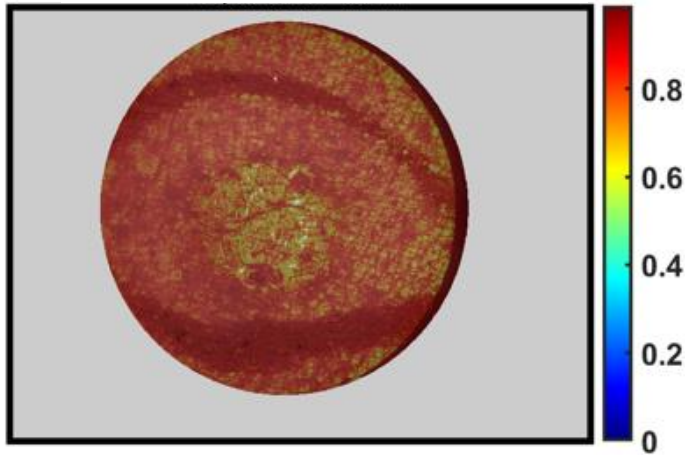
Carcinome basocellulaire

**POLADERME**

Orientation de l'axe rapide du retardeur (deg) – 680 nm




Dépolarisation – 680 nm

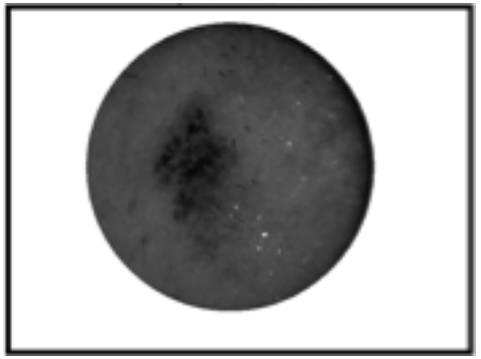



*Courtesy J. Zallat*

# Polarimetric signatures for skin lesions

Visuel standard

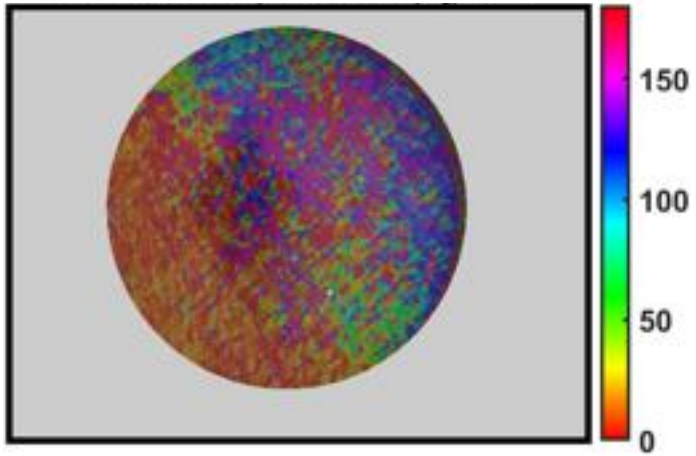
Intensité



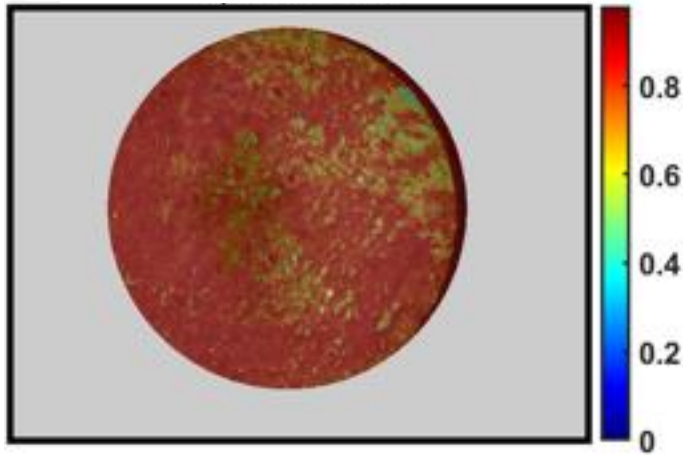
Mélanome

**POLADERME**

Orientation de l'axe rapide du retardeur (deg) – 680 nm

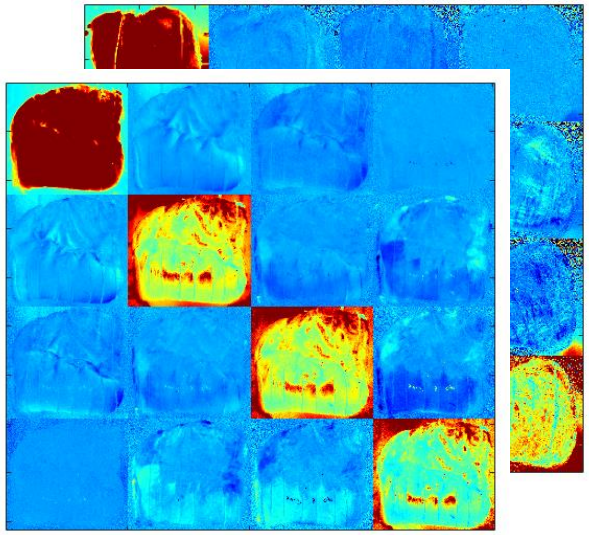



Dépolarisation – 680 nm



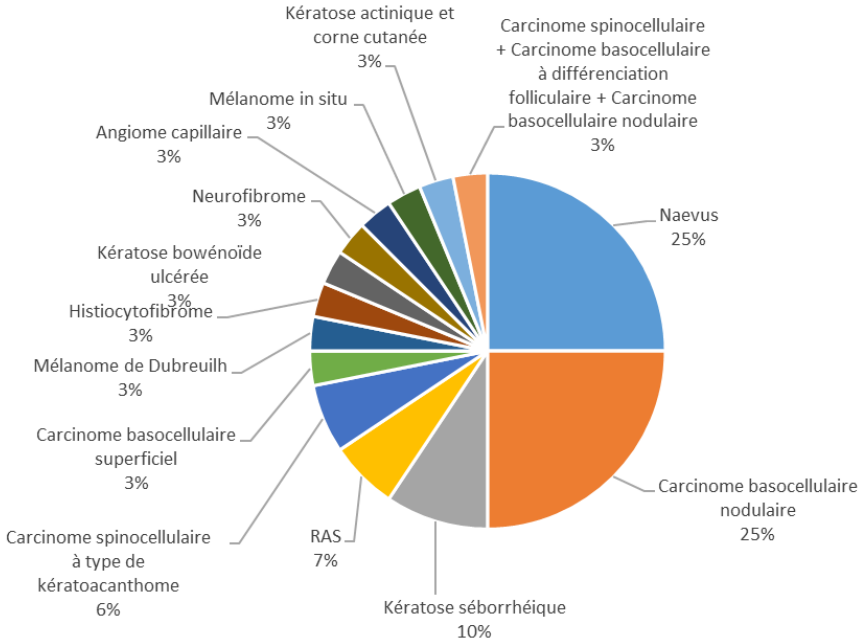

*Courtesy J. Zallat*

# Polarimetry and machine-learning



Database of polarimetric images

...



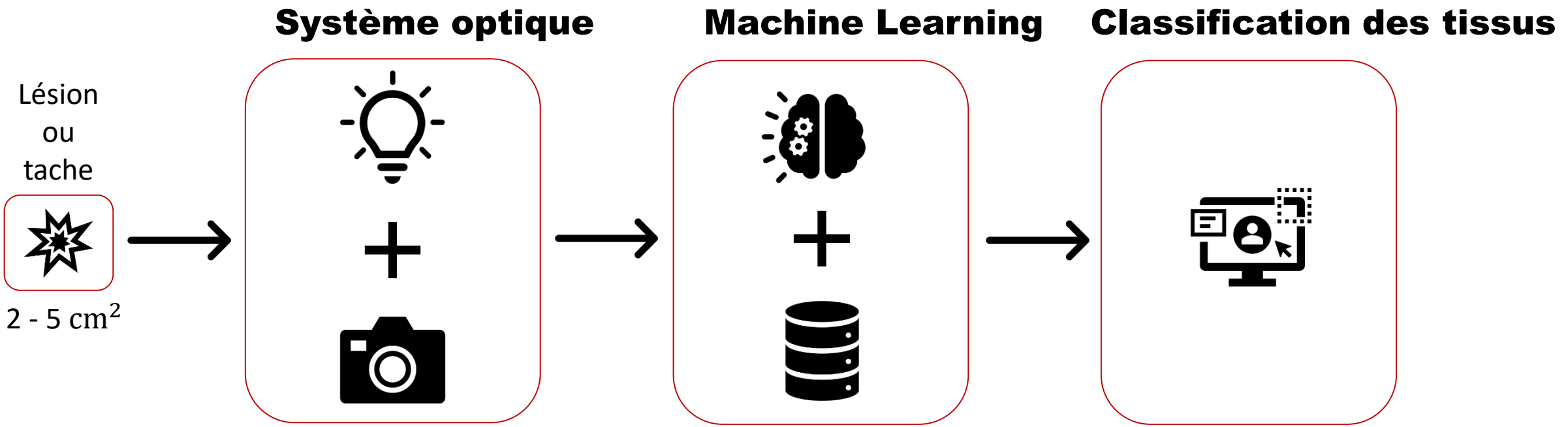

Ground truth labelling

## Problem : Scarcity of (clinical) data

- ~~Complexity of the prototype~~
- ~~Manpower for data collection~~
- ~~Ground truth expensive (histology)~~


*Courtesy J. Zallat*

# La solution Poladerme




*Courtesy J. Zallat*

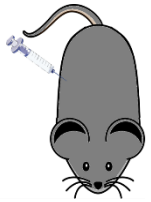
# Conclusion Poladerme

| | Dermatoscope | POLADERME |
|---|---|---|
| Grossissement | ✓ | ✓ |
| Éclairage | ✓ | ✓ |
| Analyse de la qualité du collagène | ✗ | ✓ |
| Vascularisation | ✗ | ✓ |
| État de surface de la peau | ✗ | ✓ |
| Orientation des fibres | ✗ | ✓ |
| Information biomécanique | ✗ | ✓ |

*Courtesy J. Zallat*

# Outlook Poladerme

**2017**: Prototype de laboratoire



**2019**: Études préliminaires sur des souris et des humains

2021

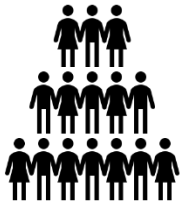
Démarrage de l'entreprise, 1er année

TRL


Miniaturisation et fabrication

Certification CE, classe IIa, EN 60601, EN 62304

CE



Études cliniques

*Courtesy J. Zallat*

# « Take-home » messages

**Optical Imaging can provide:**

- Label-free contrasts, sensitive to the micro-organization and chemical composition of tissues !
- Histological insights *in-vivo* !
- Video-rate imaging !
- A broad range of complementary techniques (not all described in this talk)

Limitations and challenges:

- “Medical is hard” – technical hurdles + tricky to find the right business model + slow adoption of new techniques
- What can be published ≠ what can be marketed

# A bright future for optical medical imaging

**Optical Biopsy:**

- Optical imaging for prevention/screening, conventional medical imaging for treatment
- “Virtual staining” for histopathology
- Low-resource settings

**ML&AI:**

- Increased information content through optical techniques → diagnostic aid extracted using machine-learning algorithms

**Point-of-Care testing:**

- Shortage of doctors, medical deserts
- Availability of smartphones (light source + camera + computing power)

# Thank you for listening !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