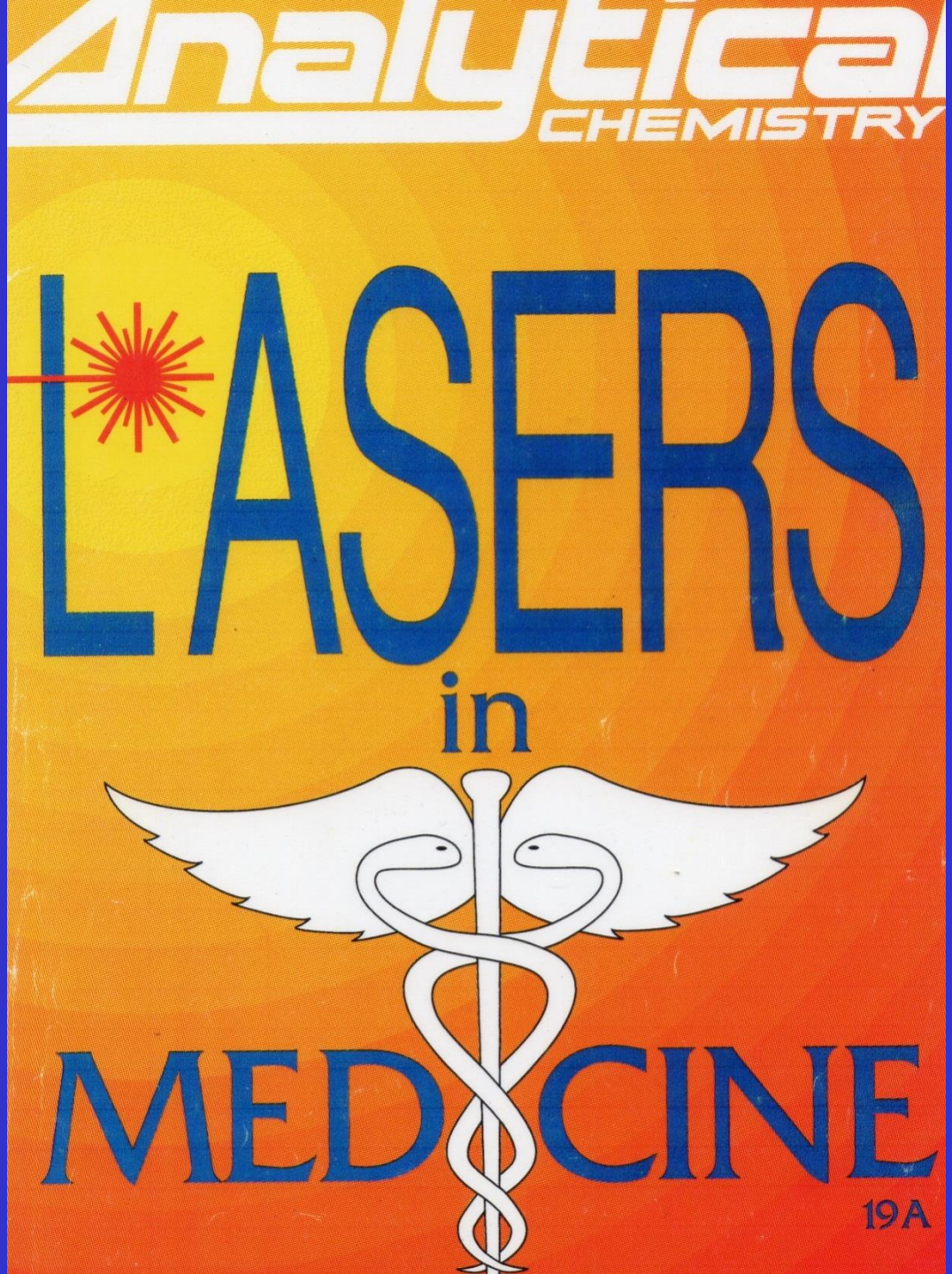
BIOFOTONIK I LUND

Sune Svanberg

Atomfysik, LTH
LLC/LUMLAC
Lunds Universitet

LUMLAC: www.mlc.lu.se



Analytical Chemistry Review by Lund University Researchers (1989)

Lund Laser Medicine Group 1983 - Medical Laser Centre 1991 -

Laser-Induced Fluorescence Studies of Hematoporphyrin Derivative (HPD) in Normal and Tumor Tissue of Rat

Appl. Spectr. 1984

J. ANKERST, S. MONTÁN, K. SVANBERG, and S. SVANBERG

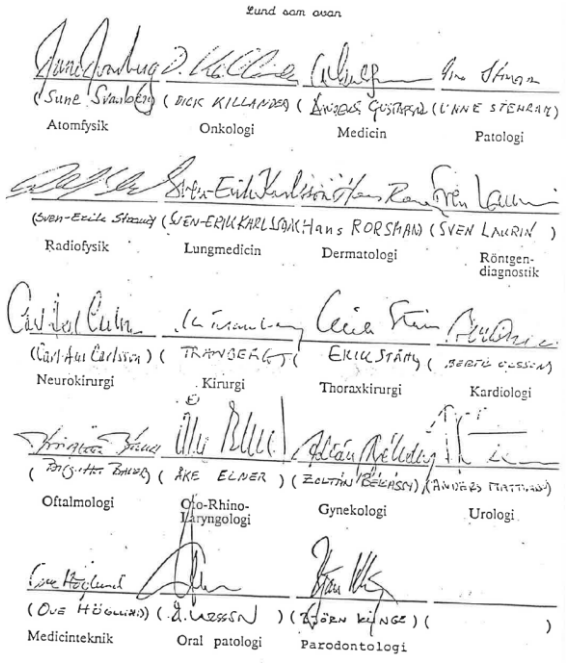
Multicolor imaging and contrast enhancement in cancer-tumor localization using laser-induced fluorescence in hematoporphyrin-derivative-bearing tissue

Optics Lett. 1985

S. Montán, K. Svanberg,* and S. Svanberg

1990 LUMLAC Proposal

Framställan om inrättande av ett för Medicinska och Tekniska Fakulteten gemensamt Medicinskt Lasercentrum



Present biophotonics in Lund (partial list)

N. Reistad, Chr. Sturesson *et al. Tissue spectr.*

V. Fellman, E.Krite-S. et al., *oxygenation*

S. Kröll, L. Edvinsson et al., *Slow light appl.*

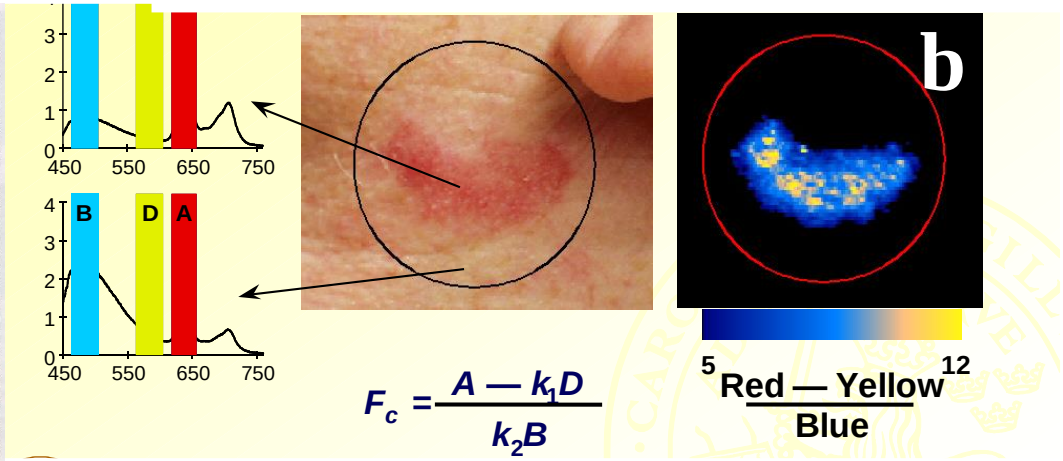
M. Malmsjö, N. Reistad et al. *Clin. Ph.acoust.*

J. Bood et al. *GASMAS*

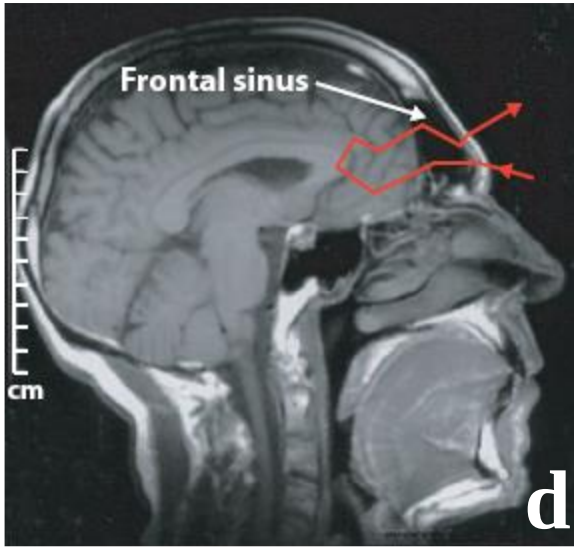
N. Bendsoe, Persson et al. *Dermal PDT*

Spectracure AB, Gasporox AB, GPX Medical ..

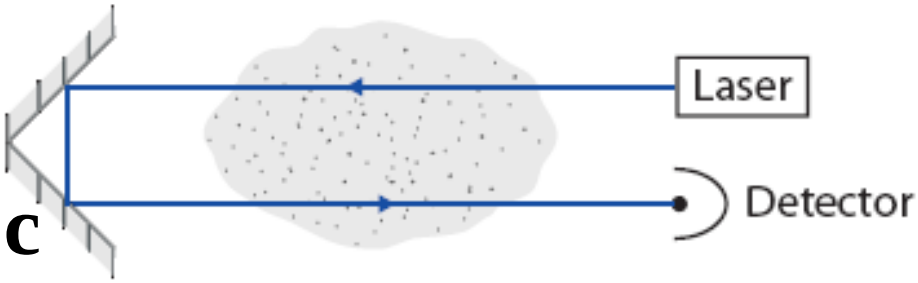
Example of Cross-Disciplinary Approach at Lund University: Environmental Monitoring connected to Biophotonics



Medicine



Environment

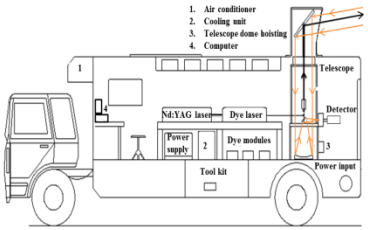


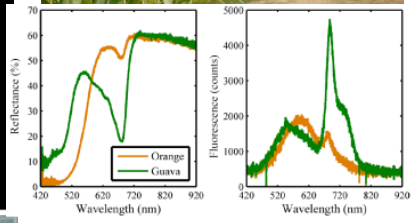
Along the same lines:

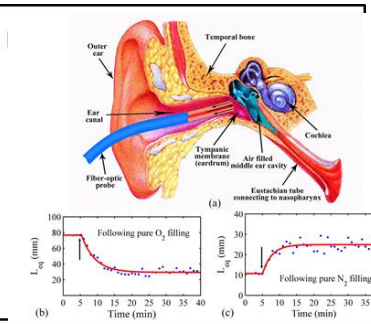
Interdisciplinary Sensing Group in Applied Laser Spectroscopy
South China Normal University, Guangzhou

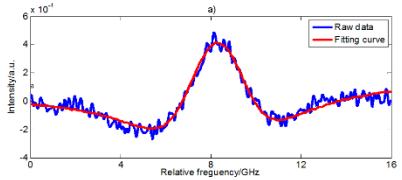
(Katarina Svanberg, Sune Svanberg; LU researchers with part-time China affiliation)

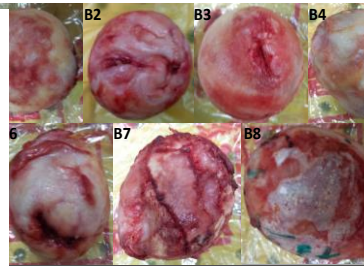
Environment - Ecology - Agriculture - Food Safety - Biomedicine

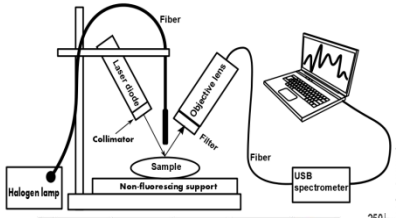


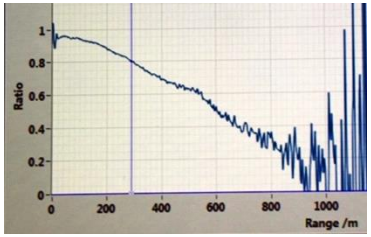


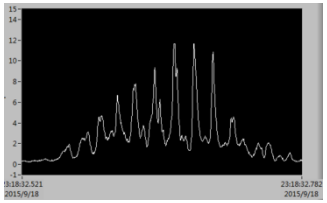


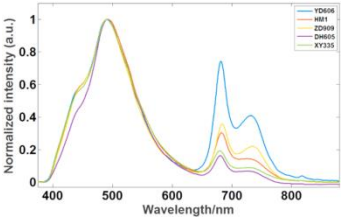


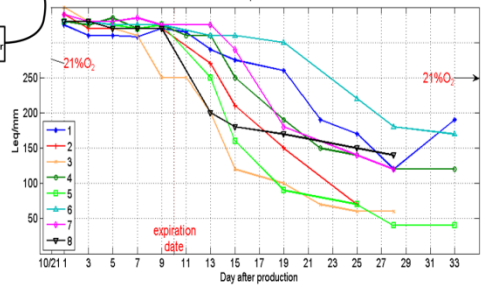




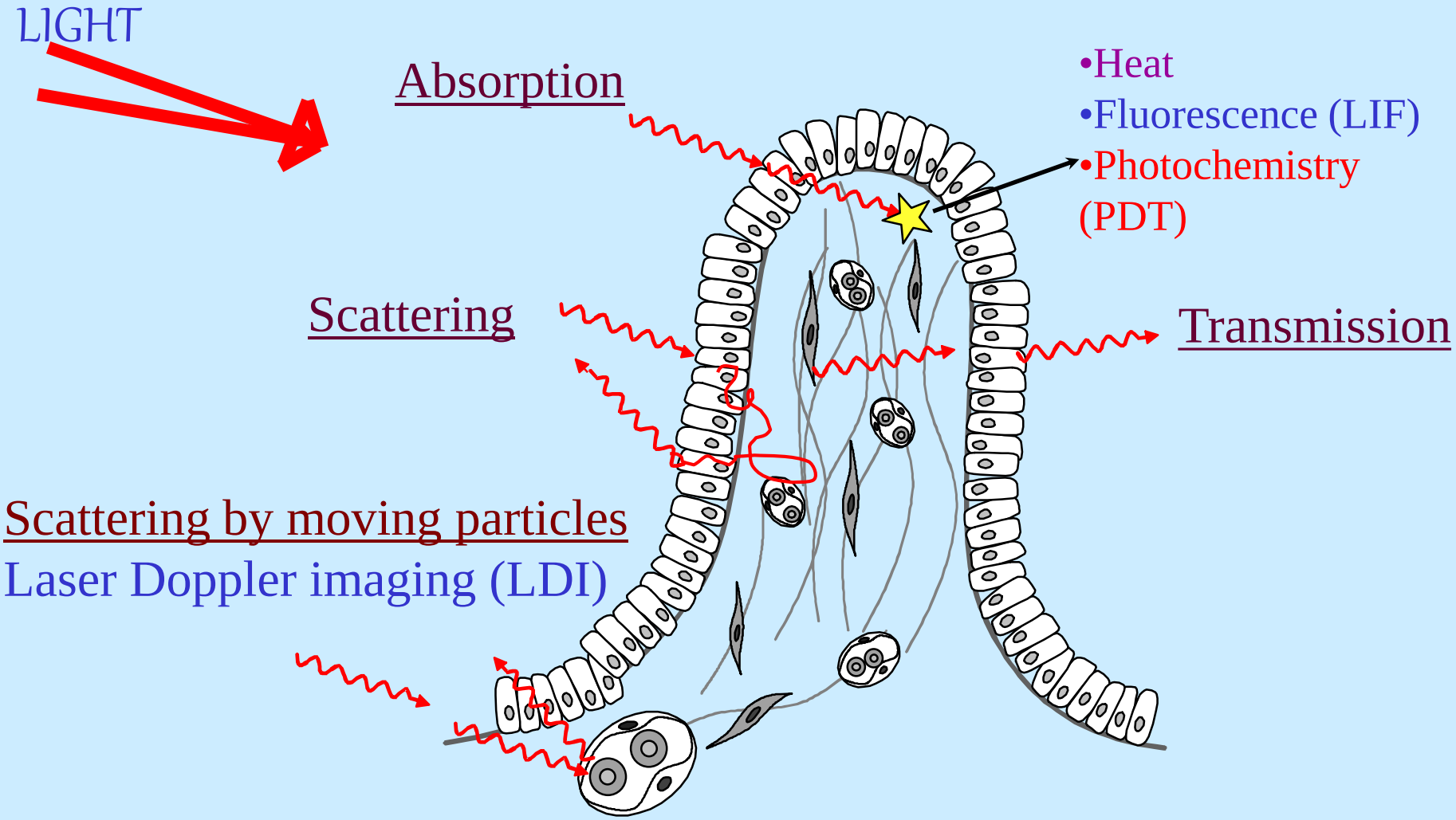








Light-tissue interaction



Ingrid Wang

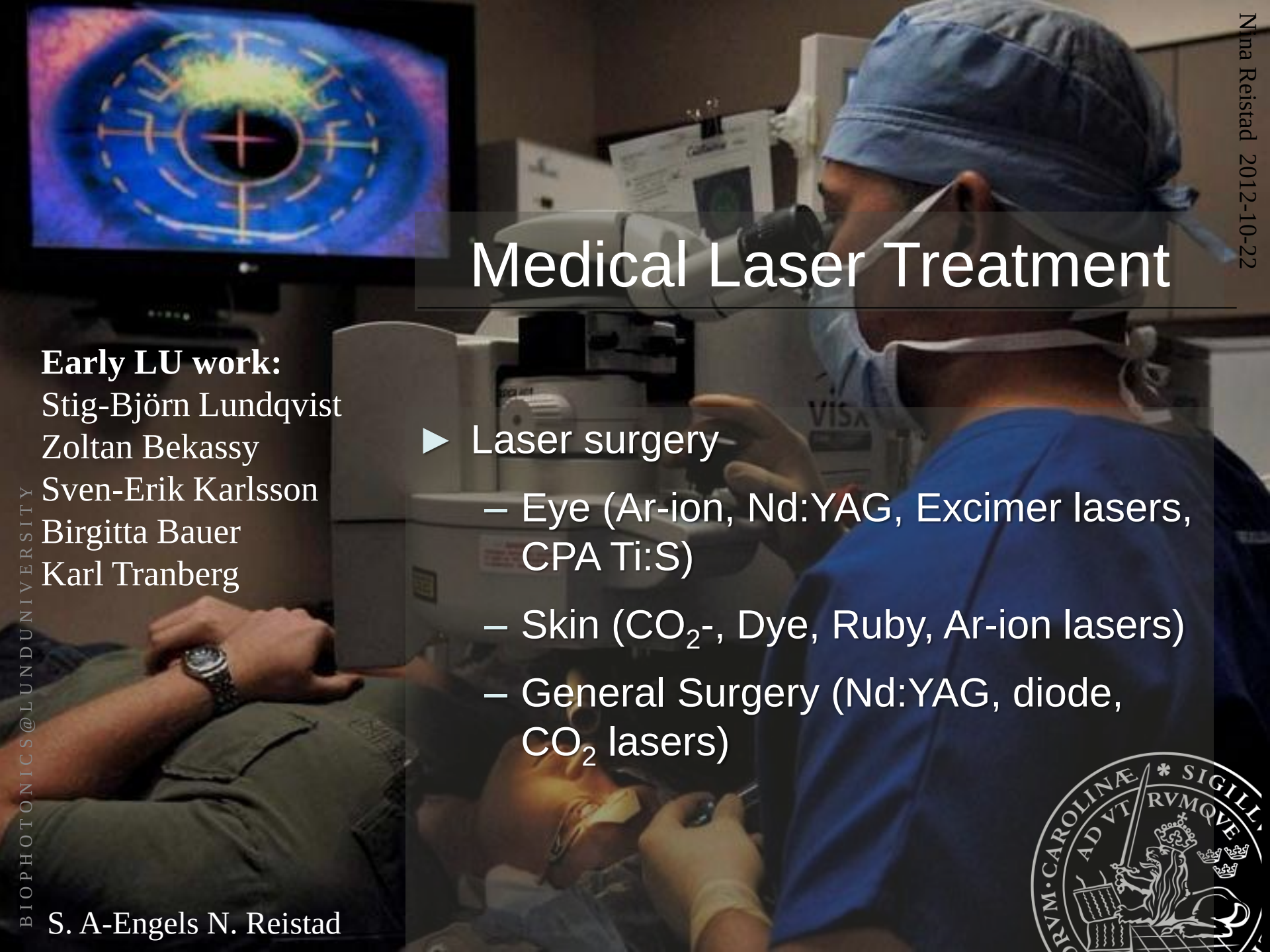
Tissue optics equations

$$I(\rho, d, t) = (4\pi Dv)^{-3/2}\, t^{-5/2} \times \exp\left(-\mu_a v t - \frac{\rho^2}{4Dvt}\right) \times \sum_{k=0}^{+\infty}\left[z_{-k}\exp\left(-\frac{r_{-k}^{\,2}}{4Dvt}\right) - z_{+k}\exp\left(-\frac{r_{+k}^{\,2}}{4Dvt}\right)\right],$$

$$\langle t\rangle = \frac{\sum_{k=0}^{\infty}\left[\frac{z_{+k}}{r_{+k}}\exp(-\mu_{\text{eff}}\, r_{+k}) - \frac{z_{-k}}{r_{-k}}\exp(-\mu_{\text{eff}}\, r_{-k})\right]}{2vD\sum_{k=0}^{\infty}\left[\frac{z_{+k}}{r_{+k}^{\,3}}(1+\mu_{\text{eff}}\, r_{+k})\exp(-\mu_{\text{eff}}\, r_{+k}) - \frac{z_{-k}}{r_{-k}^{\,3}}(1+\mu_{\text{eff}}\, r_{-k})\exp(-\mu_{\text{eff}}\, r_{-k})\right]},$$

$$I(\rho, d) = \frac{1}{2\pi}\sum_{k=0}^{\infty}\left[\frac{z_{-k}}{r_{-k}^{\,3}}(1+\mu_{\text{eff}} r_{-k})\exp(-\mu_{\text{eff}} r_{-k} - \frac{z_{+k}}{r_{+k}^{\,3}}(1+\mu_{\text{eff}} r_{+k})\exp(-\mu_{\text{eff}} r_{+k})\right].$$

Monte Carlo simulations

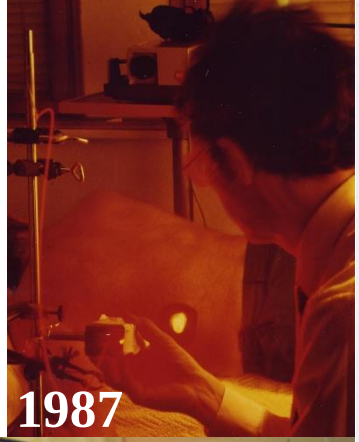


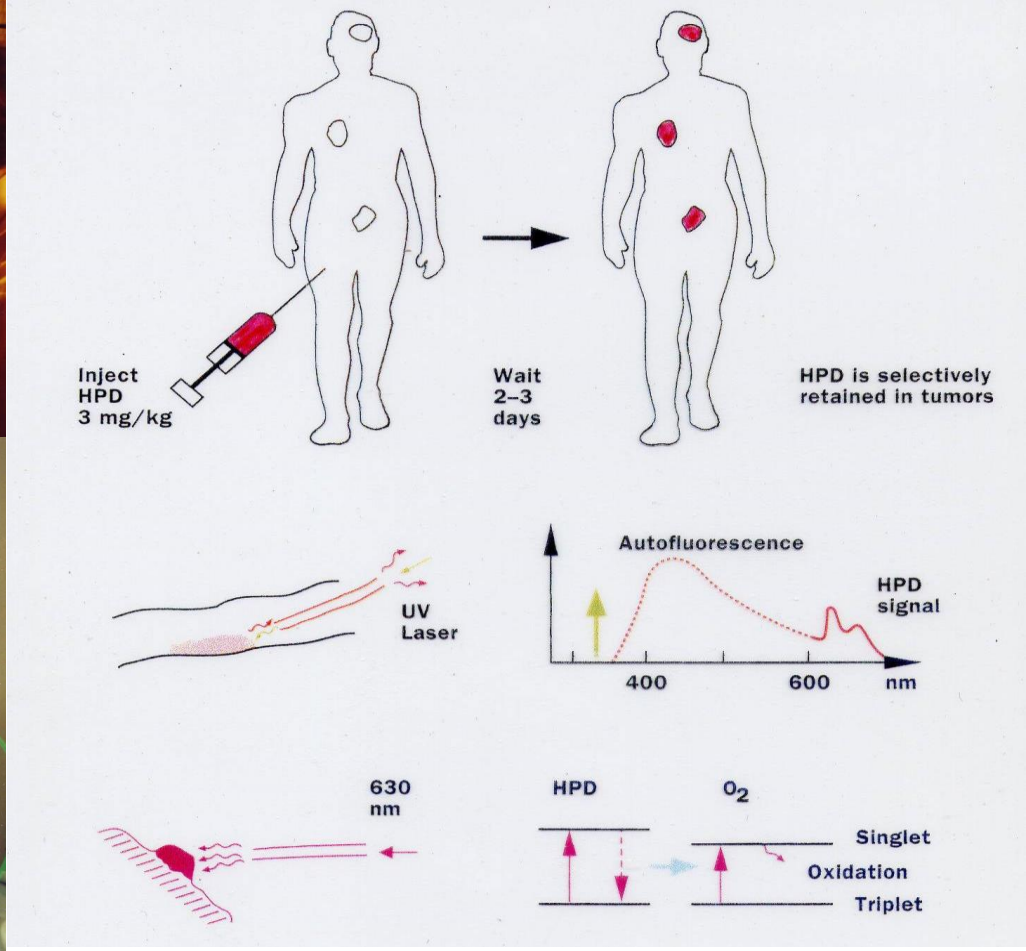
Medical Laser Treatment

Early LU work:
Stig-Björn Lundqvist
Zoltan Bekassy
Sven-Erik Karlsson
Birgitta Bauer
Karl Tranberg

- Laser surgery
  - Eye (Ar-ion, Nd:YAG, Excimer lasers, CPA Ti:S)
  - Skin (CO_2-, Dye, Ruby, Ar-ion lasers)
  - General Surgery (Nd:YAG, diode, CO_2 lasers)

Photodynamic therapy (PDT) of malignant tumours

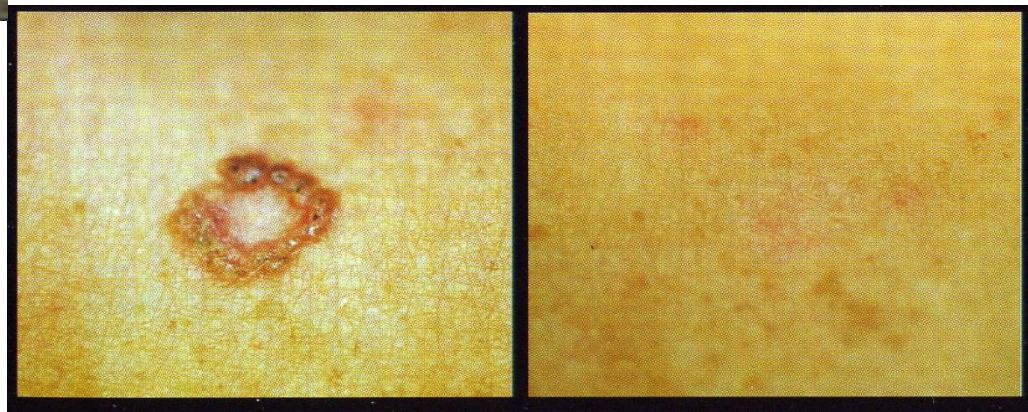




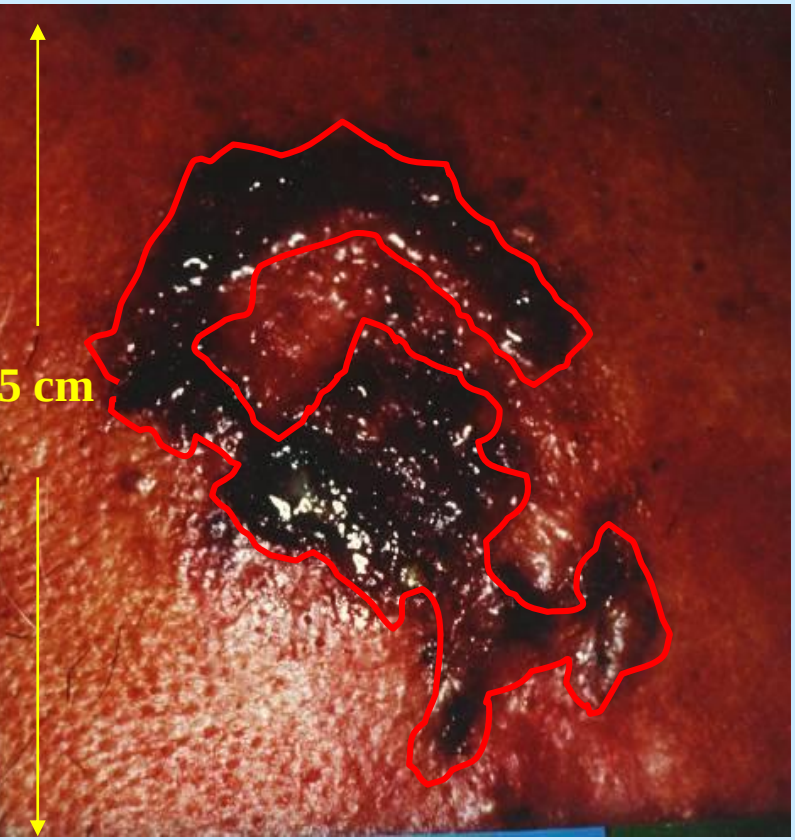
Coll.: D. Killander, T. Andersson, N. Bendsoe

PDT of basal cell carcinoma and squamous cell carcinoma

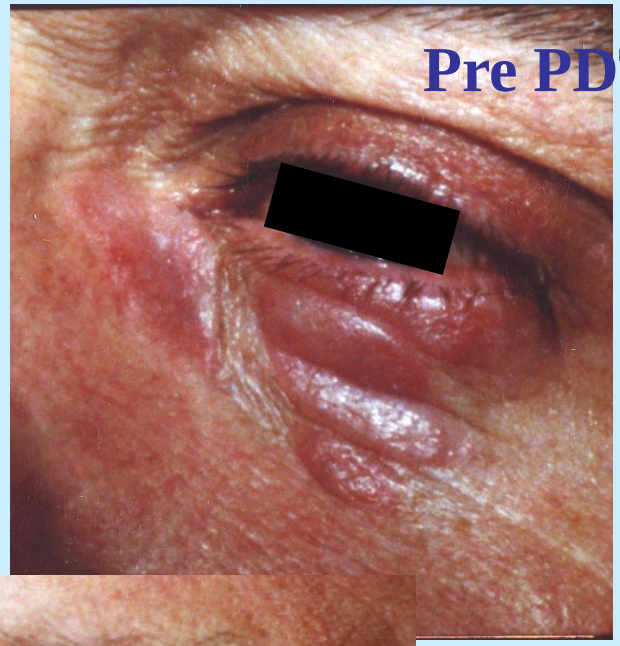
Br. J. Derm. (1994)

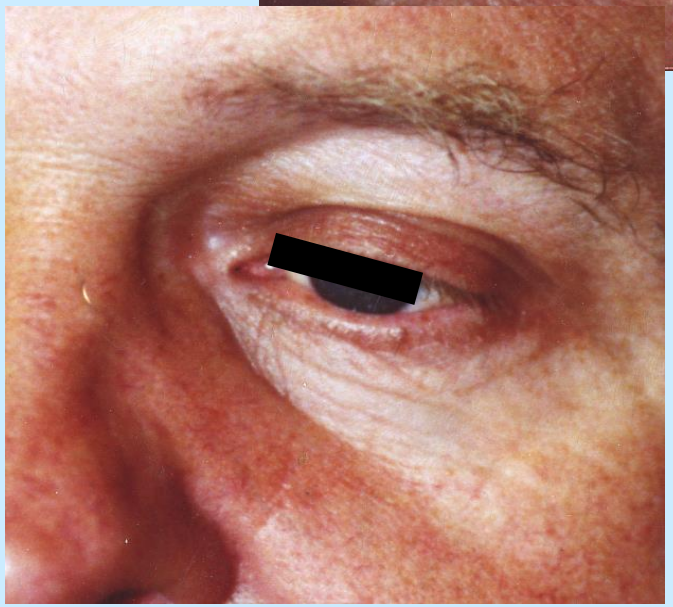


Photodynamic Therapy – a local tumour treatment with selectivity
Interaction involving: light, sensitizer and tissue oxygen



Nodular basal cell carcinoma



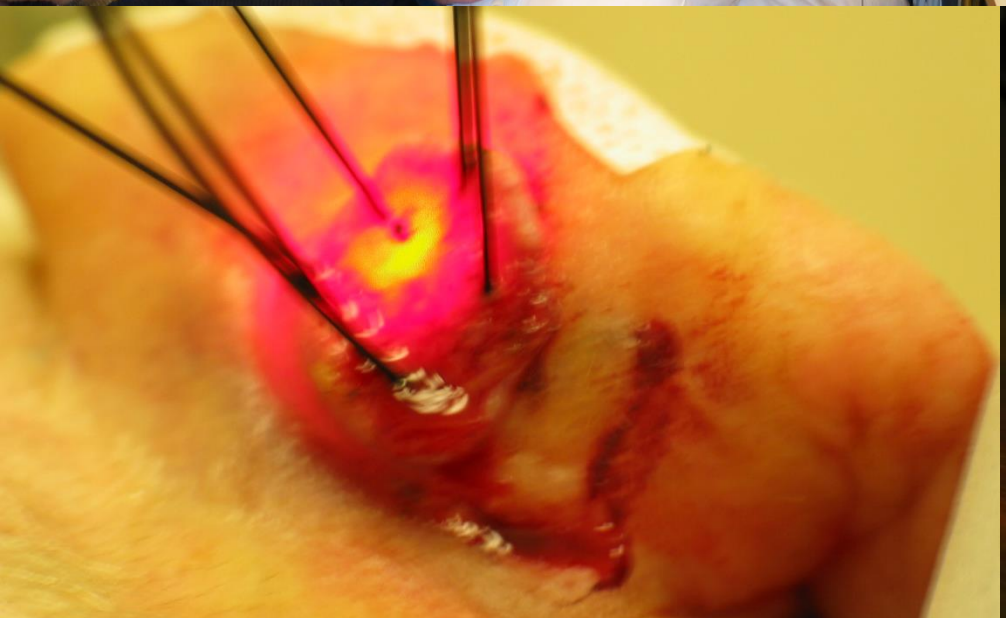


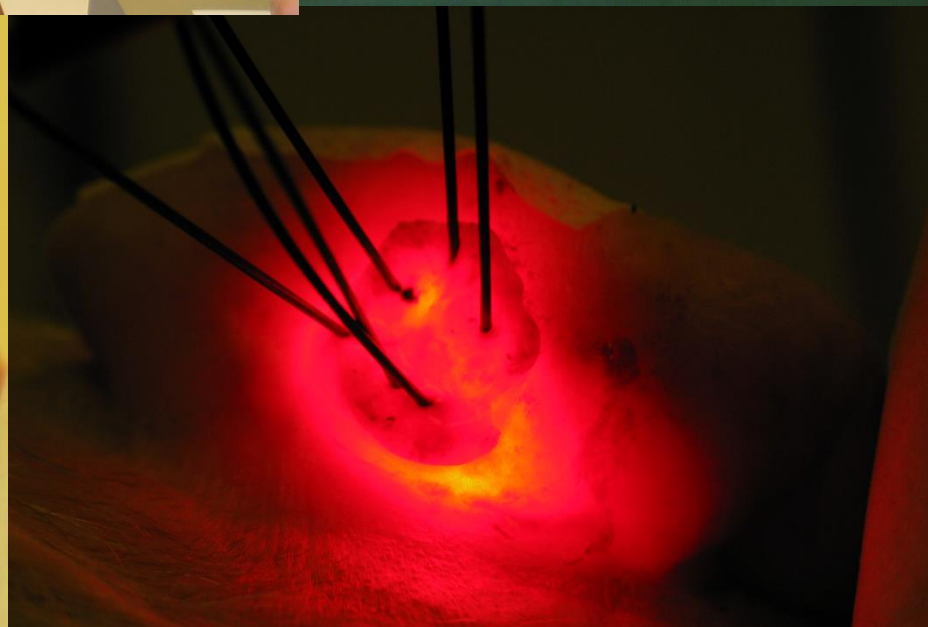
9 months post PDT

In Lund we have PDT-treated 2500 skin malignancies & performed Phase III clinical trials.

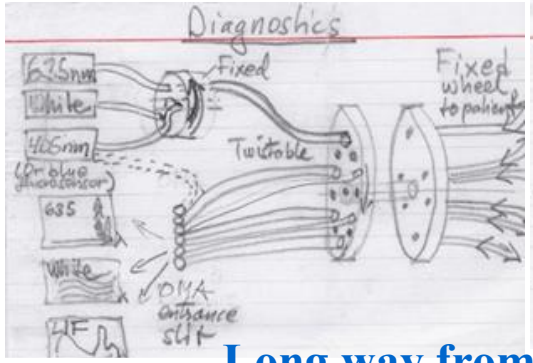
1. I. Wang, B. Bauer, S. Andersson-Engels, S. Svanberg and K. Svanberg, Photodynamic Therapy Utilizing Topical δ-Aminolevulinic Acid in Non-Melanoma Skin Malignancies of the Eyelid and the Periocular Skin, Acta Opthal. Scand. **77**, 182 (1999)

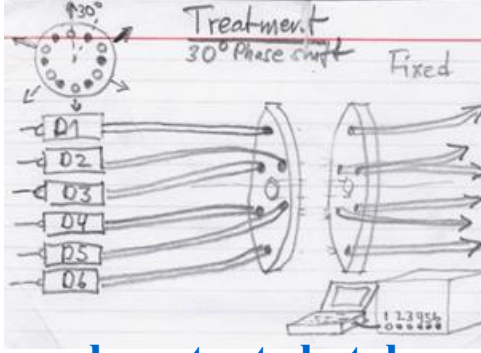
Interstitial Photodynamic Tumour Therapy



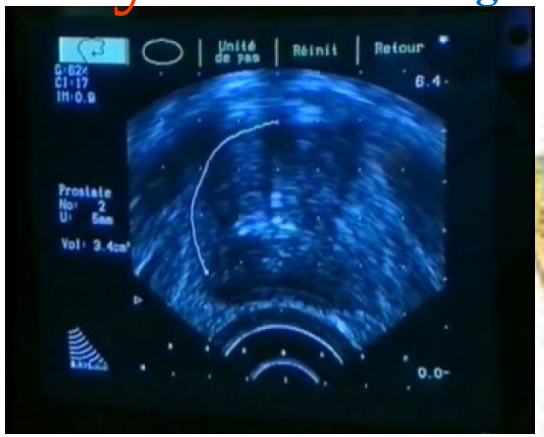


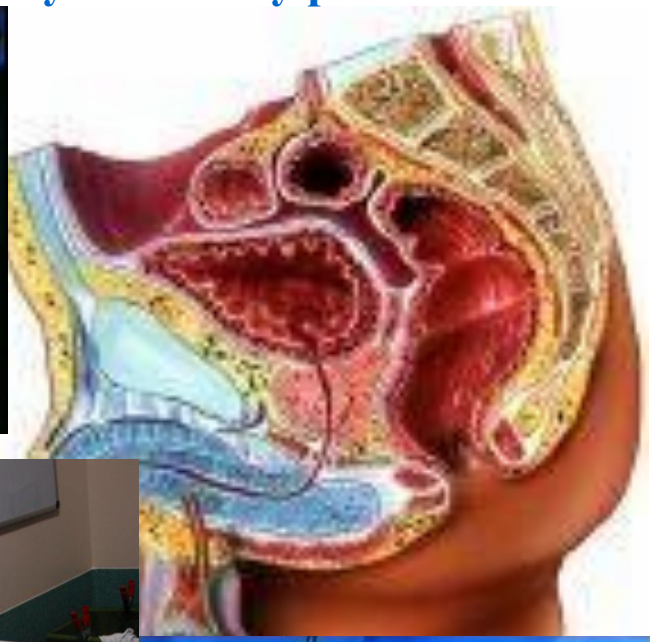
PDT interstitial treatment of recurrent prostate cancer integrated with dosimetry

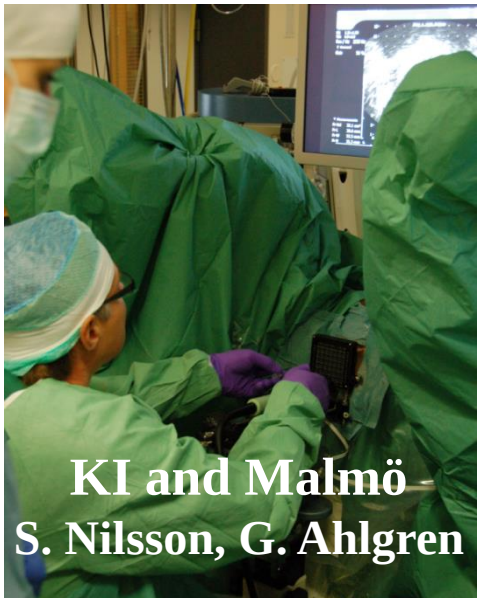




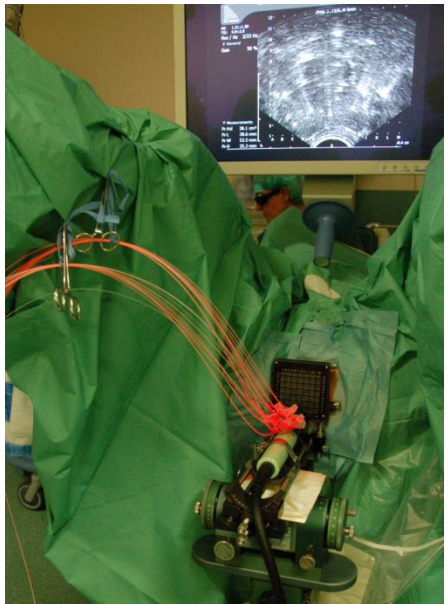
Long way from early patent sketch …

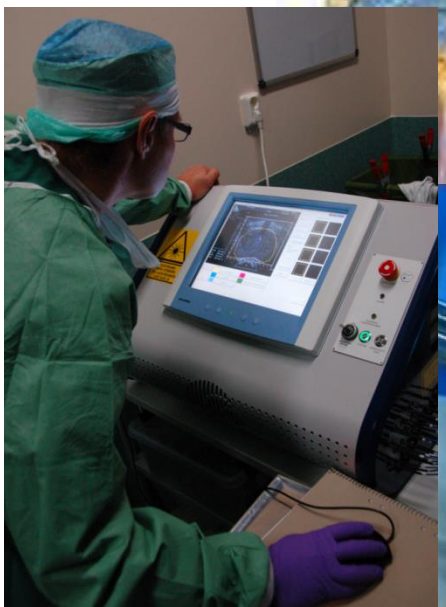




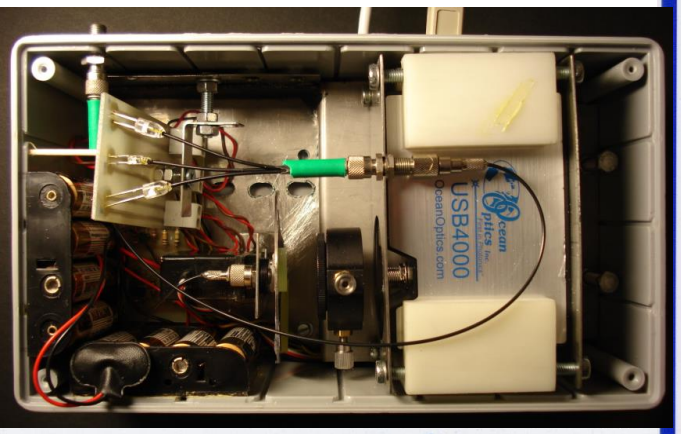


KI and Malmö
S. Nilsson, G. Ahlgren

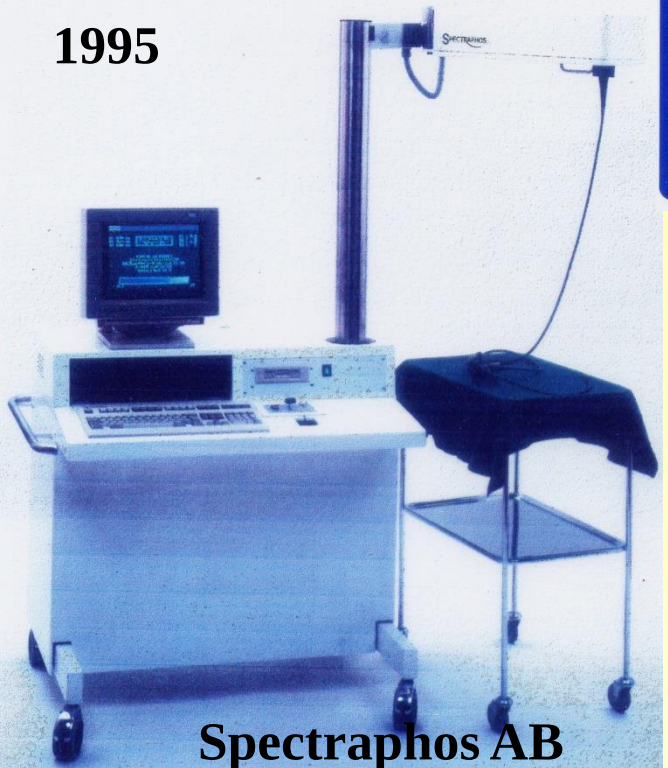




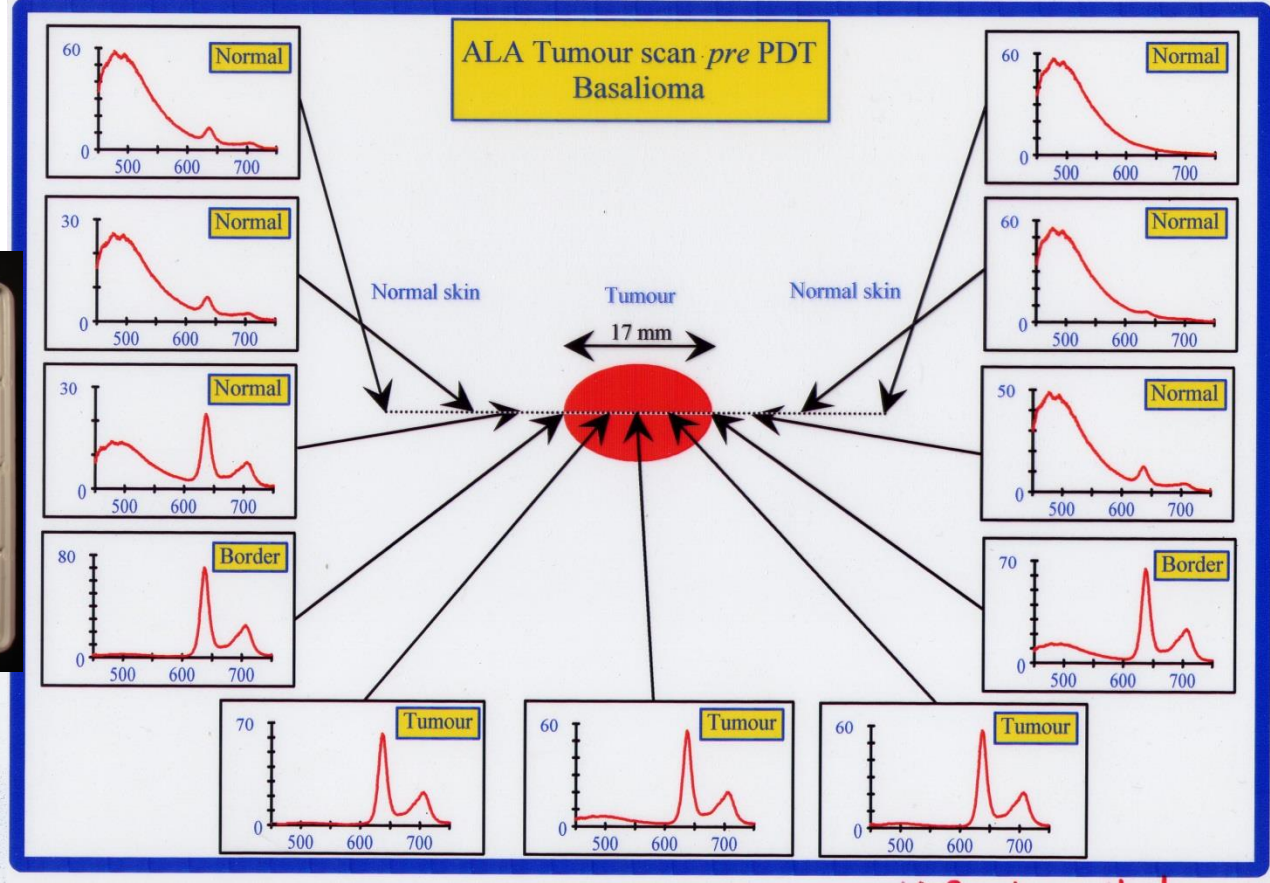
Fluorescence Diagnostics of Malignant Disease

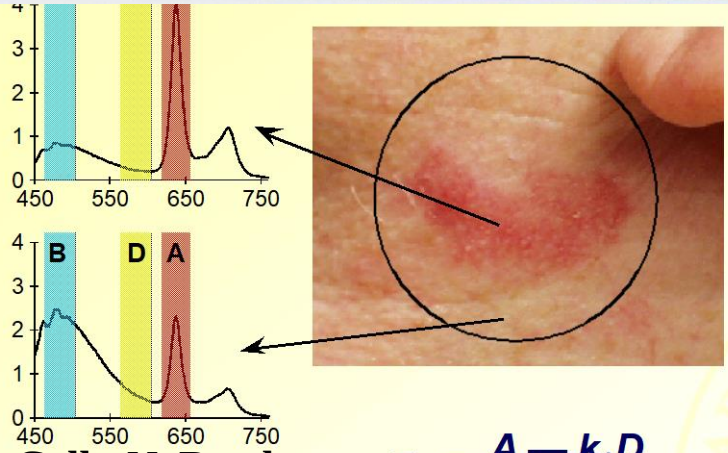


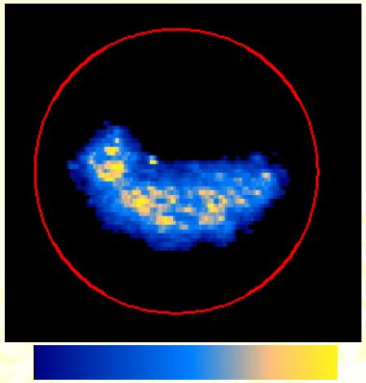
1995



Spectraphos AB







$$F_c = \frac{A - k_1 D}{k_2 B}$$

$$\frac{\text{Red} - \text{Yellow}}{\text{Blue}}$$

Coll.: N. Bendsoe, L. Salford, S.E. Karlsson

Flow cytometry in cancer research (laser-induced fluorescence labelled malignant cells)

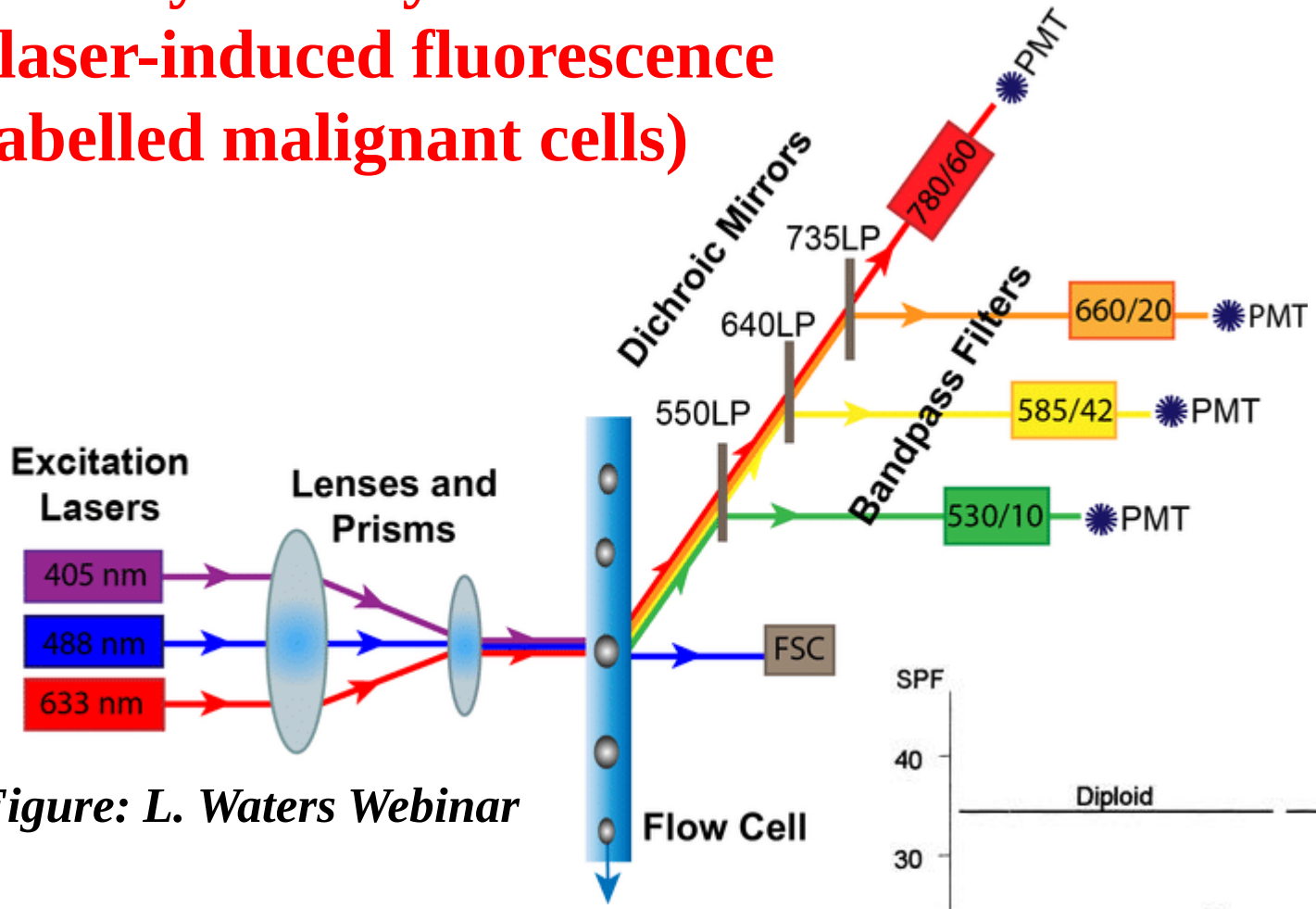
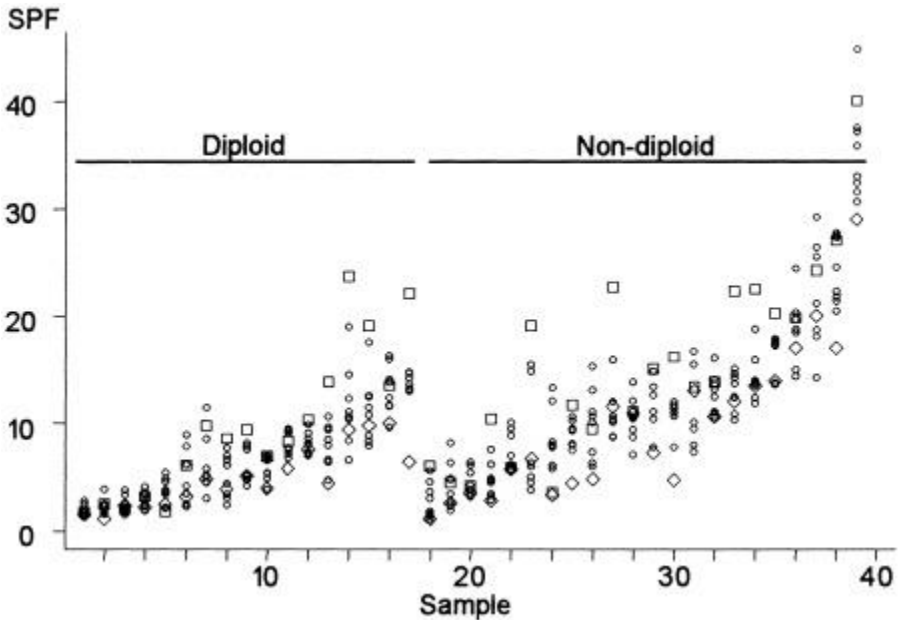


Figure: L. Waters Webinar



Baldetorp *et al.* (2013), and numerous studies before and after (with Killander, Fernö, Olsson….)

Från ett föredrag av Doc. Nina Reistad, 2016

Diffuse reflectance spectroscopy (DRS)

Vascular Research in Ophthalmology

Department of Ophthalmology (Faculty of Medicine)

- **Malin Malmsjö**, Professor, Senior Consultant (överläkare)
- **Karl Engelsberg**, Senior Consultant, Senior Researcher
- **Jonas Blohmé**, Senior Consultant, Senior Researcher
- **Rafi Sheikh**, Resident (ST-läkare), PhD-student
- **Khashayar Memarzadeh**, Specialist Consultant (specialistläkare), PhD-student
- **Ulf Dahlstrand**, Resident Consultant, PhD-student

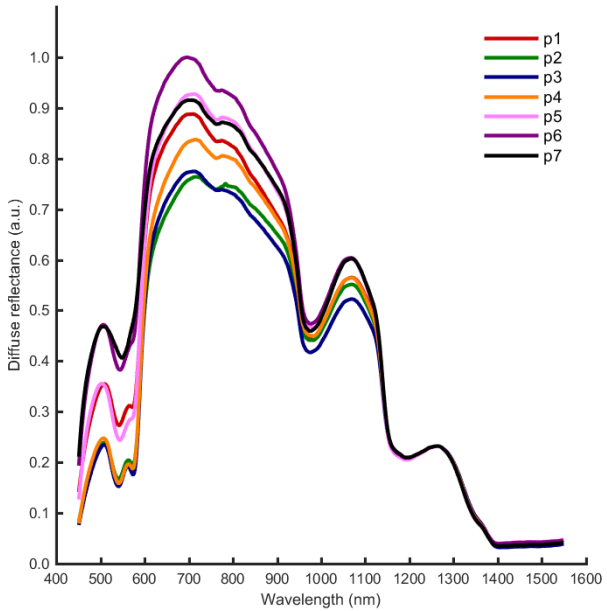
Liver Surgery Research

Department of Surgery (Faculty of Medicine)

- **Christian Sturesson**, Associate Professor (docent), Senior Consultant (överläkare)
- **Jan Nilsson**, Resident (ST-läkare), PhD student
- **Magnus Bergenfeldt**, Associate Professor (docent), Senior Consultant (överläkare)
- **Pehr Rissler**, PhD (Dept. of Pathology)

Blood perfusion measurements in eyelid flaps
Diffuse reflectance measurements (Malmsjö, Reistad et al.)

- The spectrum changes as the blood flow decreases



- Quantification using multivariate techniques

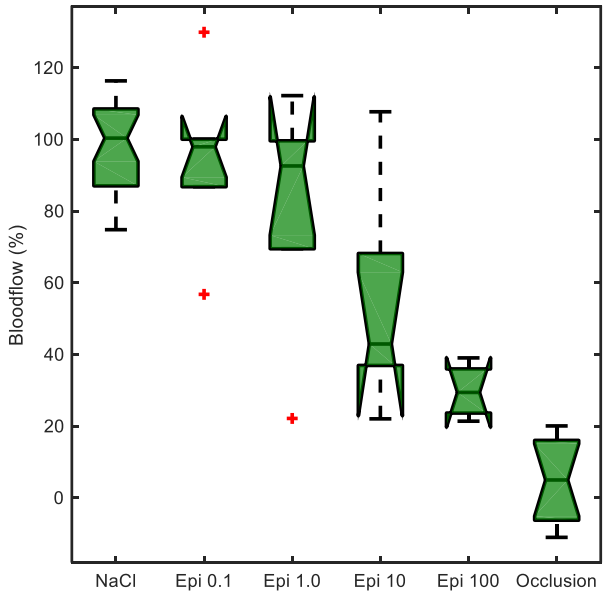
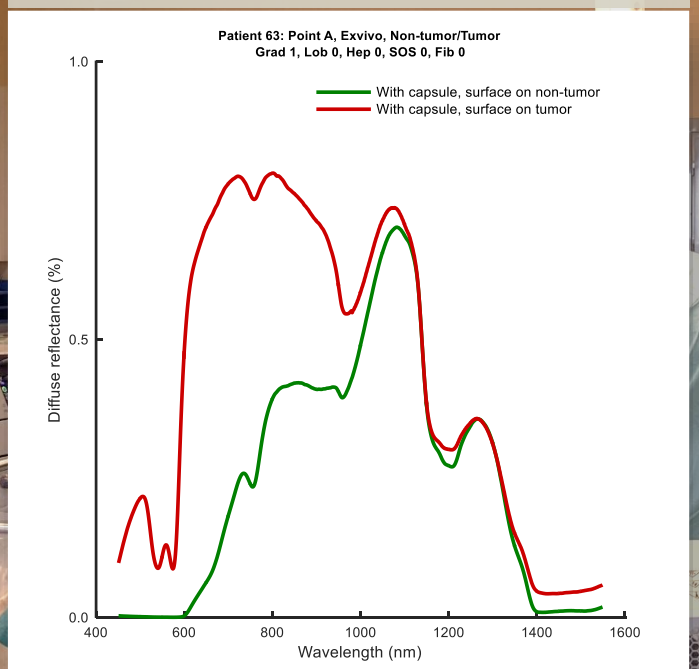


PHOTO: RAFI SHEIKH 2015

Optical signature of liver tumor tissue
Diffuse reflectance measurements (Sturesson, Reistad et al.

- Comparison of typical optical signature of tumor and non-tumor, steatosis stage 1



- Classification using multivariate analysis

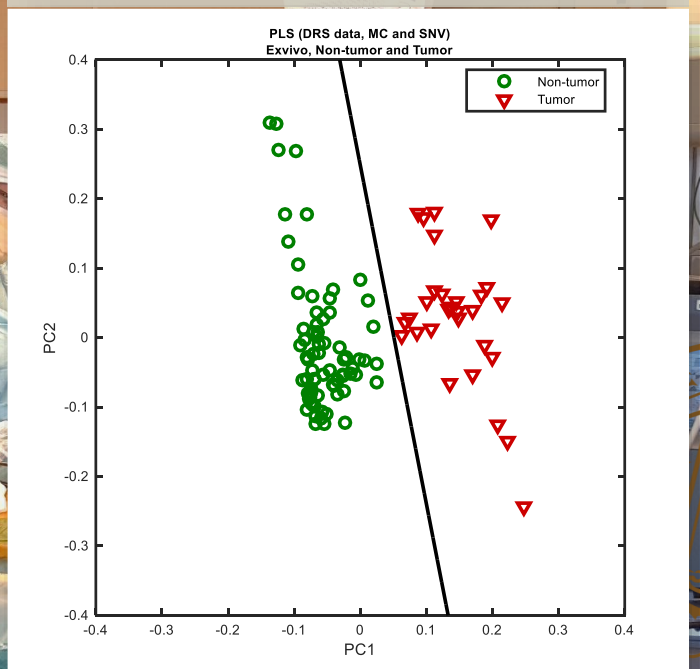
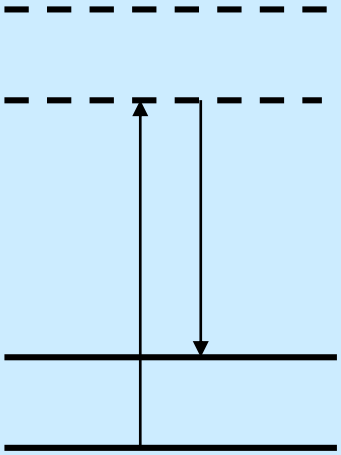


PHOTO: NINA REISTAD 2015

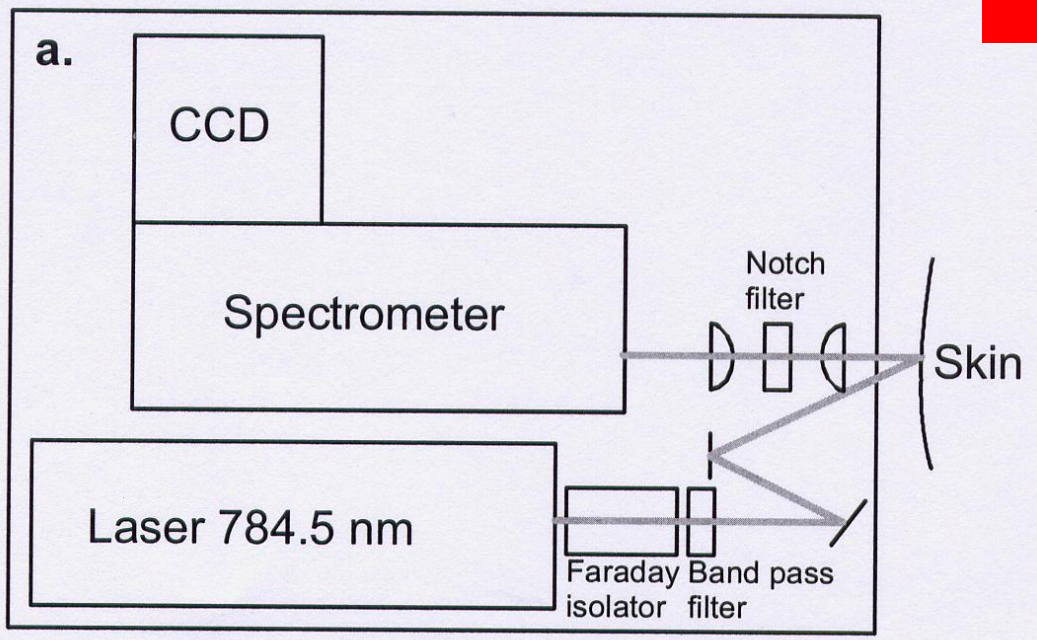
Raman Spectroscopy

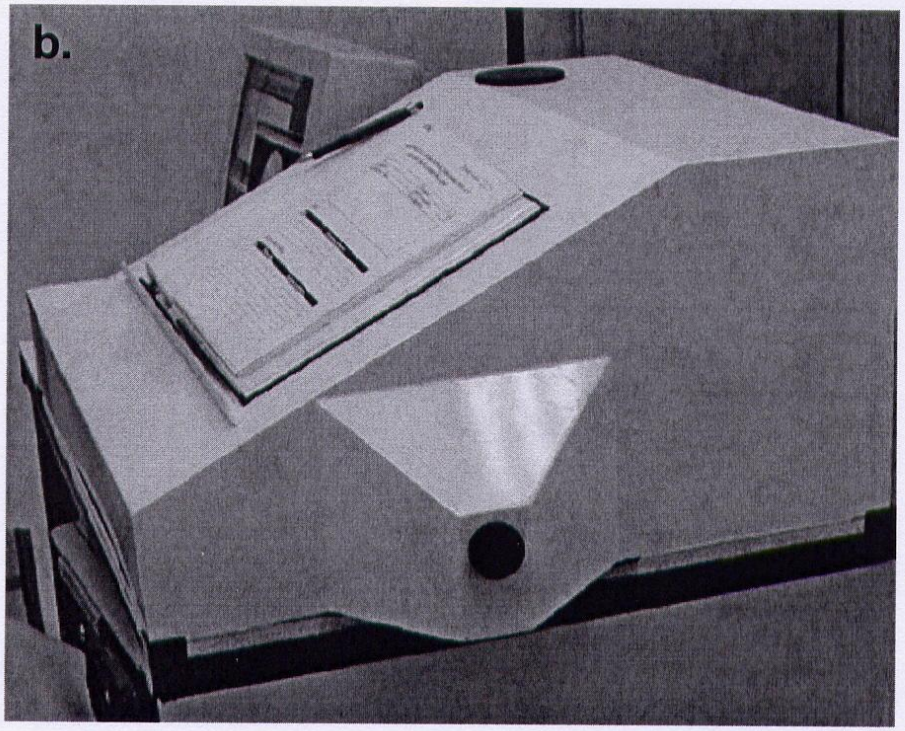


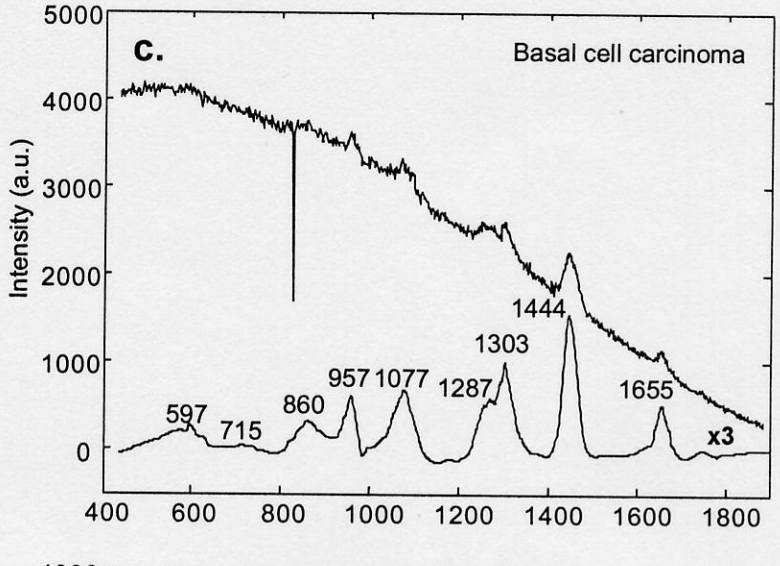
S. Pålsson *et al.* (2003)

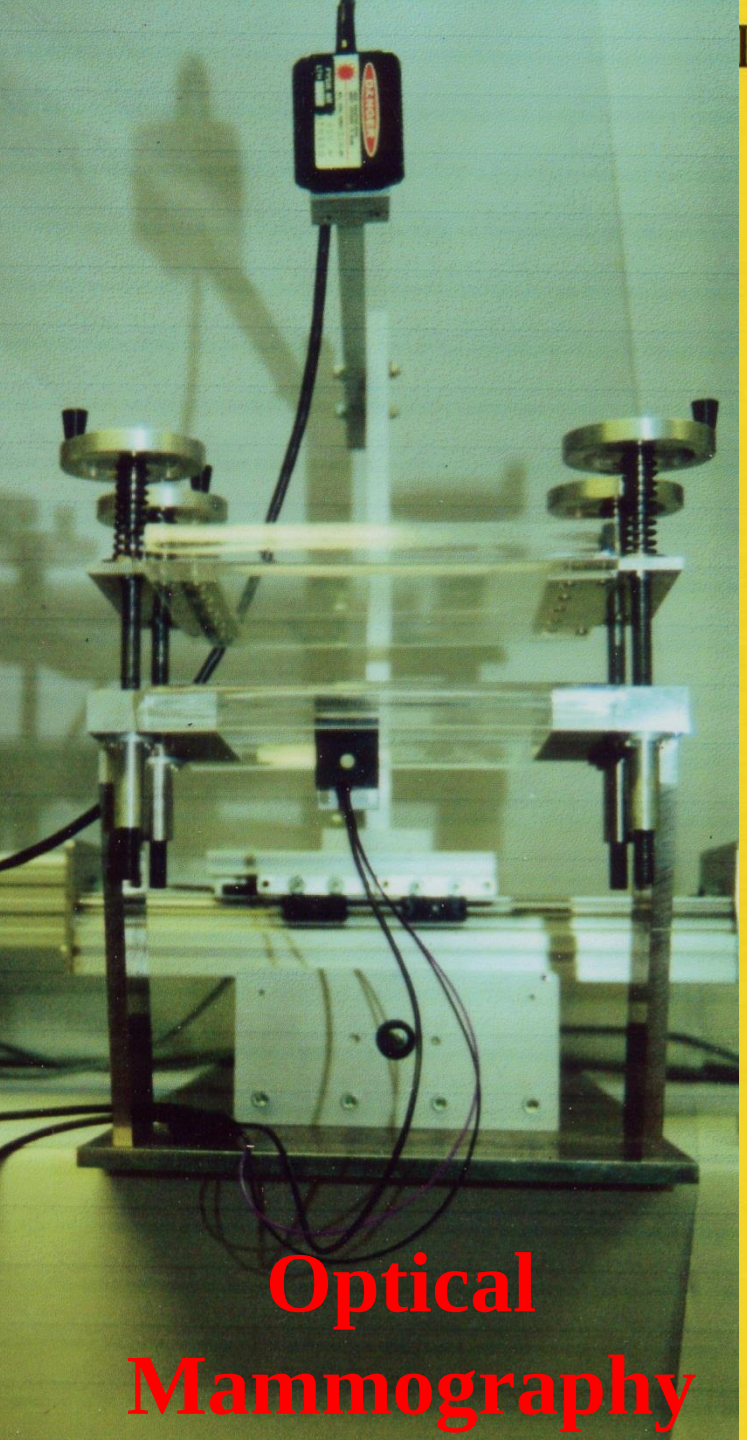
Clinical study on 64 patients

N. Bendsoe et al.





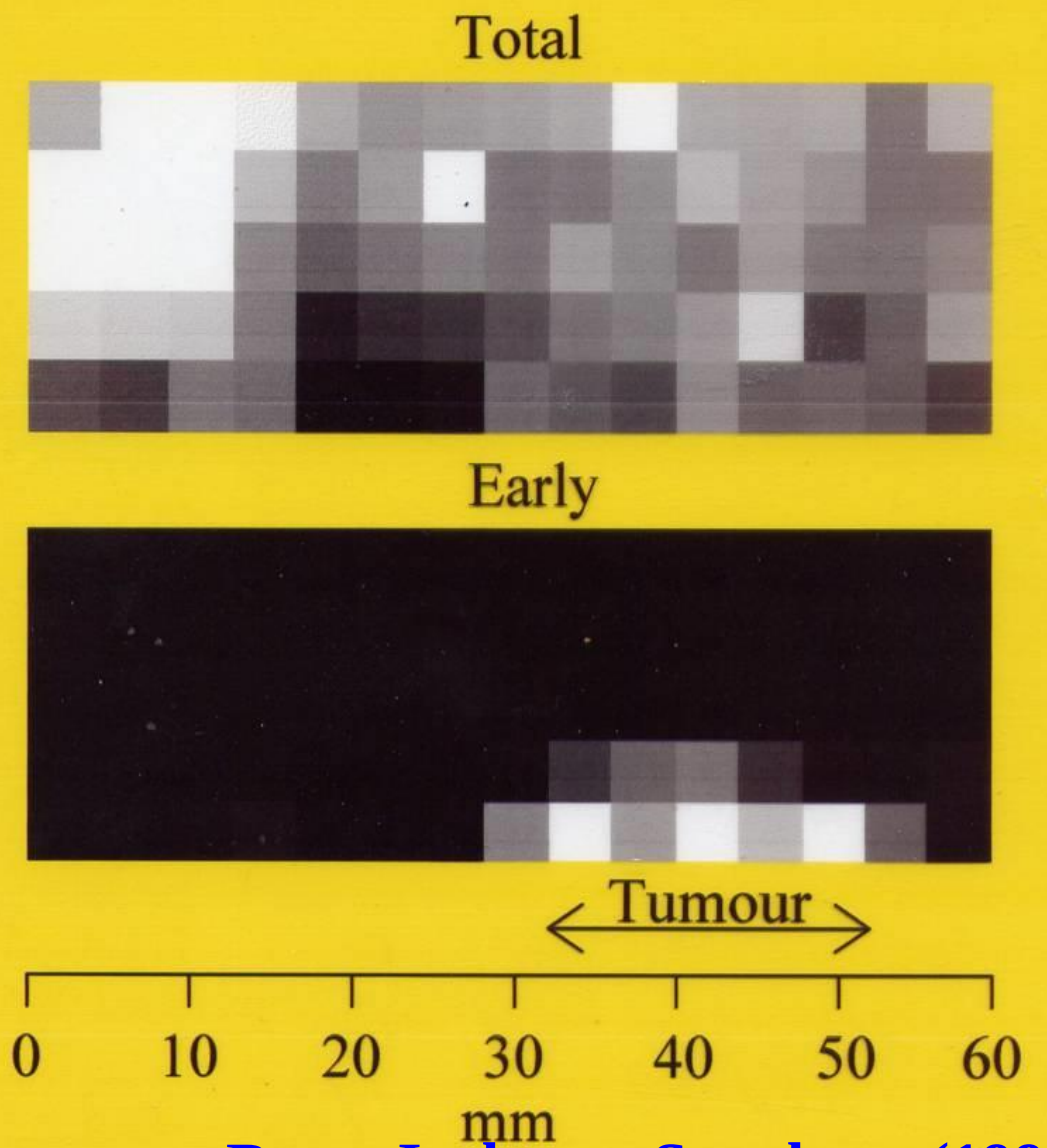




Optical Mammography

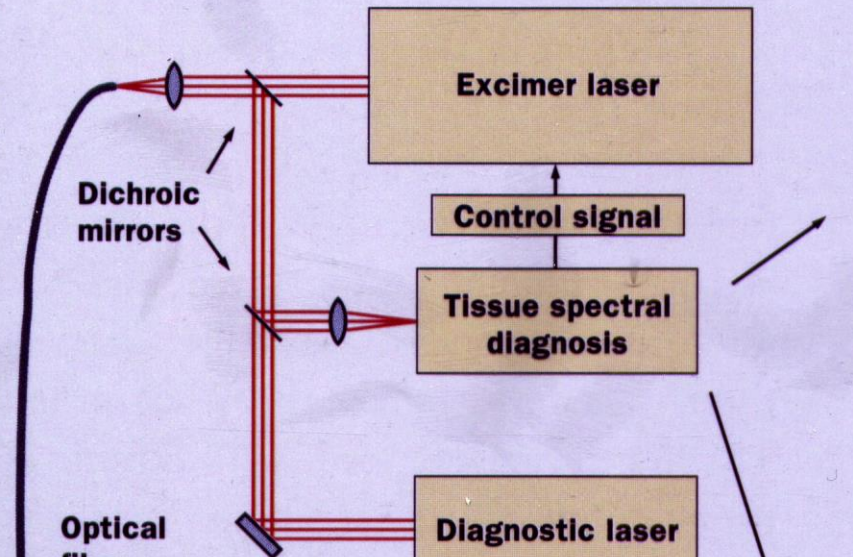
Picosecond Diode Laser Transillumination

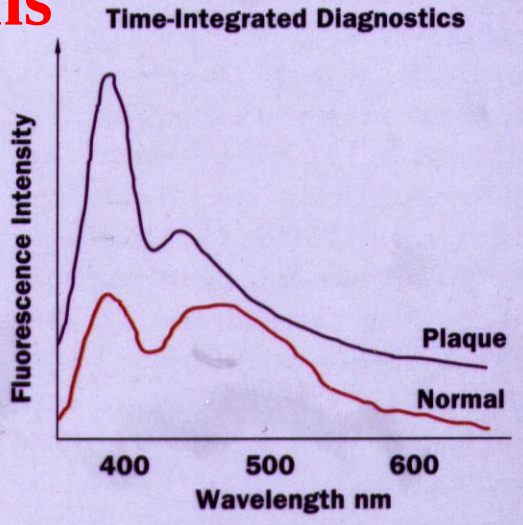
Image of ductal cancer in female breast

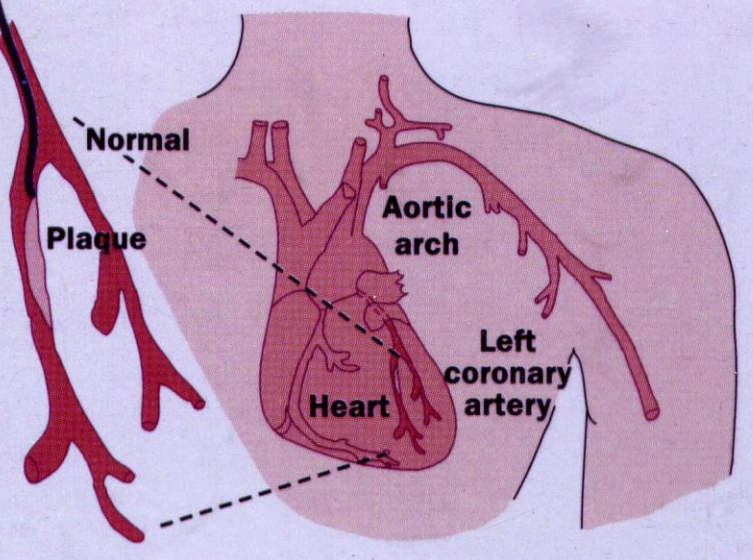


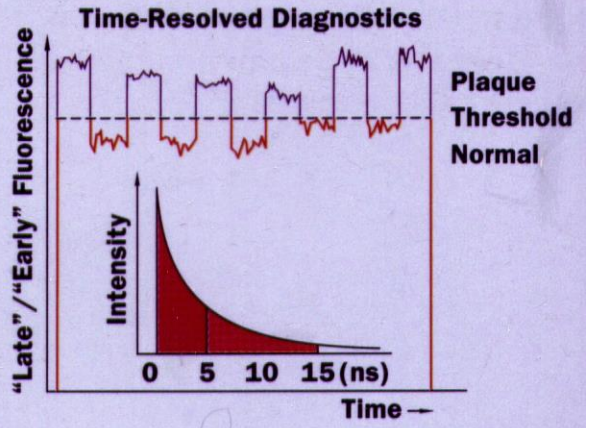
Berg, Jarlman, Svanberg (1993)

Cardiovascular applications



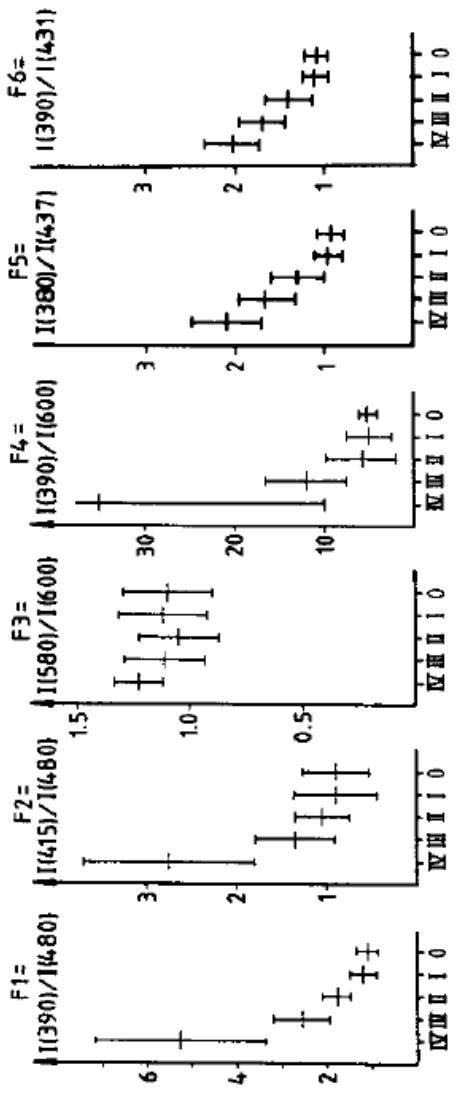




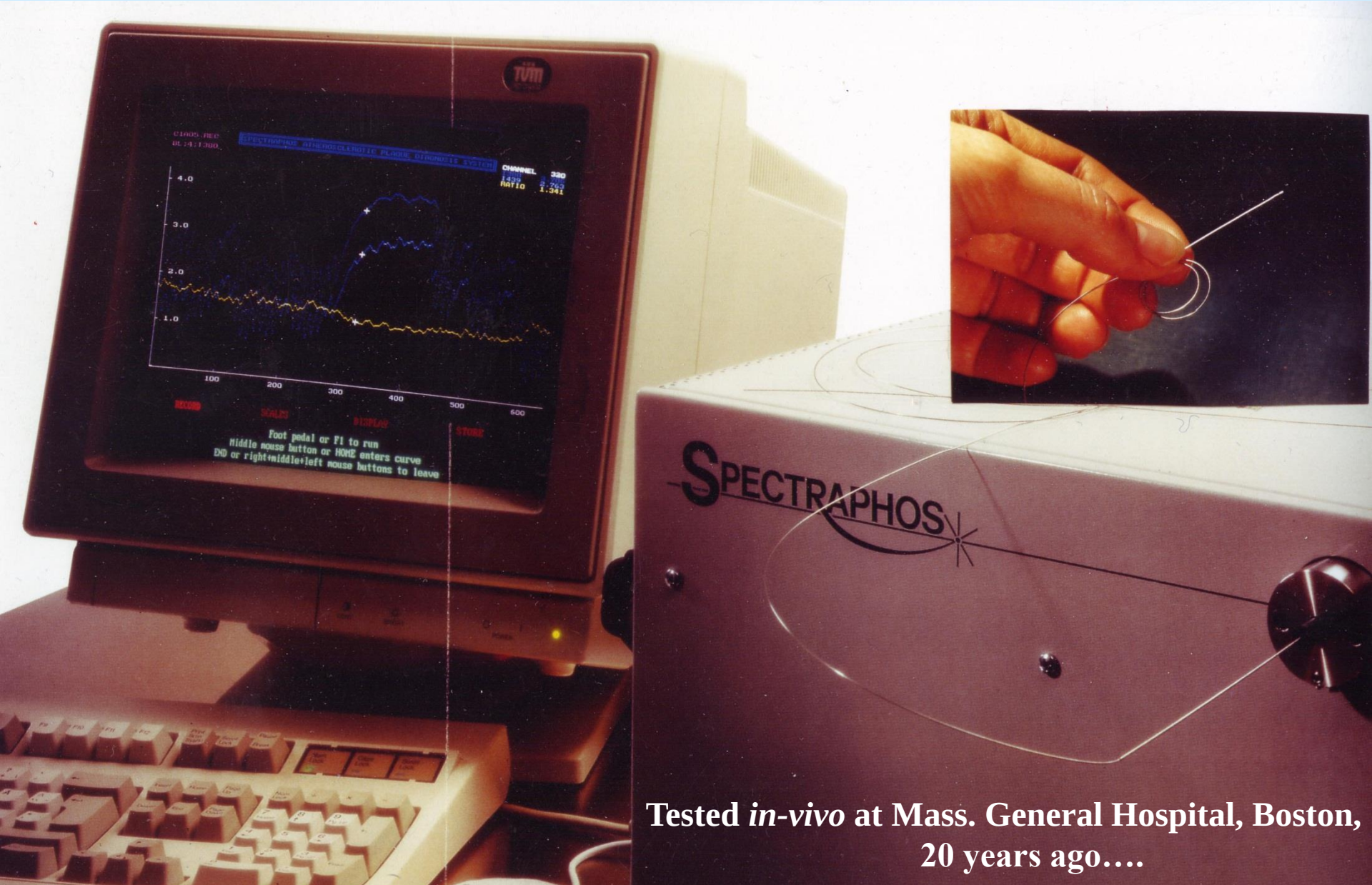


Collaboration: A. Gustafsson, S. Steen

Vessel spectroscopic diagnostics

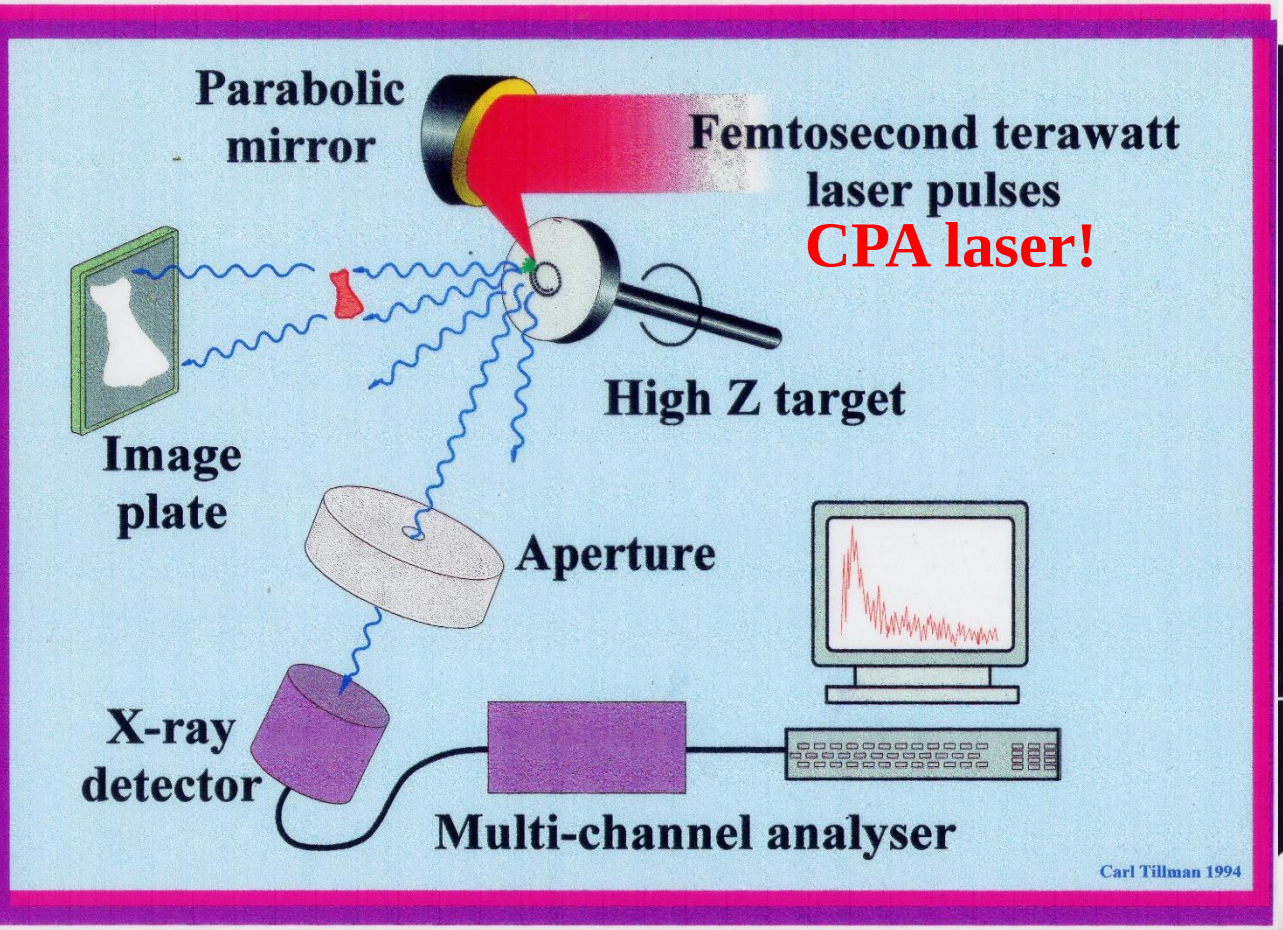


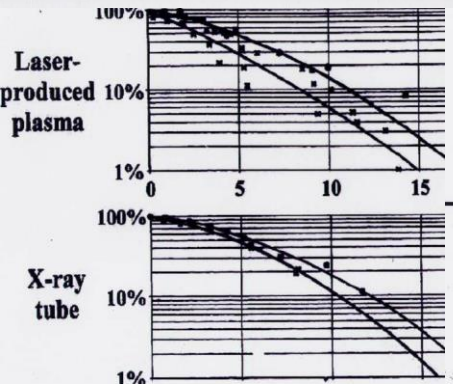
Atherosclerotic coronary artery real-time diagnostics (spectral and temporal)

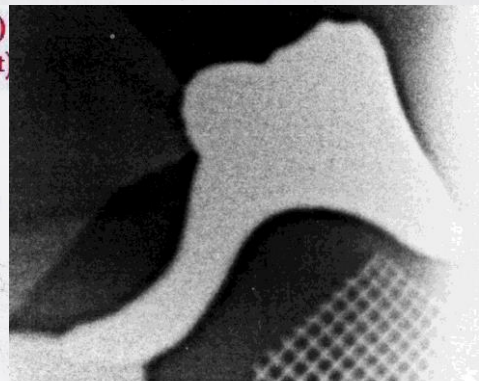


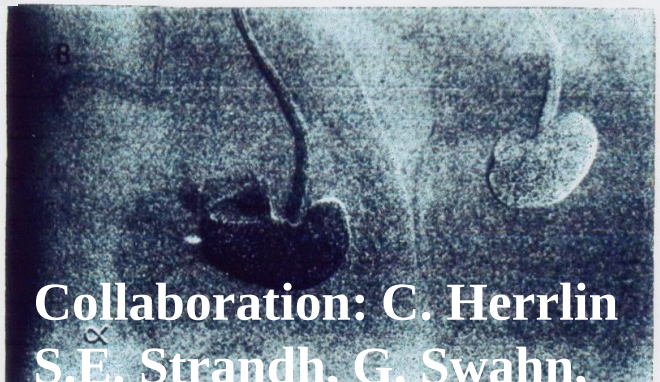
Tested *in-vivo* at Mass. General Hospital, Boston, 20 years ago….

Laser-produced hard X-rays



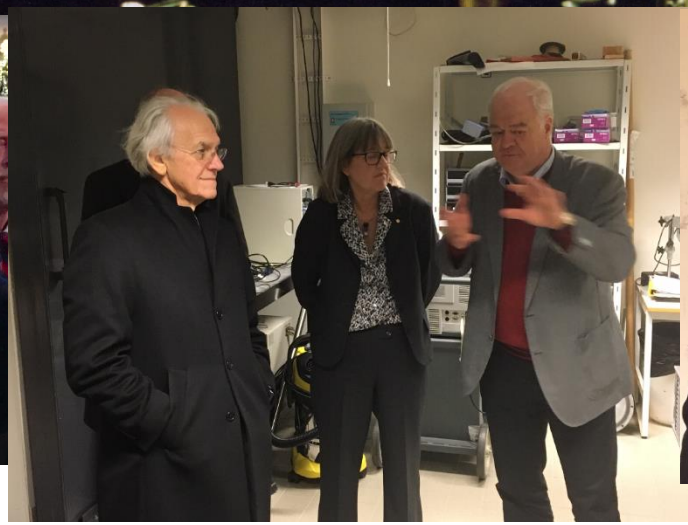


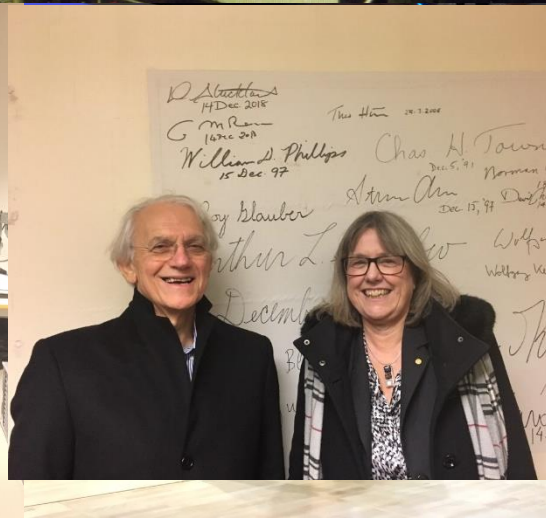




Lund Titanium-sapphire CPA Terawatt Laser

10^{+12} W x 10^{-13} s = 0.1 J !!!



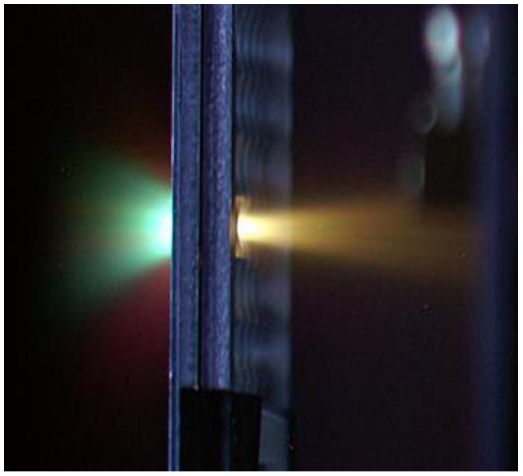


The Lund High-Power Laser Facility

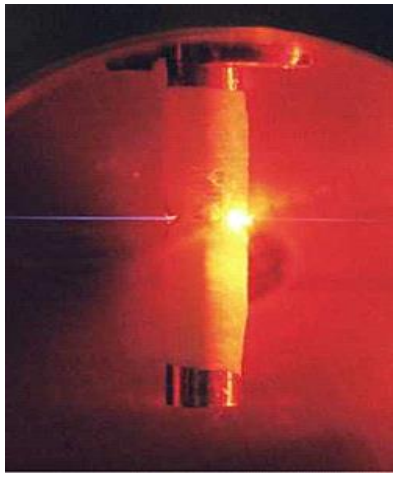
Research with high intensity, short laser pulses and VUV/XUV radiation

Claes-Göran Wahlström et al.

200 MeV Electrons

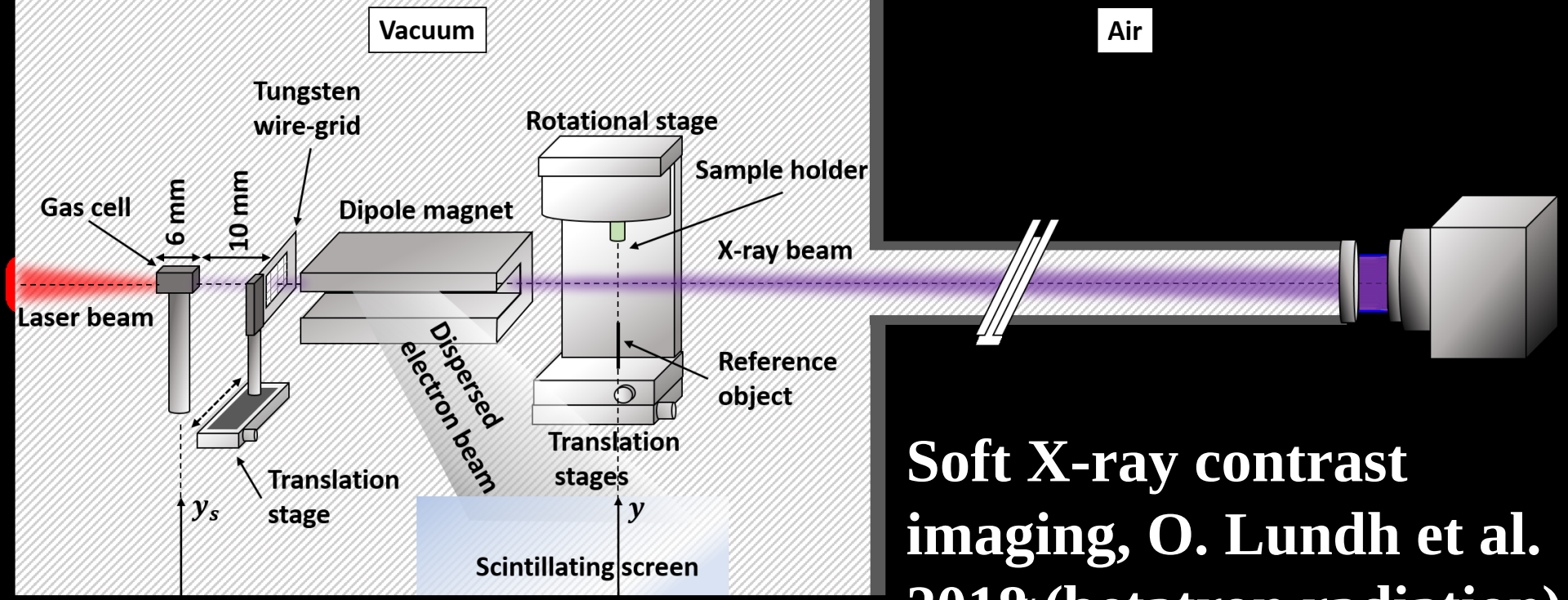


10 MeV Protons

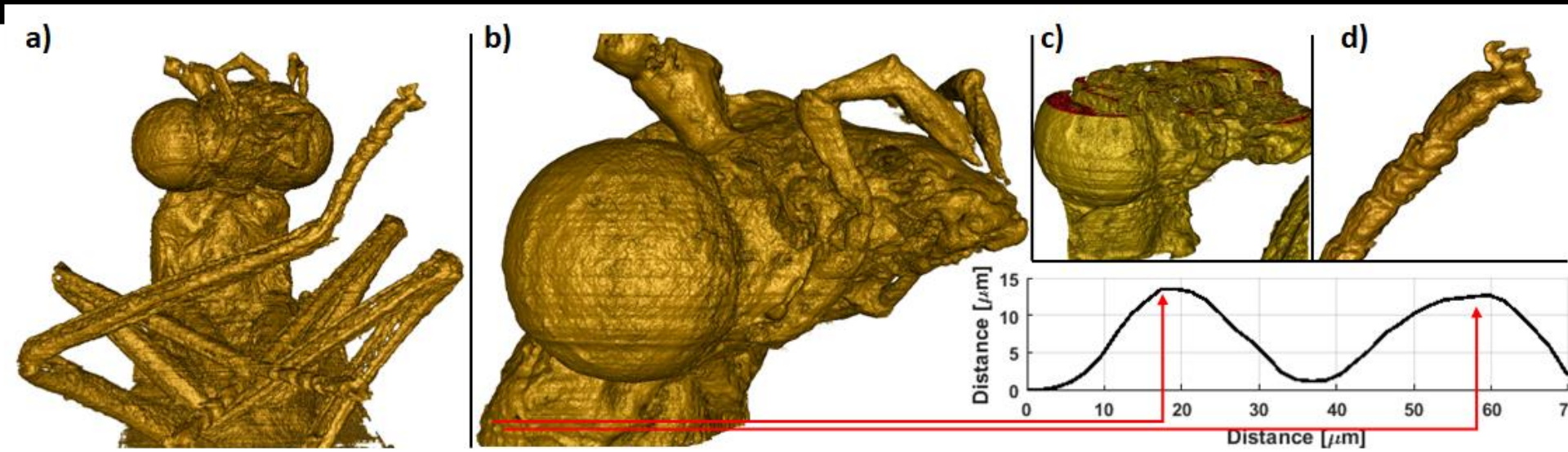


130 as Attosecond pulses

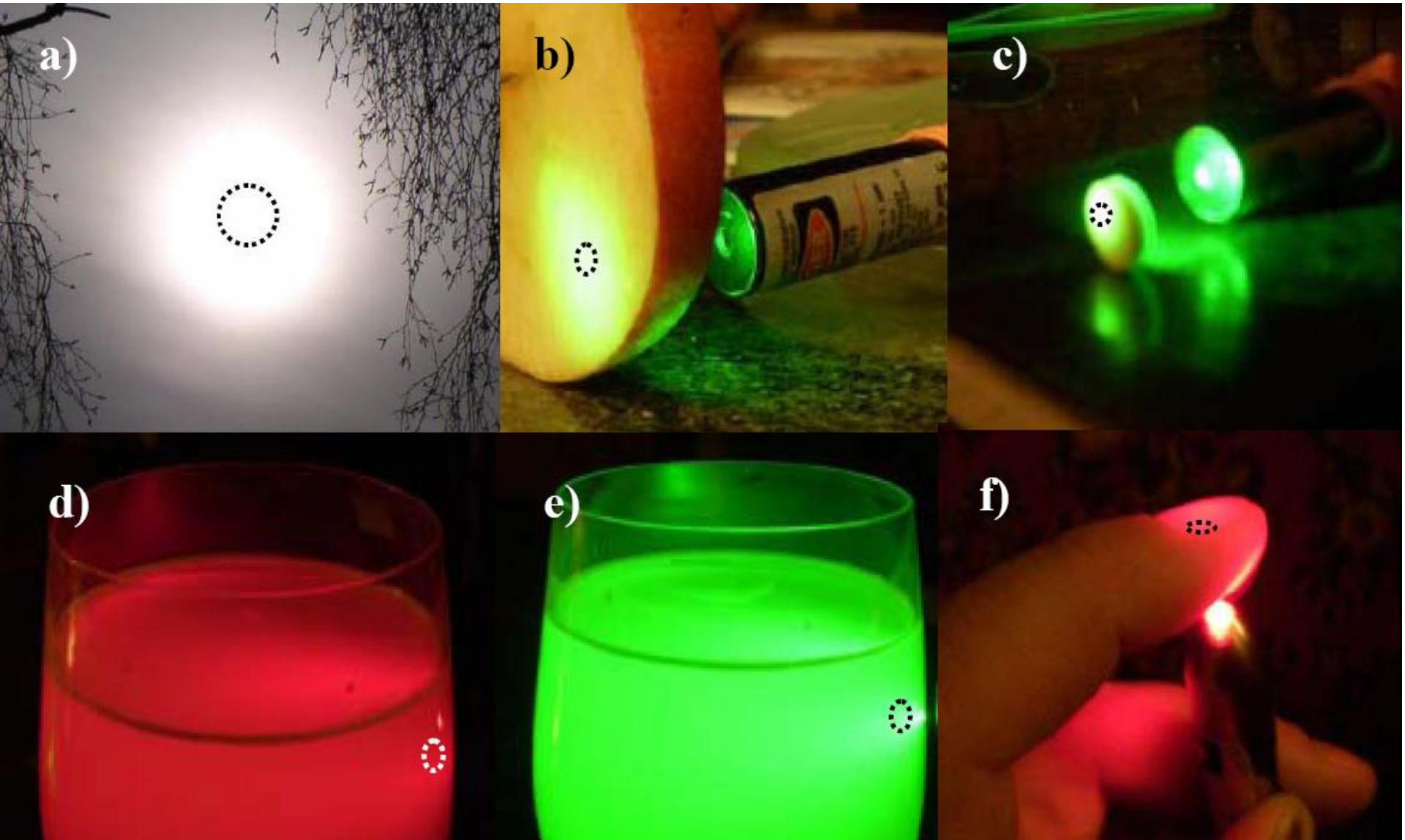
18.9 nm X-ray laser



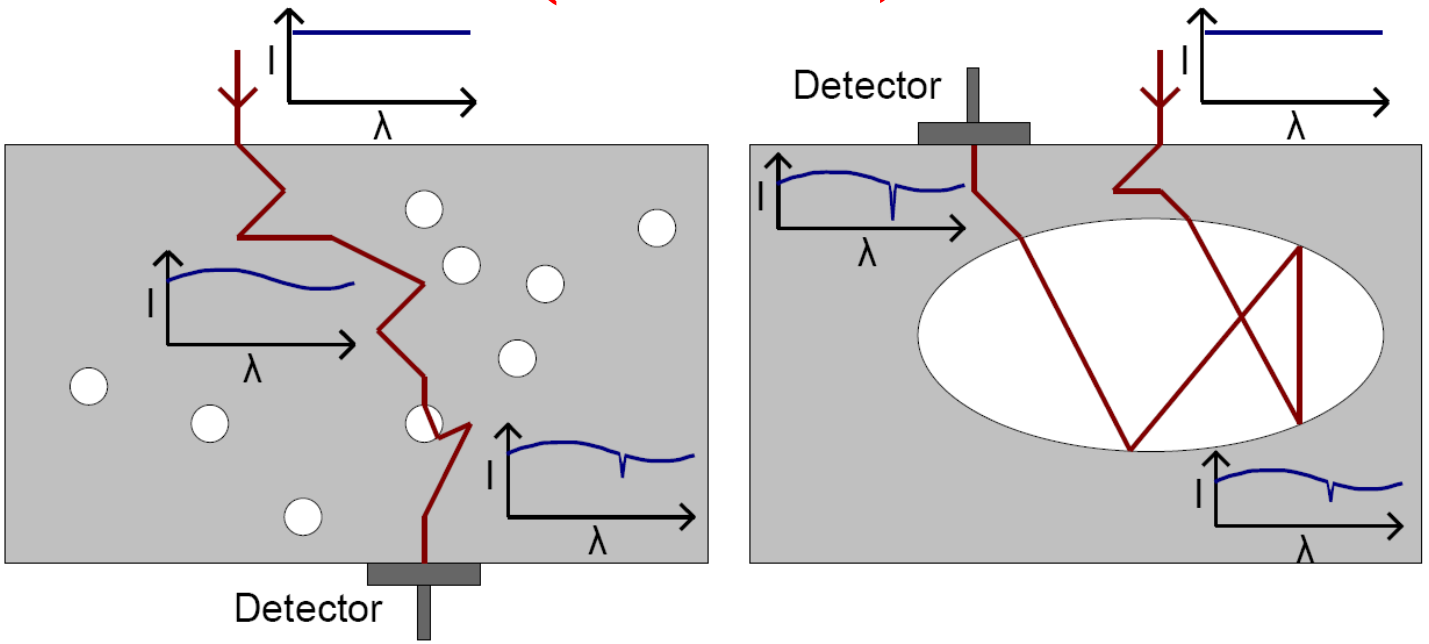
Soft X-ray contrast imaging, O. Lundh et al. 2018 (betatron radiation)



Optics in scattering media

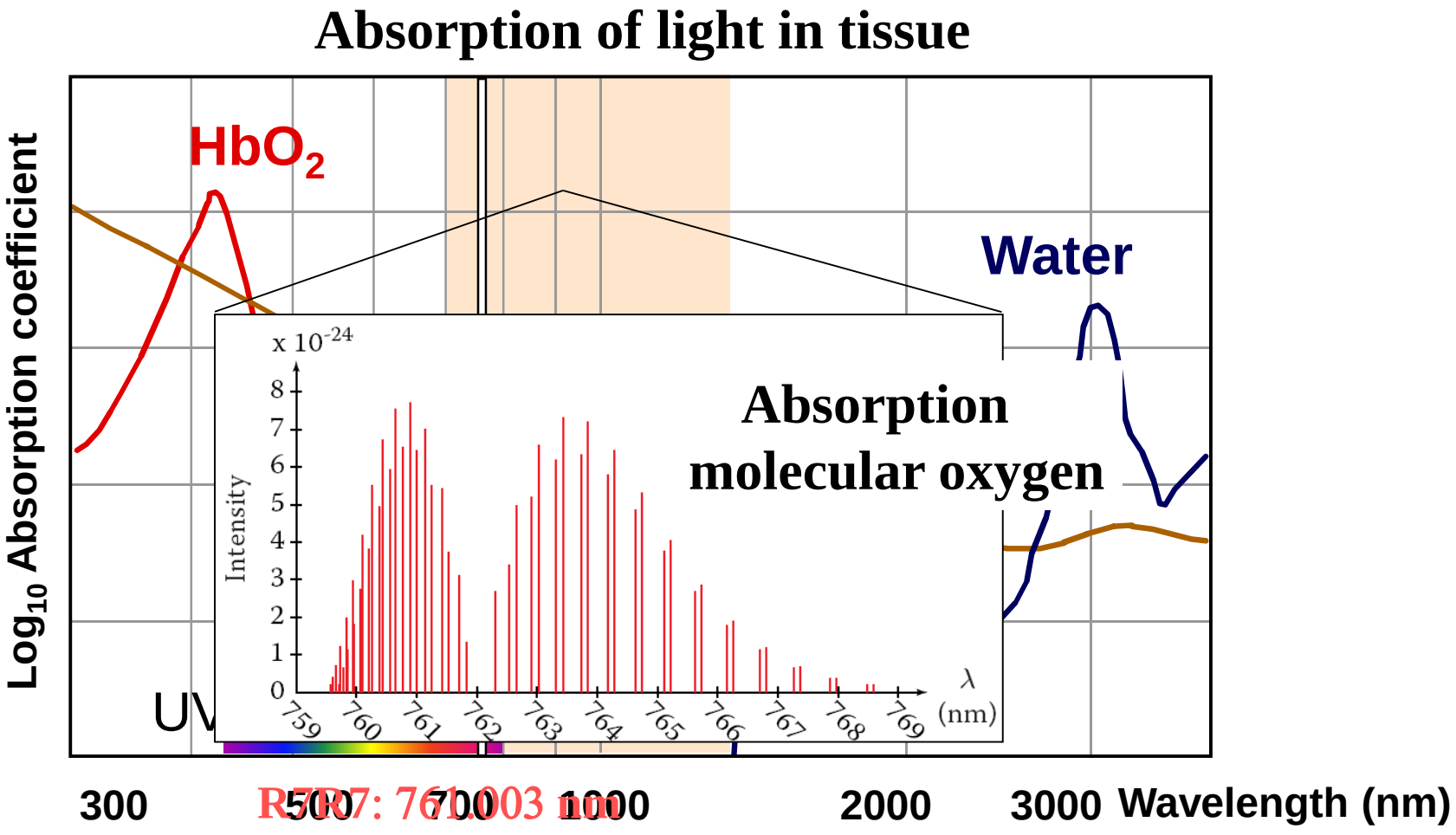


Gas in Scattering Media Absorption Spectroscopy (GASMAS)



Lewander

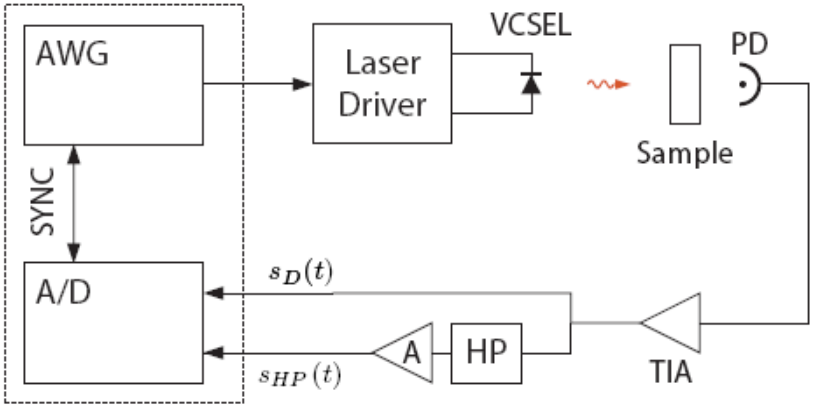
Tissue and Free-Gas Absorption

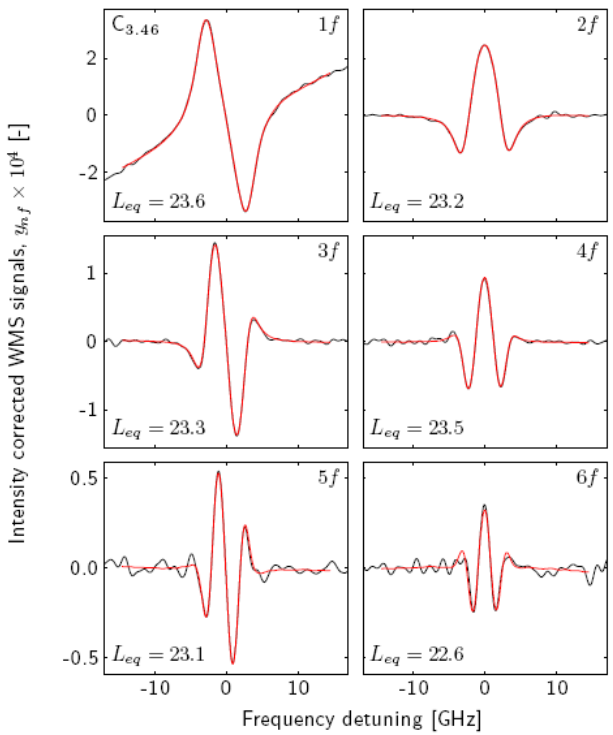


Spectroscopy on Pharmaceutical Tablets – Coll. AstraZeneca

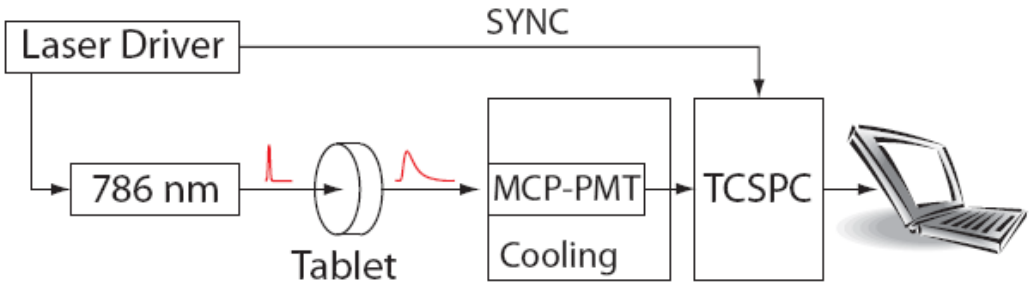
Porosity studies/delayed release

Frequency domain, oxygen

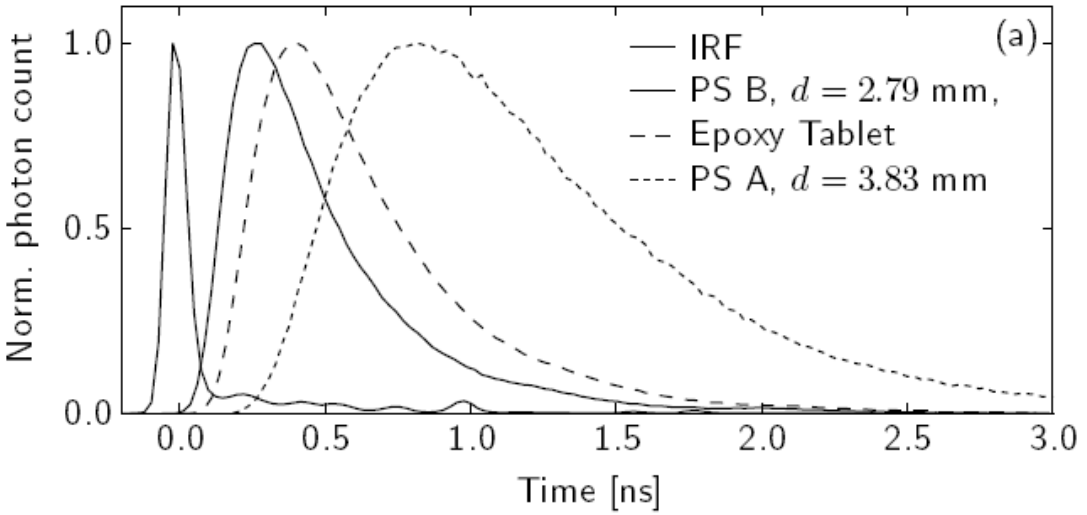




Time domain, TOF/Lidar



T. Svensson et al.



Follow-up: Alignment-free multi-pass gas cell made of nanoporous ceramics -750 times path enhancement !!

Svensson *et al.* PRL (2011)

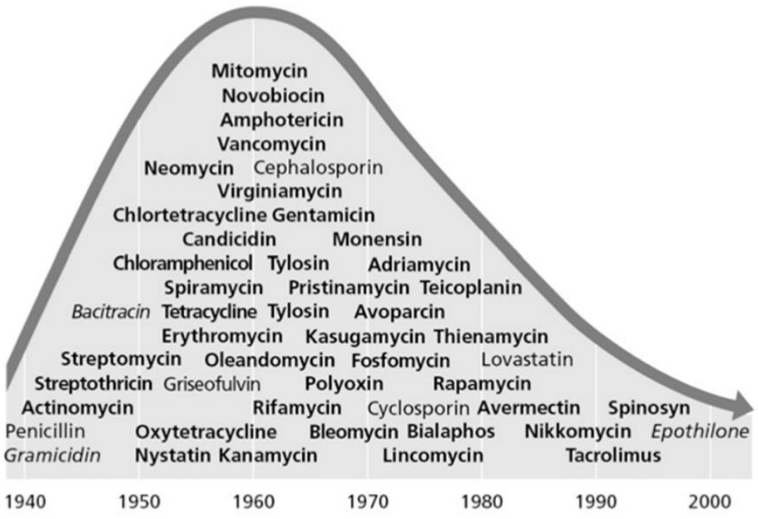
Fighting antibiotics resistance

A global challenge !

Antibiotics only work on bacteria – not on virii !

Sinusitis - Otitis

Alexander Flemming NP1945

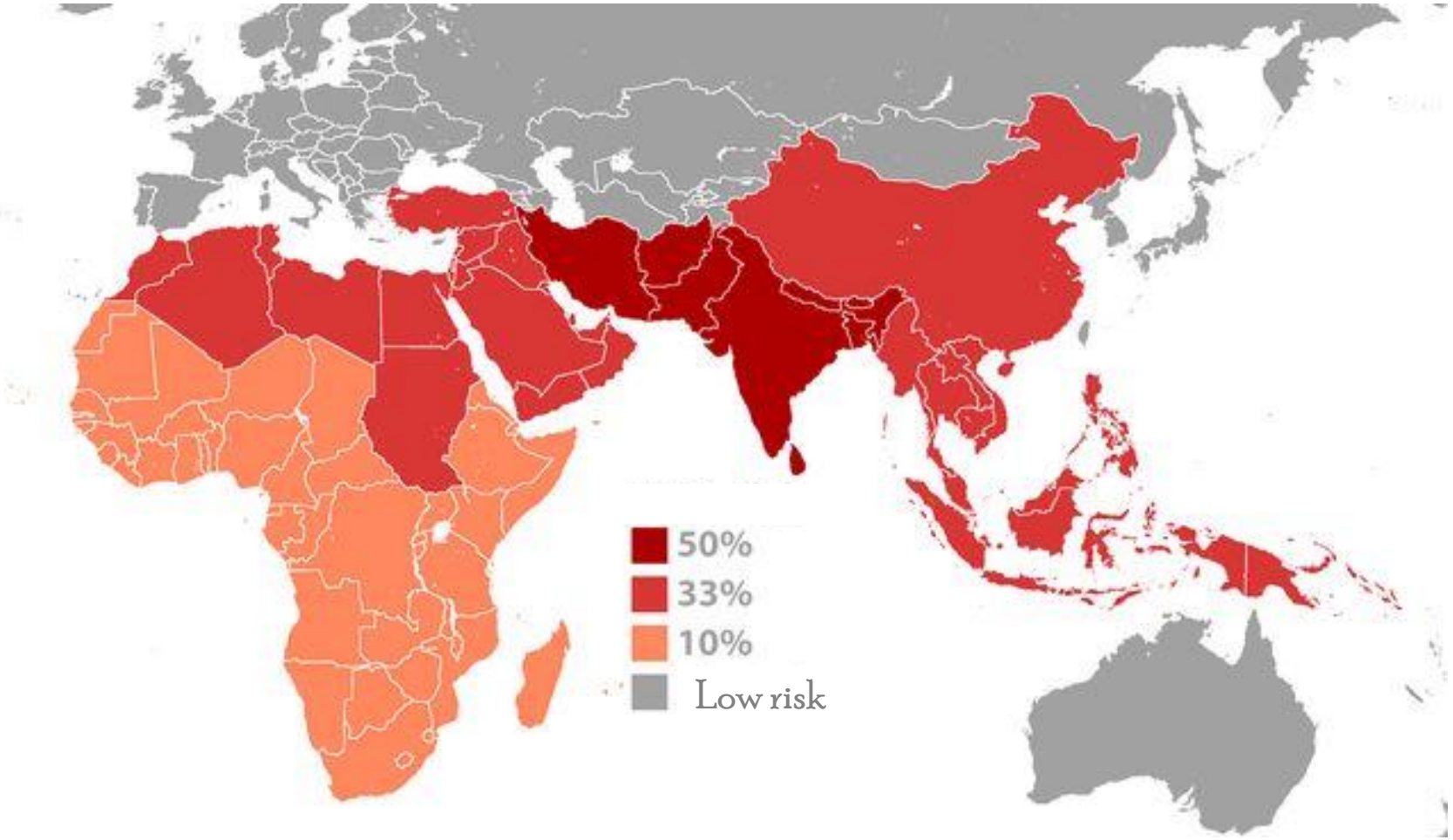


Pharmacy

in Guangzhou; free availability!

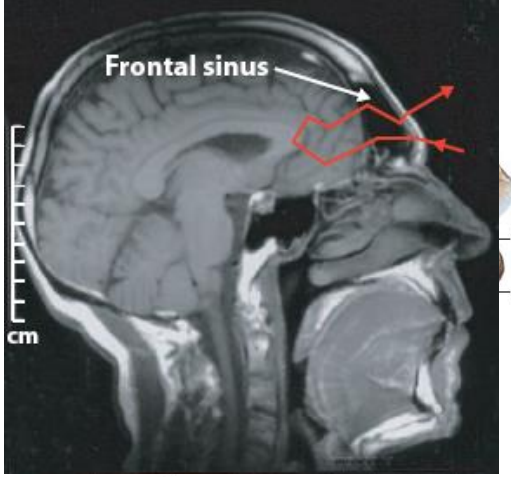
Very few new antibiotics are developed

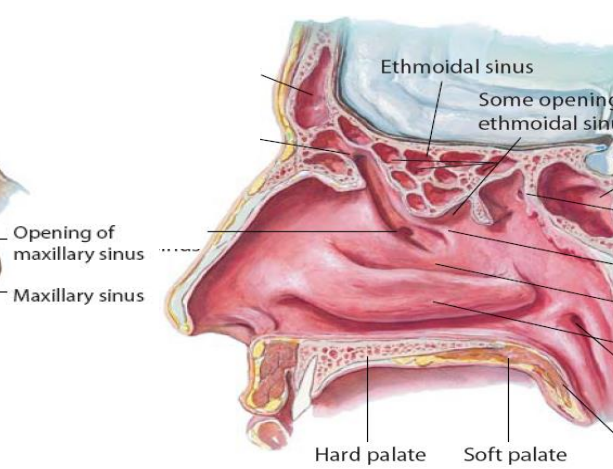
Percentage of carrier of antibiotic resistant bacteria ALARMING!

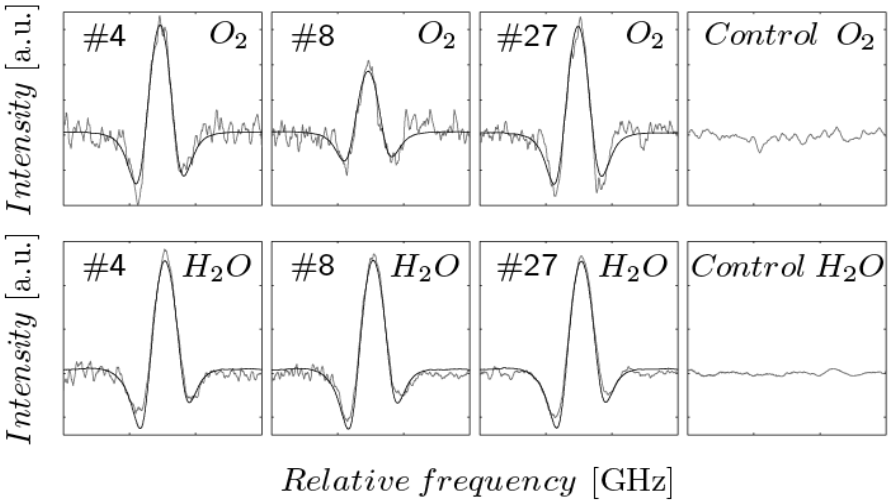


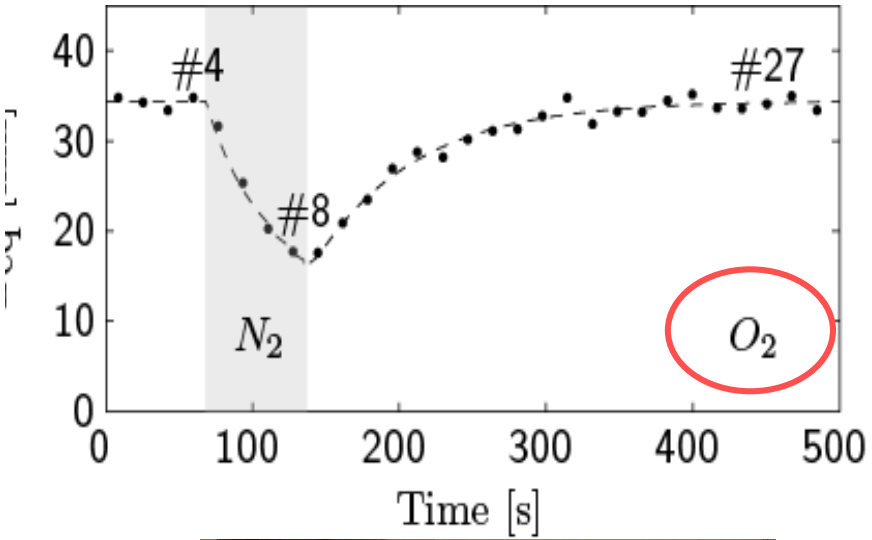
Fighting Antibiotics Resistance

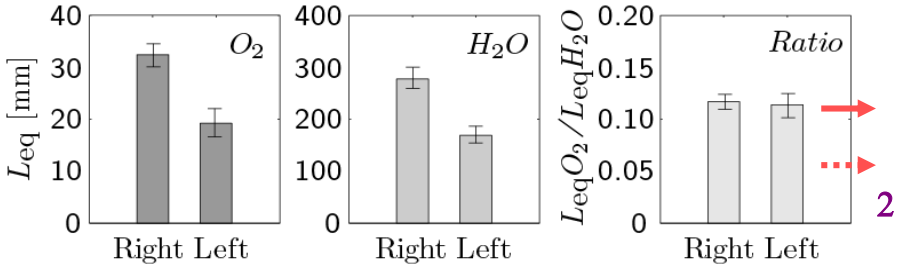
Sinusitis diagnostic by laser-spectroscopic measurement of oxygen and water vapour









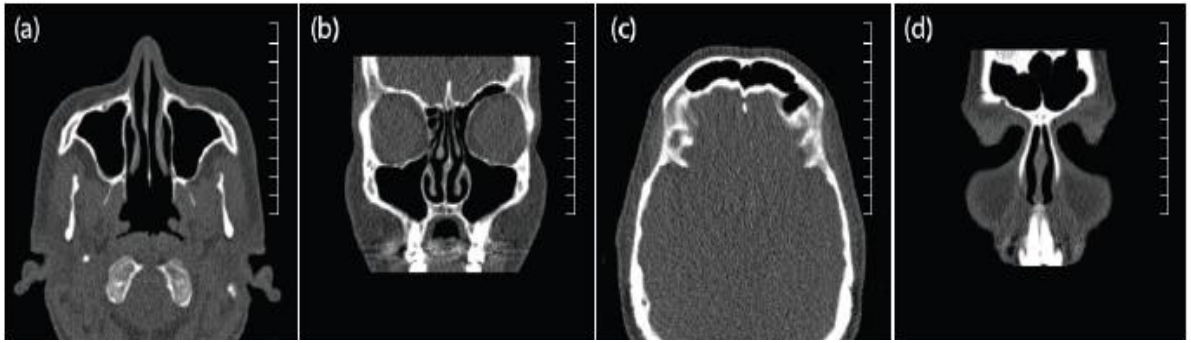


Persson et al. J. Biomed. Optics (2007); Rhinology 2012

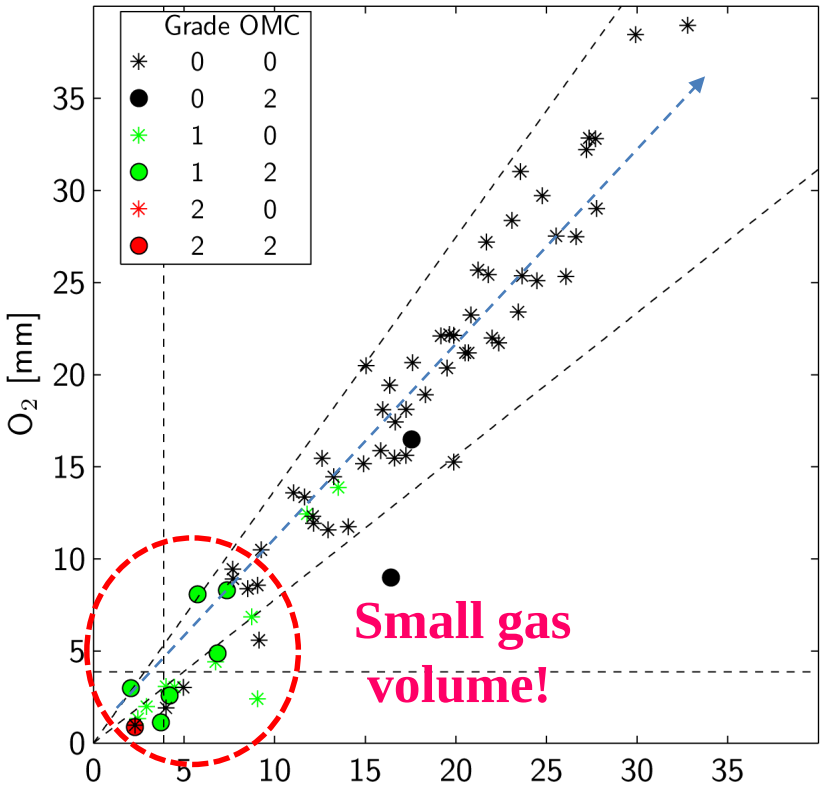
Clinical study on 40 patients

Lewander, Lindberg *et al.* Rhinology (2012) – Results comparable to CT

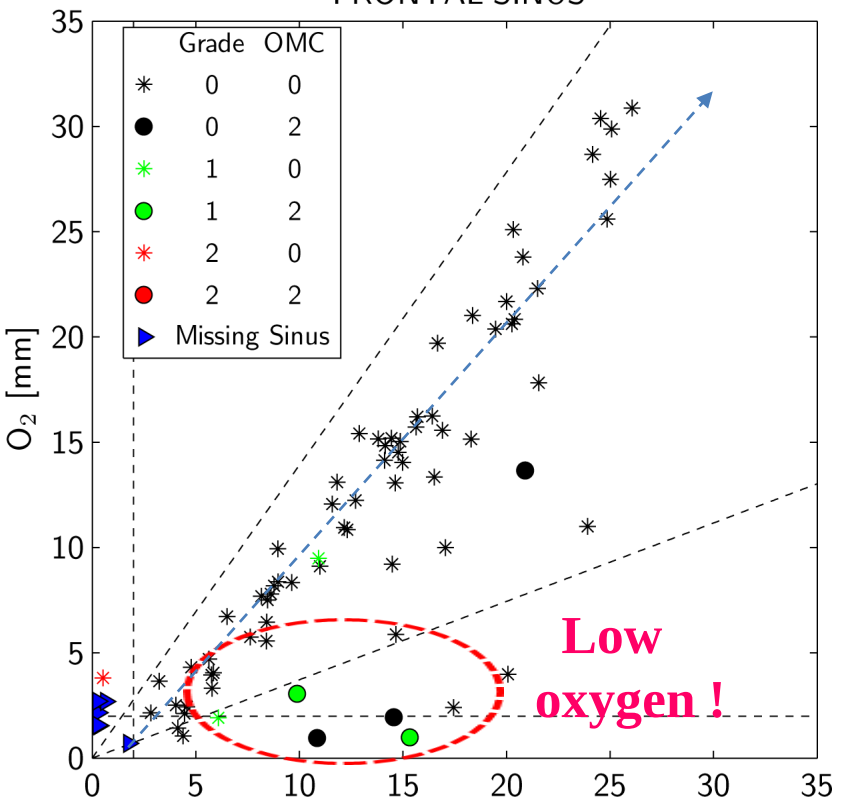
Collaboration:
S. Lindberg
R. Siemund



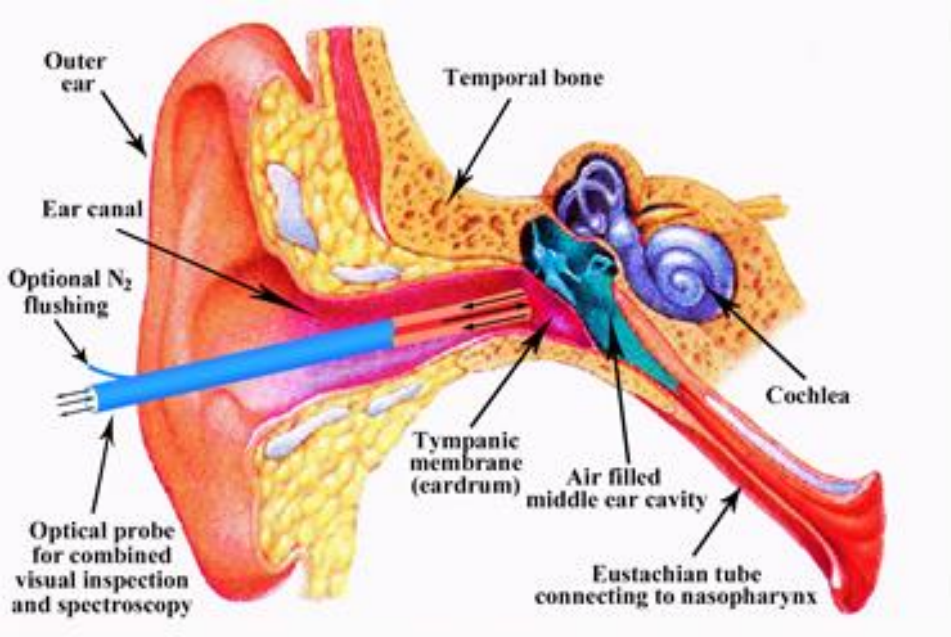
MAXILLARY SINUS

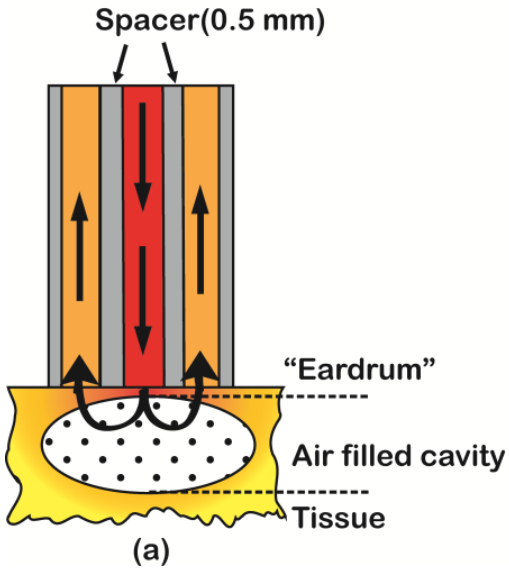


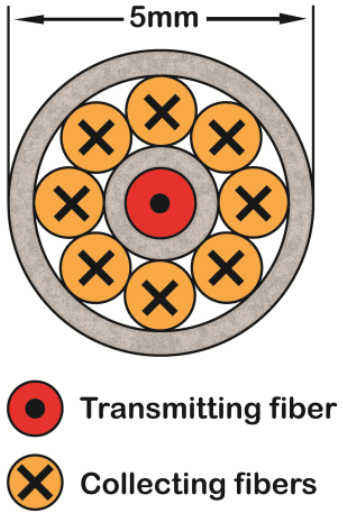
FRONTAL SINUS



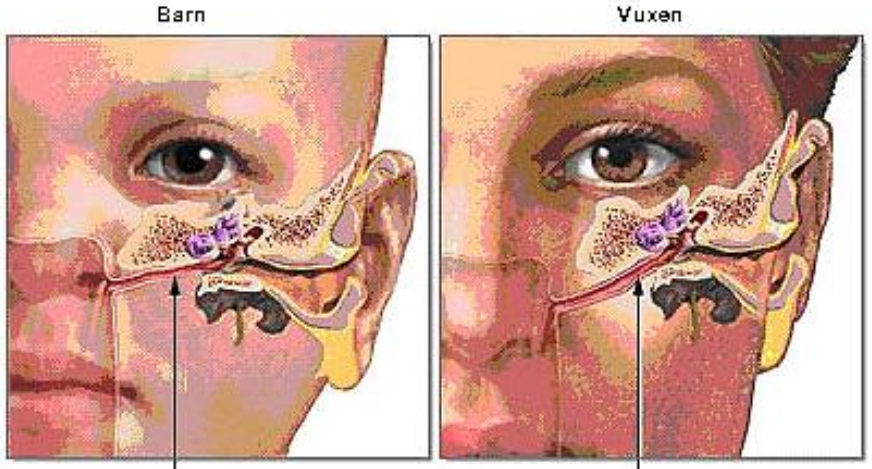
Middle Ear Diagnostics



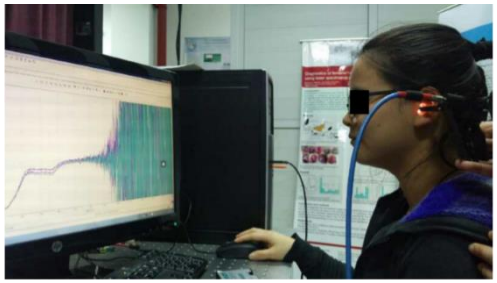


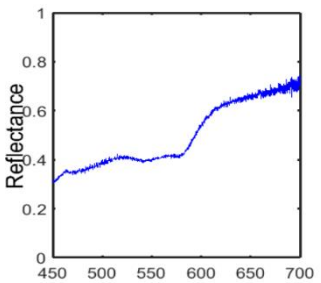


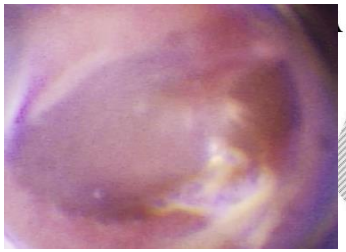
Middle ear infection (otitis)

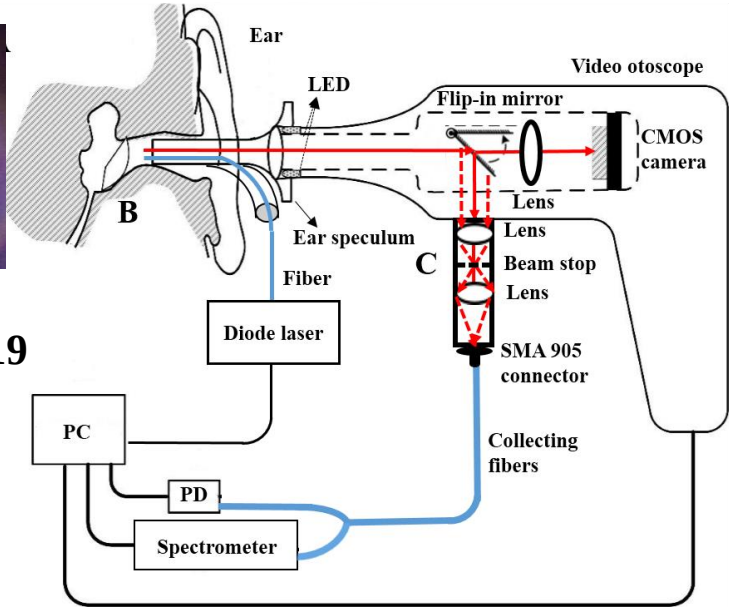


Ear-drum color monitoring



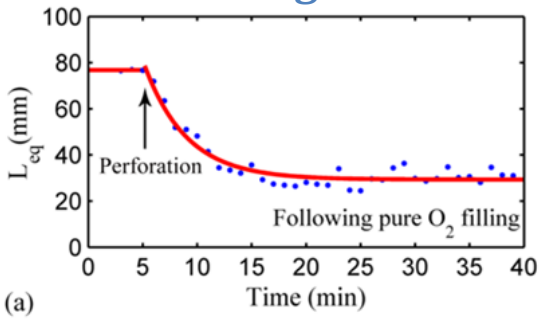


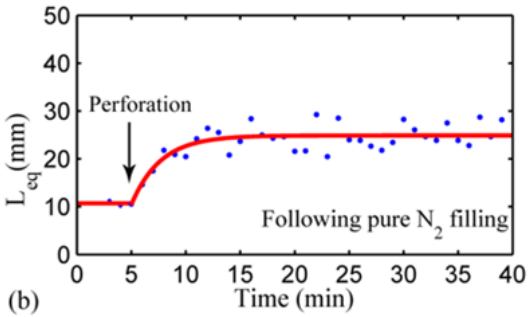




GASMAS Phantom experiments: Zhang *et al.*, 2016 Hu et al. 2019

Gas signal comes from behind the drum!





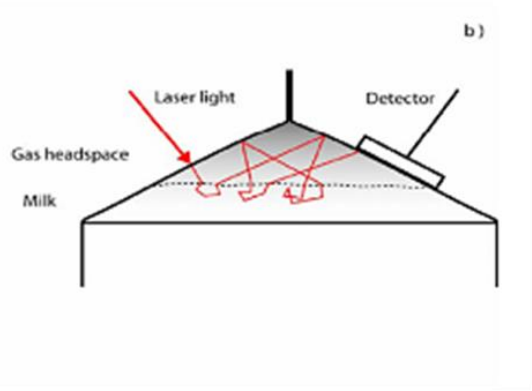
Food safety

FOOD MONITORING – FOOD SAFETY - FRESHNESS

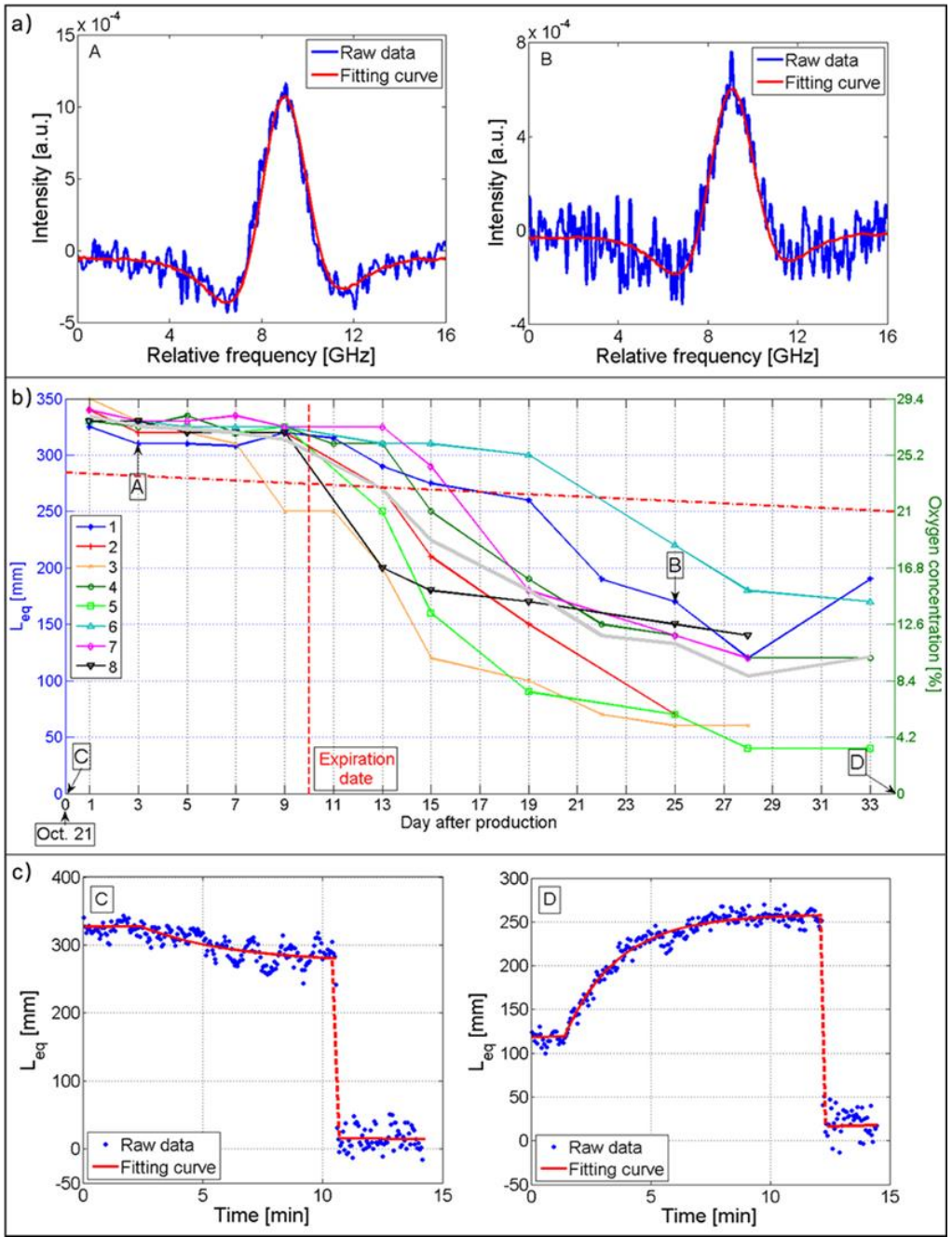
Most food is packed in modified atmosphere (low O_2, high N_2, CO_2)

Milk, bread, meat, eggs ..

Lewander *et al.*; Li *et al.*

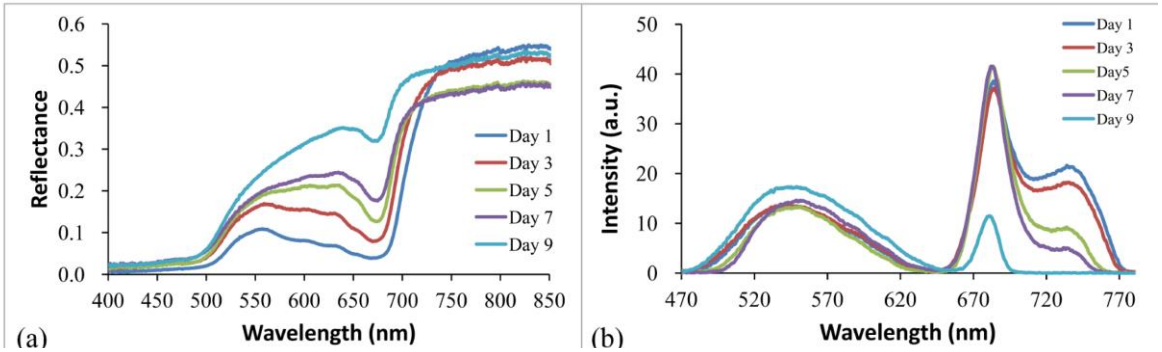


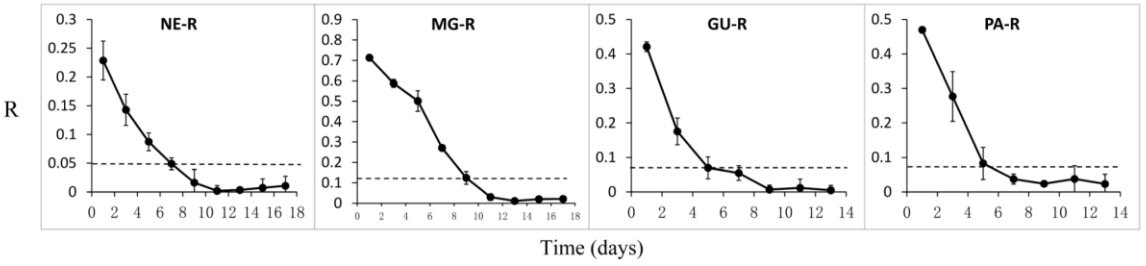
European SAFETYPACK project

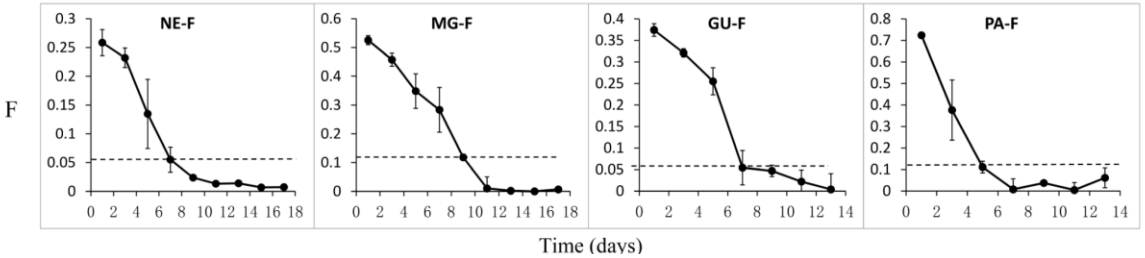


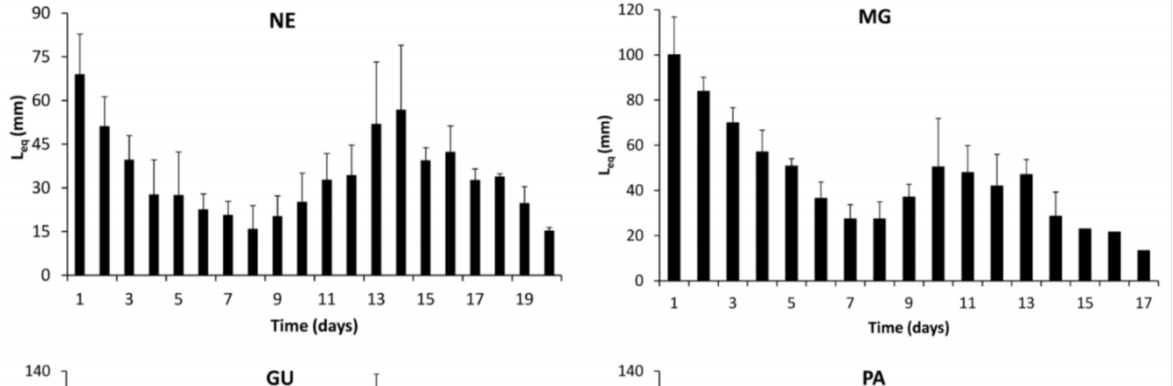
Fruit maturing

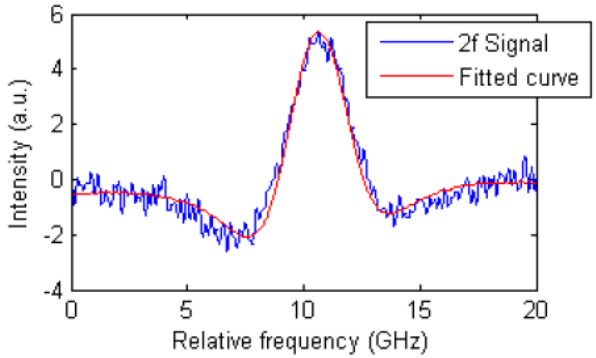
(Zhang *et al.* 2014)







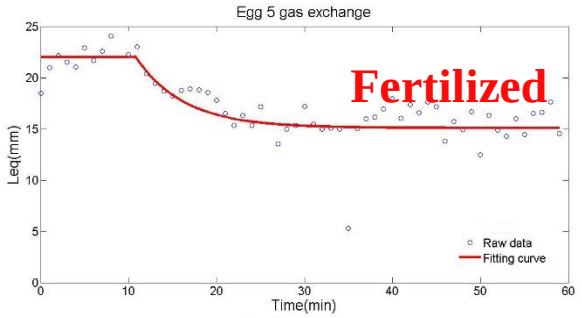


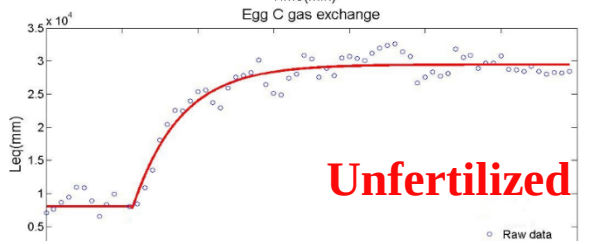


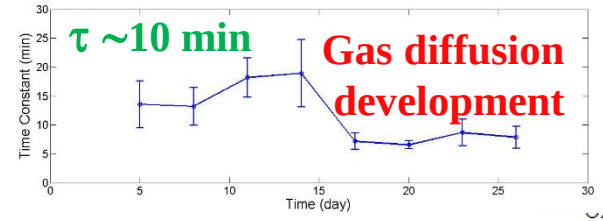
Detection of free oxygen and water vapor in hen eggs

Exploration of diagnostics possibilities

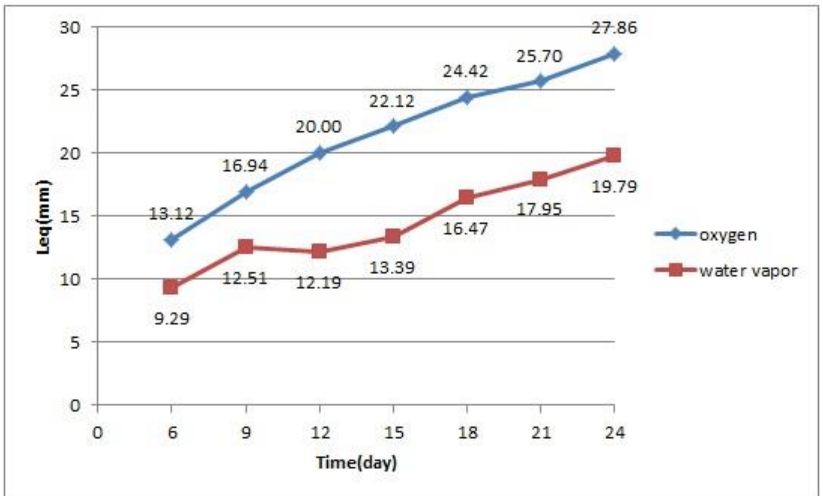
Li *et al.* J. Biophotonics 2017; 2018



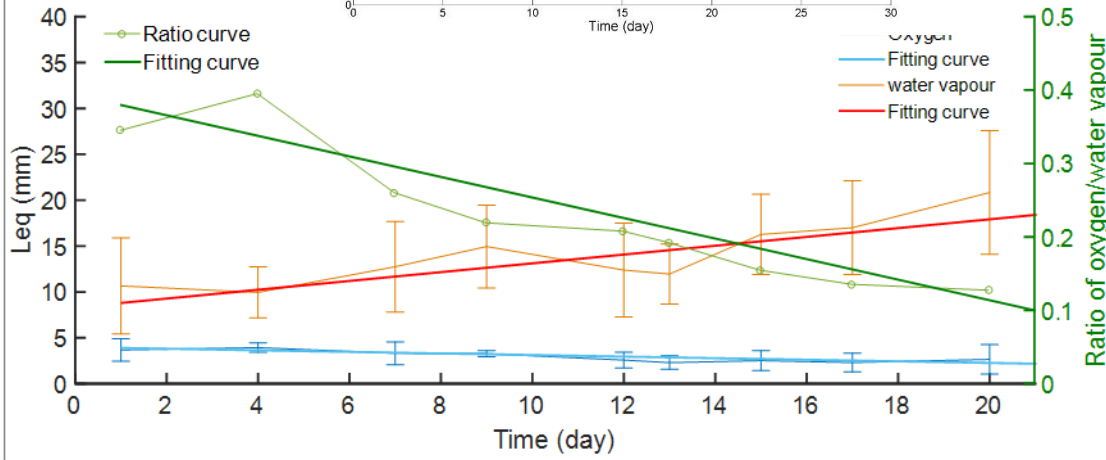




Unfertilized

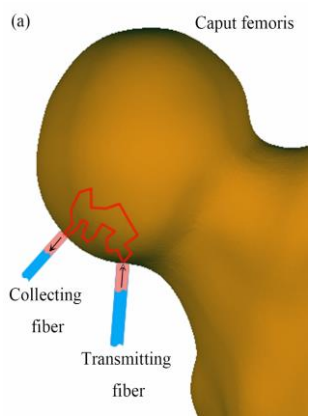


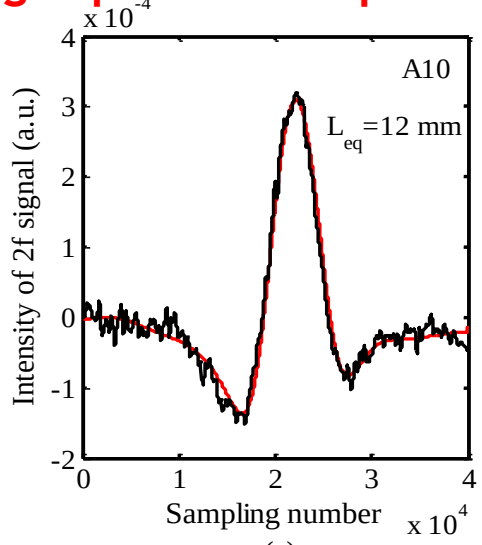
Fertilized



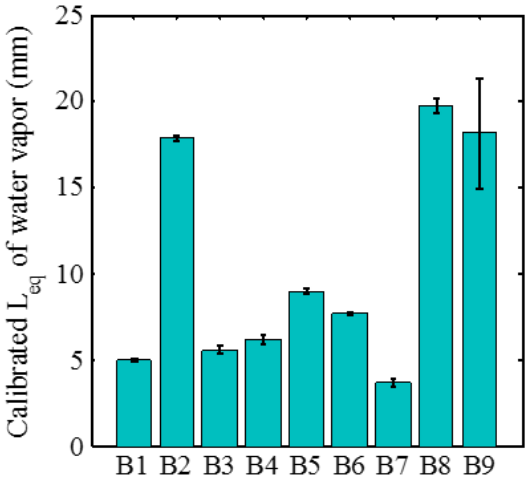
Hip replacement - developing GASMAS for diagnostics

Degradation is accompanied with gas-pore development and impaired blood flow



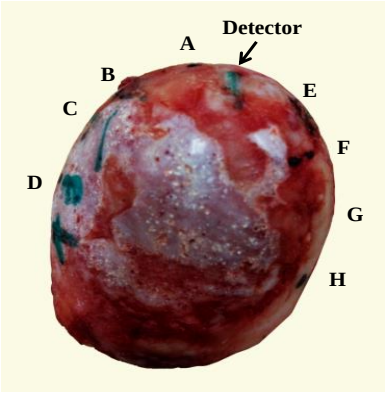


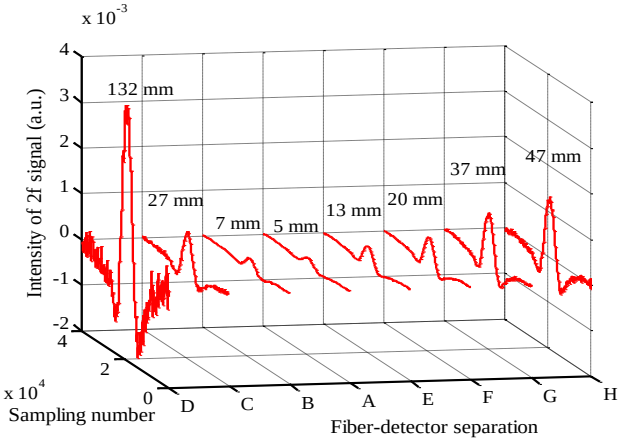
(a)

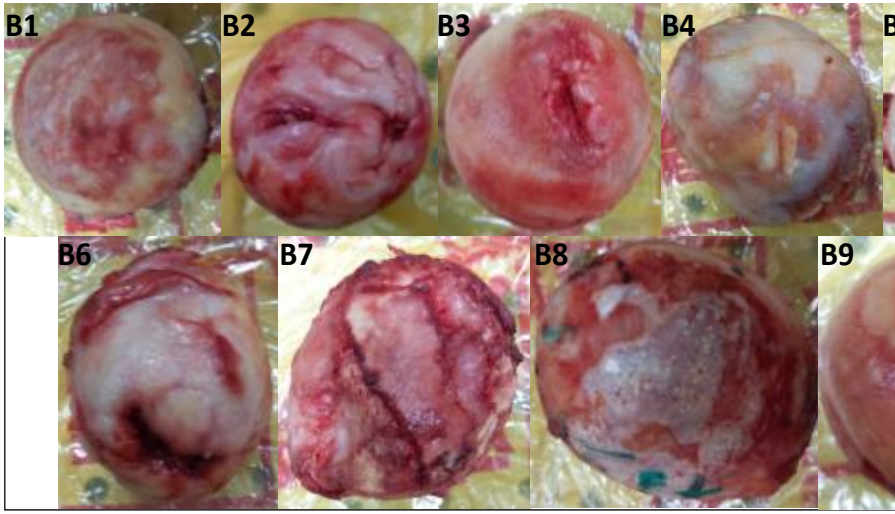


(b)

Lin *et al*. J. Biophotonics (2017)







Combine with Laser Doppler Blood Flow Measurement:

$$\frac{\Delta f}{f} = \frac{v}{c}$$

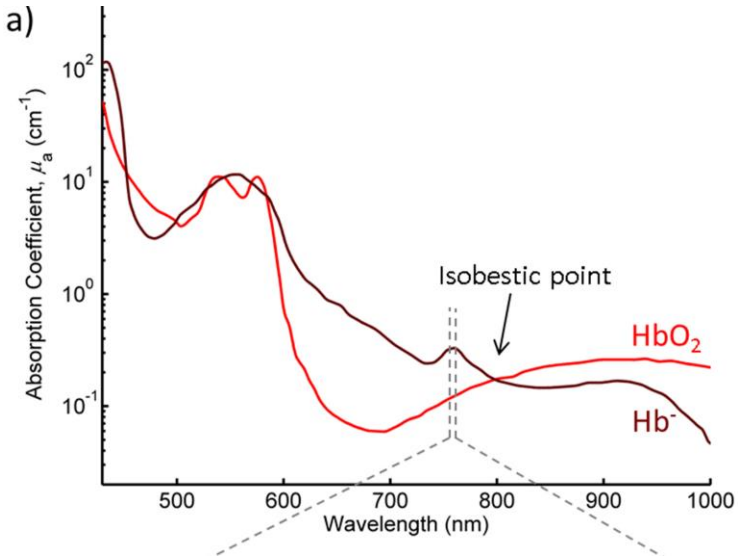
Comes for free!

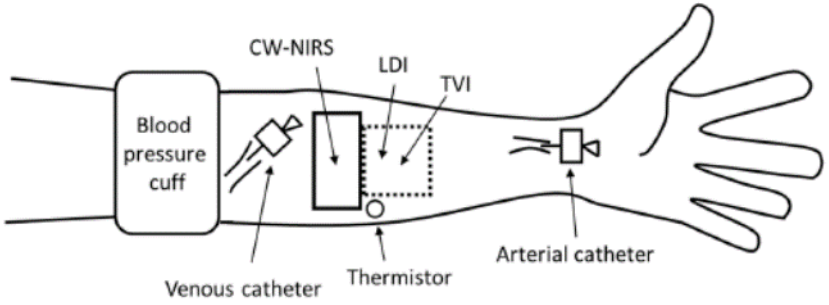
Patient oxygenation monitoring

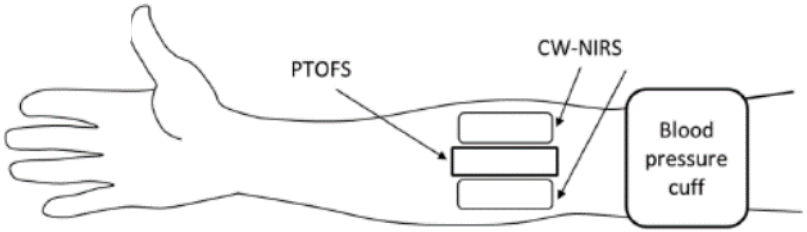
in general, and in intensive care

Steady-state or time-resolving diagnostics?

Different approaches…

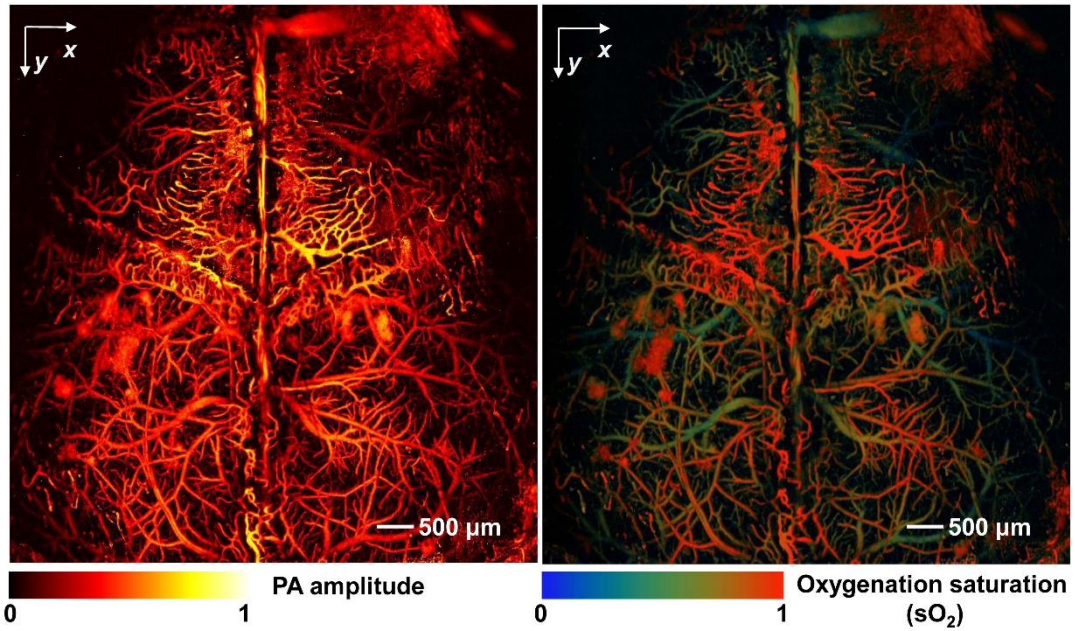




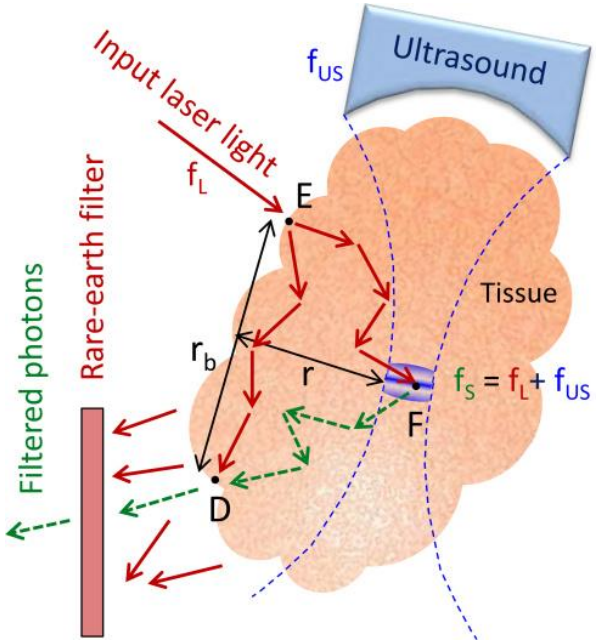


Krite Svanberg et al. (2015, and to appear)

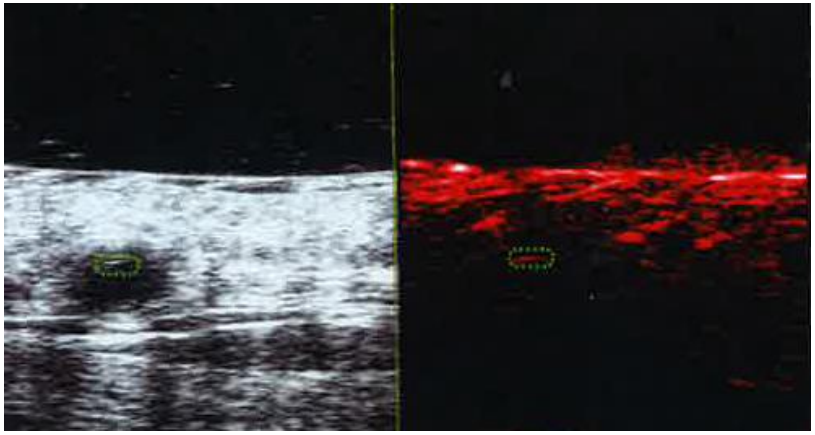
Photoacoustics for oxygenation studies



Lihong Wang *et al.*

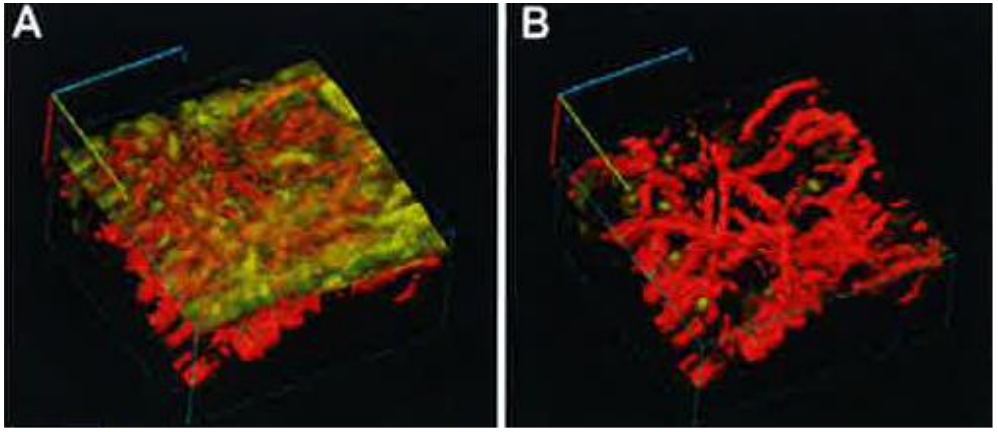


Walther, Kröll *et al.*, BOE (2017)



Temporalis arthritis

Scheikh, Malmsjö *et al.* (2018)

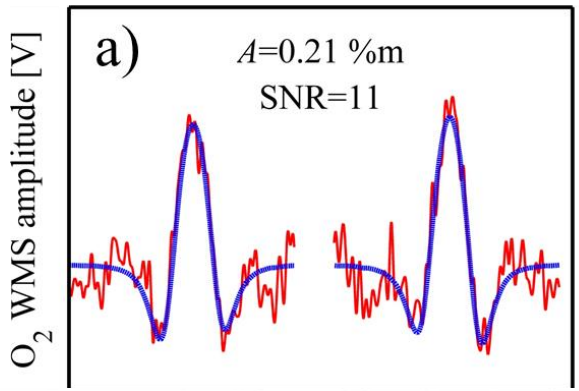


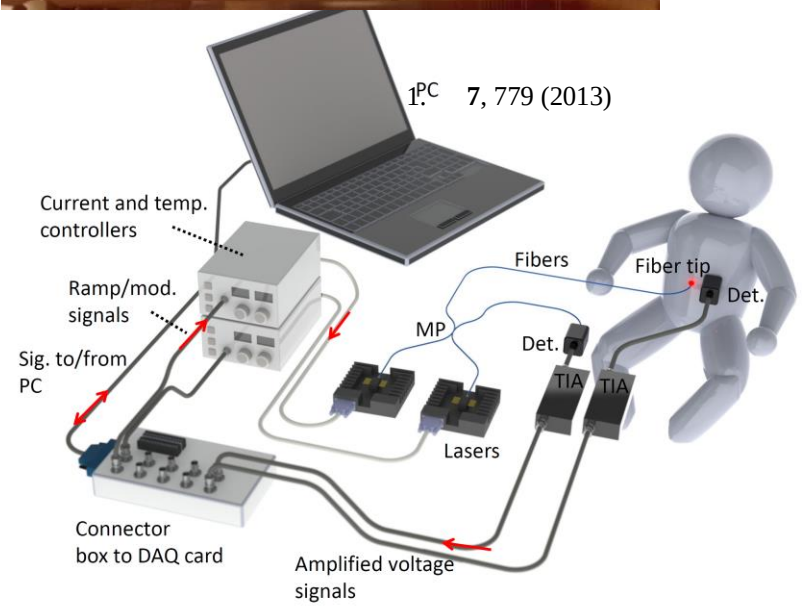
Skin vascular bed

Neonatal/Premature child monitoring

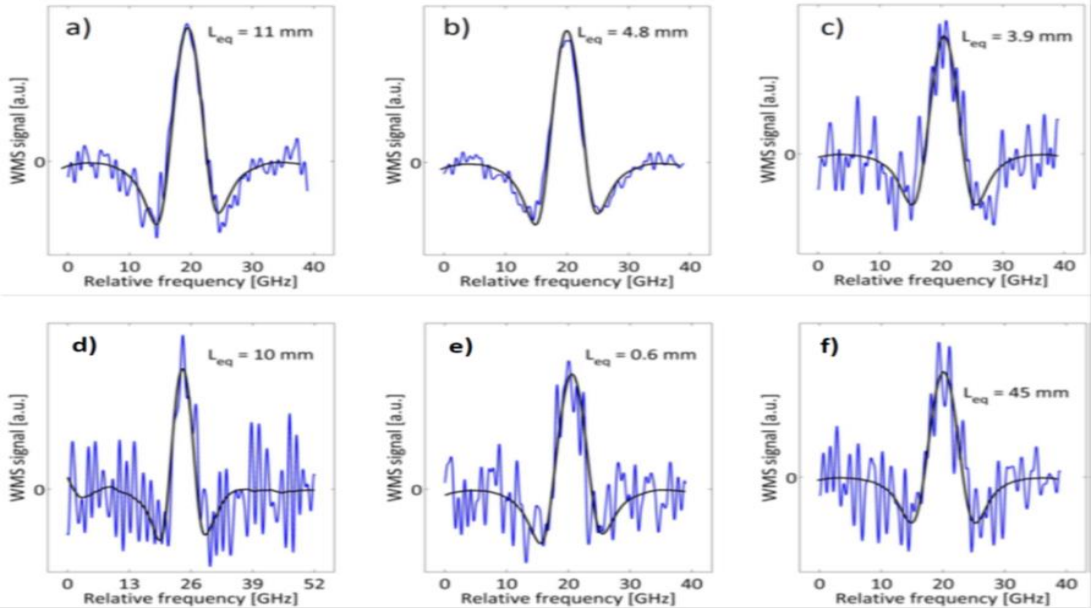
Lack of surfactant – lung problem! Eliminate X-rays! 24 h cot-side monitoring of O_2

P. Lundin *et al.*, V. Fellman, Krite-Svanberg *et al. (2015), and ongoing …*





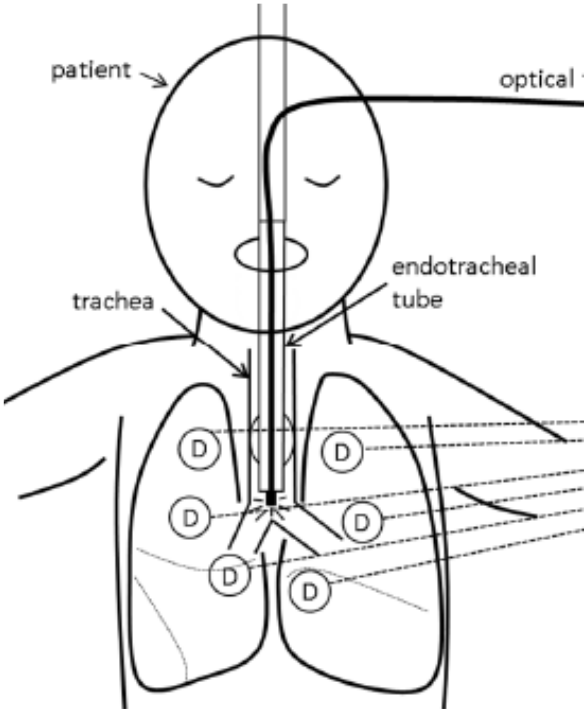
1. **7**, 779 (2013)

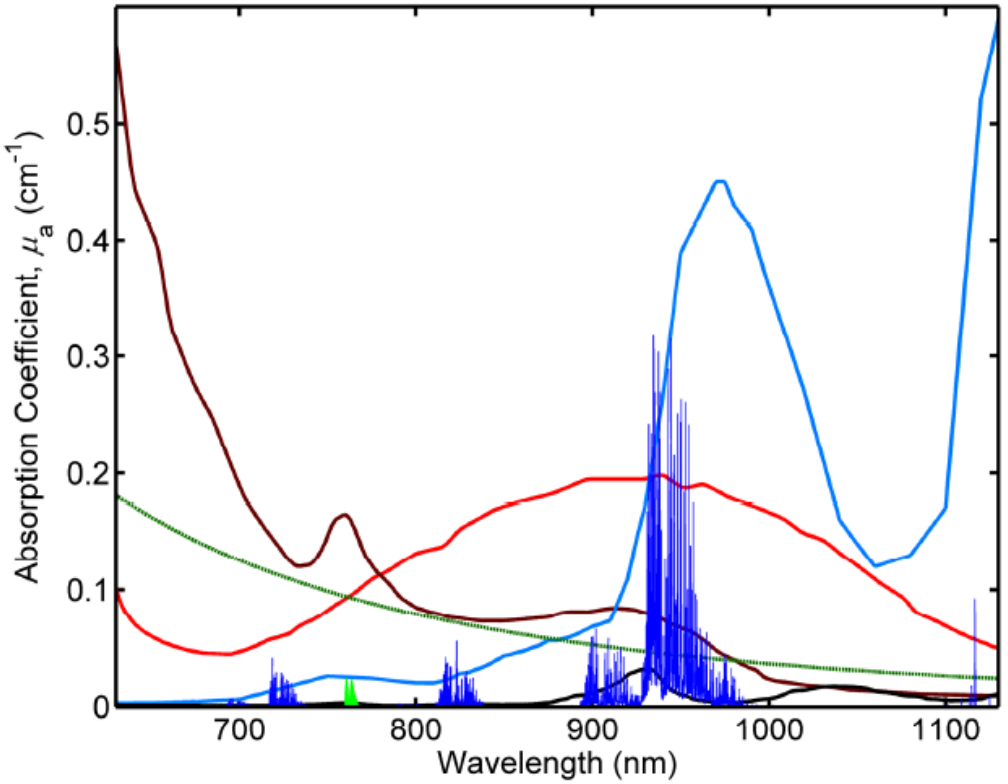


GASMAS Reviews: **S. Svanberg, Laser and Photonics Reviews 7, 779 (2013)**

K. Svanberg, S. Svanberg, in *Frontiers in Biophotonics for Translational Medicine*, in U.S. Dimish and M. Olivo (eds) (Springer, Singapore 2015) 307-321

Adult free-oxygen-in-lung monitoring?
With respirator feed-back?



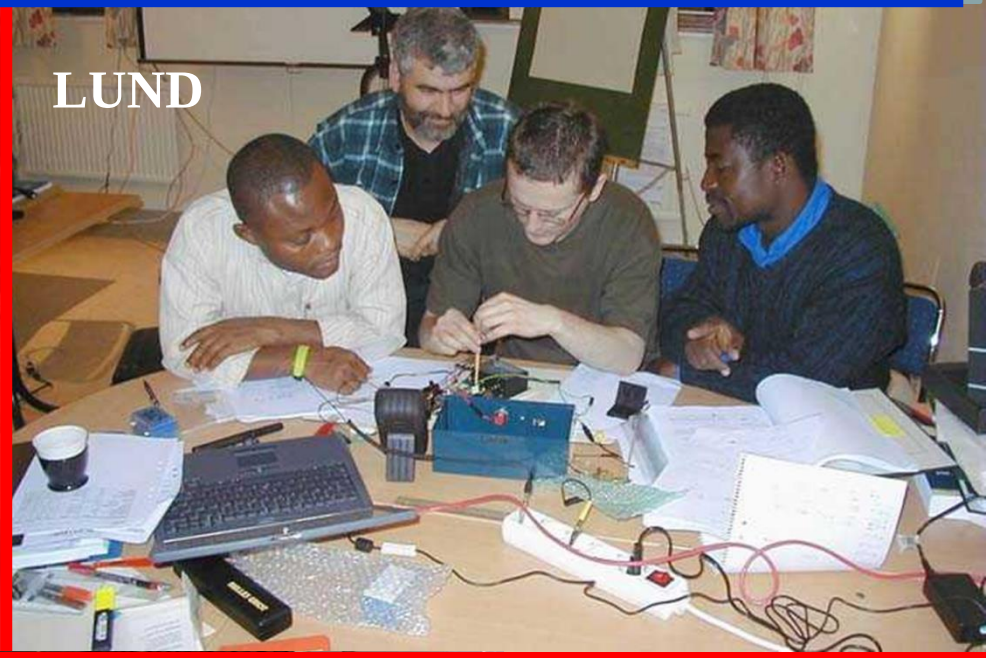


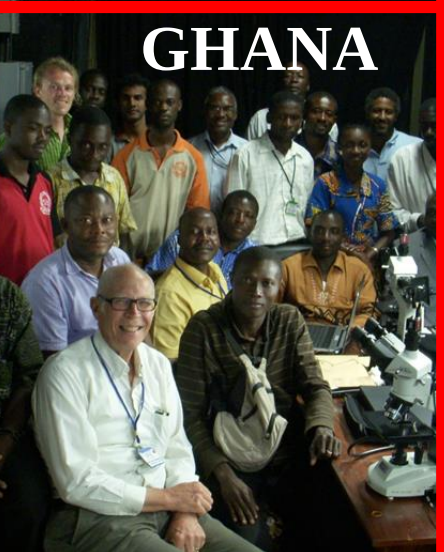
E. Krite Svanberg, S. Svanberg
SE 1500335-3 (2015)

Broad- and narrow-band absorption:
De-oxygenated blood
Oxygenated blood
Free Oxygen
Water vapour

Going beyond the borders…..

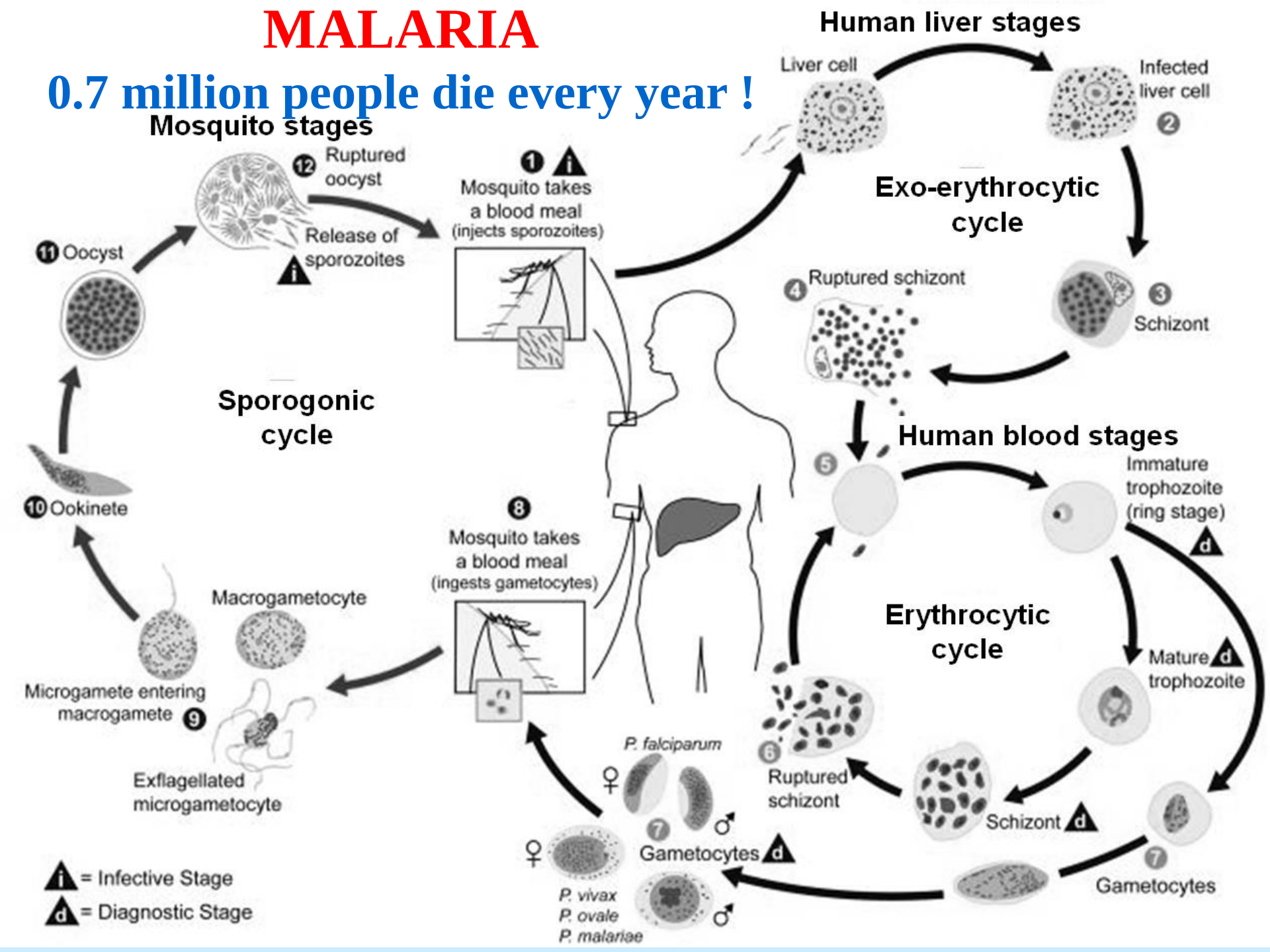
Realistic Applications for the Developing World



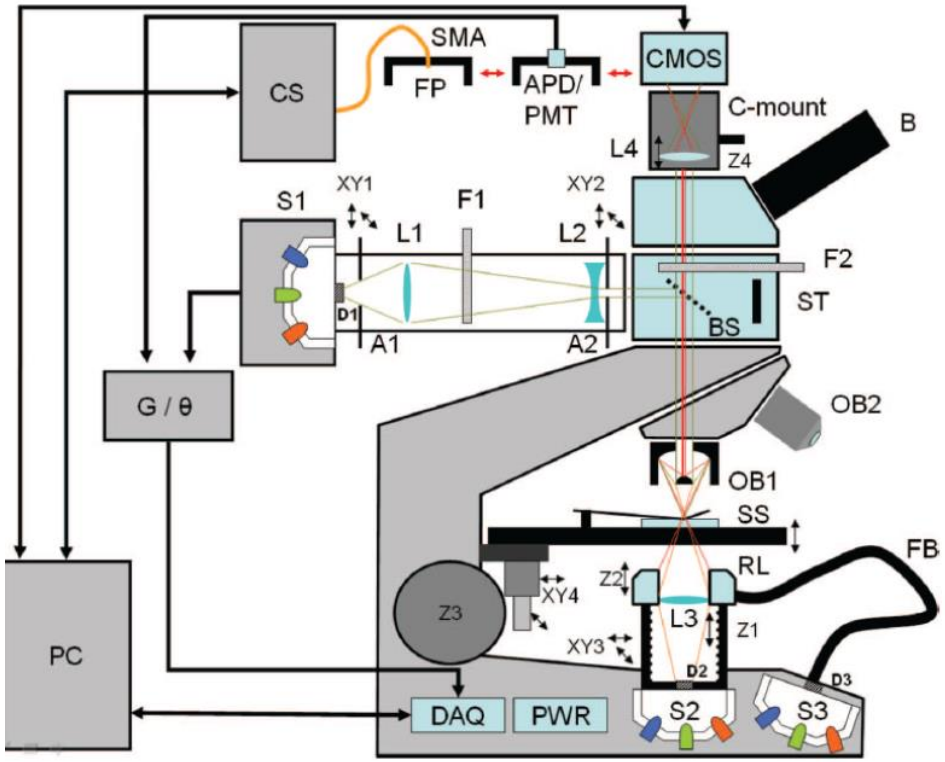


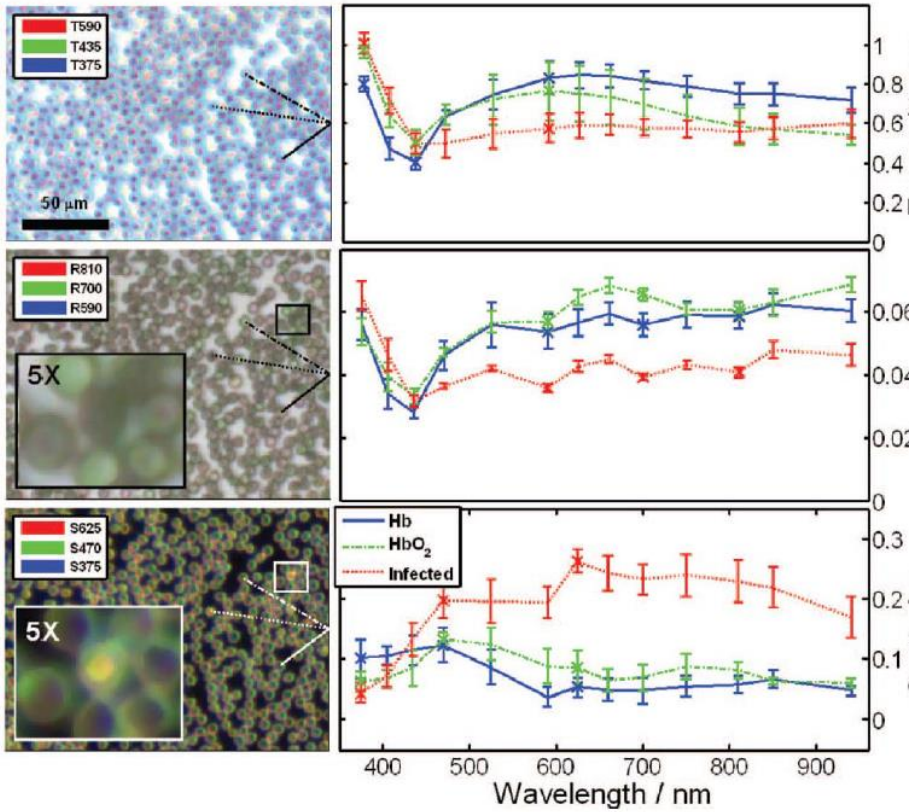
MALARIA

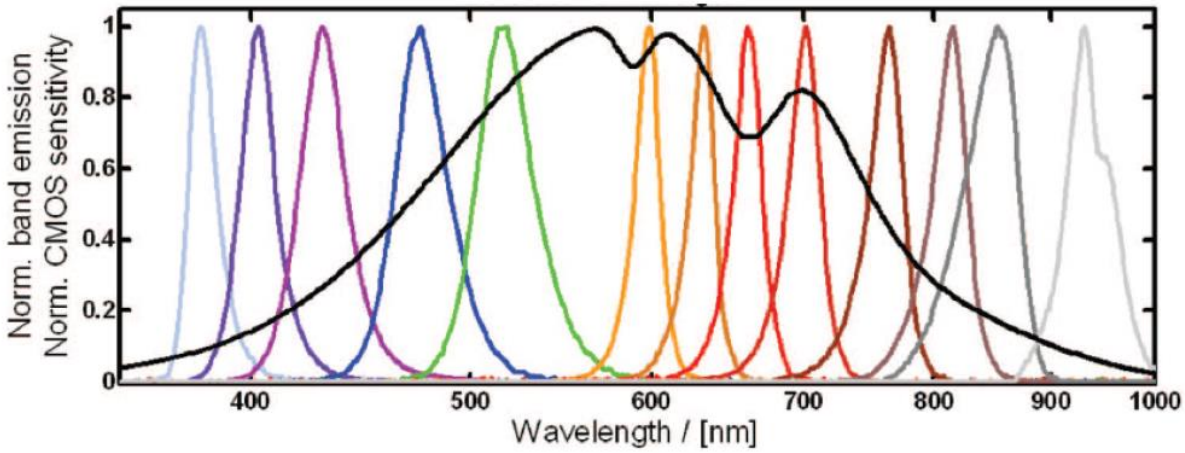
0.7 million people die every year !



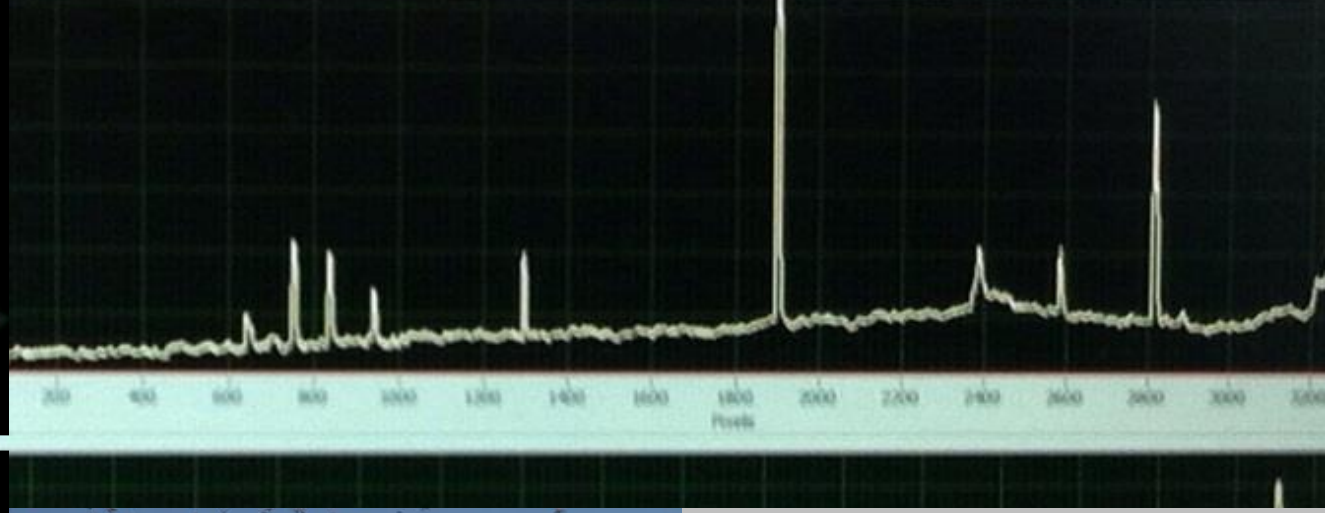
LED Multispectral microscopy malaria detection





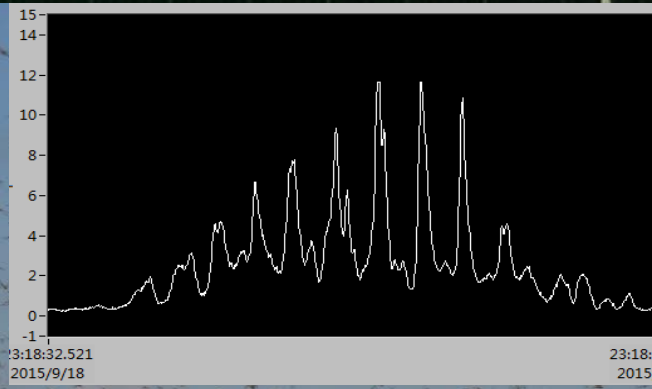


Brydegaard et al.



Insect monitoring

Pollinators
Disease vectors
Agricultural pests
Brydegaard et al.



Review of what was done and activities now

What do we presently have in Lund?

Academically:

Slow-light photoacoustic imaging: S. Kröll *et al.*
Clinical multispectral photoacoustic imaging; M. Malmsjö
Newborn baby lung monitoring by GASMAS
Diffuse and time-resolved tissue reflectance: Reistad et al.
Scattering media light propagation: Berrocal *et al.*
Agricultural/disease vector insect monitoring: Brydegaard
Laser-based proton/electron acceleration/X-ray generation

Industrially (7+ PhD trained in Biophotonics)

SpectraCure: Interstitial photodynamic therapy (IPDT)
GPX Medical: Neonatal, ENT diagnostics with GASMAS
Gasporox: Food and drug packaging (TDLAS, GASMAS)

Potential new/revived collaborations (partial list) ?

Neurosurgery: LIF, Raman, IPDT (AF, FF, Spectracure)

Orthopedy: GASMAS (AF, GPX)

ENT: GASMAS (GPX, AF, FF)

Lung: GASMAS, also on larger children (IC, Pediatrics, GPX, FF)

Oxygenation: PAI, TOFS, GASMAS (AF, IM, IC, Pediatrics)

Small animal imaging: PAI, DRS (IM, AF, IC)

Tissue optics: MC (Spectracure, FF

Microscopy: (oncology, KF, Mathematics)