





2443-19

Winter College on Optics: Trends in Laser Development and Multidisciplinary Applications to Science and Industry

4 - 15 February 2013

Biomedical applications (part 1+2)

K. Svanberg

Lund University Hospital

Sweden

Biomedical Applications

Biophotonics – Bridging the gap between medicine & physics

Katarina Svanberg

Department of Oncology, Lund University

Centre for Electromagnetic and Optical Research

South China Normal University, Canton, China





Networking and science walk together

Take always advantage of meeting people

Listen to people – learn from them (provided they have something important to teach you)

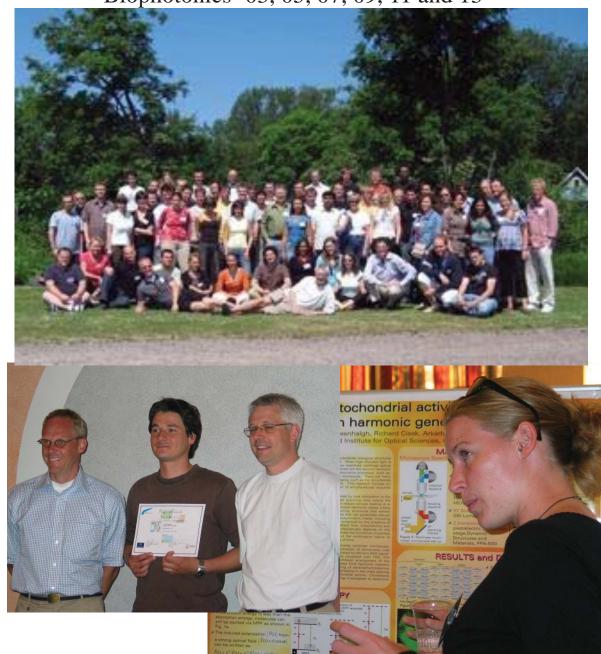
Be aware of your own competence – in particular you women

Work for improving the conditions for all of us



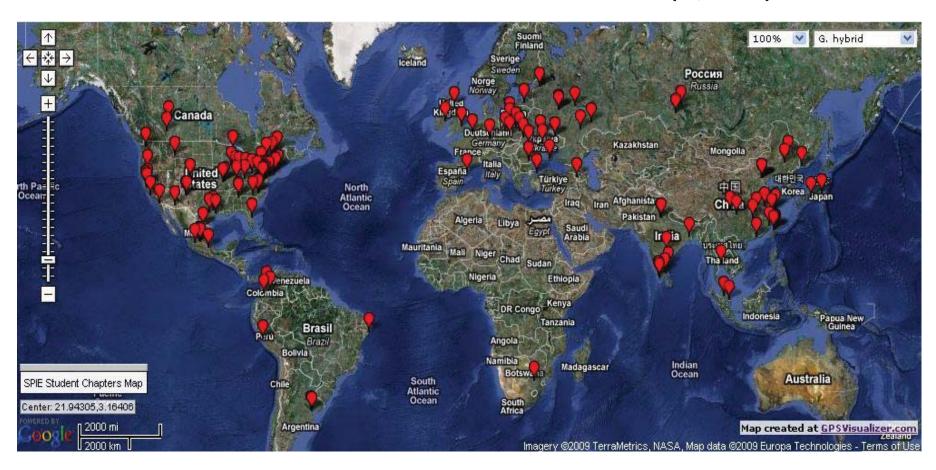


International Graduate summer school - Biophotonics' 03, 05, 07, 09, 11 and 13



SPIE - The International Society for Optics and Photonics

- 195 Student Chapters, 27 countries
- 2,400 students involved in chapters
- 27% of SPIE Members are students (4,300)





The SPIE and the OSA student chapter at Osaka University together with the two Presidents Katarina Svanberg and Chris Dainty. Also seen are Elisabeth Rogan, CEO of OSA and Satoshi Kawata, the senior leader of the SPIE chapter



Student Chapters – the SPIE version

- 5,200 student members
- 180 student chapters in 36 countries: activity grants, training & networking
- 44 student events/training at conferences in 2012
- \$350,000 is scholarships awarded annually
- Discounted memberships for students & early career
- Travel for 160 students to attend leadership training annually





Laura Mihai – the SPIE student chapter leader, Bucharest University, Romania

Mihai Pascu and Clementina Timus from the Institute of Laser, Plasma & Radiation Physics,
Bucharest University
together with Katarina Svanberg



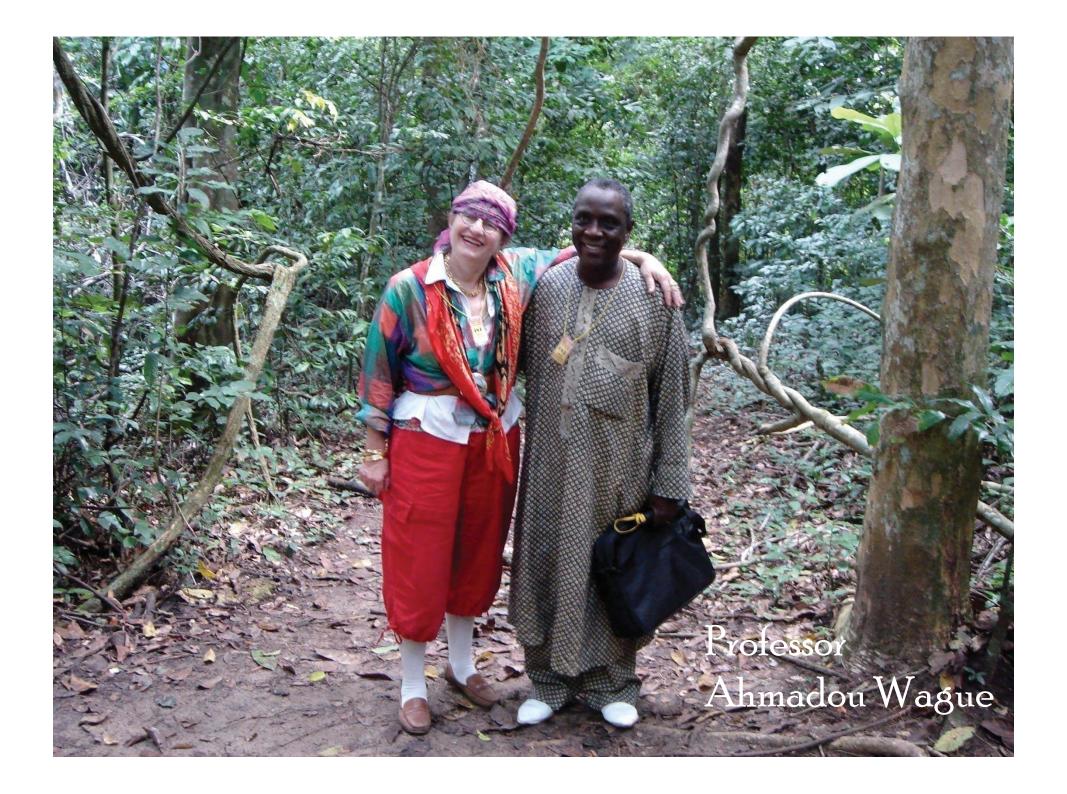


Accidental meetings may make the whole diffence



Sune Svanberg at his desk as a very young scientist







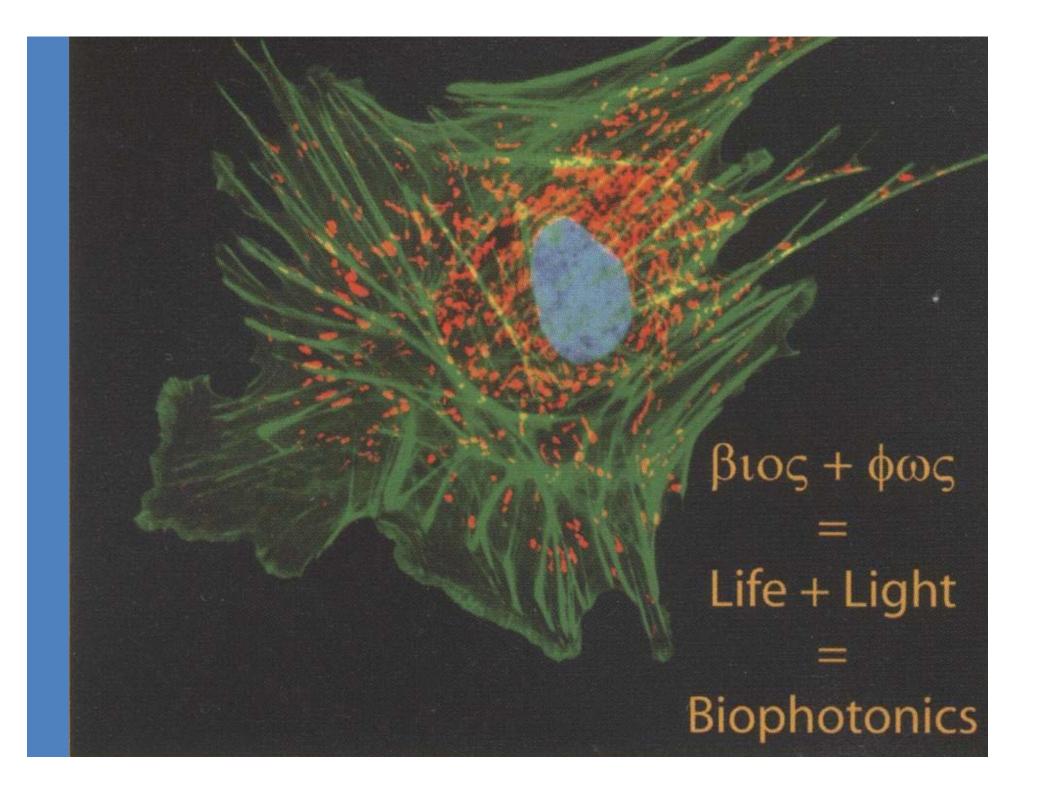




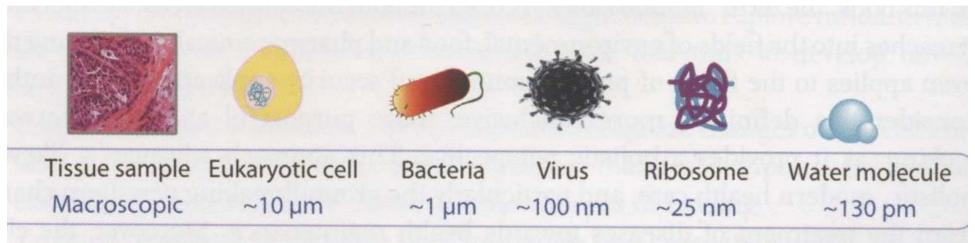
Ragnhildnew born Little Sister

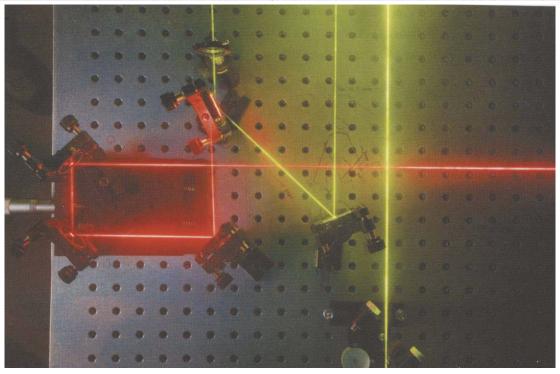
Soon opening her eyes to the world We as scientists can help to make the world a little bit better place to live for all of us!



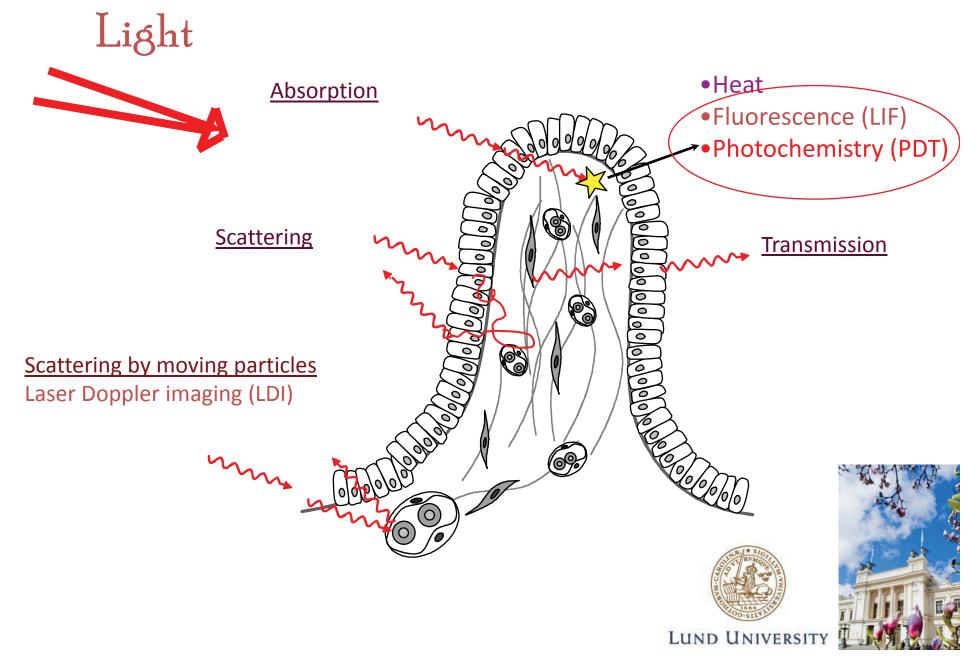


Biological objects + light = BioPhotonics



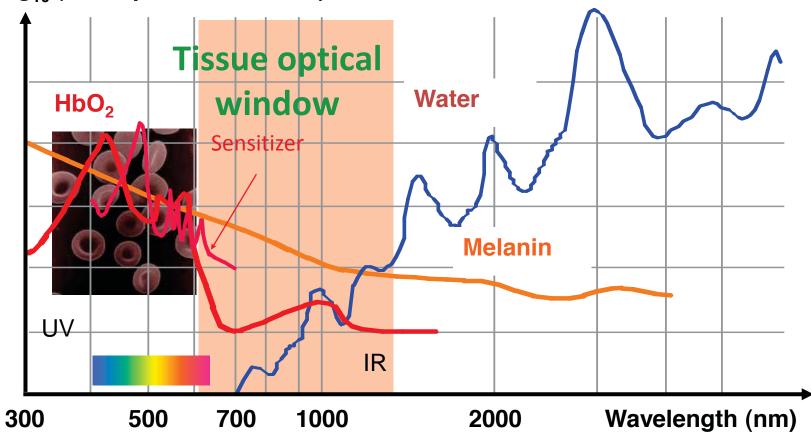


Light-tissue interaction

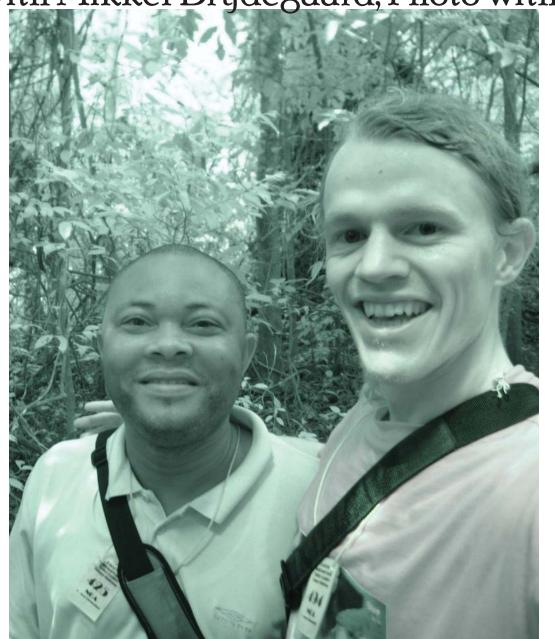


Light interaction with biological tissue The main absorbers

Log₁₀ (Absorption coefficient)



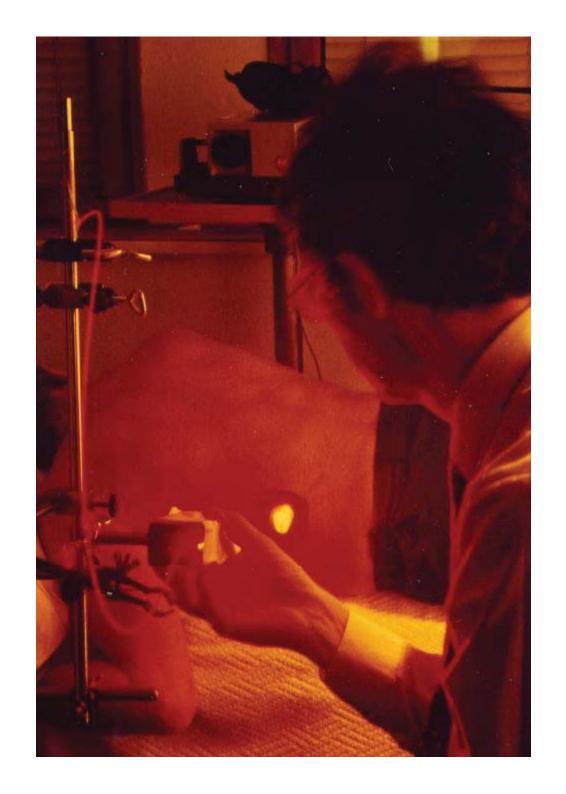
ICTP representative – Benjamin Anderson from Ghana together with Mikkel Brydegaard; Photo with an IR filter



We started
Biomedical Optical
Research in 1982

1st clinical PDT session in Scandinavia was performed by us in 1987

Lund University Medical Laser Centre was established in 1991



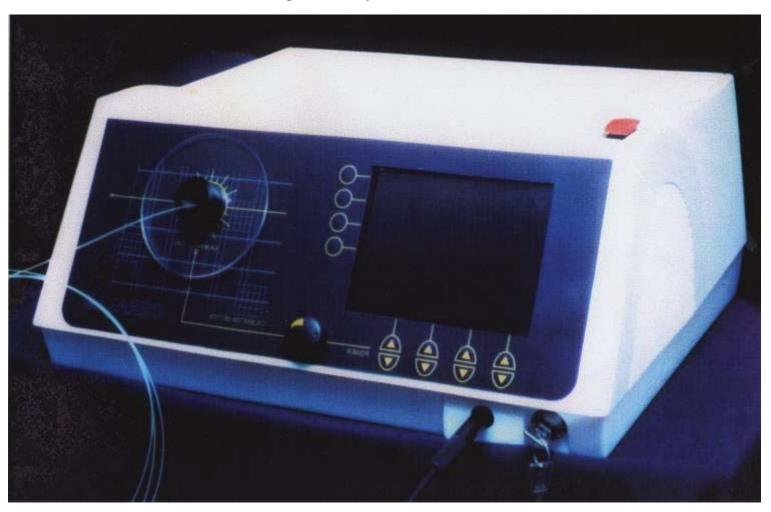
PDT treatment at the
Lund University Hospital
(Oncology Department)
with a frequency doubled
Nd:YAG laser
pumping a tunable
dye laser



635 nm

532 nm

Clinically adopted diode laser



CeramOptec/BioLitec



Lund Biophotonics Group

Stefan Andersson-Engels Katarina Svanberg Sune Svanberg

Dmitry Khopyar Märta Lewander Erik Alerstam Johan Axelsson Niels Bendsøe

Haichun Liu Hayian Xie Emilie Krite Svanberg Pontus Svenmarker Tomas Svensson

Gabriel Somesfalean Zuguang Guan Jonas Johansson Peter Andersen Can Xu Mikkel Brydegaard







































Lund University

Medical Laser Centre



For the future, the network's overall goal remains unchanged. Europe holds a strong position in biophotonics research. We will continue to build on this world-class resource in order to address the 'Grand Challenge' of sustainable health care. «

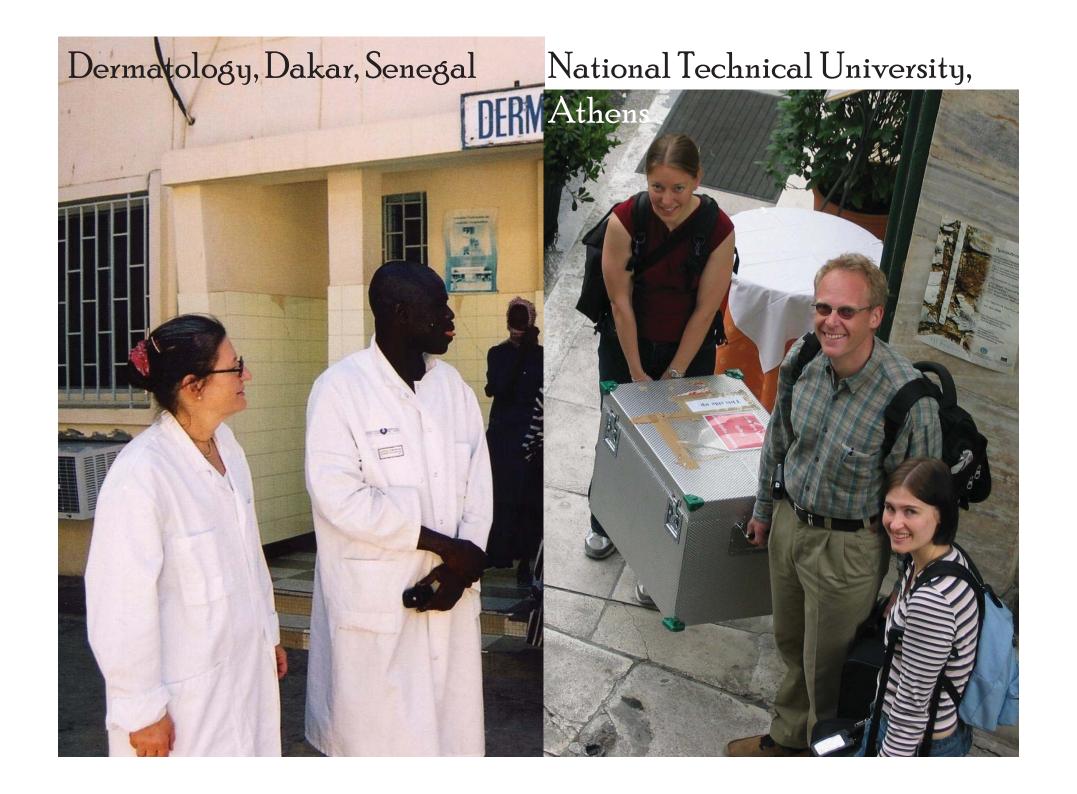
Cross disciplinarity is the key





Biolitec & Friedrich Schiller University, Jena, Gernany

Oncology
Physics
Dermatology
Cell biology
Industry







Universities and hospitals
where we performed
joint clinical and preclinical

work

•Radiumhospitalet, Oslo, Norway

•Karolinska Hospital, Stockholm

•Latvian Oncology Center, Riga

•Vilnius University, Lithuania

•London Medical College, GB

•Lübeck University, Germany

•St Pieter Hospital, Leuven, Belgium

•Friedrich Schiller University, Jena, Germany

•Padova University, Italy

•Porto Univeristy, Portugal

•National Technical University, Athens, Greece

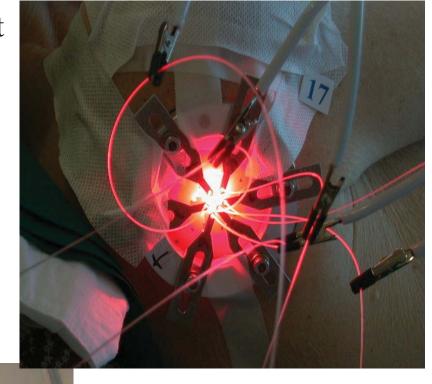
•Cheik Ante Diop Hospital, Dakar, Senegal



Joint clinical/scientific collaboration at Latvia Oncology Centre, Riga







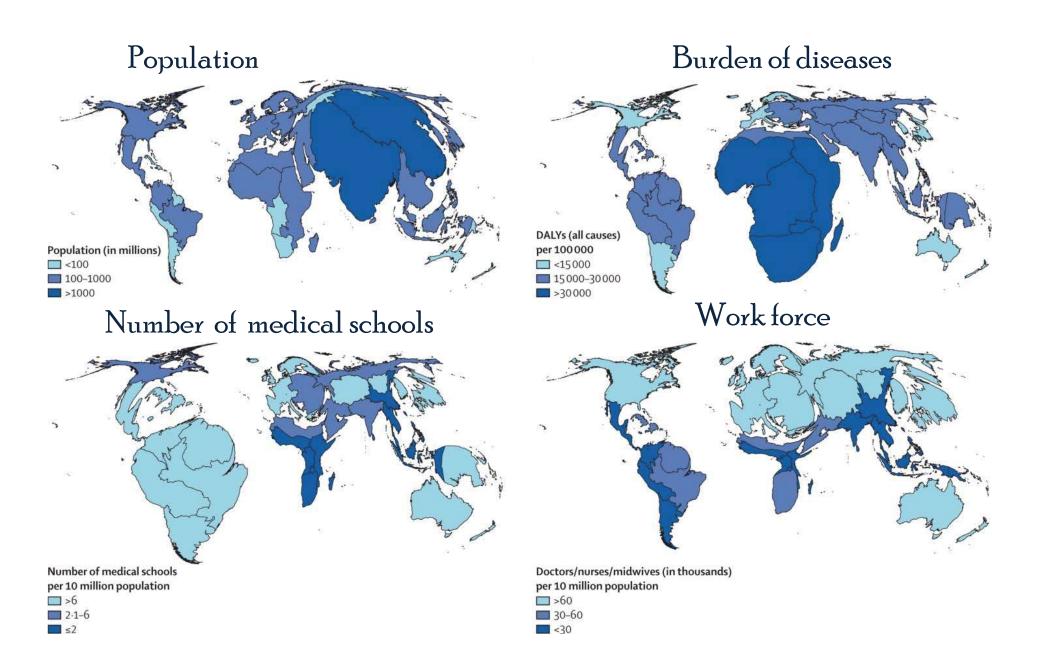
RIGA

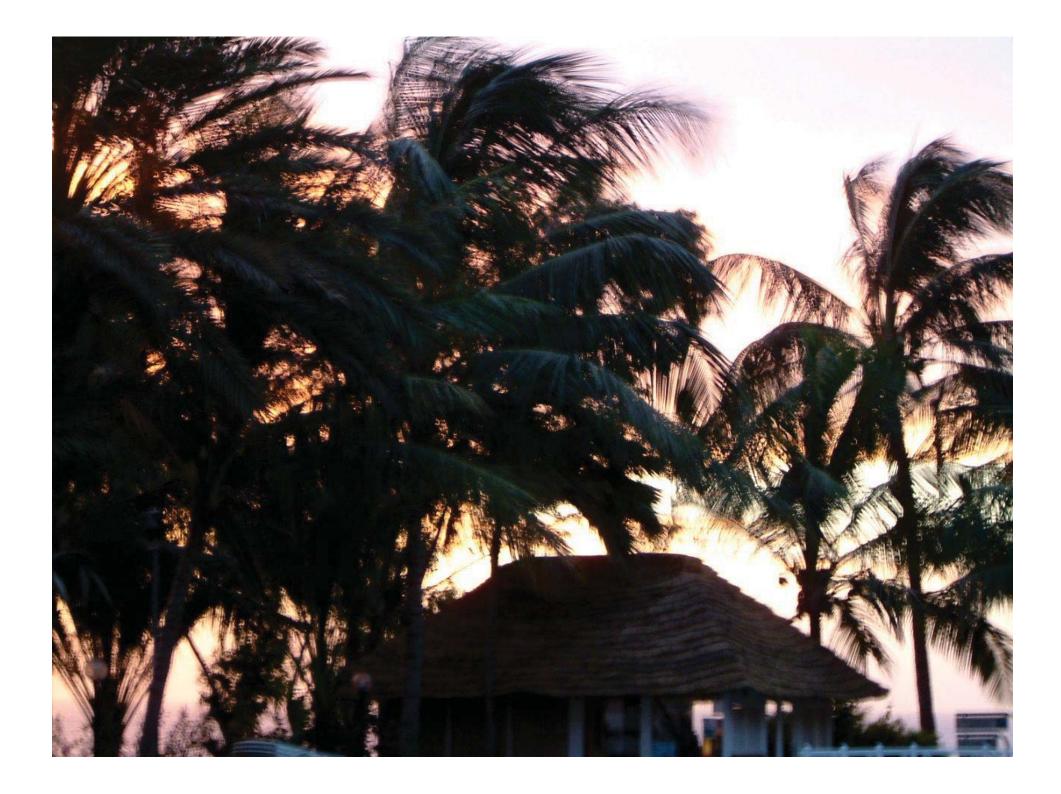
Alexander Derjabo, Janis Kapostins Janis Spigulis

LUND

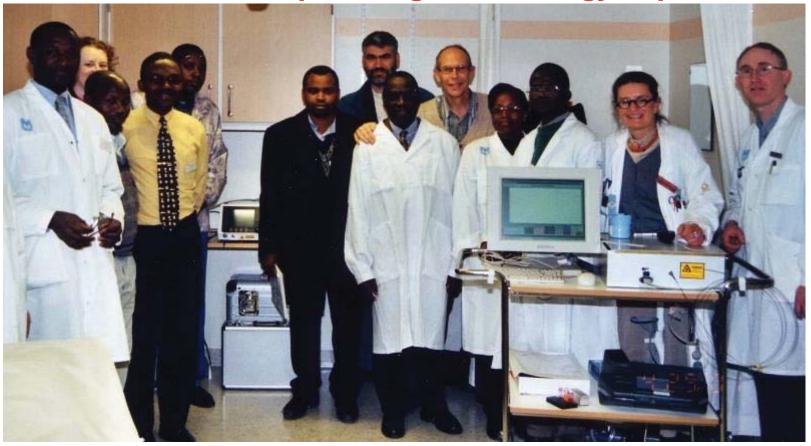
Katarina Svanberg Niels Bendsoe, Thomas Johansson, Marcelo Soto Thomson, Sune Svanberg

The global perspective





African-Lund Workshop visiting the Oncology Department



FROM LEFT TO RIGHT: Malick Diop, Sara Pålsson, Ababakar Abdalla, Kenneth Kaduki, Almamy Konte, K. Dzinavatonga, Jaidane Nejmedinne, Ahmadou Wague, Sune Svanberg, N. Ndolovu, M. Mathuthu, Katarina Svanberg and Niels Bendsoe.

Senegal, Kenya, Zimbabwe, Ghana, Sudan, Tunisia, Equador

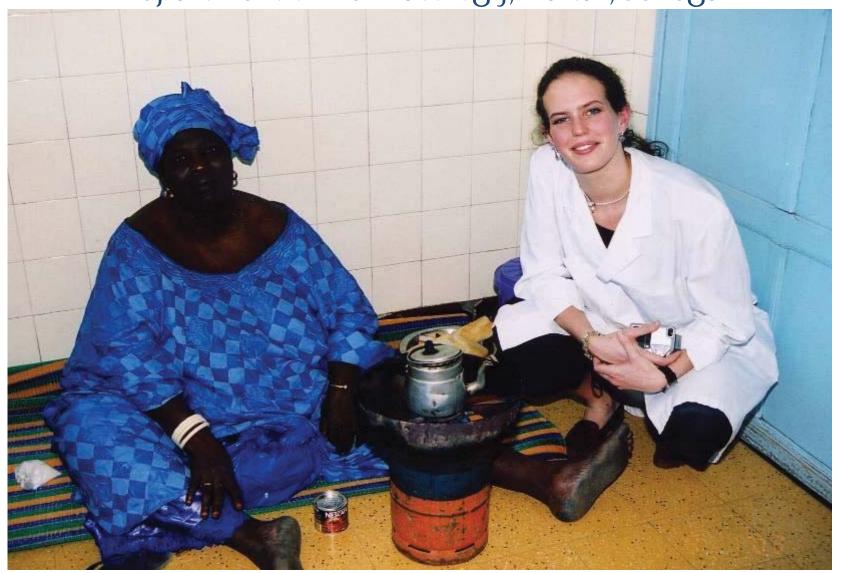




Discussing treatment possibilities



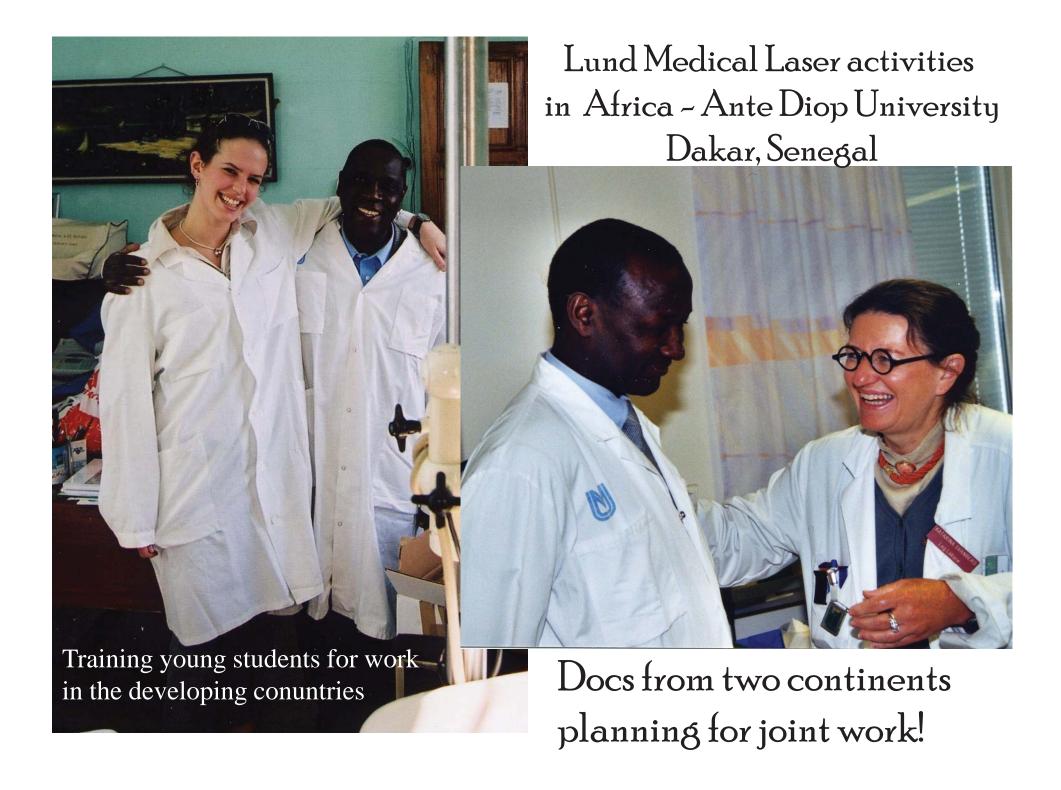
The African wife cooking food for her husband at the Department of Dermatology, Dakar, Senegal

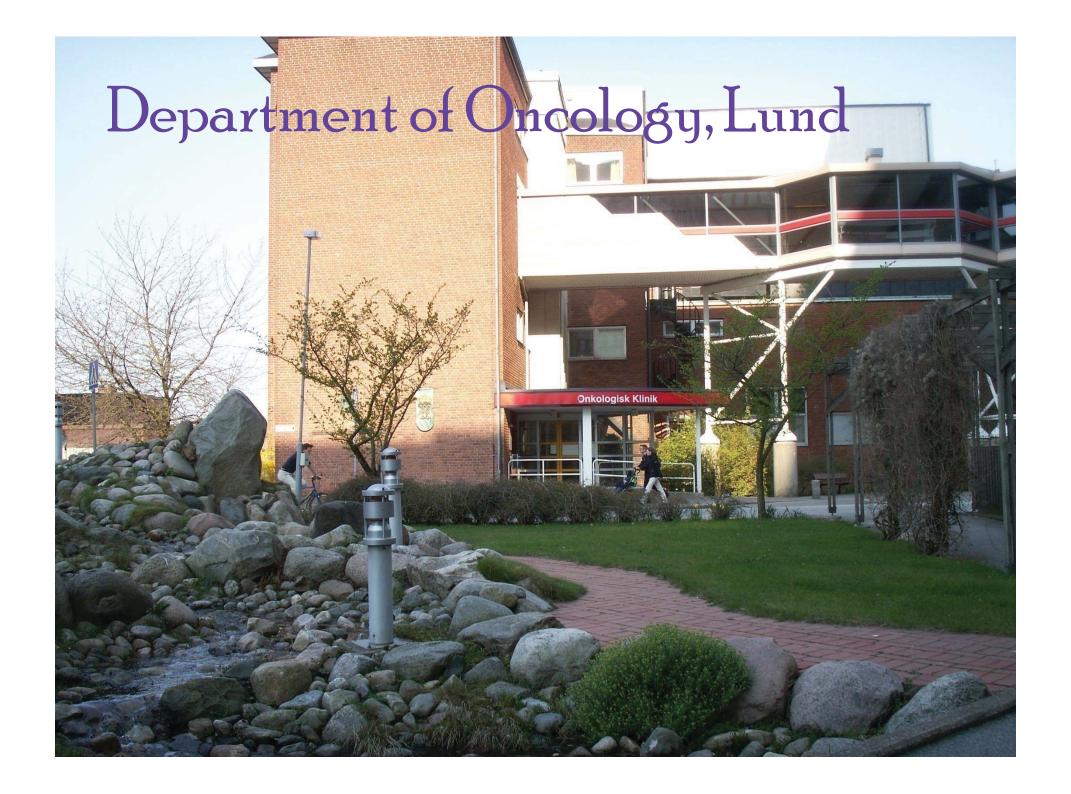


Wives never give up to support their husbands!

Photodynamic Therapy at the Arsitide le Dantec University Hospital Dakar, Senegal







Cancer in Europe

4-5 new diagnosed cancers/1000 persons each year – 1 person every 15 minutes in Sweden (9 milj)

The cancer incidence varies from region to region Highest incidence in the urban areas
The highest incidence of breast- and prostate cancer
in big cities

Cancer In the US
Approximately 1.2 million people/year are diagnosed with cancer.

Approximately 30 % of all deaths in the Western World are caused by cancer.

Only cardiovascular disease causes more deaths.

Epidemiology The cancer incidence is increasing

Urbansation fast food

obesity

pollution

family structure

Social habits **SMOKING**

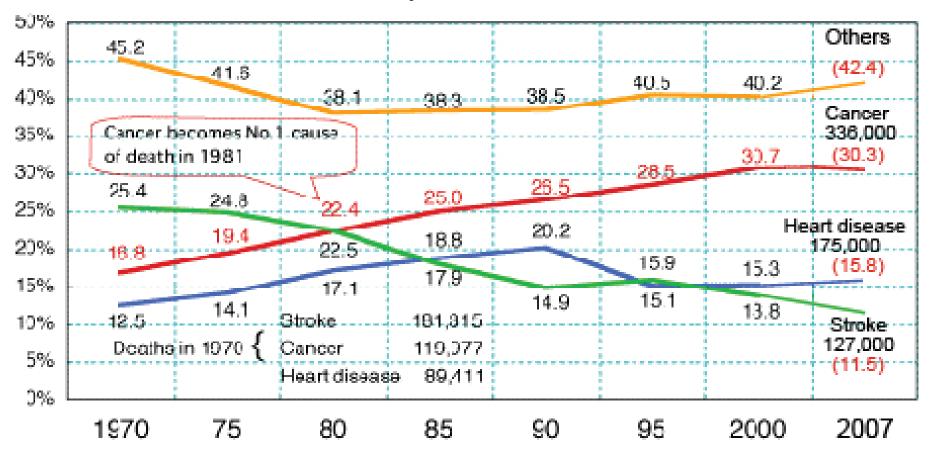
giving birth to children at later age

anticonceptual treatment

less breast feeding

Life aspect AGE

Death rates in Japan for various diseases



Approximately 30 % of all deaths in the Western World are caused by cancer.

Only cardiovascular disease causes more deaths.

The ten most common malignancies world wide causing cancer related deaths

M en Women

Lung Breast

Prostate Cervix

Large intestine Large intestine

Stomach

Mouth & throut Lung

Liver Ovary

Oesophagus Mouth & throut

Urinary bladder Uterus

Lymphoma Lymphoma

Leukemia Leukemia

Skin cancer is an increasing problem with increasing costs!

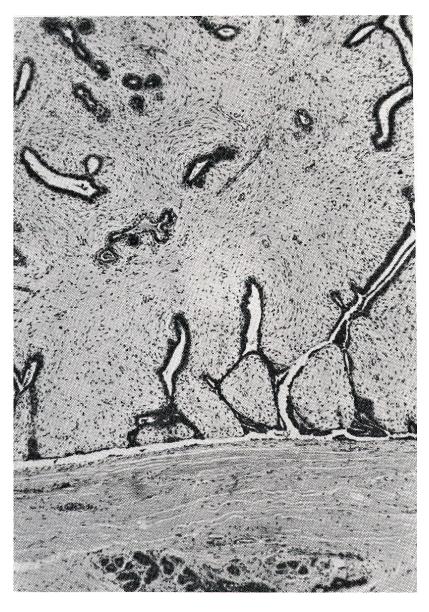


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Modified from Ringborg *et al.*

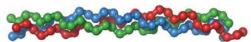
Medical Laser Centre

Katarina Svanberg



A benign tumour
(an adenoma)
clearly separated from the
normal non-affected tissue
below the tumour

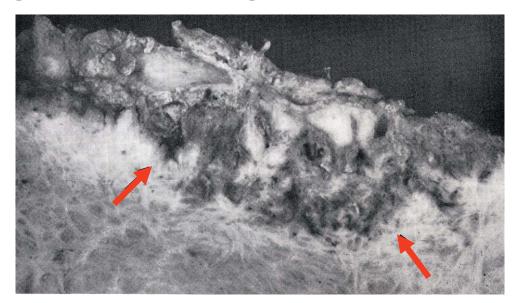
The "line" in between is composed of collagen



Never a cross over of tumour cells through the border line



Benign and malignant neoplasias



Benign lesion is:

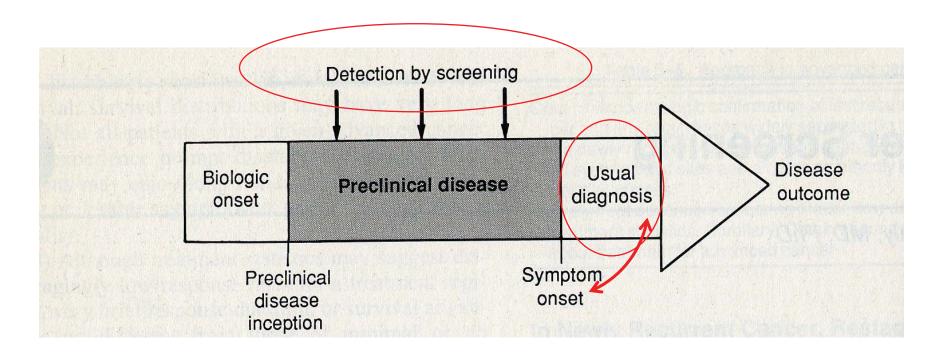
- not life-threatening
- •is slow growing
- •will not disseminate (no metastasis)
- •is amenable to remove with full cure for the patient

Malignant lesion has the potentials of:

- rapid growth
- •invasion
- destruction of adjacent structures
- dissemination (metastasis)
- •killing the patient!

Modified from Robbins *et al.*

The goal is to find the cancer early as this improves the prognosis for the patient



Modified from G.R. Weiss

5-year survival for different staging in lung cancer

(histopathologically non-small lung cancer)

Stage I		T1N0M0		T2N0M0
		60%		38%
Stage II		T1N1M0		T2N1M0
		34%		24%
Stage IIIa		T3N0M0 22%	T3N1M0 9%	T1-3N2M0 13%
Stage IIIb		T4N0-2,M0		T1-4N3M0
		7%		3%
Stage IV	M1			
	1%			

Optical tissue diagnostics

Spectroscopic techniques:

Fluorescence

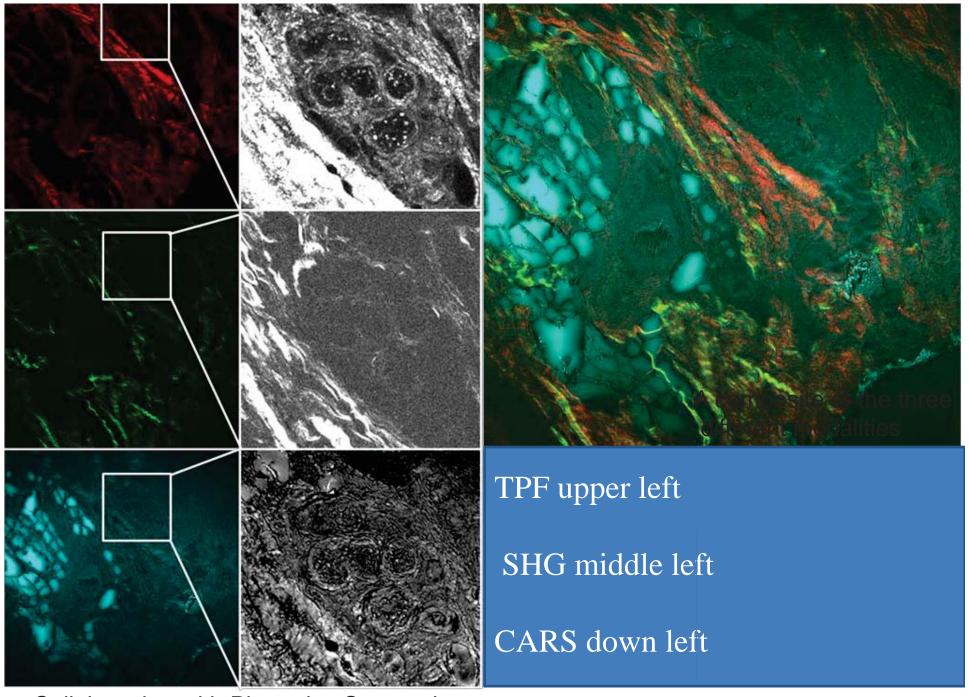
Reflectance

Elastic Scattering

Raman

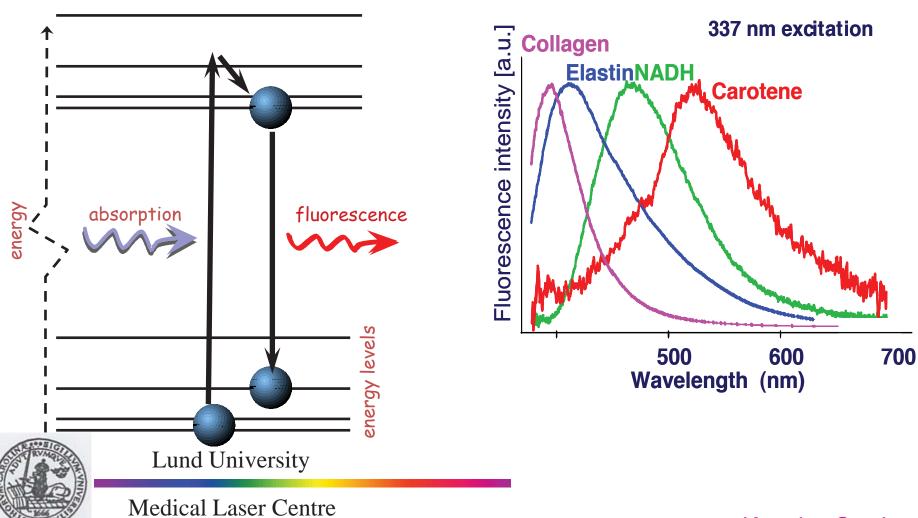




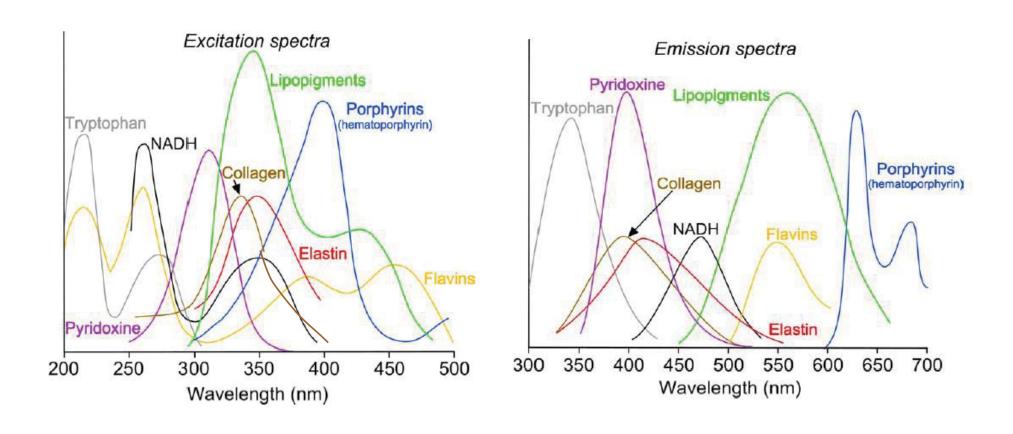


Collaboration with Photonics Center, Jena

Fluorescence excitation & emission Autofluorescence



Excitation and emission spectra for endogenous and exogenous fluorophores



Choice of wavelength

Fluorescence detection

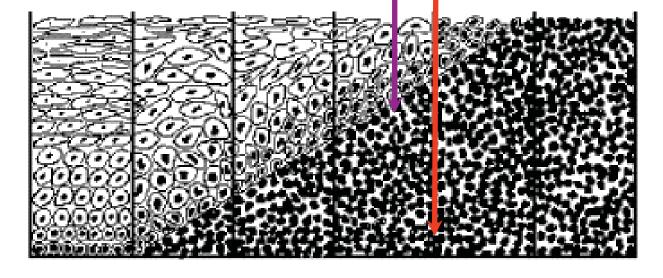
UV or near-UV excitation light (337 - 405 nm)

Shallow penetration – premalignant or carcinoma *in situ* detection

Upwelling fluorescence not "diluted" from deeper tissue

Photodynamic therapy
"Red" light (635 ~ 750 nm)

-to match the absorption peak of the photosensitizers-to obtain deep tissue penetration(TUMOUR THERAPY)

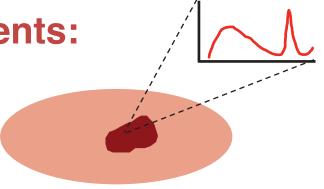


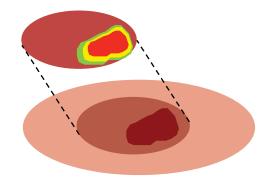


Different geometries

Point measurements:

- All colours
- In one single point





Imaging measurements

- One or few colours
- Over the whole area

Tissue fluorophores/chromophores

Endogenous Tissue Fluorophores

Extracellular

<u>Intracellular</u>

Collagens

Elastin

mucin

NADH/NAD+

Oxidised flavins

Keratin

Melanin

Porphyrins

Lipofucin

Vitamin B derivatives

Cholosterols

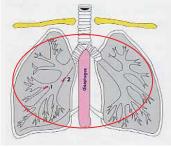
Aromatic amino acids

Example of clinical applications

Endoscopic diagnostics

& treatment

Bronchus



Surface (direct) detection & treatment

Cervix



Oesophagus



ENT



Large intestine - colon





Lund University







Katarina Svanberg

Skin cancer – related costs

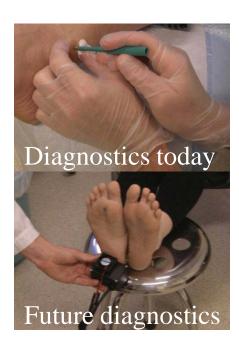
Approximately 150 000 benign naevi are excised yearly to a cost of 30 000 000 Euro in Sweden 49/50 persons are operated "unnescessarily"

Total costs for skin cancer treatment each year:
125 000 000 Euro – Sweden
1 000 000 000 Euro - Germany

Better diagnostics/treatment needed



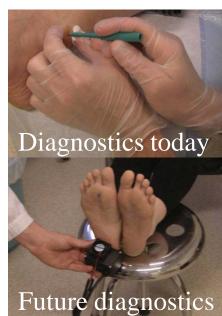
Lund University



Challenges of today in the clinic



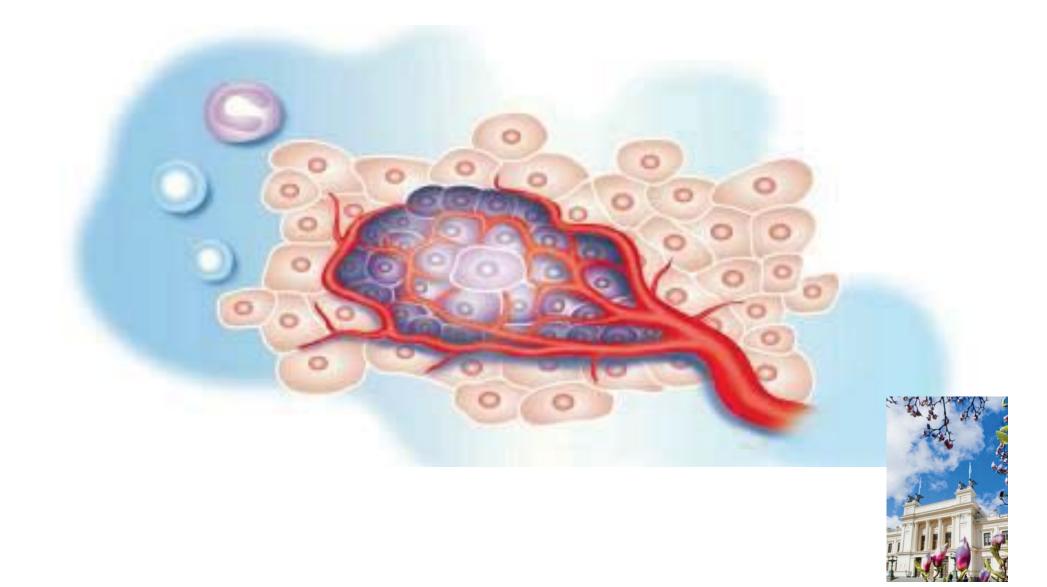
Field cancerisation – how to localise areas to treat – target decision Katarina Svanberg



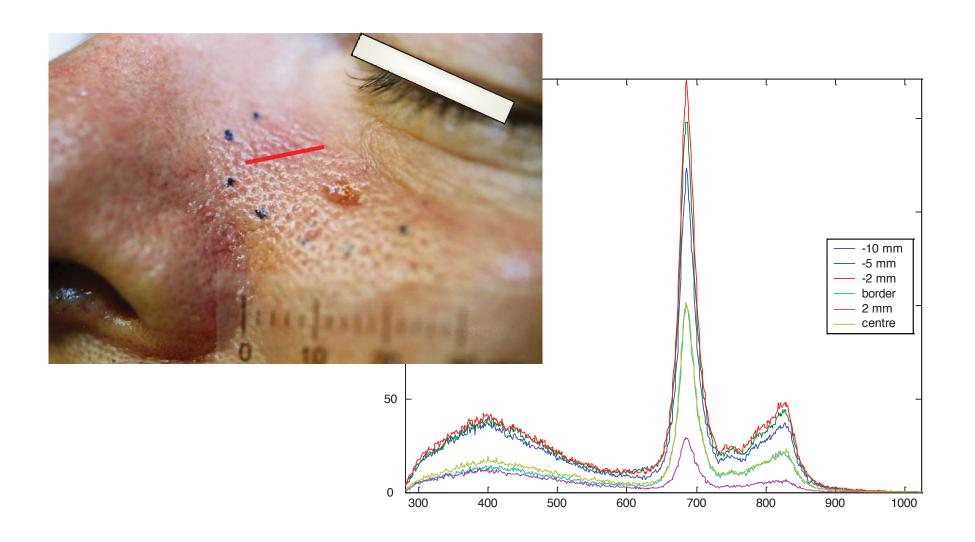
Challenges of today in the clinic



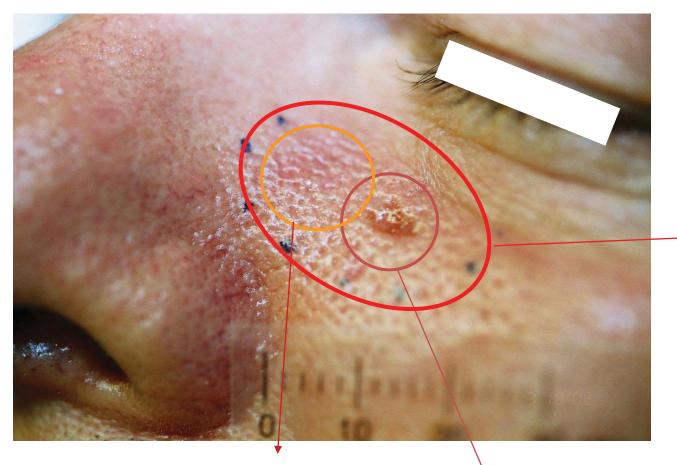
Tumour borders?



Where are the tumour borders?



Treatment target definition



Interactively defined treatment borders

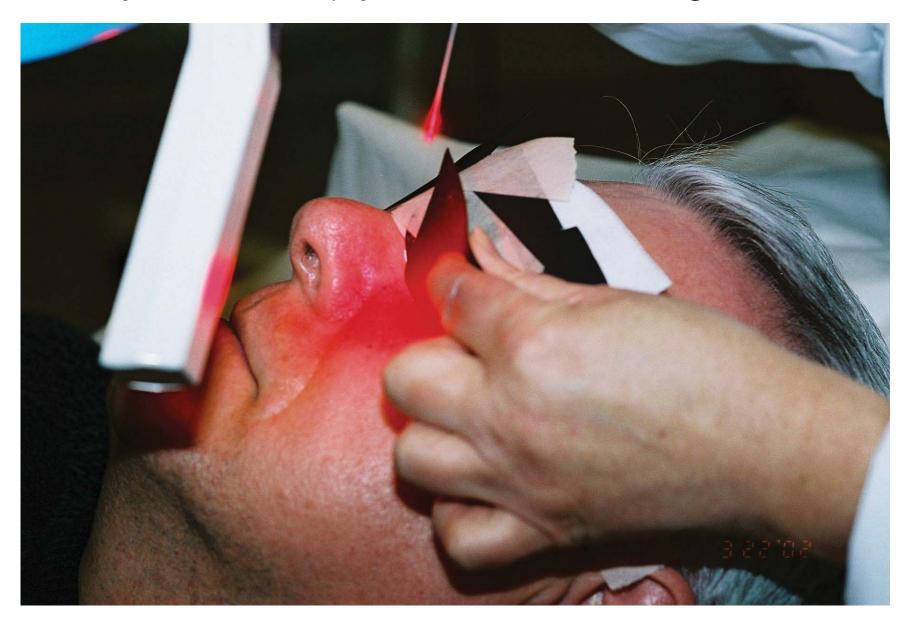
By fluorescence revealed additional tumour area

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Clinically judged tumour borders



Photodynamic Therapy with interactive target definition



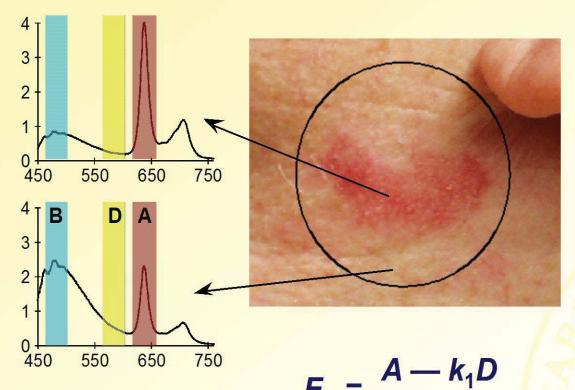
Fluorescence measurements tumour border detection

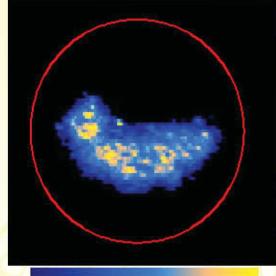




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Multicolour Fluorescence Imaging

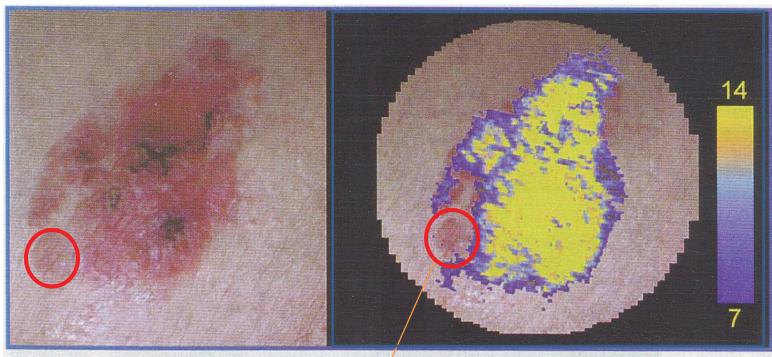




⁵Red — Yellow Blue



Benign – Malignant?



A basal cell carcinoma (left) as seen through a fluorescence imaging system (right) provides a clear delineation of the lesion.

Benign naevus





Traditional diagnosis versus optical characterisation





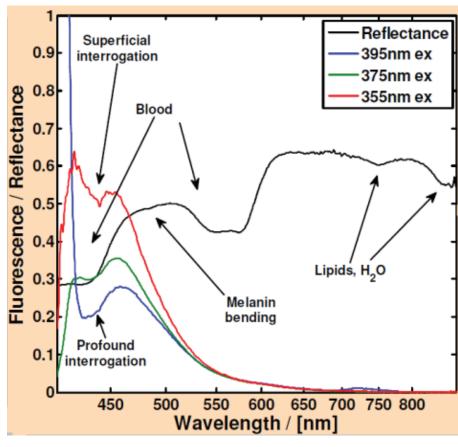
Punch biopsy

Optical detection

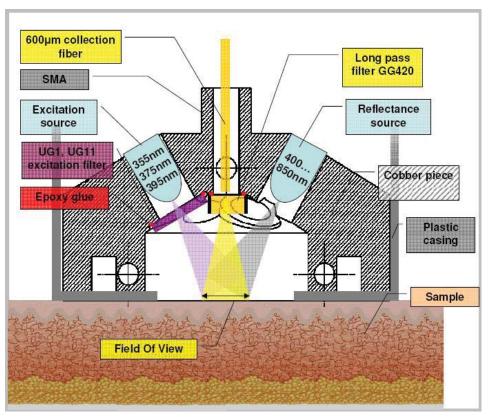
Equipment developed by Mikkel Brydegaard et al.

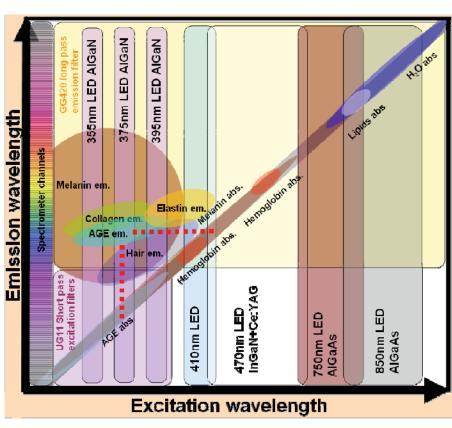
LED based multiple exctation fluorescence and reflectance sensor





Monitoring system for multiple excitation fluorescence and reflectance monitoring





Efforts in improving women health Cervical tissue detection to prevent development of cancer





Lund University



Optical Tissue Diagnostics of cervical precancer & cancer

111 patients included



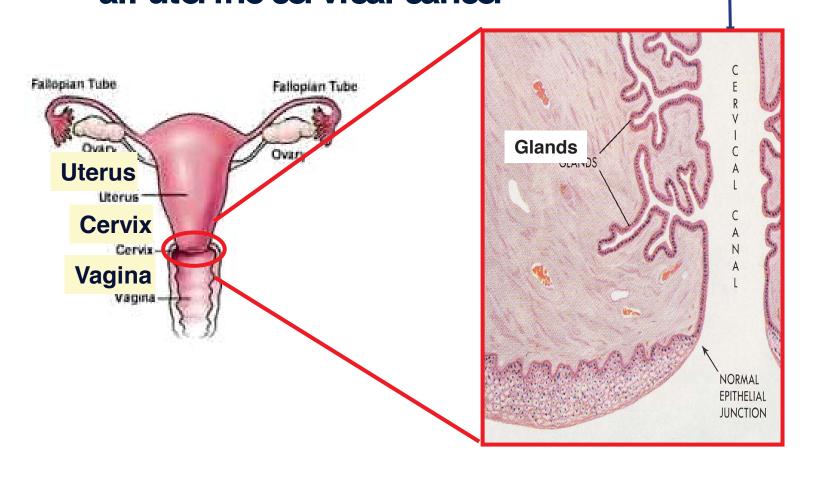
Lithuanian Oncology Centre

Out patient clinics

Vilnius University Hospital – The Gynaecology Department

The transition zone – site for 95% of all uterine cervical cancer

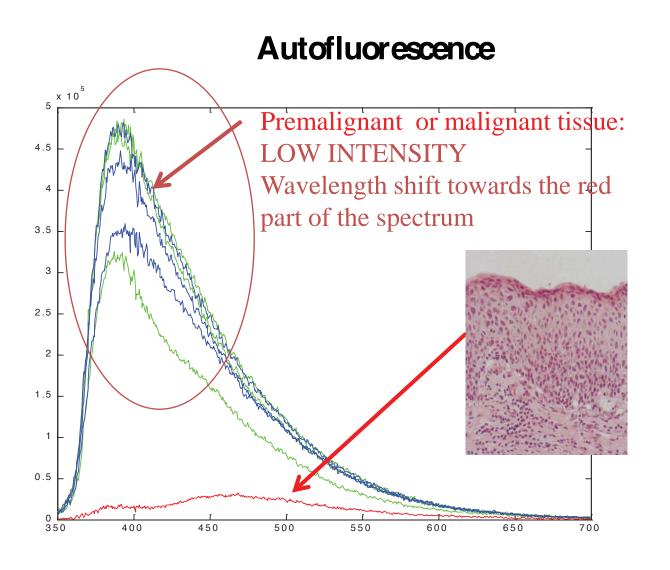
Cervical canal





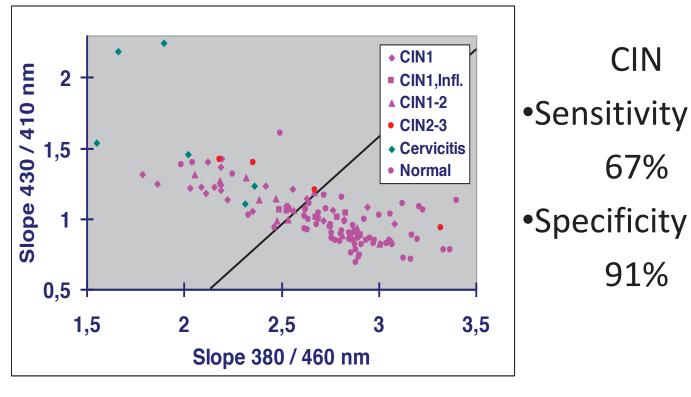
Lund University

Optical Tissue Diagnostics in the Uterine Cervical Area



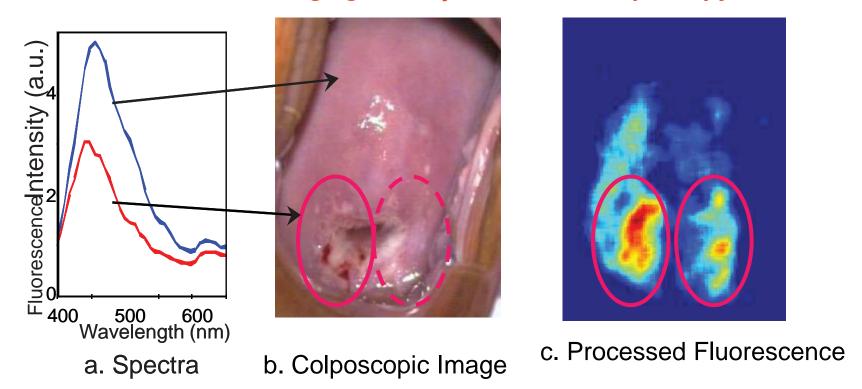
Separate inflammation from neoplasia

Laser-induced **autofluorescence** data – cervicitis/precancer



Exc. 337 nm

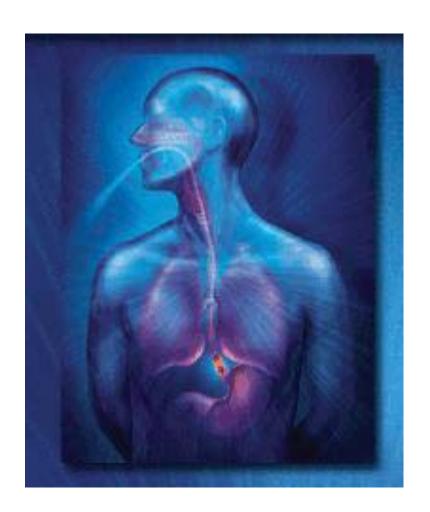
Real-time fluorescence imaging in conjunction with colposcopy



Treatment considerations!

Collaboration with STI Inc., Honolulu, USA

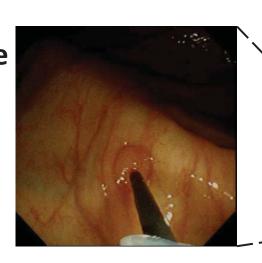
Barret's oesophagus – guided biopsy sampling in the metaplastic mucosa



Picture from Axcan Pharma Inc.

Clinical measurements at Karolinska Hospital, Stockholm

The probe fibre in contact with a polyp



Non-neoplastic: Neoplastic:







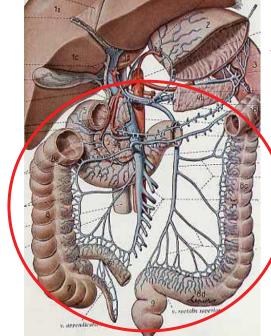


Separate metaplasia/hyperplasia from neoplasia

Large intestine - colon

What is the interpretation if the clinical appearance is

Various kinds of polyps



Neoplastic

Non-neoplastic

Adenomatous polyps
Villous adenomas
(in particular flat sessile lesions - often overseen in colonoscopy)

Hyperplastic or metaplastic

10% Carcinoma in situ in these

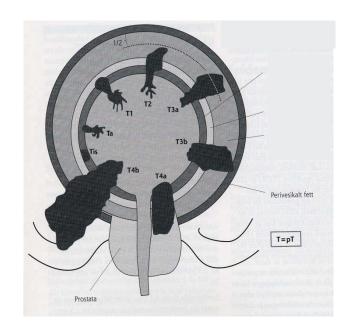
PDT treatment

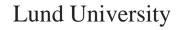
Multiple polyp resection Tumour bed illumination

Visualise precancer (dysplasia) & non-invasive tumours

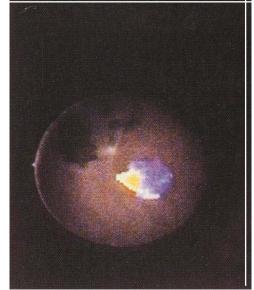
Ca *in situ* (Tis)

Urinary bladder tumour detection







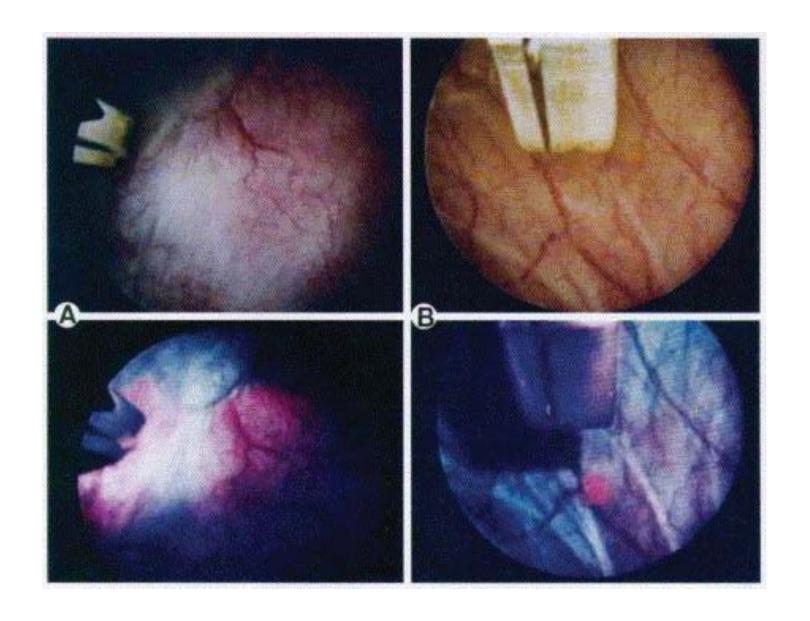


Endoscopic view

Fluorescence image



Medical Laser Centre

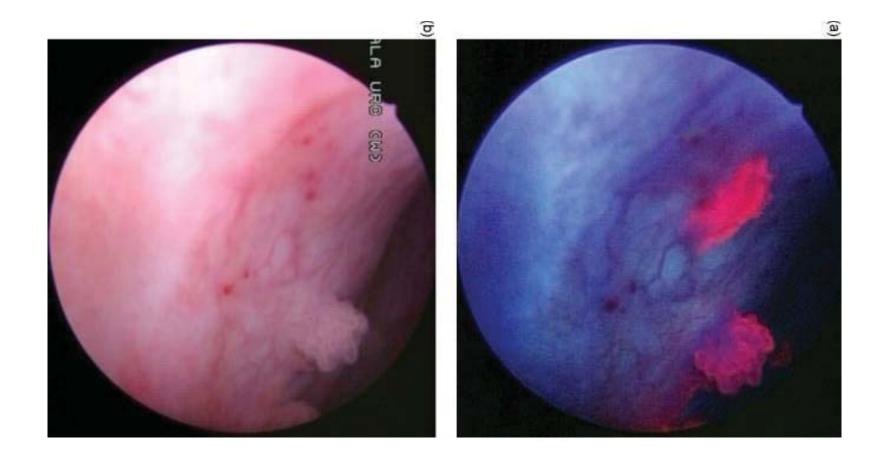


Herbert Stepp et al.

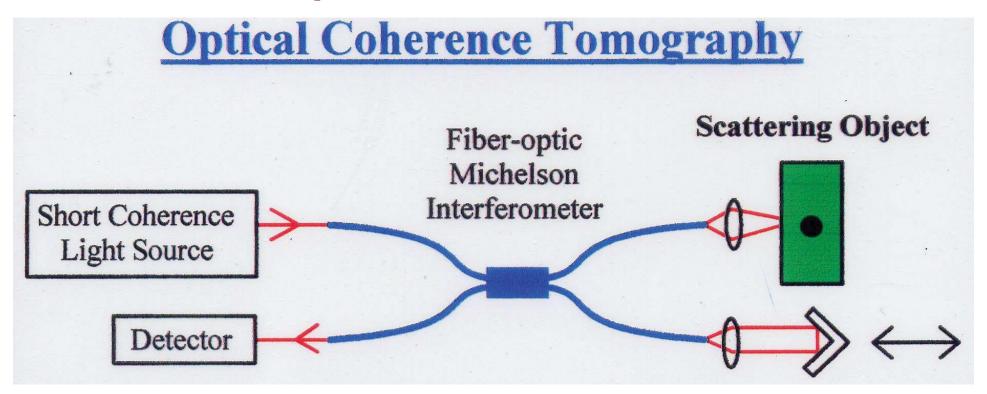
School by Hon Forms, Barbaro Homerost, Notehold Savingartina and residual literals

Photodynamic Therapy with ALA





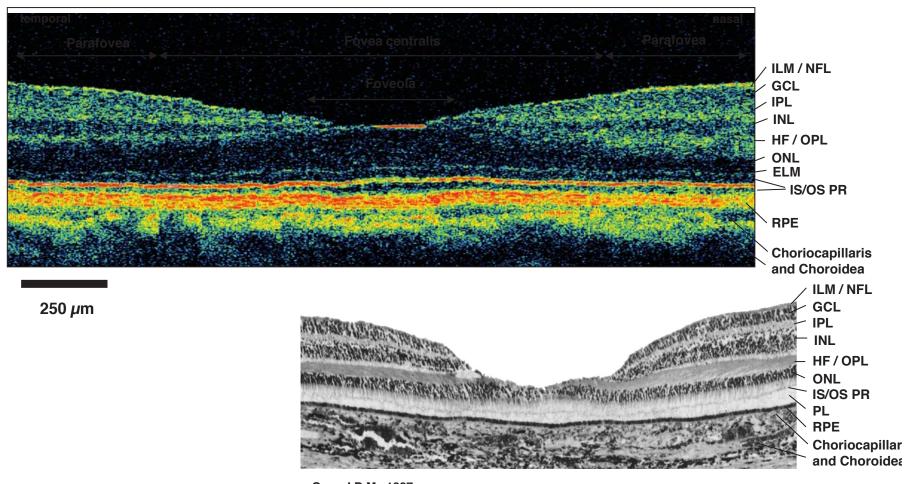
A success development of a photonics-related technique introduced in the clinic



Fujimoto et al.

Ophthalmology Vessels Skin

In Vivo Ultrahigh Resolution OCT versus Histology



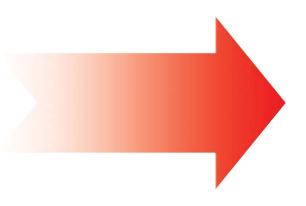
Gass J.D.M., 1997

Photodynamic therapy Three crucial components in PDT

Sensitiser







Tumour Destruction



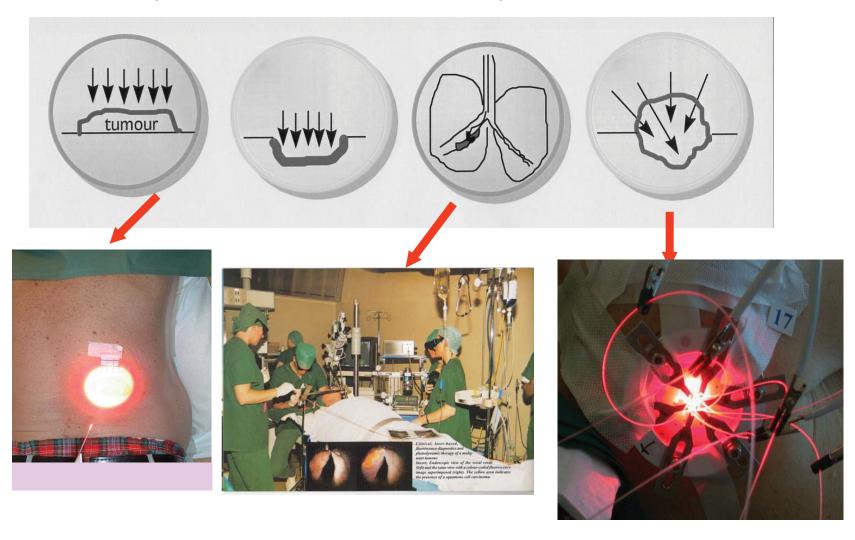
Primary effect (~days) – Direct tumour cell toxicity Secondary effect (~ weeks) – Vascular damage, Apoptosis



Lund University

Various PDT-modes for light delivery

Superficial Tumour bed Endoscopical Interstitial



Tumour localising agents - photosensitisers (PDT) tumour markers (LIF)

	RED Absorption Peak
Haematoporphyrin derivative (HpD), (Photofrin)	630 nm
δ-aminolevulinic acid (ALA)	635 nm
Mesotetrahydroxyphenychlorin (mTHPC), (Foscan)	652 nm
Tin Etiopurpurin (Pyrlytin)	660 nm
Benzoporphyrin, (Verteporfin)	690 nm
Phthalocyanins	720 nm
Lutetium texaphyrin (Lutrin)	732 nm
Bacteriochlorophyll (Tookad)	760 nm



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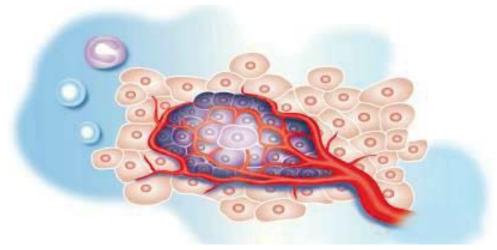
Why selectivity?

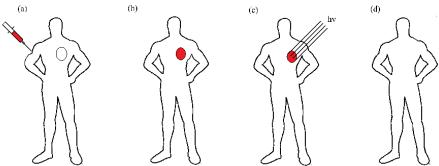
Affluent blood flow to the tumour – insufficient blood flow from the tumour (trapping)

Leaky blood vessels in the tumour

Lower pH in tumour

For ALA an enzymatic response





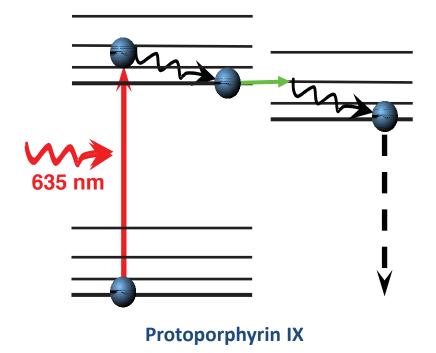
The tumour destruction process

The sensitizer molecule gains excess energi by light excitation

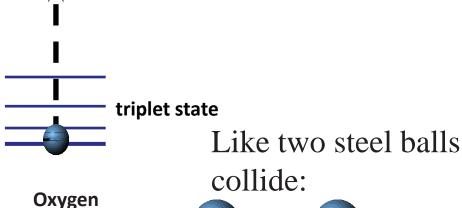
The excess energi



Tissue triplet oxygen is transformed to cytotoxic singlet oxygen





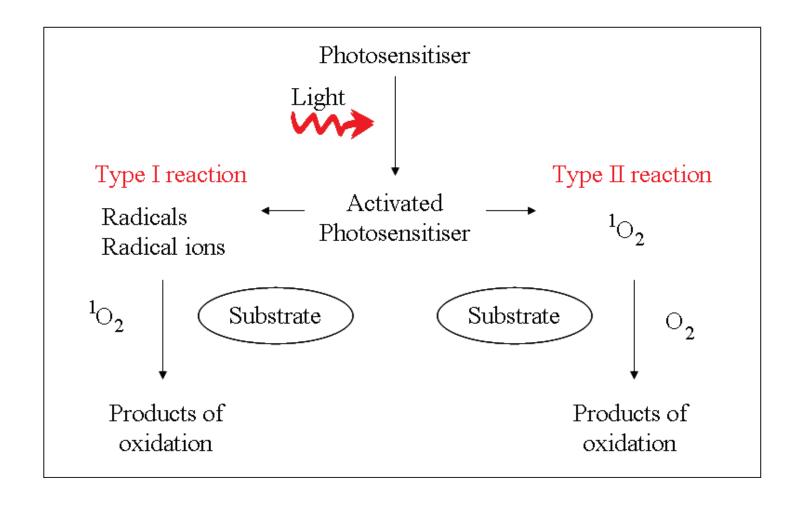






Lund University

Type I and Type II reactions in PDT



Photodynamic Therapy

PDT characteristics:

- •Tumour selectivity
- •Can be repeated
- No accumulated toxicity
- •Fast healing
- •Minimal scaring
- Organ function is retained

Systemically given it

causes skin sensitisation



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

Katarina Svanberg

Indication for PDT

Primary and/or Recurrent skin malignancies

- •Large lesion >4 cm
- •Multiple lesions
- •Sensitive location
 Face
 Pretibial etc
- •Underlying cartilage
 Ear
 Nose
- Elderly people
- Excellent cosmetic outcome
- Short healing time
- •Comparable respons to conventional techniques



What are the indications for PDT of skin malignancies?

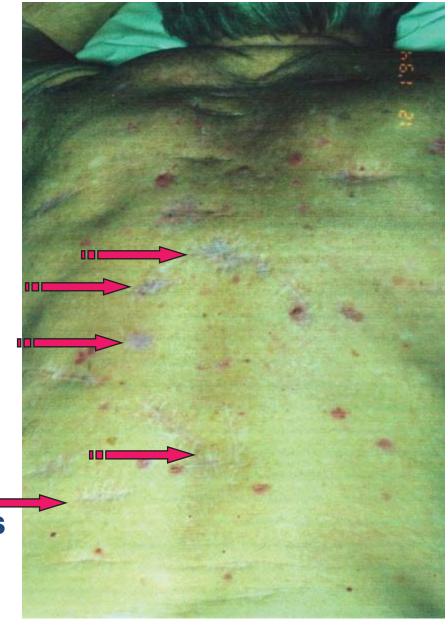
e.g.,

•Multiple skin lesions

Large skin lesions(diameter 5 cm or more)

•Lesions in sensitive areas

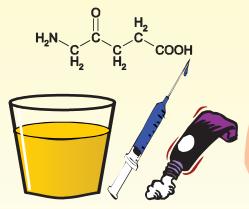
Surgical scar



Superficial basal cell carcinoma

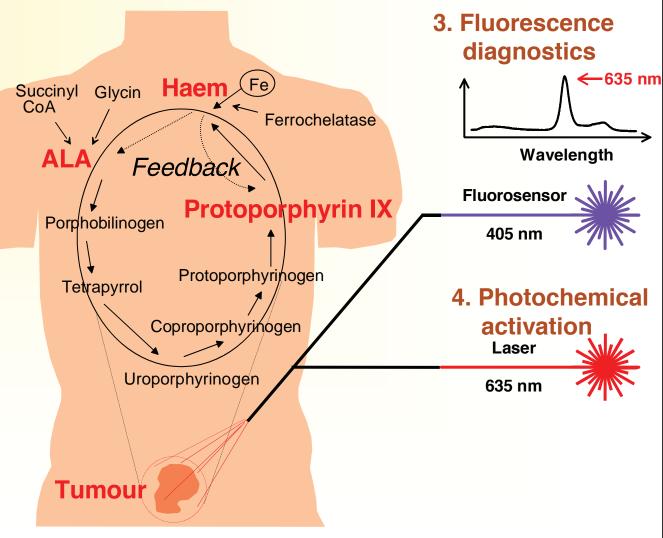
Photodynamic therapy (PDT)

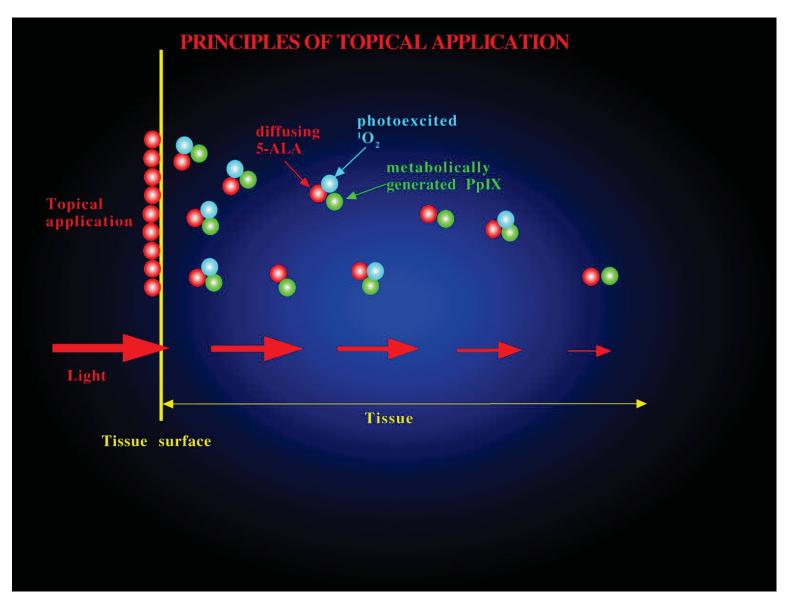




2. Build-up of Protoporphyrin IX

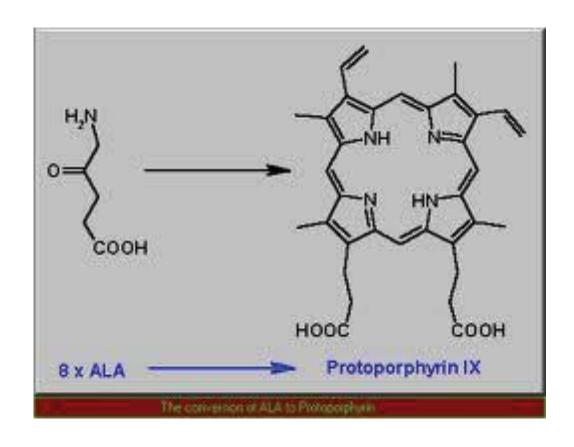




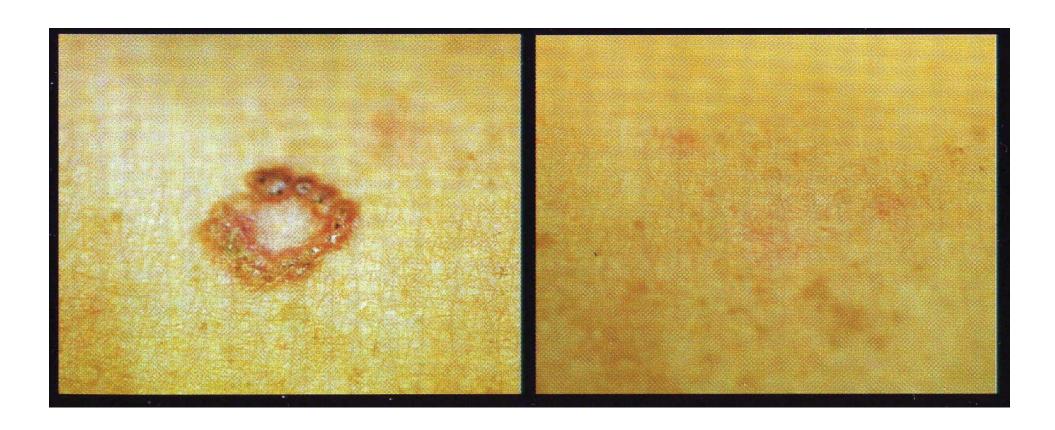


From L. O. Svaasand

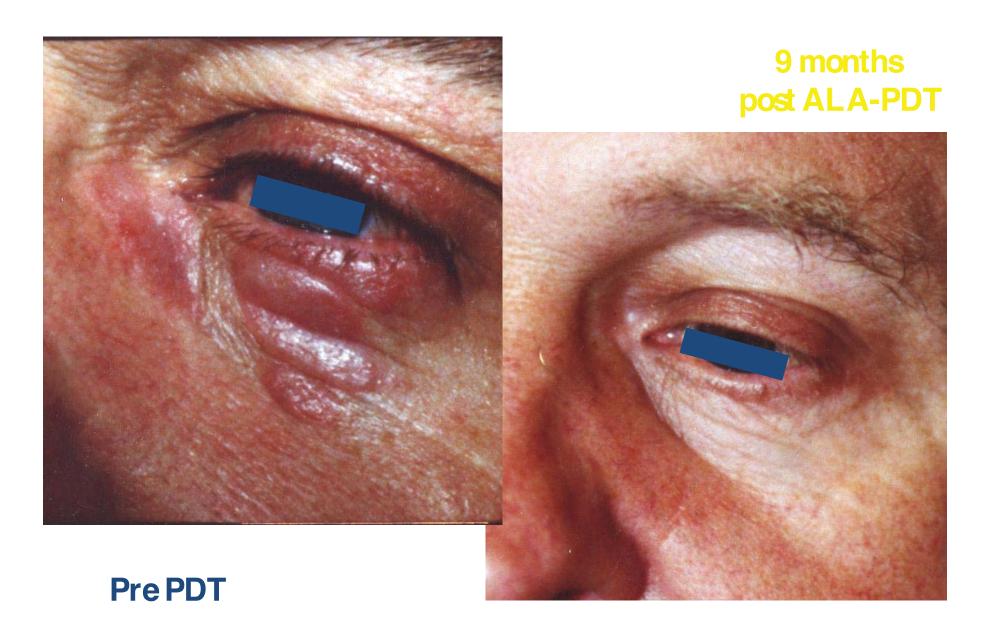
ALA to Protoporphyrin IX in several enzymatically generated steps



ALA PDT Treatment of a nodular Basal Cell Carcinoma – one of our first patients



Histopathology showed compete response; some elastosis



Cutaneous T-cell lymphoma

ALA-PDT of a squamous cell carcinoma

Prior to ALA-PDT

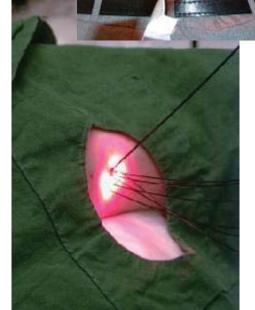
3 months post
ALA-PDT



W

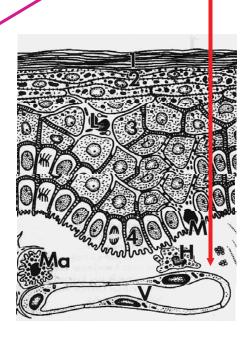
How to overcome the limited penetration with superficial illumination?

Tissue penetration



Interstitial PDT

Up to cm:s



Up to mm:s



Lund University

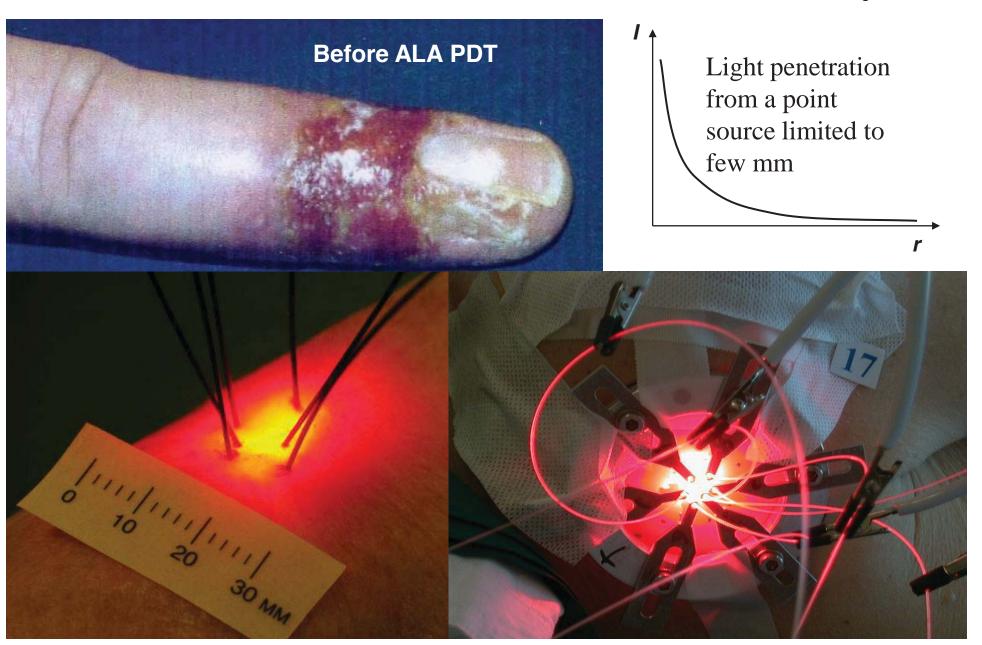
Medical Laser Centre



Optical fibres inserted into the tumour mass

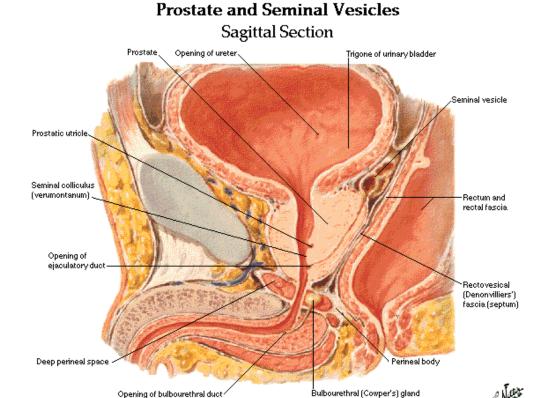
Motivation for Interstitial PDT

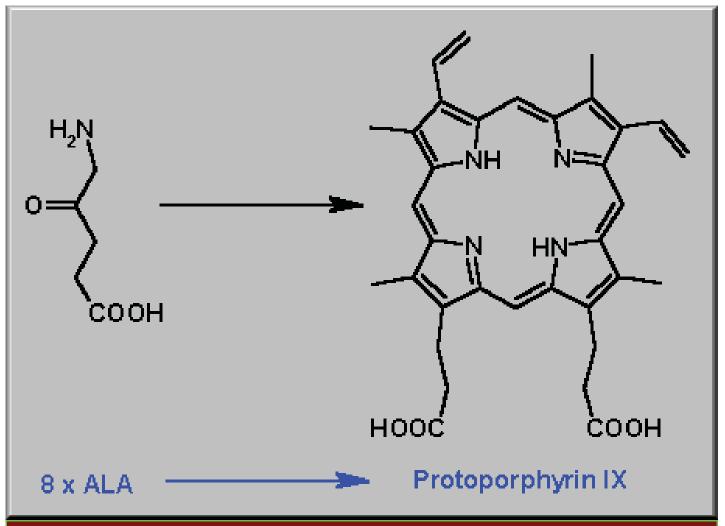
Johansson et al. JBO (2006) Wang et al. Br. J. Dermatol. (2001) Stefan Andersson-Engels



Challenging indication for PDT

- Prostate recurrent cancer post XRT
- •The alternative is hormone therapy
- M ore toxic than anticipated





The conversion of ALA to Protoporphyrin

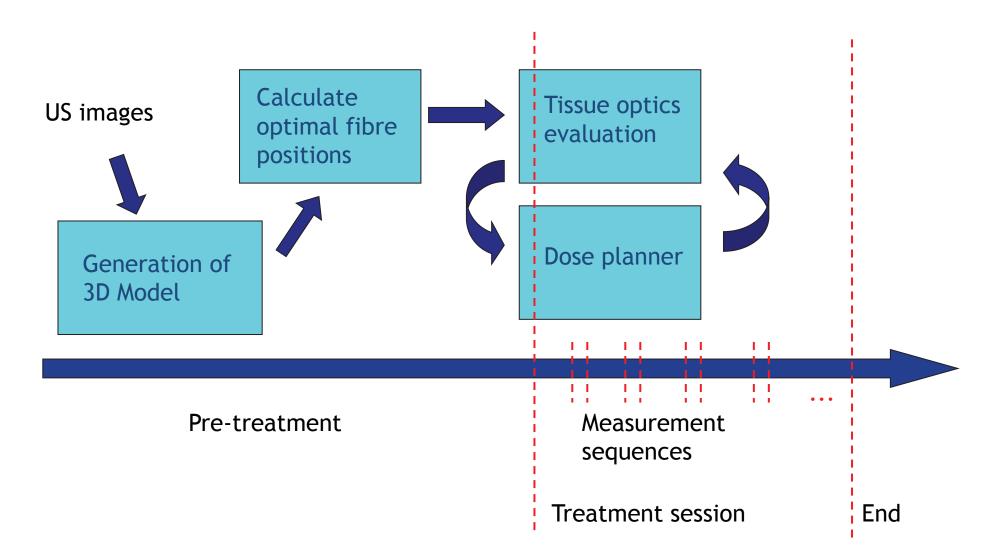
Fiber-based laser therapy system for interstitial PDT

The instrument:

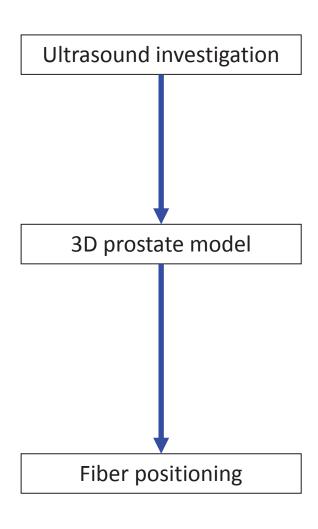


- 18 combined treatment/monitoring fibres
- Therapeutic light: 652 nm for mTHPC
- On-line treatment control based on therapeutic light transmission
- Applied to prostate cancer therapy

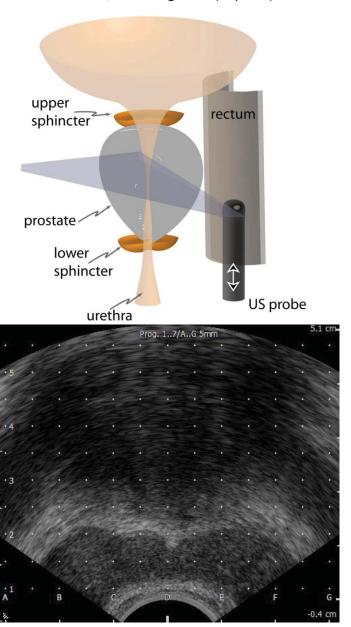
IDOSE – Flow chart



Pre-Treatment Planning

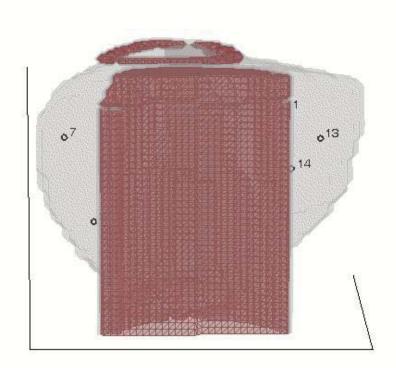


Stefan Andersson-Engels Johan Axelsson Johansson et al. Med. Phys. (2008) Axelsson, Swartling et al. (in press)

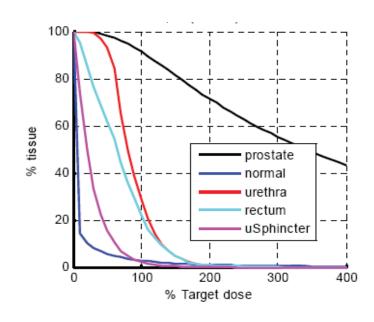


The treatment geometry

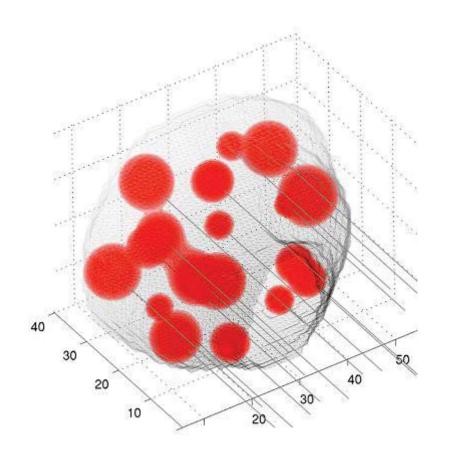
- Optical fibres are **positioned to optimize treatment** of prostate gland with minimal effect on nearby organs at risk
- 18 fibres allow low-resolution **tomographic reconstruction** of the important treatment parameters

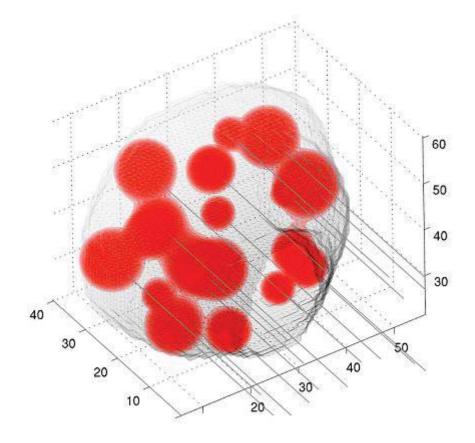


Dose Volume Histogram

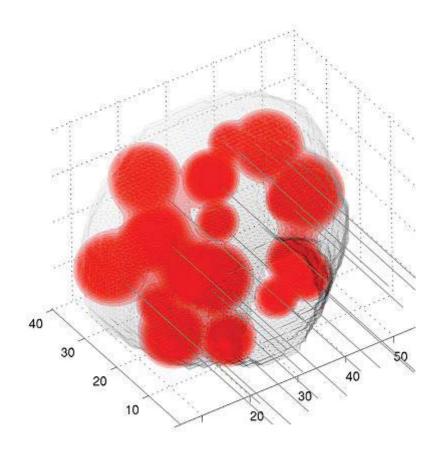


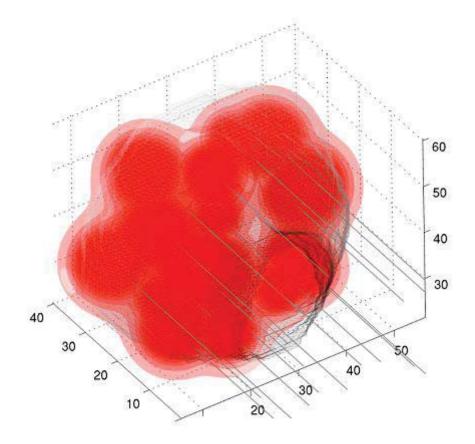
Stefan Andersson-Engels Johan Axelsson



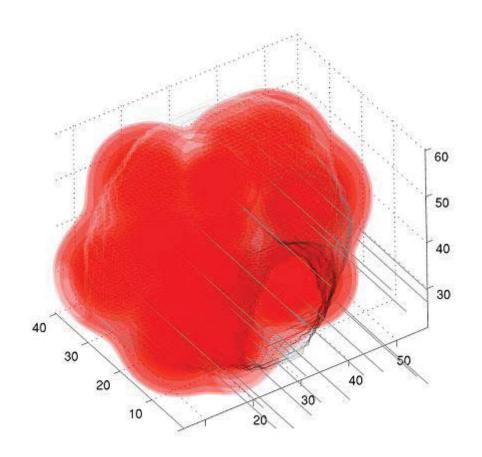




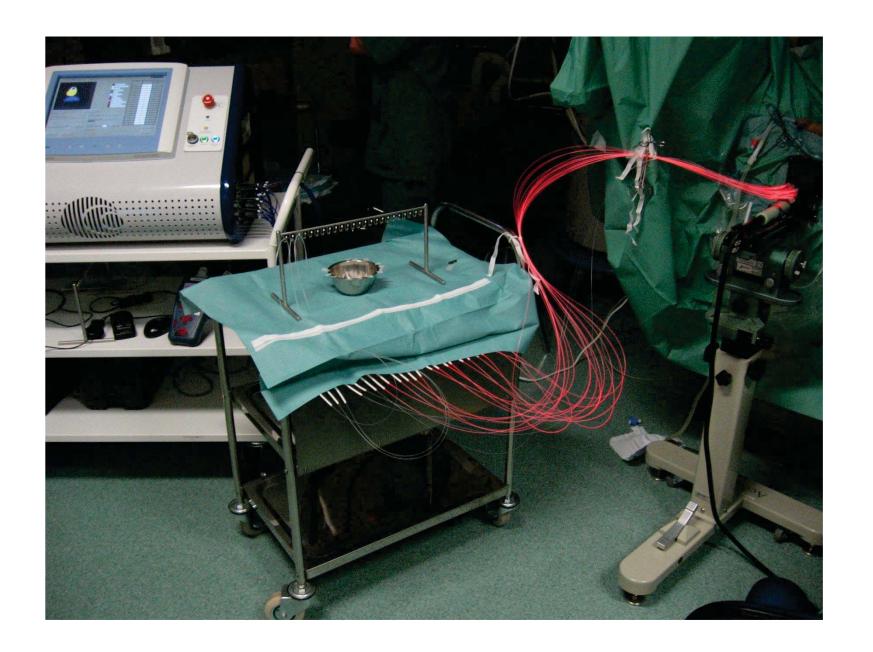






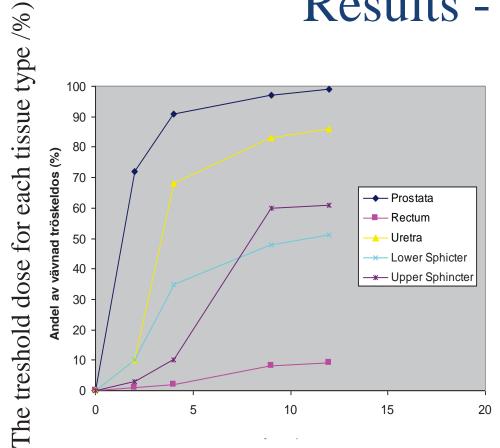








Results - dosimetry



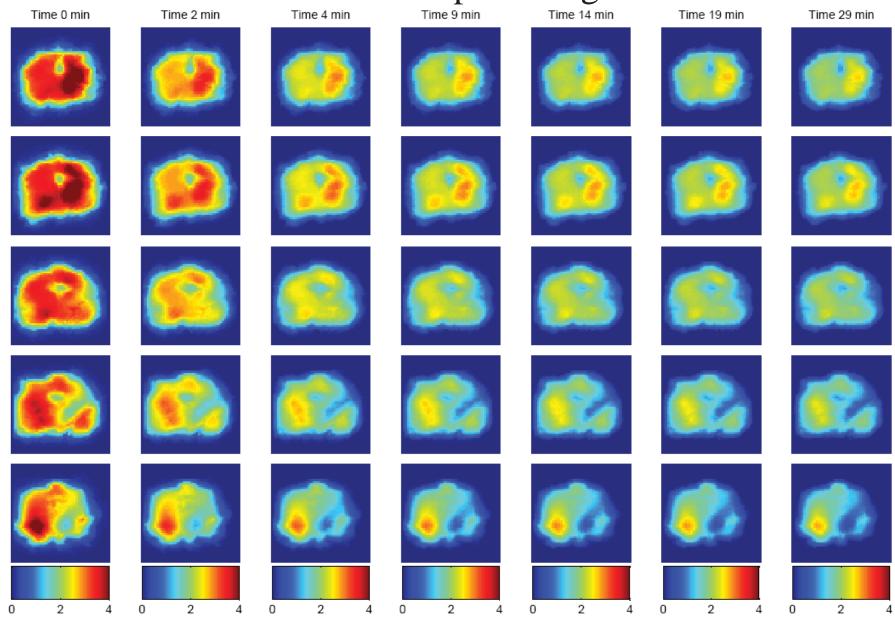
patient 1 patient 2 Percentage of organ above threshold dose (%) patient 3 80 patient 4 70 60 50 30 20 10 urethra u sphincter I sphincter prostate rectum

Laser illumination time (min)

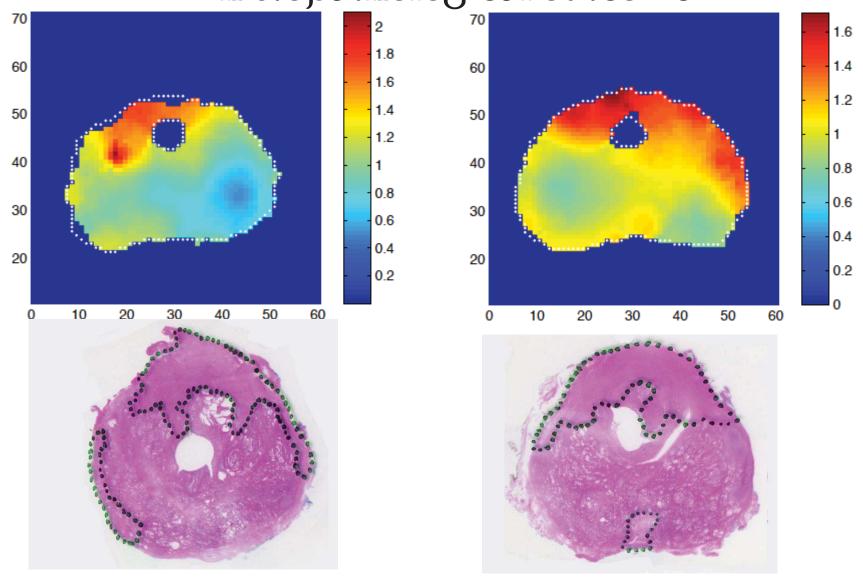
Tissue	
type	Acc. limit
prostate	>95
urethra	<90
rectum	<80
u	
sphincter	<80
I sphincter	<50



3 D mapping of the fluorescence of the sensitiser Foscan in the treated prostate gland



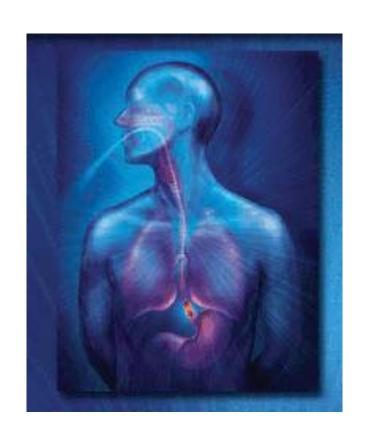
Correlation in between sensitiser content & histopathological outcome



Challenging indication for PDT

Barrets Oesophagus

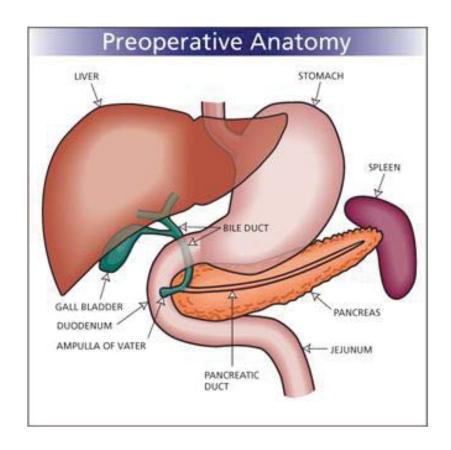
- •A precancerous condition for adenocarcinoma
- Caused by GERD
- •The alternative is mechanical mucosectomy





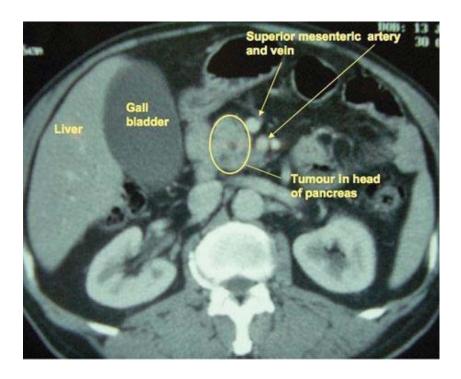
Challenging indication for PDT

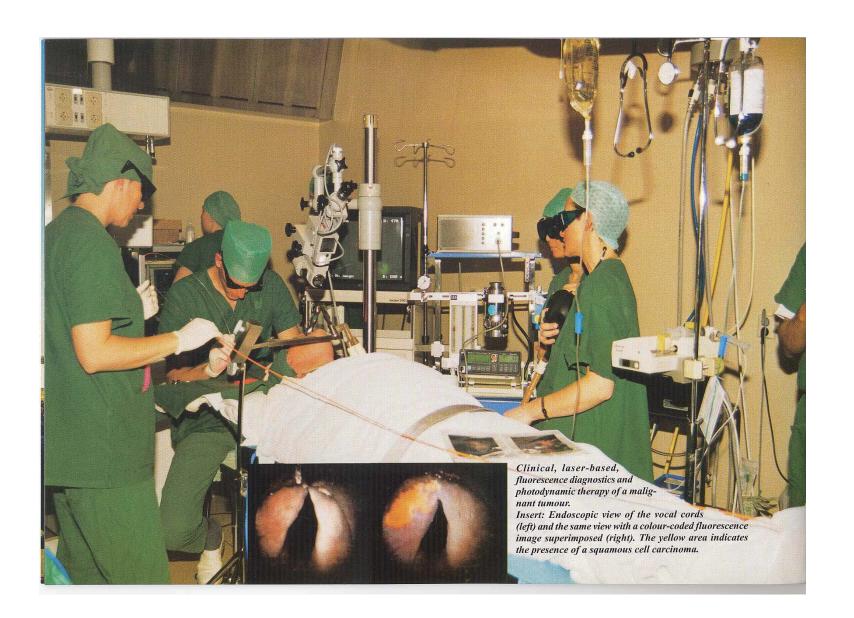
Pancreas cancer



- Lund University
- Medical Laser Centre

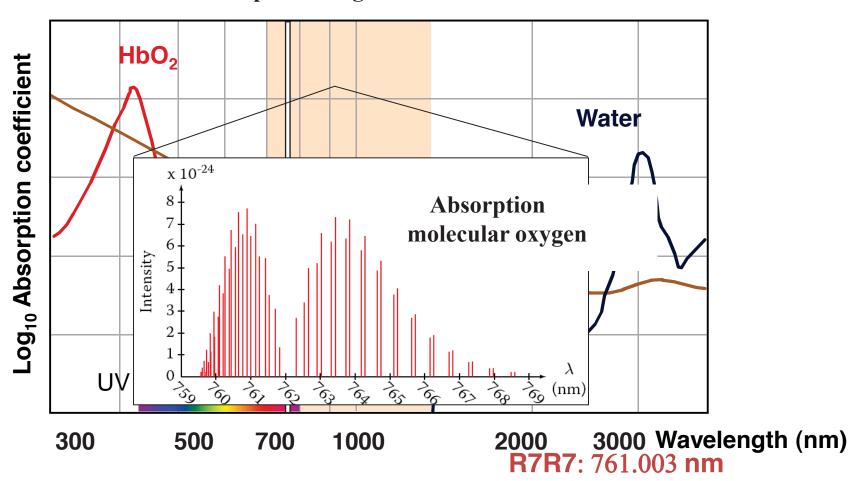
- Poor prognosis
- Late diagnosis
- •10-15% are operable at diagnose
- To shrink the tumour
- •To make the tumour operable



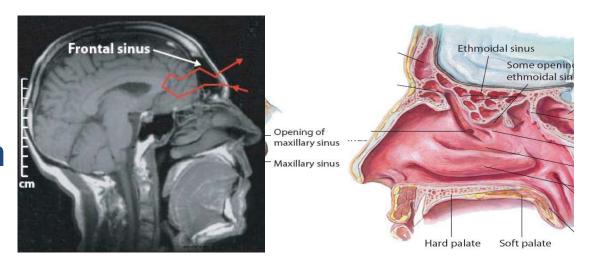


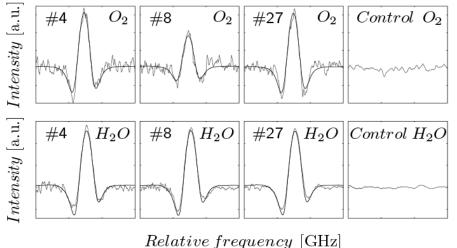
Tissue Absorption

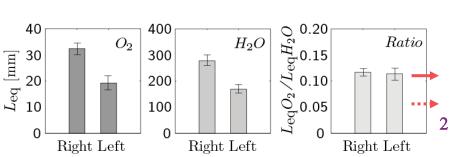
Absorption of light in tissue

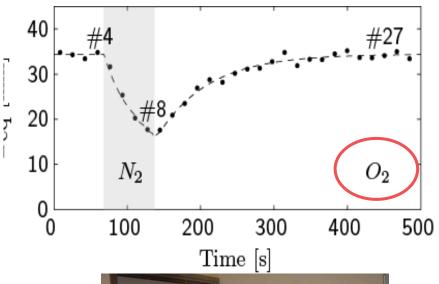


Sinusitis diagnostic by laser-spectroscopic measurement of oxygen and water vapour

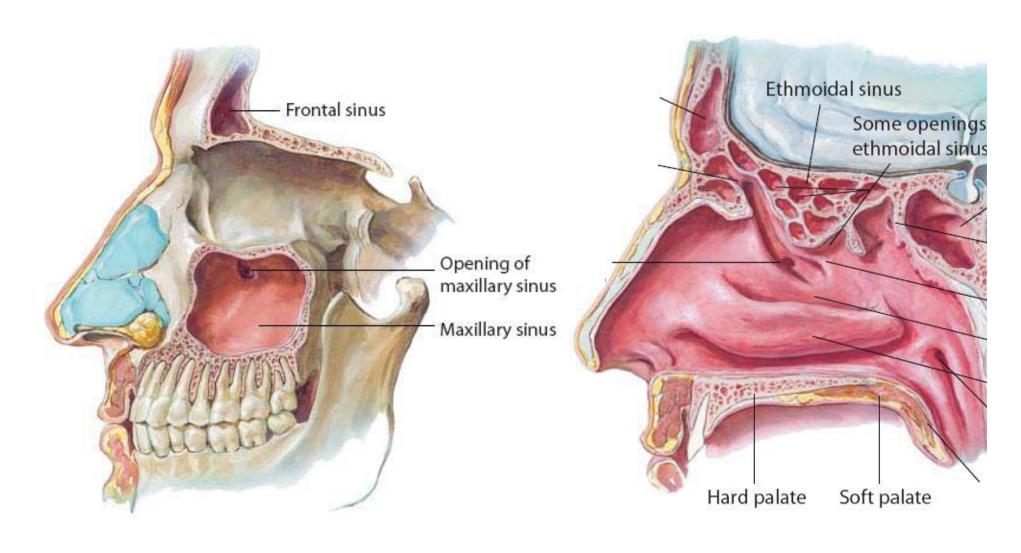








Gas in Scattering Media Absorption Spectroscopy (GASMAS) for paranasal sinus detection



Paranasal sinuses

Sinusitis: Inflammation in the paranasal sinuses

Common disease

No easy diagnostic tool available

Obstruction & blockage

Diagnostic methods

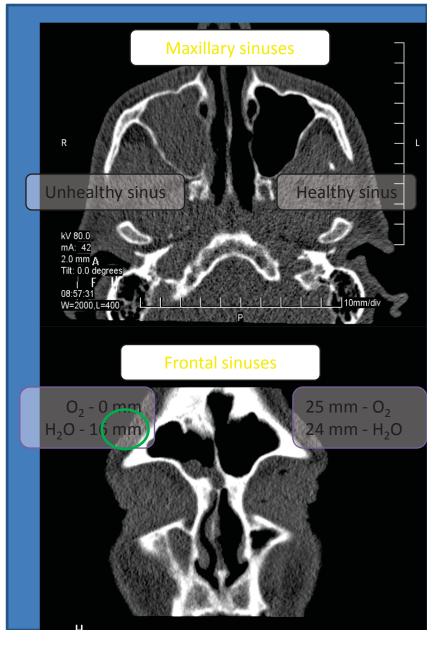
Computer tomography

Endoscopy

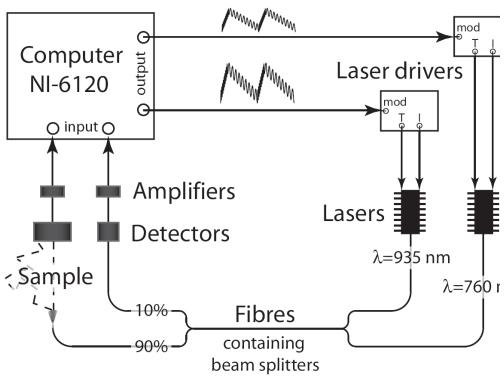
Frontal Sinus

Maxillary Sinus

Lewander et al.

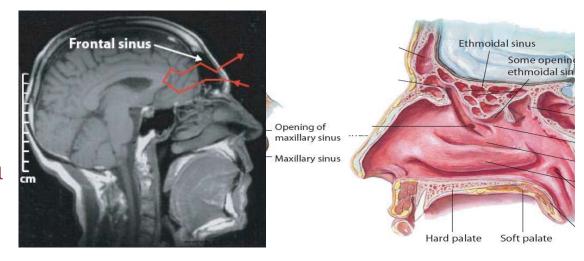


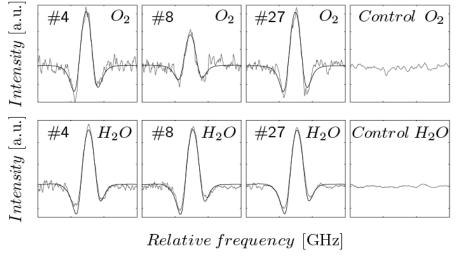
Clinical trial on 40 patients referred to CT scanning

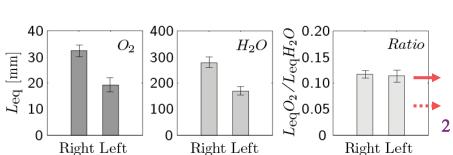


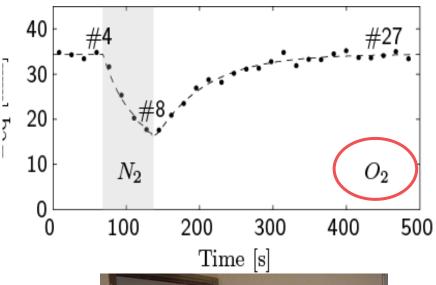


Sinusitis diagnostic by laser-spectroscopic measurement of oxygen and water vapour

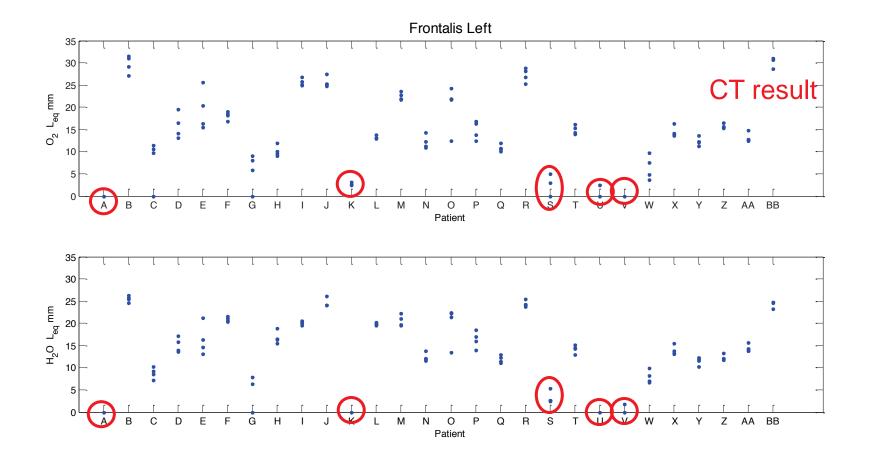












GASMAS correlation to CT scan results Lewander et al. 2009

Pediatrics and Neonatology

Clinical challenges ~24 h non-invasive surveillance Spectroscopic techniques

Spectroscopic techniques \sim as compared to conventional techniques for surveillance

Back ground in detection of sinusitis with GASMAS Gas in Scattering Media Absorption Spectroscopy



Preterm born babies

- Born before the 37th week of pregnancy
- 8-10% of all pregnancies in the US
- Not fully developed organs
- -in particular the lungs
- Low weight





Lund University

Medical Laser Centre

Preterm born babies

Respiratory distress syndrome (RDS)

- a breathing disorder
- more often if born ≥6 weeks early
- 50% week 26-28; 25% week 30-31
- lack of alveoli liquid coating surfactant
- collapse of the lung alveoli
- insufficient oxygen saturation
- damage to organs
 - in particular the brain





Preterm born babies

Respiratory distress syndrome (RDS)

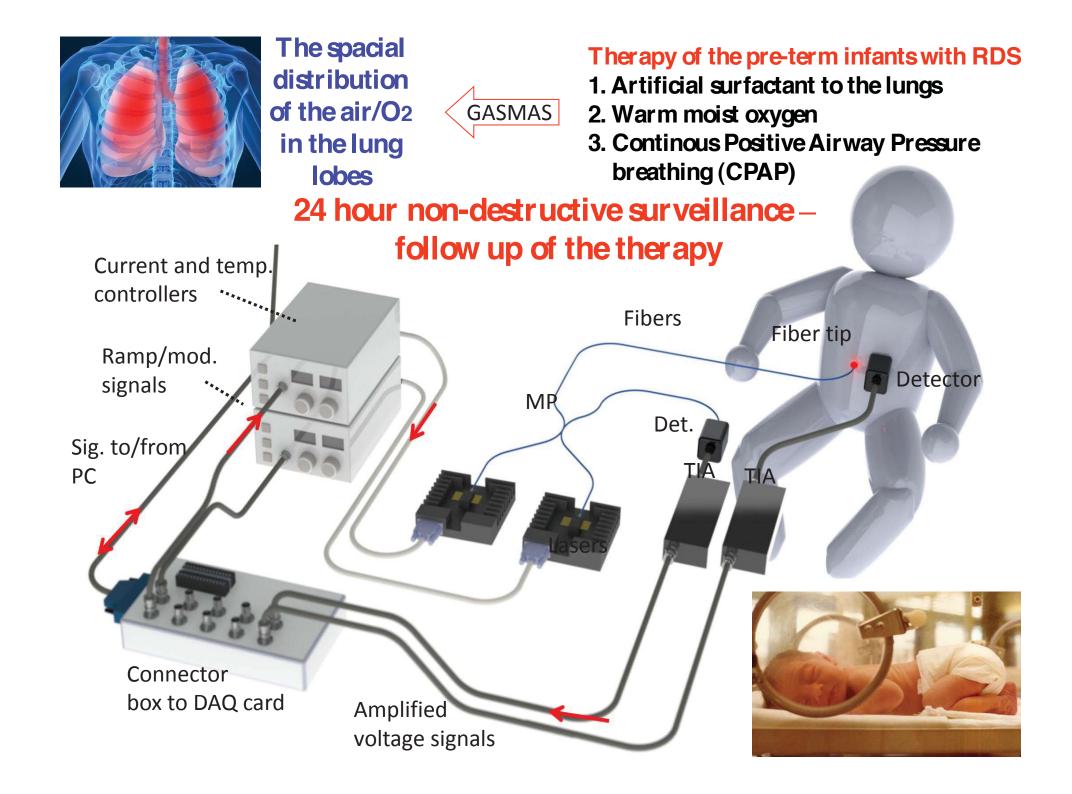
Conventional surveillance of the babies:

Blood sampling for oxygen gas analysis

X-ray-based investigations (CT)









Ultra sound image taken over the stomach area with the intestines (2 weeks old non-preterm baby)



Science certainly brings people together!



