The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific and
Cultural Organization

IAEA
International Atomic Energy Agency

1932-10

Winter College on Micro and Nano Photonics for Life Sciences

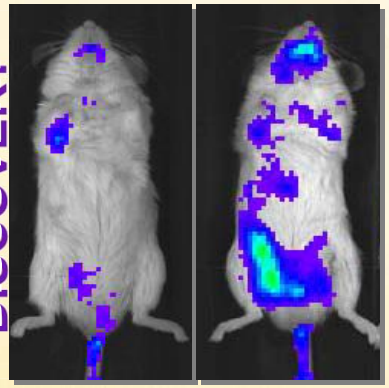
11 - 22 February 2008

Bioscience and Medicine Lecture I

Dennis Matthews
NSF Center for Biophotonics
UC Davis, Sacramento
CA, U.S.A.

EDUCATION

DISCOVERY



TECHNOLOGY

A Survey of the Field of Biophotonics and its Applications to Bioscience and Medicine – Lecture 1

Dennis Matthews, PhD

UCDAVIS
UNIVERSITY OF CALIFORNIA

Center for BIOPHOTONICS Science & Technology
NSF

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Winter College on Micro and Nano Photonics for Life Sciences

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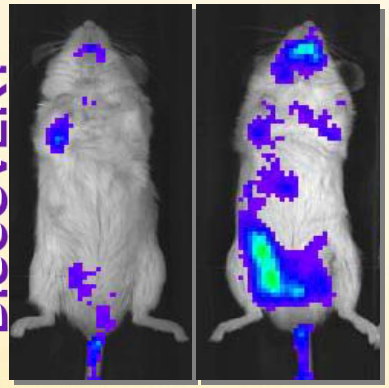
EDUCATION

Applications of biophotonics to nanoscale imaging and sensing – ICTP Lecture 2/3

DISCOVERY



Applications of Ultrafast Lasers to Bio and Medicine – ICTP Lecture 3 ?

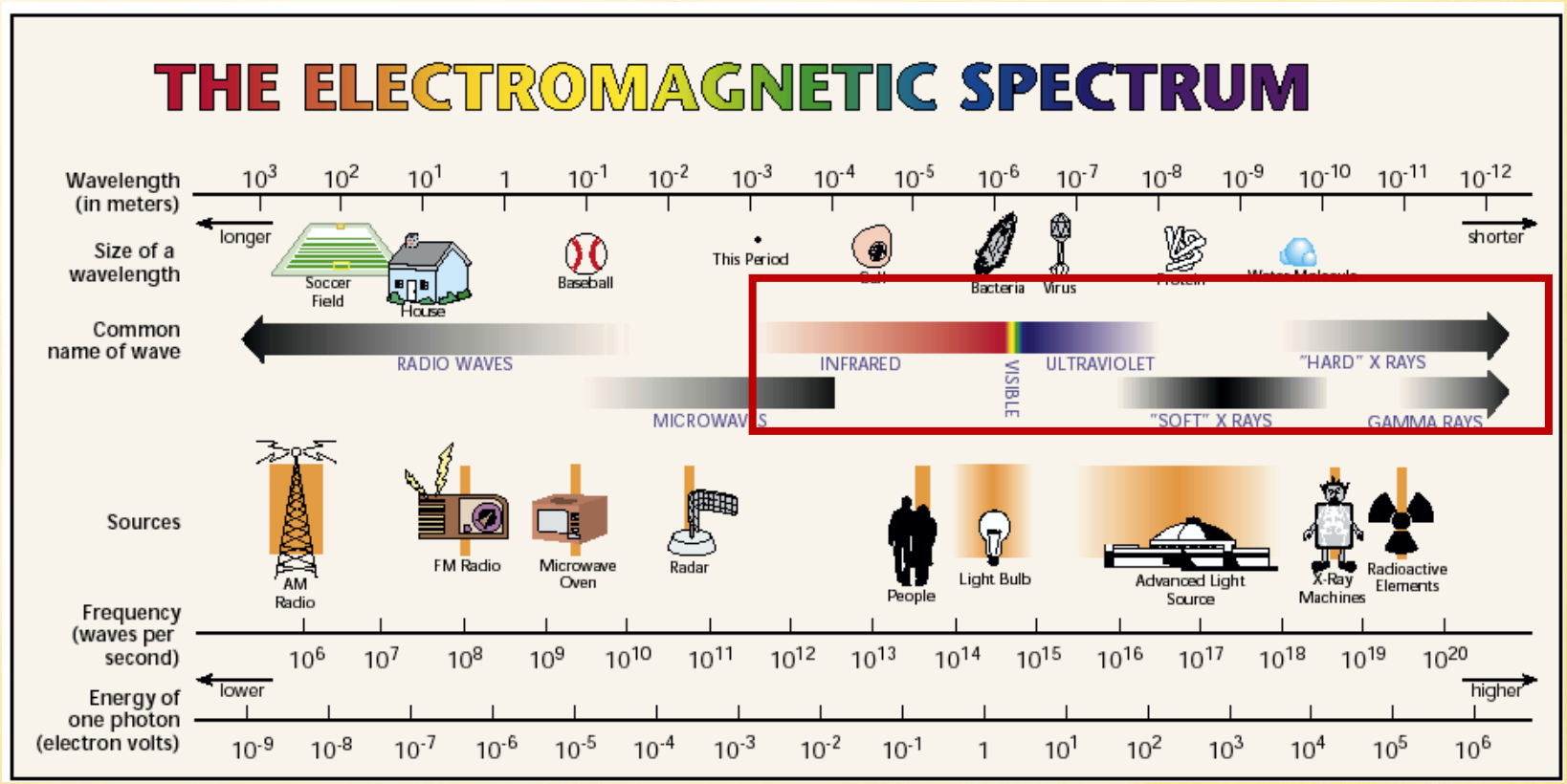
TECHNOLOGY

Principal Points for this Lecture

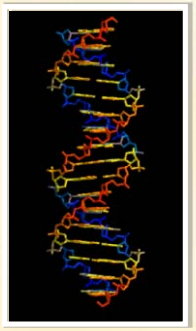
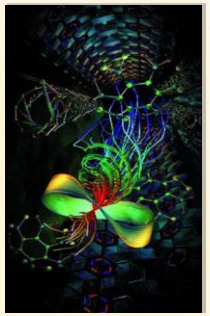
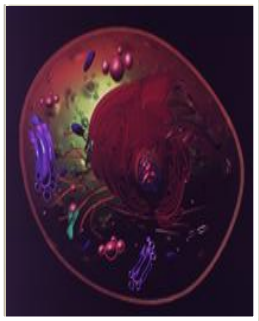
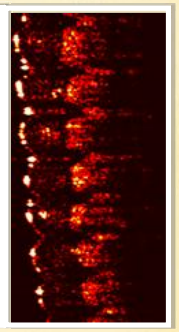
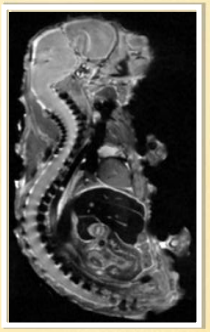
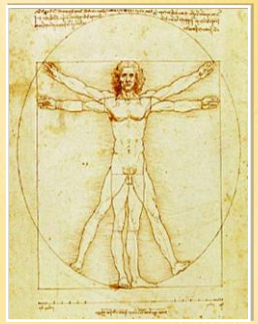
- Introduce you to the field of biophotonics and its applications in bioscience and medicine
- Describe our recent market study for biophotonics devices
- Introduce our http://www.BiophotonicsWorld.org web portal for the worldwide research, education and industry community
- Introduce you to our NSF Center for Biophotonics
- Describe some grand challenges in bioscience and medicine that can be met using biophotonics devices, present and future
- Speculate on the future of biophotonics R&D

What is Our Definition of Biophotonics?

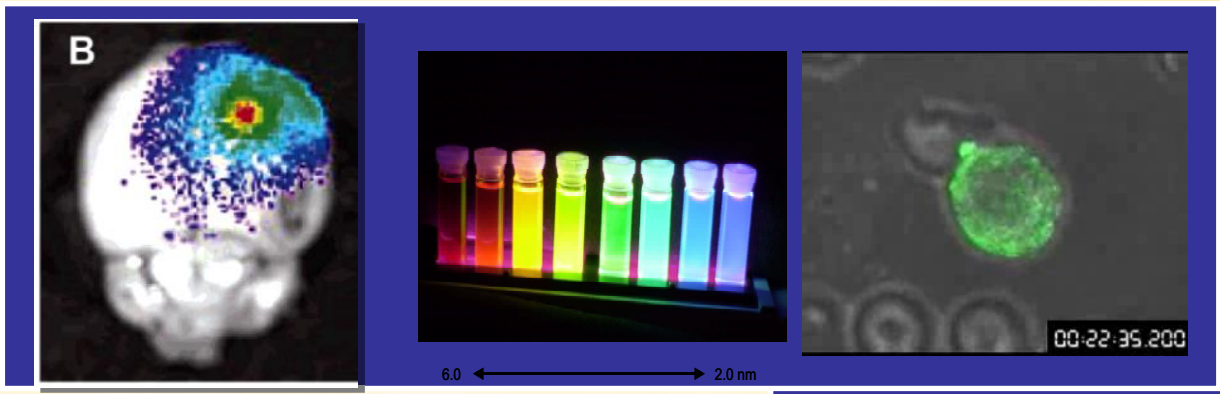
The application of light and other forms of radiant energy to the life sciences and medicine



Applications of Biophotonics

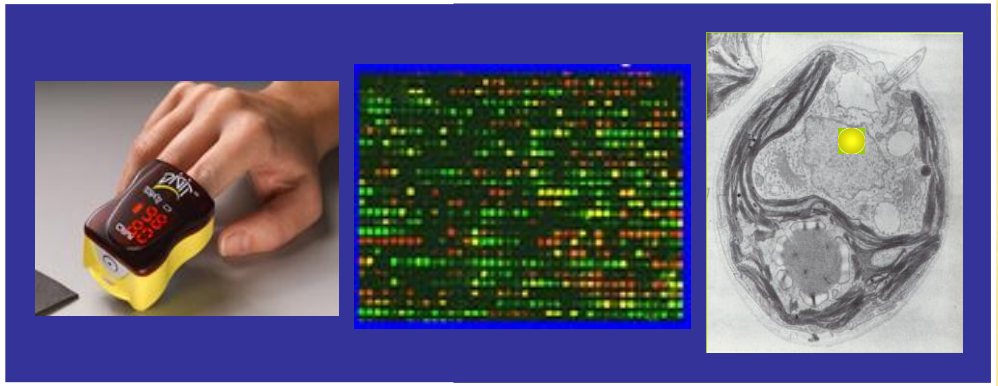
Discipline	Physics, chemistry, biology, medicine, engineering, robotics					
	Molecular Biology	**Cell Biology**	**Histopathology**	**Embryology**	***In vivo***	**Medicine**
				 			
Org. level	**DNA**	**PROTEIN**	**CELL**	**TISSUE**	**EMBRYO**	**ANIMAL**	**HUMAN**
Information	**GENOMICS**	**PROTEOMICS**	**CYTOMICS**	**HISTOMICS, PHENOMICS**			**CLINICAL**
Imaging	**MICROSCOPIC**			***MESOSCOPIC***			**MACROSCOPIC**

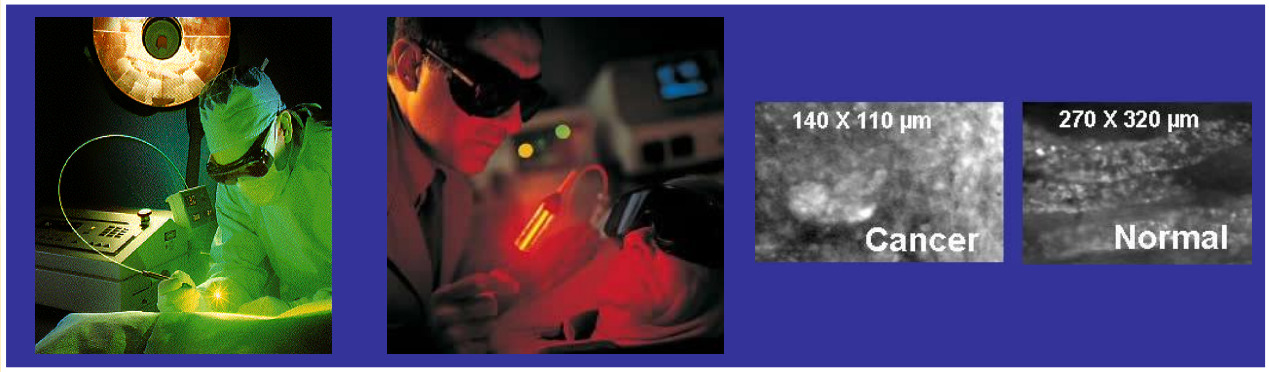
What is Biophotonics?



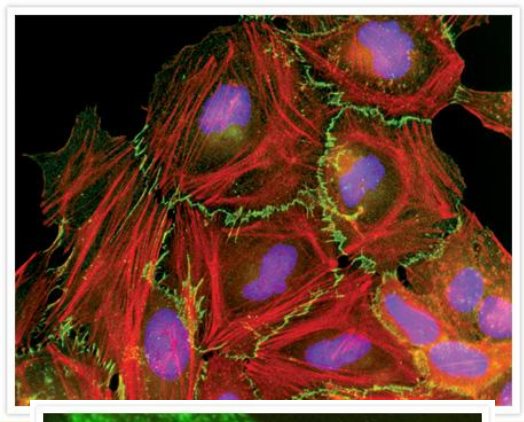
Imaging Tools

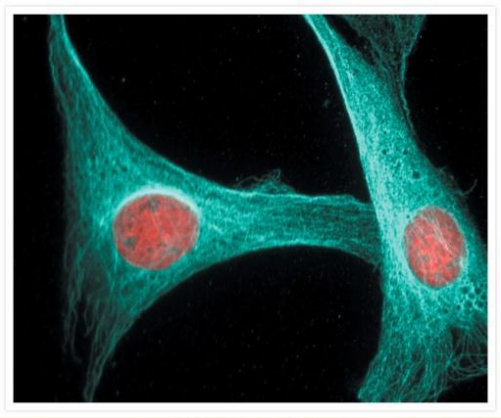
Sensors and Assays

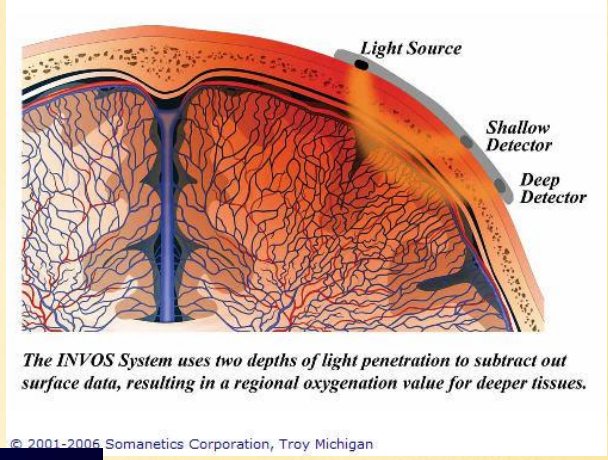




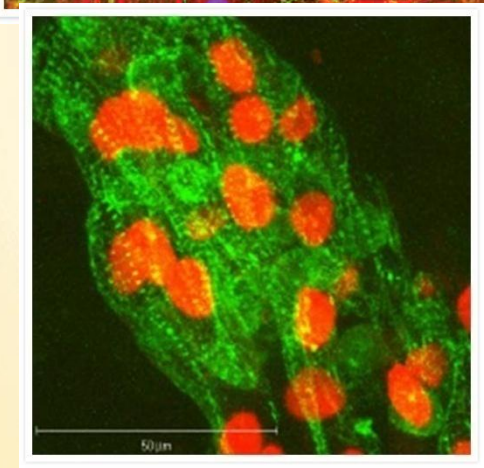
Cinical Diagnostics and Therapy

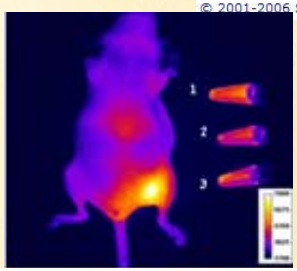


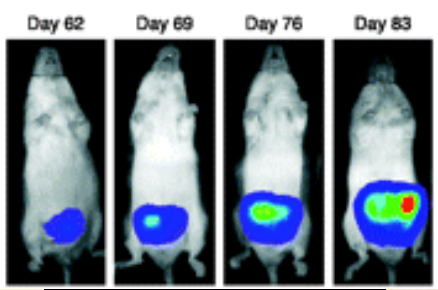


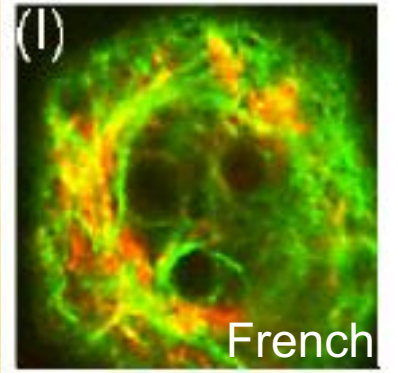


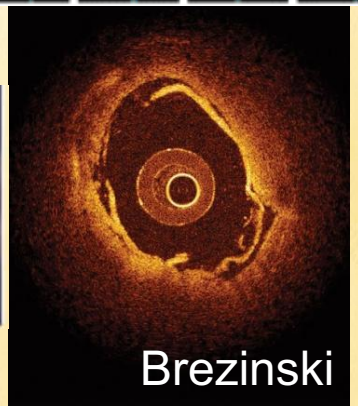
The INVOS System uses two depths of light penetration to subtract out surface data, resulting in a regional oxygenation value for deeper tissues.

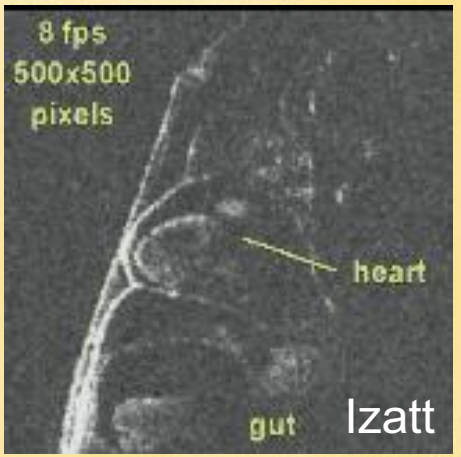












Biophotonics: Methods and Technologies

Imaging, Microscopy, Spectroscopy

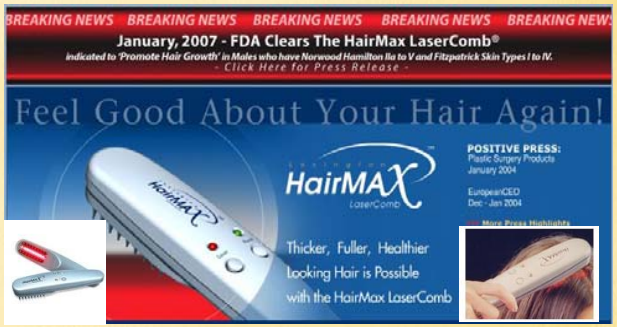
- Absorption, fluorescence
- Fluorescence lifetime imaging
- Illumination sources
- Transmission, trans-illumination
- Phase contrast
- Confocal, 2D and 3D spinning disk
- Spectral imaging
- Point spread function engineering
- Multiphoton: fluorescence, SHG, CARS
- Raman
- THz imaging
- TIRF (total internal reflection)
- Intra-vital
- Bioluminescence
- Optical coherence tomography

Sensors/Assays/Probes

- Elisa
- Sandwich fluoroimmunoassay
- Microarrays
- FISH (fluorescence in situ hybridization)
- SPR (surface plasmon resonance)
- Fluorescent probes, organic, genetically modified
- Quantum dots, nanoparticles
- SERS (surface enhanced raman scattering)
- Fiber-optic biosensors
- Flow cytometry
- Lab-on-a-chip
- Gene sequencing

Medical Diagnostics & Therapies

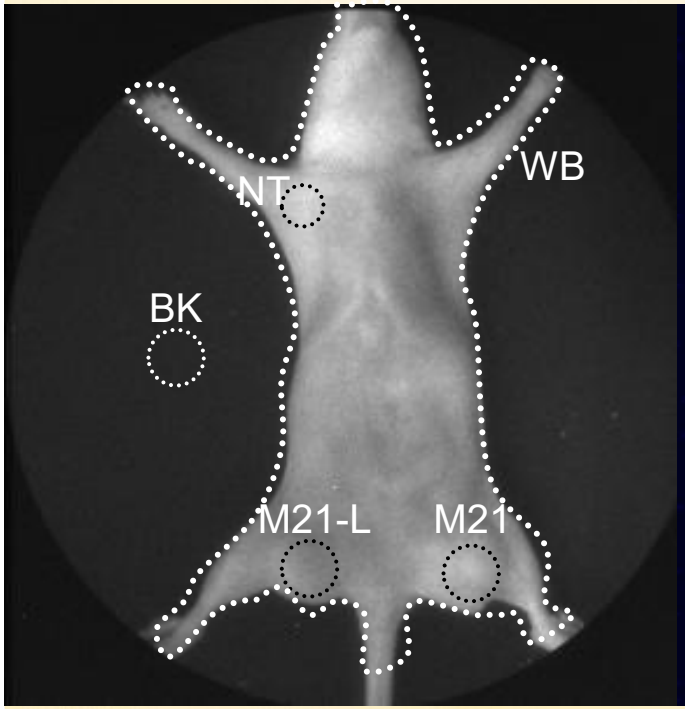
- Finger and Cerebral pulse oxymetry
- PDT (photodynamic therapy)
- Optical biopsy
- Laser capture microdissection



Translational

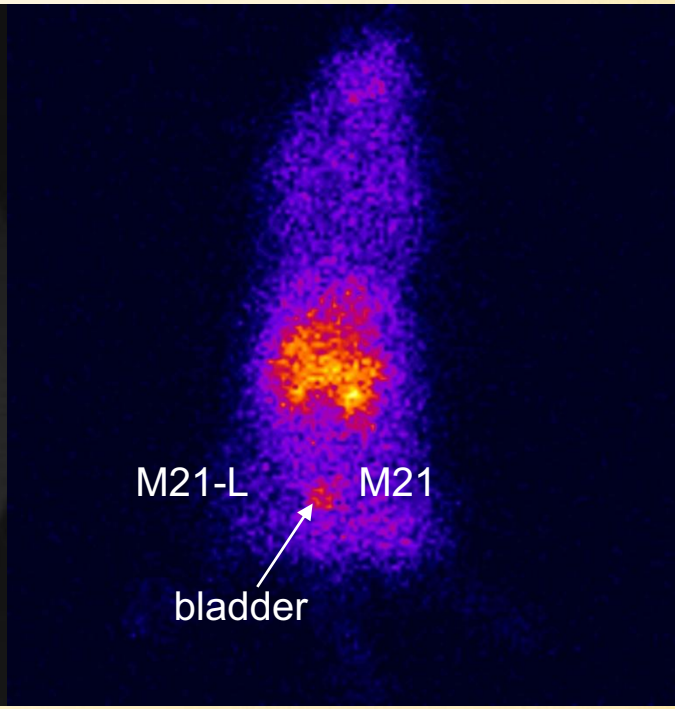
Optical Imaging is Fast!

Optical Imaging



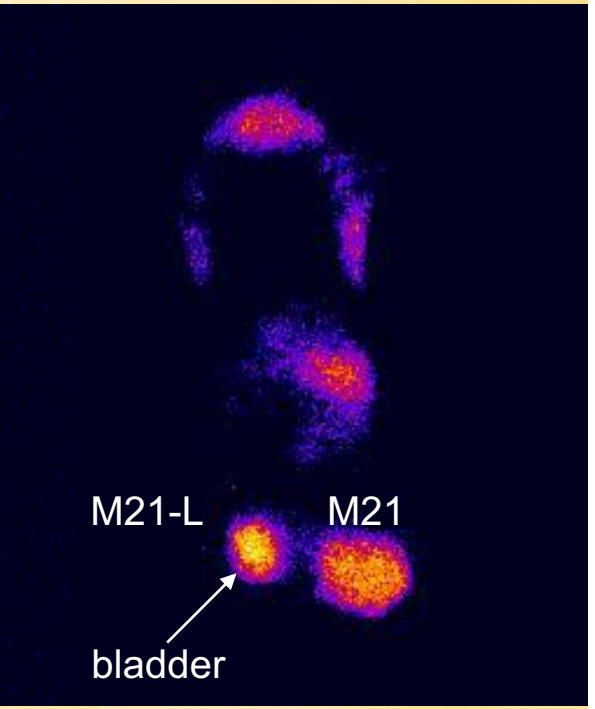
100 milliseconds

Gamma scintigraphy



15 minutes

Fluorescent Imaging

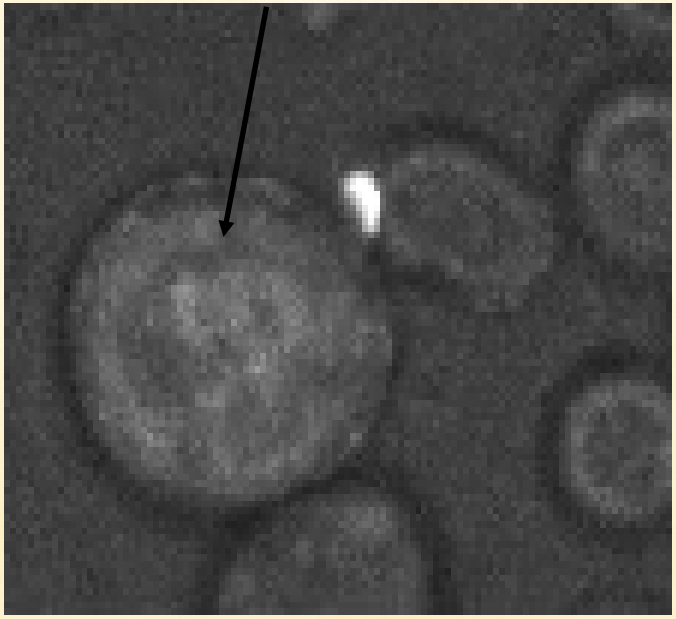


800 milliseconds

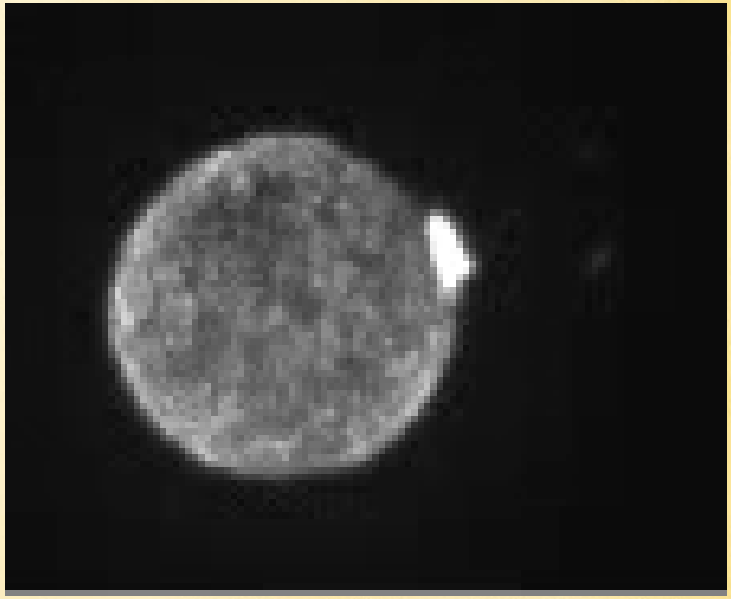
Houston, J.P., Ke, S., Wang, W., Li, C. and E.M. Sevick-Muraca, Journal of Biomedical Optics, 10, 054010, 2005.

Understanding Disease: microscopy of Cell-Cell Transmission of Infection with GFP Labeled HIV matrix Protein*

HIV-infected Jurkat T-cell



Compressed time Movie of the infection

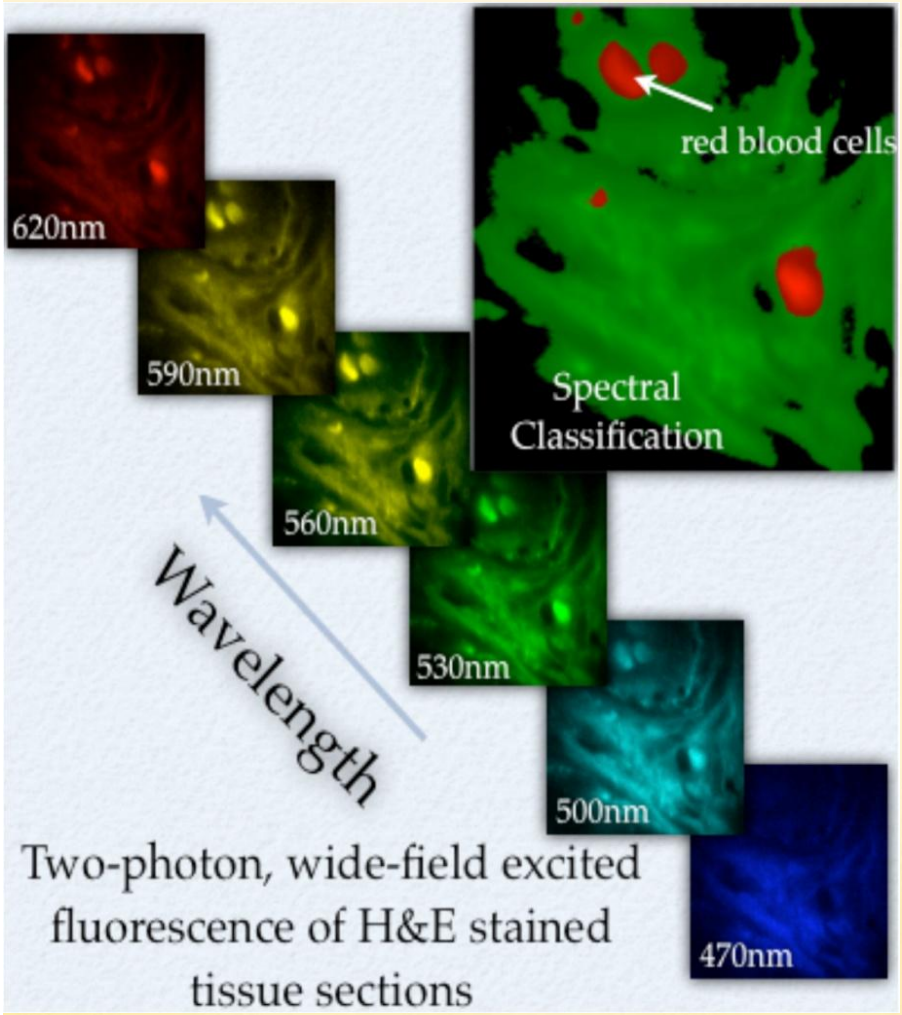


Fluorescence movie obtained with CBST real-time confocal microscope. 30 fps 3D frames collapsed to 1.3 s maximum intensity projection frame. Total length: 54 min.

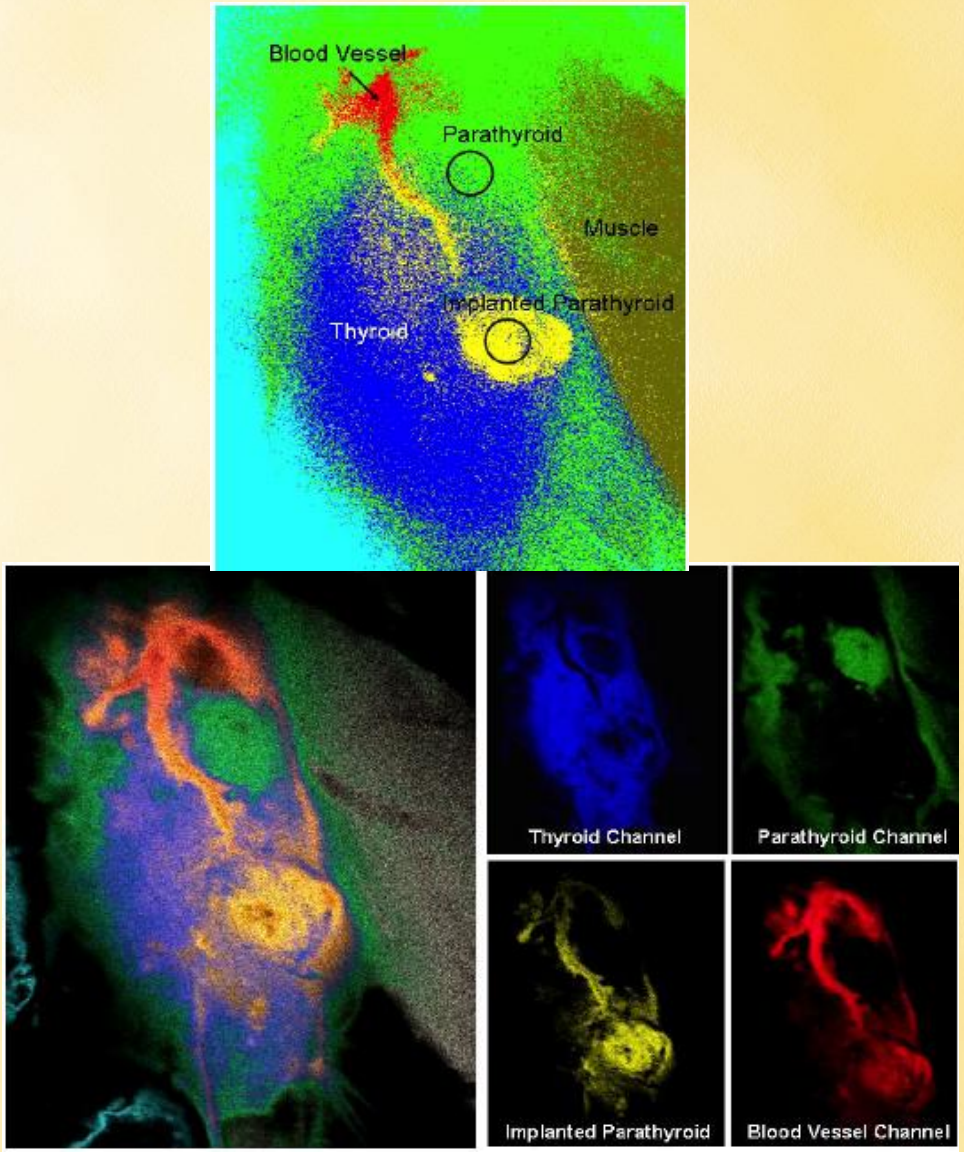
* Labeling by Dr. Ben Chen of Mt. Sinai

Spectral Imaging: from bench to surgical applications

Thyriod/parathyroid identification in rat *in vivo*

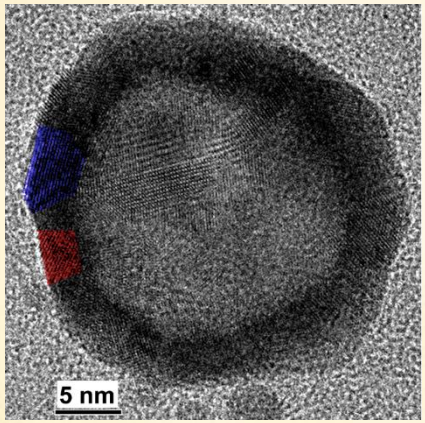


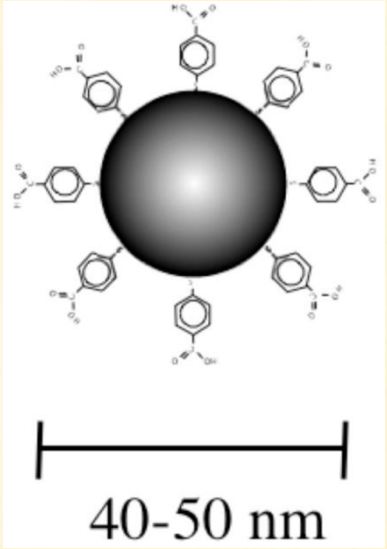
•Wachsmann-Hogiu et al, Proc. SPIE 6441, 644105 (2007)

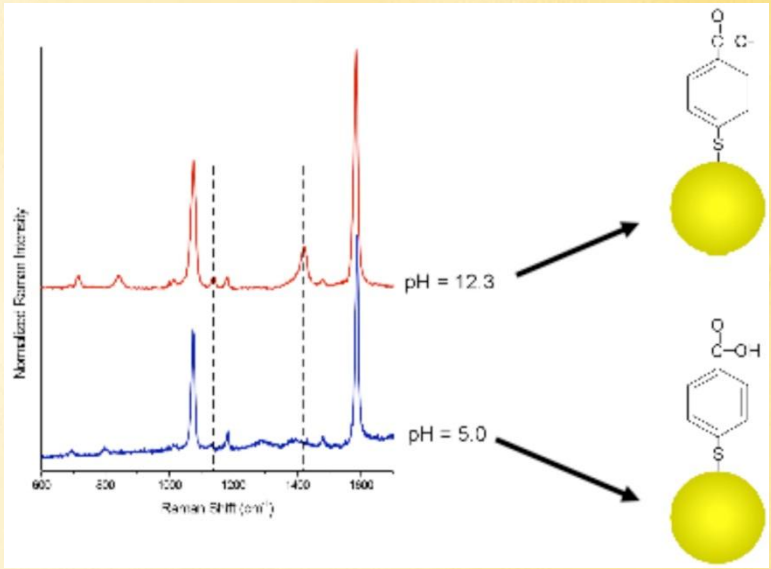


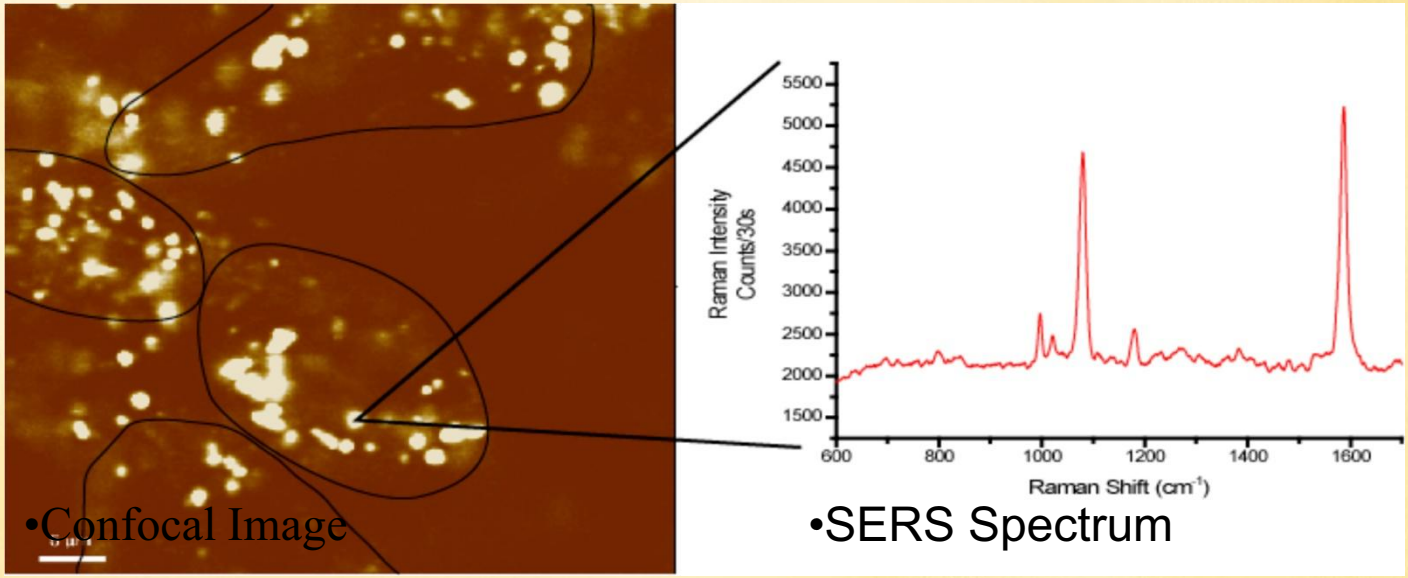
•J. Jeong et al, Proc. SPIE 6441. 64411N-1 (2007)

Sensors: passive uptake of functionalized nanoparticles by Chinese Hamster Ovary Cells (CHO): Nanoparticle sensors for intracellular use







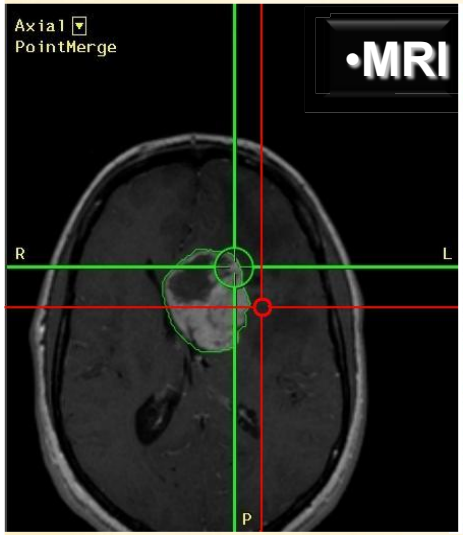


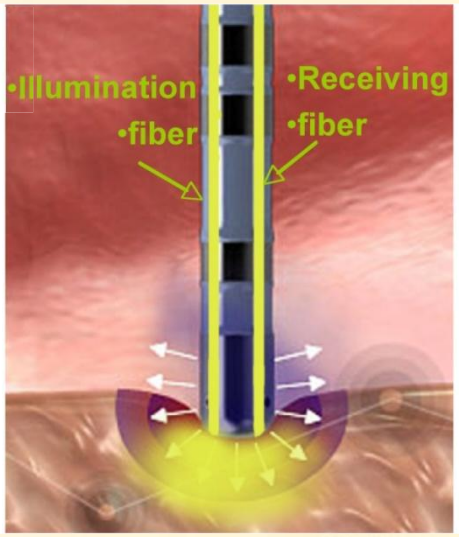
•Confocal Image

•SERS Spectrum

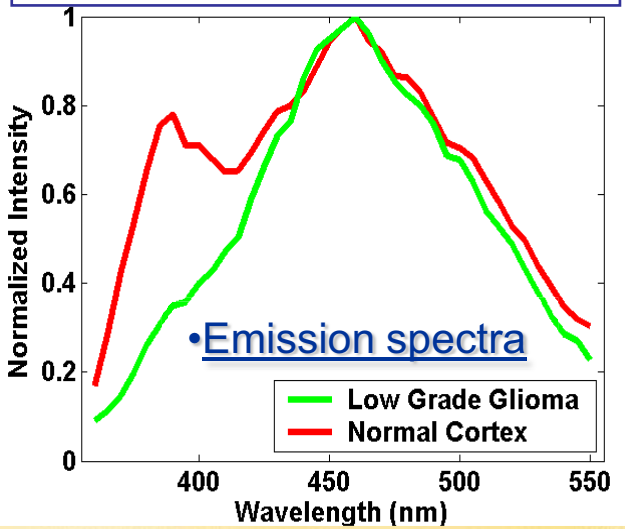
•Talley et al., Anal. Chem. 76, 7064-7068 (2004)

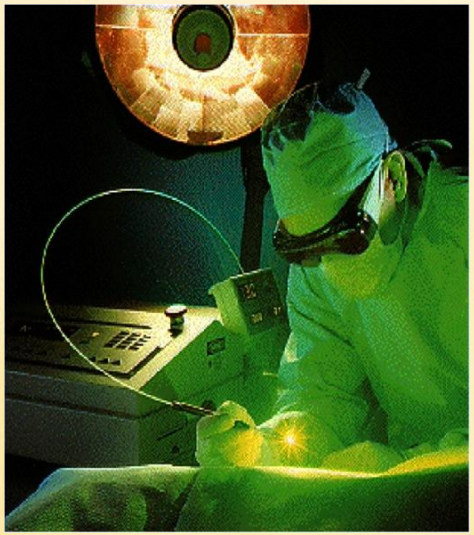
Clinical applications

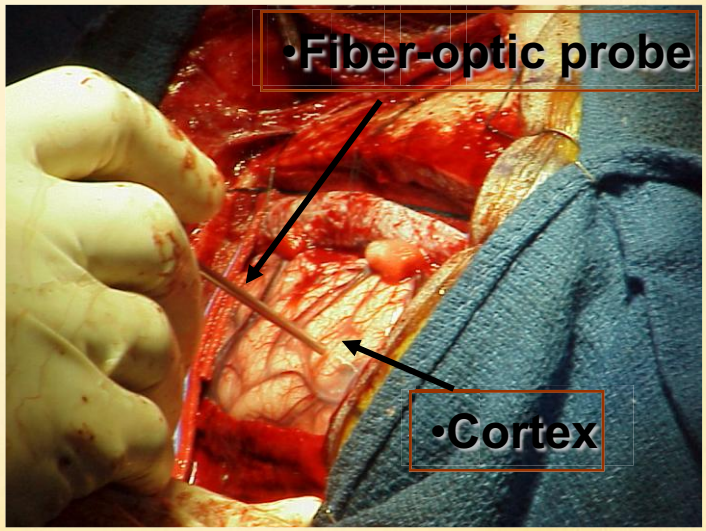


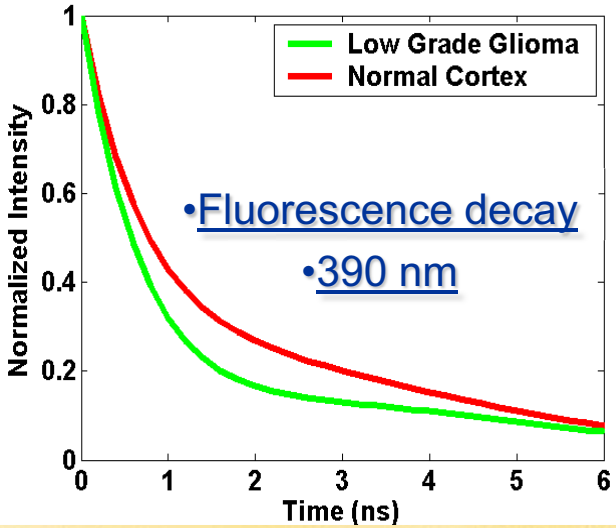


Fluorescence diagnostic signature.









CURRENT LANDSCAPE

WHAT IS BIOPHOTONICS REALLY USED FOR IN THE CLINICAL SETTING IN 2008?

WHAT MEDICAL SPECIALTIES ARE THE BIG USERS?

DERMATOLOGY OPHTHALMOLOGY

WHAT ARE THE HOME RUNS TO DATE?

WHAT ARE THE 'PIVOTAL CHALLENGES" THAT HELP DRIVE BIOPHOTONICS?

Courtesy of B. Wilson

PORT WINE STAIN

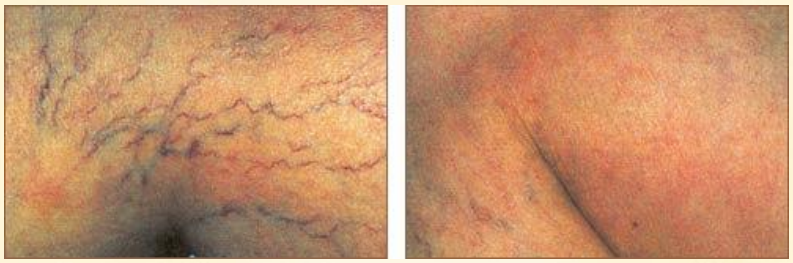
ACNE

ROSACEA

ANGIOMAS

Courtesy of B. Wilson

SPIDER VEINS



HAIR REMOVAL

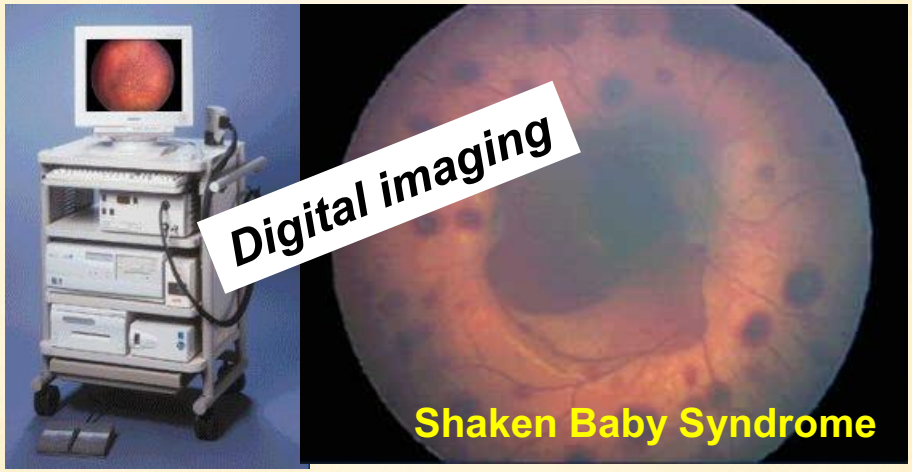
REJUVENATION

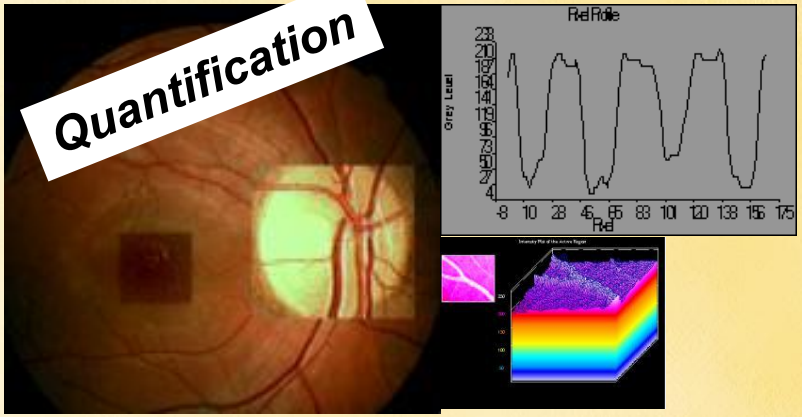
PIGMENTATION

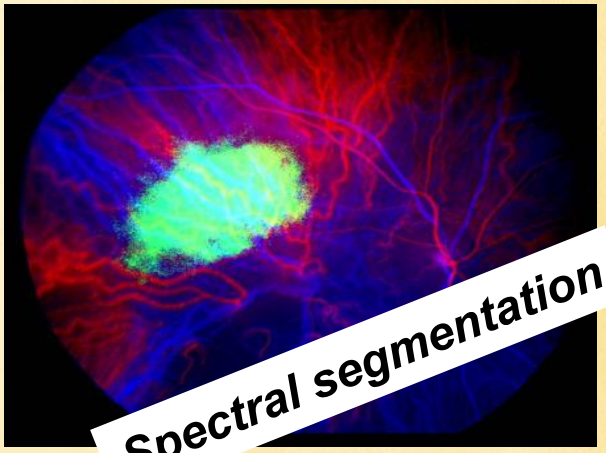
TATTOO REMOVAL

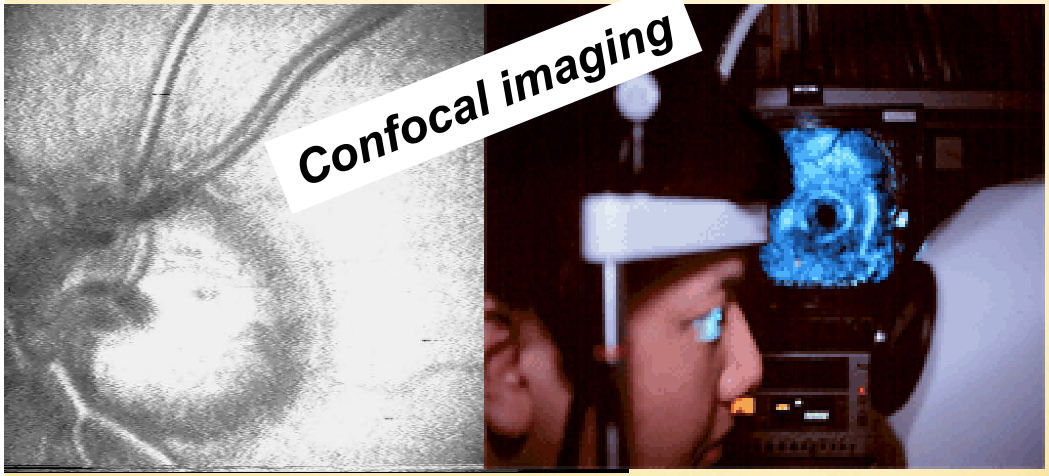
Courtesy of B. Wilson

Ophthalmology/diagnostic

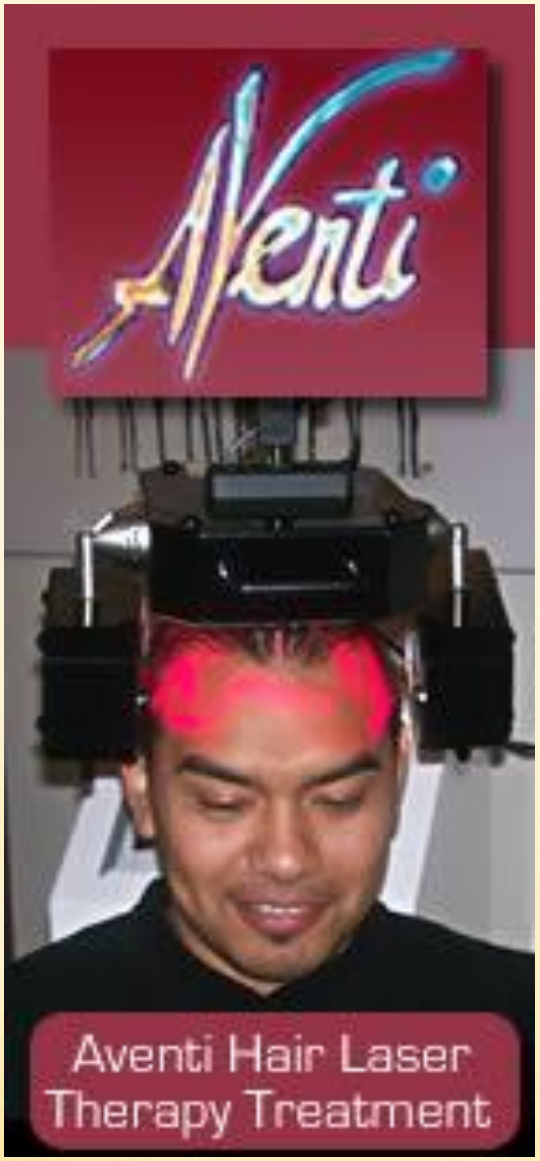








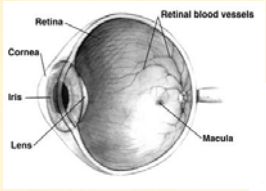
Courtesy of B. Wilson



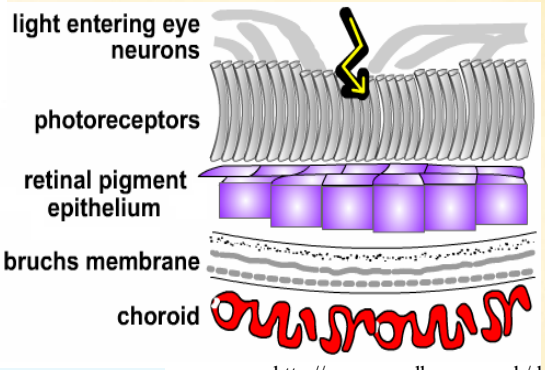
Courtesy of B. Wilson

Courtesy of B. Wilson

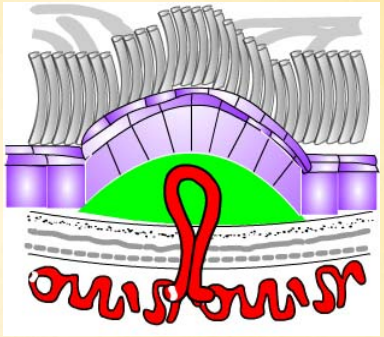
Example: Age-related macular degeneration



Normal eye



Neovascular AMD (CNV)



http://www.goodhope.org.uk/departments/eyedept/armd%20pathol.htm

http://www.charles-retina.com/images/normal.jpg

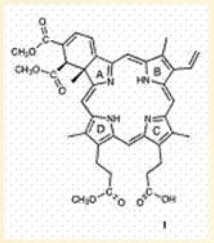
http://www.bostonretinalimplant.org/img/photos/wet-armd.jpg

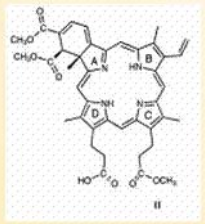
- Worldwide ~3 million cases of neovascular AMD (~1.6 million in US)
- 500,000 new cases of per year (200,000 in US)
- ~40% over the age of 75 will develop AMD and over 1/3rd between 55 & 74
- Aging population is increasing……..

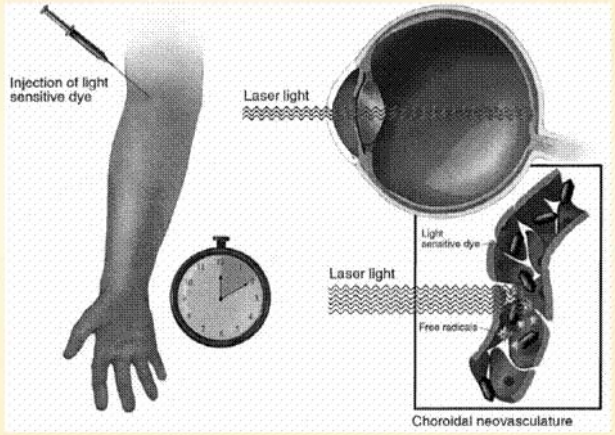
Courtesy of B. Wilson

Schmidt-Erfurth U, Hasan T, Gragoudas E, Michaud N, Flotte TJ, Birngruber R.
Vascular targeting in photodynamic occlusion of subretinal vessels
Ophthalmology. 1994 101:1953-61

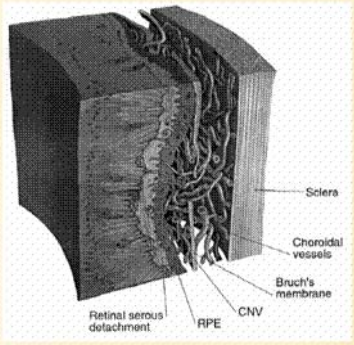
Neovascular Photodynamic Therapy using Visudyne







Renno and Miller, Adv. Drug Deliv. Rev., 2001



- FDA approval in 2000
- treatment demonstrated efficient neovasculature closure
- gold standard

>2M patients treated to date

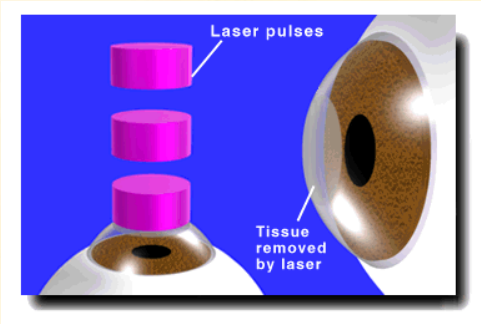
Sales ~B$0.5/yr

drug-device combination

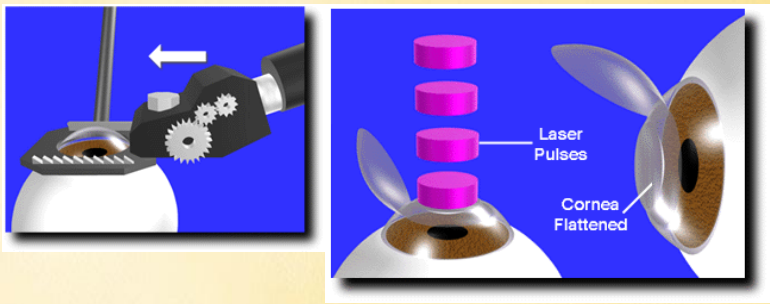
Courtesy of B. Wilson

Example: Corneal reshaping

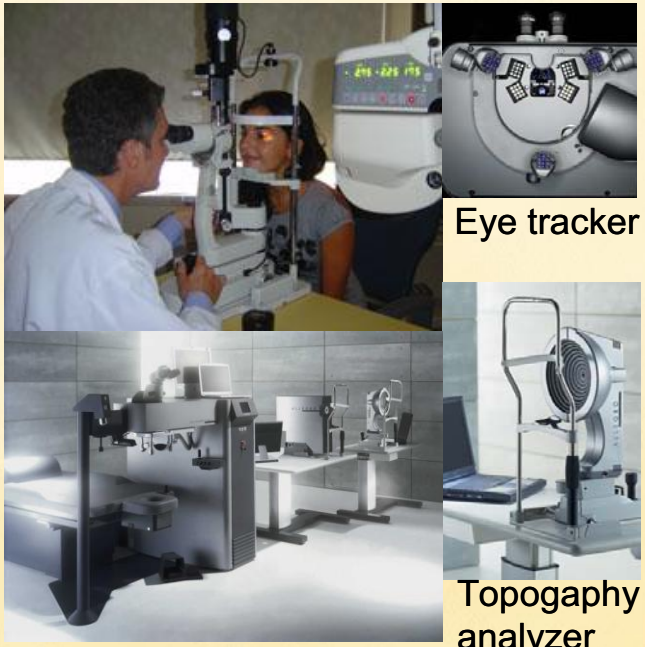
PRK



LASIK



Sophistcated technolgies



Eye tracker

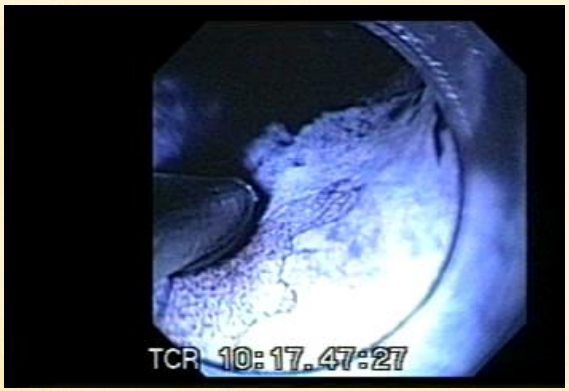
Topogaphy analyzer

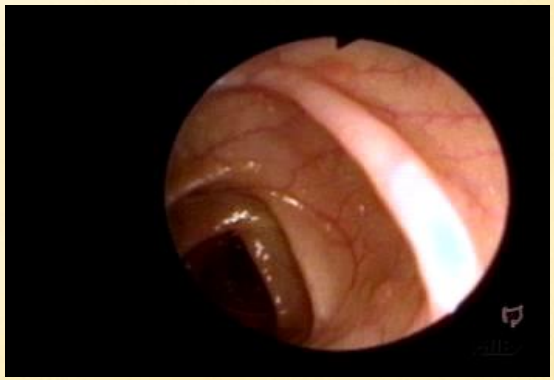
Laser system

Fully commercial and ubiquitous

Courtesy of B. Wilson

Example: Endoscopic diagnostics and therapeutics





Confocal

autofluoresecnce

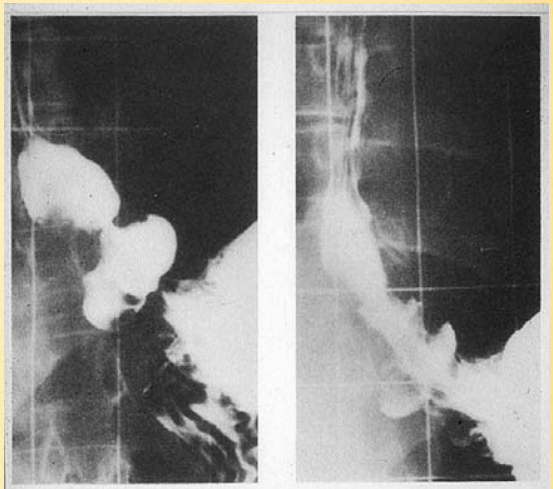
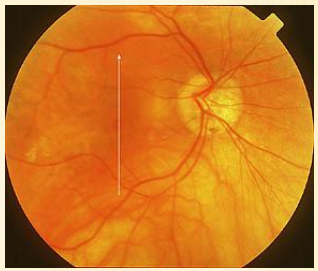
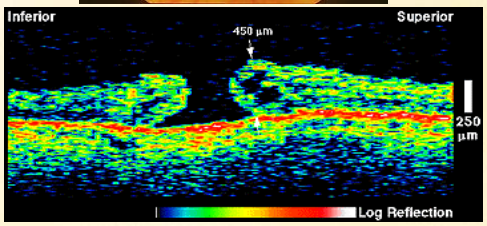


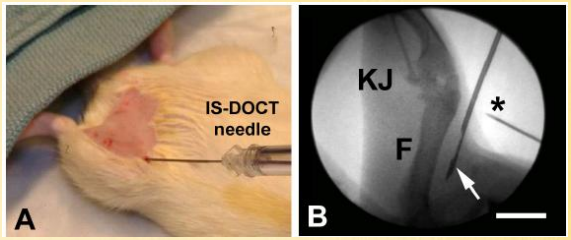
Figure 5.5 Carcinoma of the oesophagus before and after treatment with the Nd–YAG laser (photograph courtesy of Dr S G Bown).

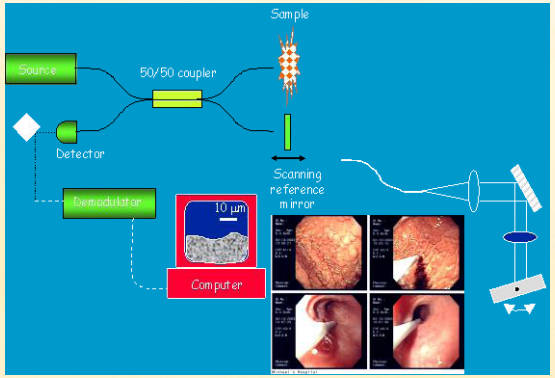
Courtesy of B. Wilson

Example: Optical Coherence Tomography





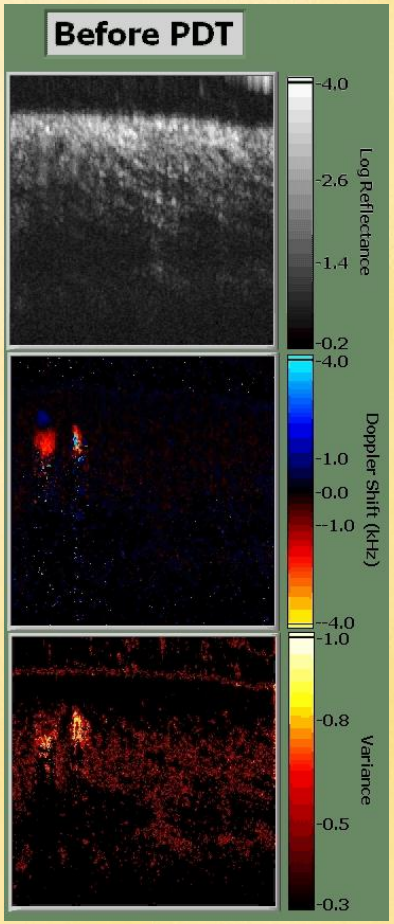


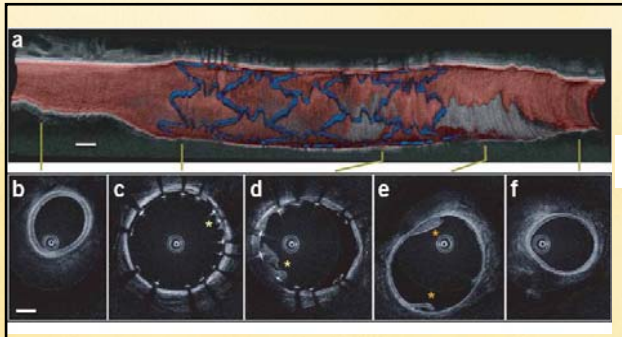


Intraocular
endoscopic
Intravascular
interstitial

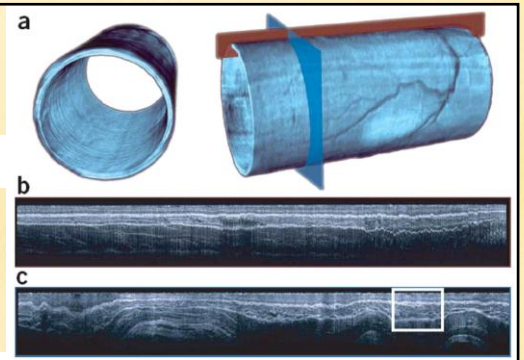
structural
blood flow
…

THERAGNOSTICS





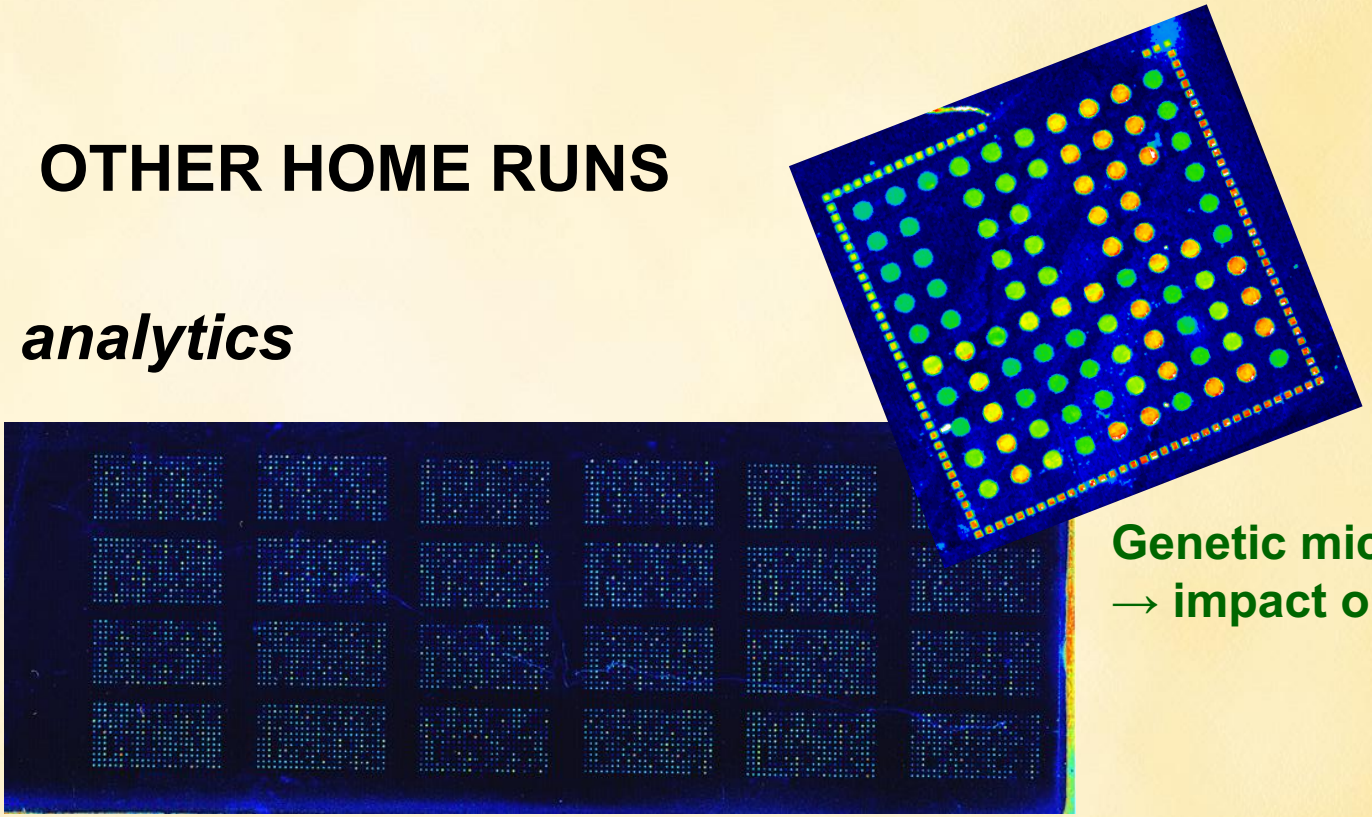
MGH



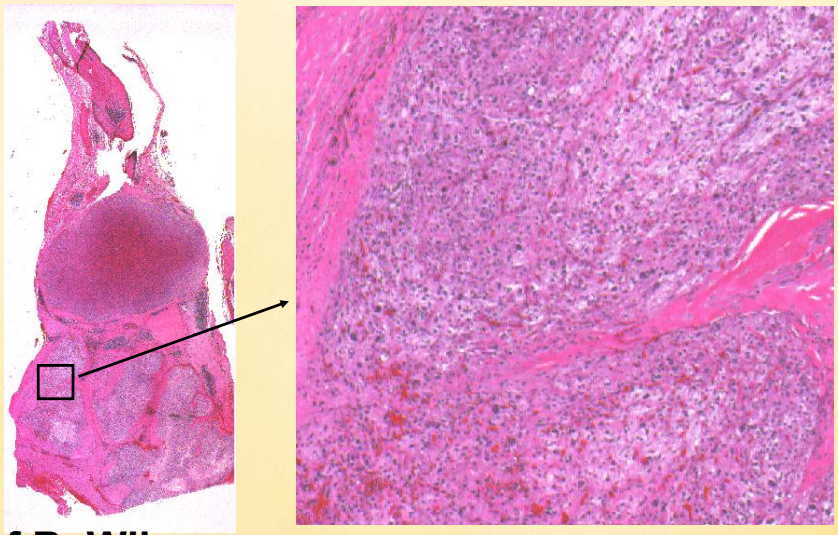
Courtesy of B. Wilson

OTHER HOME RUNS

analytics



Genetic microarrays
→ impact on drug discovery



Optical Microscopy
→ pathology

Courtesy of B. Wilson

Worldwide Research Institutions

Biophotonics Imaging Laboratory
University of Illinois at Urbana-Champaign

New York State Center for Advanced Technology in Photonics Applications at the City University of New York

Wellman Center for Photomedicine

ICFO Institut de Ciències Fotòniques

BIOP.DK

Britton Chance 生物医学光子学研究中心
Britton Chance Center for BioMedical Photonics

ICIP CIPI

CBST

The University Of Queensland Australia

Forschungsschwerpunkt Biophotonik

Photonics Research Ontario

Biophotonics and Laser Science Solutions

BIOPHOTONICS
National Yang Ming University

DRBIO Research WEBB GROUP

Beckman Laser Institute
University of California · Irvine

Lund University Medical Laser Centre

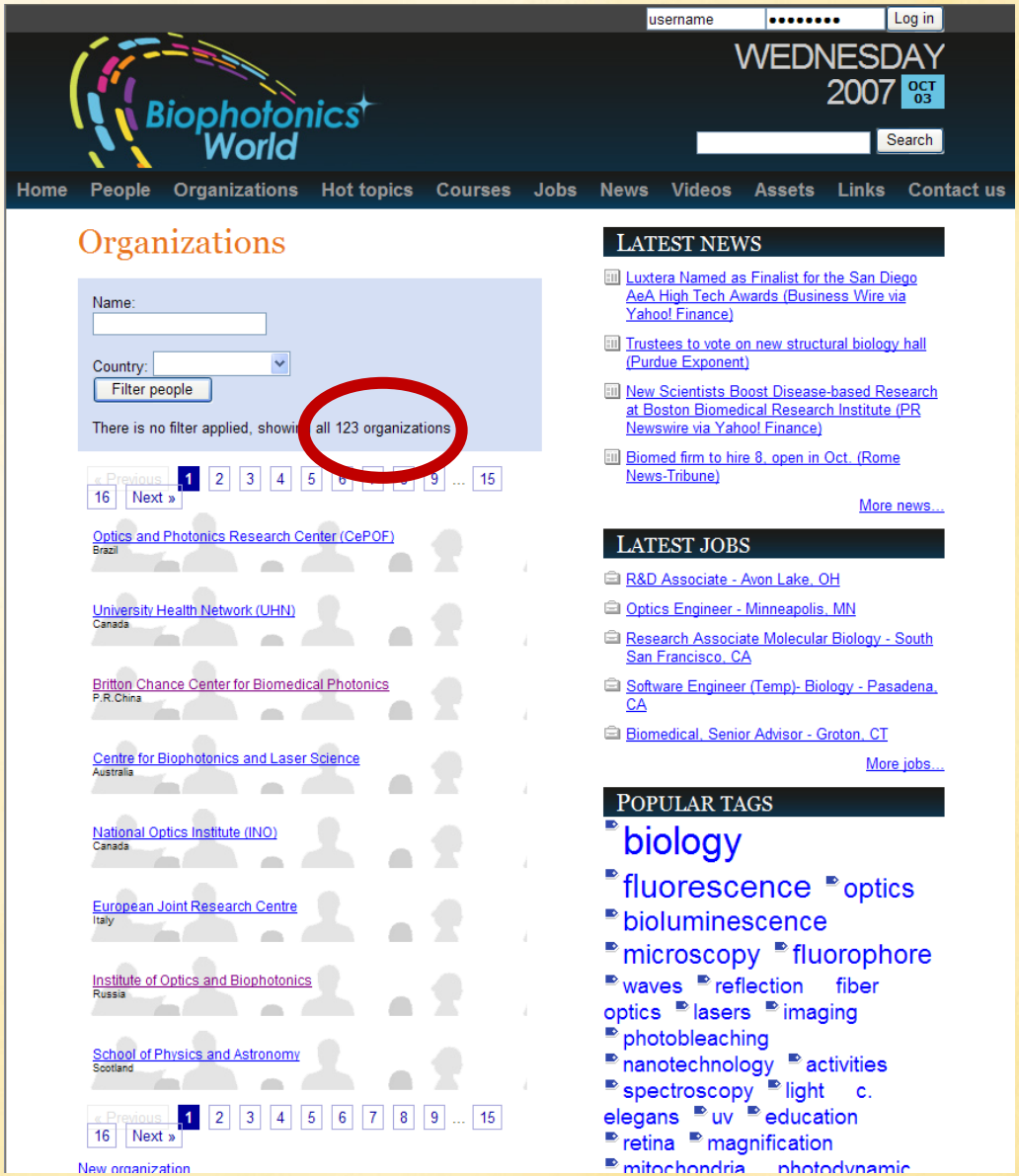
Director Dr. Katarina Svanberg, Department of Oncology
Chairman Professor Stefan Andersson-Engels, Division of Atomic Physics

Institut für Physikalische Chemie
Friedrich-Schiller-Universität Jena
Arbeitsgruppe Prof. Dr. Jürgen Popp
Mikro- & Biospektroskopie

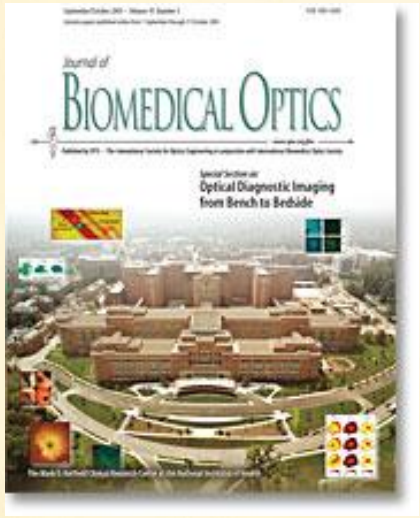
Center for Advanced Research in Photonics
Chinese University of Hong Kong (CUHK)

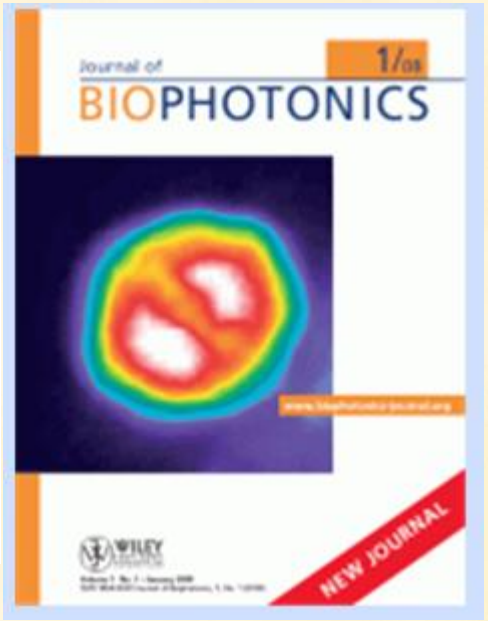
Кафедра Оптики
и Биомедицинской Физики

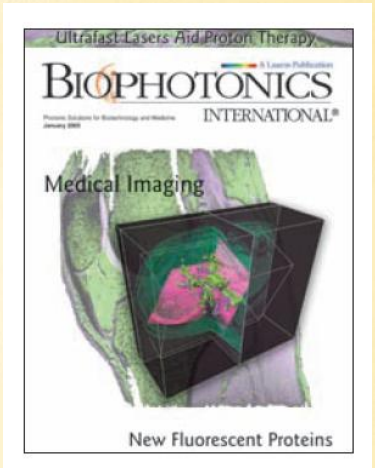
123 Academic Biophotonics Research Facilities now registered on www.biophotonicsworld.org

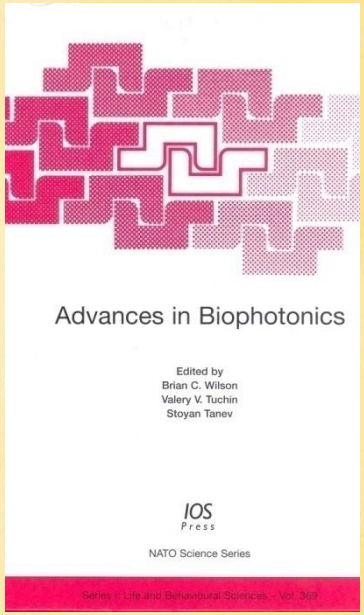


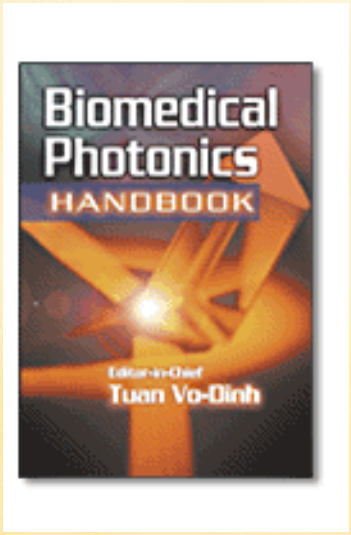
Selected Examples of Biophotonics Literature

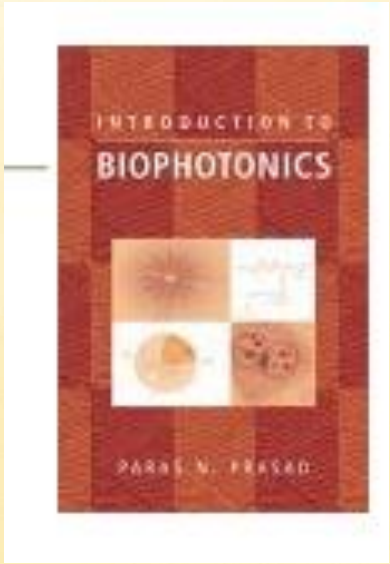


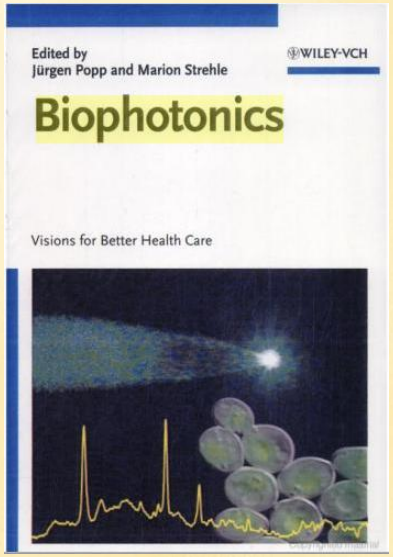


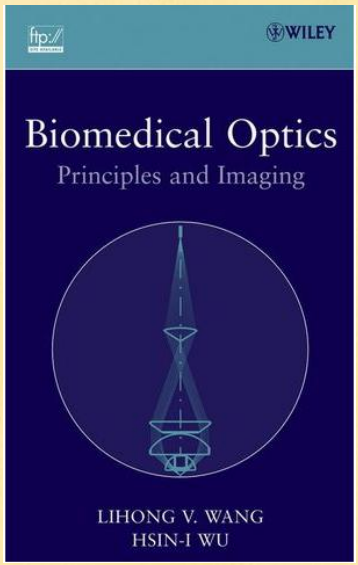












Biophotonics Conferences

APBP 2007
3rd Asian and Pacific Rim Symposium on Biophotonics
&
Biophotonics Downunder II

OWLS 9
The 9th International Conference on Optics Within Life Sciences, Taipei, Taiwan
November 26th~29th, 2006

International Conference "LASER OPTICS 2008"
St.Petersburg, Russia, June 23-28, 2008

LALS 2007
11-14 June 2007
Moscow, Russia

The International Society for Optical Engineering

Biophotonics Conference:
Entrepreneurship, Medicine & Light

April 28, 2005
Brown University Faculty Club
1:00-6:00pm
Buffet Dinner to follow

MEETING ANNOUNCEMENT

Second San Antonio Biophotonics Symposium
at
The University of Texas at San Antonio

INTERNATIONAL INSTITUTE OF BIOPHYSICS

Summer School 2003
Biophotonics and Applications of Biophotons

BiOS 2008
Part of SPIE Photonics West
19 - 24 January 2008
San Jose Convention Center
San Jose, California, USA

Biophotonics: Technology and Applications

Date:	07 December 2006
Venue:	Institute of Physics, London
Organised by:	Instrument Science and Technology Group

NATO Advanced Study Institute

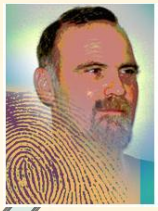
BIOPHOTONICS:
From Fundamental Principles to Health, Environment, Security and Defence Applications

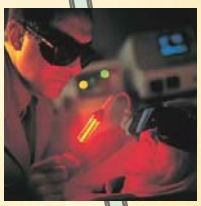
September 29-October 9, 2004
Crowne Plaza Hotel, Ottawa, Ontario, Canada

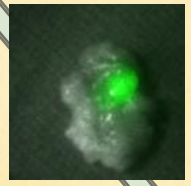
Biophotonics colloquium Paris 2003:
spotlight on biochips

PARIS BIOPHOTONIQUE 2003

Biophotonics market is > $53B/yr worldwide*







Non-medical applications

Biometric devices

UV sterilization equipment

Biosensing devices

>$1,146M

Tests &Components

Optical instruments

Molecular biology Probes

X-ray diffractometers

Fiber Optic sensors

>7,230M

Medical Therapeutics

Surgical equipment

PDT instrumentation

UV illuminators

Low-level laser therapy

Radiation-based therapy

>8,210M

Medical Diagnostics

In vitro diagnostics

Imaging

Endoscopes

Optical biopsies

Advanced imaging

>37,134M

Graduate School of Management UCDAVIS

Research performed as a class project by UCD Graduate School of Management MBA Students and Mentors: Lauren Fix, Gabriela Lee, Lisa Conroy, George Lui, Kaiyu Chu, Chris Truesdell. Instructor: Professor Richard Dorf. Now published in 30 Optik & Photonik June 2007 No. 2

> 250 companies surveyed

Abbott Diagnostics
AccSys
Acutronic Medical Systems AG
Advanced Cytometry Instrumentation
Advanced Medical Optics
Advanced Refractive Technologies
Advanced Research Technologies
Affinity Sensors
Affymetrix
Agilent Technologies
Akceli
Alcon - Surgical
Alerion Biomedical
Amnis
Analog Devices
Analogic
Analytical m-Systems
Anaspec
Andor Technology
Applied BioPhysics
Applied Biosystems
Applied Cytometry Systems
Applied Photophysics
Applied Scientific Instrumentation
Arkray
ARRYX, Inc.
Arturus Bioscience
Askion
Asylum Research
Avicenna
AVIV Instruments
Barco
Bayer
Beckman Coulter
Becton Dickinson
Beecher Instruments
Biacore International
Biodesign International
Bio-Logic SAS
bioMerieux SA
Bioptechs
Bioptigen
Bio-Rad
BioSense Serve
Biosite
Boston Electronic Corp
Boston Scientific Corporation
Bristol-Myers Squibb
BriteSmile
Bruker AXS
Bruker Biosciences
Bruker Optics Inc
Hamamatsu Photonics
Henry Schein, Inc
Hitachi Chemical Diagnostics
Hitachi High Technologies
Hitachi Kokusai Electric
Hitachi Medical Systems America
Hologic Inc
Horiba Jobin Yvon
HTS Biosystems
Huntsman Corp
IBIS Technologies
Illix (Canada)
Illumina
ILT
Imaging Diagnostic Systems
Imalux
Immune Source Immunotech
InfraMed Imaging
Inndrenex (subsidiary of BioGenex)
Intel
IntraLase
Inverness Medical Innovations
Invitrogen Corp - Molecular Probes
Ionscope Limited
ISCO International
Jackson Immunoresearch
JDS Uniphase Corporation
Johnson & Johnson
JPK Instruments
Karl Storz
Kinetic Systems, Inc
KinTek Corp
Laser Drive, Inc
Laser Light Canada
Laser Physics
Laserscope
LCA Vision Inc
Leica Microsystems, Inc
Life Wave
LightLab Imaging
Linos Photonics Inc
Ludl Electronic Products Ltd
Nellcor
NeoSensor Limited, Farfield Group
Newport
Nikon
Nonin Medical
Nova Biomedical
Novacam Technologies
Ocean Optics
Oculir
Olis
Olympus
Omega Optical
Optiscan Inc
Ortho-Clinical Diagnostics
OSI Systems
P.A.L.M. Microlaser Technologies
Palomar Medical Technologies
Partec
Pasco
Pavilion Integration Corp.
Pegasus Scientific
Pentax
Perkin Elmer
PharMingen
Philips Medical Systems
PhotoMedex
Photon Technology International
PI (Physik Instrumente) LP
PicoQuant GmbH
Ploenix Flow Systems
Polymicro Technologies LLC
Polysciences
Positive Light, Ing.
Power Technology, Inc
Prairie Technologies
Prior Scientific Inc
Prizmatix S. Pozner Tech Ltd
Prolinx
QBiogene
Qiagen
Qlt Inc
Quantech Ltd
Quantel SA
Spotlight surgical
SRU Biosystems
STMicroelectronics
Stratagene
Stryker Corporation
Sutter Instrument Co
Sybron Dental Specialties
Syngenta
Sysmex
Teleflex Incorporated
Texas Instruments
Therakos
ThermoElectron Corp
Thermomicroscopes
Thorlabs
ThreeFold Sensors
Toptica Photonics AG
Toshiba Medical Systems
Tree star
Triple-O Microscopy GmbH
Tyco Healthcare Group
Union Biometrica Inc, Holliston, MA
Unitron
Varian Medical Systems
Vector Laboratories
Veridex
Verity Software House
Virtek Vision International
VisEn Medical
Warner Instruments
Waters
WITec Wissenschaftliche
Xenogen

Biophotonics Growth Rates versus Market Sector

Industry Segments Relevant to Biophotonics	Components within Segment	Forecast (in Millions of USD)		Annual Growth Rate (A=average, C=compound)	
		US	World	US	World
Microscopes and accessories	Microscopes		2,770 in 2009		11% AAGR
Medical lasers	Laser illumination, Lasers for OCT, Surgical lasers, Dermatology lasers, Cosmetic lasers, Dental lasers, Would care lasers, Lasers for low-level laser, therapy, Lasers for benign prostatic, hyperplasia	2,086 in 2006	3,209 in 2006	12% CAGR 2003 - 2006	12% CAGR 2003 - 2006
DNA sequencing	DNA sequencing		17,500 in 2009		17.6% AAGR
In Vitro Diagnostics	Clinic biochemistry, Immunoassays, Blood testing, Nucleic acid diagnostics, Flow cytometers	17,700 in 2009		6.1% in 2004	5% in 2005
Endoscopes	Endoscopes (excludes visualization equipment)	513.5 in 2012		1.9% CAGR 2005 - 2012	
Medical imaging equipment	X-ray, PET, CT, MRI, ultrasound	9,500 in 2008 1,900 X-ray 1,775 MRI 1,775 ultrasound 4,050 other		7.6% 2003 - 2008 4.6% X-ray 5.3% MRI 6.2% ultrasound 11.2% other (PET more than 3X)	7% through 2007
Patient monitoring systems	Pulsed oximetry, IR body temperature sensors, Blood glucose monitors, Cardiac and multi-parameter, monitoring systems with fiber optic sensors, Bili light, Slit lamps, Borescopes, fiberscopes, videoscopes	8,200 in 2008		6.7%	
Radiation-based therapy and therapeutic imaging	X-ray and laser therapeutic radiation	5,700 in 2009		7.6% AAGR	
Adjunctive therapies: photodynamic, electromagnetic, radioimmunotherapy, and angiogenesis inhibitors	PDT instrumentation and therapeutic agents	8,800 in 2009		39.2%	

TABLE 3: **Market size forecasts and annual growth rates of various industry segments relevant to biophotonics.**

Lee et al., Optik & Photonik June 2007 No. 2

BiophotonicsWorld
What is it?

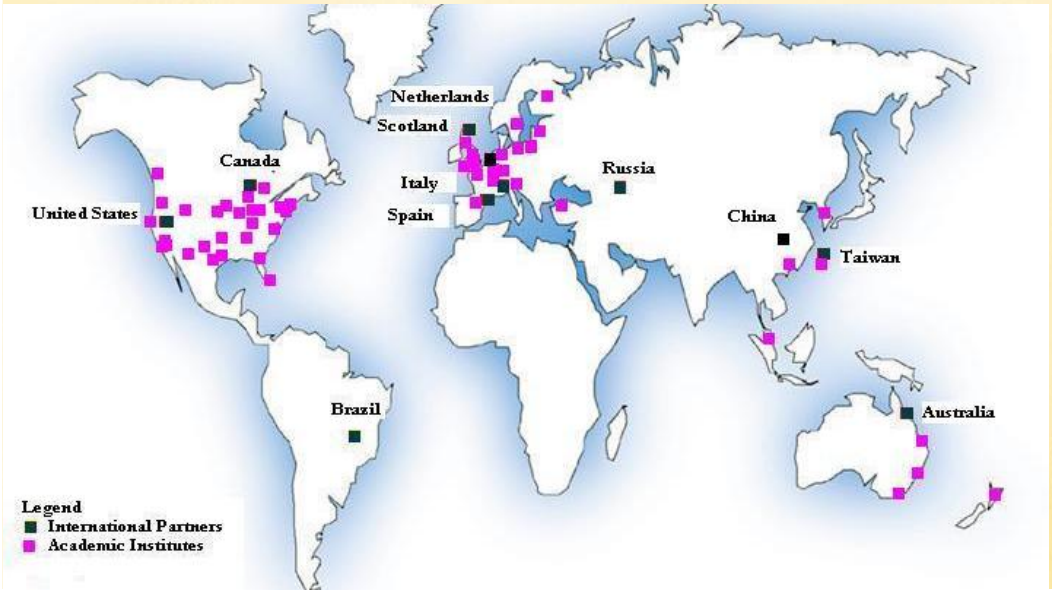
your portal to biophotonics
Biophotonics World

- **A resource for biophotonics teaching and learning**
  - What is Biophotonics? Common and not so common examples, Lessons plans and activities, Video lectures, Connect and share with other educators
- **A clearinghouse and discussion forum for the latest research in the field**
  - Who is doing what, where? What topics are most important in the field? Connect and share with other researchers
- **Who and where are the industries? What are the latest products?**

PLUS…

a meeting place for educators, researchers, and industry and government representatives

a place to find the latest news and job opportunities in the field.



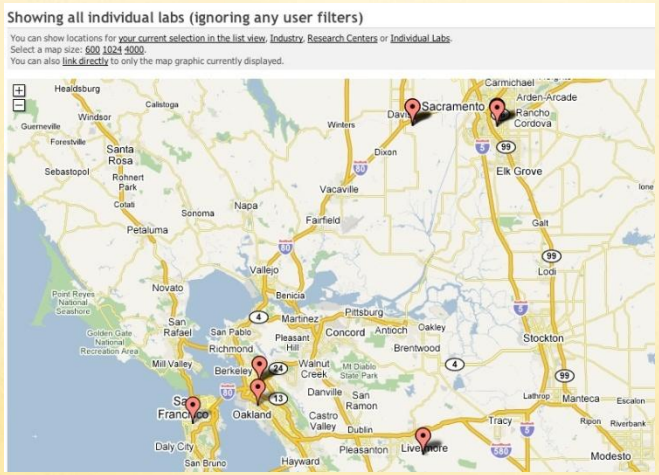
Nodes in 11 countries and growing!

Center for BIOPHOTONICS Science & Technology

ICIP CIPI

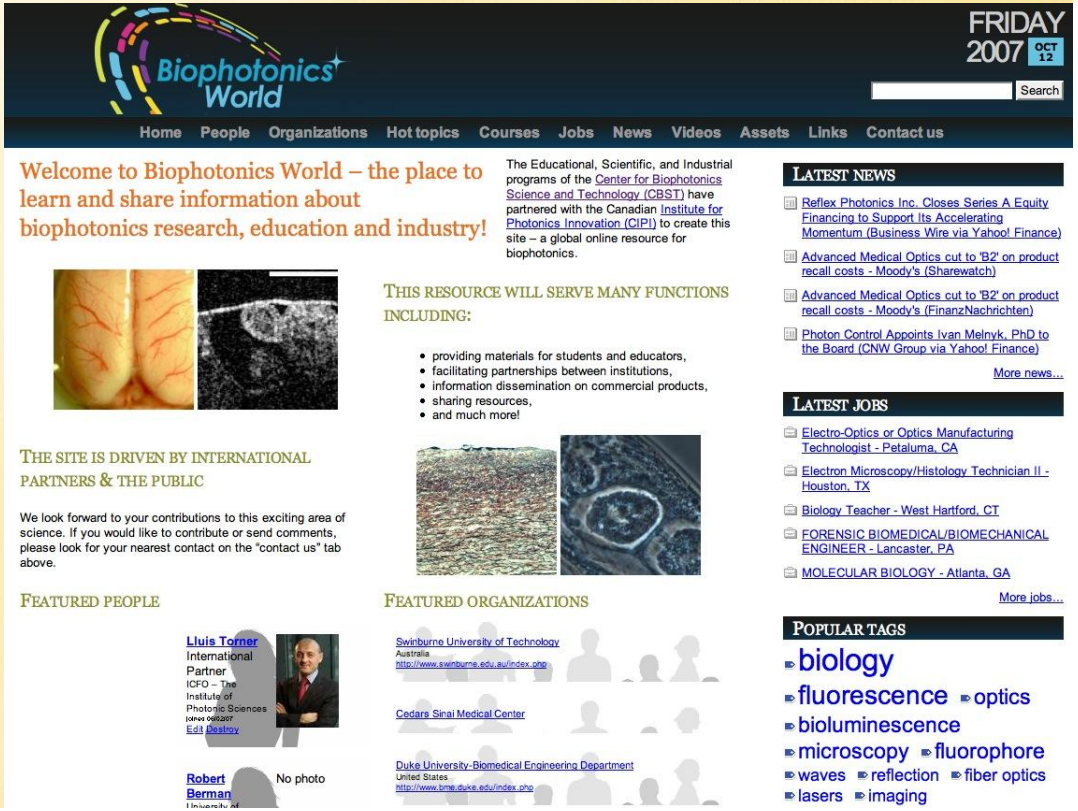
BiophotonicsWorld
Future

- Foster community of interested users
- Increase number of nodes and members
- Increase content and functionality based on initial user feedback
- Develop international governing structure
- Seek substantial external funding through grants and foundations
- Partner with one or more journals focused on biophotonics

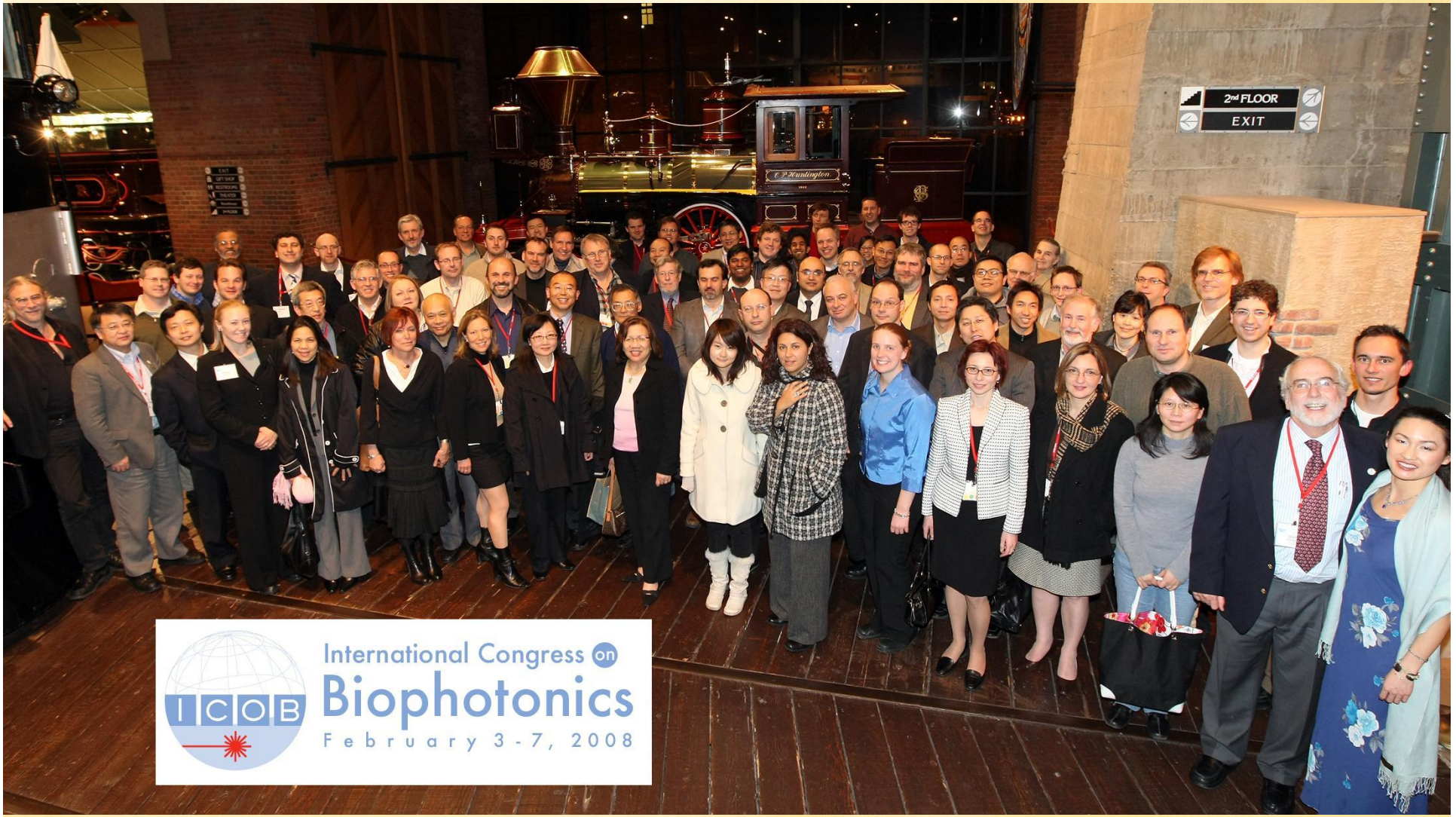


Center for BIOPHOTONICS Science & Technology

ICIP CIPI



Major Challenges in Bioscience and Medicine

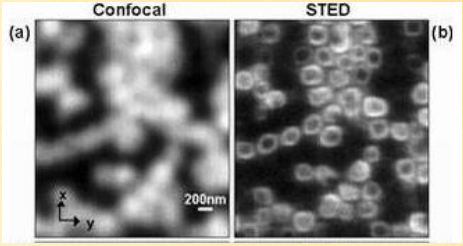


More Grand Challenges for Biophotonics (from BP world)

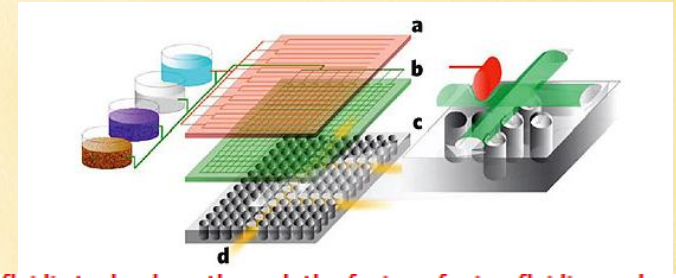
- **Image-guided surgery at the cellular level of precision**
- **Personal implantable or wearable continuous-operation biological marker sensor to predict onset of diseases such as cancer, stroke, heart attack, etc.**
- **Smart tissue welding system to re-unite all types of tissue including severed nerves and spinal cords.**
- **Rapid ER assays to diagnose and distinguish acute bacterial or viral infections**
- Bioscience: To understand the structure, dynamics and function of every element of the living cell, including every aspect of the cell membrane, the molecular structure and dynamics within the cell and the relationship of proteins to genetic functions
  - Inter-intracellular communication
  - Relationship of structure and dynamics to evolution, immortality, and cell death
  - Origin of degenerative diseases
- Medical Science - To develop Automated Pathology for non-invasive, *in situ*, multi-disease diagnosis of the most debilitating diseases at the earliest stages (Molecular or cellular level), including spatial identification:
- **Develop photo-activatable molecular machines ("Nano-bots") to conquer disease**
- **Develop a photonics based method to detect and treat metastases at the time Cancer is diagnosed**
- **Detection/imaging changes in brain function at the micro level that accompany degerative diseases such as Alzheimers**
- **Non touch arterial blood pressure determination**
- **…..**

Future Directions in Biophotonics*

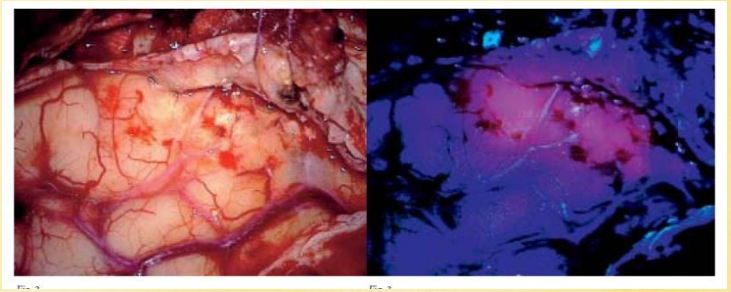
- Microscopic Imaging
  - Biomolecular imaging with X-diffraction
  - Non-linear imaging devices
    - Unlabeled viral, bacterial dynamics
    - In vitro imaging of protein complexes
  - ……
- Sensors/Assays/Probes
  - POCT Devices (Optofluidic Lab on a Chip)
  - Highly targeted nano-particle probes
  - Probeless, Raman Flow Cytometry
  - Personal health monitors, metabolometers
  - High speed wide field array readers
  - ……
- Clinical Diagnostics/Therapy
  - Real time pharmaco-kinetics
  - Biodosimeters (radiation,viral, bacterial)
  - Response to therapy monitors
  - POCT devices for diagnoses, staging
  - Image-guided micro/nano-surgery
  - Non-invasive cancer, etc. therapy
  - Stem cell ID, tracking
  - Self-reporting *In Vivo* Nano-clinics



From Stefan Hell, Phys Rev Letts, 2005.



Developing optofluidic technology through the fusion of microfluidics and optics
Demetri Psaltis, Stephen R. Quake and Changhuei Yang
Nature **442**, 381-386(27 July 2006)



Fluorescence-guided malignant glioma resection, courtesy of Zeiss Inc.

* Caveat - I am better at attempting to create the future than predicting it!

Principal Points for this Talk

- Biophotonics is a critical and growing component of bioscience and medicine
  - study of living organisms at dimensions of e-microscopy, surgery at subcellular precision…
- Biophotonics as a business is >$50B/yr with 5-40% growth, lots of room for startups and new products
- Please use our http://www.BiophotonicsWorld.org web portal to understand and contribute to the field.
  - who is doing, what, where and why?
- There are plenty of grand challenges in bioscience and medicine that can be met using biophotonics devices, present and future
  - Wearable health monitors? Cure for presbyopia? Non-invasive surg? Artificial Pancreas? POC diagnostics/pathology?....
- Speculate on the future of biophotonics R&D.
  - We will study life at the dimension of molecular machines
  - Diagnose and treat with a hand-held lab/therapy device (tri-corder!)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