The Abdus Salam International Centre for Theoretical Physics

United Nations Educational, Scientific and Cultural Organization

IAEA International Atomic Energy Agency

1932-11

Winter College on Micro and Nano Photonics for Life Sciences

11 - 22 February 2008

A Survey of the field of Biophotonics and its Applications to Bioscience and Medicine Lecture II

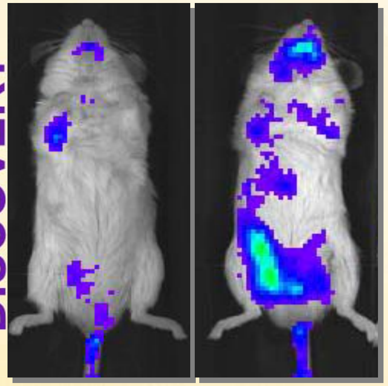
Dennis Matthews

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

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

EDUCATION

DISCOVERY



TECHNOLOGY

Dennis Matthews, PhD

UCDAVIS
UNIVERSITY OF CALIFORNIA

Center for BIOPHOTONICS Science & Technology

NSF

http://cbst.ucdavis.edu • dlmatthews@ucdavis.edu • 011(916)734-4342

Work supported by the National Science Foundation Cooperative Agreement No. PHY-0120999

Winter College on Micro and Nano Photonics for Life Sciences

ICTP The Abdus Salam International Centre for Theoretical Physics

UC DAVIS

Lawrence Livermore National Laboratory

Berkeley University of California

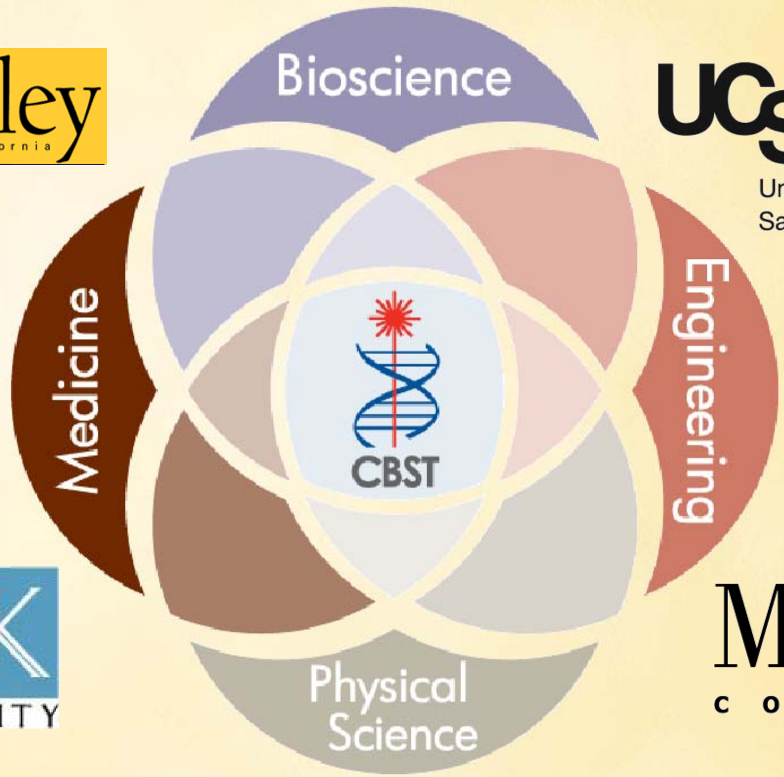
UCSF University of California San Francisco

Alabama A&M University

STANFORD UNIVERSITY

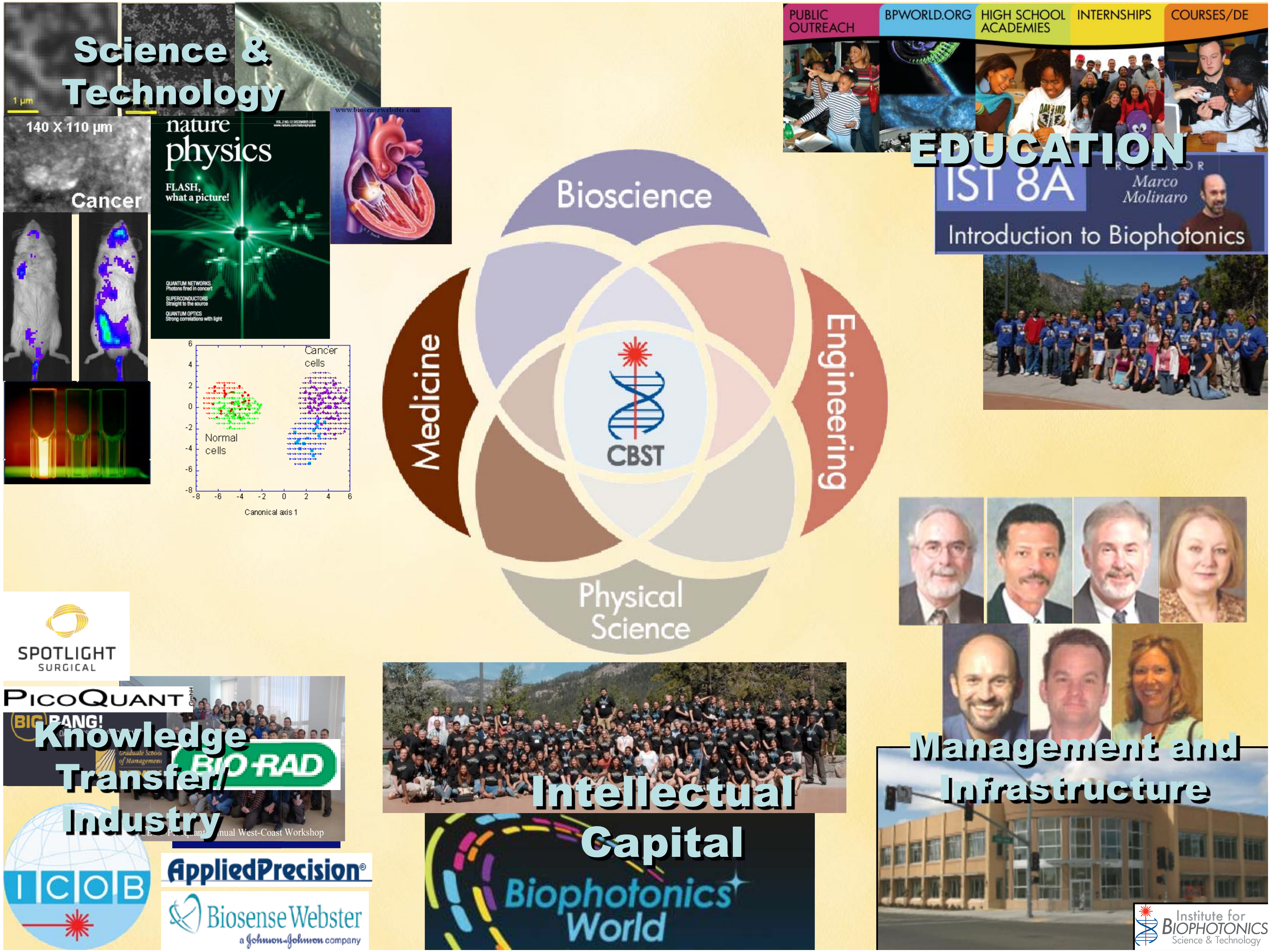
FISK UNIVERSITY

MILLS COLLEGE



UTSA

MISSION: To develop and apply photon-based technologies to Biosciences and Medicine


Science & Technology
1 µm
140 X 110 µm
Cancer
nature physics
FLASH, what a picture!
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PROFESSOR Marco Molinaro
Introduction to Biophotonics
Bioscience
Medicine
Engineering
Physical Science
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BIG BANG!
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BIO-RAD
Annual West-Coast Workshop
ICOB
AppliedPrecision
Biosense Webster
a Johnson & Johnson company
Intellectual Capital
Biophotonics World
Management and Infrastructure
Institute for BIOPHOTONICS Science & Technology

CBST, Oak Park Facility Summary

UCDAVIS

Center for Biophotonics Science & Technology

The CBST Oak Park facility is the central location for CBST research activities. This ~10,000 sq.ft., multi-user, state-of-the-art facility is a catalyst for collaborative efforts in biophotonics research and education.

CBST Facility

Facility description

Research labs - designed for the development of novel biophotonics tools and their applications;
Biochemistry lab - bio-hoods, cell culture, sample storage, and wet bench space for sample prep;
Education rooms - video/computer equipment and biophotonics hands-on demos;
Engineering room - light machining tools for prototyping and instrument development;
Offices, student, meeting, and seminar rooms.

Facility management

A facility committee made up of CBST senior management, PIs, and main operators meets regularly to address issues such as common use and maintenance of the equipment, instrumentation needs and problems, safety, data collection and handling. A written policy for the use of the facility will be approved by this committee.

CBST Research Labs

Non-Linear Microscopy Lab

CARS ratiometric scanning microscope
CARS spinning disk confocal microscope
High-power femtosecond laser microscope
Multi-Photon Microscope

Single Molecule Spectroscopy Lab

TCSPC microscope
Laser trap Raman spectroscopy system
Till Photonics robotic microscope
Nipkow spinning-disk confocal microscope

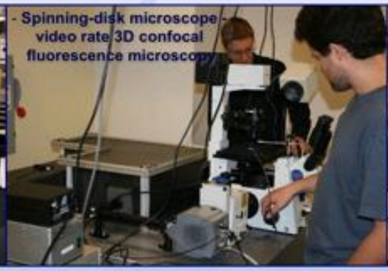
Advanced Imaging Lab

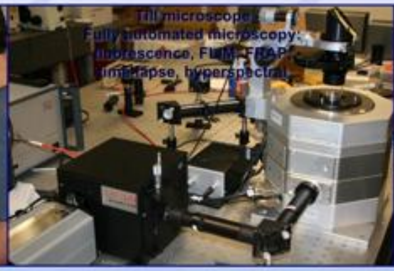
OMX
AFM
Fluorimeter
UV-Vis spectrometer

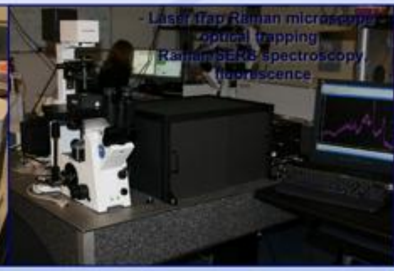
Instrument Development Lab

FLIM clinical system
Robotic DNA/protein array printer

Red italics: instruments to be finalized within one year

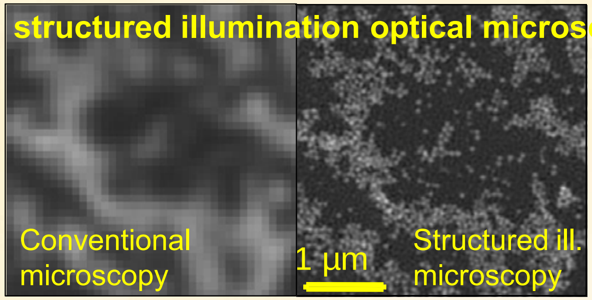




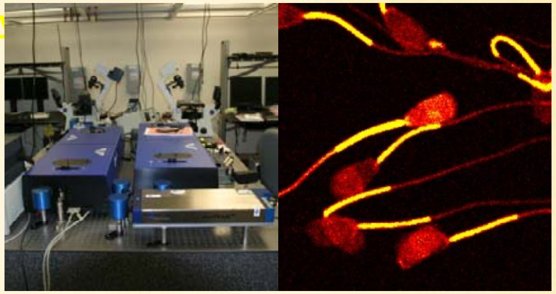


CBST Science and Technology Themes and Projects

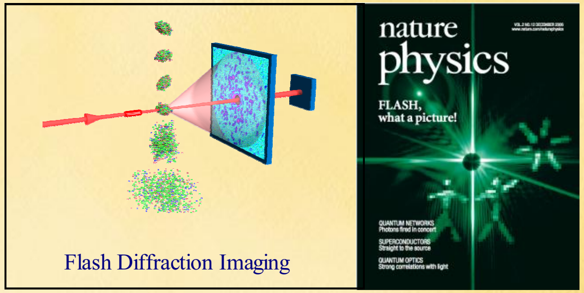
Advanced Microscopy and Spectroscopy



Ultra-resolution optical microscopy

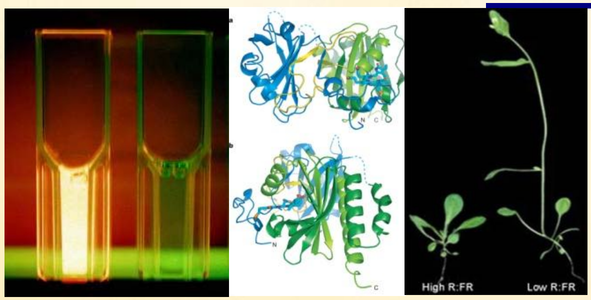


CARS and other label-free microscopies

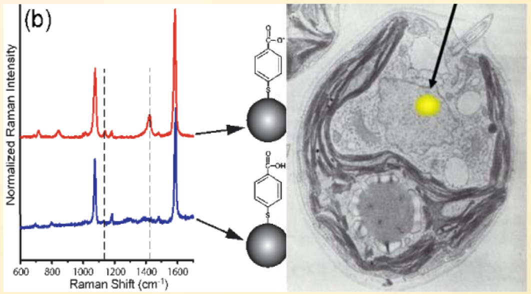


Structure of individual cells and biomolecules by lenless x-ray diffraction imaging.

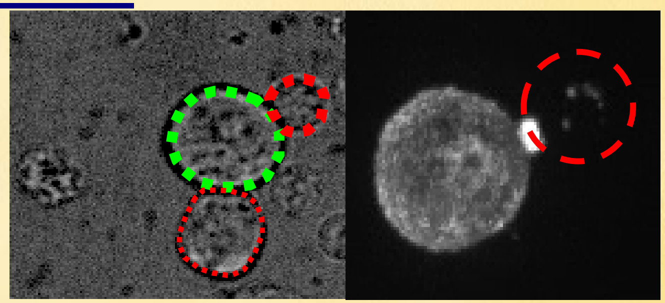
Molecular and Cellular Biophotonics



Engineered phytochromes produce versatile optical labels and modulate plant behavior.



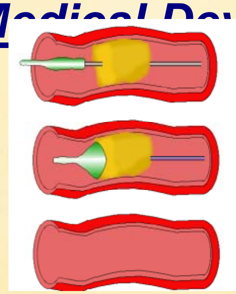
Nanoparticle intra- and inter-cell sensing and tracking.



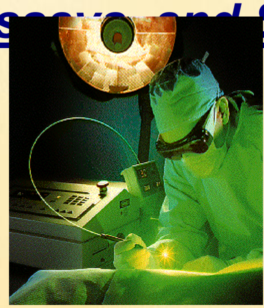
3D RT tracking viral infections in-vitro: Transfer of GFP-GAG HIV from infected cells

Medical Devices, Assays, and Sensors

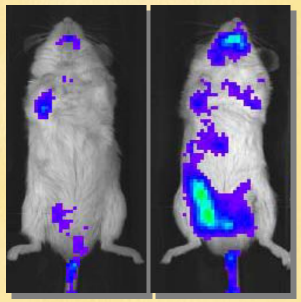
An optical probe for controlling treatment of heart arrhythmias.



SMP tools for vascular interventional surgery



Light based diagnostics and therapies for surgery



Bioluminescent in vivo and in vitro protease assays

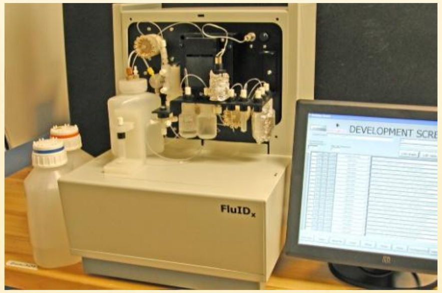
Applying Biophotonics to POCT Needs – Current Devices & Concepts

Early prototype , Real-time PCR device

Handheld RT - PCR for first responders

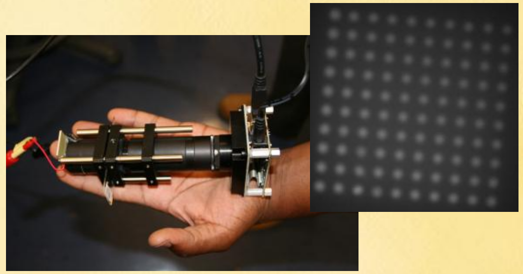
Autonomous airborne disease detector

Laser bioaerosol mass spectrometry



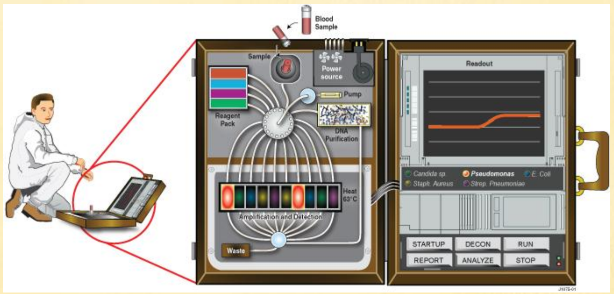
Point-of-Care Influenza Detection - FluIDx

Center for BIOPHOTONICS Science & Technology

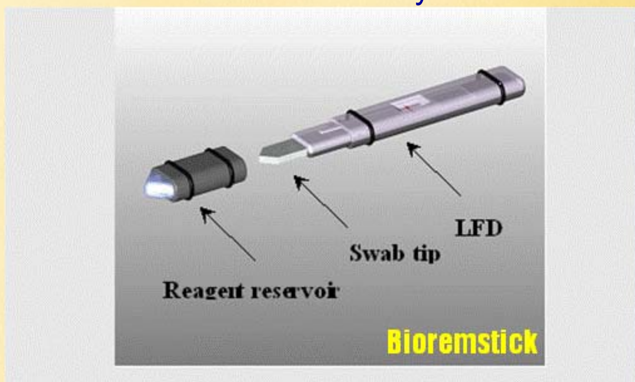


Portable microarray readers

Disposable infectious disease detector



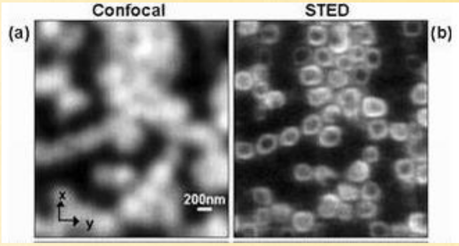
Field-portable isothermal RT PCR



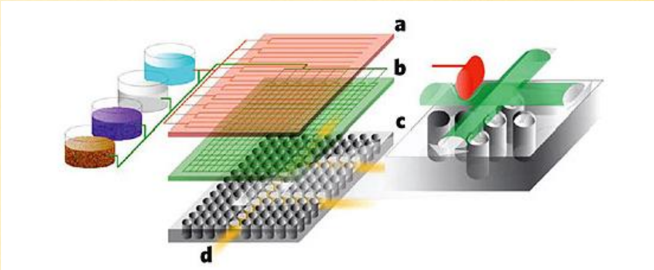
Disposable Radiation Biodosimeters

Future Directions in Biophotonics*

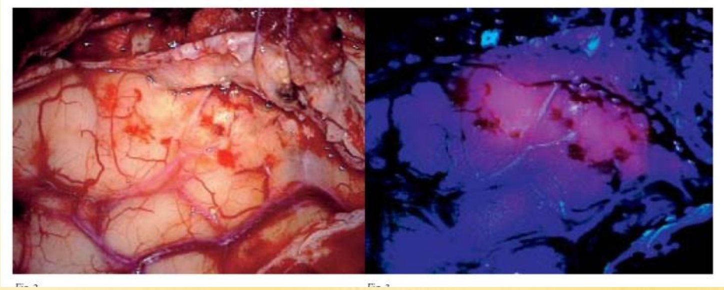
- Microscopic Imaging
  - Biomolecular imaging with X-diffraction
  - Non-linear imaging devices
    - Unlabeled viral, bacterial dynamics
    - In vitro imaging of protein complexes
  - ……………………..
- Sensors/Assays/Probes
  - POCT Devices (Optofluidic Lab on a Chip)
  - Highly targeted nano-particle 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.

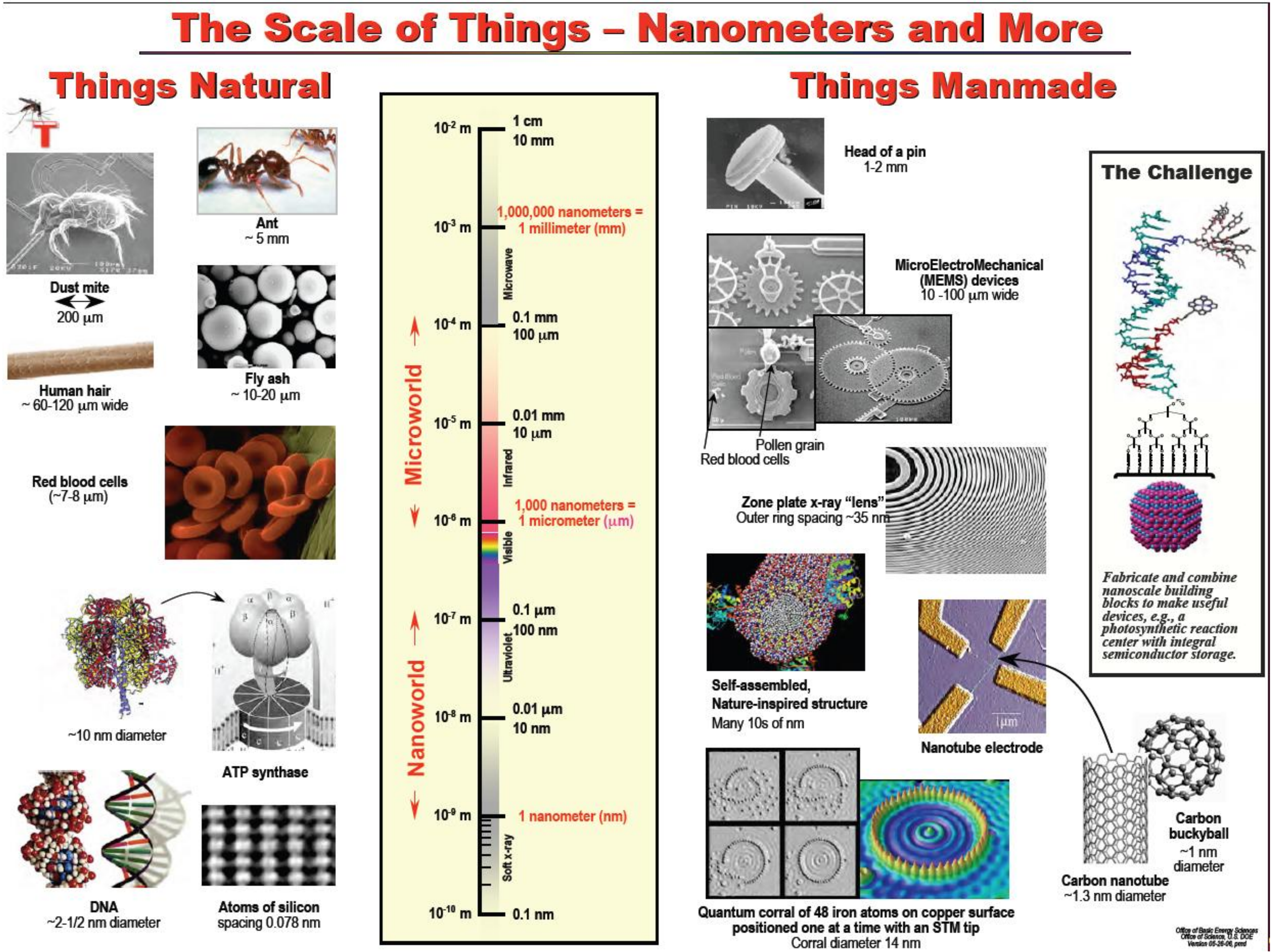


Developing optofluidic technology through the fusion of microfluidics and optics
Demetri Psaltis, Stephen R. Quake and Changhuei Yang
Nature **442**, 381-386(27 July 2006)



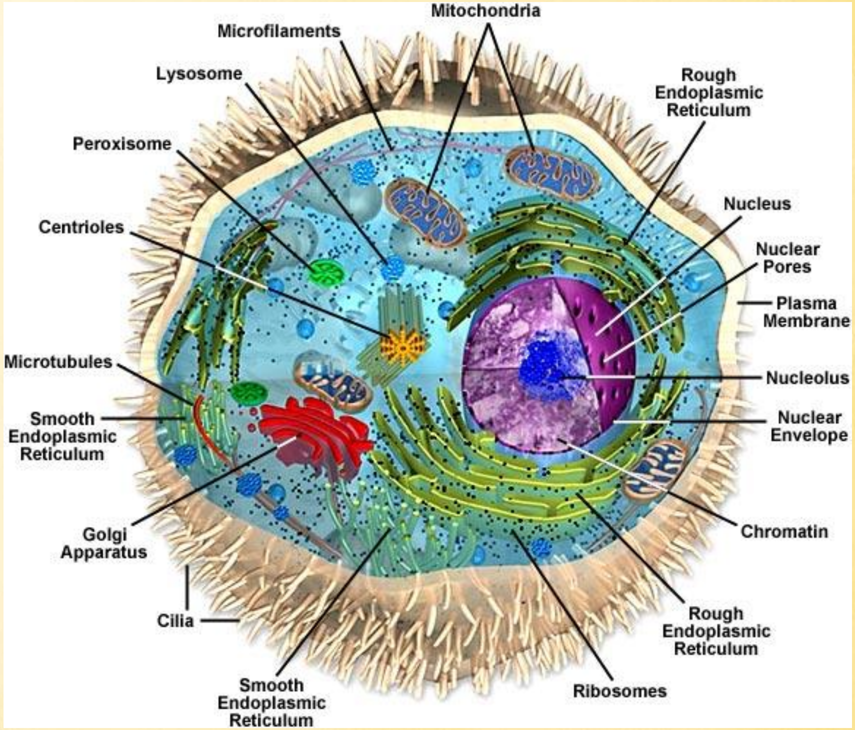
Fluorescence-guided malignant glioma resection, courtesy of Zeiss Inc.

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

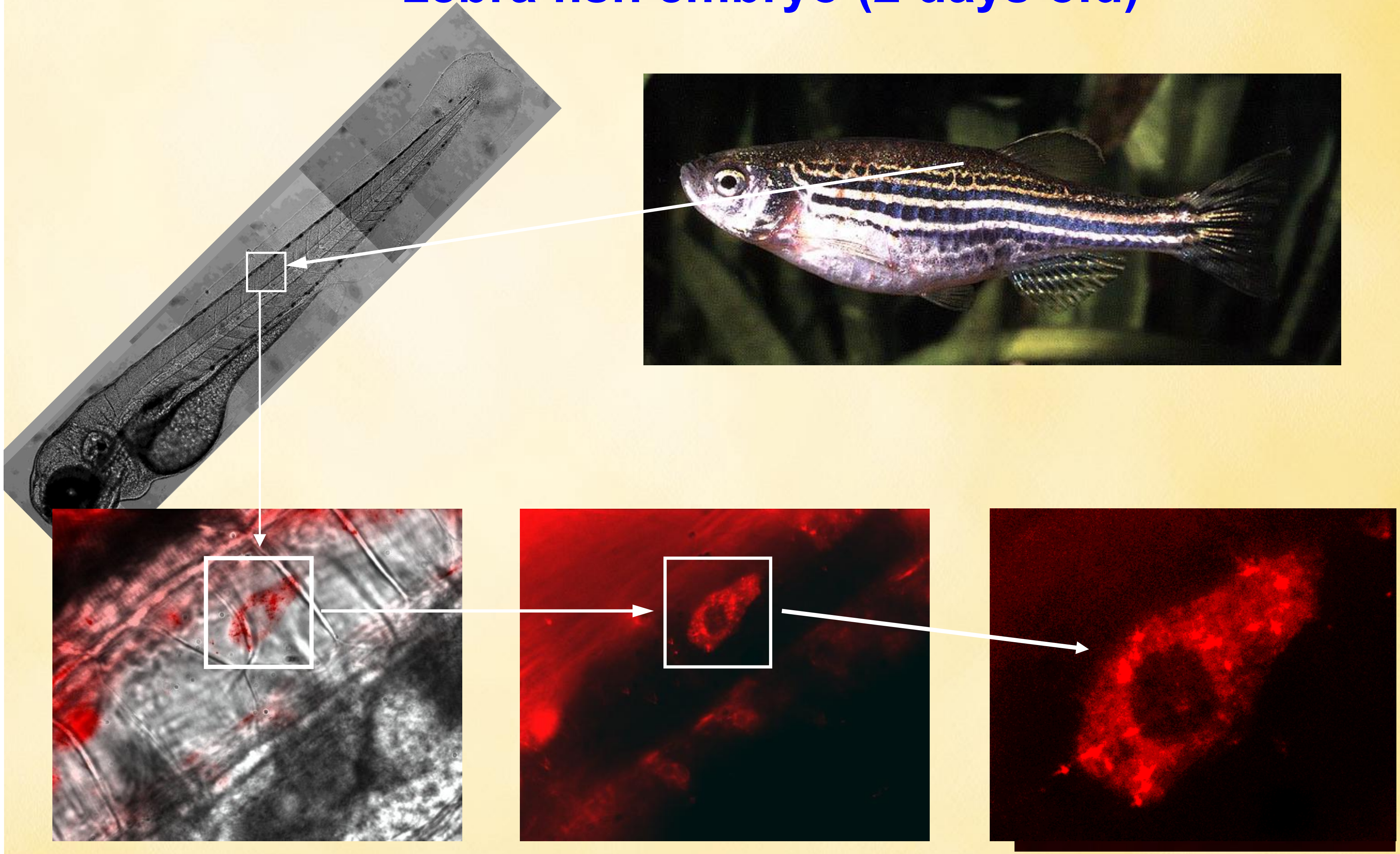

The Scale of Things – Nanometers and More
Things Natural
Things Manmade
Dust mite
200 µm
Ant
~ 5 mm
Human hair
~ 60-120 µm wide
Fly ash
~ 10-20 µm
Red blood cells
(~7-8 µm)
~10 nm diameter
ATP synthase
DNA
~2-1/2 nm diameter
Atoms of silicon
spacing 0.078 nm
10⁻² m
1 cm
10 mm
10⁻³ m
1,000,000 nanometers =
1 millimeter (mm)
Microwave
10⁻⁴ m
0.1 mm
100 µm
10⁻⁵ m
0.01 mm
10 µm
Infrared
Microworld
1,000 nanometers =
1 micrometer (µm)
10⁻⁶ m
Visible
10⁻⁷ m
0.1 µm
100 nm
Ultraviolet
Nanoworld
10⁻⁸ m
0.01 µm
10 nm
10⁻⁹ m
1 nanometer (nm)
Soft x-ray
10⁻¹⁰ m
0.1 nm
Head of a pin
1-2 mm
MicroElectroMechanical
(MEMS) devices
10 -100 µm wide
Pollen grain
Red blood cells
Zone plate x-ray "lens"
Outer ring spacing ~35 nm
Self-assembled,
Nature-inspired structure
Many 10s of nm
Nanotube electrode
Quantum corral of 48 iron atoms on copper surface
positioned one at a time with an STM tip
Corral diameter 14 nm
Carbon nanotube
~1.3 nm diameter
Carbon
buckyball
~1 nm
diameter
The Challenge
Fabricate and combine nanoscale building blocks to make useful devices, e.g., a photosynthetic reaction center with integral semiconductor storage.
Office of Basic Energy Sciences
Office of Science, U.S. DOE
Version 05-26-06, pmd

Live cell imaging requires the development of optical microscopy methods with several capabilities

- Specificity
- Sensitivity
- Dynamic live cell imaging
- Long term live cell imaging



Single cell / single vesicles visualization inside live zebra fish embryo (2 days old)



Laurent Bentolila / Shimon Weiss

Biophotonics Nano-Scale Imaging Modalities

Abbe's Law for transverse resolution is : $\Delta x, \Delta y = \lambda/(2n\sin\alpha)$

1. Best optical microscope (n=1.56, α= 68 deg, λ= 400 nm min for live cells) yields
   - $\Delta x \sim 150$ nm, in practice

2. Super-resolution Microscopy techniques ($\Delta x > 20$ nm is achieved or achievable)

   Far-field imaging of fluorescence probe-tagged objects ($\Delta x > 20$ nm is achieved or achievable, S. Hell et al., Science 316 1153 (2007)):

   - Two Photon Scanning 4-Pi microscopy
   - Reversible Saturable Optical Transitions (RESOLFT)
     - Stimulated Emission Depletion (STED) microscopy
   - Photoactivated Localization Microscopy (PALM)
   - I^5M (3-D widefield fluorescence interferometric imaging)
   - Saturated Structured Illumination Microscopy – widefield imaging (Δx = 46 nm now and 23 nm achievable theoretically, Gustaffson et al., PNAS 2005)

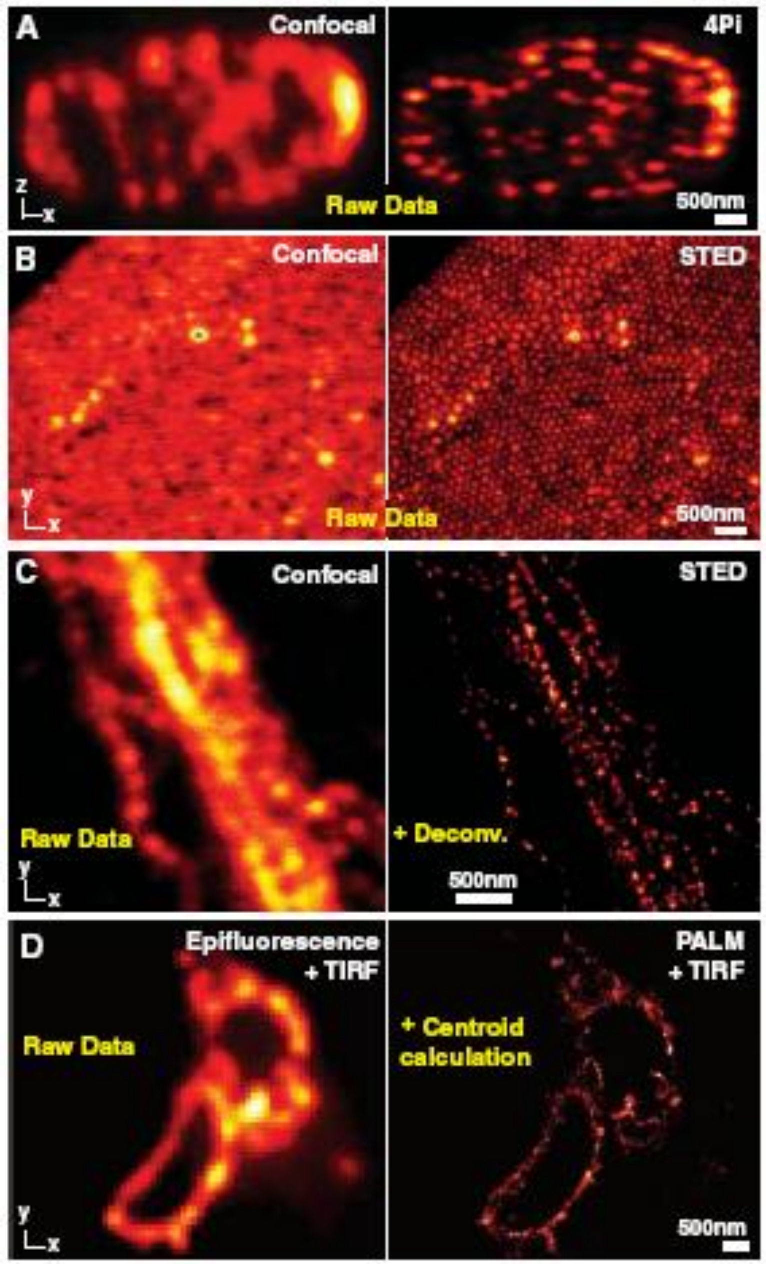
   $$\Delta x \approx \frac{\lambda}{\pi n \sin\alpha \sqrt{I_0/I_{sat}}}$$

   Negative permittivity / permeability optics, i.e., superlenses (Δx= 40 nm achieved to date, Fang et al. Science 308 (2005)).

   Near field scanning optical microscopy (NSOM), Δx = 20-200 nm achieved, ? for live cell imaging.

3. Lens-based soft x-ray imaging (limited to resolution of Fresnel zone plate lens , Δx = 15 nm now, 10nm is planned). Specimens are cryofixed, but unlabelled.

4. Lensless Diffraction Imaging (diff-lim imaging already achieved, ultimately, Δx = 0.1 nm)

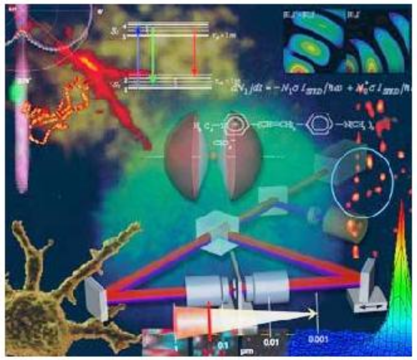


Far-Field Optical Nanoscopy

Stefan W. Hell SCIENCE VOL 316 25 MAY 2007

Department of NanoBiophotonics

Director: Prof. Stefan W. Hell

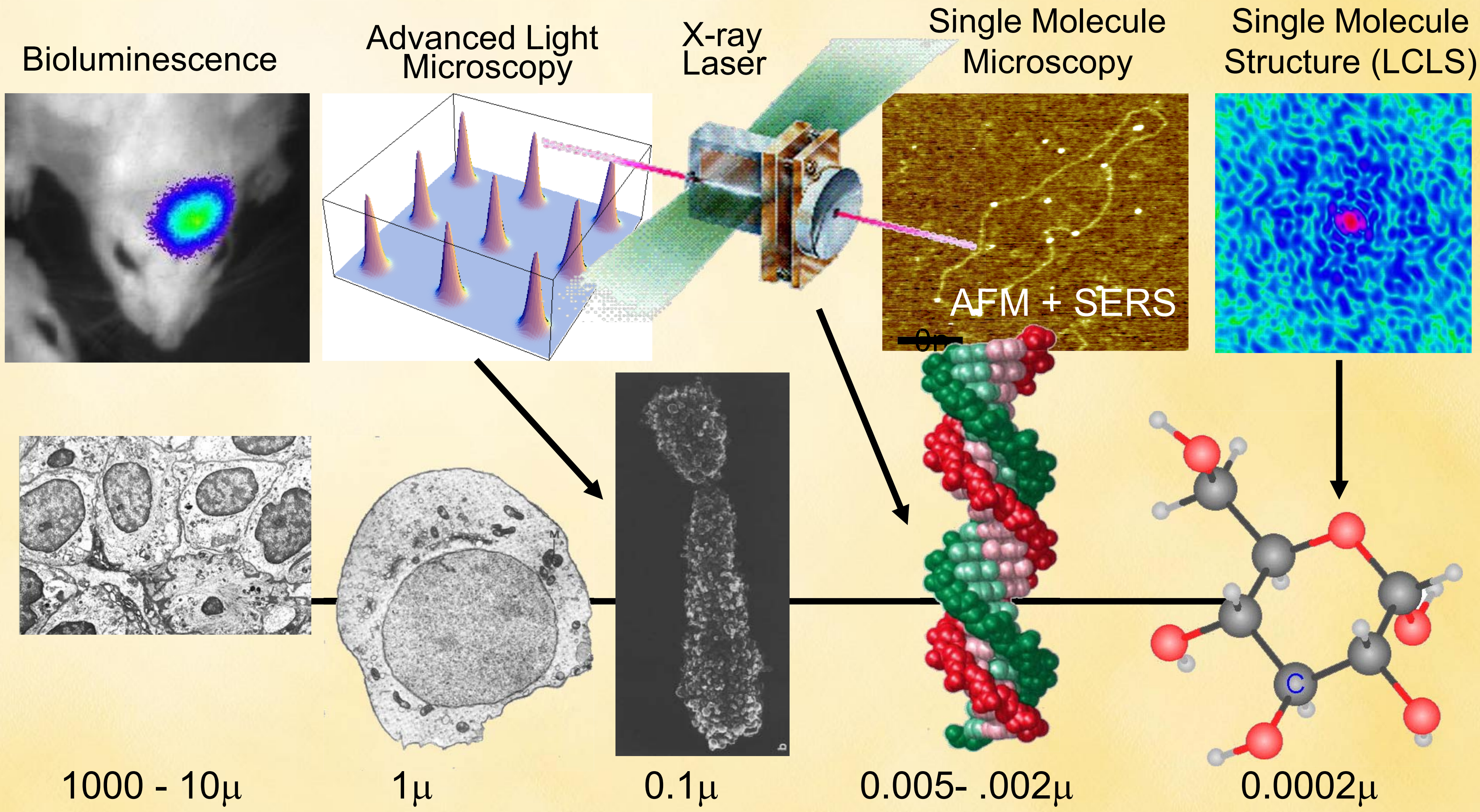


We are a group
of

physicists, biologists, chemists, and engineers

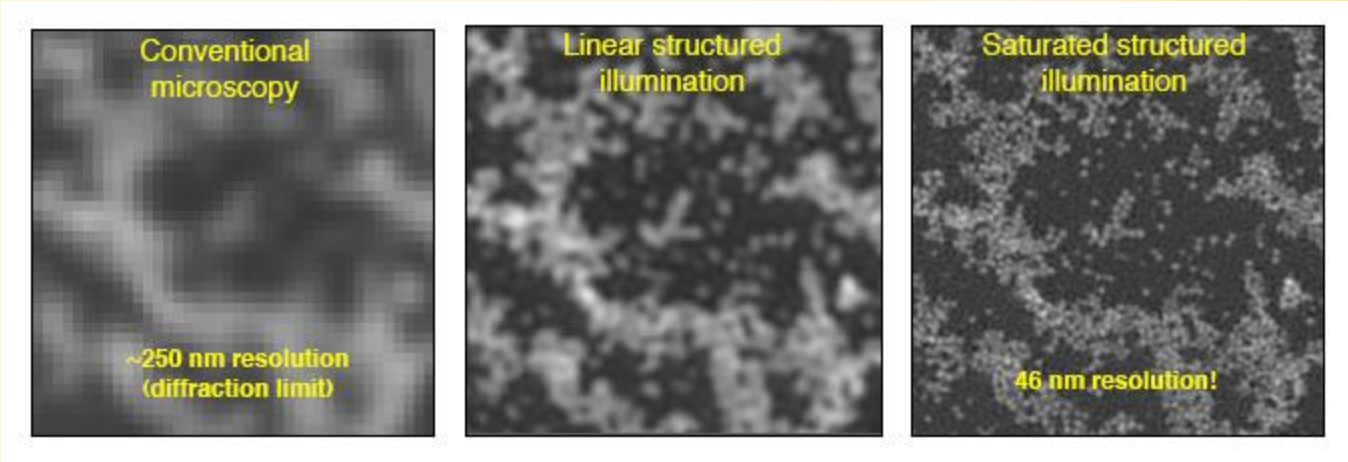
conceiving
inventing and utilizing
optical microscopes
with resolution at the nanometer scale
to
advance life sciences

CBST focuses on imaging & detection from live organisms to single biomolecules



tools

Light Microscopy Beyond the Classical Diffraction Limit



→ $R \sim R_{CD}/??$

$R_{CD} = 1.22\ \lambda/NA_{total}$ $R \sim 0.5\ R_{CD}$ $R \sim 0.2\ R_{CD}$

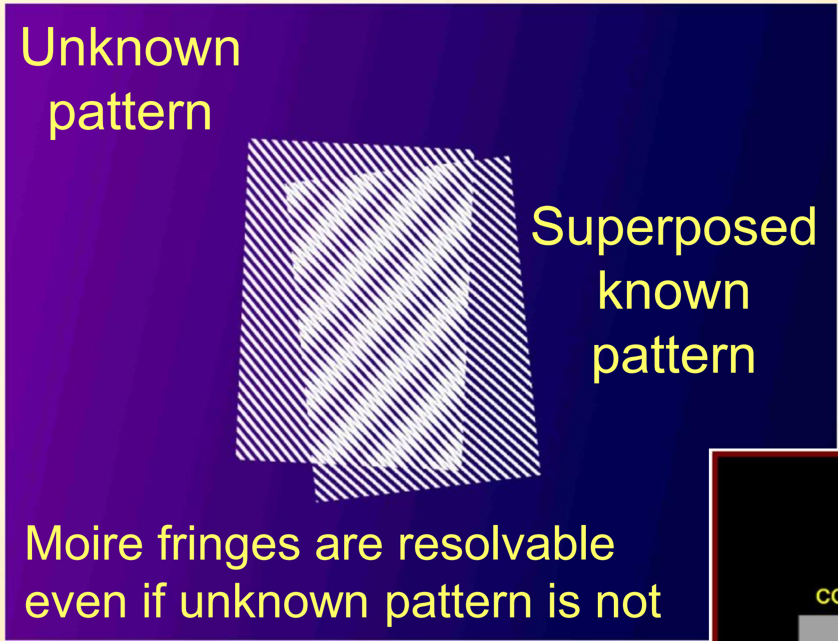
Mats Gustafsson, Lin Shao, Lukman Winoto, Peter Kner, David Agard, John Sedat,
UC San Francisco

Eugene A. Ingerman, UC Davis

Stephen Lane, Thomas Huser, LLNL

Work supported by the National Science Foundation
Cooperative Agreement No. PHY-0120999,
and by the Keck Foundation

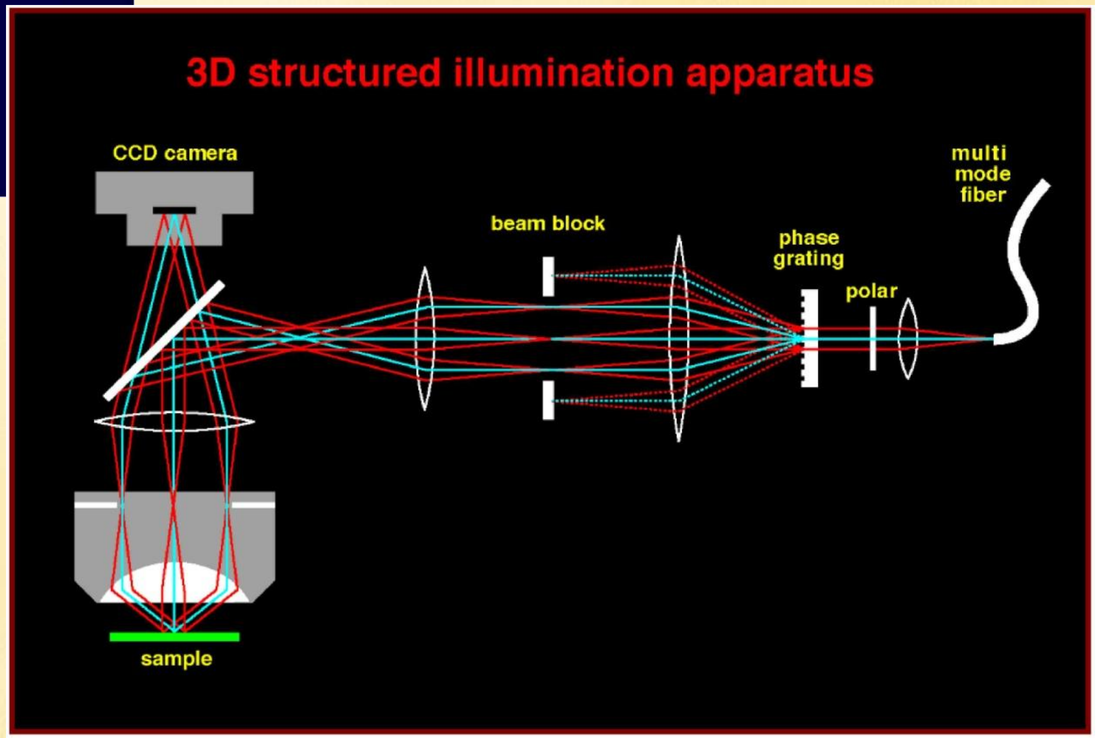
Structured Illumination Microscopy Enables Sub-diffraction-limit Imaging



$\lambda_{beat} = \lambda_1 \lambda_? / (\lambda_? - \lambda_1)$

λ_1 , λ_{beat} are known, so can get $\lambda_?$

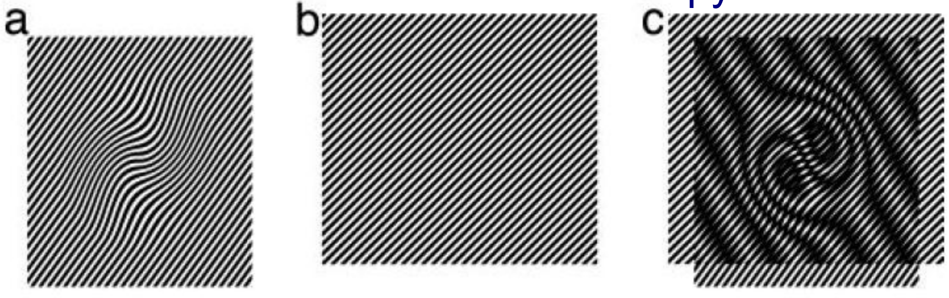
The trick: Beat a source of known spatial frequency against an unknown! This concept can be applied to microscopy

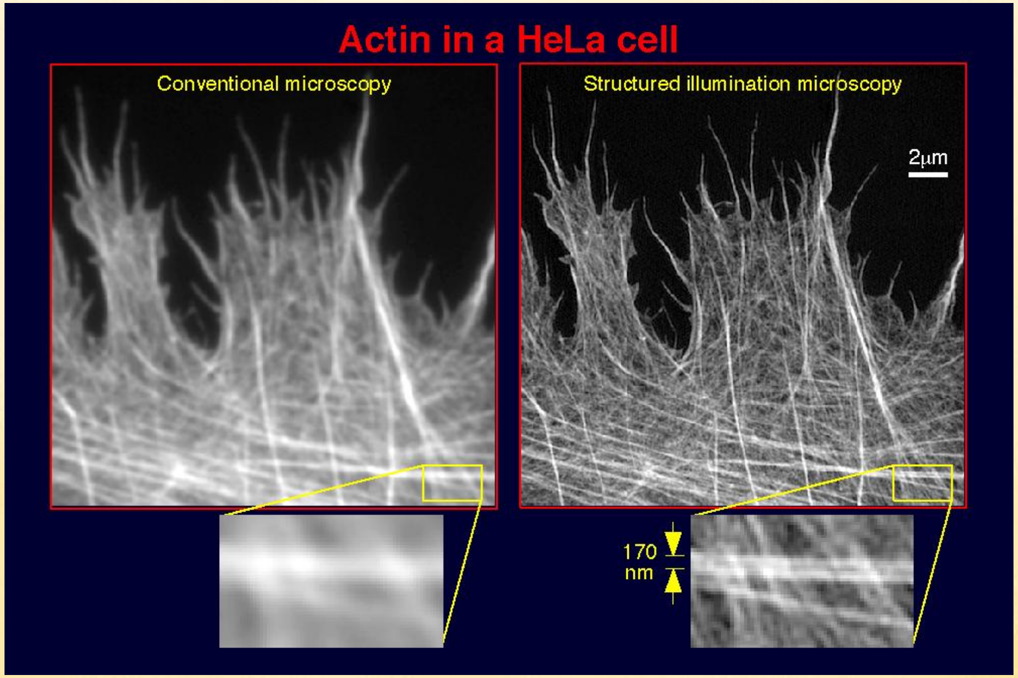


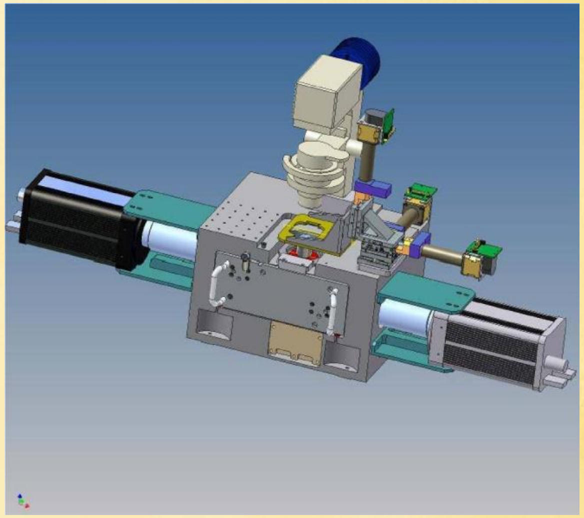
Courtesy J. Sedat, M. Gustafsson, D. Agard, *UCSF*

With an NSF MRI grant we are commercializing and will have first super-resolution OMX microscope , Feb 2008 delivery

structured illumination microscopy







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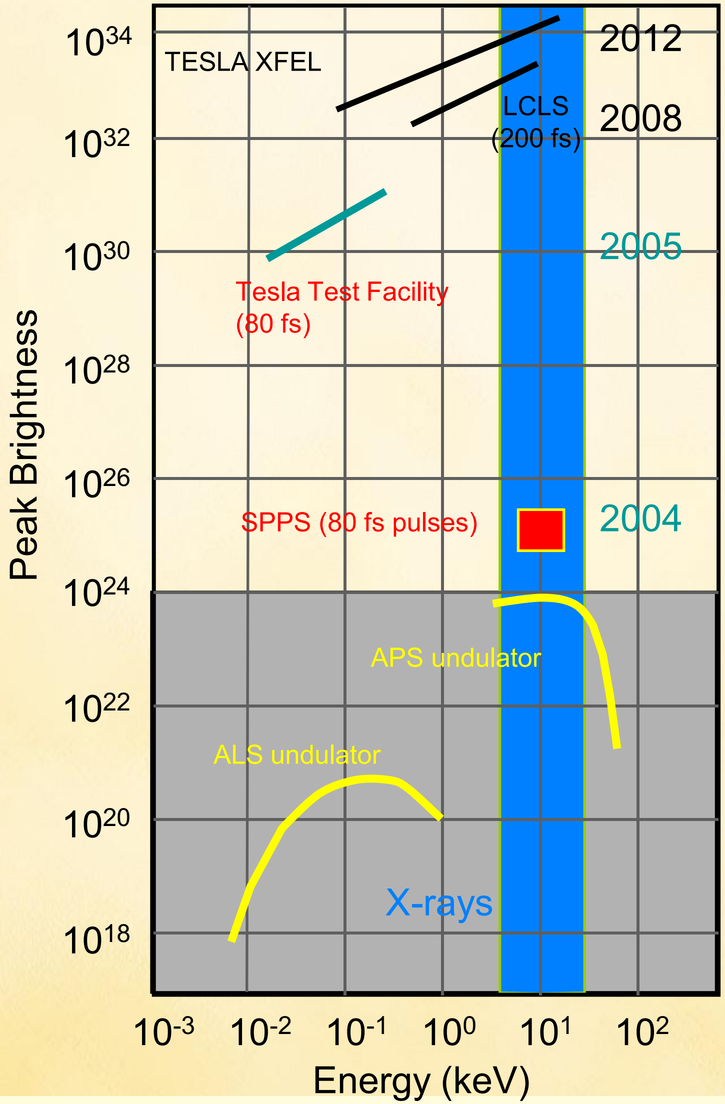
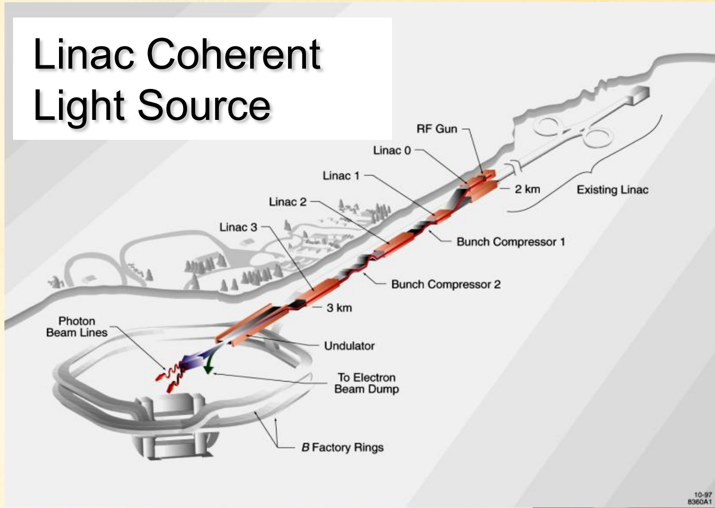
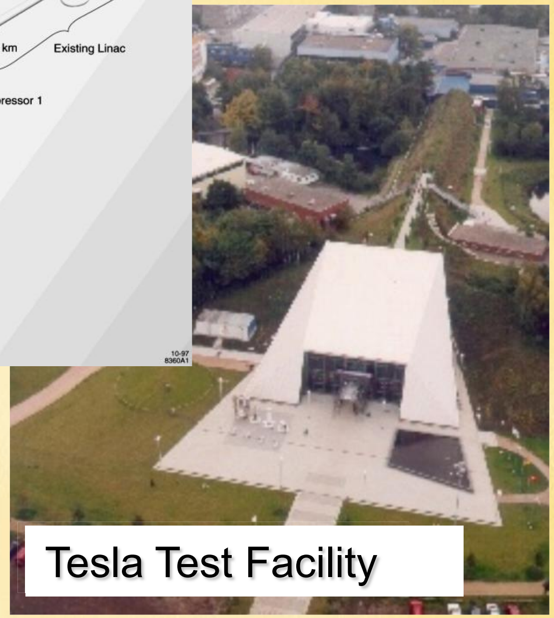
We are entering a new era in x-ray science





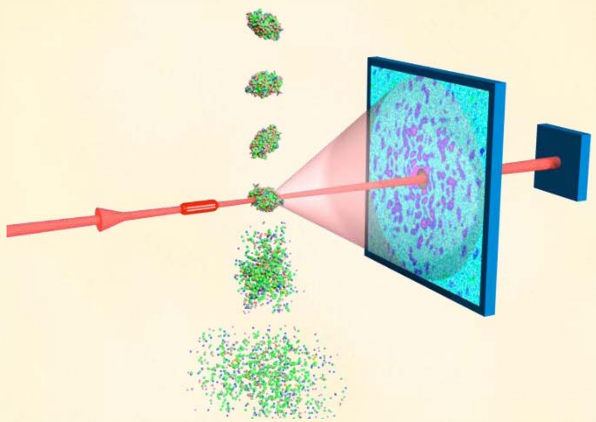


- femtosecond
- 10^{13} photons
- Angstrom wavelength

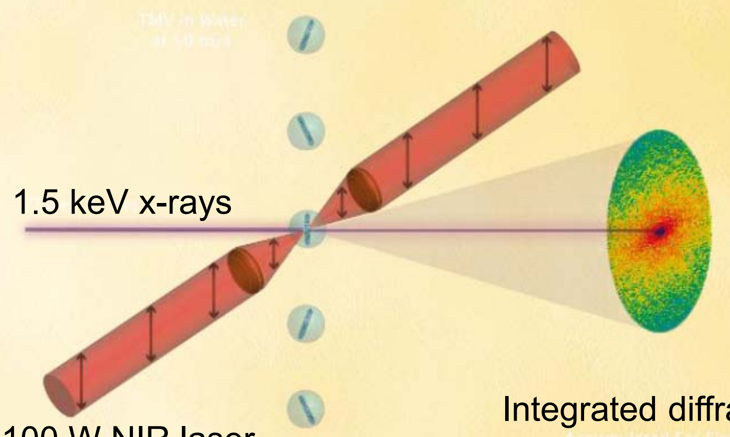
This short-pulse high-fluence x-ray regime is completely unexplored

H. Chapman et al, LLNL, UCD, Stanford, Uppsala

Coherent Diffraction Imaging

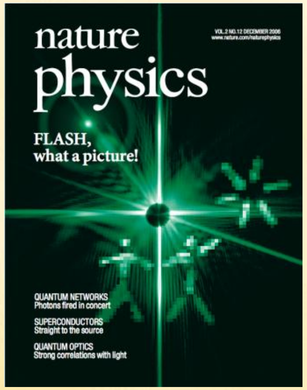


Flash Diffraction Imaging



Serial Diffraction Imaging

Goal: Determine the structure of protein molecules by diffraction imaging



"Femtosecond diffractive imaging with a soft-X-ray free-electron laser" H. Chapman et al, December 2006

"A unified evaluation of iterative projection algorithms" S. Marchesini Review of Scientific Instruments 78 (2007) 011301

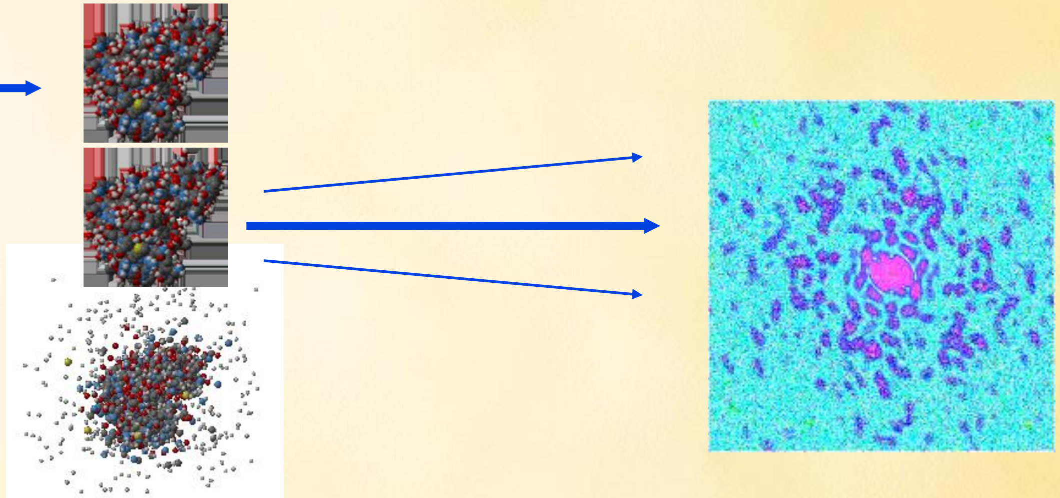
Atomic-resolution imaging of macromolecules will become possible with flash imaging

Diffraction from a single molecule:

10 fs pulse

Just after pulse

Long after pulse



Noisy diffraction pattern

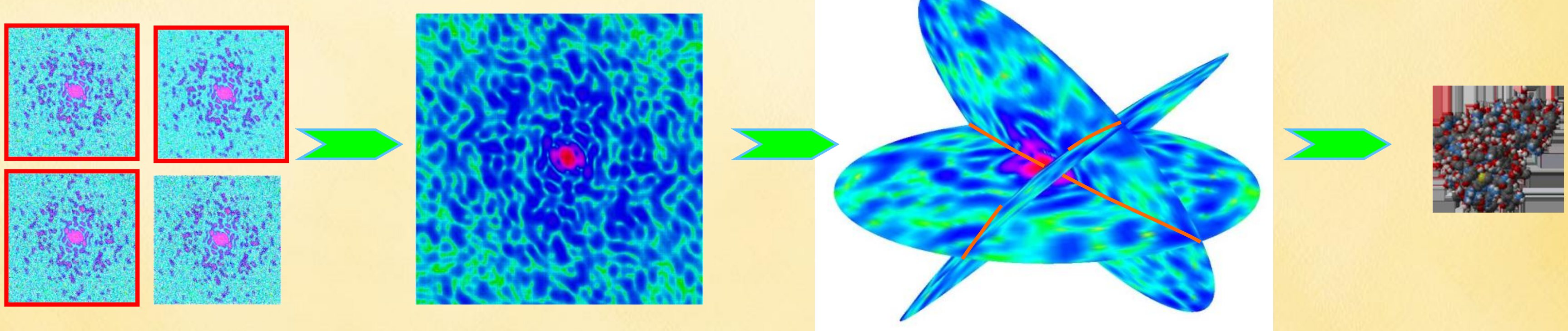
Combine 10^5 to 10^7 measurements into 3D dataset:

Classify

Average

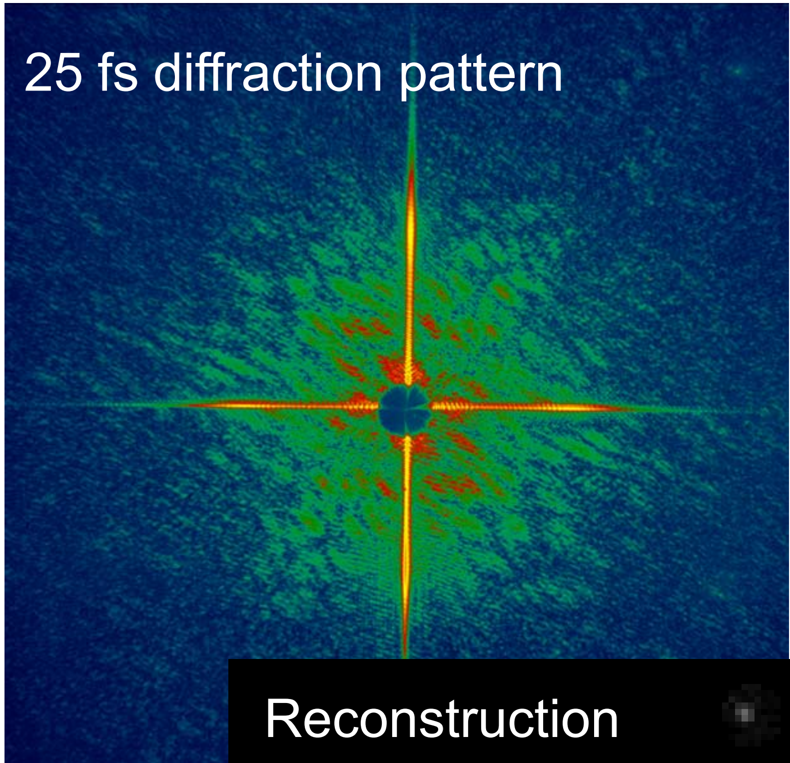
Combine

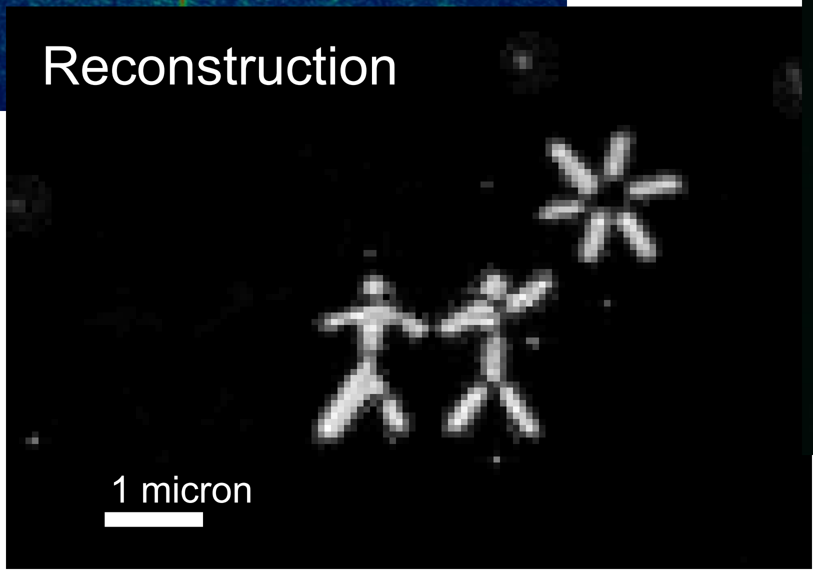
Reconstruct

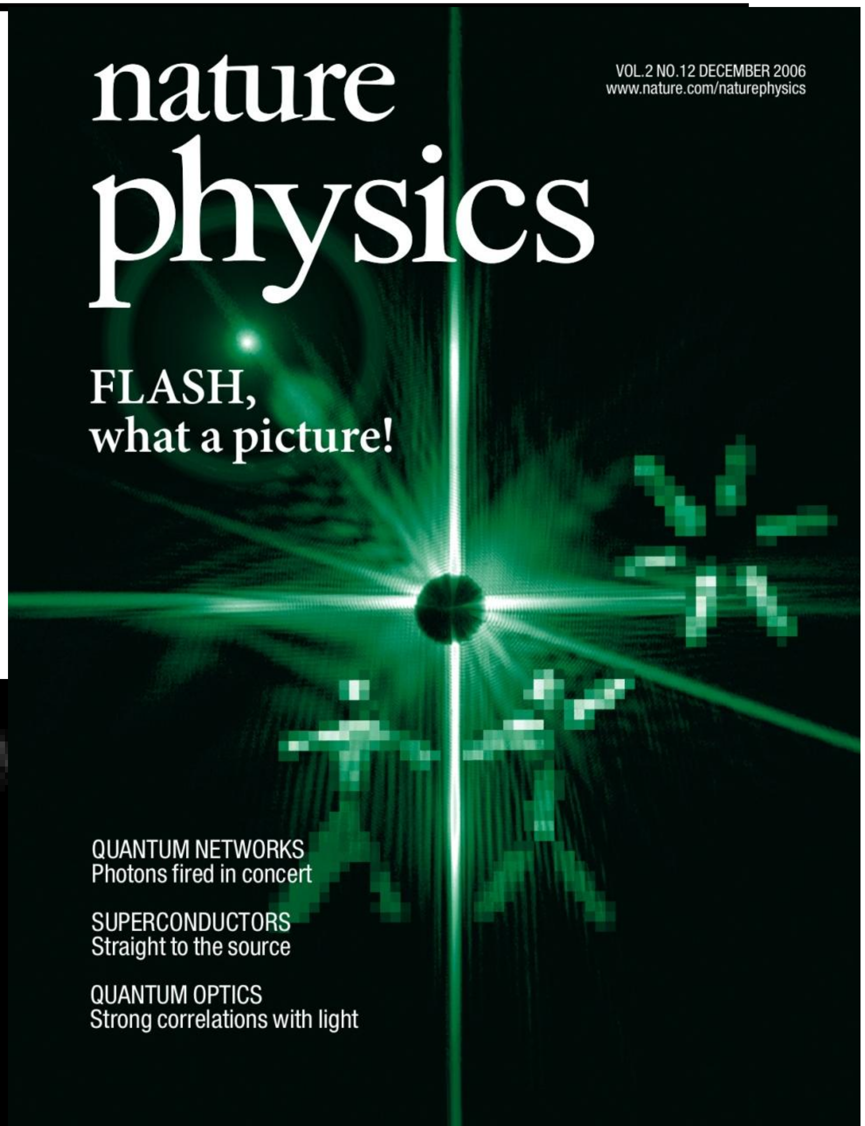


H. Chapman et al, LLNL, UCD, Stanford, Uppsala

Coherent X-ray Diffractive Imaging with the FLASH free-electron laser has been demonstrated

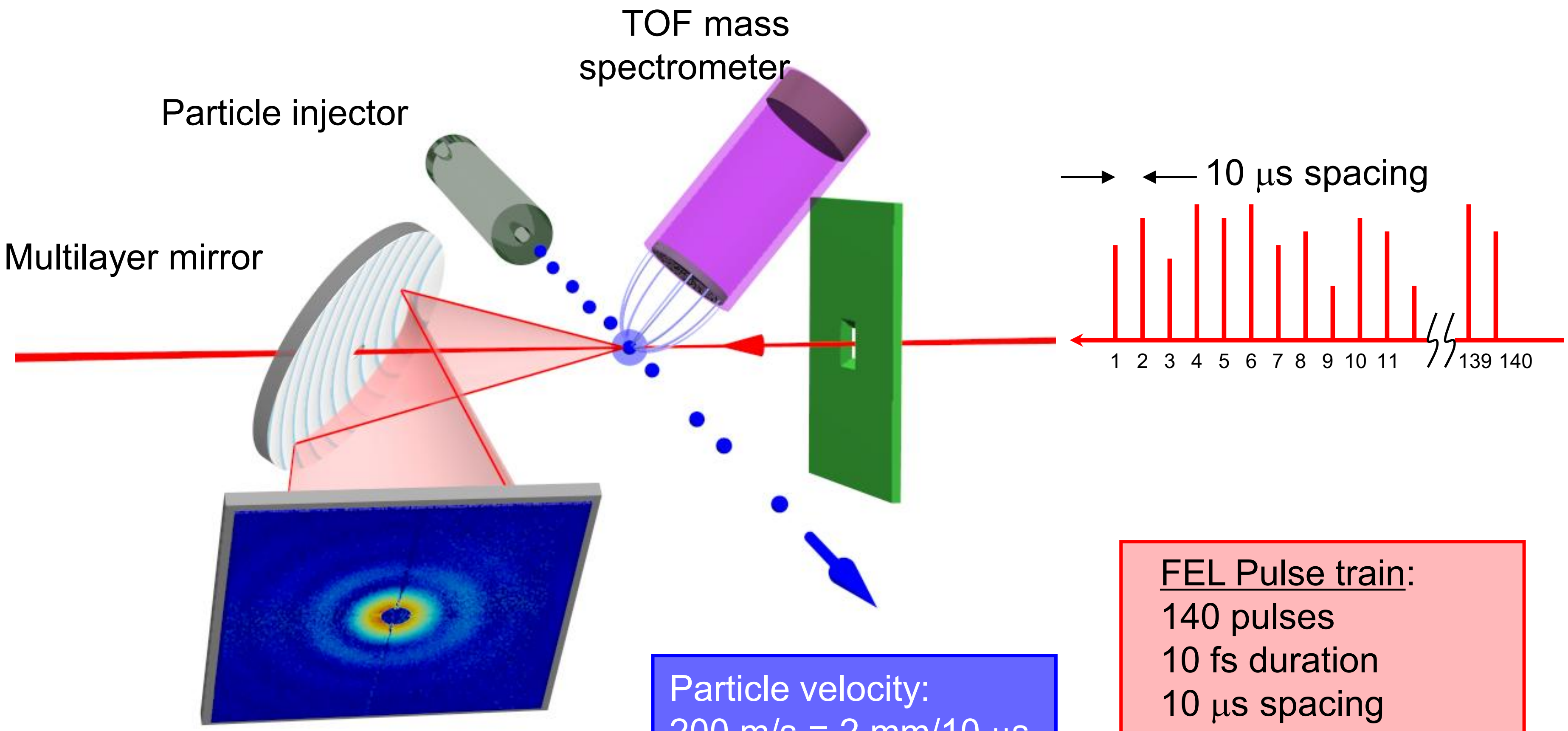






Chapman et al, Nature Phys **2** 839 (2006)

Single-particle FEL diffraction of "on-the-fly" particles has been demonstrated for the first time

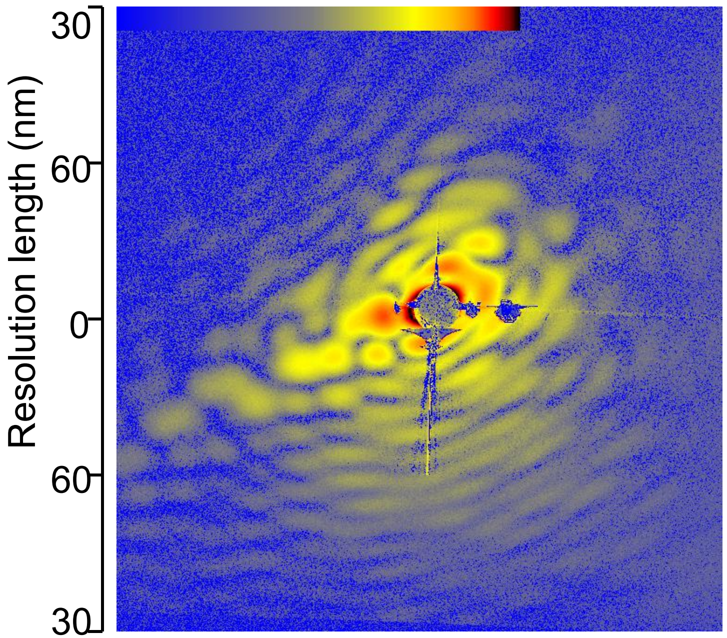


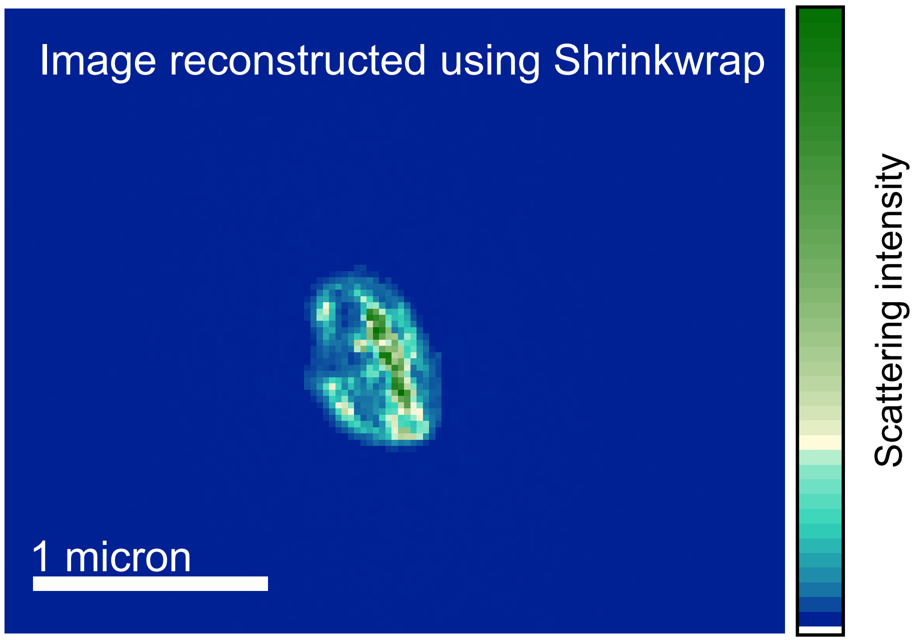
Single particle diffraction pattern (one hit + 269 no-hits)

Particle velocity:
200 m/s = 2 mm/10 μs
(c.f. 20 μm beam)

FEL Pulse train:
140 pulses
10 fs duration
10 μs spacing
~20 μJ/pulse
13.5 nm wavelength

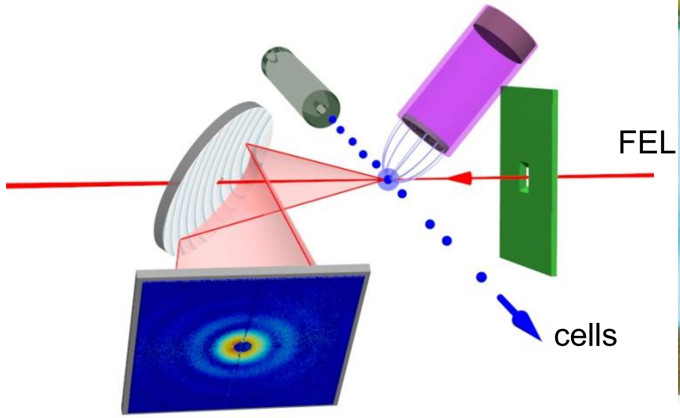
We have x-ray imaged unstained living cells – first step to imaging proteins.

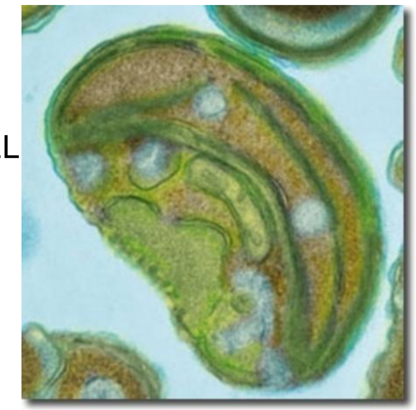




Single shot ~10 fs diffraction pattern recorded at FLASH (DESY) at a wavelength of 13.5 nm of a picoplankton organism.

This cell was injected into vacuum from solution, and shot through the beam at 200 m/s





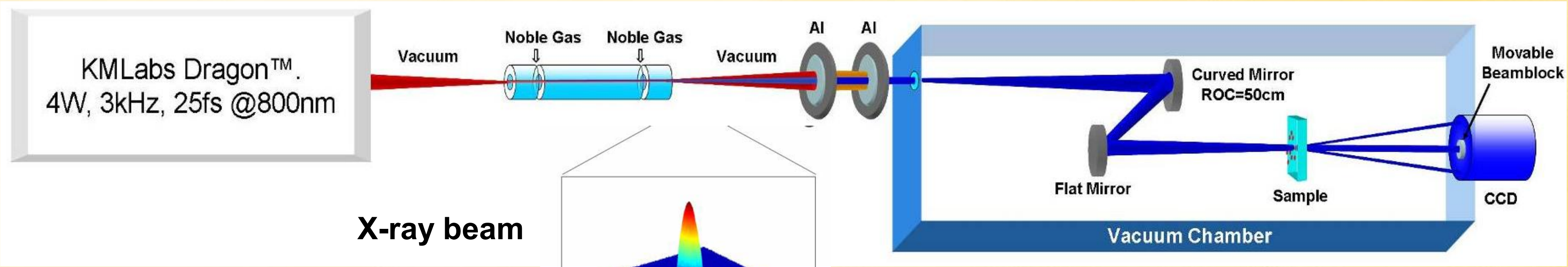
Ostreococcus TEM section
(Wenche Eikrem and Jahn Throndsen, University of Oslo)

J. Hajdu, I. Andersson, M. Svenda, M. Seibert (Uppsala)
S. Boutet (SLAC)
M. Bogan, H. Benner, U. Rohner, H. Chapman (LLNL)

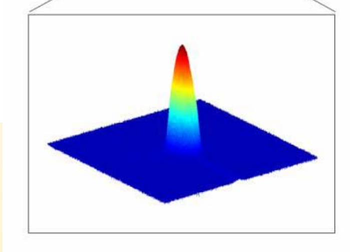
CBST
Stanford Linear Accelerator Center

Multiphoton Harmonic Generation

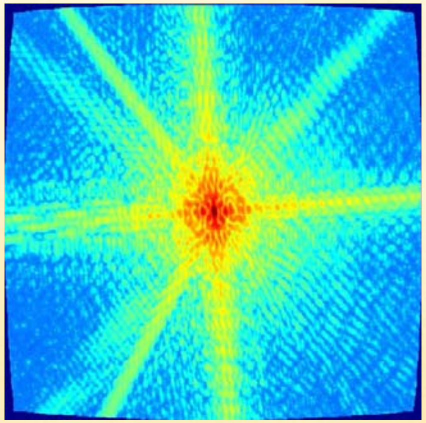
Tunable coherent light source from fundamental to 25th or more harmonic – Table top coherent x-ray source for diffraction imaging

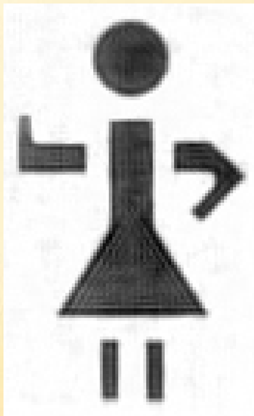


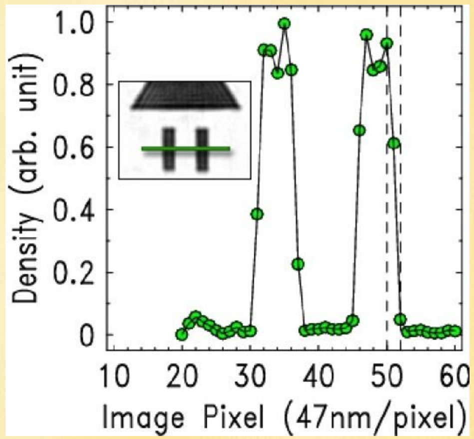
X-ray beam



Anne Sakdinawat, Dave Attwood (**Berkeley**)
Mario Marconi, Jorge Rocca, Carmen Menoni (**CSU**)
Changyong Song, John Miao (**UCLA**)
Richard Sandberg, Daisy Raymondson, MM, HK (**JILA**)







1 µm

sample (SEM image) diffraction pattern reconstruction

Phys. Rev. Lett. **99**, 098103 (2007); PNAS **105**, 24 (2007); Nature, News & Views **449**, 553 (2007); Nature Photonics (Feb. 2008)

Nano-scale imaging with Biophotonics

Photon-based imaging enables the study of living organisms

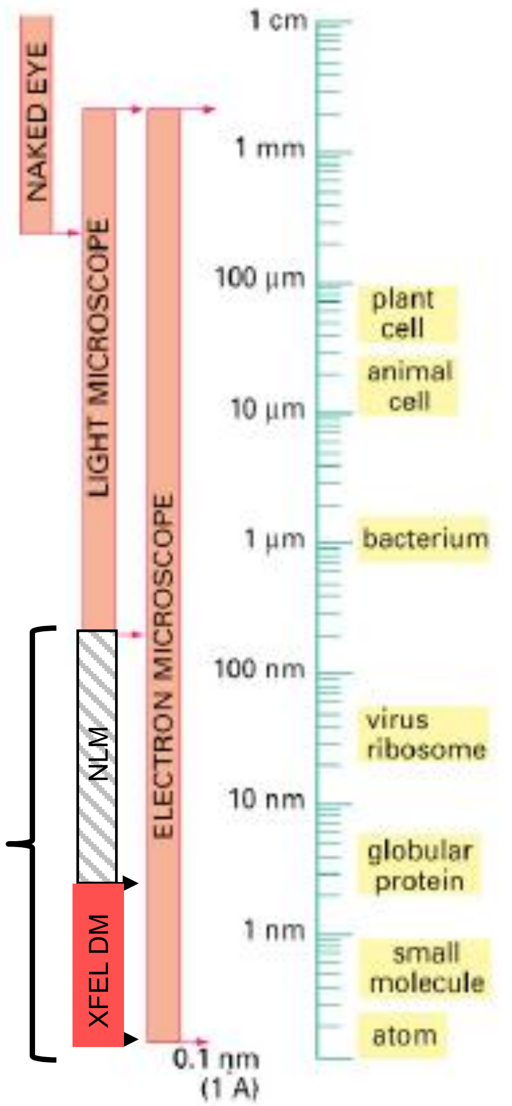
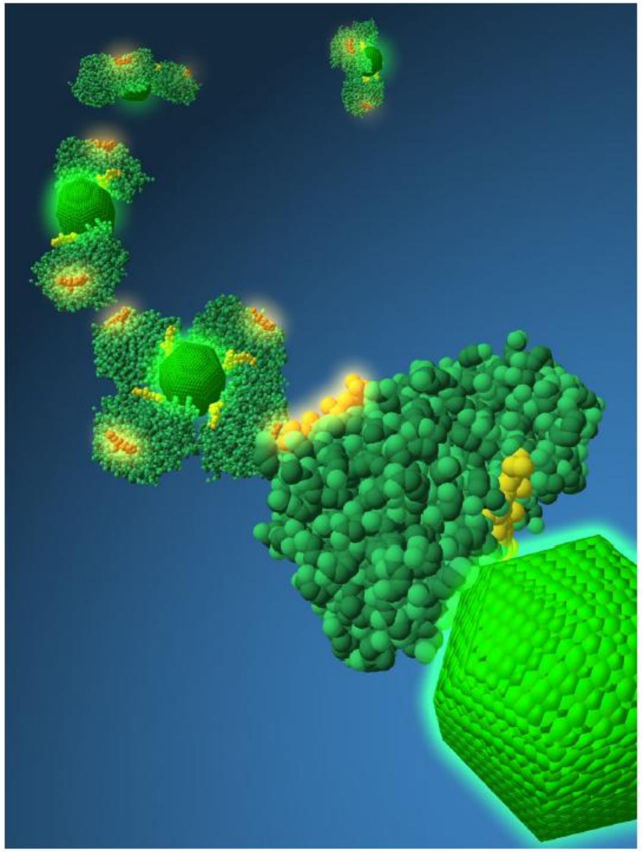


Figure 9–2. Molecular Biology of the Cell, 4th Edition.

Nano-scale sensing with Biophotonics



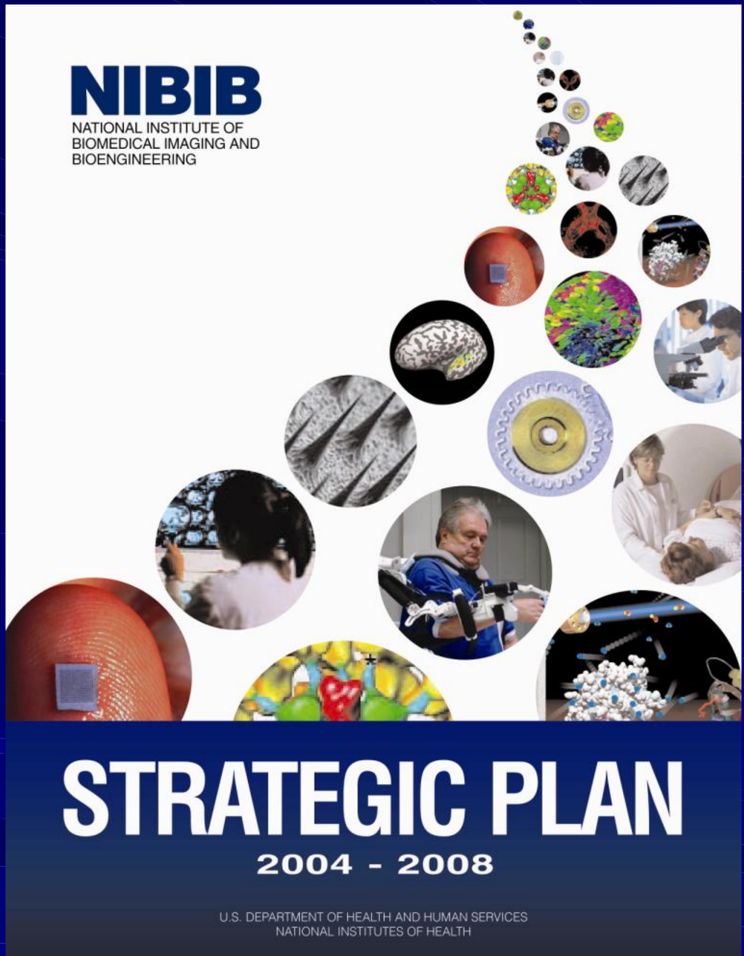
Quantum Dot Nanosensors

The sensor consists of CdSe/ZnS core/shell quantum dots (shown as large, dimpled green crystals) covered in maltose binding protein (clusters of small green spherical elements). Added analyte displaces a dye-labeled analog in the protein-binding pocket, changing the yellow fluorescence of the nanosensor.

Courtesy of NRL tech transfer

Motivations

NIBIB Strategic Plan I – Foster Point of Care Testing

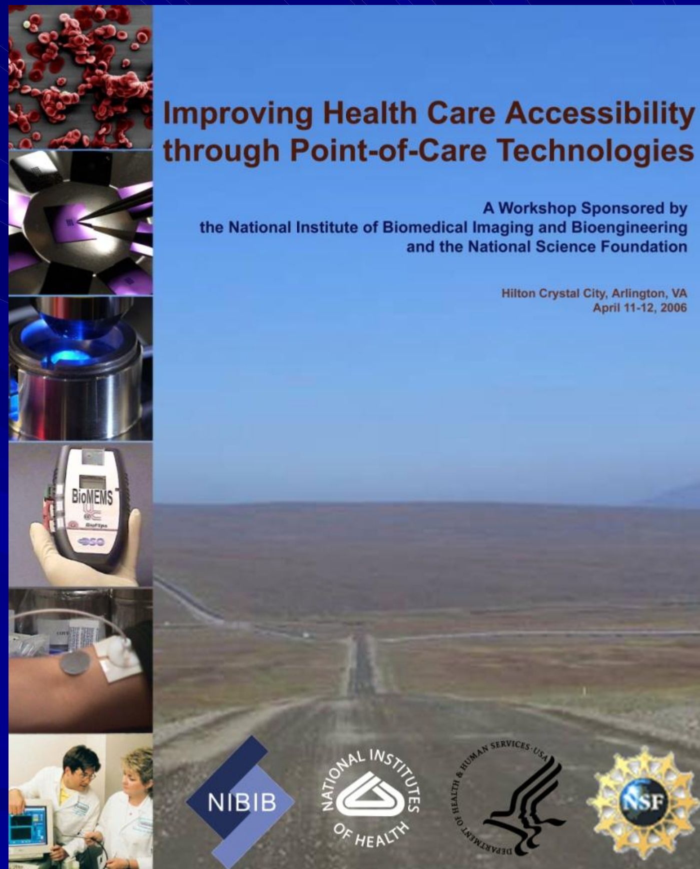


- Promote development of low-cost technologies
- Reduce health disparities
- Accelerate translation of technologies to improve human health
- Partner with industry
- Develop interdisciplinary training and research programs

NIBIB/NHLBI/NSF Workshop
“Improving Health Care Accessibility through Point-of-Care Technologies”

Technologies: sensors and microsystems, low-cost imaging, noninvasive monitoring and telehealth/informatics

Health Care Settings: primary care, EMS, home/community-based, developing countries



April 11-12, 2006

www.nibib.nih.gov/NewsEvents/SympReports/2006Apr11

NIBIB Point-of-Care Technologies Research Network

Center to Advance POC Dx for Global Health

Program for Appropriate Technology in Health
PI: Bernhard Weigl

- Improving availability, accessibility, and affordability of POC tests for infectious diseases in low resource settings
- Whole-blood processing device for CD4+ cell purification and cell count
- Multiplex immunoassay for antenatal screening for HIV, syphilis and malaria

Center for POC Technologies Research for Sexually Transmitted Diseases

Johns Hopkins University
PI: Charlotte Gaydos

- Development of POC tests for STDs for use in primary care, ED, and home care settings
- Testing of assay performance with trained and untrained users
- Evaluation of home delivery of OTC assays to end users

Rapid Multipathogen Detection for POCT and National Disaster Readiness

University of California-Davis
PI: Gerald Kost

- Improving the accessibility, portability, and field robustness of POC devices in critical-emergency-disaster care settings
- Isothermal loop-mediated amplification assays and POC system for simultaneous detection of pathogens
- Environmental stress testing of POC devices

POC Center for Emerging Neurotechnologies

University of Cincinnati
PI: Fred Beyette

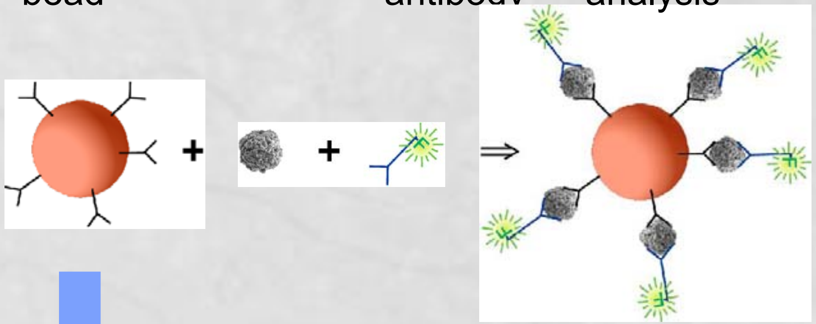
- Development of Dx technologies for neurologic emergencies
- Spectrophotometric quantification of metabolites in CSF for diagnosis of subarachnoid hemorrhage
- Cross-disciplinary training in device innovation and entrepreneurship

NIBIB

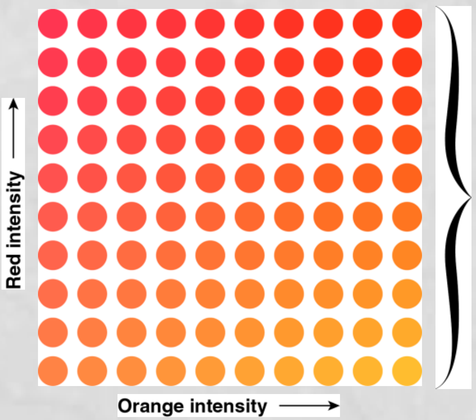
National Atlas of the United States

Immunofluoroassay (sandwich assay) technology allows many biological agents to be detected at the same time

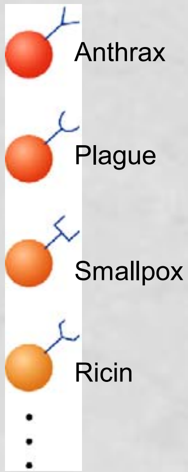
Capture bead | Bioagent | Labeled antibody | Color analysis



Adding a color code (optical bar code) to the capture bead enables individual ID



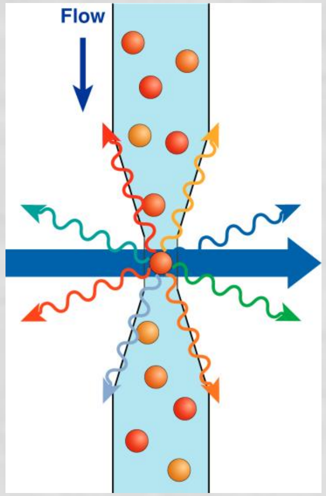
Liquid Array



Different antibodies on each bead enables deeply multiplex detection

Beads can be analyzed by flow cytometry

at rates up to 2,000/s



100's of different pathogens can be detected in a single assay

CBST
CENTER for BIOPHOTONICS SCIENCE and TECHNOLOGY

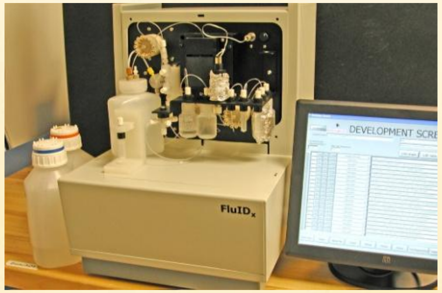
Applying Biophotonics to POCT Needs – Current Devices & Concepts

Early prototype , Real-time PCR device

Handheld RT - PCR for first responders

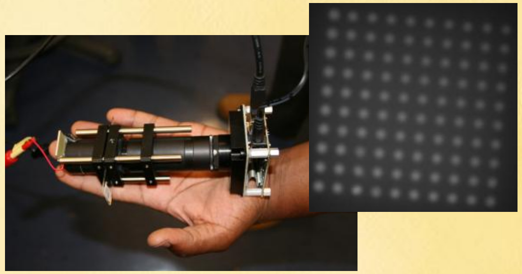
Autonomous airborne disease detector

Laser bioaerosol mass spectrometry



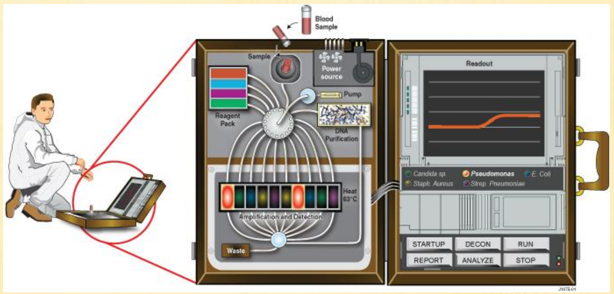
Point-of-Care Influenza Detection - FluIDx

Center for BIOPHOTONICS Science & Technology

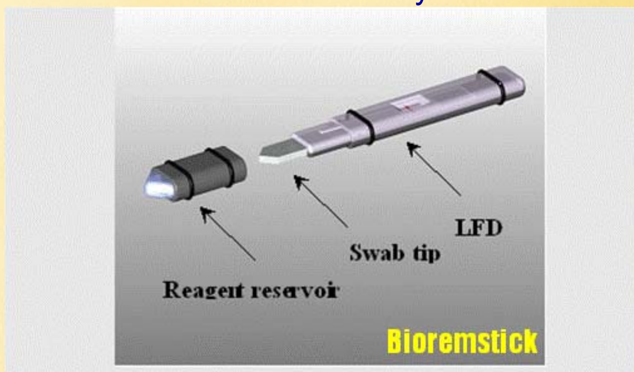


Portable microarray readers

Disposable infectious disease detector

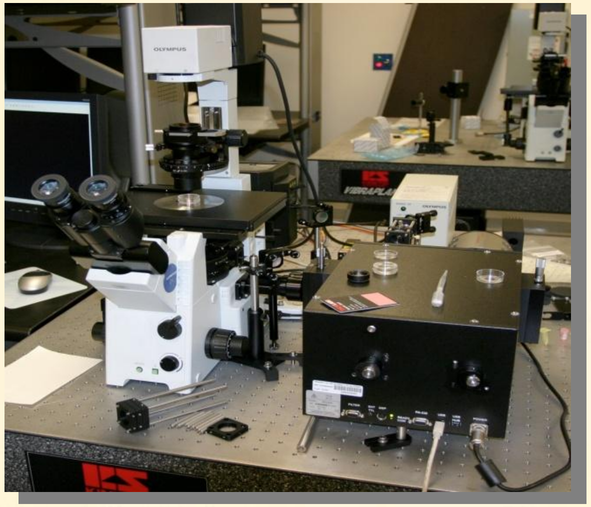


Field-portable isothermal RT PCR



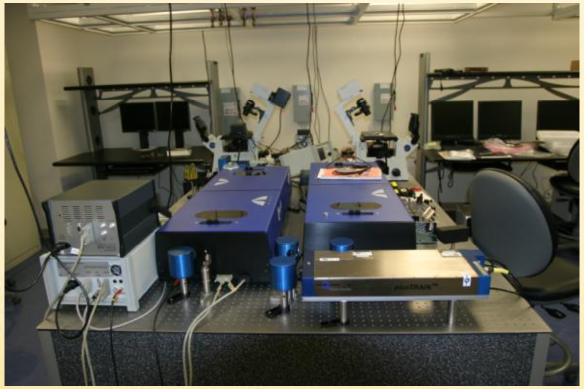
Disposable Radiation Biodosimeters

Raman Imaging and Cytometry,

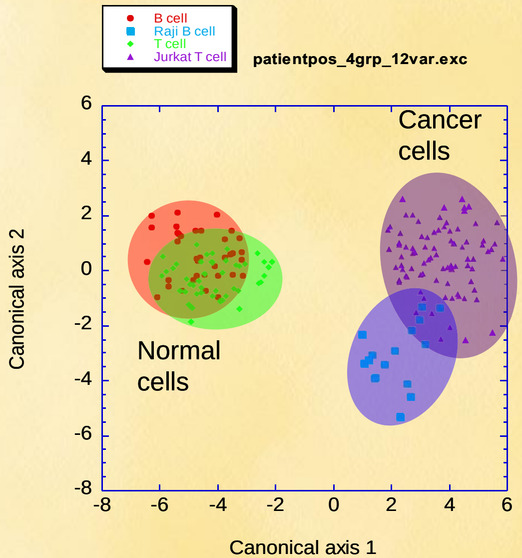


Laser-tweezers Raman system

Optically trapped T cell

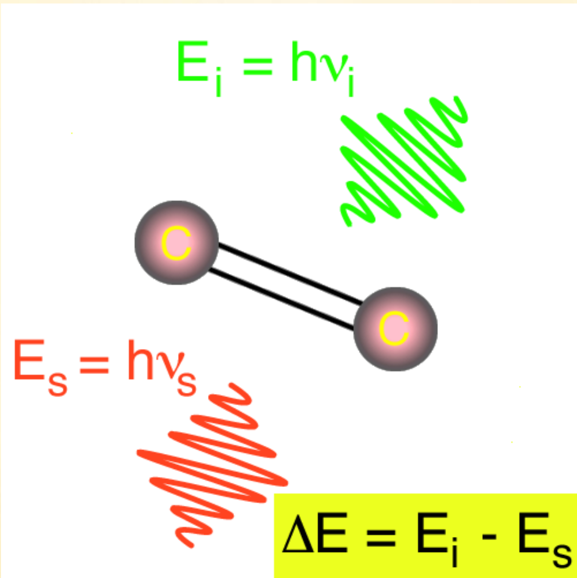


Ratiometric CARS (Coherent Anti-Stokes Raman Spectroscopy) Imaging System

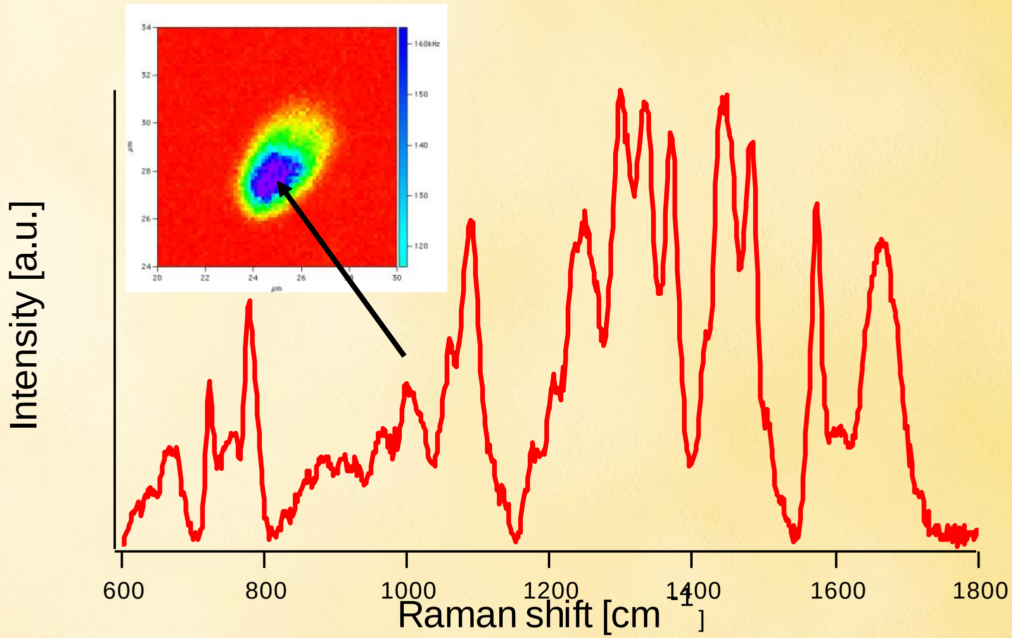


Goal: Develop and apply new Raman-based tools and techniques for analyzing single cells

Raman spectroscopy probes bonds in molecules and provides characteristic chemical information about compounds



Raman spectrum of a single sperm cell



Raman spectroscopy provides

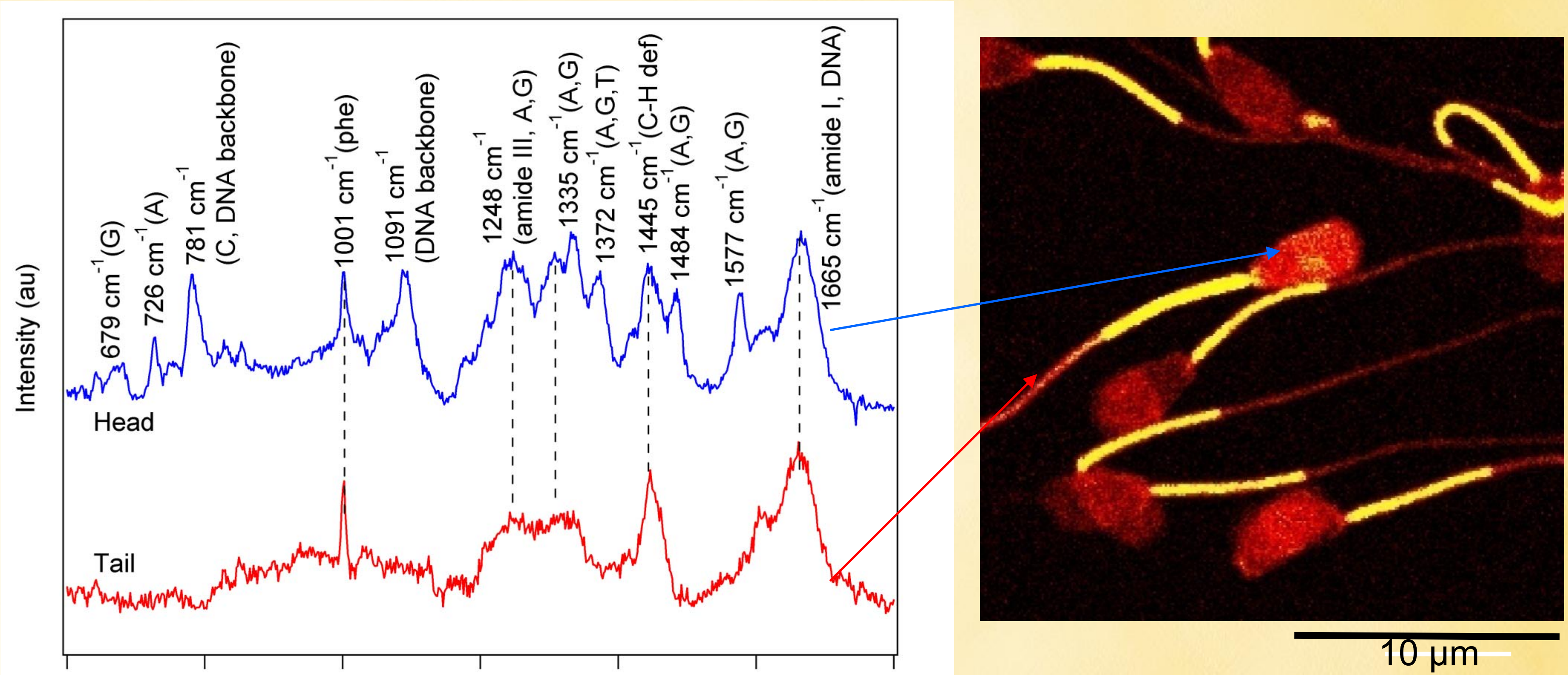
- fingerprint spectra (molecular identity)
- information about 3d structural changes
  (orientation, conformation)
- information about intermolecular interactions
- dynamics

Advantages of Raman spectroscopy

- non-destructive, non-invasive
- works in-situ and in-vitro for biological samples
- works under a wide range of conditions:

(temperature, pressure)

Confocal Raman spectroscopy provides chemical information on microscopic samples with high spatial resolution

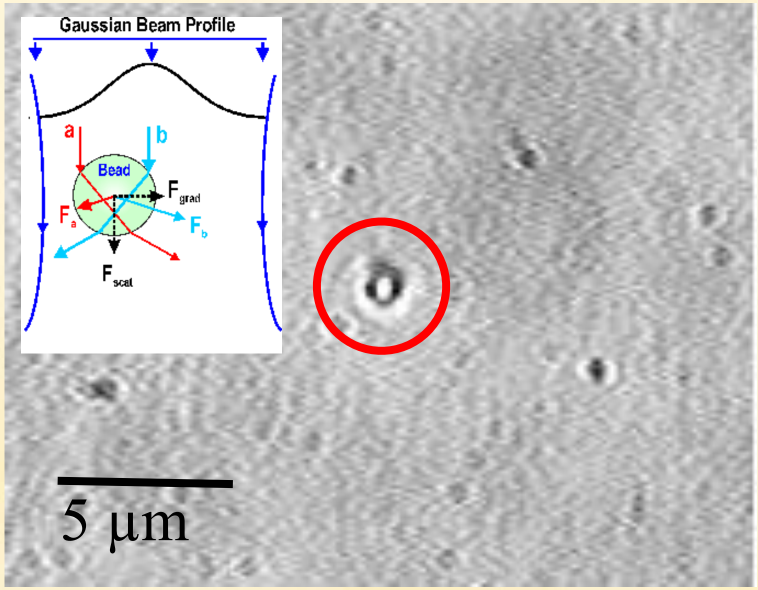


Bovine sperm cells

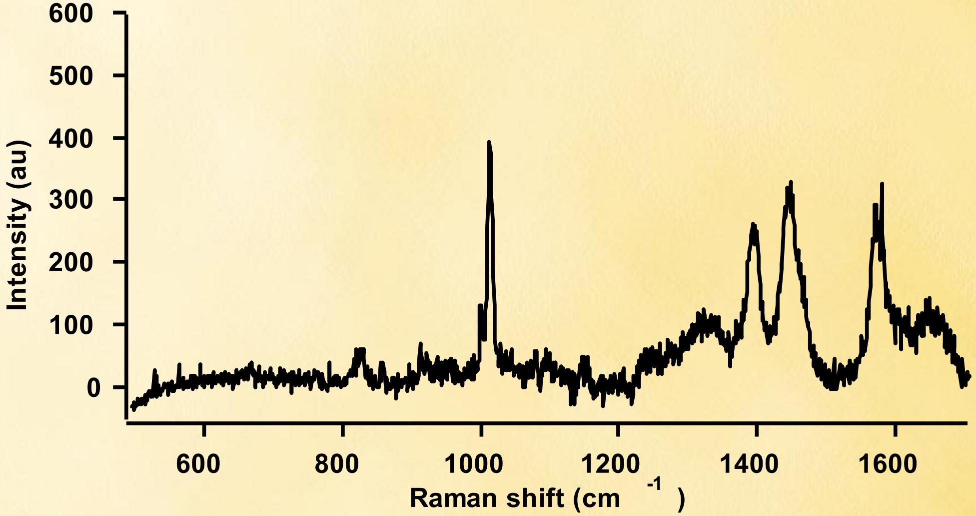
Resolution: ~ 1 µm laterally, 5 µm vertically (100x air objective)
Spectra with excellent S/N require ~ 5 min integration at 1 mW,
(488 nm Ar^+ laser excitation)

Laser tweezers Raman spectroscopy provides an even easier way to handle individual biological samples in their native environment

Optically trapped bacterial spore (B.g.)



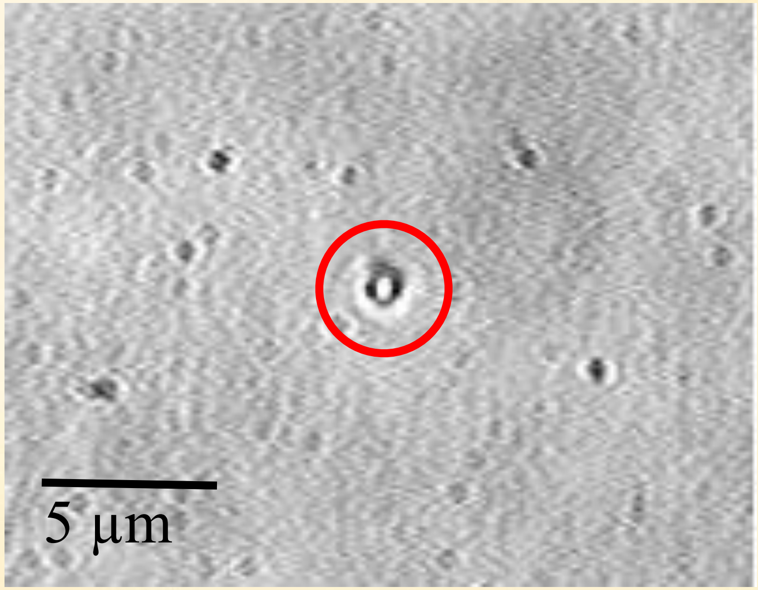
Raman spectrum of the bacterial spore (20s acq. time)

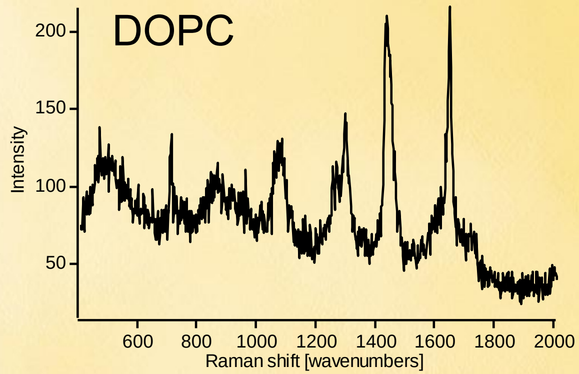


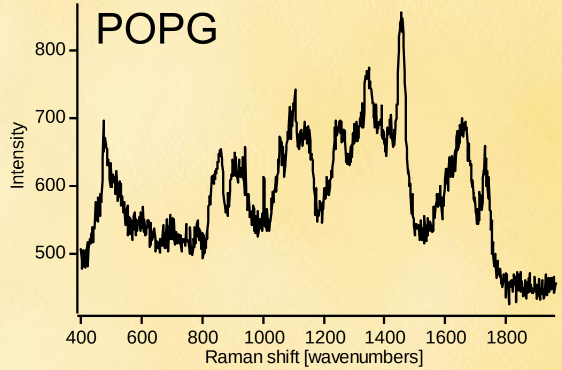
Advantages:
- fast, easier sample handling
- no substrate (lower background)
- native environment
- only low power necessary (1 mW)

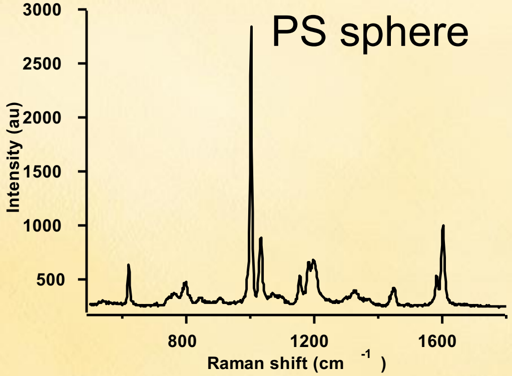
Chan et al, Anal. Chem. **76**, 599-603 (2004)

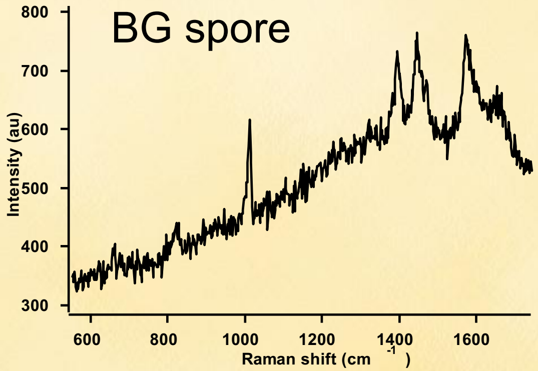
We can optically trap individual cells and particles and obtain their Raman spectrum in as little as 5s

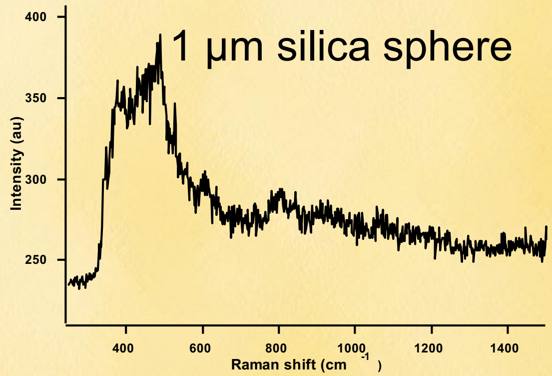






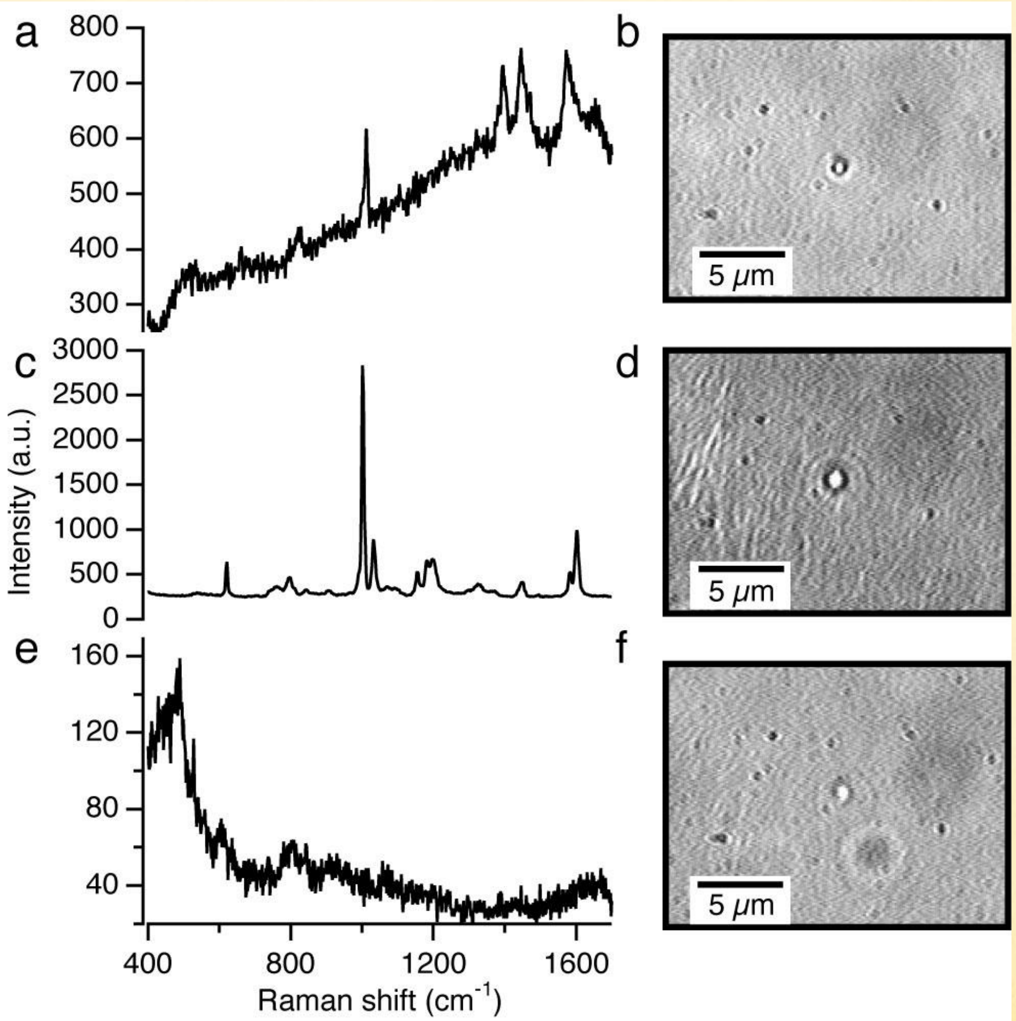




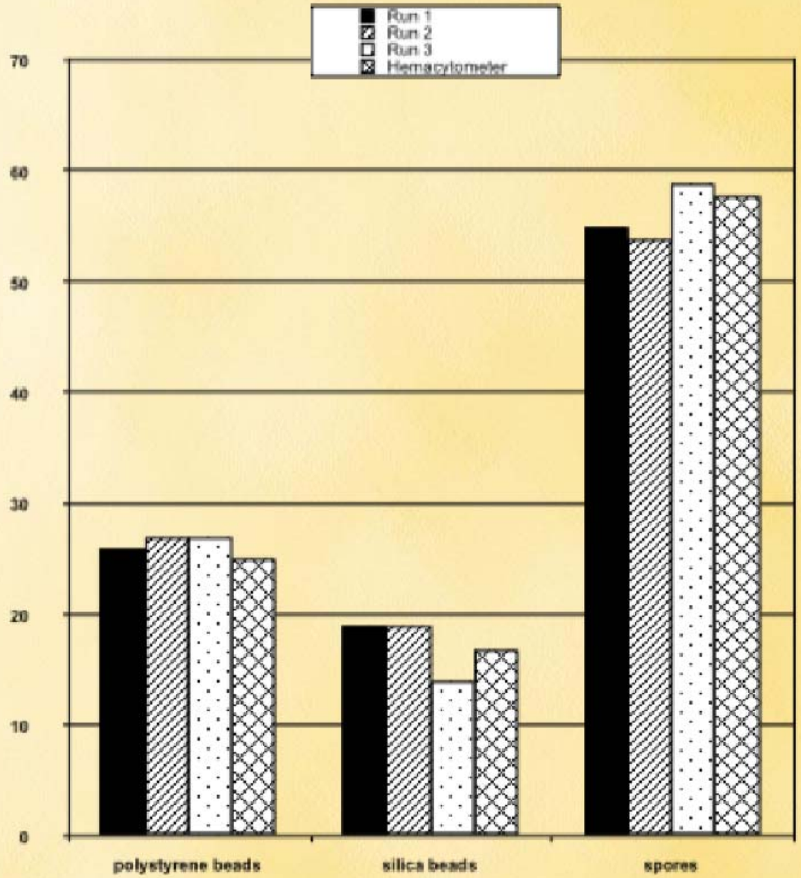


Laser tweezers Raman spectroscopy enables the rapid analysis of complex, mixed samples

Mixed, aqueous samples of bacillus spores, polystyrene beads, and silica microspheres



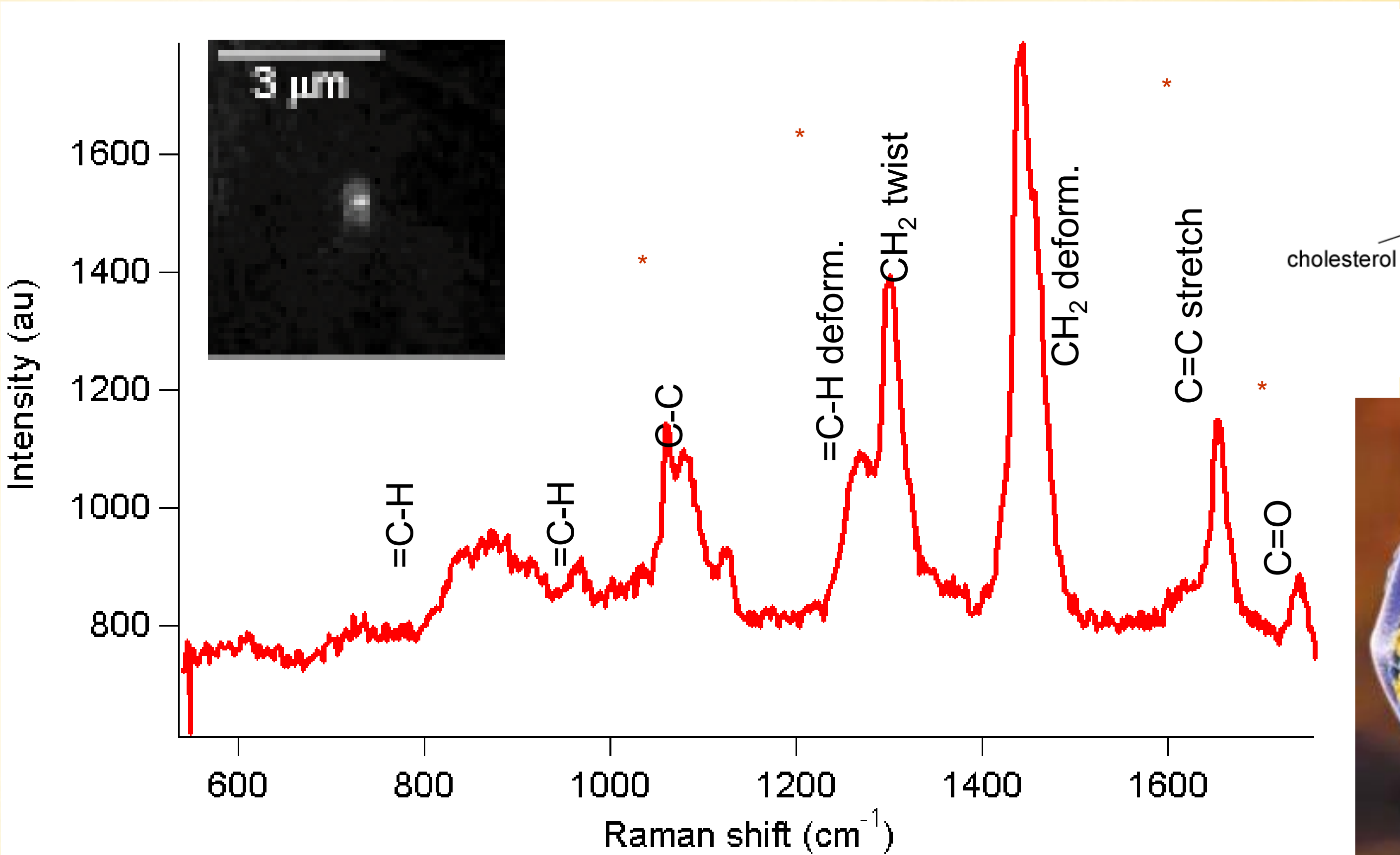
Relative concentration distribution

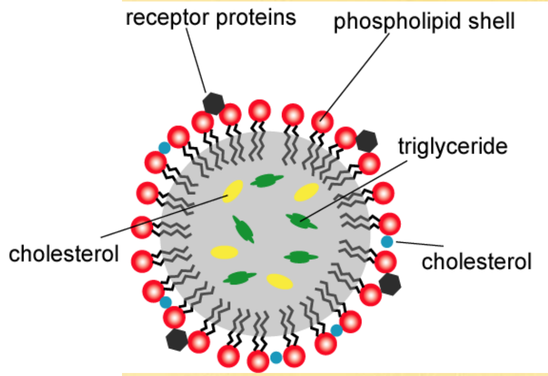


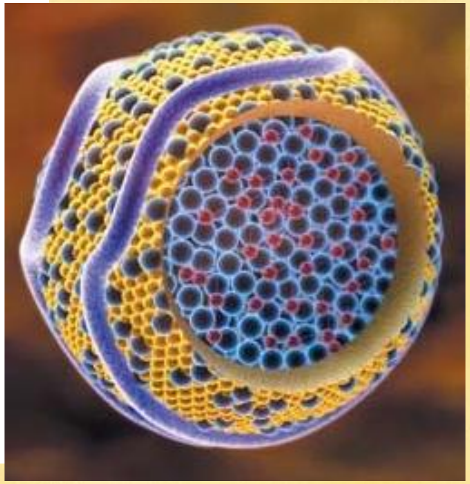
Chan et al., *Anal. Chem*. **85**, 599-603

Application Atherosclerosis: we found that we can obtain Raman spectra of individual lipoproteins

30 seconds acquisition time





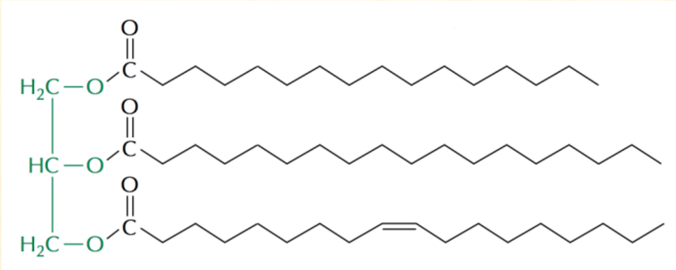


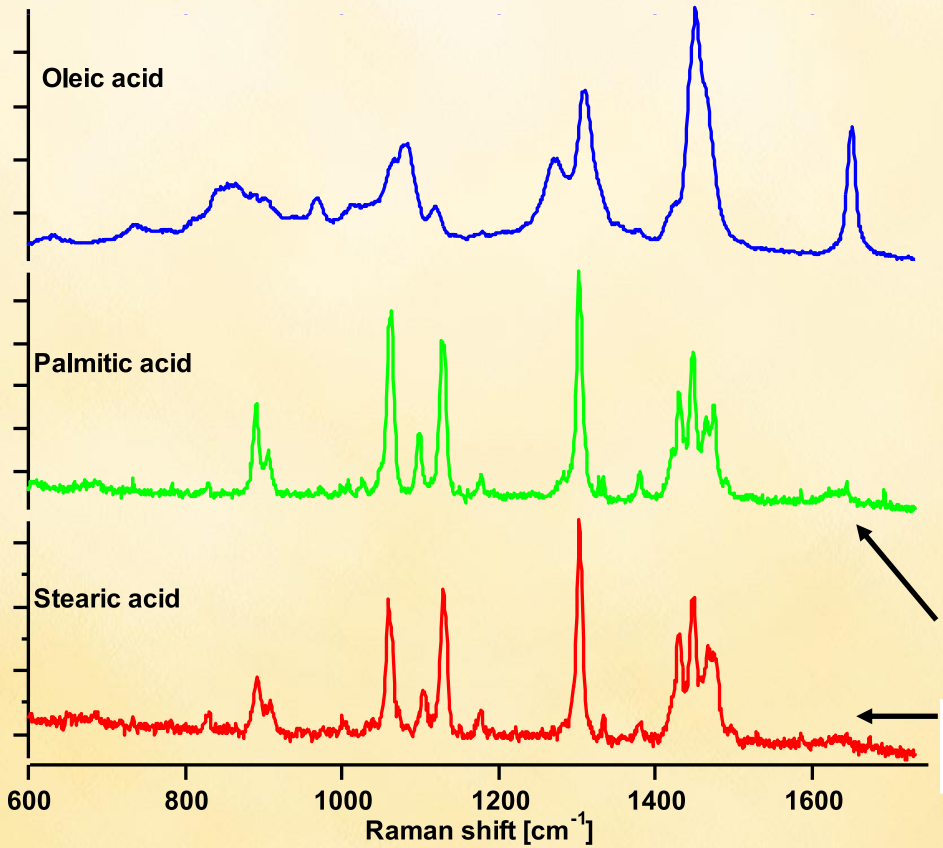
Raman peaks from triglycerides, cholesterol, phospholipid shell, and protein receptors are difficult to isolate from each other

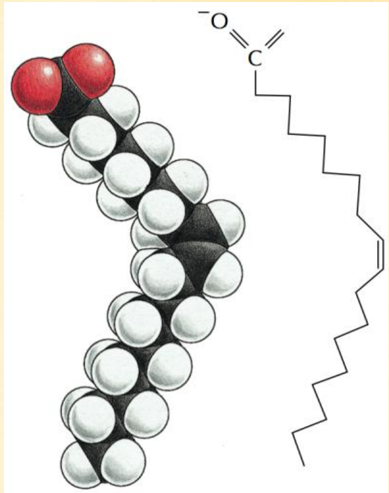
Chan et al., Anal. Chem. **77**, 5870-5876 (2005)

Raman spectra of fatty acids are indicative of the degree of saturation

Triacylglycerol

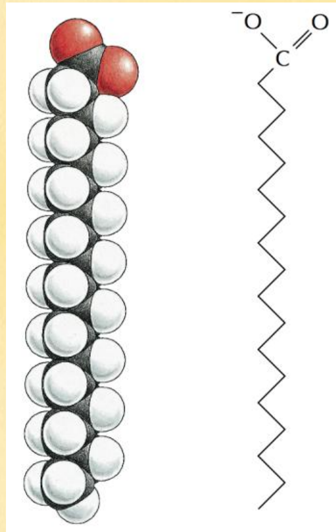


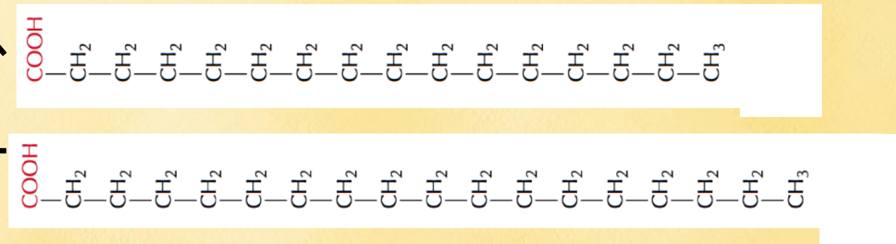




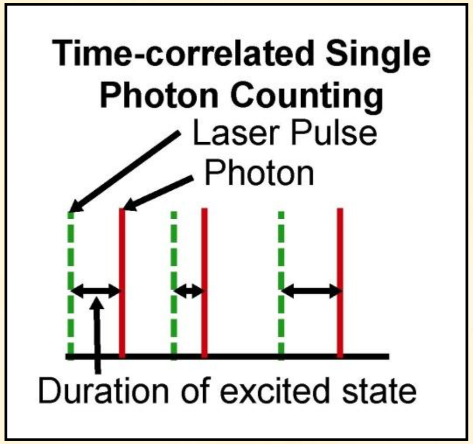
Oleic acid

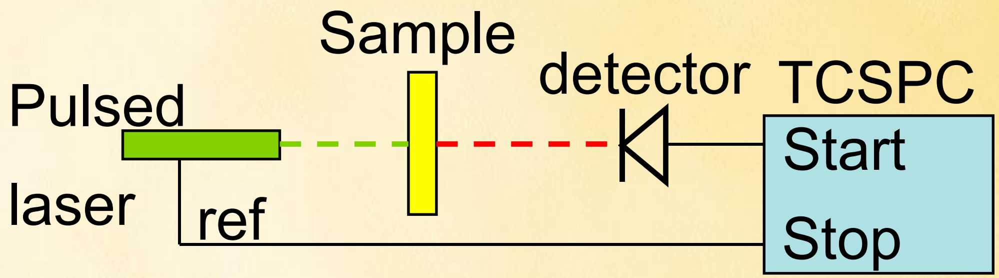
Stearic acid

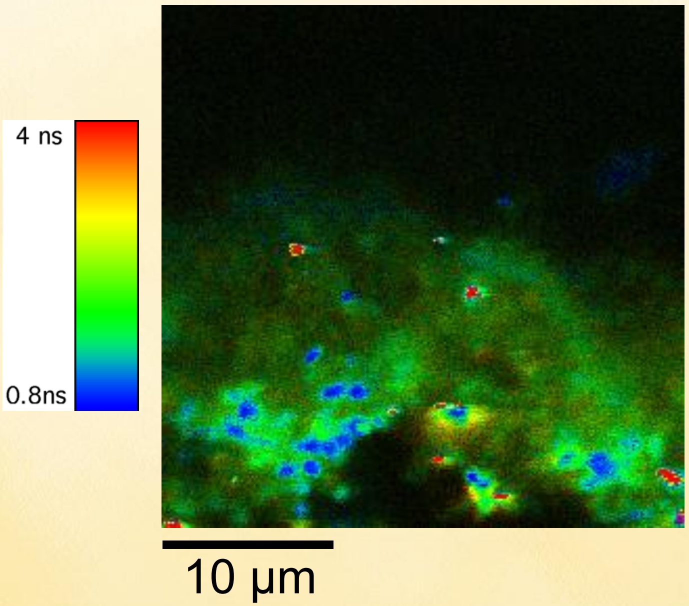


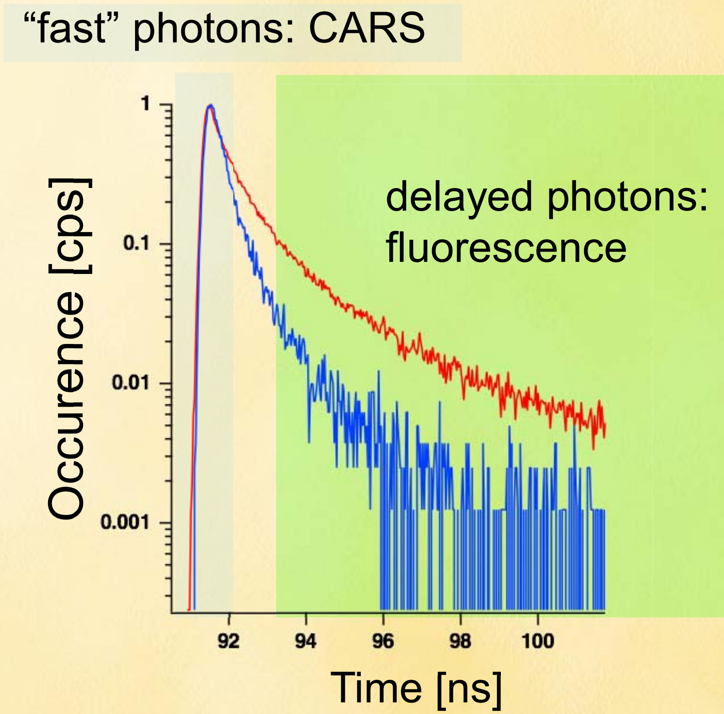


We have developed a unique CARS capability: Time-correlated single photon counting (TCSPC) provides additional contrast



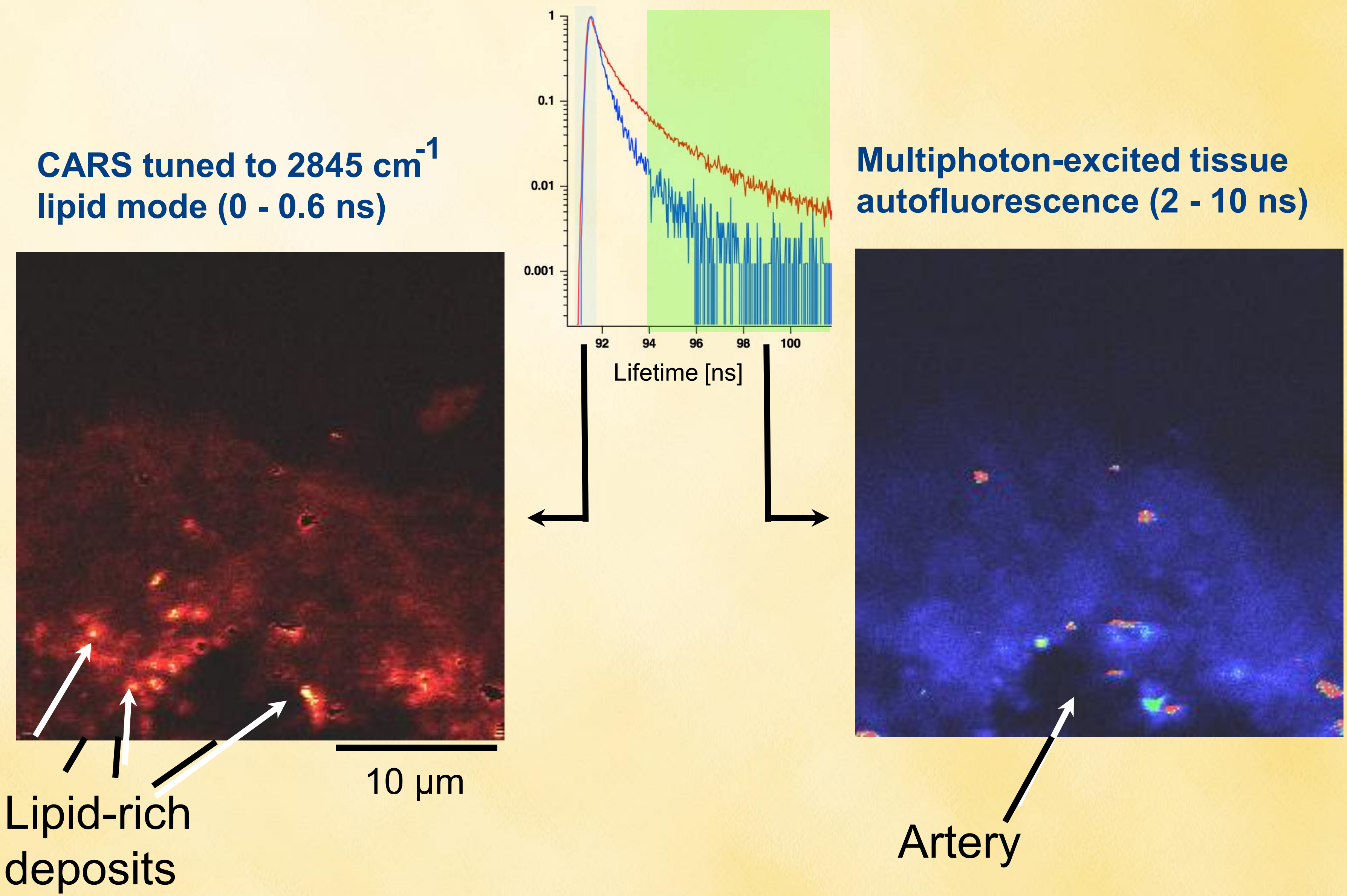






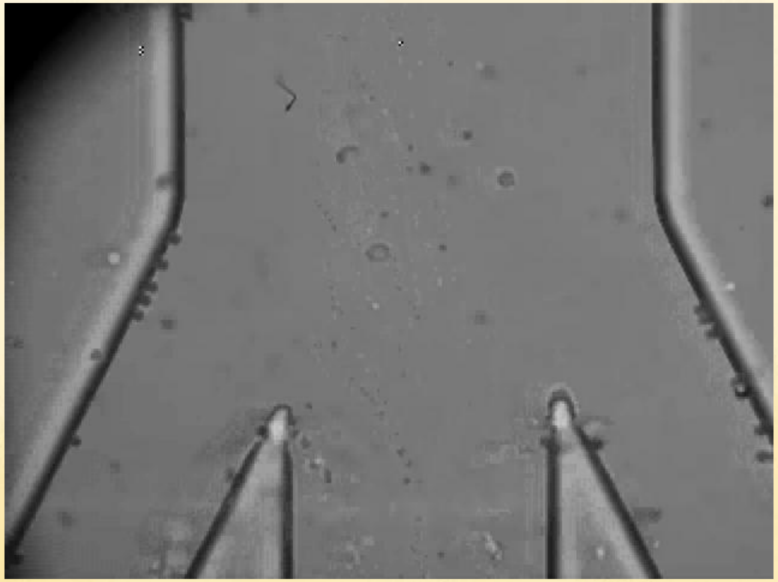
Sonny Ly, Gregory McNerney, Samantha Fore, James Chan, and Thomas Huser
Manuscript in preparation

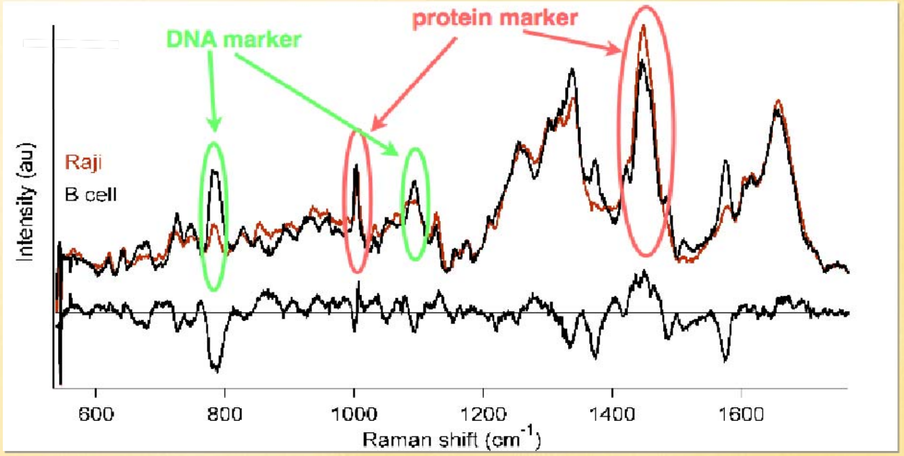
Time-gating allows us to separate CARS signals due to lipid-rich deposits from the tissue autofluorescence background



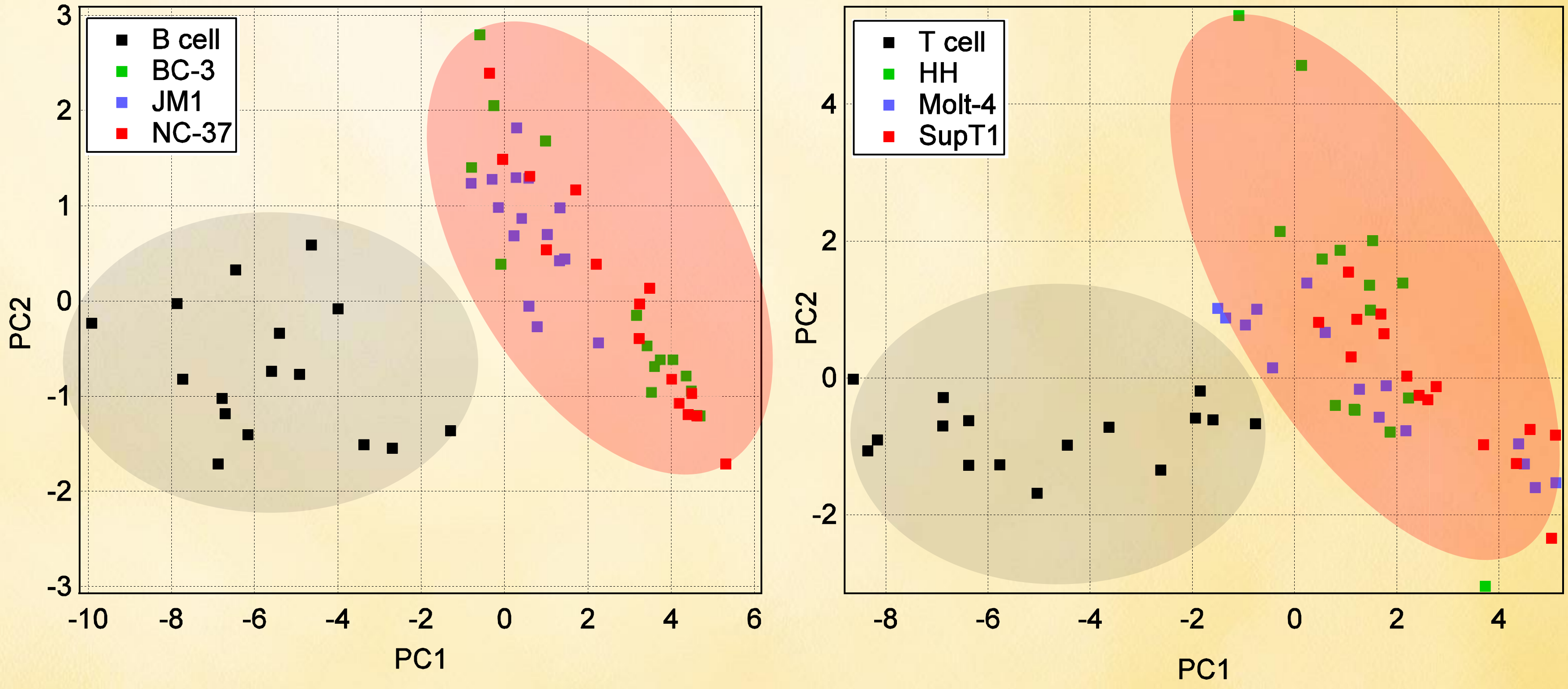
Towards Raman Flow Cytometry

Raman Cell Sorting , Thomas Huser and James Chan

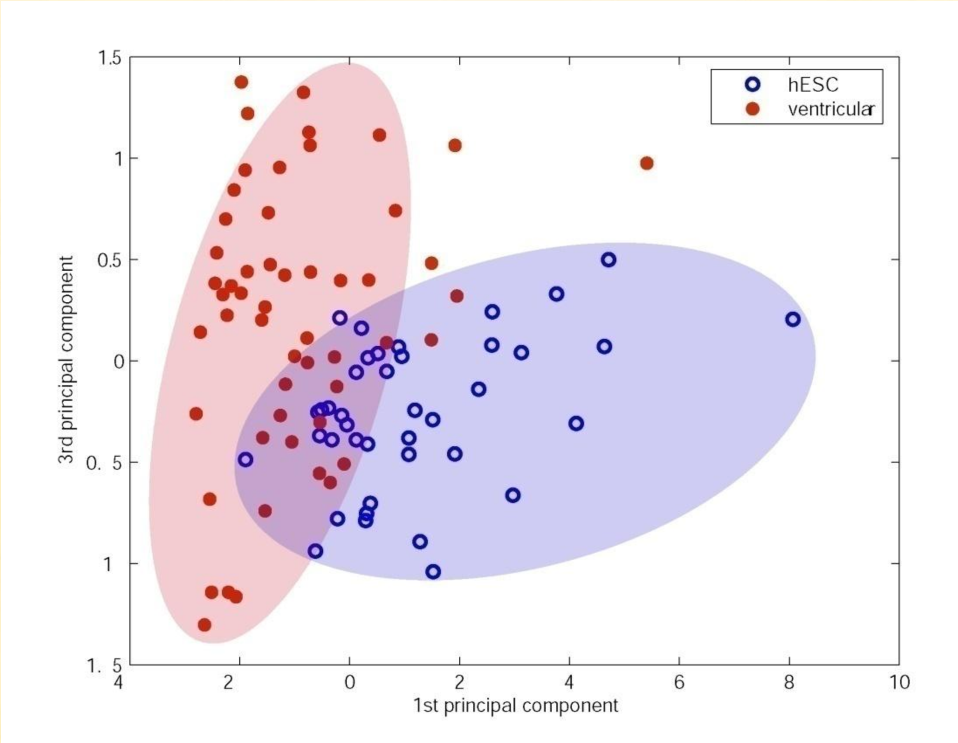


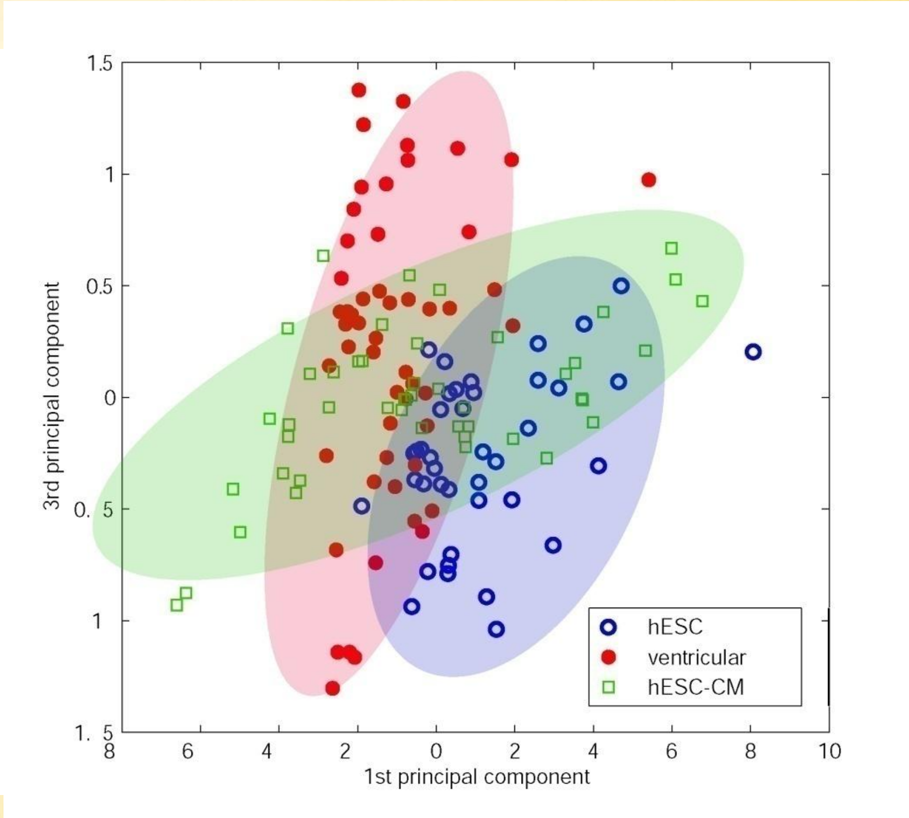


PCA shows excellent separation of normal cells and all leukemic cell types



Application of principal component analysis (PCA) shows separation of hESC and matured ventricular cell groups

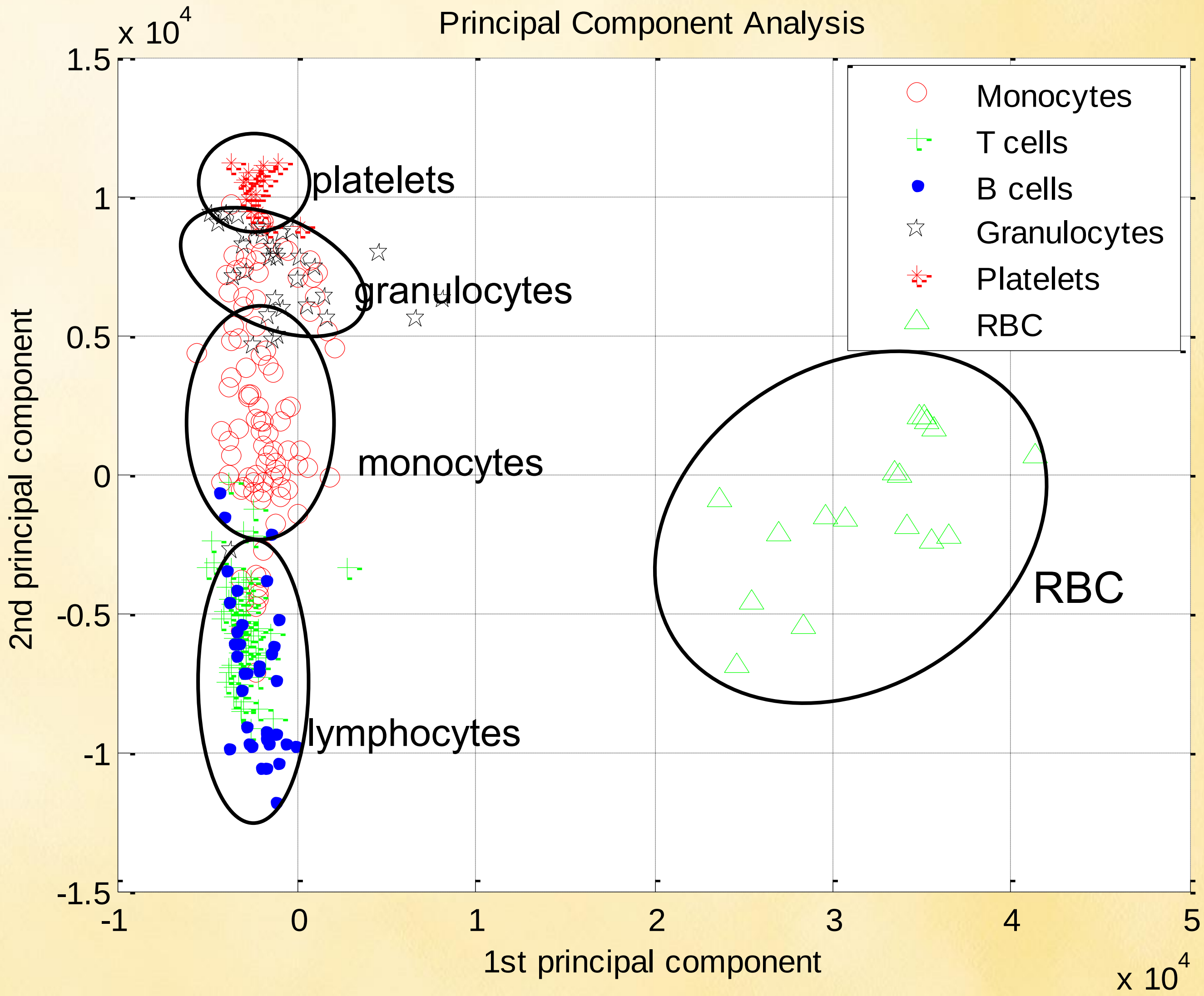




Right: hESC-derived CMs fall between fully matured cells and embryonic stem cells

(possible reasons: not fully matured and/or not 100% of hESCs were differentiated to CMs)

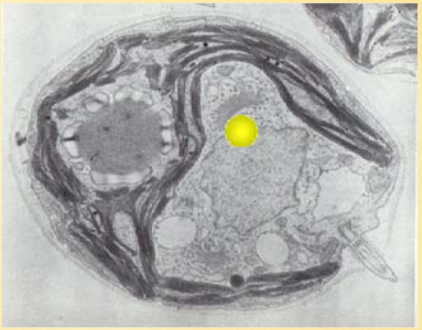
Separation of different living cell types by applying PCA to Raman spectra is demonstrated



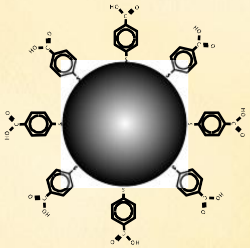
We have developed novel nanosensors for intracellular use based on surface-enhanced Raman spectroscopy (SERS)

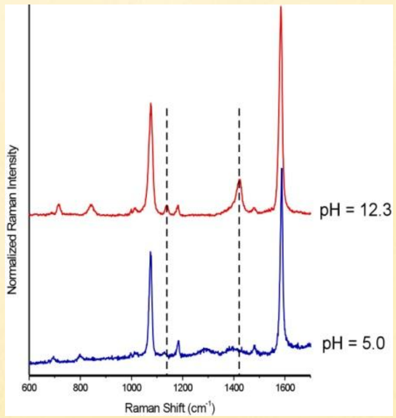
- Molecules with functional groups are attached to gold or silver nanoparticles (40-100 nm in diameter)
- The Raman spectrum of the “probe” molecule changes in response to changes in its local environment
- Nanoparticle probes can be microinjected into living cells to monitor:
  - pH, glucose, CO_2, Reactive Oxygen Species, etc.
- Advantages
  - Photostable—will not photobleach like fluorescent probes
  - Provide highly specific and quantitative information
  - Virtually background-free

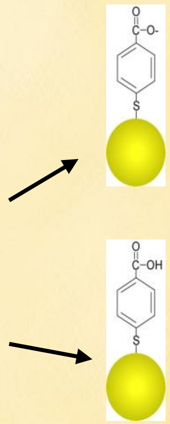
In situ nanoparticle chemical sensor

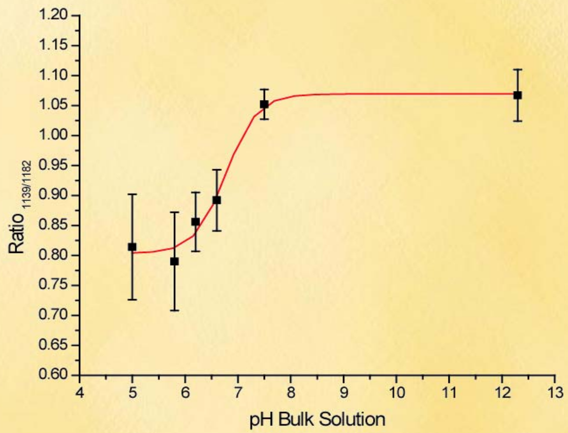


Example: 4-Mercaptobenzoic acid coated silver nanoparticles act as nano - pH sensors







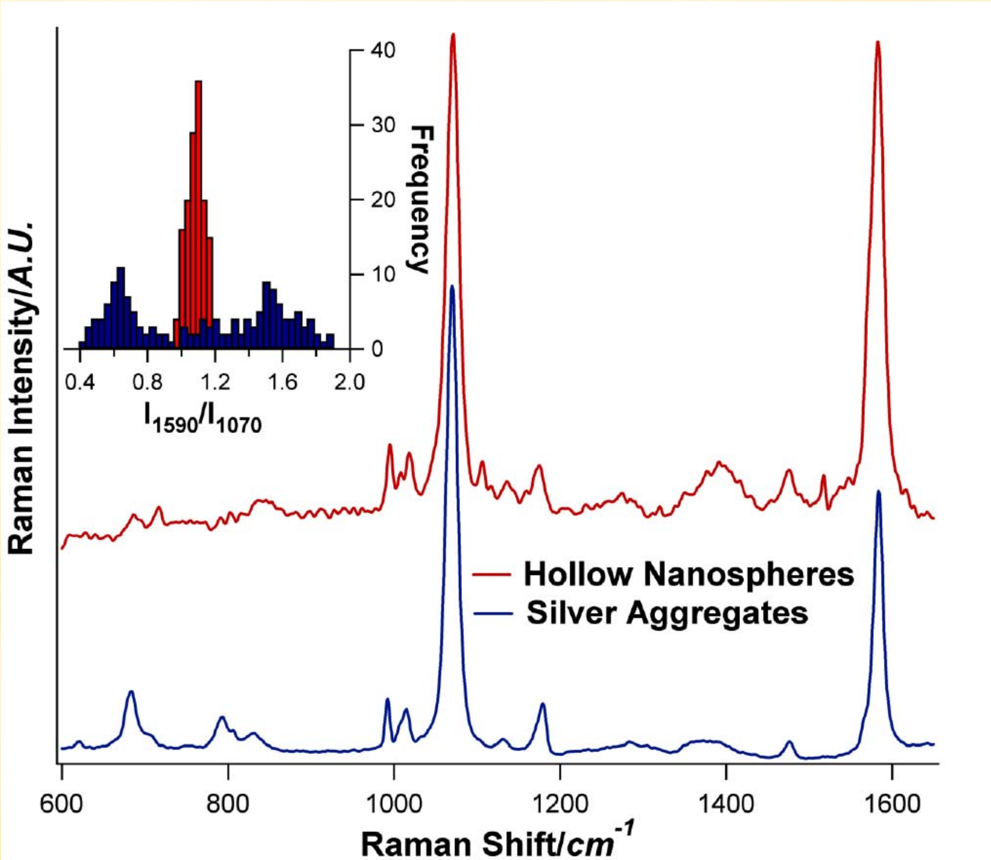


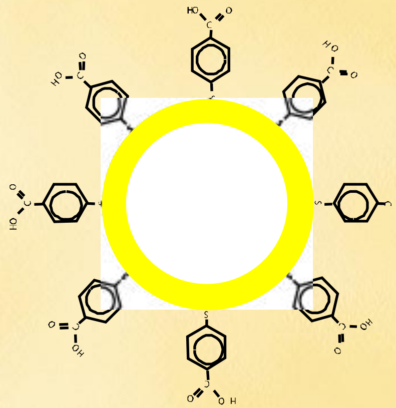
Applications:

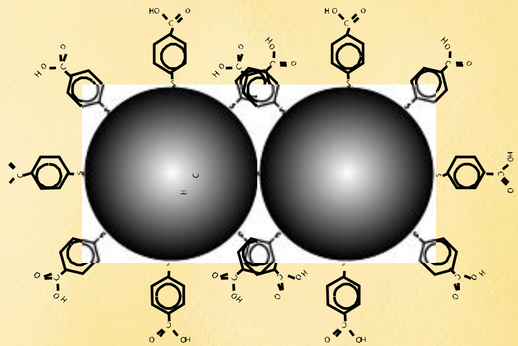
-Understanding how local pH affects cellular uptake of chemotherapeutic agents
-Monitoring reactive oxygen species concentration following low dose radiation

T. Huser, S. Lane, Tony Esposito, C. Hollars, C. Talley , J. Chan et al, LLNL/UCD

SERS signals from functionalized hollow nanospheres are much more uniform than for aggregated bulk particle clusters



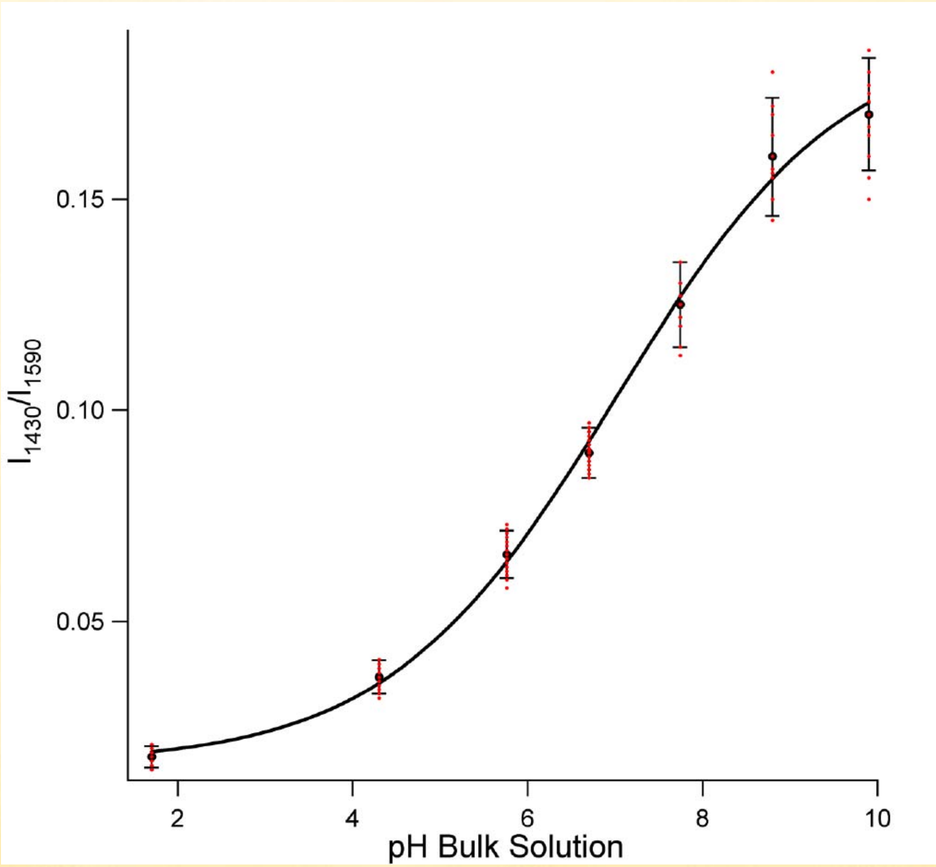


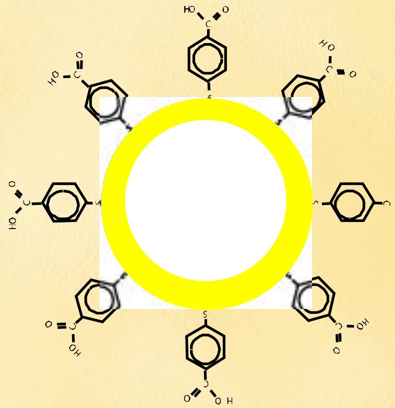


Single particle SERS spectrum of MBA on hollow nanosphere vs. SERS spectrum from a silver aggregate

Schwartzberg et al., Anal. Chem. **78**, 4732 (2006)

The SERS response / pH range of functionalized hollow gold nanospheres is highly reproducible and wider than that of silver nanoaggregates





Normalized intensity of the pH sensitive 1430 cm^{-1} peak of 20-30 particles at different pH

Schwartzberg et al., Anal. Chem. **78**, 4732 (2006)

Take-aways

- Brief Intro to our Center for Biophotonics. Network, collaborate with us and visit.
- Nanoscale imaging opens the door to understand live cell function and response to infection, mutation and therapy
- Nanosensing is a critical need for many bioscience and medical applications. New technology/methods are progressing on a broad front. Point of Care Testing will be the killer app.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