Optical Imaging for Minimally Invasive Medical Diagnosis



Using Nanotechnology to Address Gaps in Health Care Technology

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"Something there is that does not love a wall…"


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Before I built a wall I'd ask to know

What I was walling in or walling out,

And to whom I was like to give offence.

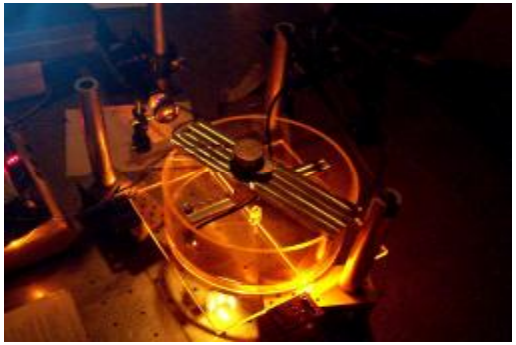
Something there is that doesn't love a wall,

That wants it down.

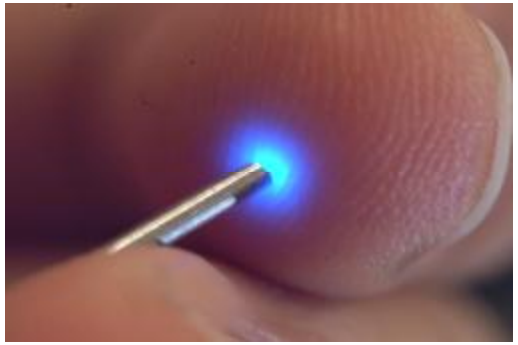
Mending Wall, Robert Frost

Optical Molecular Imaging Laboratory

We conduct interdisciplinary research at the interface of photonics, nanotechnology, and clinical medicine towards development of novel optically-based technologies for minimally invasive screening, diagnosis, and monitoring of disease



Basic Science



Technology Development

Clinical Trials

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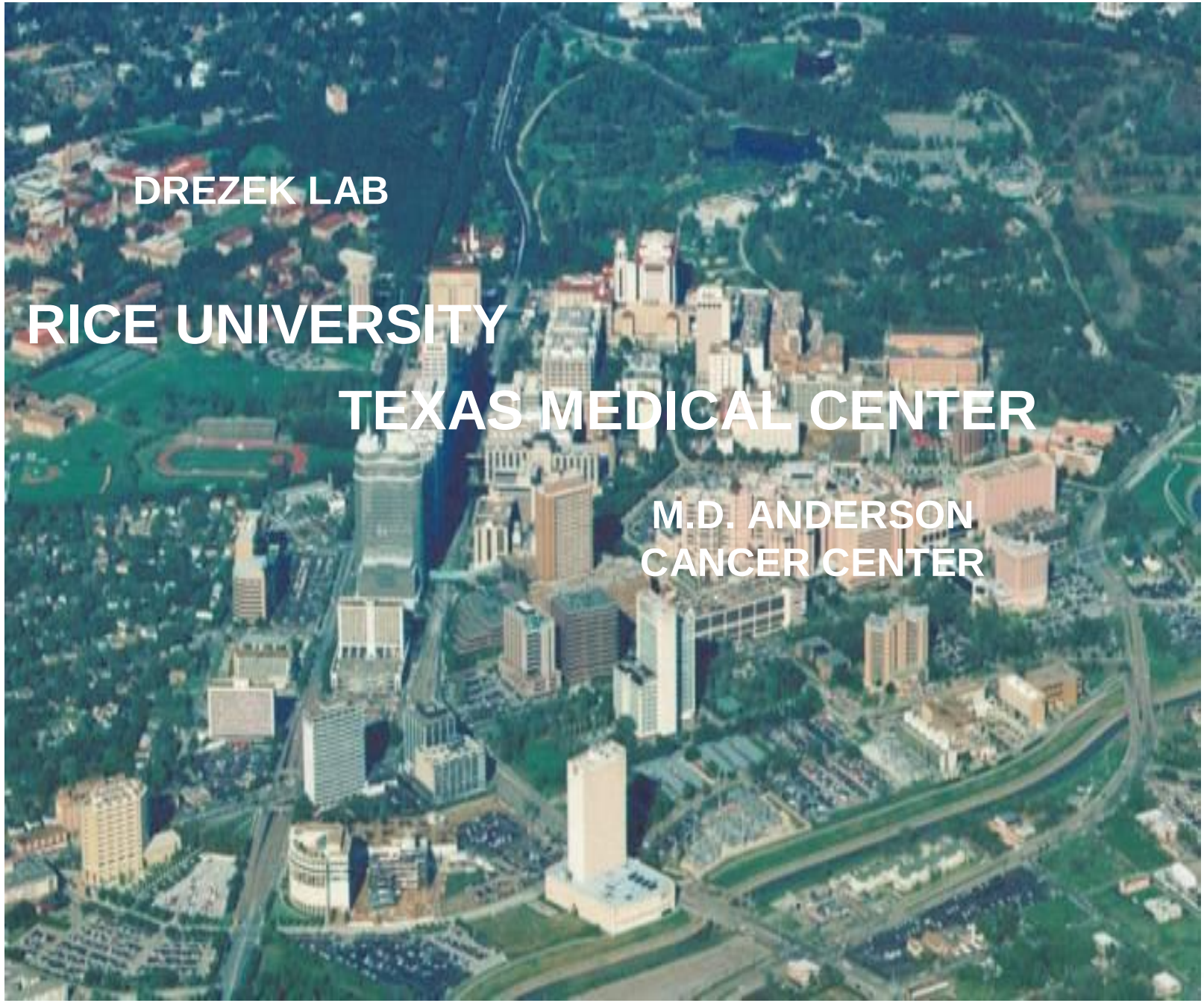
DREZEK LAB
RICE UNIVERSITY
TEXAS MEDICAL CENTER
M.D. ANDERSON
CANCER CENTER

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Questions

- Why do we screen women for cervical cancer using a test which misses almost 40% of the cases of disease?
- Why do we operate on nearly 100 women to find 1 – 3 ovarian cancers?
- Why does a breast tumor grow for 8 years before we locate it? And why is surgical lumpectomy the most common treatment for breast cancer?

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Outline of Talk

- The Cancer Problem
- Biomedical Technology: Optical Imaging
- Adding Functionality via Nanotechnology
  - Evolution of “active” nanostructures

Cancer: Statistics

1,368,030

1,334,100 new cancer cases

563,700

556,000 deaths

women: 1 in 3 lifetime risk

men: 1 in 2 lifetime risk

$189.5 billion

annual costs: $110 billion

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Cancer: Importance of Screening

- Five Year Relative Survival Rates

Organ Site	Local	Regional	Distant
Breast	**96%**	**77%**	**21%**
Ovary	**95%**	**79%**	**28%**
Colon	**90%**	**65%**	**8%**
Cervix	**91%**	**48%**	**13%**

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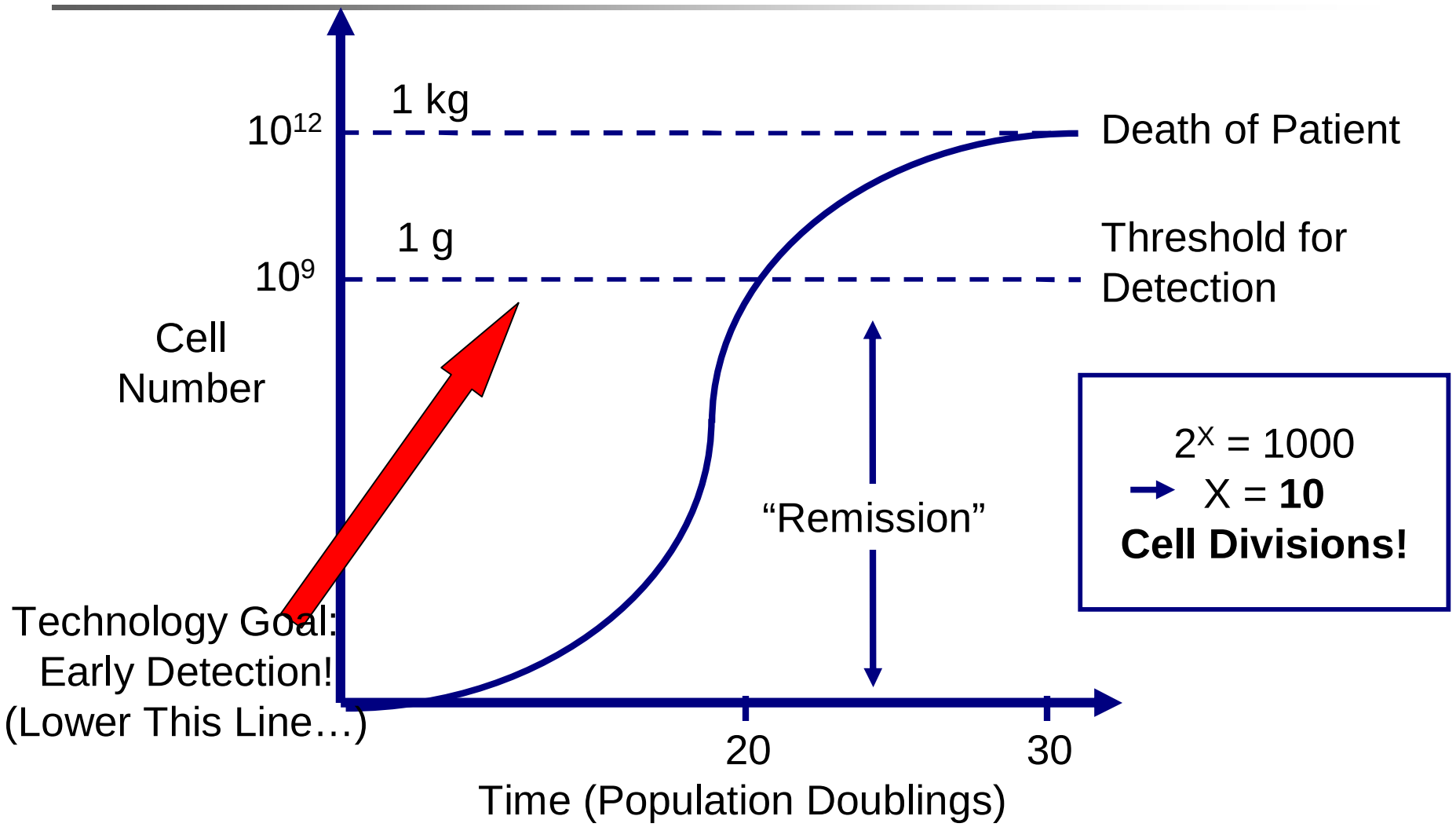
"I'd have been here sooner if it hadn't been for early detection."

Cancer: Detection Problem



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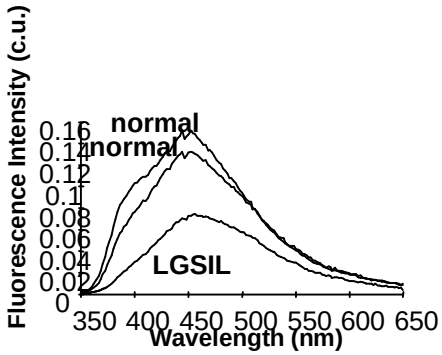
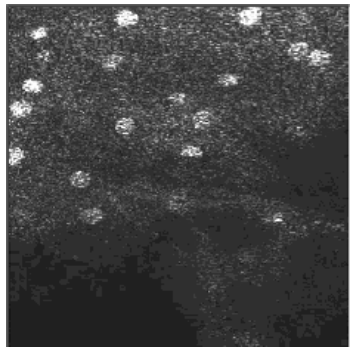
Source: Robbins, Pathologic Basis of Disease 5th Edition

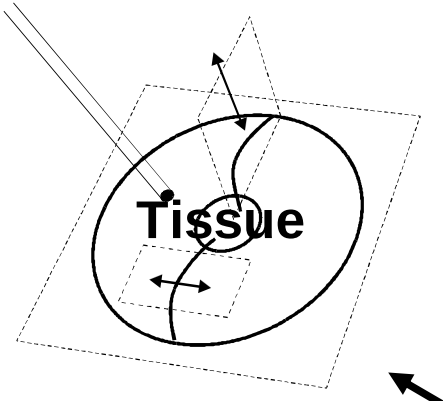
Optical Imaging Strategies

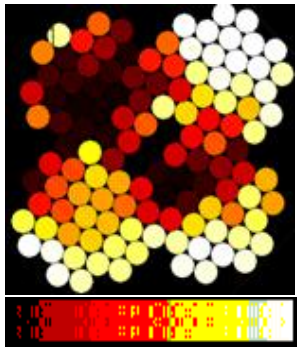


Optical Spectroscopy



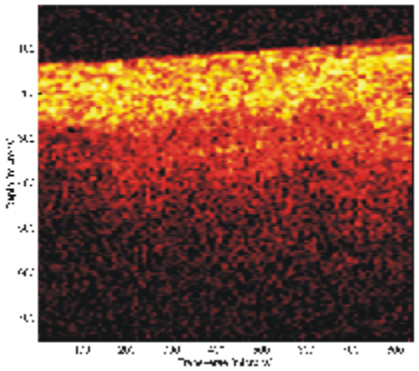
Confocal





Probability of being abnormal

Multispectral Imaging



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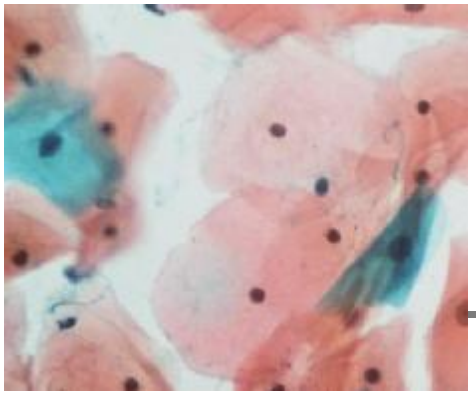
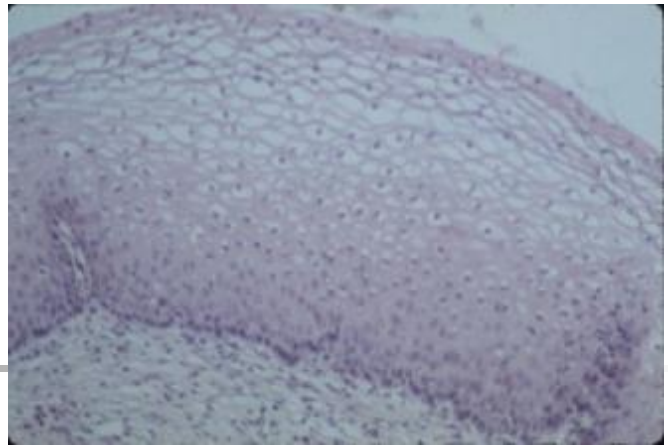
Detecting Cervical Pre-Cancer

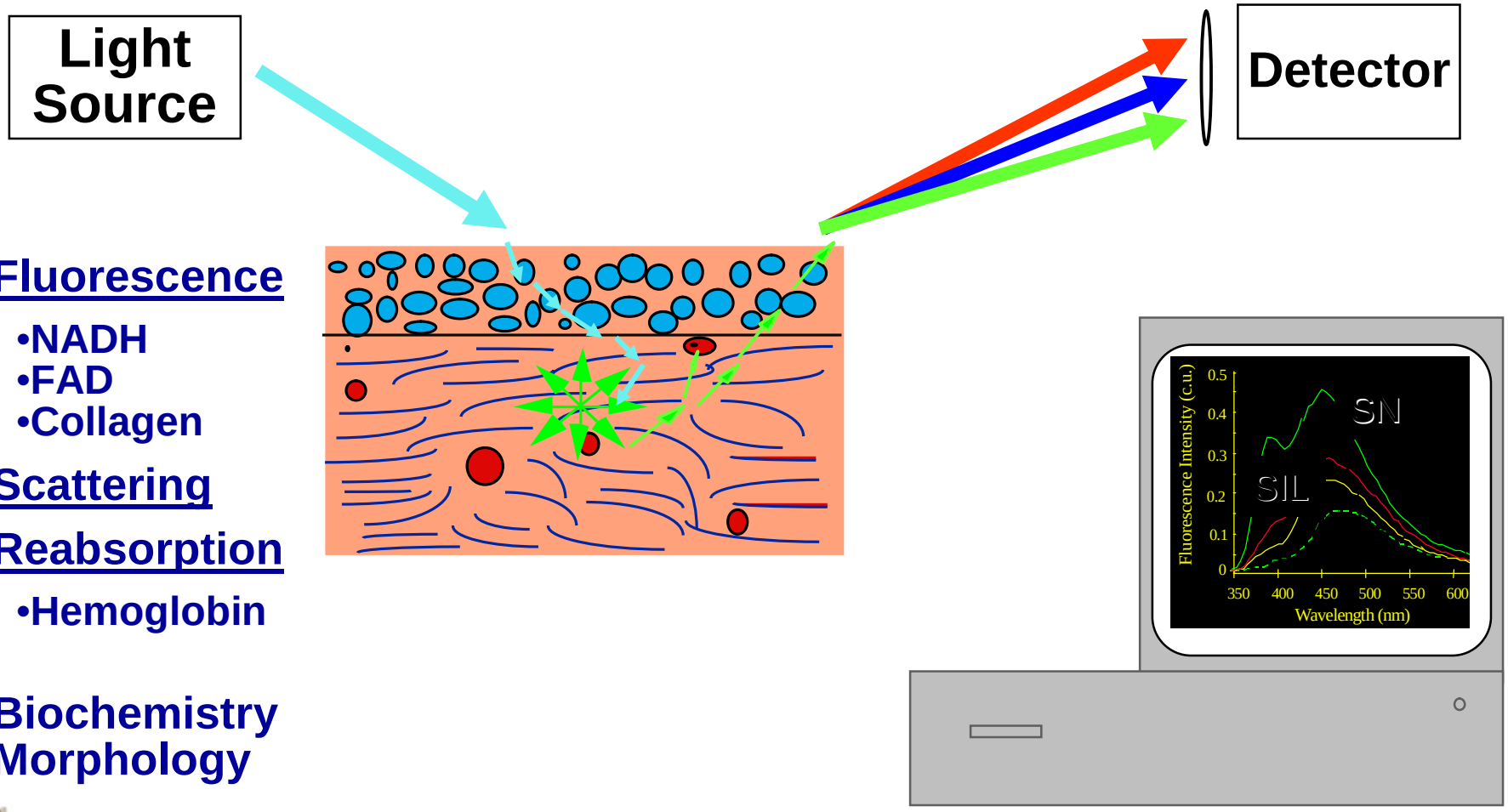


Se = 62%
Sp = 60%



Se = 95%
Sp = 44%

Fluorescence Spectroscopy



- **Fluorescence**
  - NADH
  - FAD
  - Collagen
- **Scattering**
- **Reabsorption**
  - Hemoglobin

- Biochemistry
- Morphology

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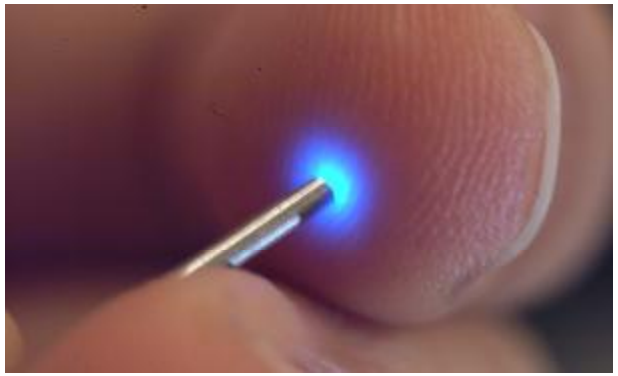
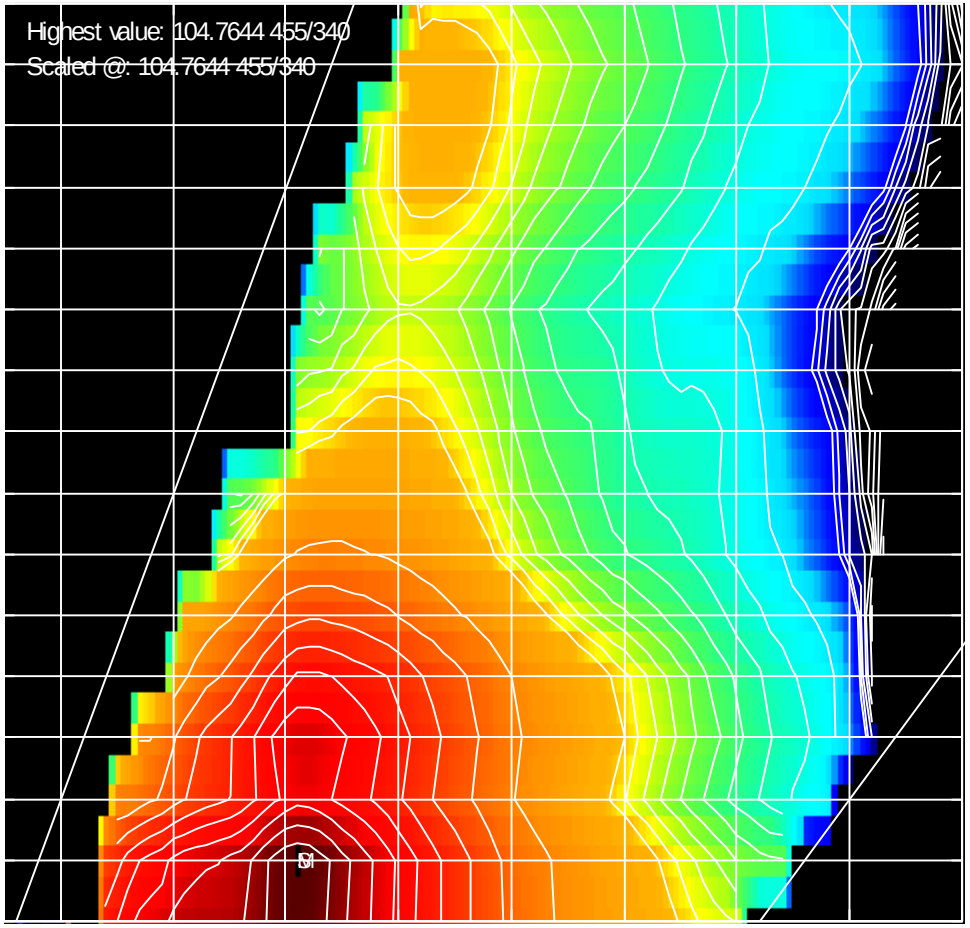
Spectroscopy Example: Point-of-Care Cervical Cancer Screening





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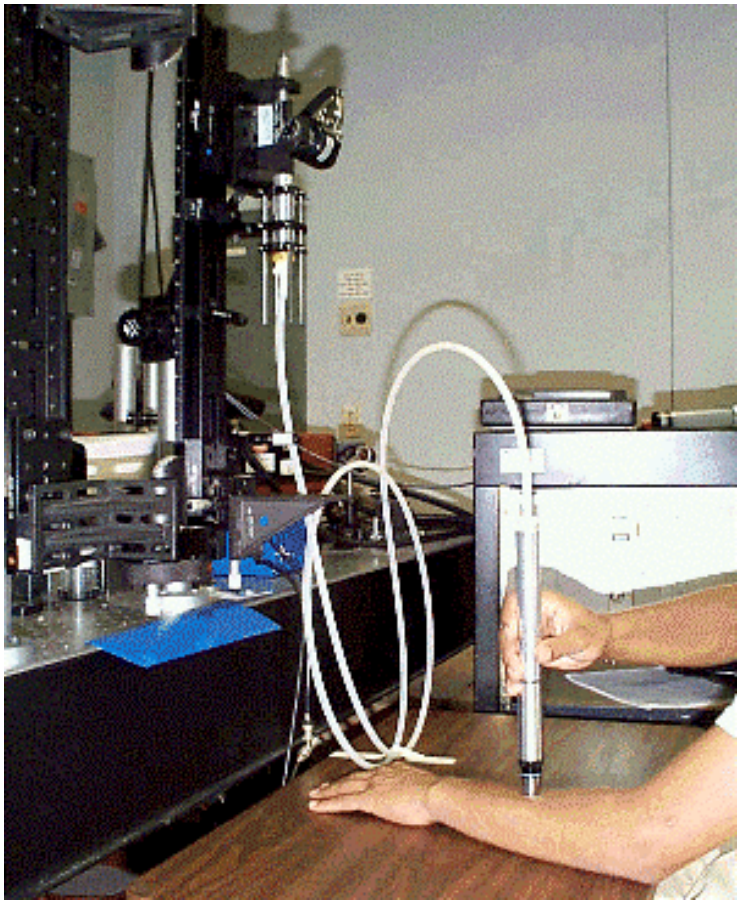
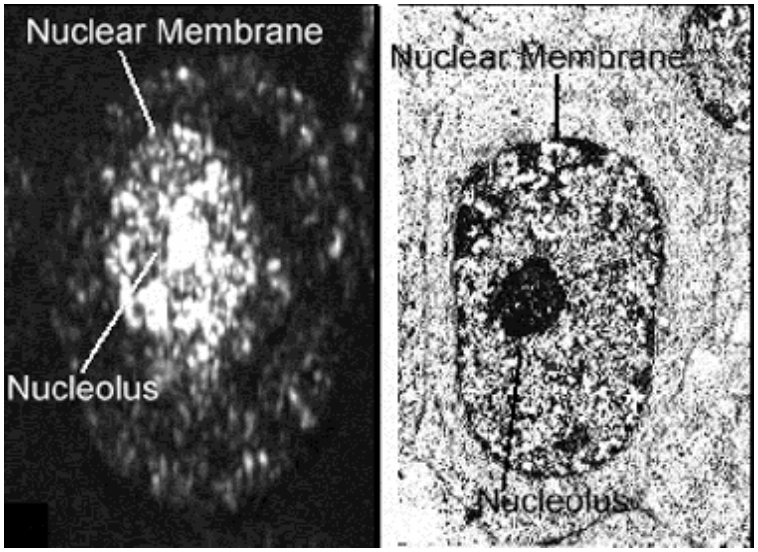
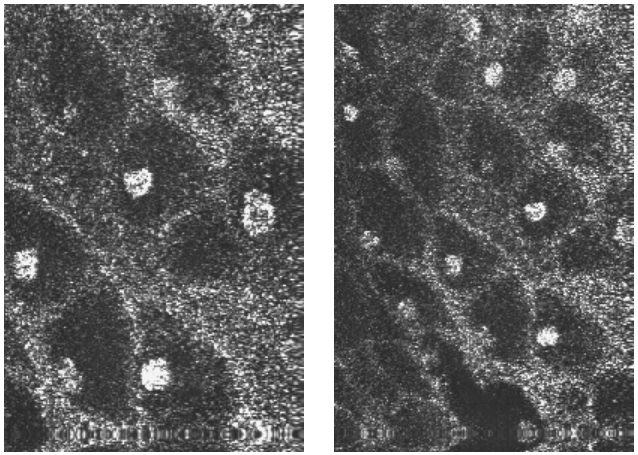
Richards-Kortum Laboratory; Utzinger Laboratory (fiber probe)



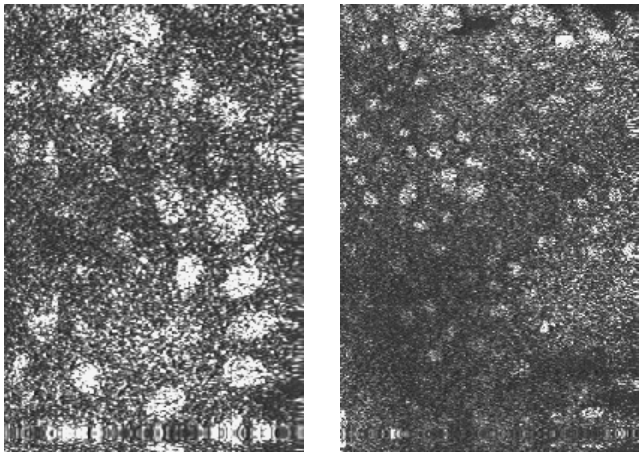
In Vivo Confocal Microscopy



Normal



Precancerous



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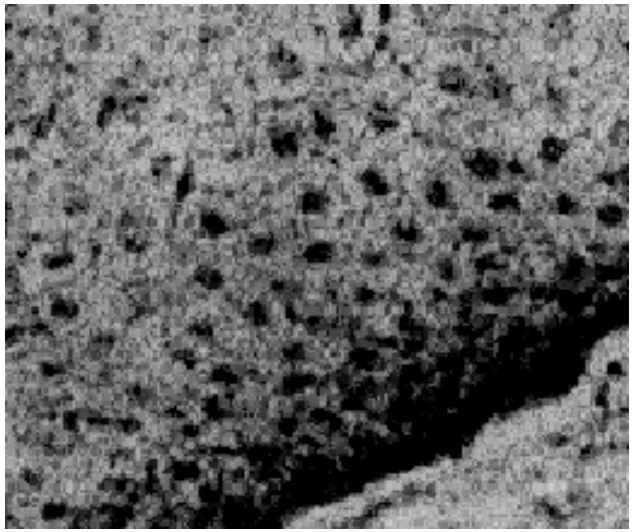
Drezek et al, Am J Obstet Gynecol (2000)

Correspondence to Histology

H&E

confocal



- Similar information content available immediately without the need to section or stain tissue

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How Does Nanotechnology Add Value?

Example: Near Infrared Confocal Reflectance Imaging

Endogenous Signal

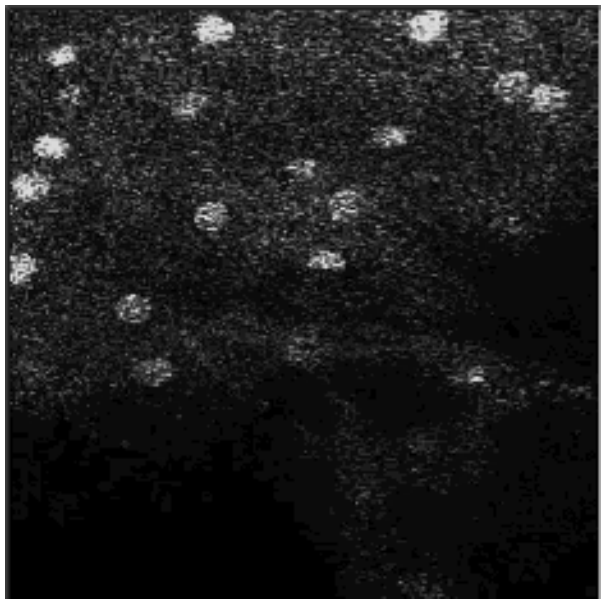

Image cell nuclei morphology

Exogenous Signal

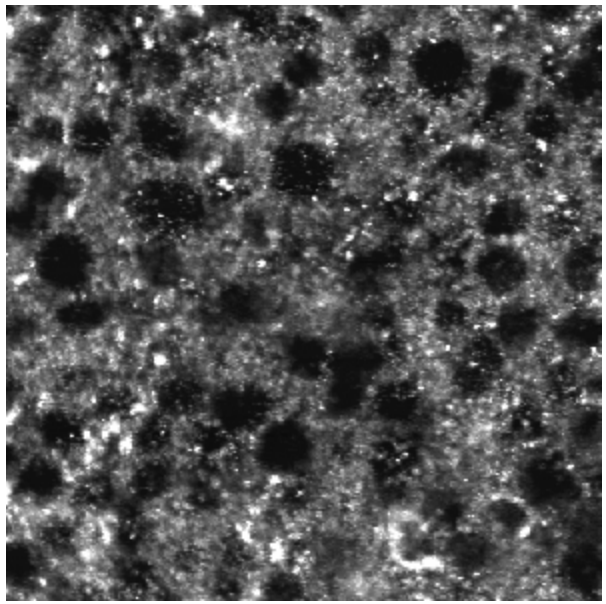

Image HER2 expression

How?

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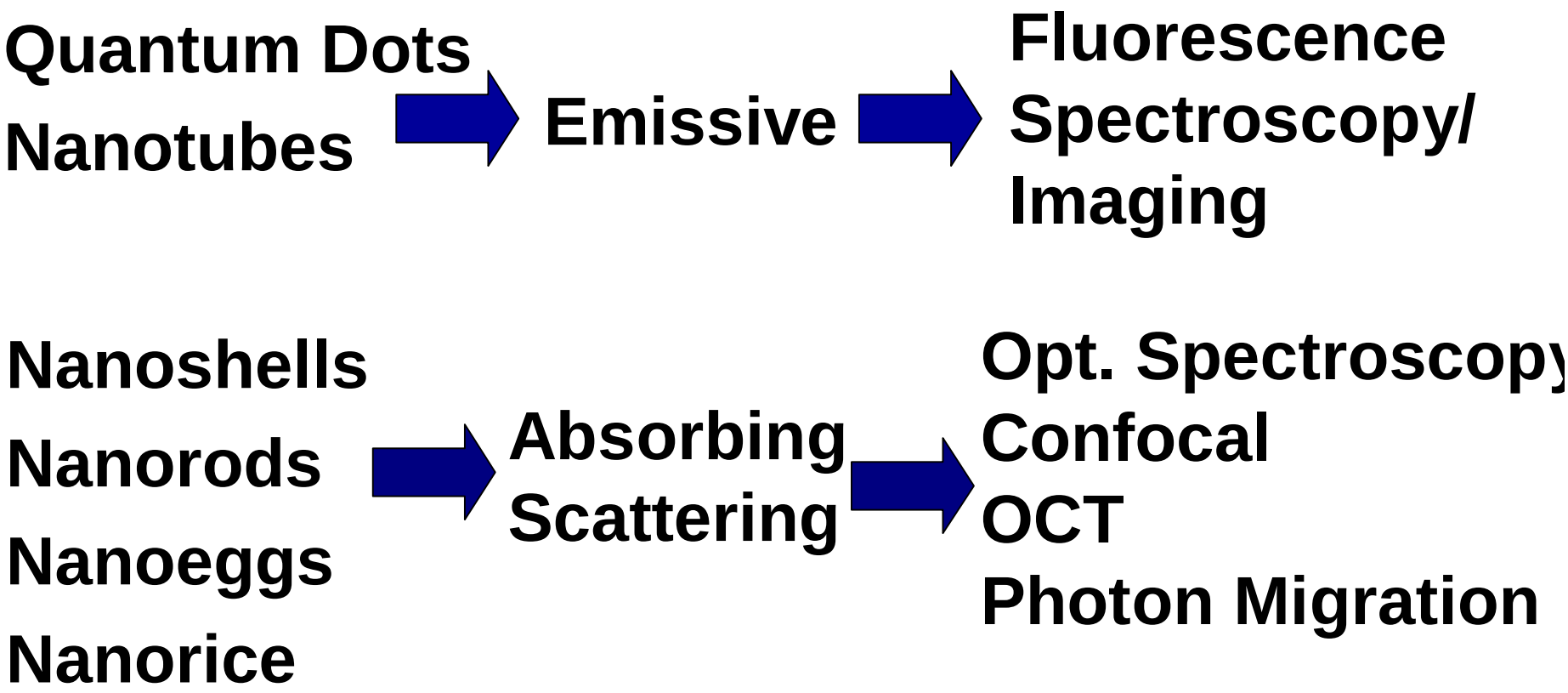
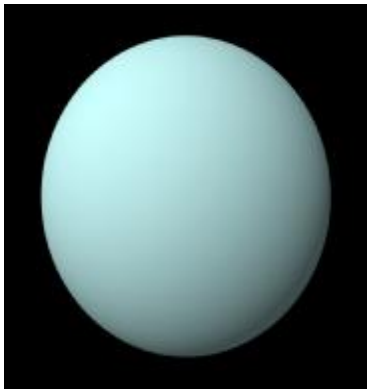
Nanomaterials



Nanoshells

Nano-engineered Core / Shell Particles



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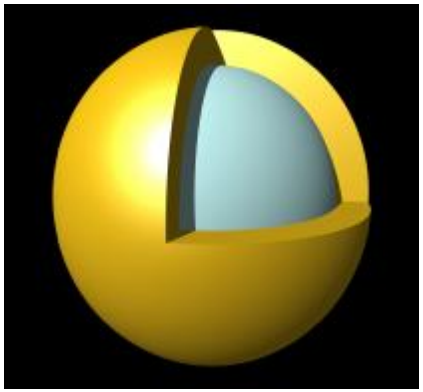
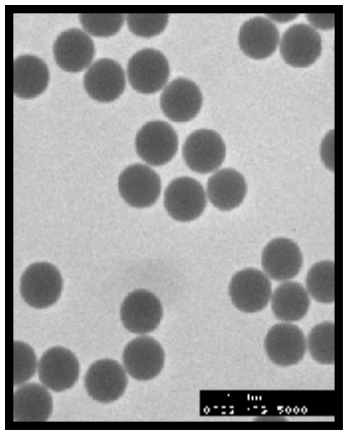


Non-Conducting Core

Metal Shell of Desired Thickness

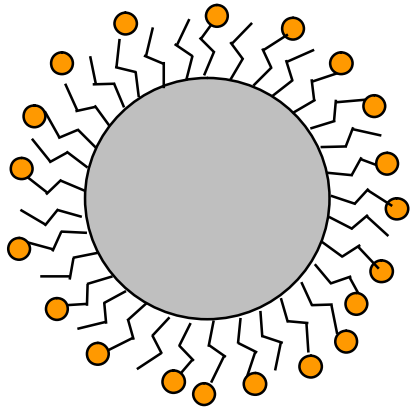
Thickness of Shell/Size of Core =
Optically Tunable Particle

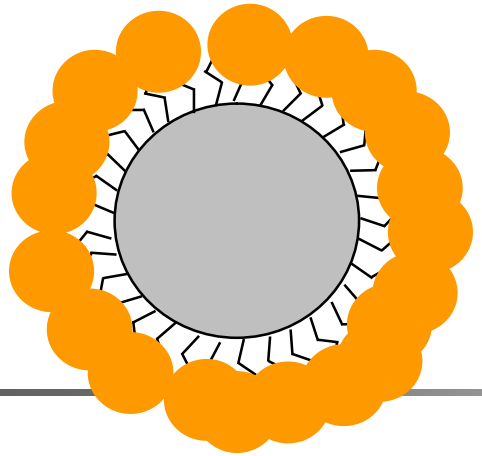
Nanoshell Fabrication



- Grow silica cores using Stöber method (basic reduction of tetraethoxysilane in ethanol).
- Coat with amino propyl triethoxysilane to terminate the surface of the nanoparticle with amine groups.

- Immerse amine coated silica particles into a bath of small gold colloid (< 2 nm).





- Reduce more gold onto seed particles until particles coalesce into a complete shell.

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Nanoshells vs. Quantum Dots

Nanoshells:

tunable plasmonic nanoparticles

~50-300 nm diameter

Quantum efficiencies ~10^{-4}

Spectral range (extinction):
500(Ag)-9000 nm

Cross sections:
~10^{-13} m^2

Quantum Dots:

tunable excitonic nanoparticles

~1-10 nm diameter

Quantum efficiencies ~ 0.1-0.5

Spectral range (emission):
400-2000 nm

Cross sections:
~10^{-19} m^2

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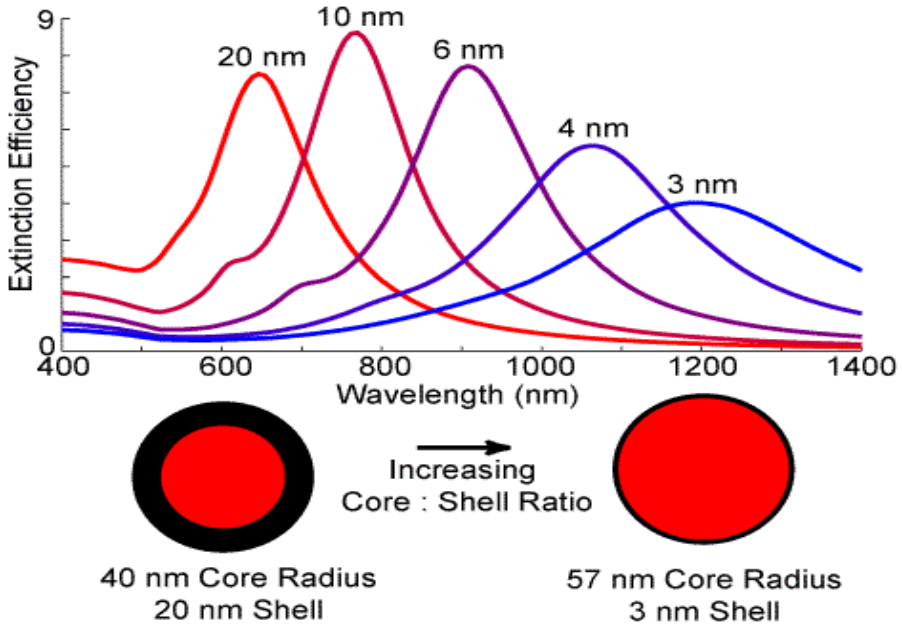
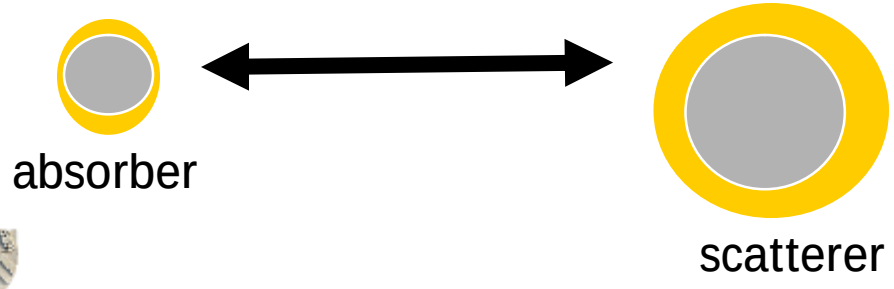
Slide provided by Naomi Halas

Nanoshell Properties for Imaging/Therapy

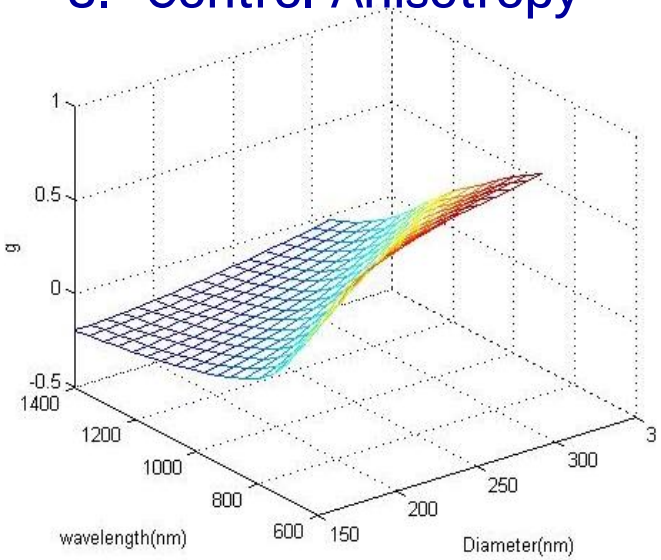
1. Control Plasmon Resonance



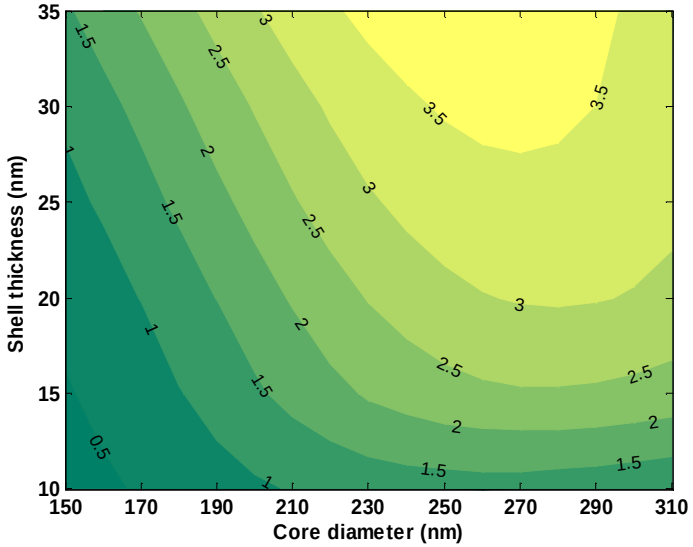
2. Control Ratio of Scatter to Absorption



3. Control Anisotropy



4. Control Backscatter



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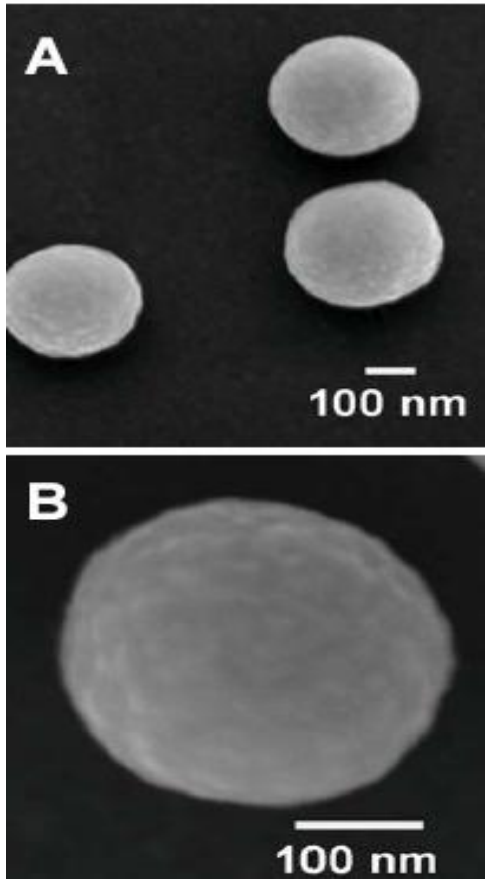
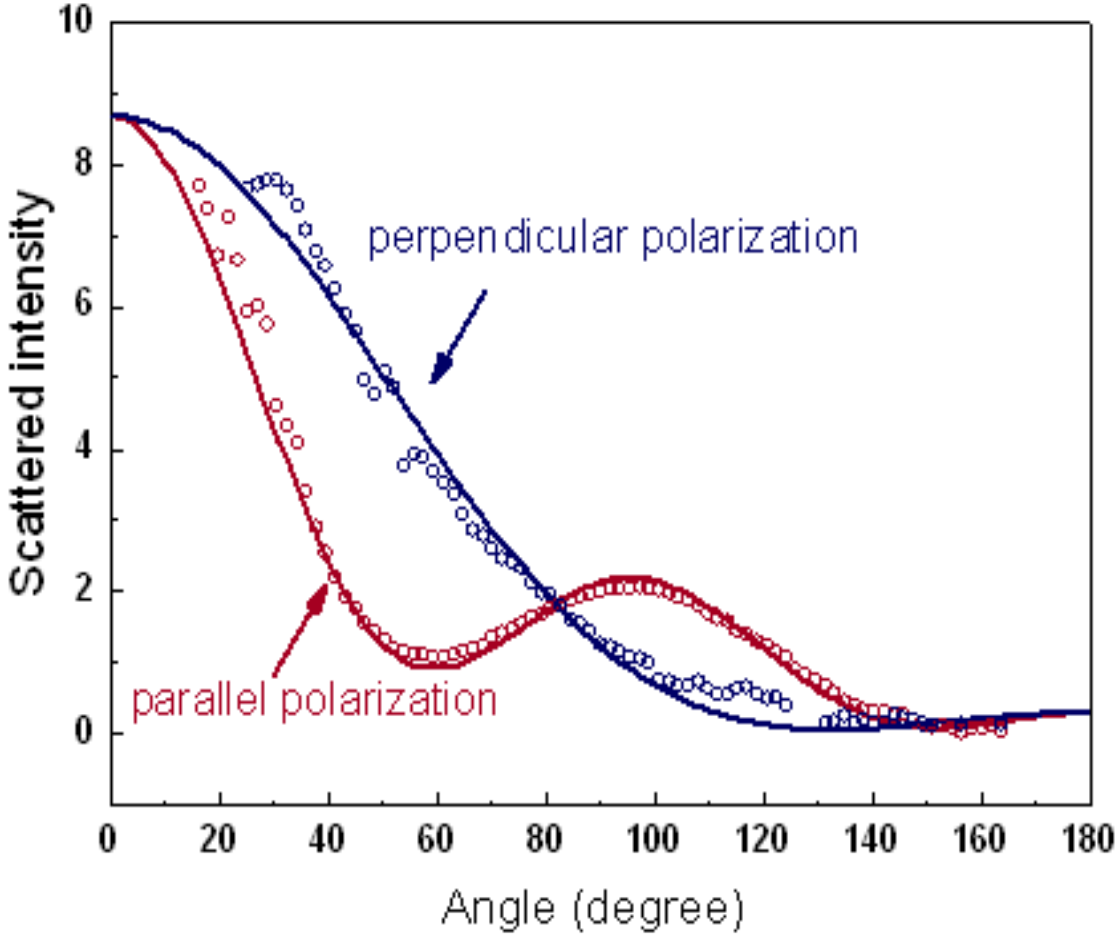
Nanoshells: Theory vs. Experiments





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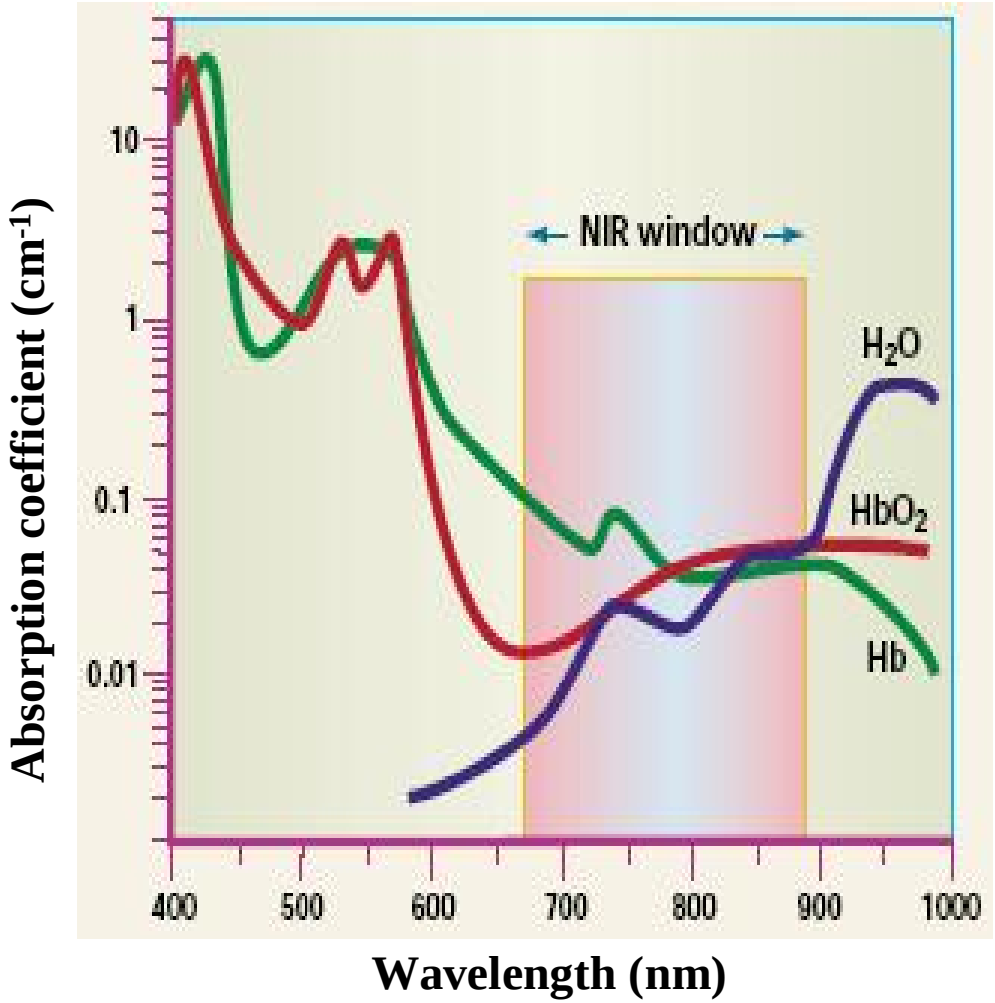
Absorption of Light in Tissue

- Absorption by many native chromophores
- Absorption **à** Heat
- Absorption is λ dependent
- NIR window
  - ~650 – 900 nm
  - Low absorption
  - High transmission



R. Weissleder, *Nat Biotechnol* 19, 316-7 (2001)

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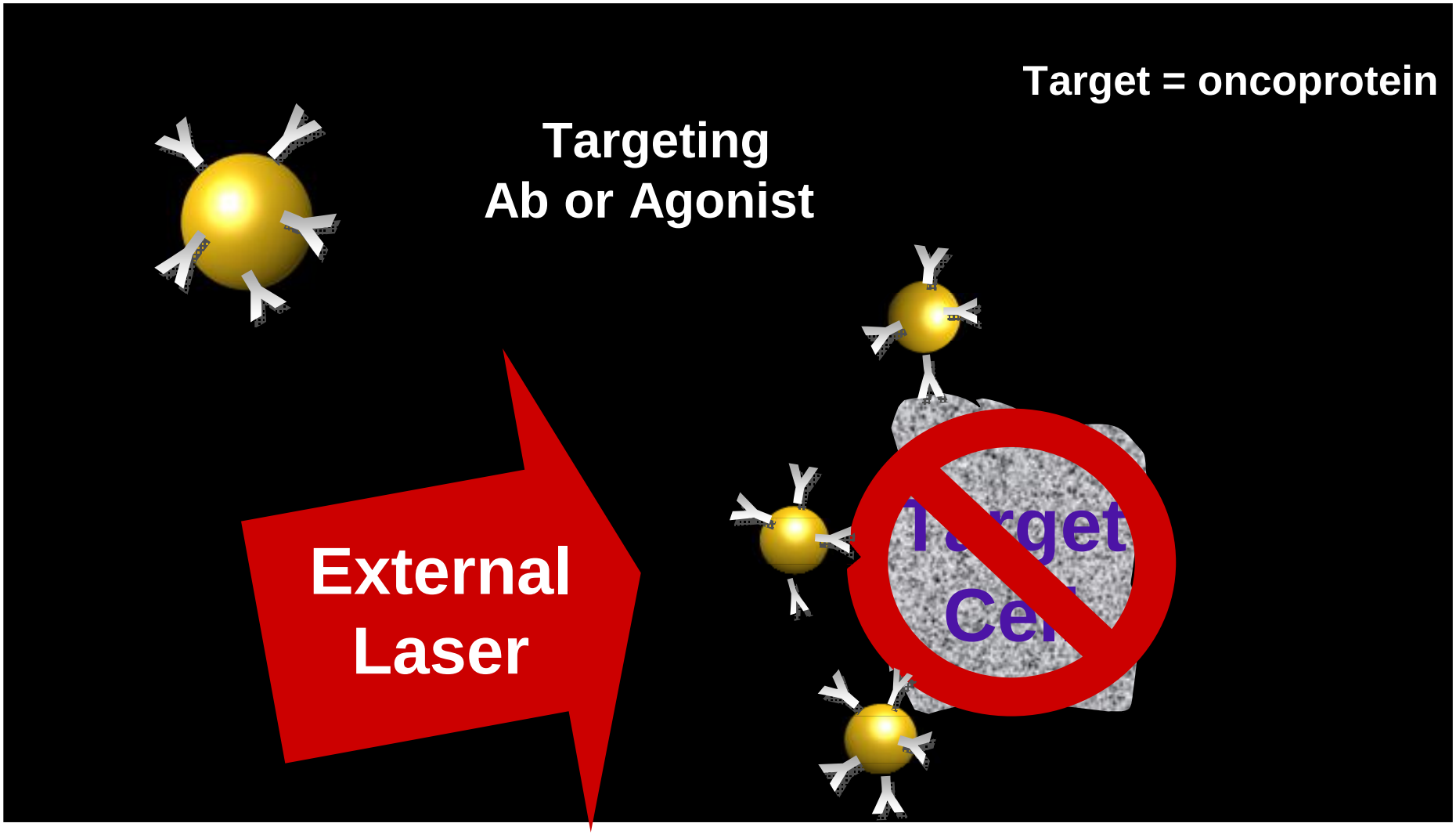
Thermal Ablation



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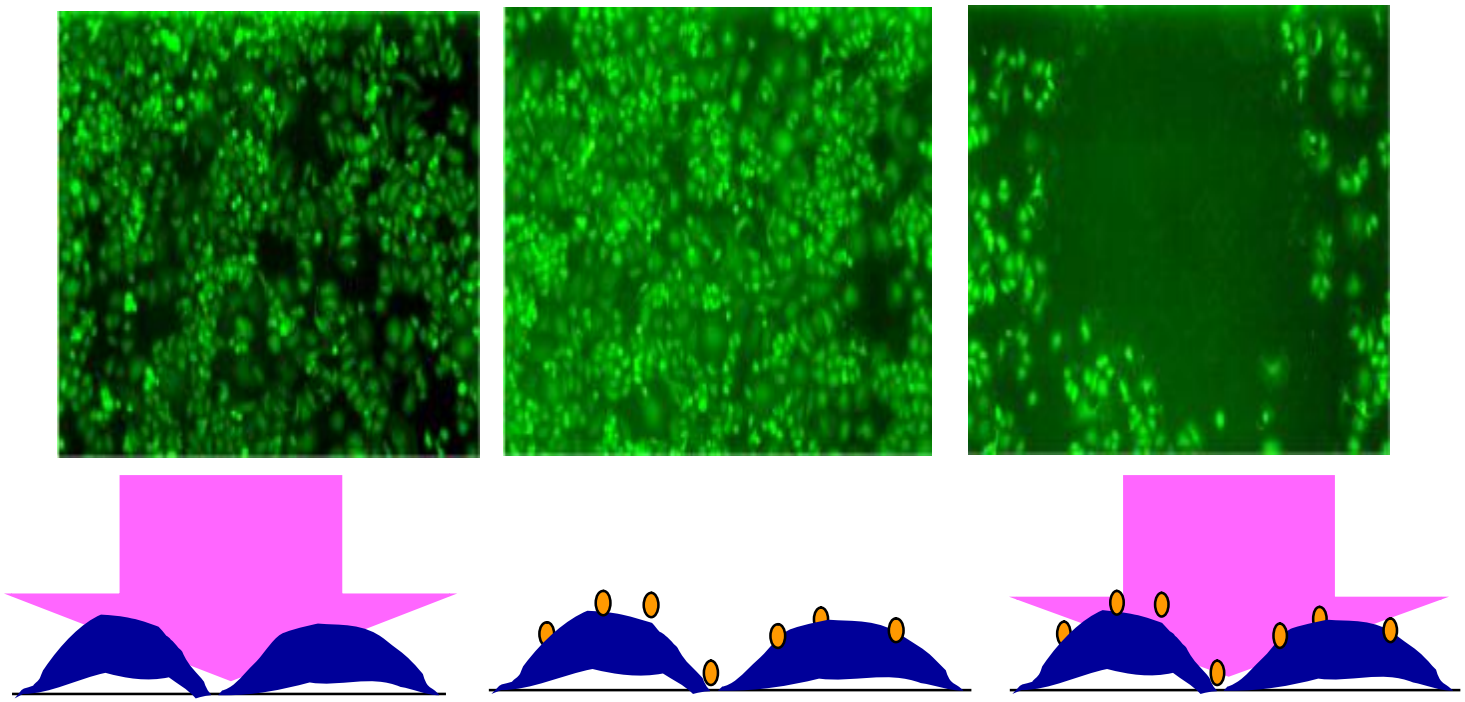
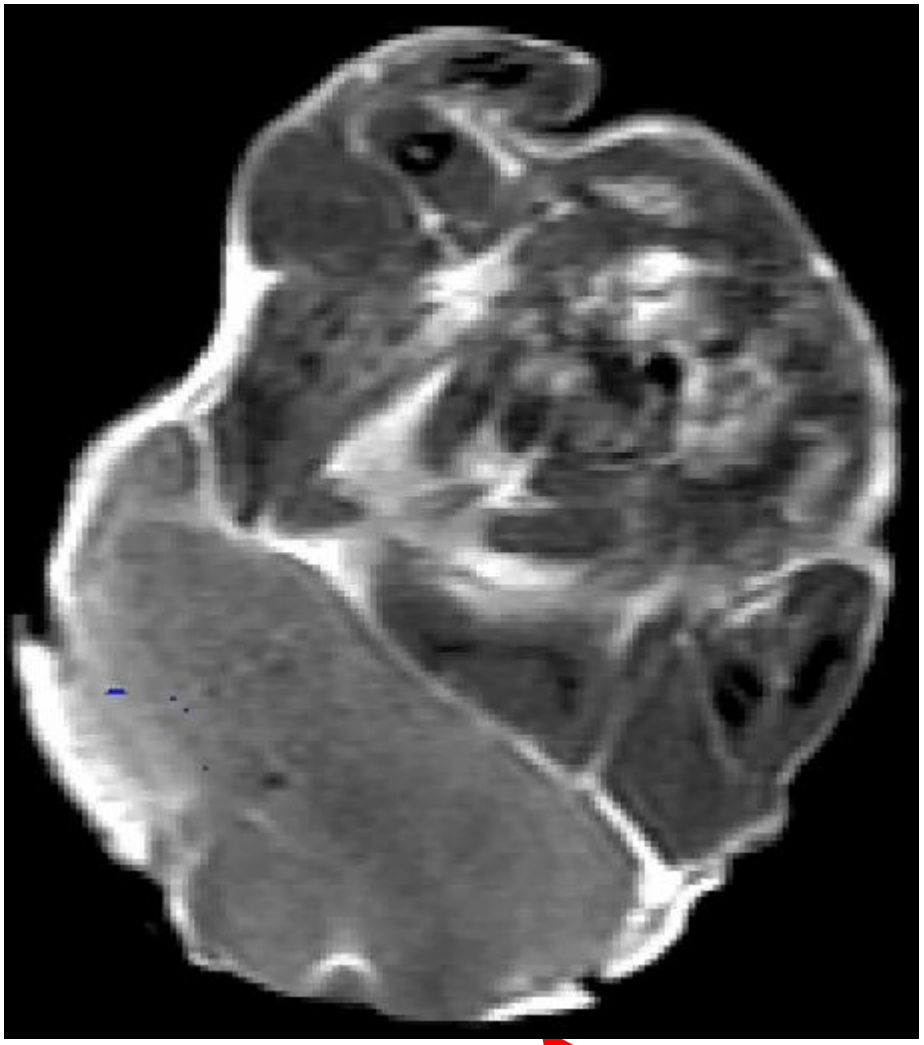
Nanoshells for Photothermal Cancer Therapy



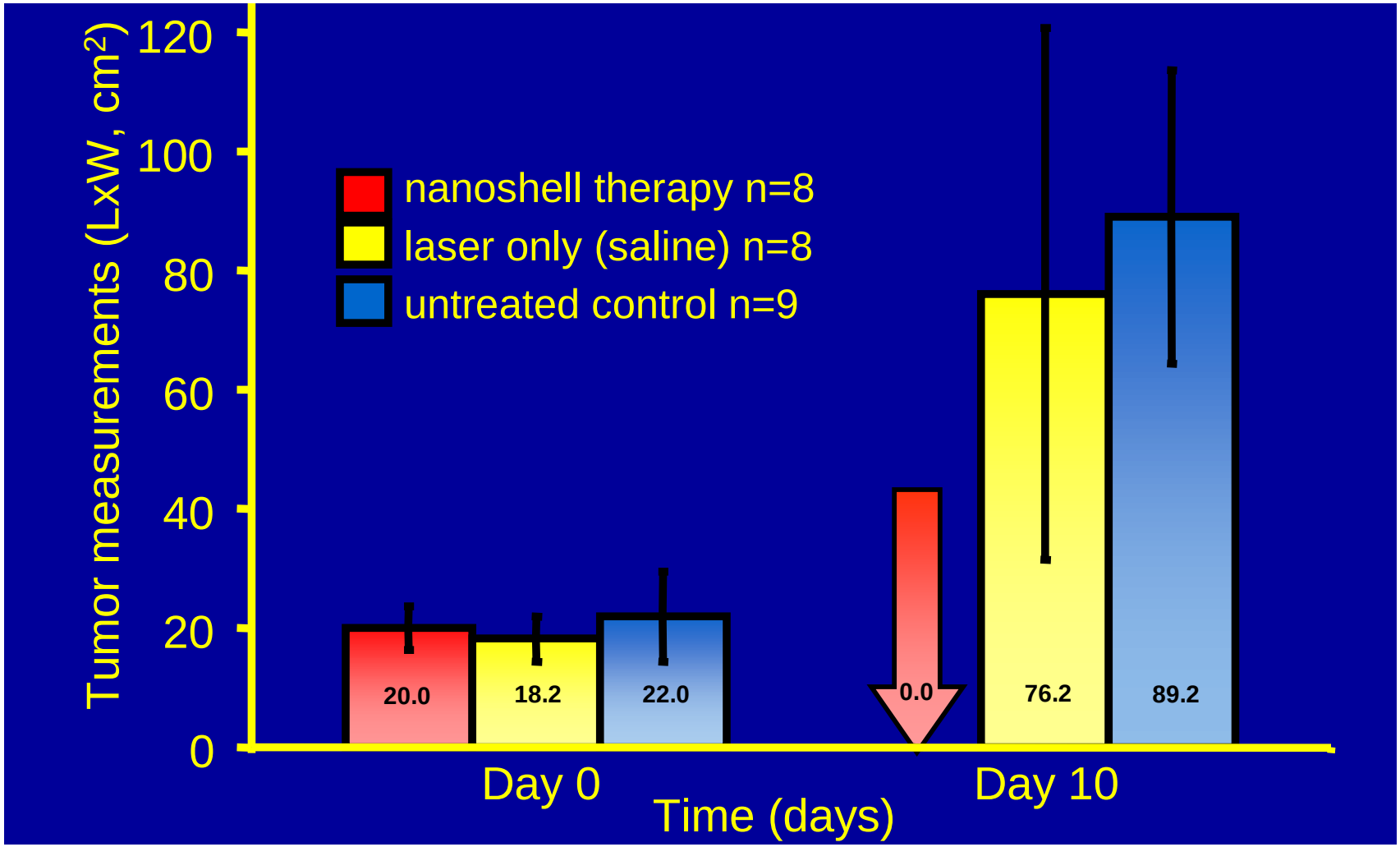
Nanoshell BNCs + near IR light =
Carcinoma cell death

Effect of Nanoshells on Mouse Tumor



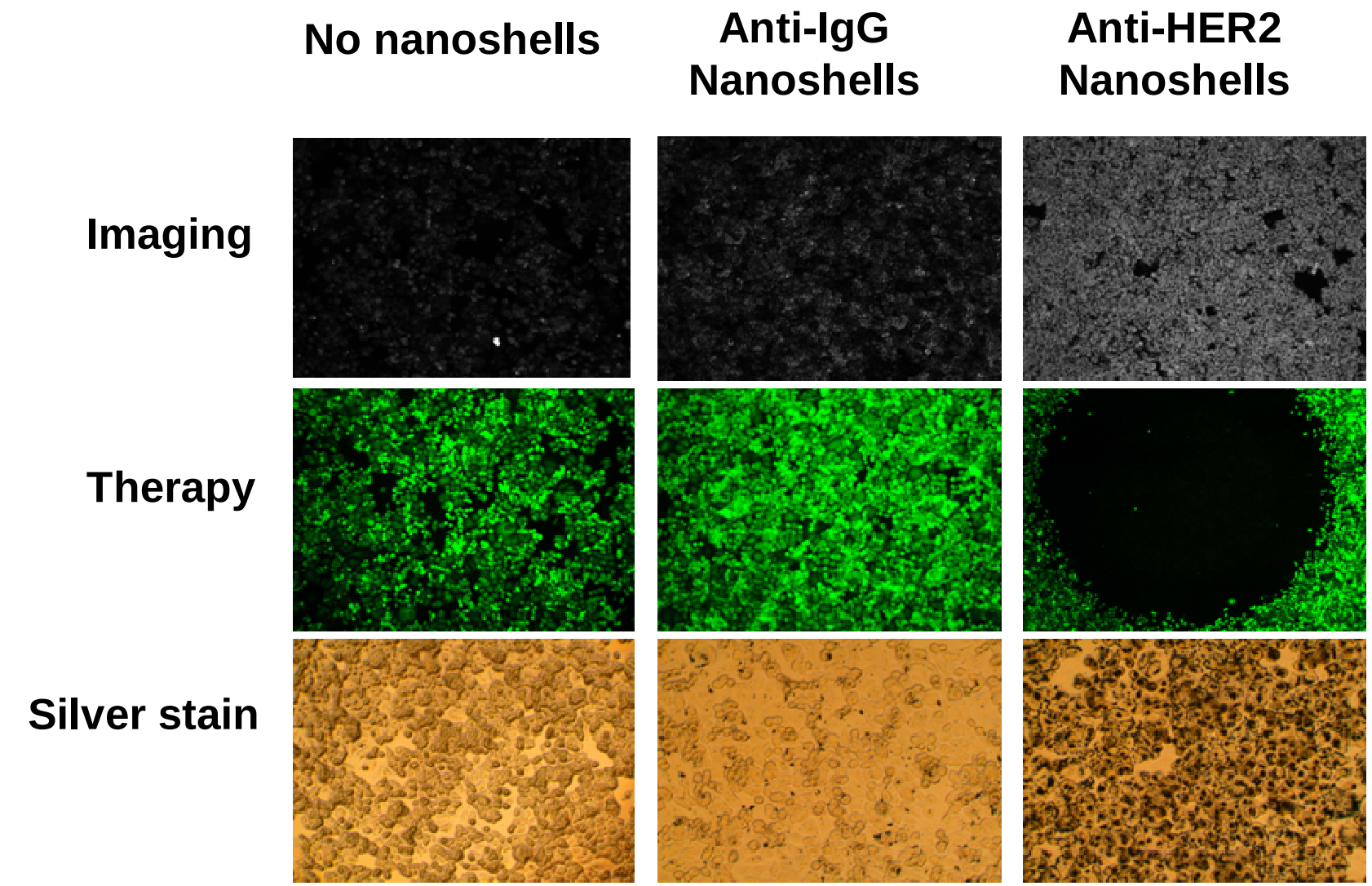
Hirsch et al, PNAS (2005).

Changes in Tumor Size



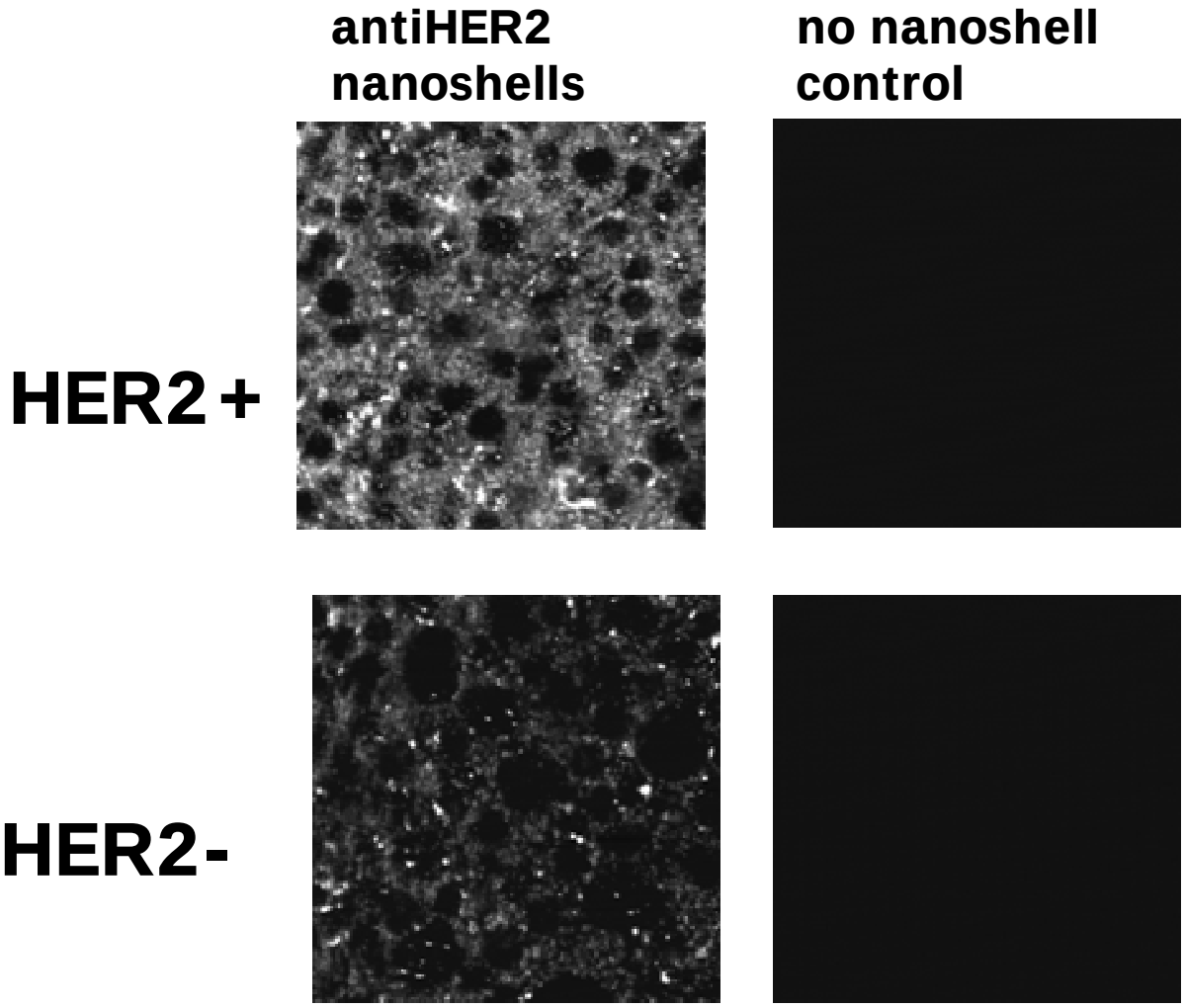
O'Neal et al, Cancer Letters 209: 171-176 (2004).

Nanoshells for Dual Imaging/Therapy



Loo et al, NanoLetters (2005)

Real-Time NIR RCM Molecular Imaging Using Nanoengineered Contrast Agents



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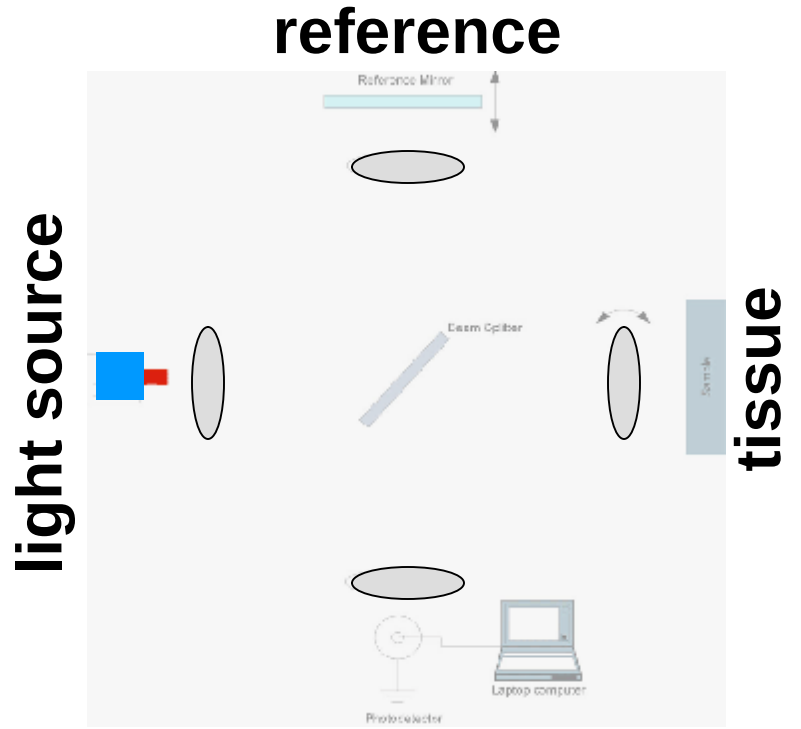
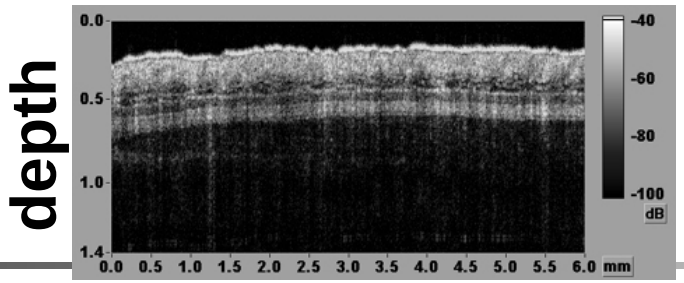
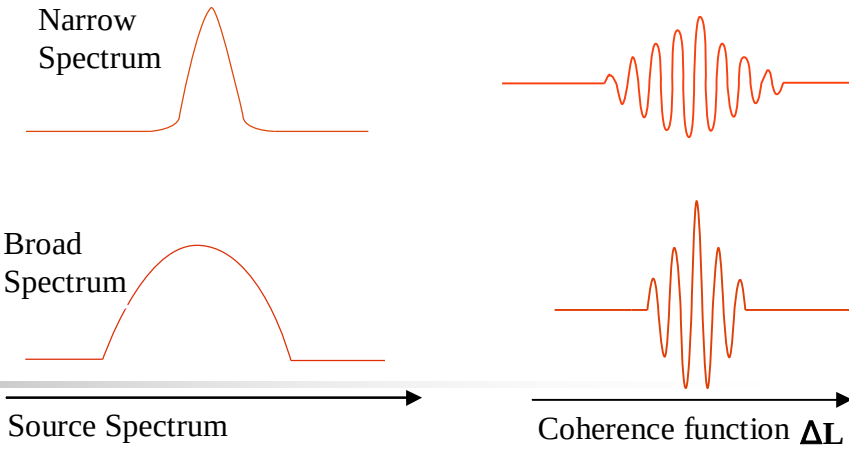
Optical Coherence Tomography

- A biomedical imaging technique that uses backreflected infrared light to perform *in situ* cross sectional imaging.
- Analogous to ultrasound B-mode imaging.
- Based on fiber optics and readily interfaced to catheters and endoscopes.
- Resolution: ~10-15 micron







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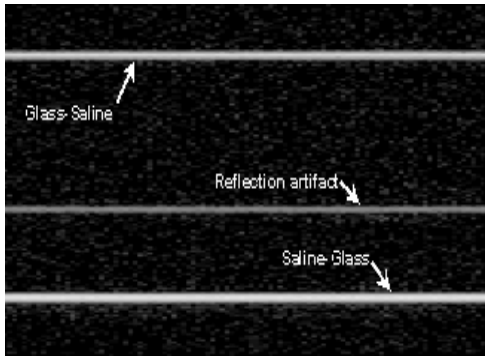
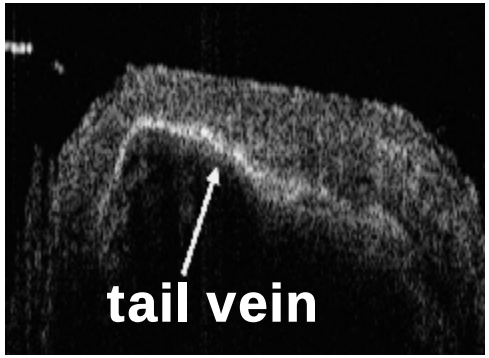
Nanoshells: Scattering Contrast Agents for OCT Imaging

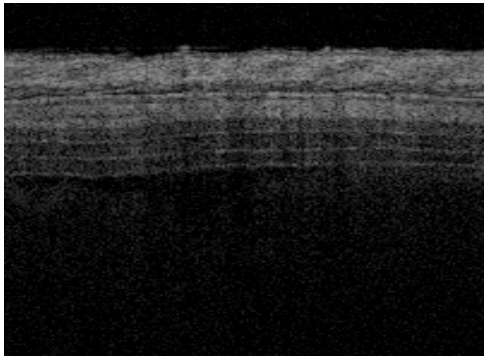
With Water



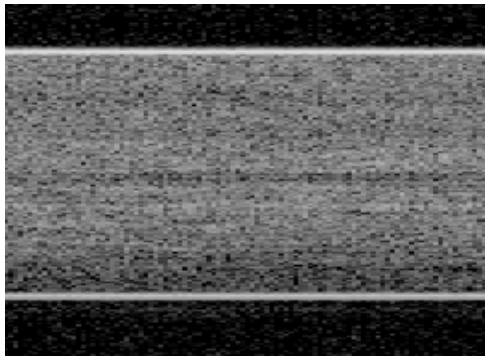
Tail Vein Injection



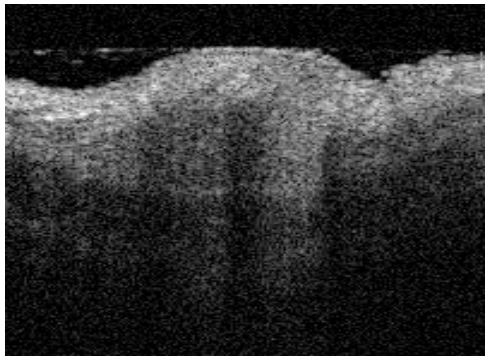
Mouse: Normal Tissue



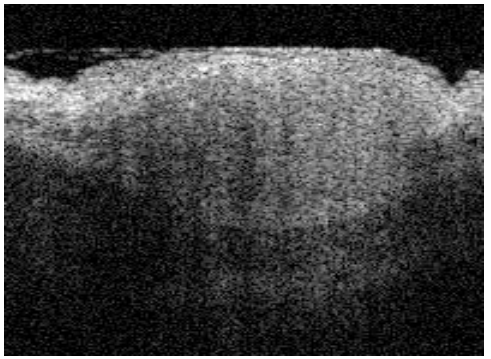
With Nanoshells (NS)



Mouse: Tumor (+NS)



Mouse: Tumor (+NS)



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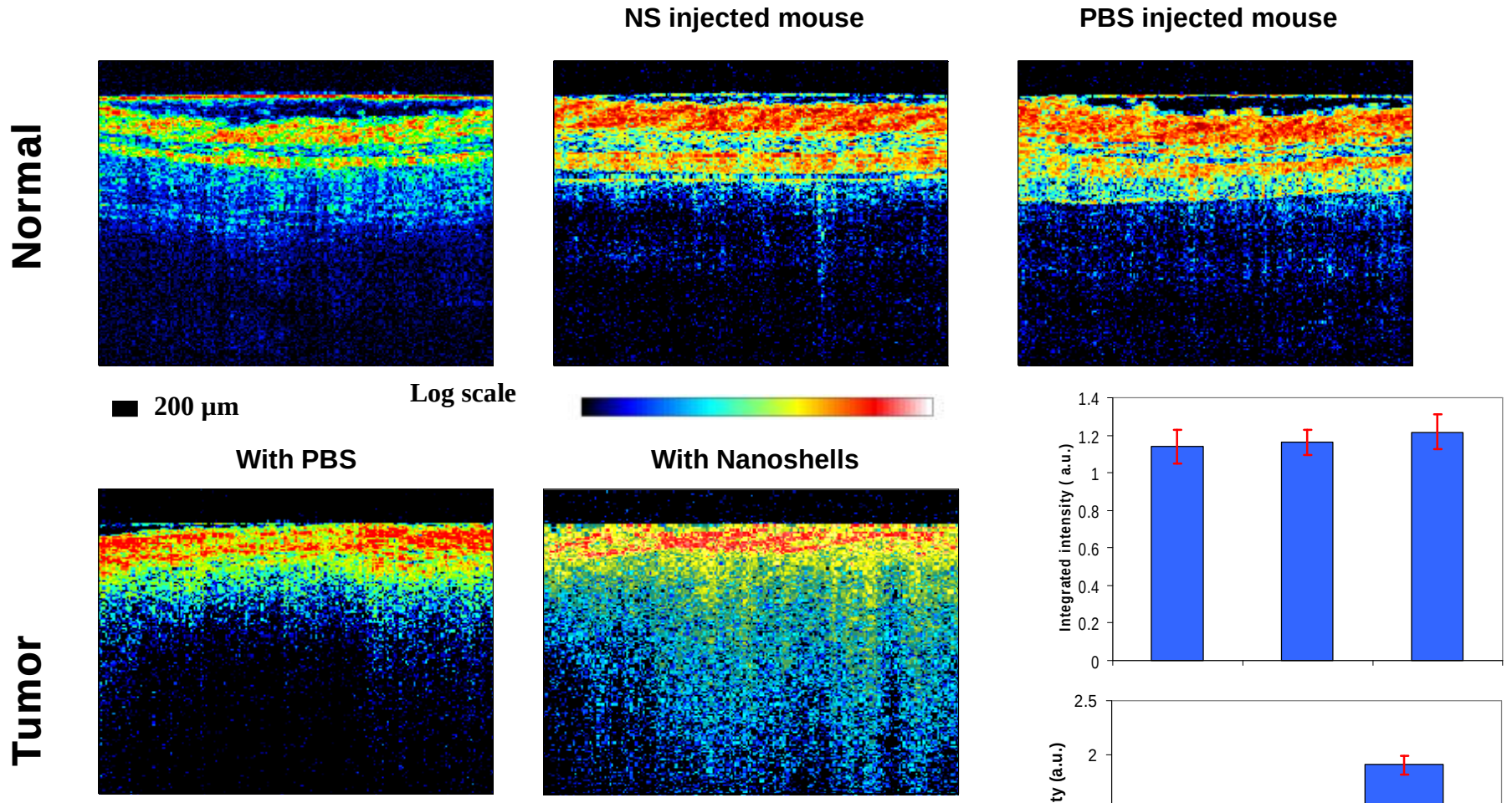
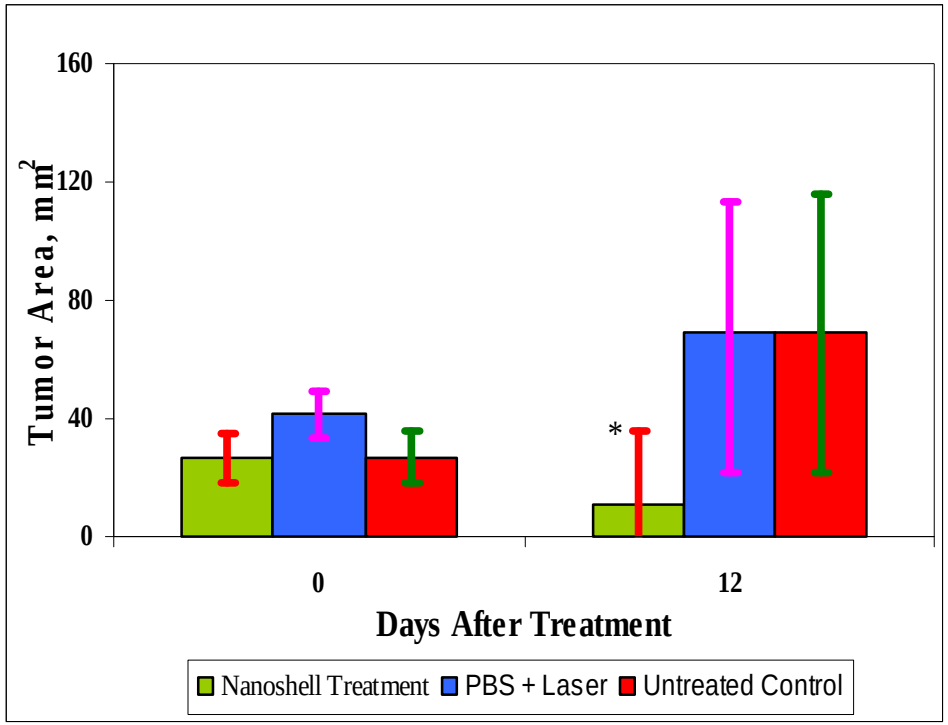
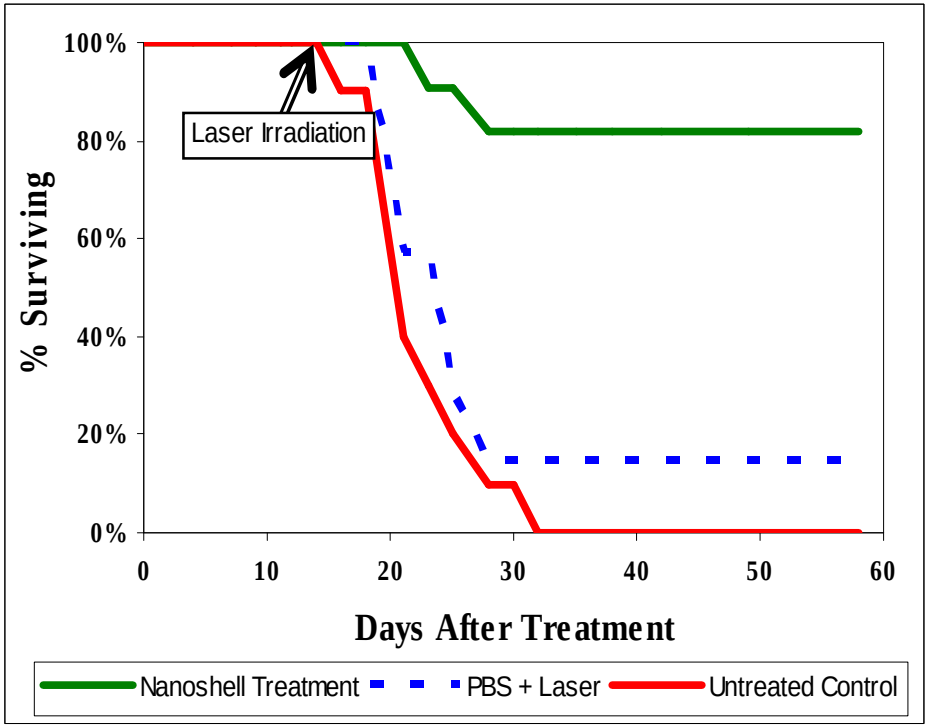
“See and Treat” Proof-of-Principle

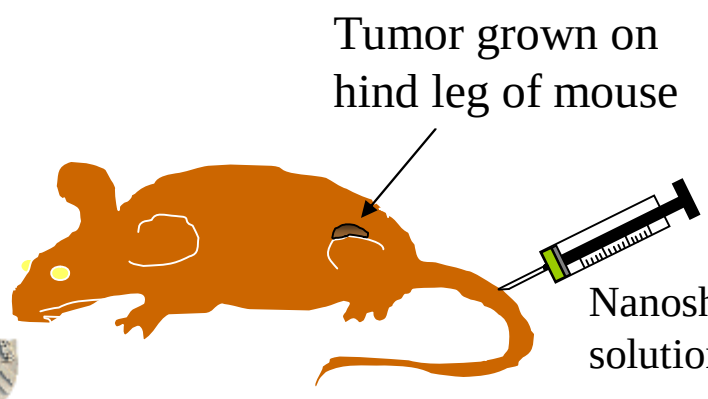


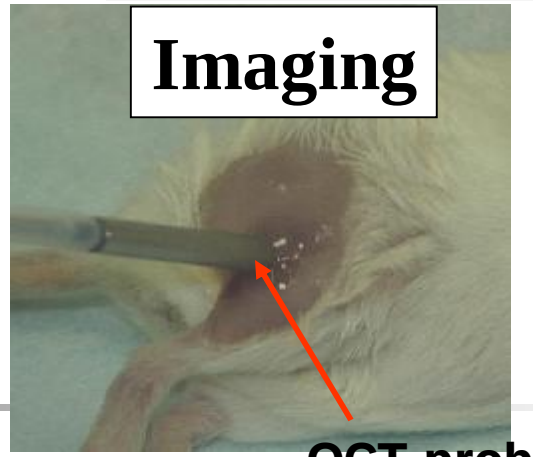
- BALB/c mice innoculated with CT-26 tumor cell line
- Tumor injection with 20-50 µl of nanoshells (PEGylated, 3E6)
- OCT imaging performed; treatment at 4 W/cm^2

In Vivo Dual Imaging/Therapy









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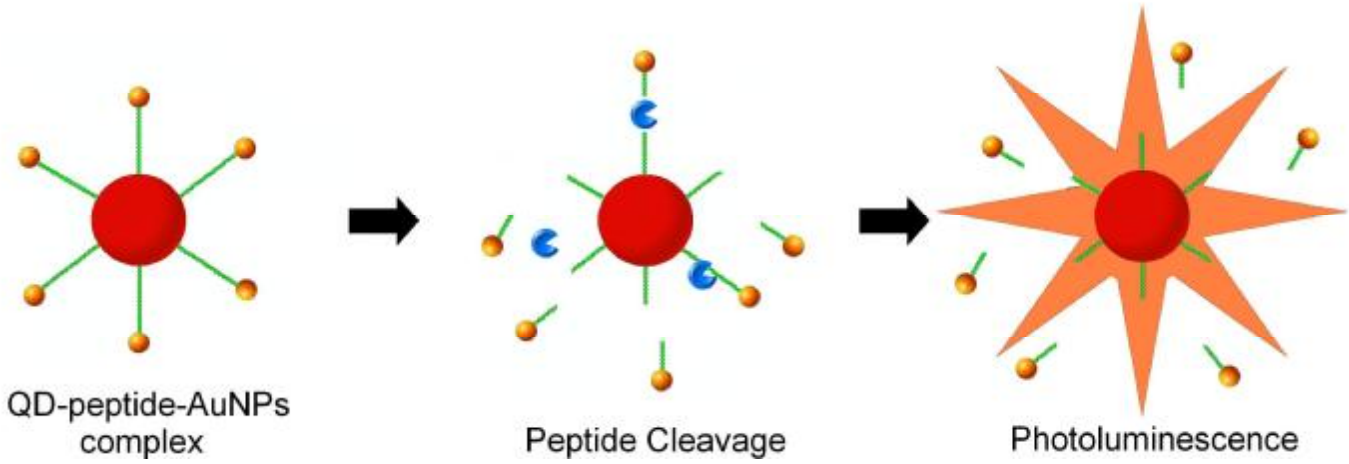
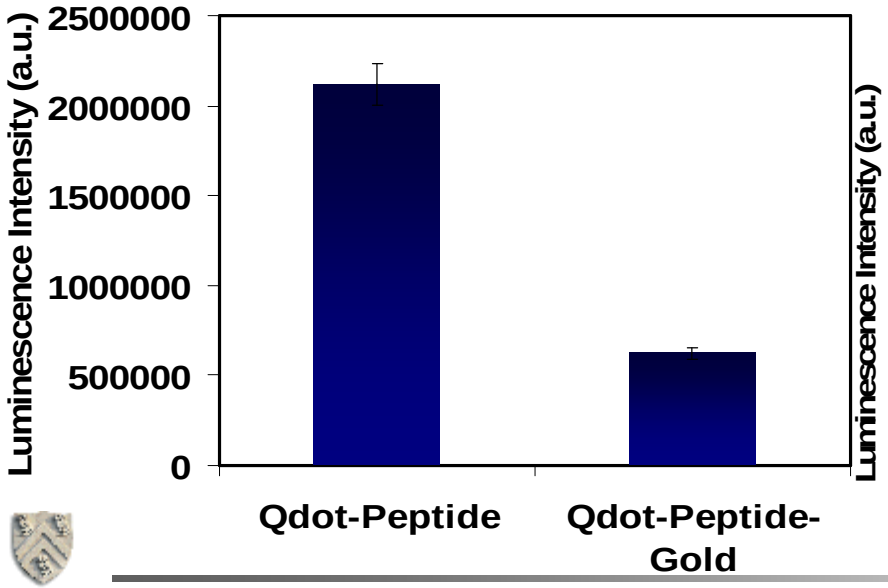
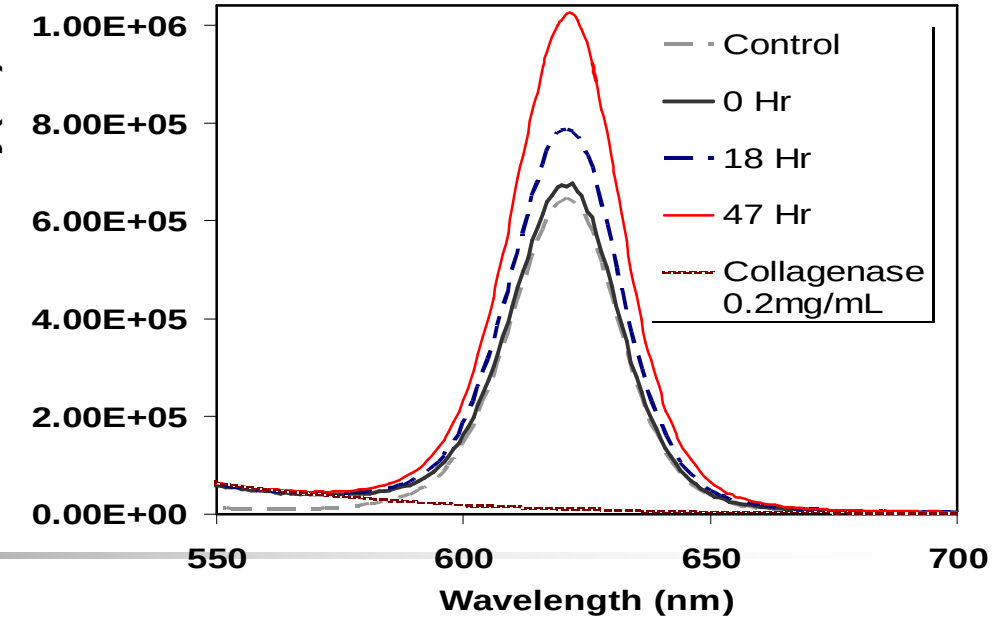
Drezek and West Labs

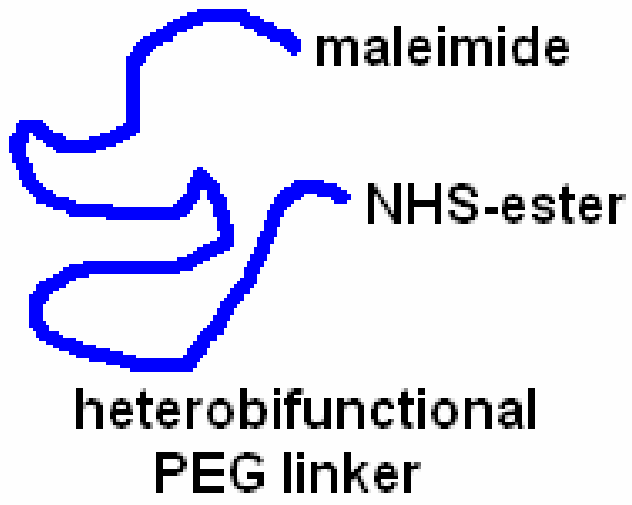
Protease-Activated Qdot Probes

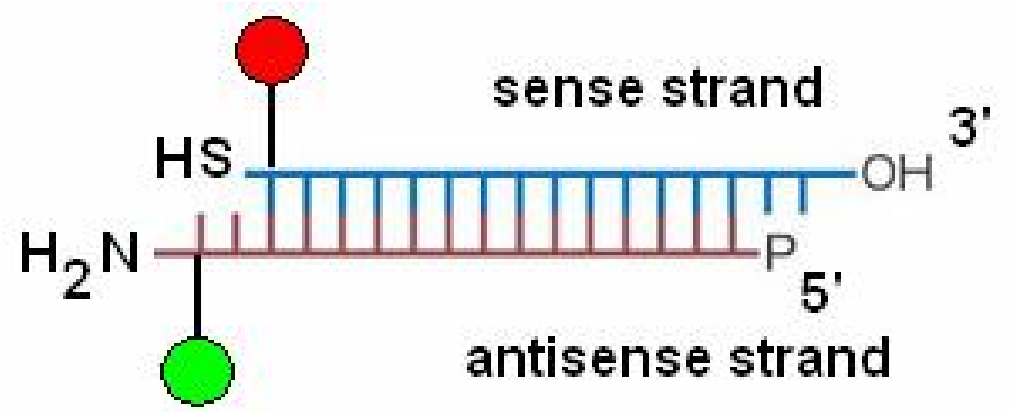






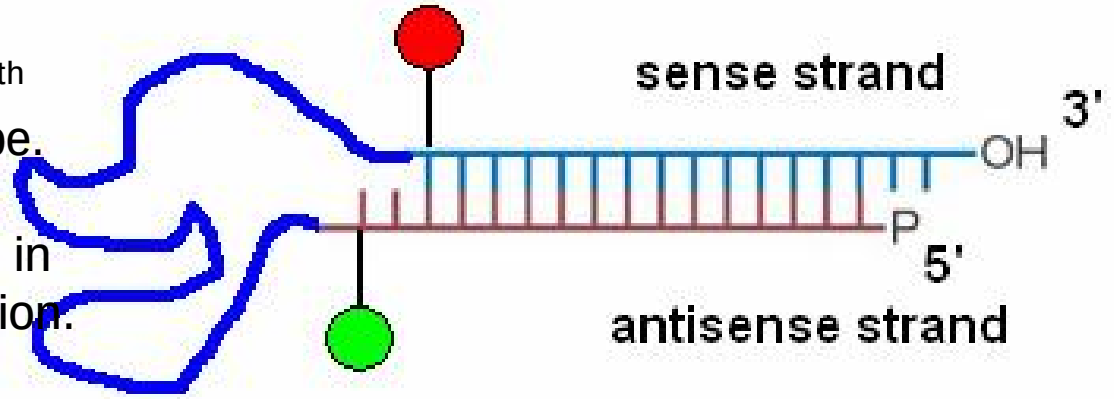
Can We Design a Probe Activated in Presence of Telomerase mRNA?





Use 2 21 nucleotide complementary strands as stem and covalently linked PEG as loop of molecular beacon.

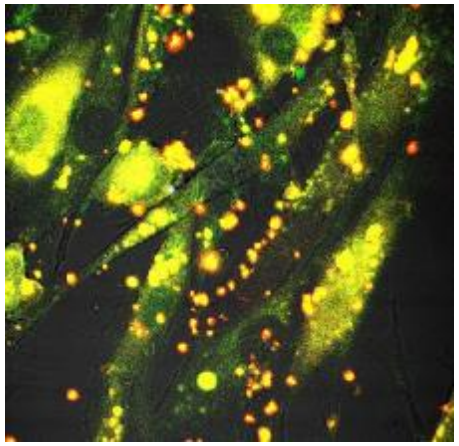
After siRNA probe incorporates into RISC, anti-guide strand cleaves at 9th position leaving 9 bp molecular probe. presence of complementary mRNA displaces anti-guide strand resulting in activation of probe for mRNA detection.

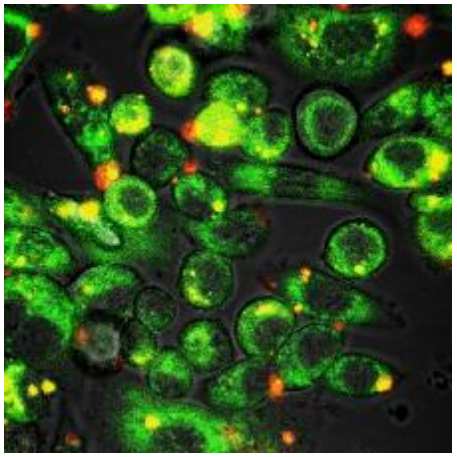


Can We Image/Silence Telomerase?

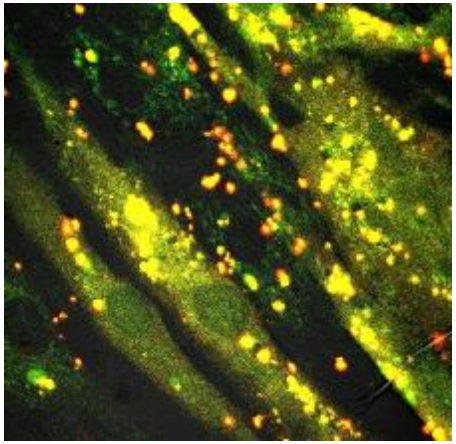
CCD-1059Sk Normal Cells **SK-BR-3 Cancer Cells**

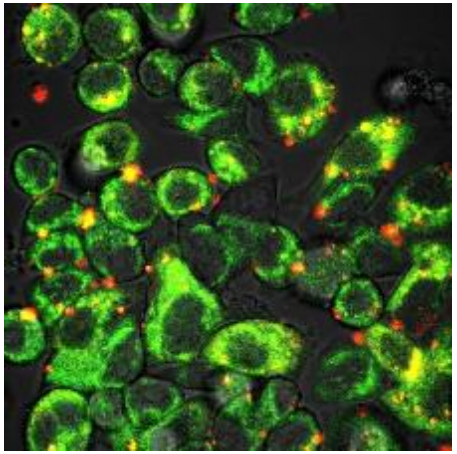
3400 MW siRNA Probe at 10 hr

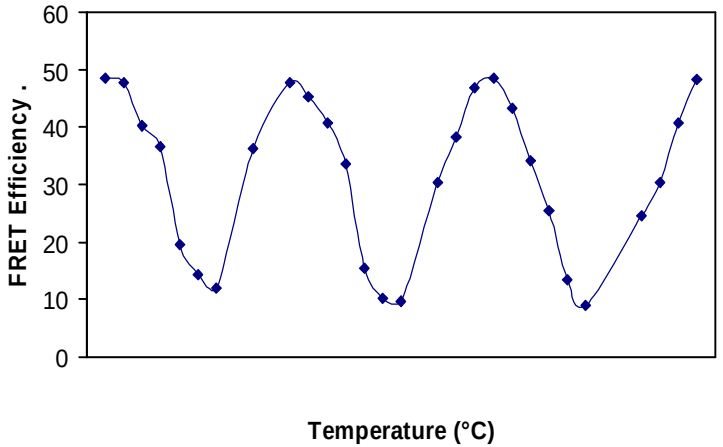


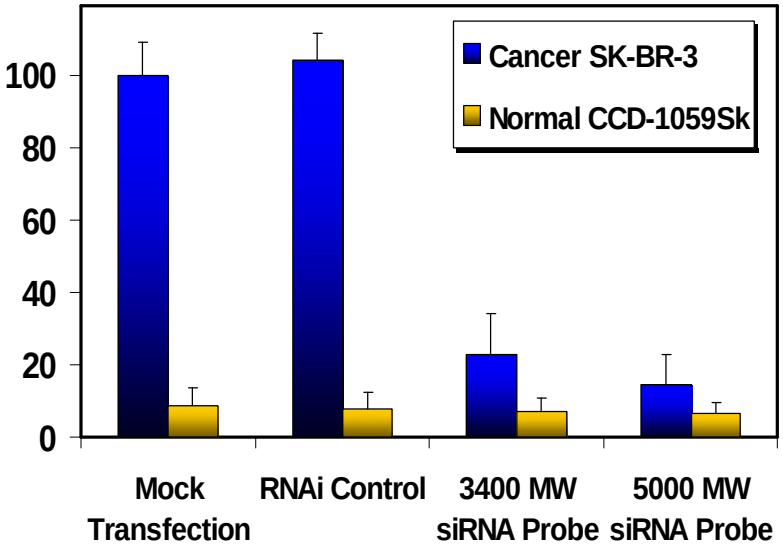


5000 MW siRNA Probe at 14 hr









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Methods to Assess New Technologies: Littenberg Model

Biologic Plausibility

Does the biology support the technology?

Technical Feasibility

Can we safely and reliably deliver technology to the patients?

Intermediate Outcomes

Sensitivity and specificity in a relevant population

Patient Outcomes

Does the technology improve the patient's health?

Societal Outcomes

Cost and ethical implications of the technology

Three Ps: Patient, Provider, Payee

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Littenberg B. Technology Assessment in Medicine. Academic Med 67:424, 1992

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CNST
Center for Nanoscale Science and Technology
Smalley/Curl Innovation Fund

Department of Defense
DOD Congressionally Directed Medical Research Program

MIRTHE
Johns Hopkins University · Rice · Princeton · The City College of New York · UMBC

The Welch Foundation

Rice IBB
Institute of Biosciences and Bioengineering

Questions?