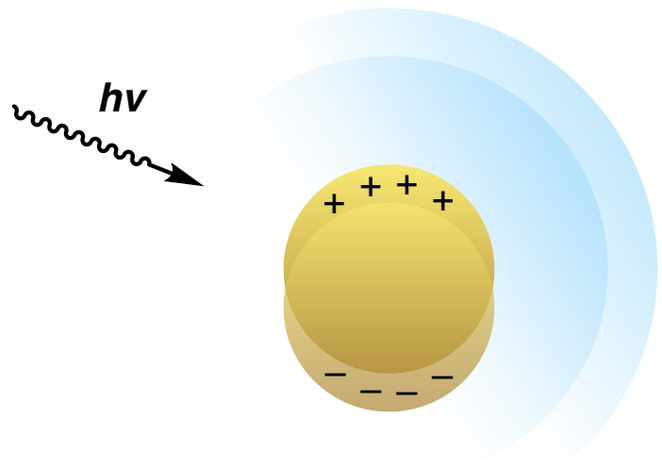
Plasmonic Gold Nanoparticles as Theranostic Agents



Agustin Millet

MacMillan Group

May 27, 2020

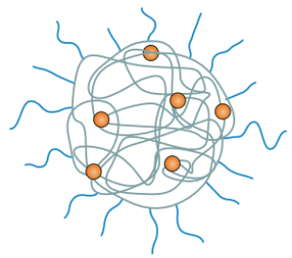
Outline

Theranostics

Definitions

The EPR effect

Most common theranostic agents

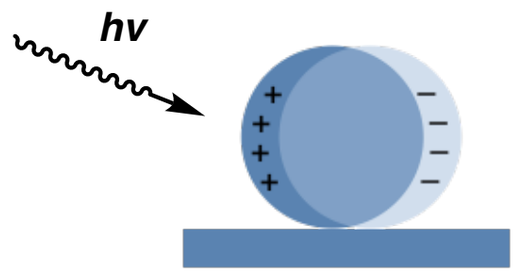


Plasmonic Resonance

History

Absorption cross-section

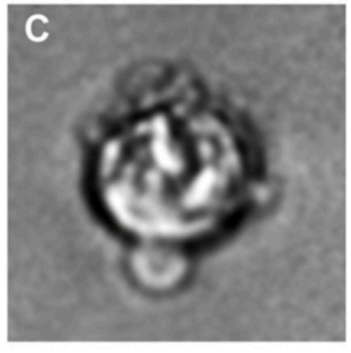
Plasmonic resonance as a function of shape, size, aggregation, and composition



Plasmonic Gold Nanoparticles in vivo

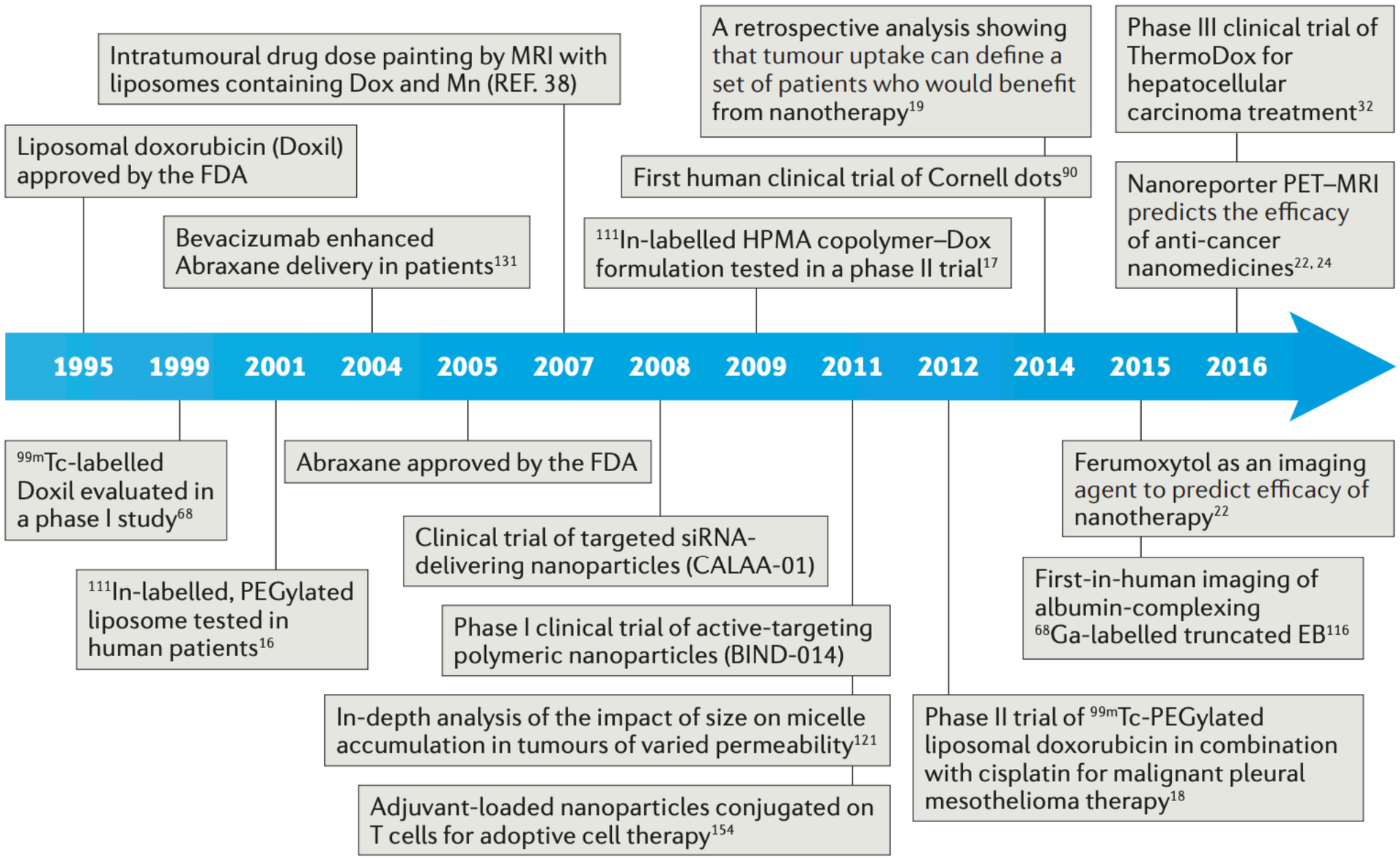
Development of a theranostic in vivo model

Plasmonic nanobubble-guided surgery



Nanotheranostics

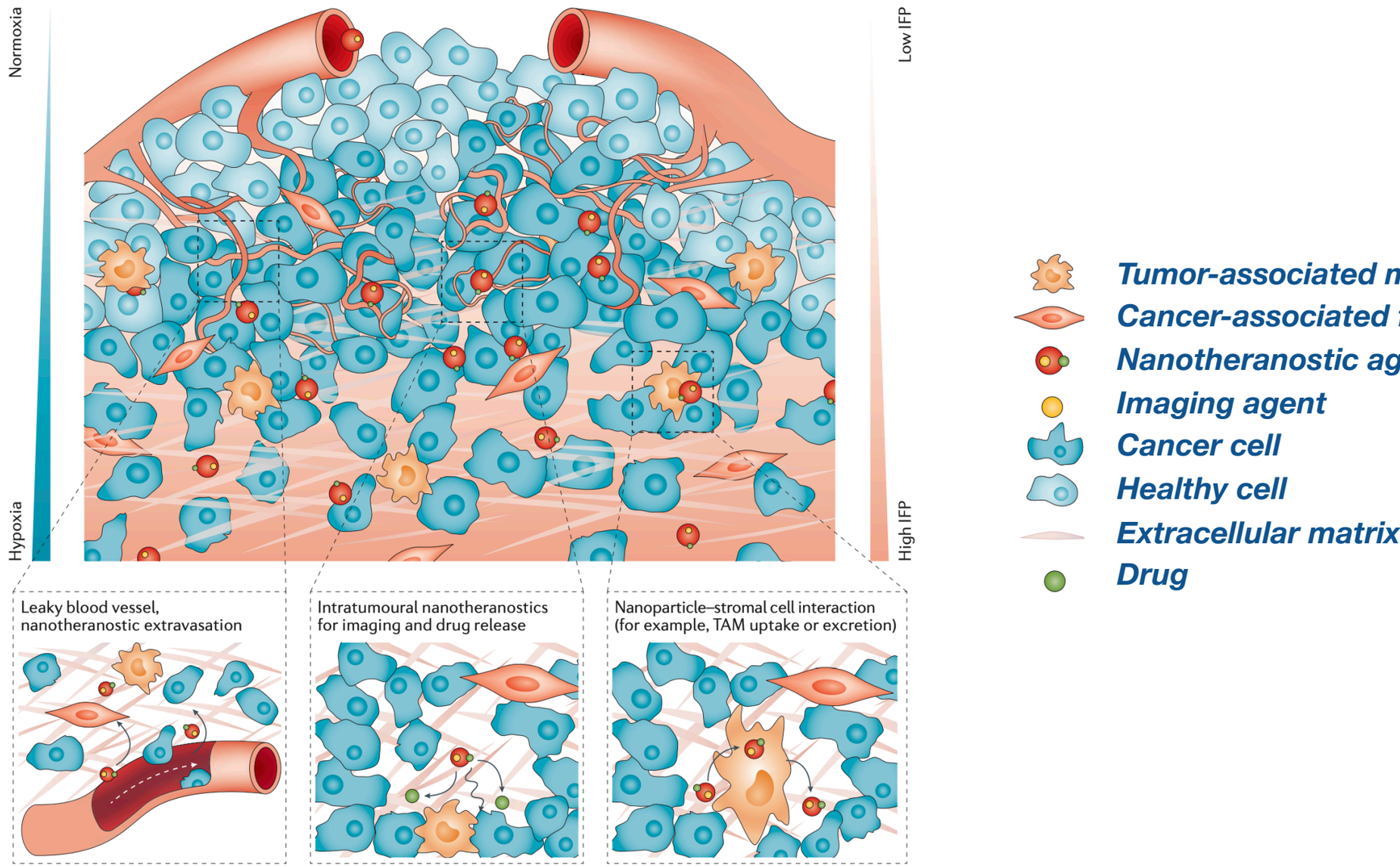
anatomy of a nanotheranostic agent



Chen, H. et al. *Nat Rev Mater*, **2017**, 2, 17024.

Nanotheranostics

the EPR effect



the average tumour uptake of nanoparticles is only 0.7% of the injected dose

Wilhelm, S. e al. *Nat. Rev. Mater.* **2016**, *1*, 16014.

Chen, H. et al. *Nat Rev Mater*, **2017**, 2, 17024.

Nanotheranostics

enhancement of the EPR effect

engineering nanoparticles

small NPs

NP shrinkage

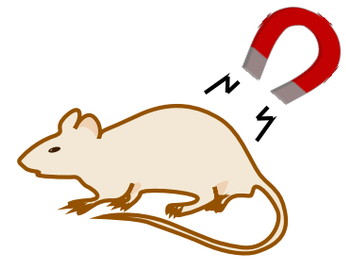
stimulus

tumor penetration

NP expansion

stimulus

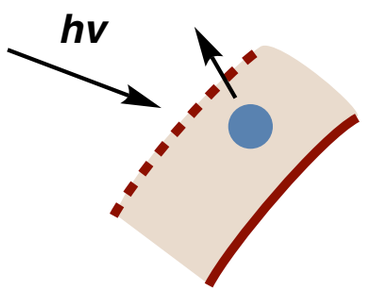
magnetic guidance



tumor retention

modulating tumor microenvironment

PDT/ultrasound



increase blood vessel leakiness

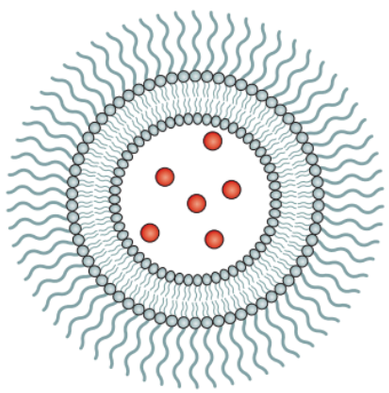
radiotherapy/immunotherapy

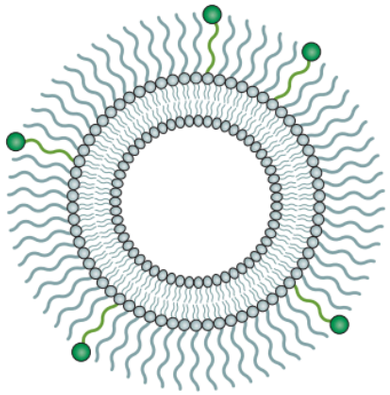
kill perivascular cancer cells

Chen, H. et al. *Nat Rev Mater*, **2017**, 2, 17024.

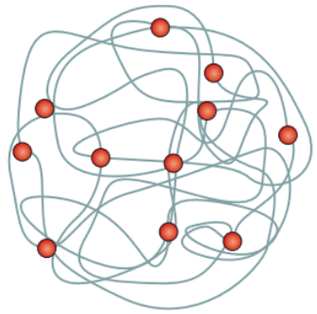
Nanotheranostics

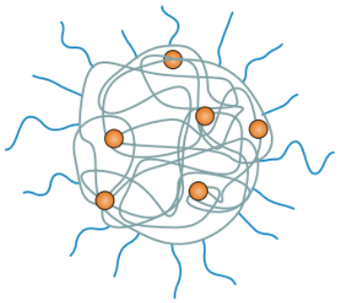
anatomy of a nanotheranostic agent



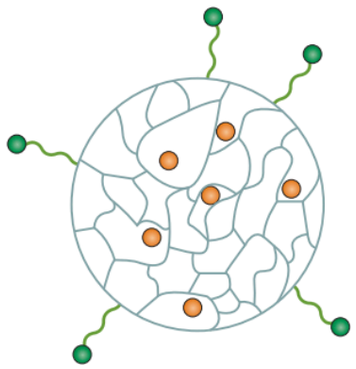


liposomes

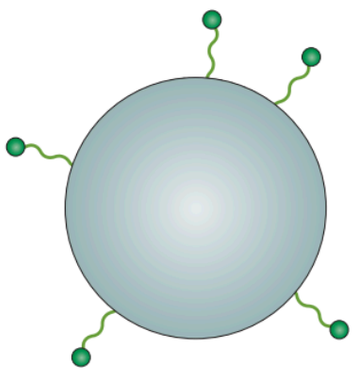


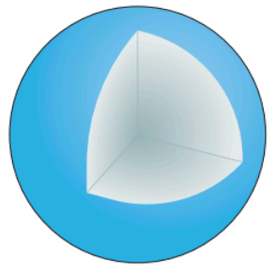


polymers



PLGA





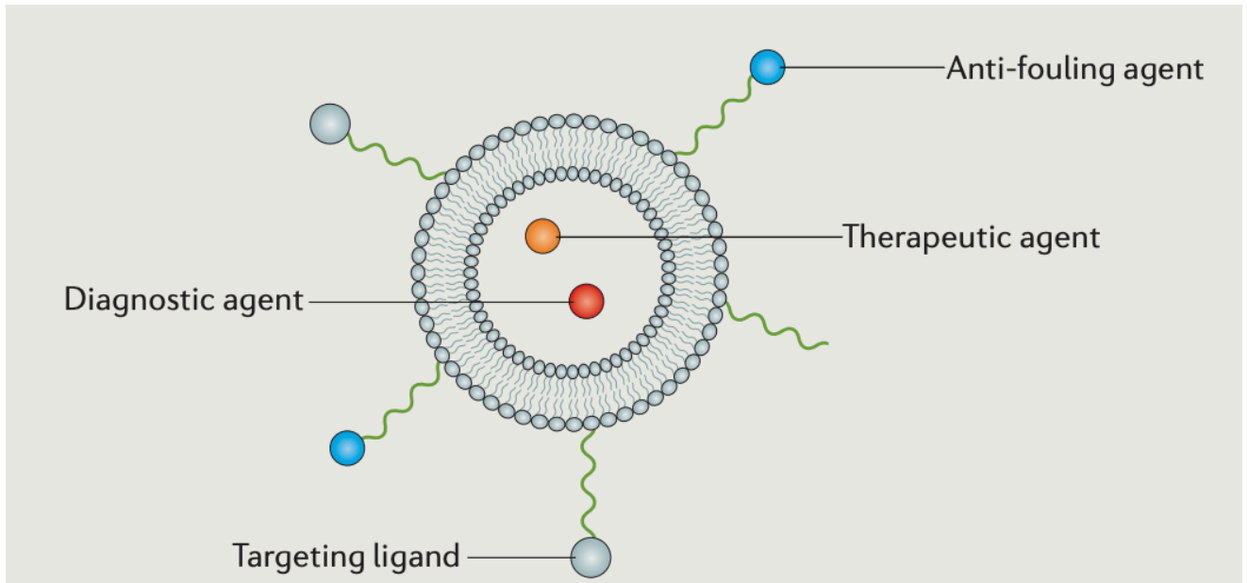
inorganic materials

Fluorophore Radioisotope MRI mediator

Chen, H. et al. *Nat Rev Mater*, **2017**, 2, 17024.

Nanotheranostics

anatomy of a nanotheranostic agent



Diagnostic agents

- Positron emission tomography: ^{64}Cu and ^{68}Ga
- Magnetic resonance imaging: Gd^{3+}, Mn^{2+}, and iron oxide nanoparticles
- Ultrasound imaging: microbubbles
- Computed tomography: I and Au
- Optical imaging: quantum dots and fluorophores
- Single-photon emission computed tomography: ^{99m}Tc and ^{123}I
- Photoacoustic imaging: Au nanostructures and porphyrin

Therapeutic agents

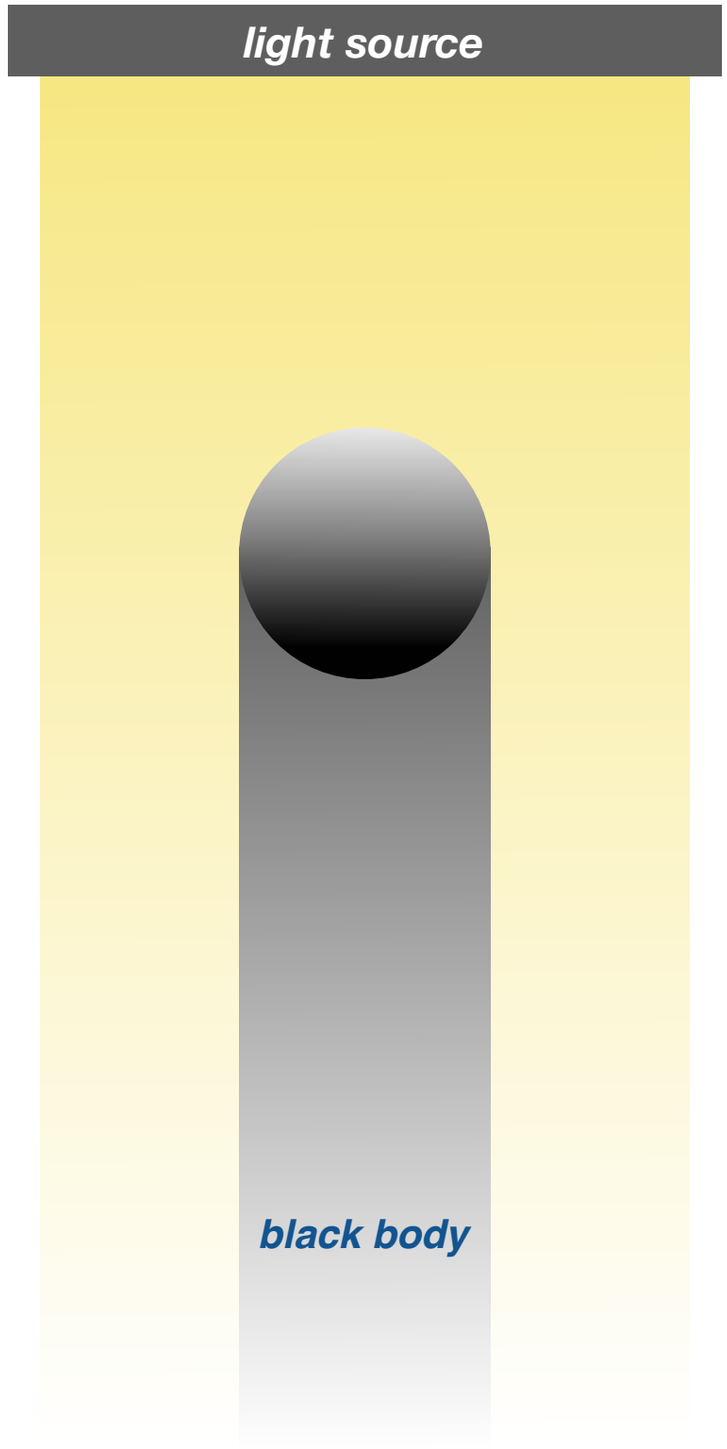
- Chemotherapy: doxorubicin and paclitaxel
- Radiation therapy: Au, Hf, and Gd
- Immunotherapy: cancer vaccines and immune checkpoint inhibitors
- Photodynamic therapy: indocyanine green
- Photothermal therapy: Au nanostructures
- Gene therapy: small interfering RNA, plasmids, and CRISPR

Chen, H. et al. *Nat Rev Mater*, **2017**, 2, 17024.

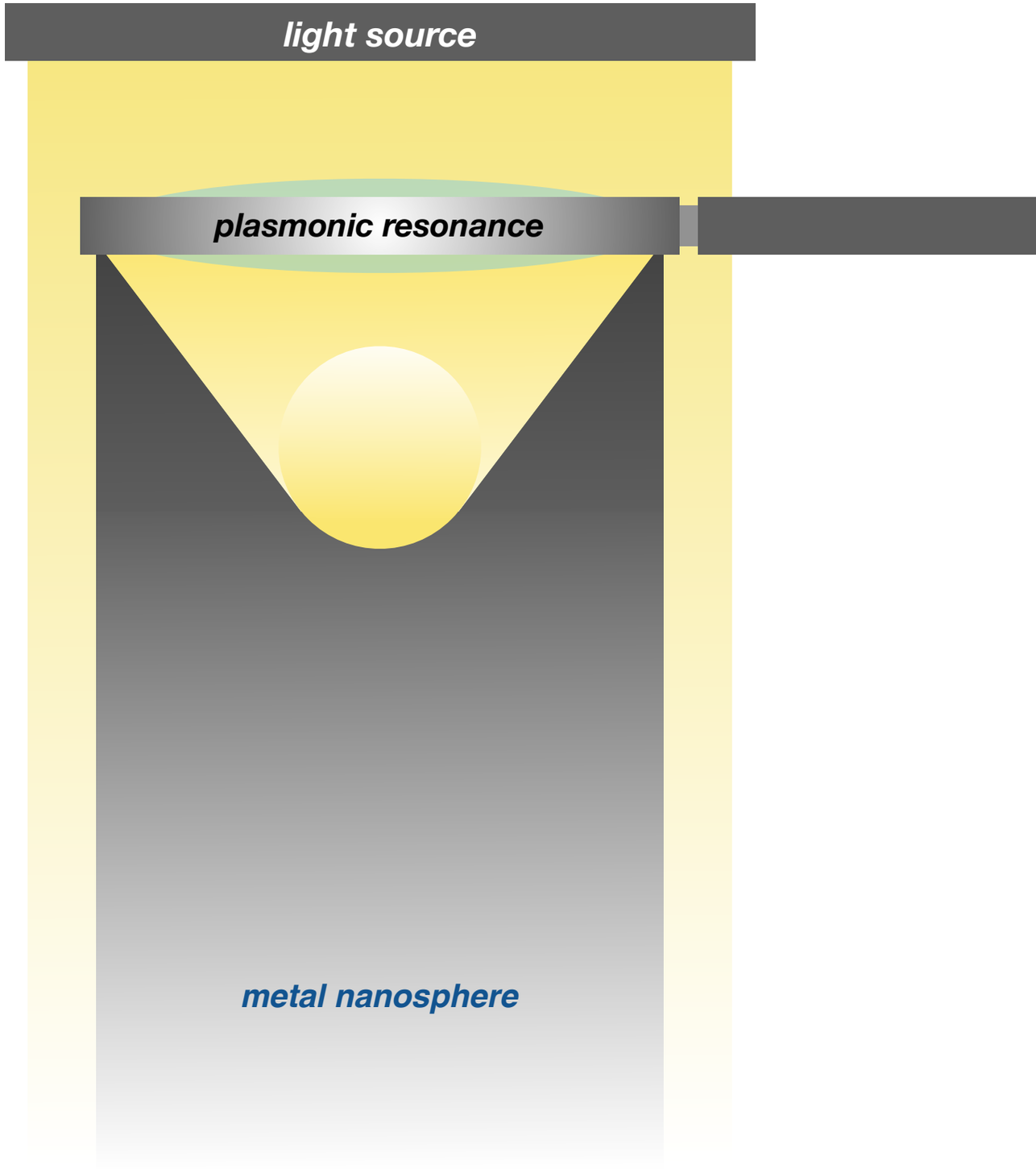
Plasmonic Nanoparticles

geometric vs optical cross-section

$\sigma_{abs} = \sigma_{geom}$



$\sigma_{abs} > \sigma_{geom}$



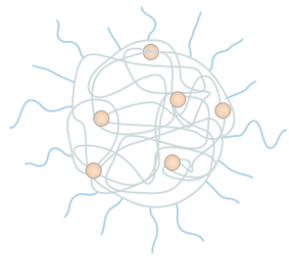
Outline

Theranostics

Definitions

The EPR effect

Most common theranostic agents

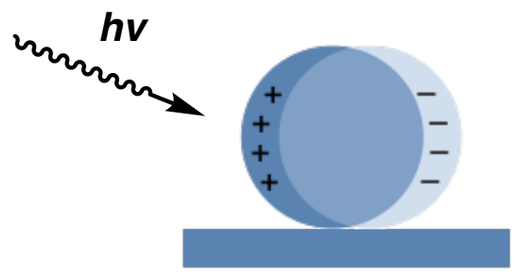


Plasmonic Resonance

History

Absorption cross-section

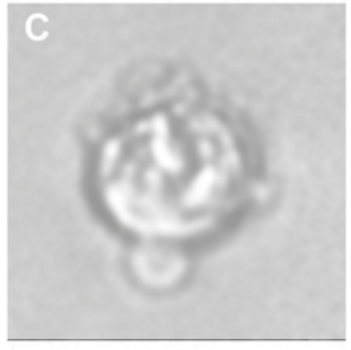
Plasmonic resonance as a function of shape, size, aggregation, and composition



Plasmonic Gold Nanoparticles in vivo

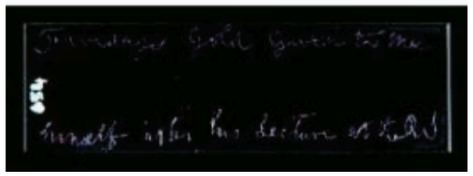
Development of a theranostic in vivo model

Plasmonic nanobubble-guided surgery



Plasmonic Nanoparticles

history

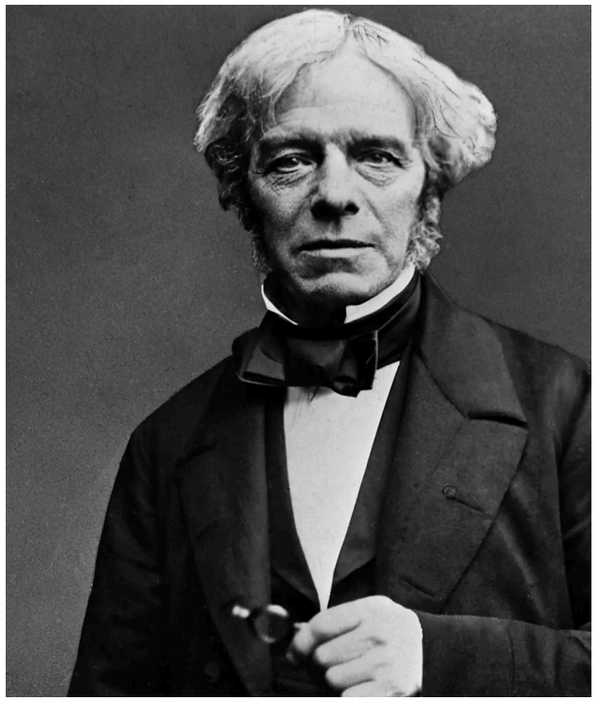


8th century BC *4th century* *17th century* *19th century*

Amendola, V. et al. *J. Phys.: Condens. Matter.* **2017**, *29,* 48.

Plasmonic Nanoparticles

history



Michael Faraday

1852: 'Experimental Relations of Gold (and Other Metals) to Light'

> ***described the Au colloid solutions as***
> ***'a beautiful ruby fluid',***
> ***and attributed the effect to***
> ***'a mere variation in the size of particles'***

Amendola, V. et al. *J. Phys.: Condens. Matter.* **2017**, *29,* 48.

Plasmonic Nanoparticles

history

1908. № 3.

ANNALEN DER PHYSIK.

VIERTE FOLGE. BAND 25.

1. *Beiträge zur Optik trüber Medien, speziell kolloidaler Metallösungen;*
von Gustav Mie.

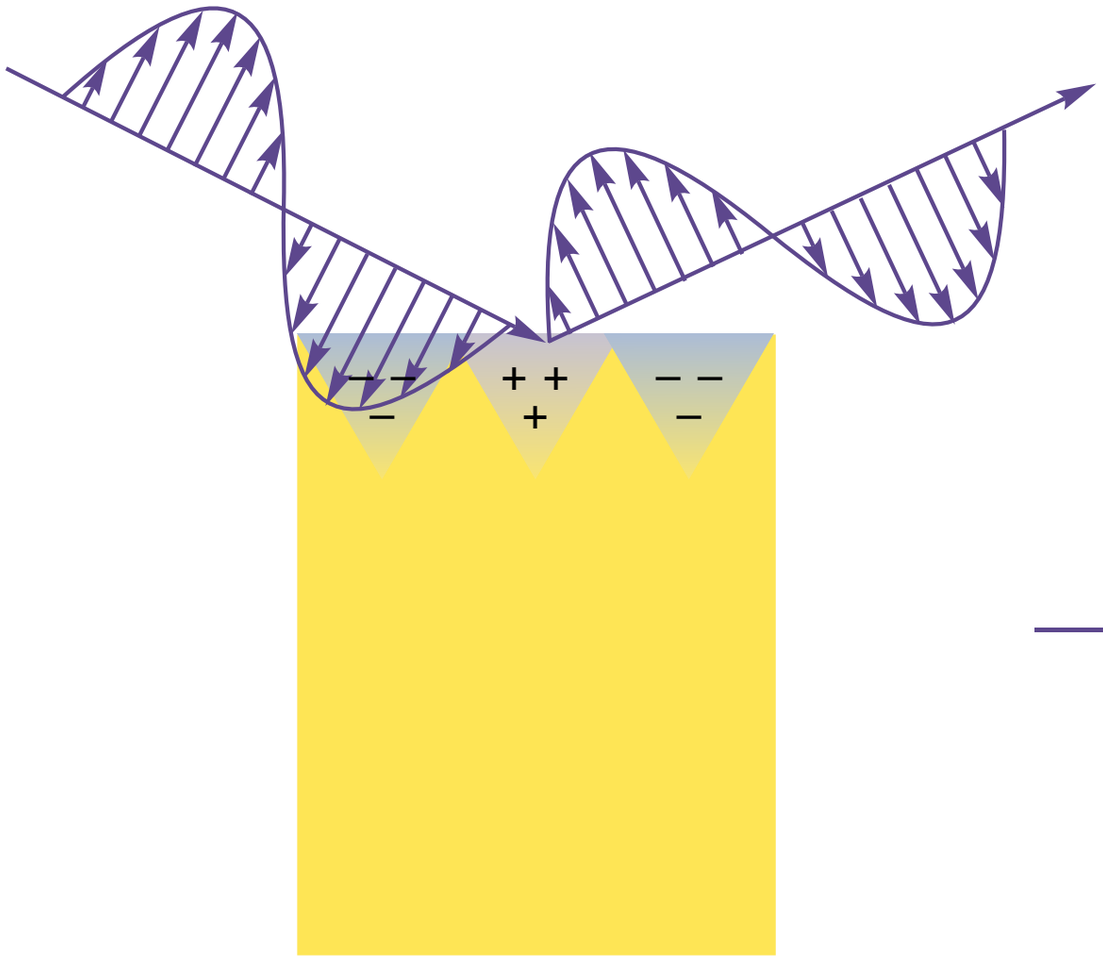
Gustav Mie

Mie theory is an exact analytic solution to Maxwell's equations for spheres with an arbitrary size

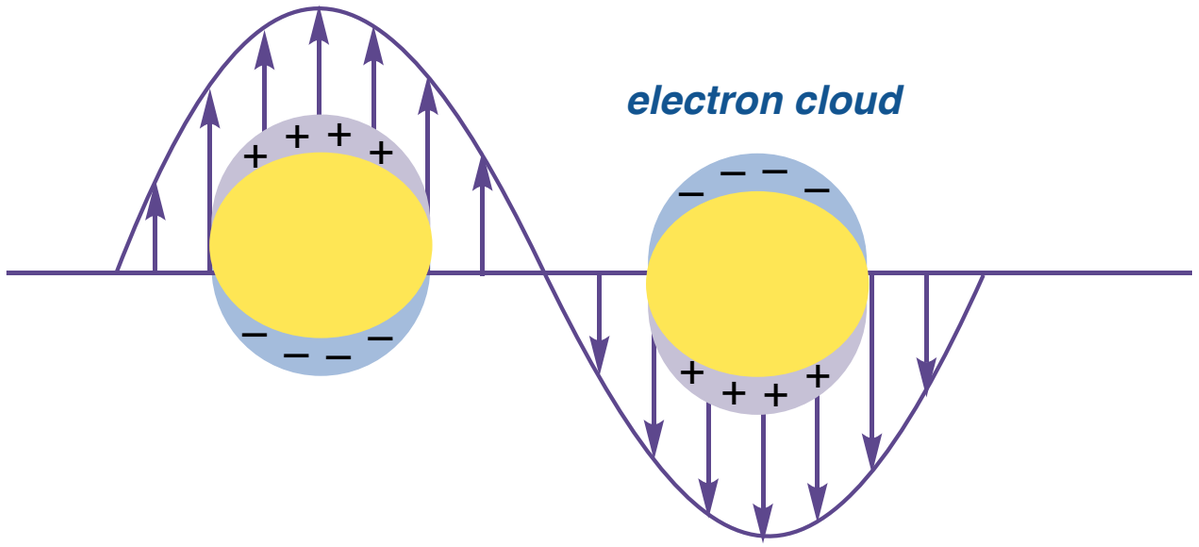
Amendola, V. et al. *J. Phys.: Condens. Matter.* **2017**, *29,* 48.

Plasmonic Nanoparticles

electronic interaction with electromagnetic field



bulk gold



metal nanospheres

Second reference - if needed Kobayashi, S. e al. *Tetrahedron* **1993***,* 1761.

First reference Cotte, M. et al. *Acc. Chem. Res.* **2010**, *43*, 705.

Plasmonic Nanoparticles

dielectric constant of noble metals

Drude's free electron model

$$\varepsilon(\omega) = 1 - \frac{{\omega_p}^2}{\omega(\omega + i\gamma_b)}$$

$$\gamma(l_{eff}) = \gamma_b + \frac{Av_F}{l_{eff}}$$

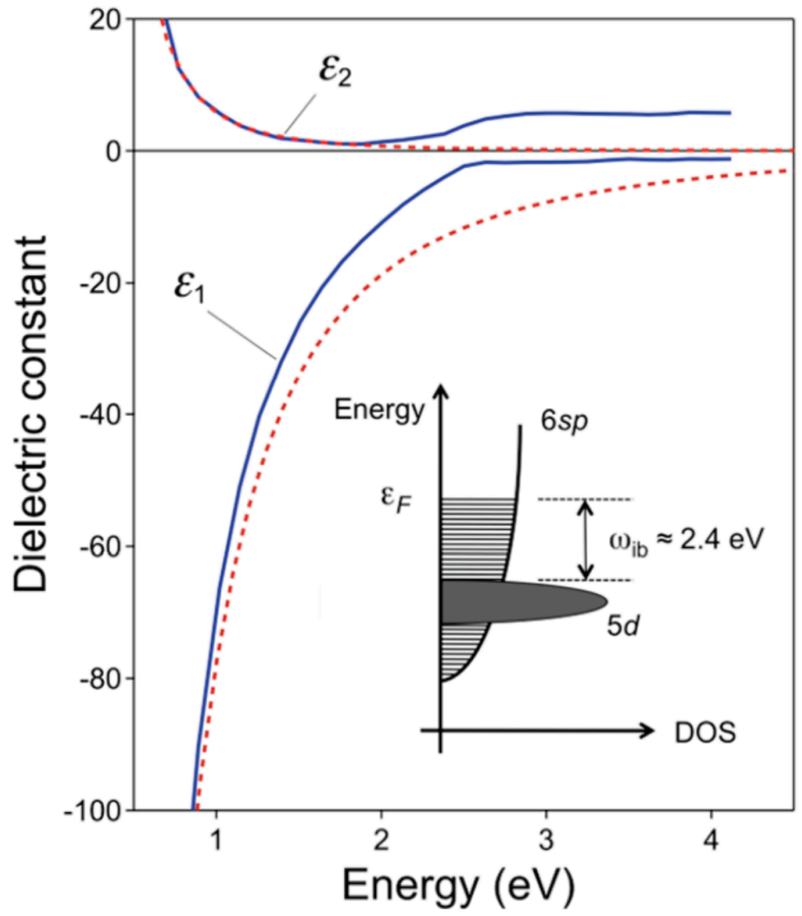
damping constant related to mean free path

4V/S

for noble metals:

$$\varepsilon(\omega) = \varepsilon^{ib}(\omega) + 1 - \frac{{\omega_p}^2}{\omega[\omega + i\gamma(l_{eff})]}$$

interband contribution (E > 55 kcal/mol)



Hartland, G. *Acc. Chem. Rev.* **2011**, *111*, 3858.

Plasmonic Nanoparticles

dielectric constant of noble metals

separating into imaginary and real components

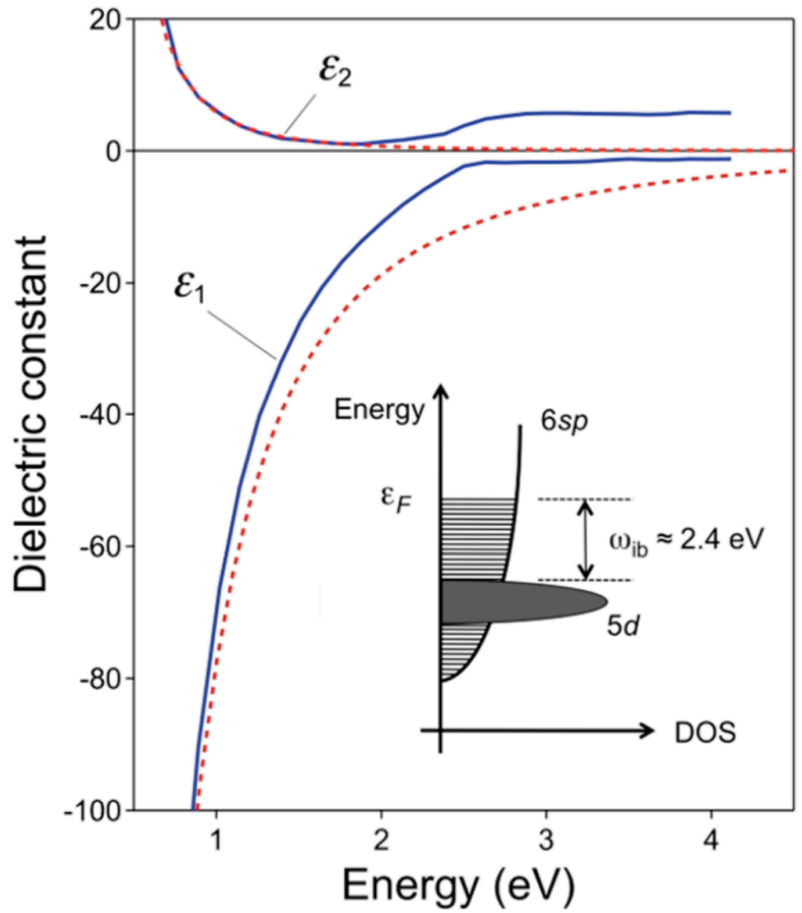
$$\omega \gg \gamma$$

$$\varepsilon_1(\omega) \approx \varepsilon_1^{\text{ib}}(\omega) + 1 - \frac{{\omega_\text{p}}^2}{\omega^2}$$ ***imaginary***

$$\varepsilon_2(\omega) \approx \varepsilon_2^{\text{ib}}(\omega) + \frac{{\omega_\text{p}}^2 \times \gamma(l_\text{eff})}{\omega^3}$$ ***real***

$$\varepsilon_1(\omega) \approx \varepsilon_1^{\text{bulk}}(\omega)$$

$$\varepsilon_2(\omega) \approx \varepsilon_2^{\text{bulk}}(\omega) + \frac{{\omega_\text{p}}^2}{\omega^3} \times \frac{A v_\text{F}}{l_\text{eff}}$$



Hartland, G. *Acc. Chem. Rev.* **2011**, *111*, 3858.

Plasmonic Nanoparticles

absorption cross-section of GNPs

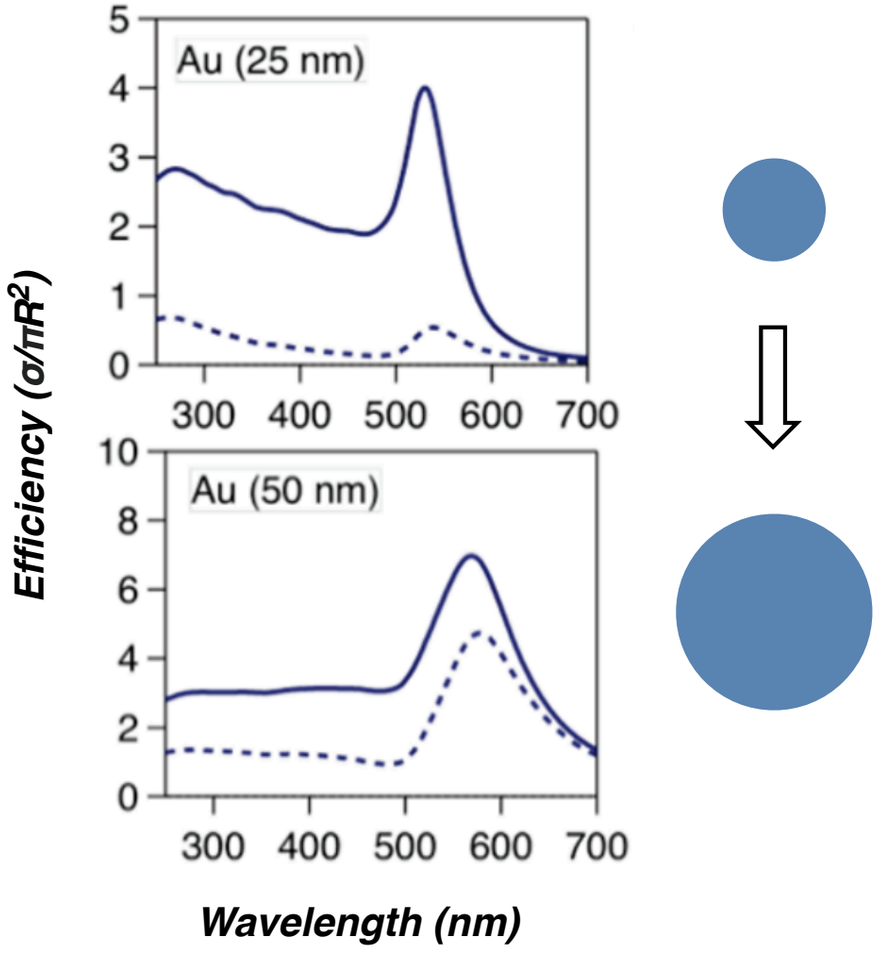
Mie theory

$$\sigma_{\text{sca}} = \frac{2\pi R^2}{x^2} \sum_{n=1}^{\infty} (2n+1)\{|a_n|^2 + |b_n|^2\}$$

$$\sigma_{\text{ext}} = \frac{2\pi R^2}{x^2} \sum_{n=1}^{\infty} (2n+1) Re[a_n + b_n]$$

$$\sigma_{\text{abs}} = \sigma_{\text{ext}} - \sigma_{\text{sca}}$$

$$\sigma_{\text{abs}} = \frac{18\pi V}{\lambda} {\varepsilon_{\text{m}}}^{3/2} \frac{\varepsilon_2}{(\varepsilon_1 + 2\varepsilon_{\text{m}})^2 + {\varepsilon_2}^2}$$



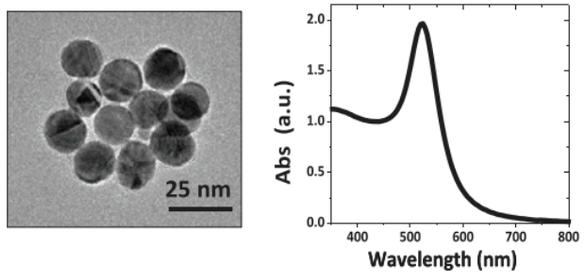
for spherical nanoparticles the plasmon resonance occurs when $\varepsilon_1 = -2\varepsilon_{\text{m}}$

Hartland, G. *Acc. Chem. Rev.* **2011**, *111*, 3858.

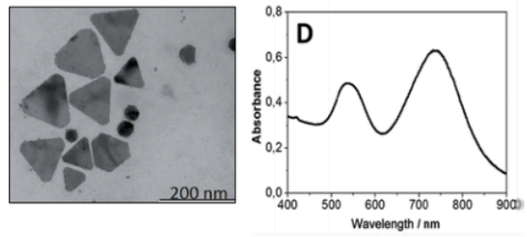
Plasmonic Nanoparticles

shape and composition

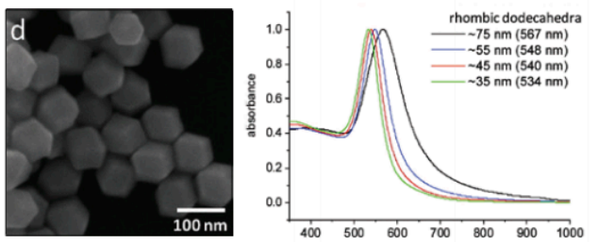
Nanospheres



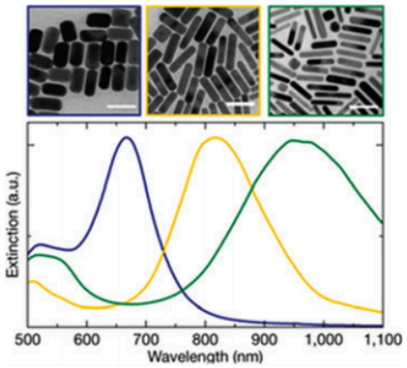
Nanotriangles/prisms



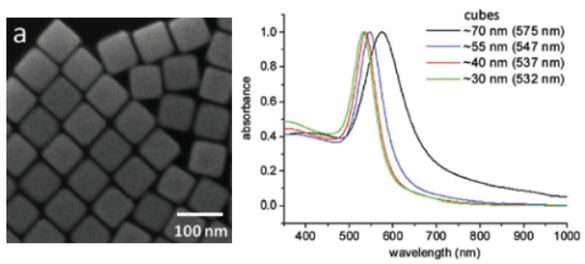
Nanododecahedra



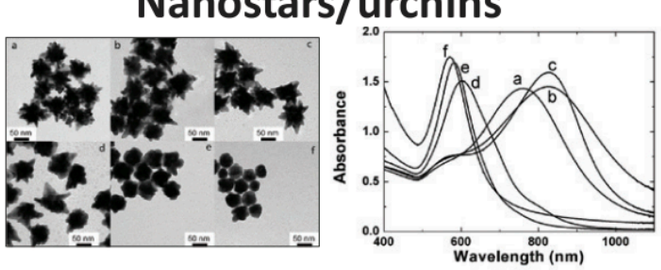
Nanorods



Nanocubes



Nanostars/urchins

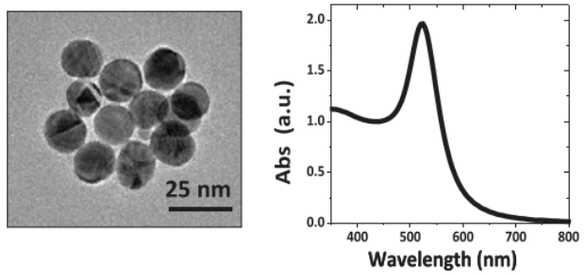


Amendola, V. et. al. *J. Phys.: Condens. Matter.* **2017**, *29*, 48.

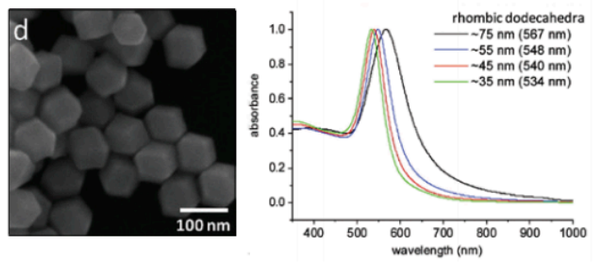
Plasmonic Nanoparticles

shape and composition

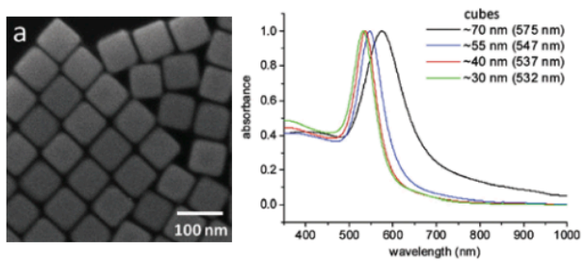
Nanospheres



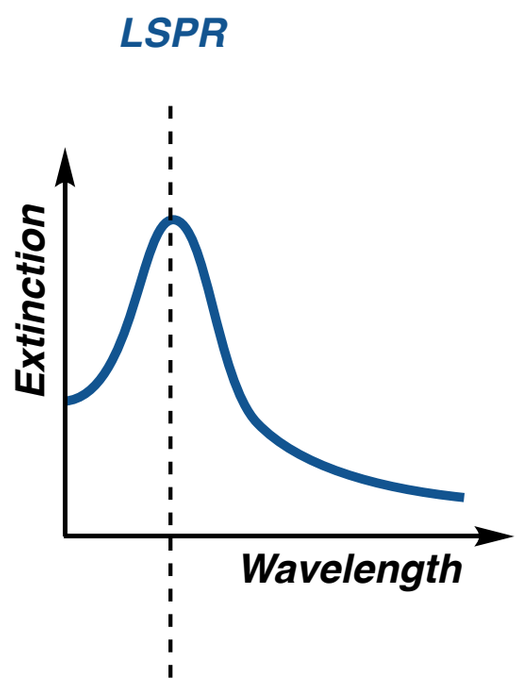
Nanododecahedra



Nanocubes



LSPR



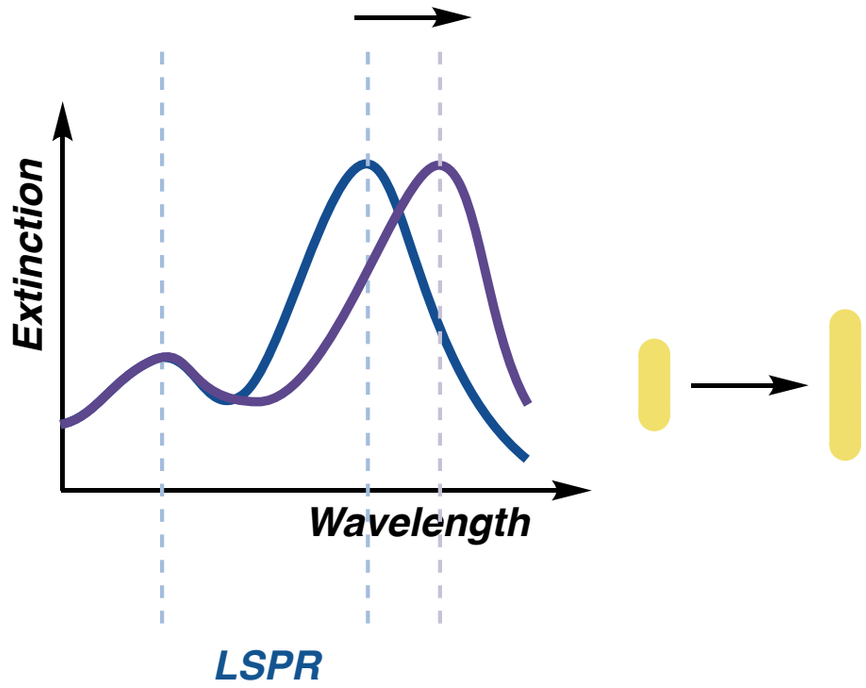
single LSPR determined by the size of the particle

Amendola, V. et. al. *J. Phys.: Condens. Matter.* **2017**, *29*, 48.

Plasmonic Nanoparticles

shape and composition

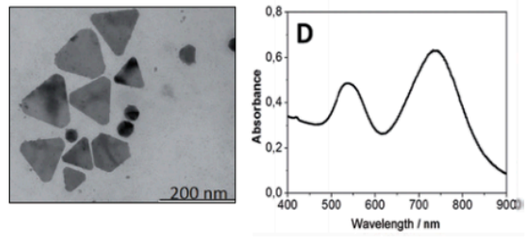
gold nanorod



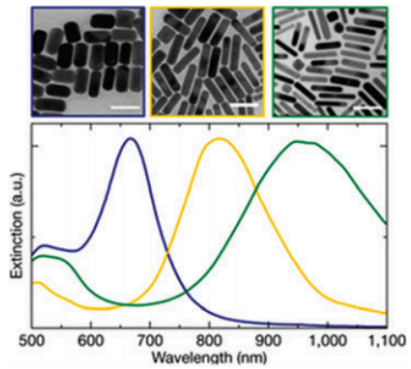
LSPR

multiple LSPRs determined by the aspect ratio of the material

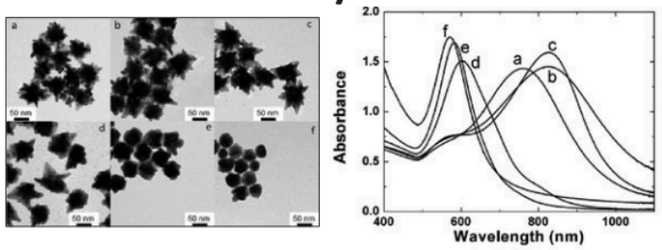
Nanotriangles/prisms



Nanorods



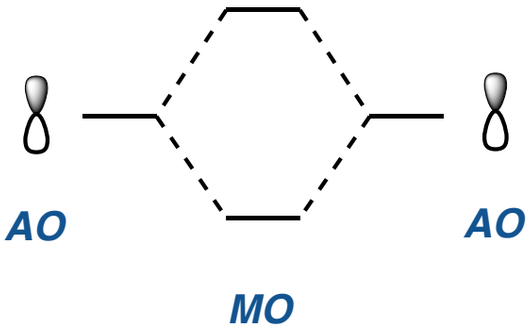
Nanostars/urchins

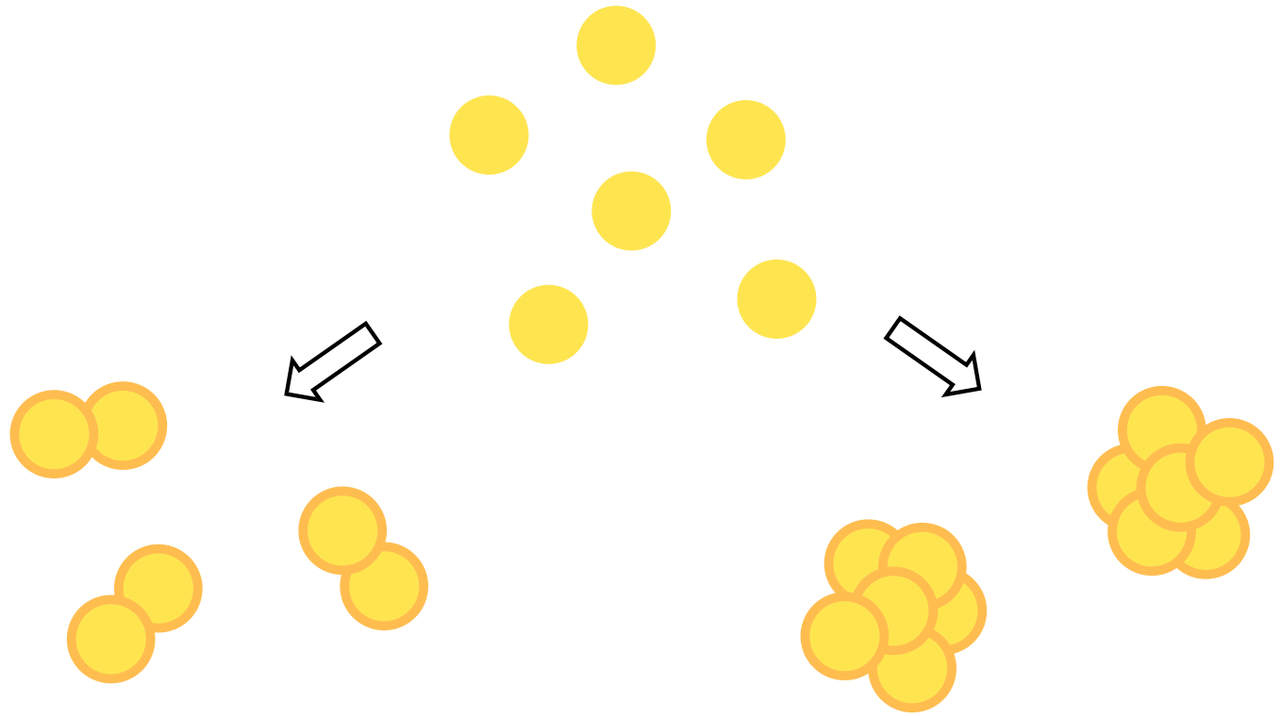


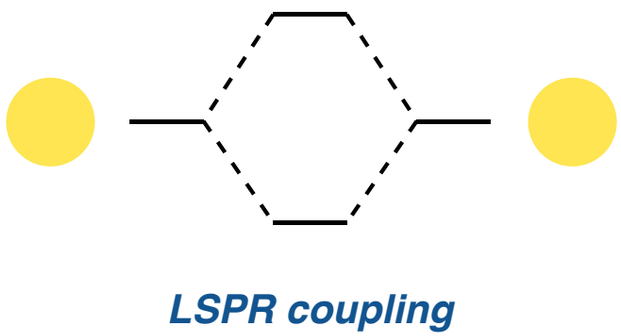
Amendola, V. et. al. *J. Phys.: Condens. Matter.* **2017**, *29*, 48.

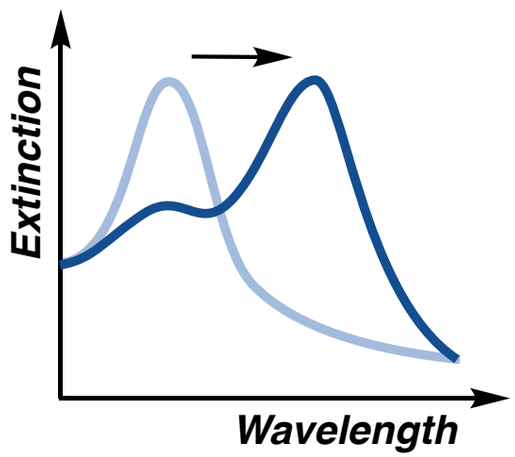
Plasmonic Nanoparticles

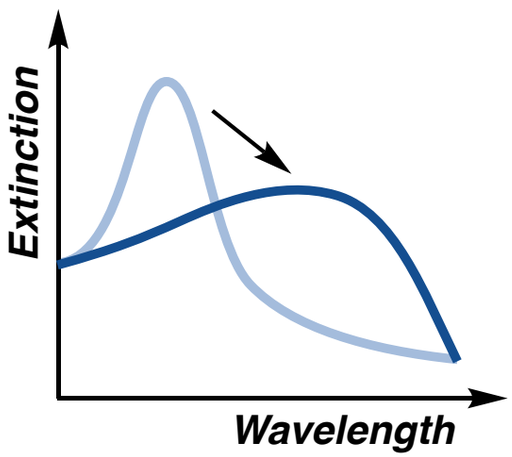
plasmon-plasmon coupling







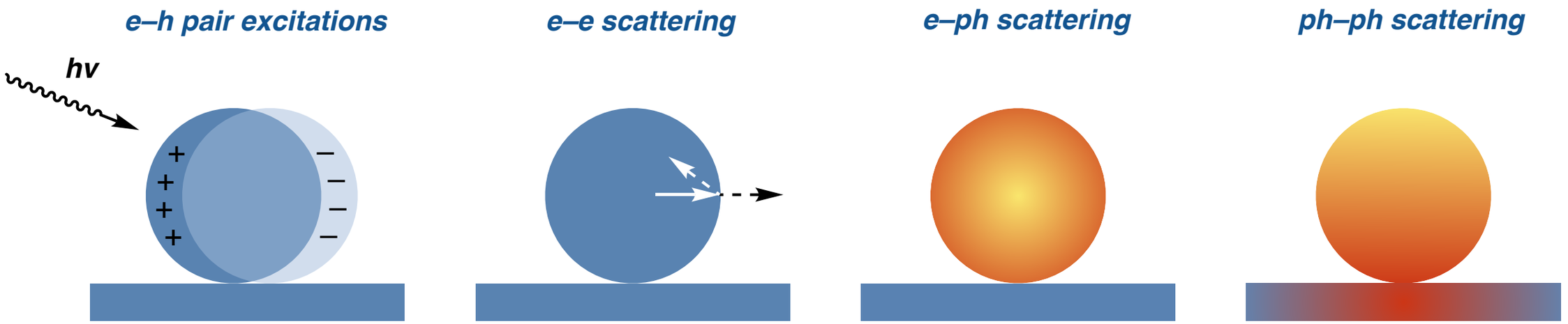


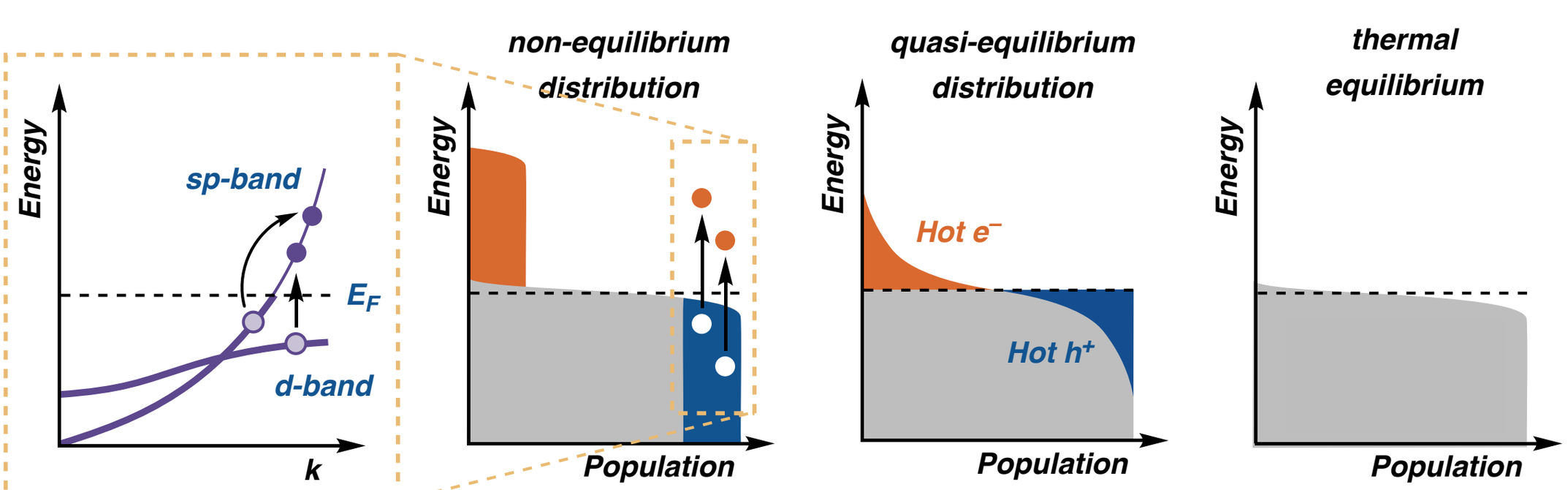


Guo, L. et al. *Nano Today* **2015**, *2*, 213.

Plasmonic Nanoparticles

plasmon excitation timeline





plasmon excitation
t = 0 s

Landau damping
t = 1–100 fs

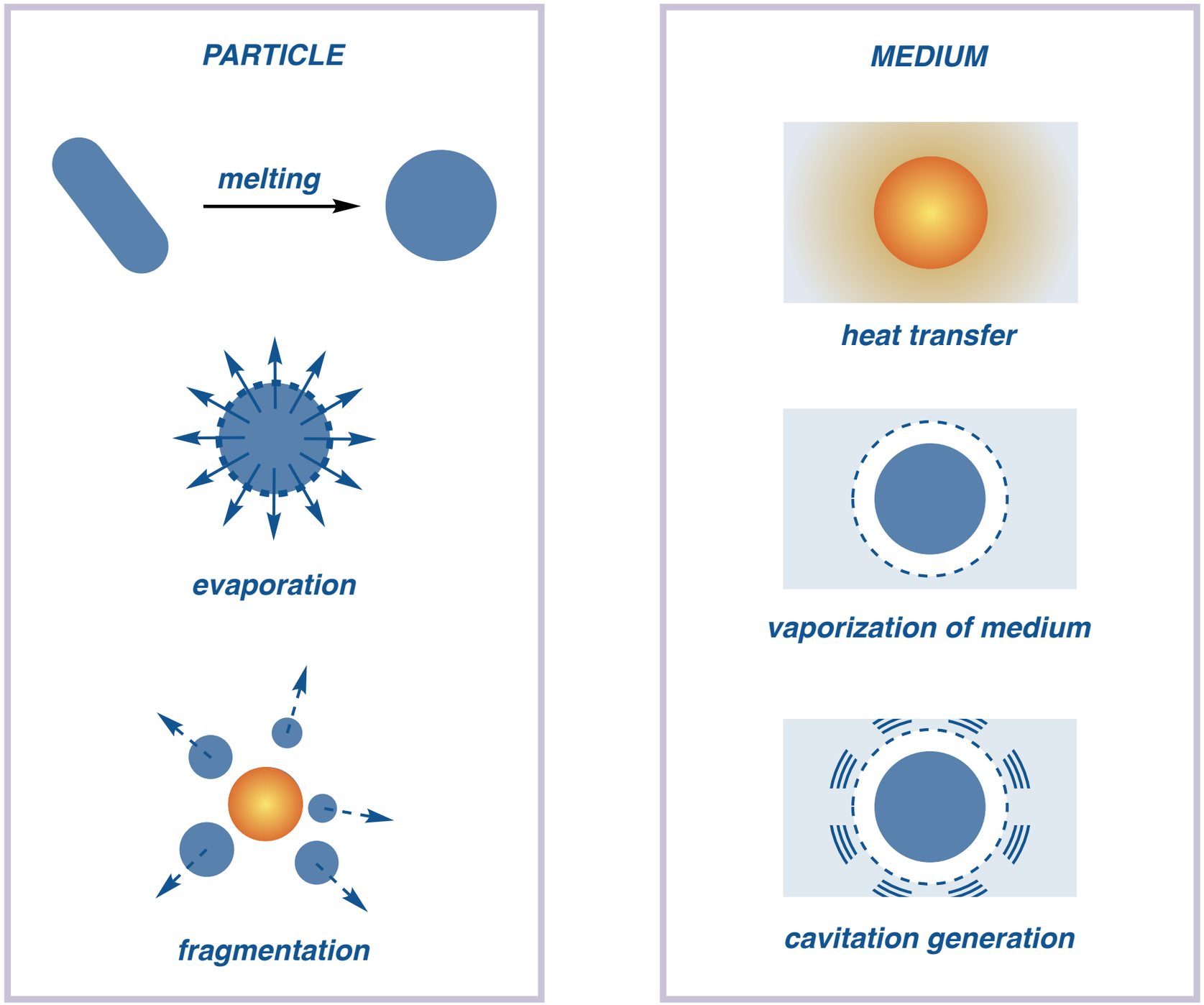
carrier relaxation
t =100 fs to 1 ps

thermal dissipation
t =100 ps to 10 ns

Brongersma, M. et al. *Nat. Nanotechnol.* **2015**, *10*, 25.

Plasmonic Nanoparticles

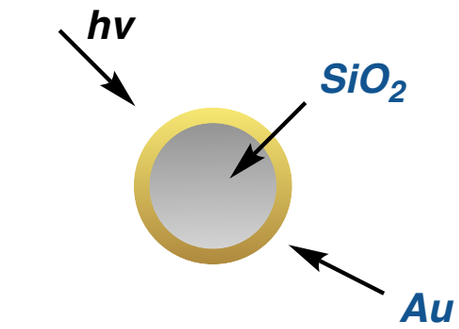
energy dissipation and the medium



Hashimoto, S. et al. *Photochem. Photobiol.* **2012**, *1*, 28.

Plasmonic Nanoparticles

photothermal ablation



gold-silica nanoshell

EPR effect

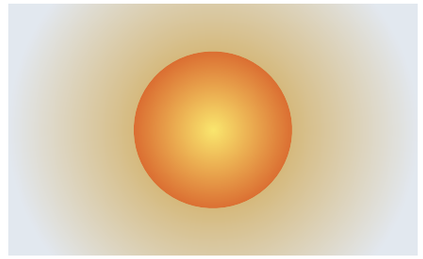
normal tissue

mild and reversible hyperthermia

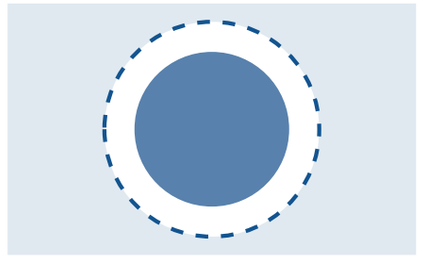
cancerous lesion

coagulative necrosis

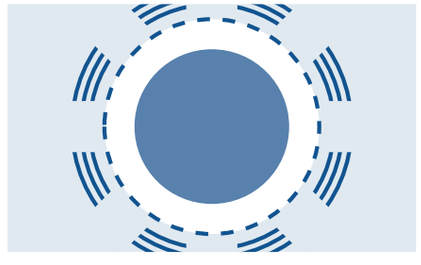
MEDIUM



heat transfer



vaporization of medium

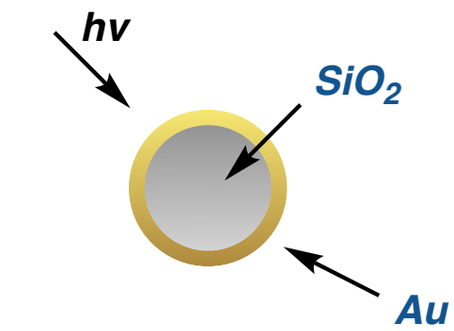


cavitation generation

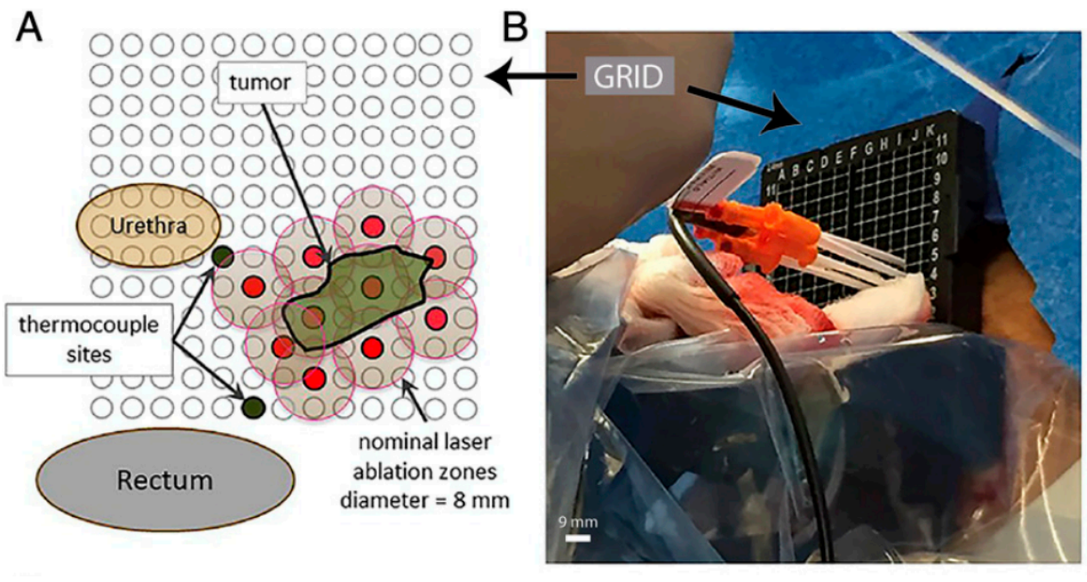
Rastinehad, A. et al. *PNAS* **2019**, *116*, 18590.

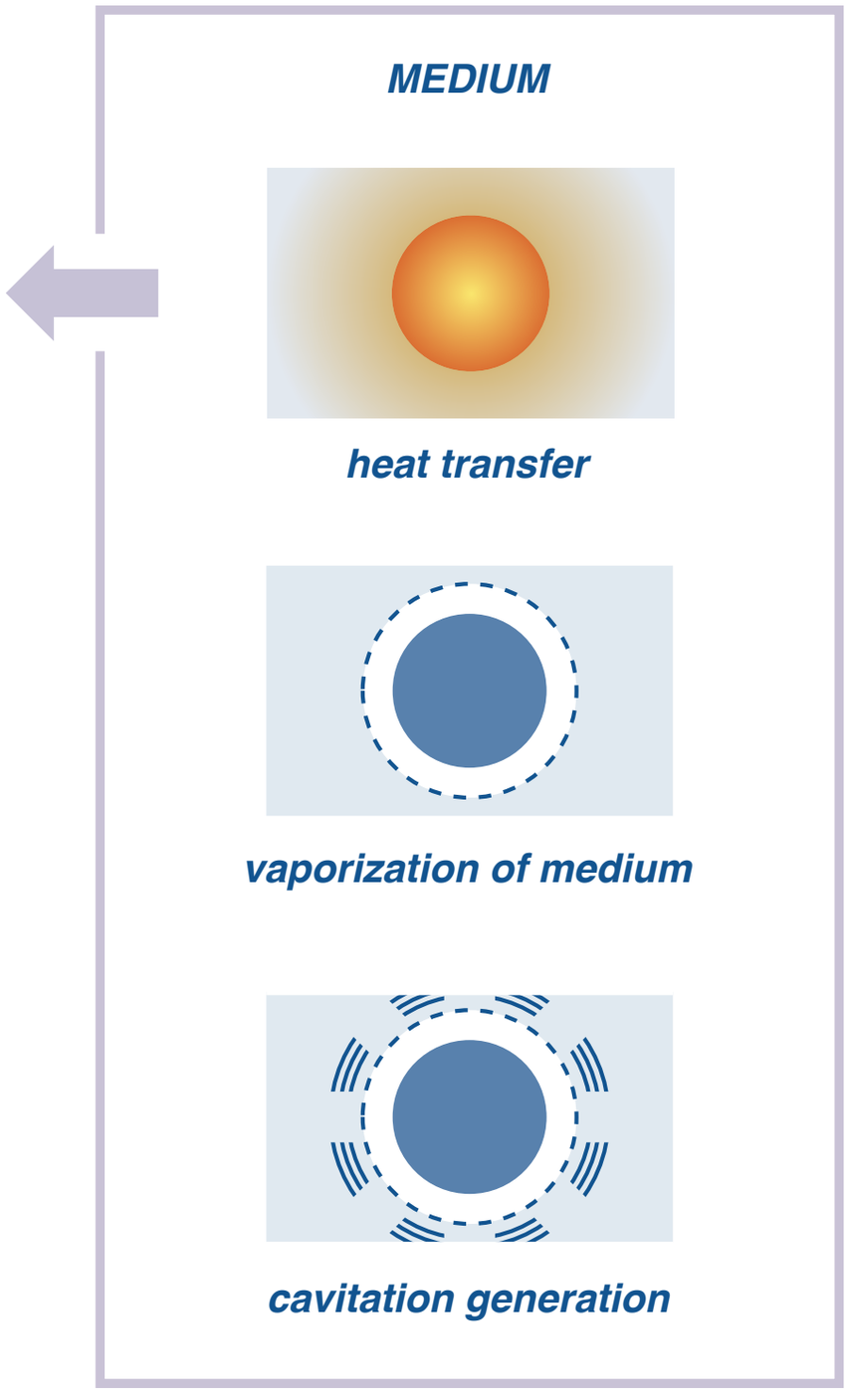
Plasmonic Nanoparticles

photothermal ablation



gold-silica nanoshell

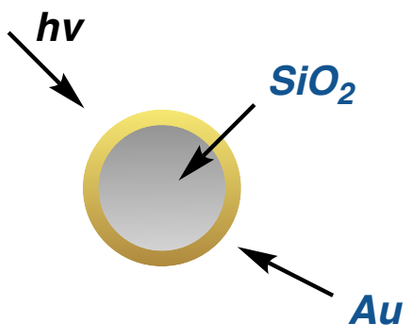




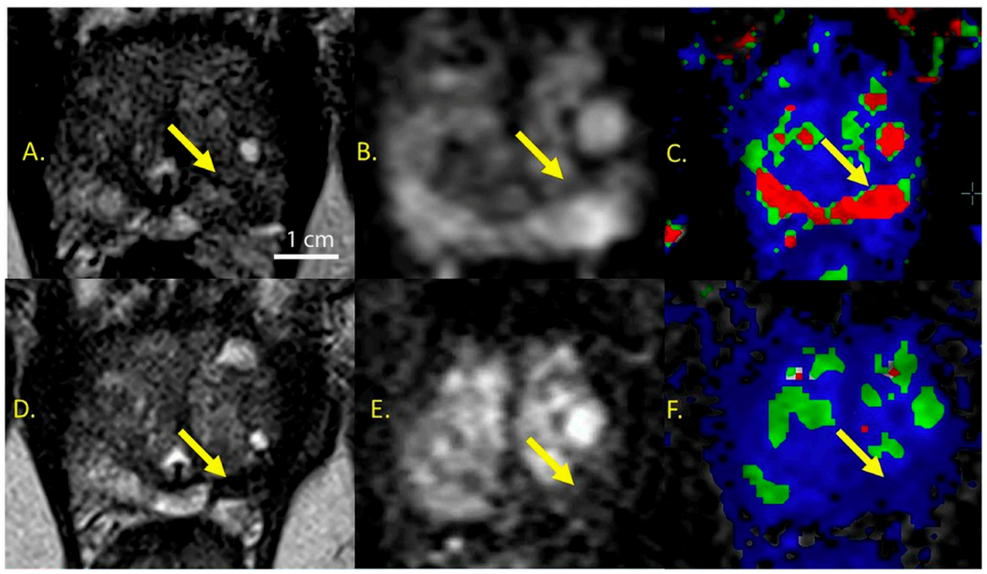
Rastinehad, A. et al. *PNAS* **2019**, *116*, 18590.

Plasmonic Nanoparticles

photothermal ablation

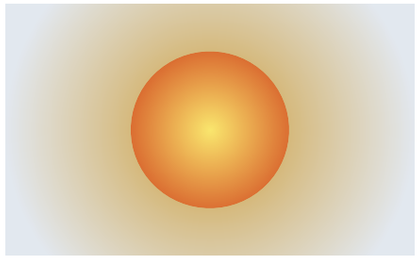


gold-silica nanoshell

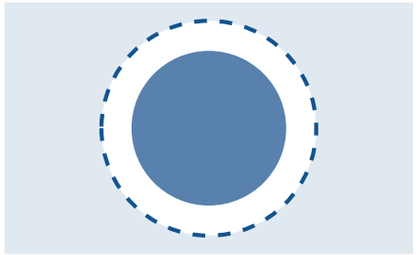


3 months after treatment:
complete removal of tumor after

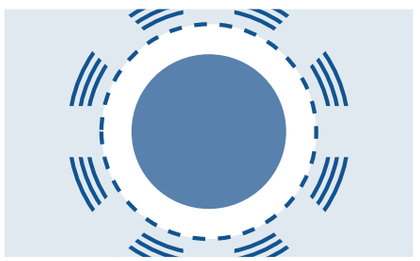
MEDIUM



heat transfer



vaporization of medium

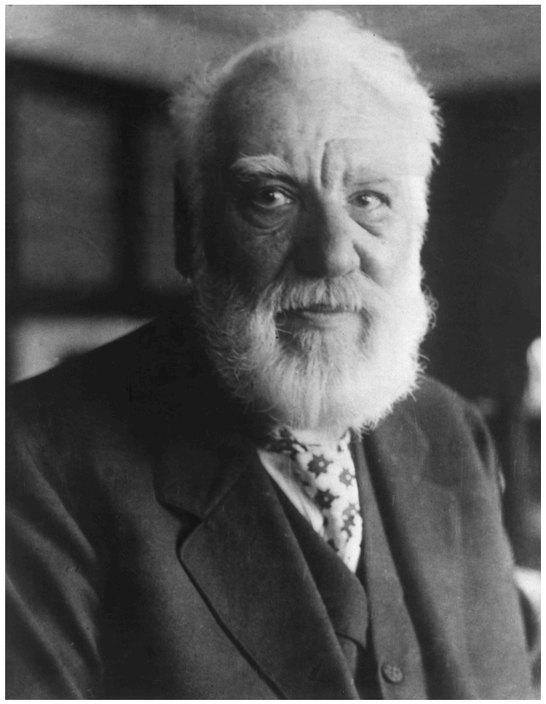


cavitation generation

Rastinehad, A. et al. *PNAS* **2019**, *116*, 18590.

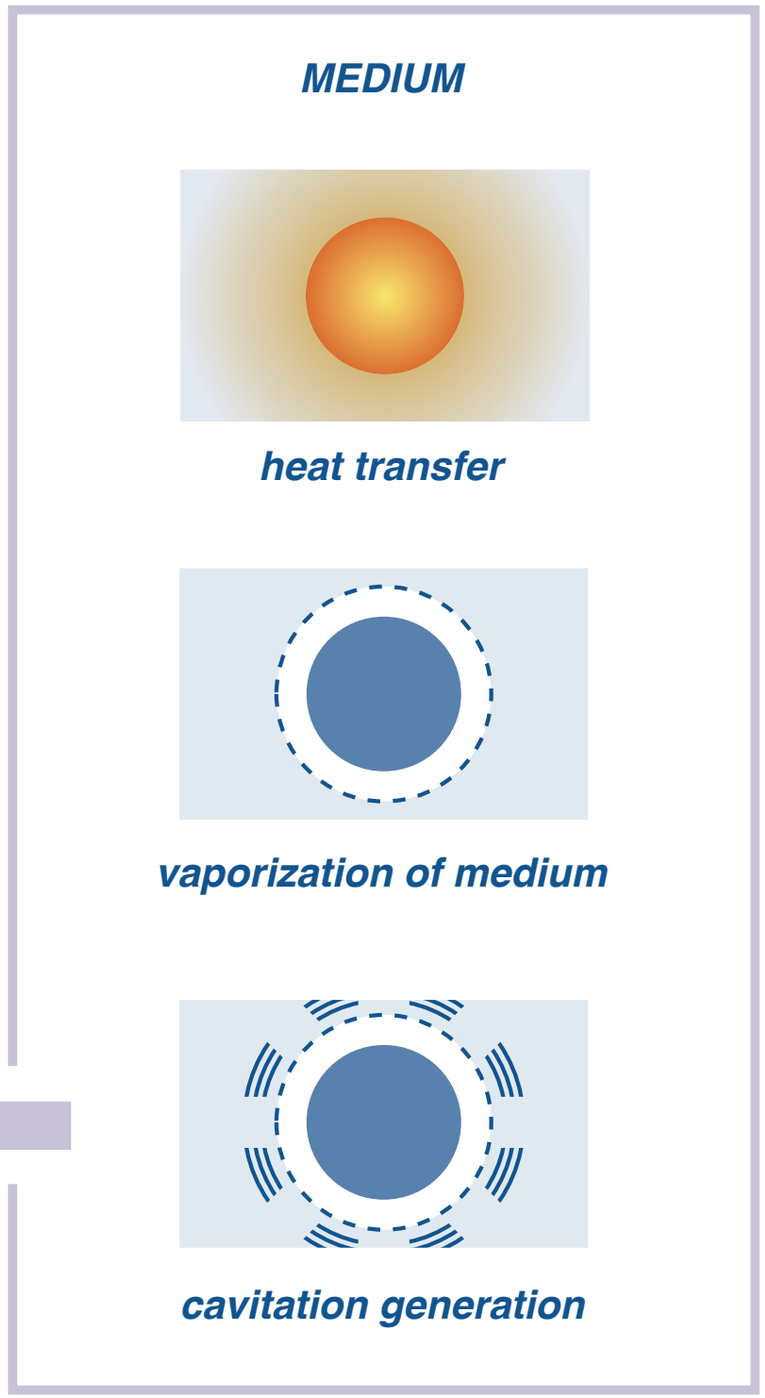
Plasmonic Nanoparticles

photoacoustic effect



ART. XXXIV.—*On the Production and Reproduction of Sound by Light;* by ALEXANDER GRAHAM BELL, Ph.D.

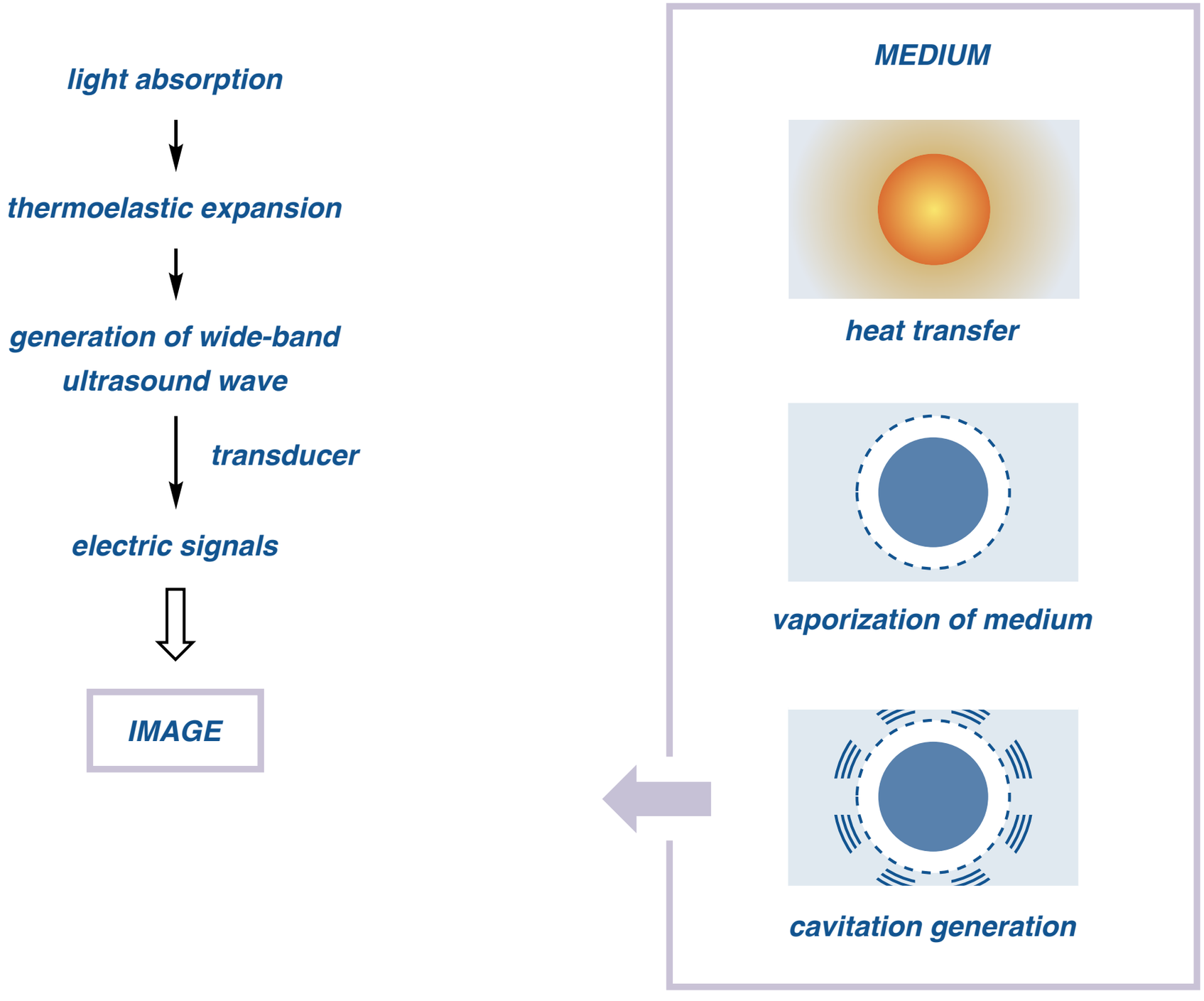
[Read before the American Association for the Advancement of Science, in Boston, August 27, 1880.]



Mallidi, S. et al. *Trends Biotechnol.* **2011**, *29*, 213.

Plasmonic Nanoparticles

photoacoustic effect



Mallidi, S. et al. *Trends Biotechnol.* **2011**, *29*, 213.

Plasmonic Nanoparticles

photoacoustic effect

light absorption

↓

thermoelastic expansion

↓

generation of wide-band ultrasound wave

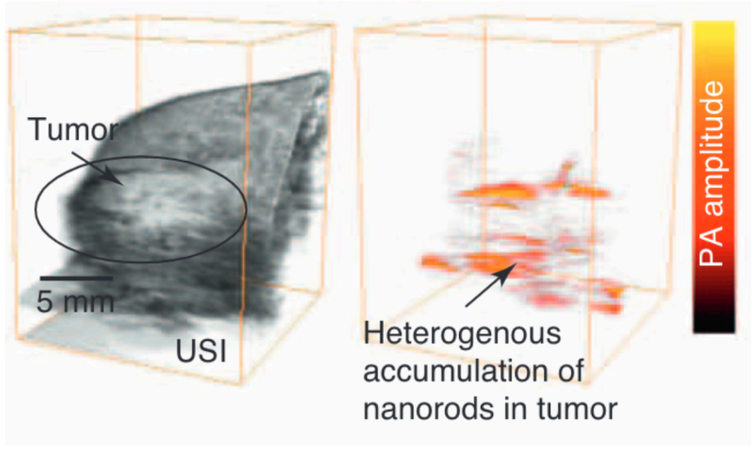
↓

transducer

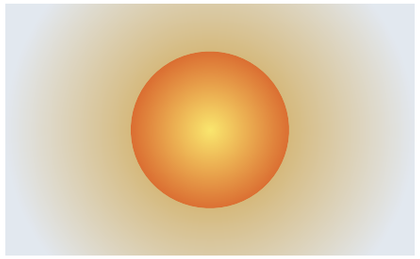
↓

electric signals

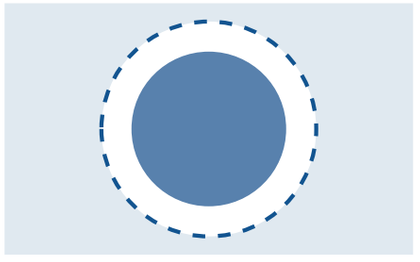
⇩



MEDIUM



heat transfer



vaporization of medium

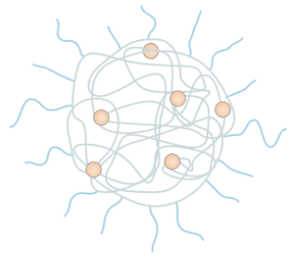
cavitation generation

Mallidi, S. et al. *Trends Biotechnol.* **2011**, *29*, 213.

Outline

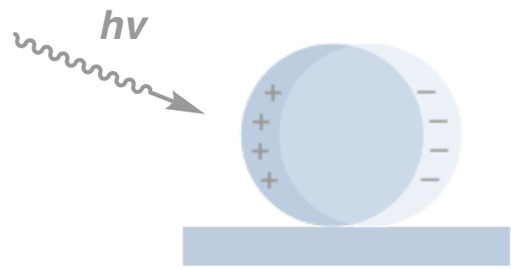
Theranostics

- *Definitions*
- *The EPR effect*
- *Most common theranostic agents*



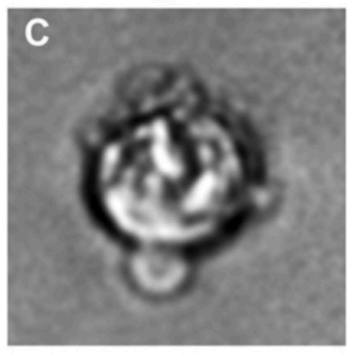
Plasmonic Resonance

- *History*
- *Absorption cross-section*
- *Plasmonic resonance as a function of shape, size, aggregation, and composition*



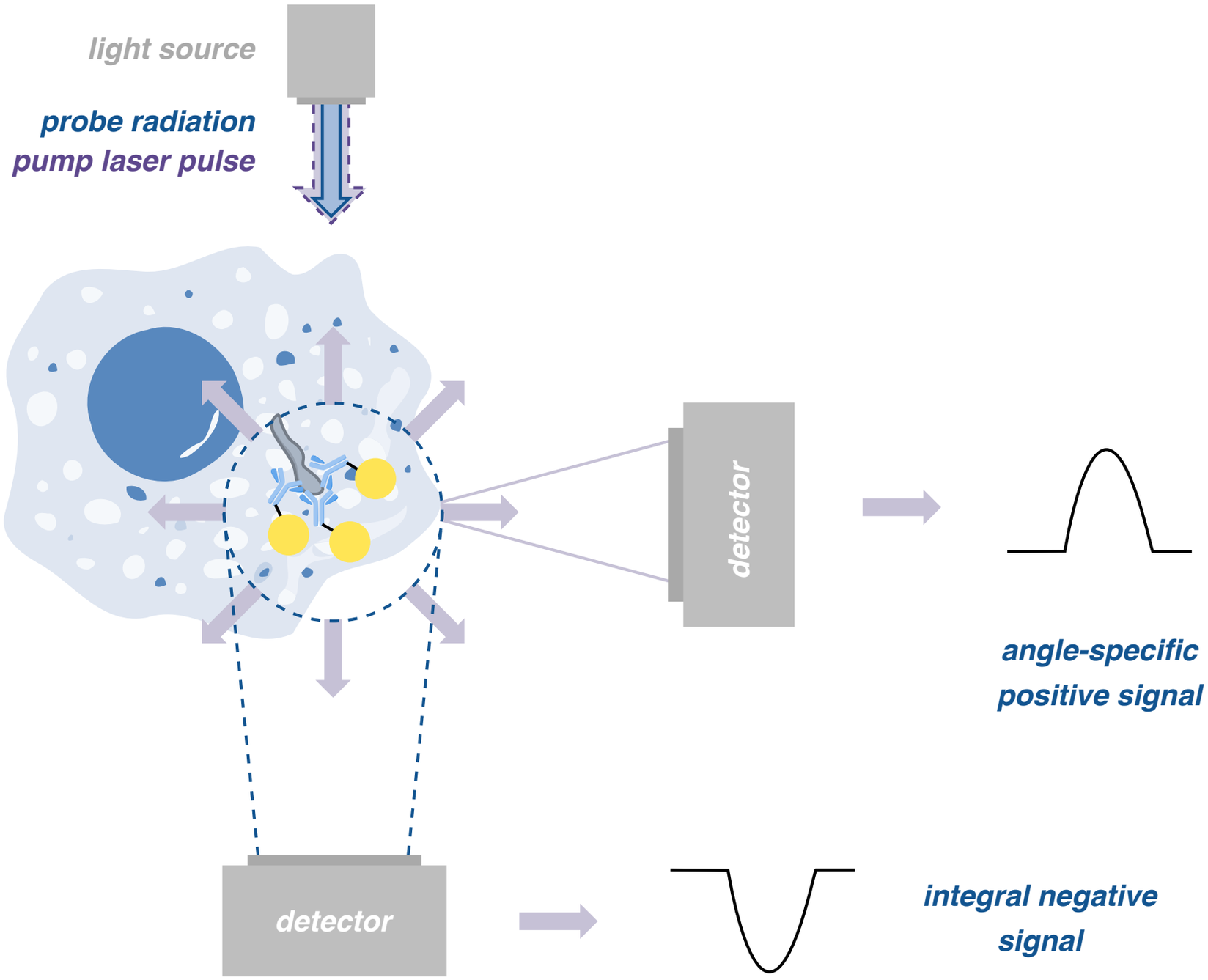
Plasmonic Gold Nanoparticles in vivo

- *Development of a theranostic in vivo model*
- *Plasmonic nanobubble-guided surgery*



GNP as Theranostic Agents

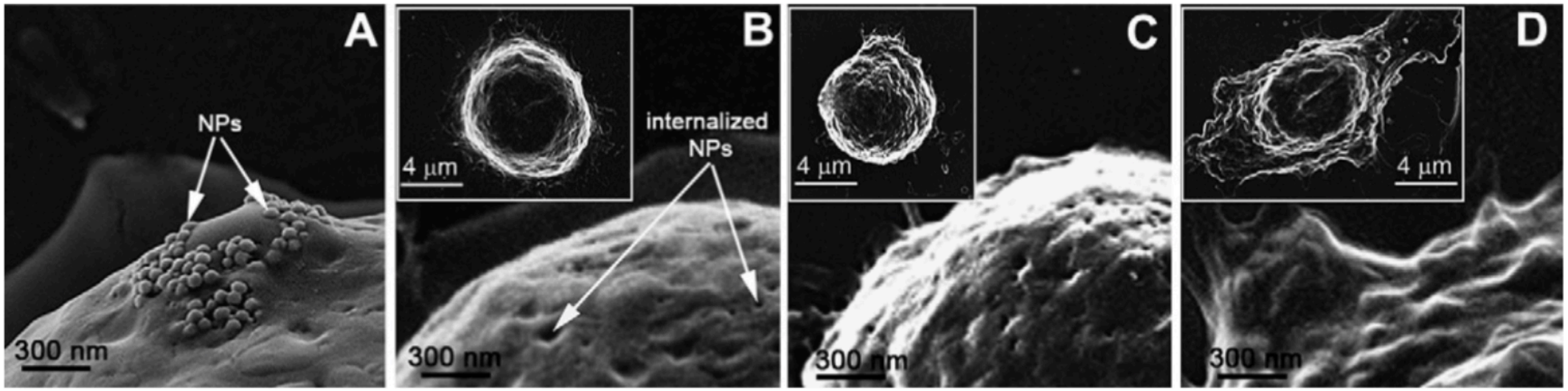
in vivo model



Wagner, D. et al. *Biomat.* **2010**, *31*, 7567.

GNP as Theranostic Agents

in vivo model



NP membrane coupling

internalization

single pump laser pulse

Diagnosis

ablative PNB

Therapy

Wagner, D. et al. *Biomat.* **2010**, *31*, 7567.

GNP as Theranostic Agents

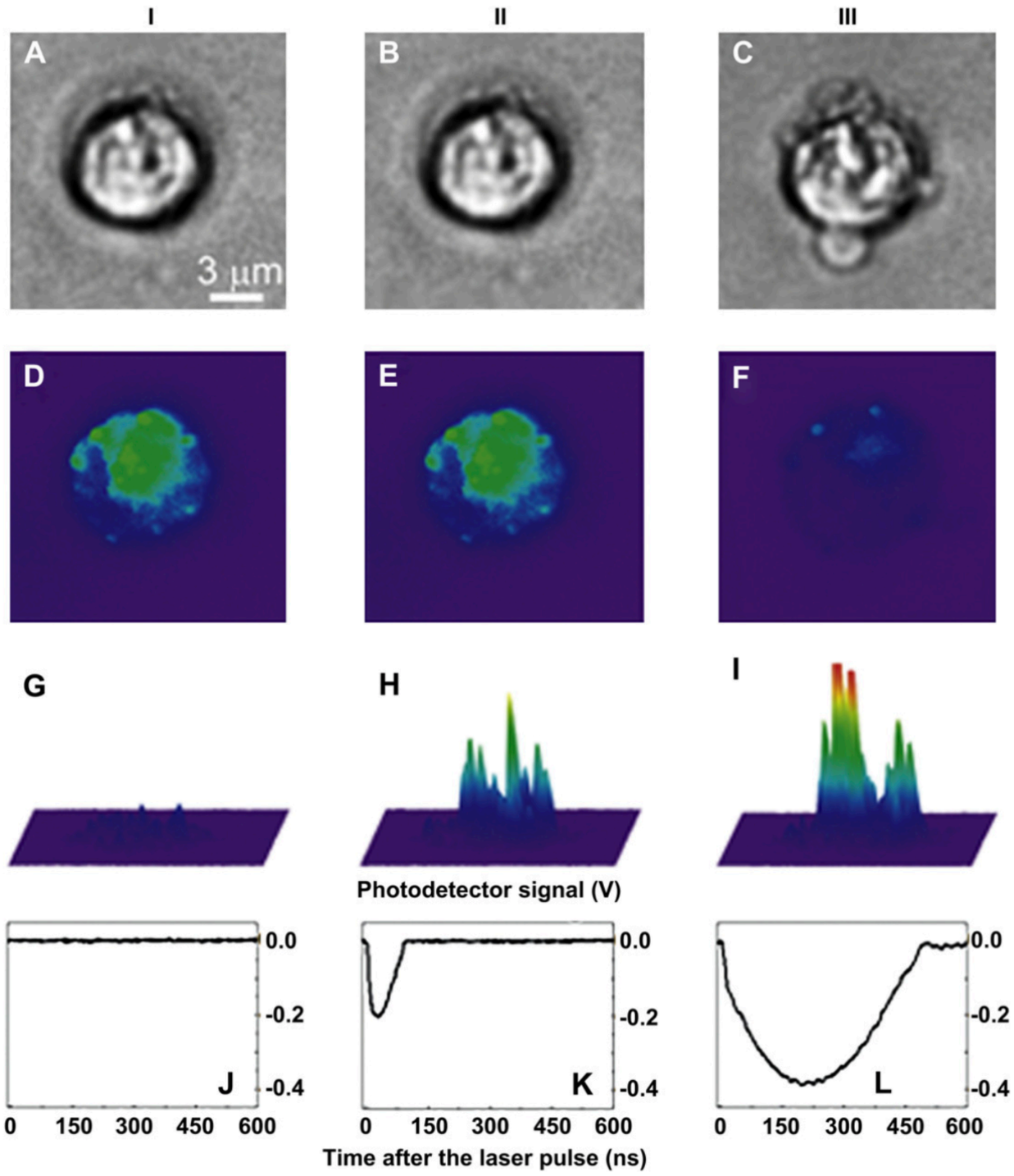
in vivo model

bright field

fluorescence of dye

side-scattering

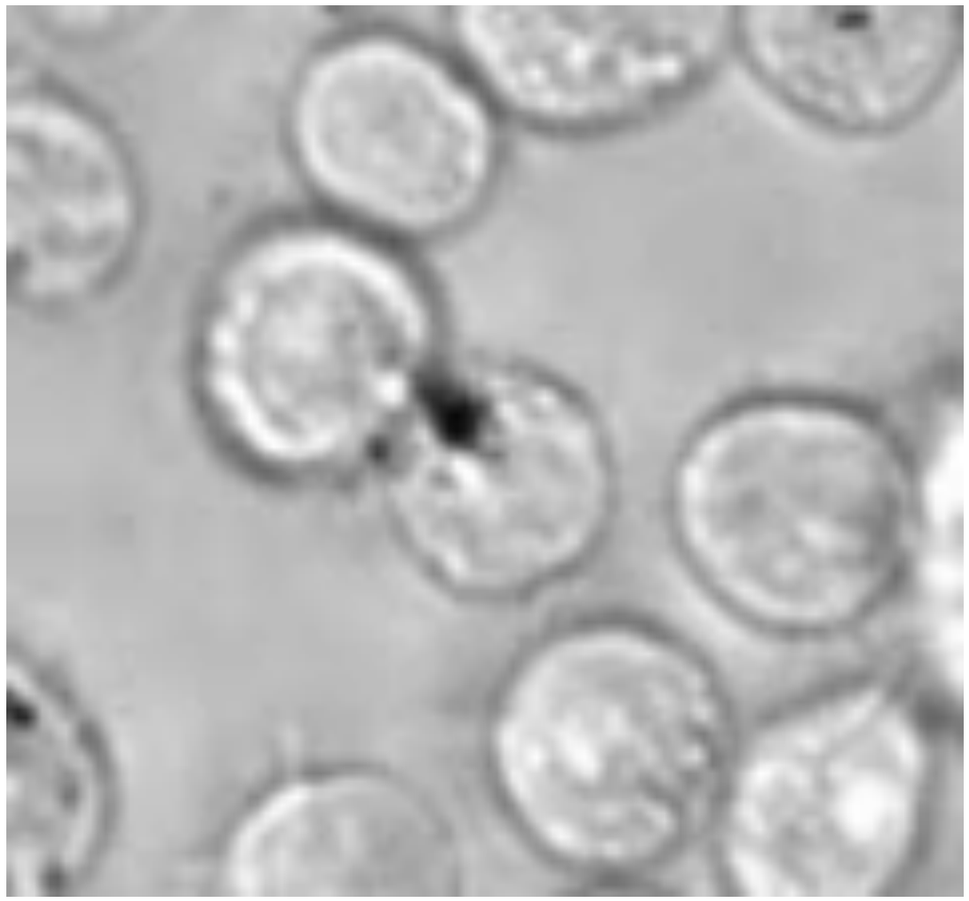
scattering time response



Wagner, D. et al. *Biomat.* **2010**, *31*, 7567.

GNP as Theranostic Agents

in vivo model



Wagner, D. et al. *Biomat.* **2010**, *31*, 7567.

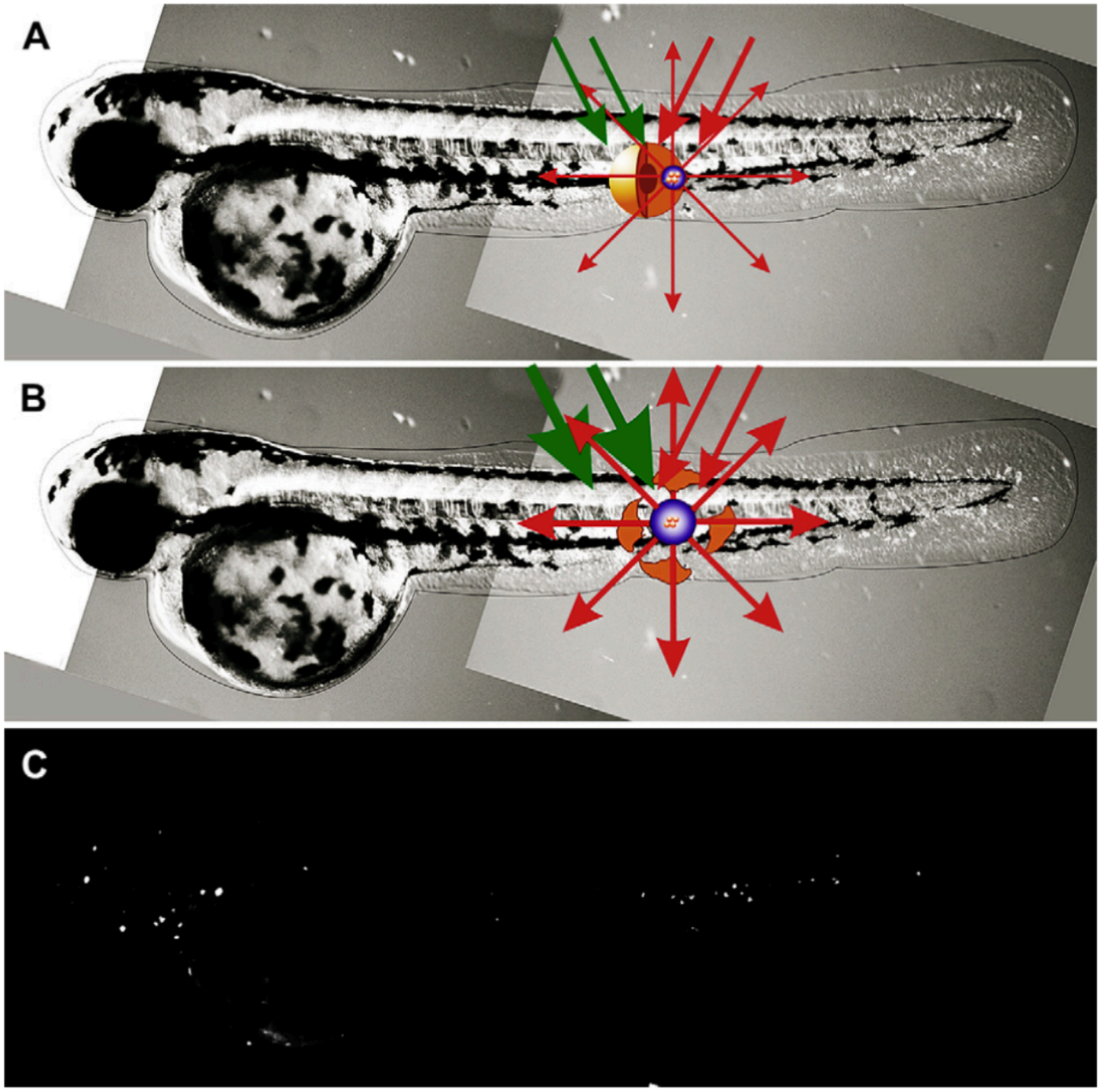
GNP as Theranostic Agents

in vivo model

Diagnosis

Therapy

labeled cancer cells



Wagner, D. et al. *Biomat.* **2010**, *31*, 7567.

GNP as Theranostic Agents

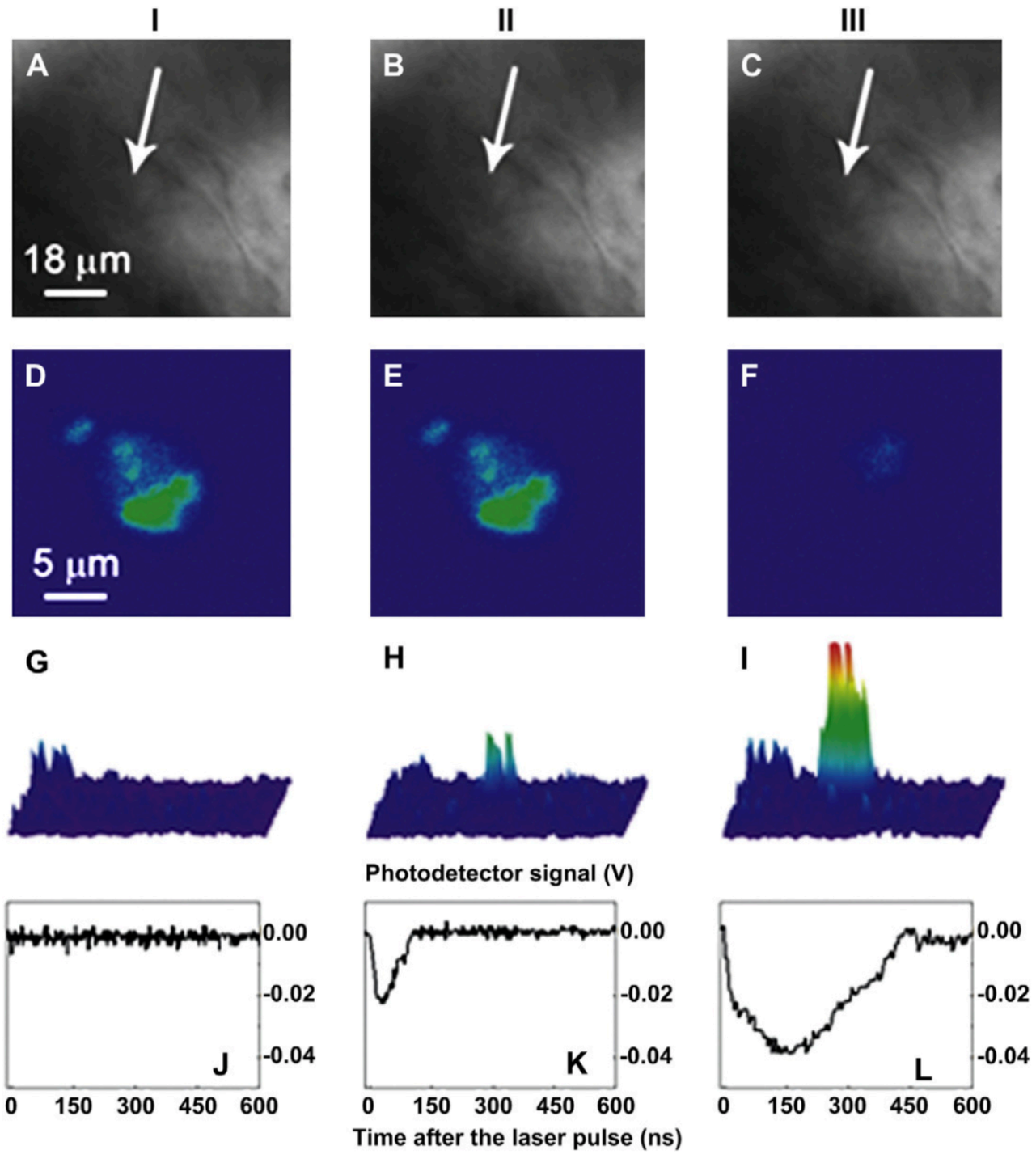
in vivo model

bright field

fluorescence of dye

side-scattering

scattering time response



Wagner, D. et al. *Biomat.* **2010**, *31*, 7567.

Plasmonic Nanobubble-Guided Surgery

motivation

microscopic (or minimal) residual disease, MRD *(head and neck squamous cell carcinoma)*	⟷	*often comprises just tens of cancer cells cause lethal recurrence*
palpation and radiographic imaging	→	*not sensitive enough*
pathological analysis of surgical margins	→	slow and often inaccurate
resect large margins of normal tissue	→	*often fails while causing high morbidity*
post-operative radiation or chemoradiation therapies	→	*increase morbidity and cost*

detect MRD in solid tissue in vivo with single cancer cell sensitivity and in real time

Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

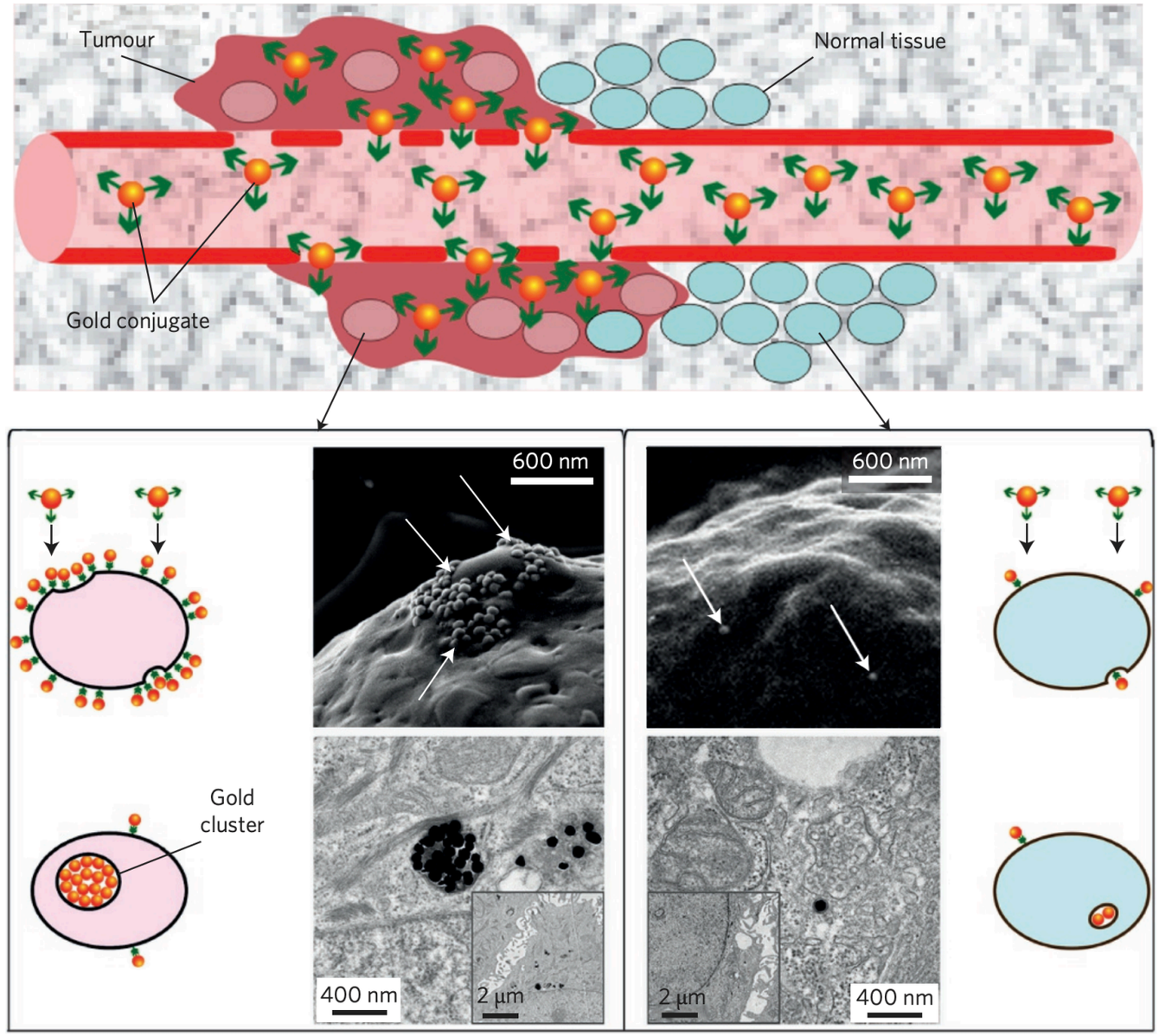
Plasmonic Nanobubble-Guided Surgery

in vivo model

EPR effect

antibody specific interactions

formation of clustres of GNPs



three consecutive stages of selectivity

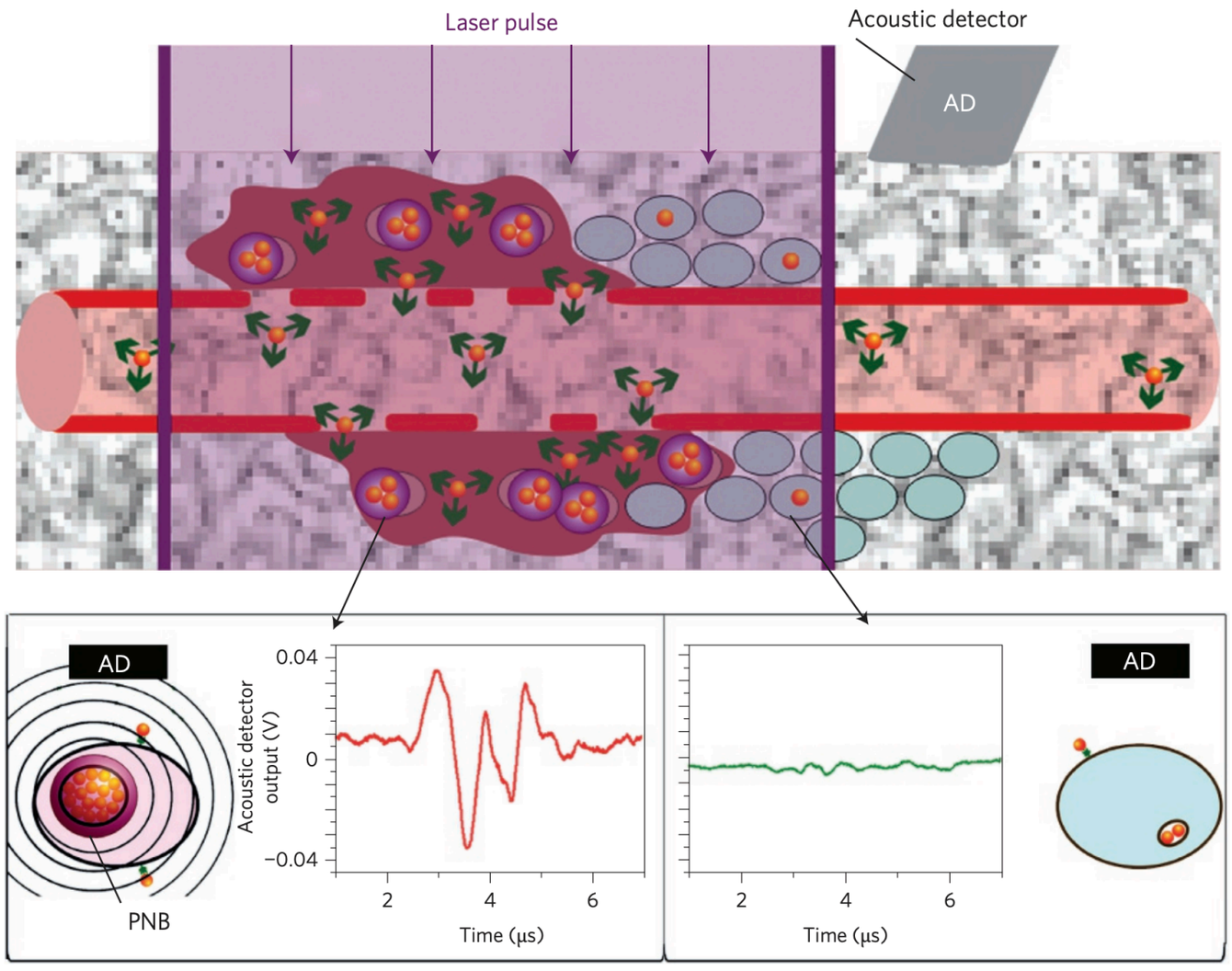
Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

Plasmonic Nanobubble-Guided Surgery

in vivo model

application of a laser pulse

PNB formation and diagnosis

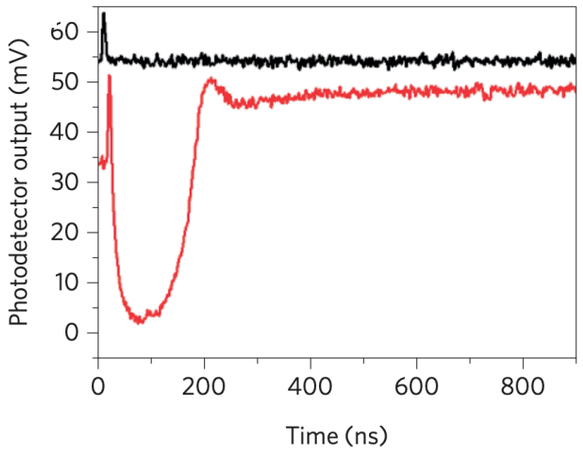


Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

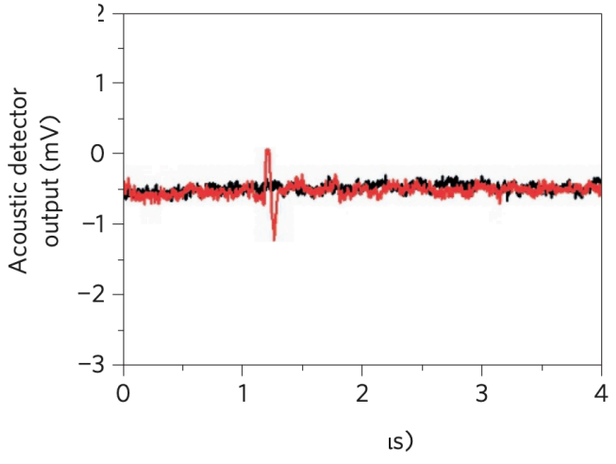
Plasmonic Nanobubble-Guided Surgery

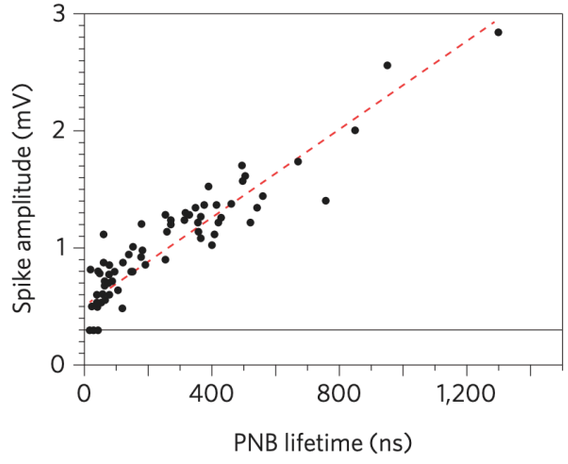
in vivo model

time response



acoustic response

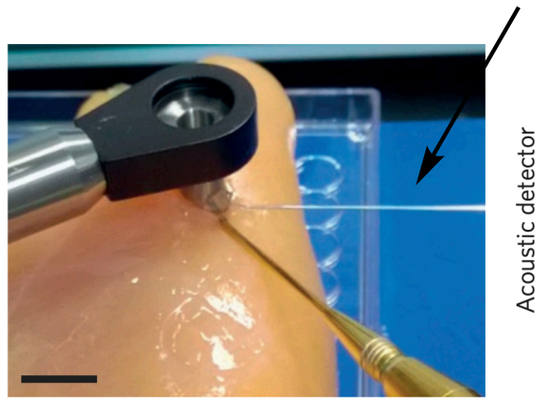




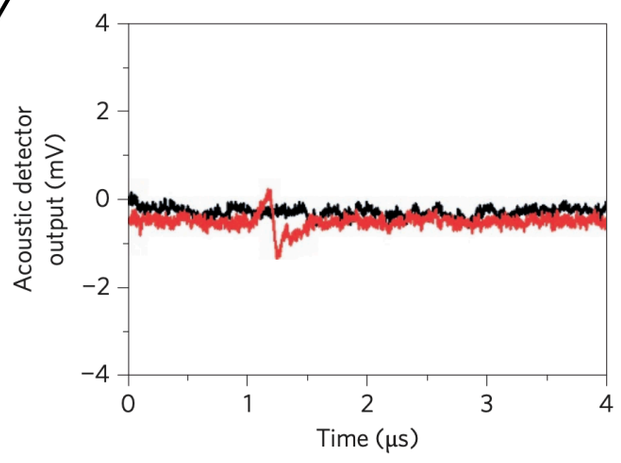
injection needle

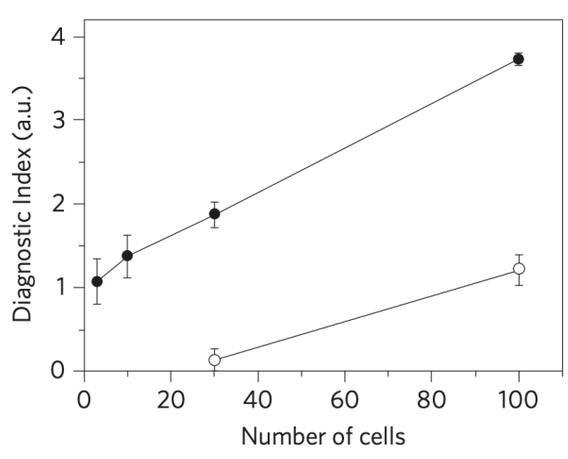
endoscope

782 nm, 30 ps,
70 mJ/cm^2



acousting sensor





1 mm

3–4 mm

control

GNP-pretreated cells

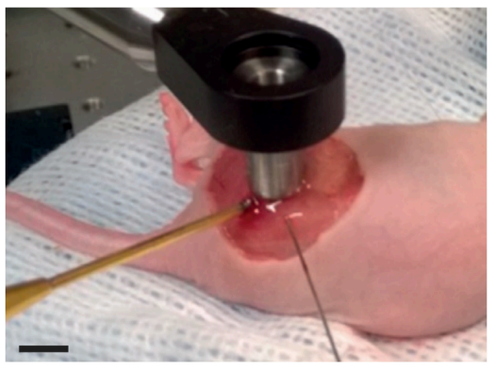
Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

Plasmonic Nanobubble-Guided Surgery

in vivo model

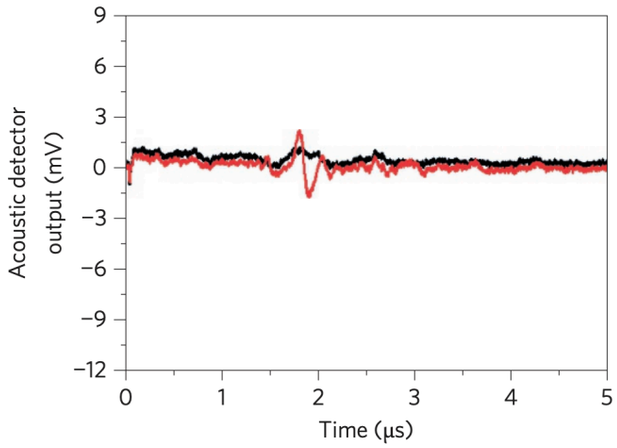
endoscope

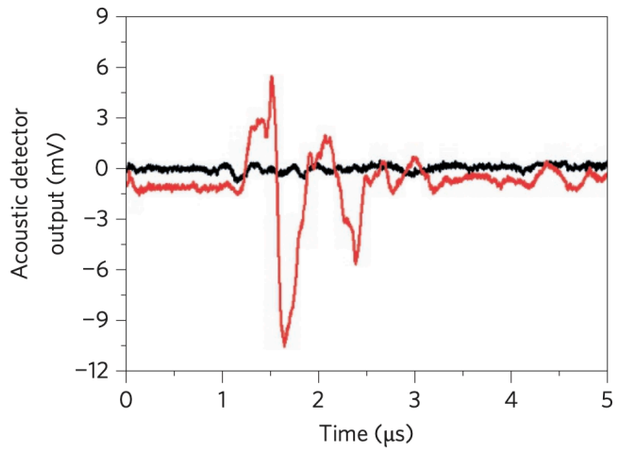
acousting sensor



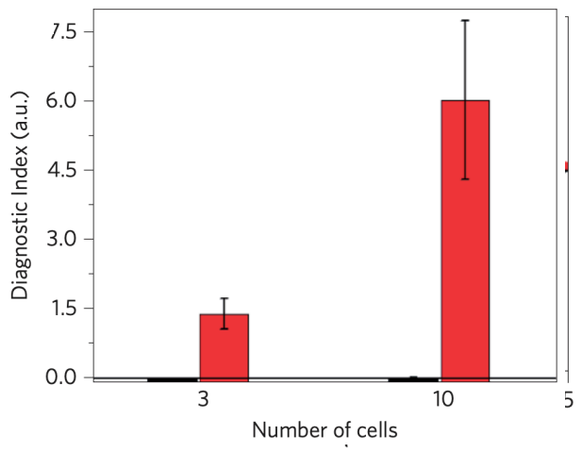
injection needle

3 cells, 1 mm





10 cells, 1 mm



as little as 3 cancer cells can be acoustically detected upon irradiation

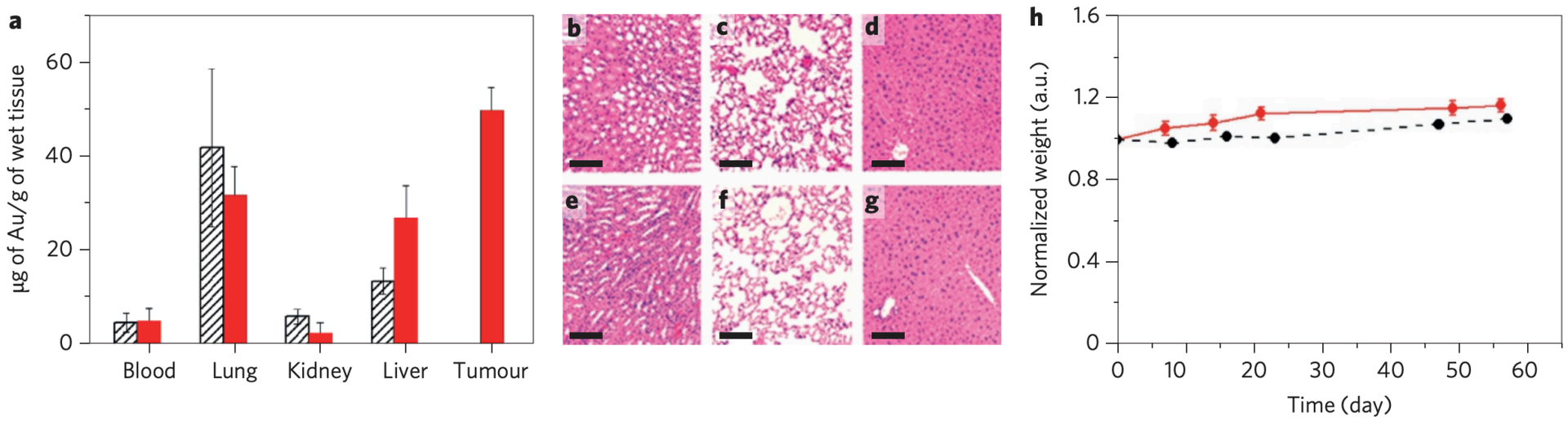
— ***before injection***

— ***GNP-pretreated cells***

Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

Plasmonic Nanobubble-Guided Surgery

in vivo model



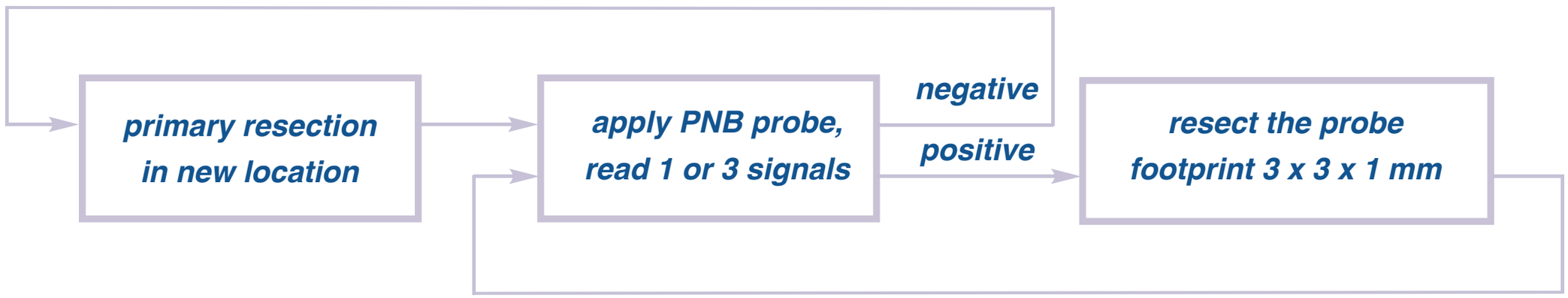
NPs accumulated primarily in the tumor and did not display any cytotoxic effects

Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

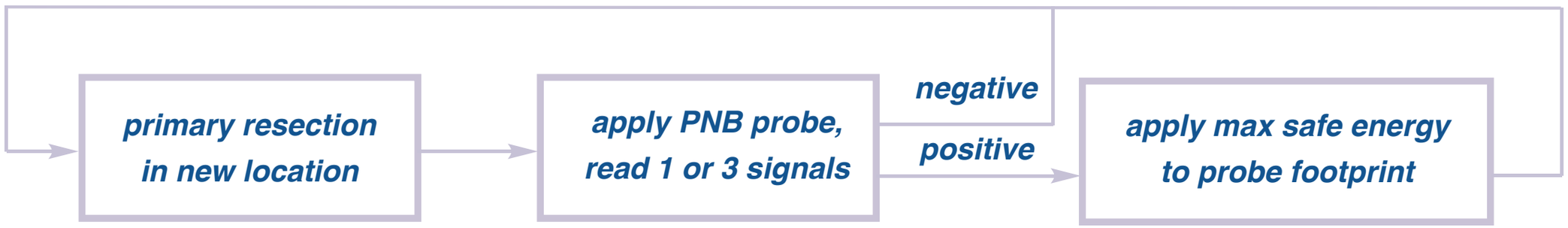
Plasmonic Nanobubble-Guided Surgery

PNB-guided surgery: algorithm

Resectable MRD



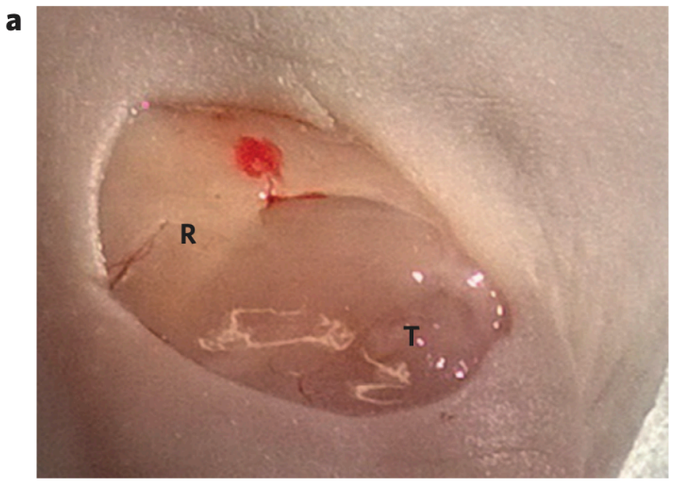
Unresectable MRD

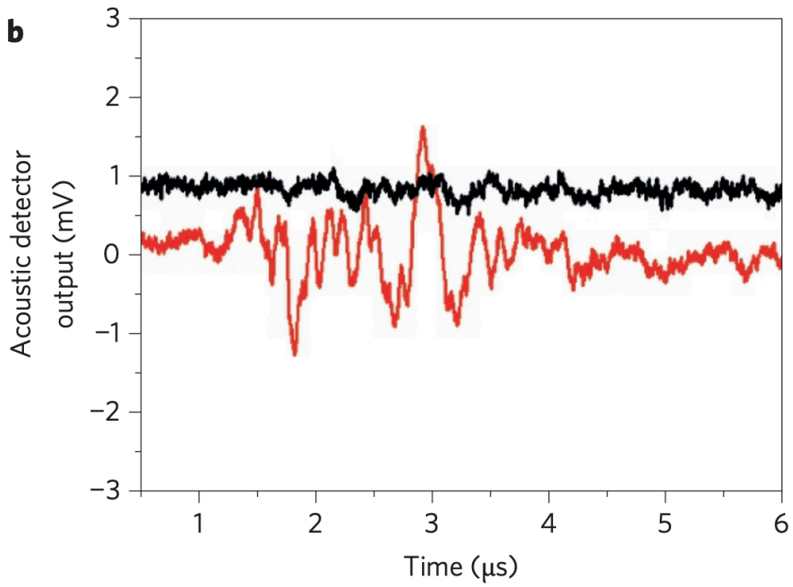


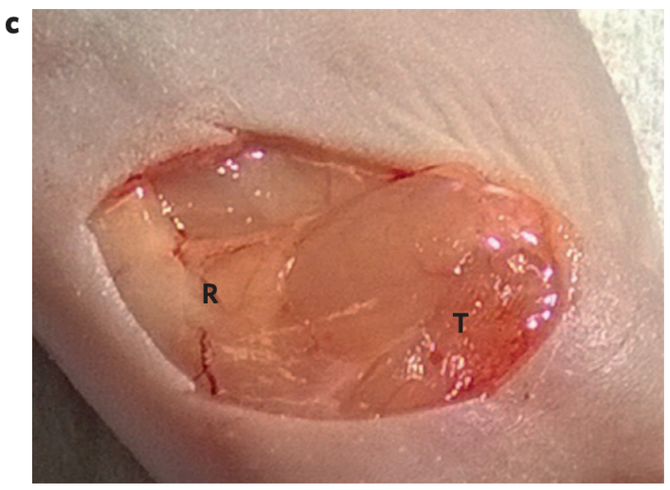
Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

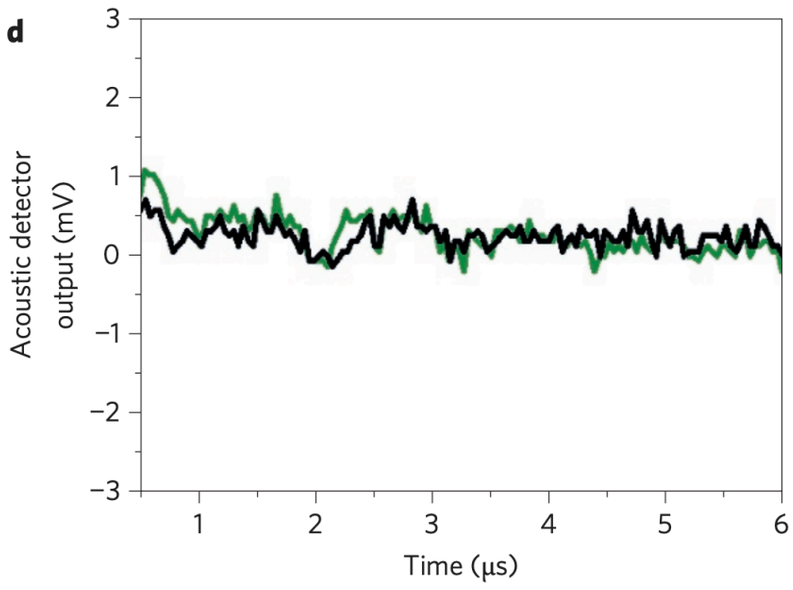
Plasmonic Nanobubble-Guided Surgery

PNB-guided surgery: Resectable MRDs









PNB generation allows for real time cancerous cell detection and treatment

Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

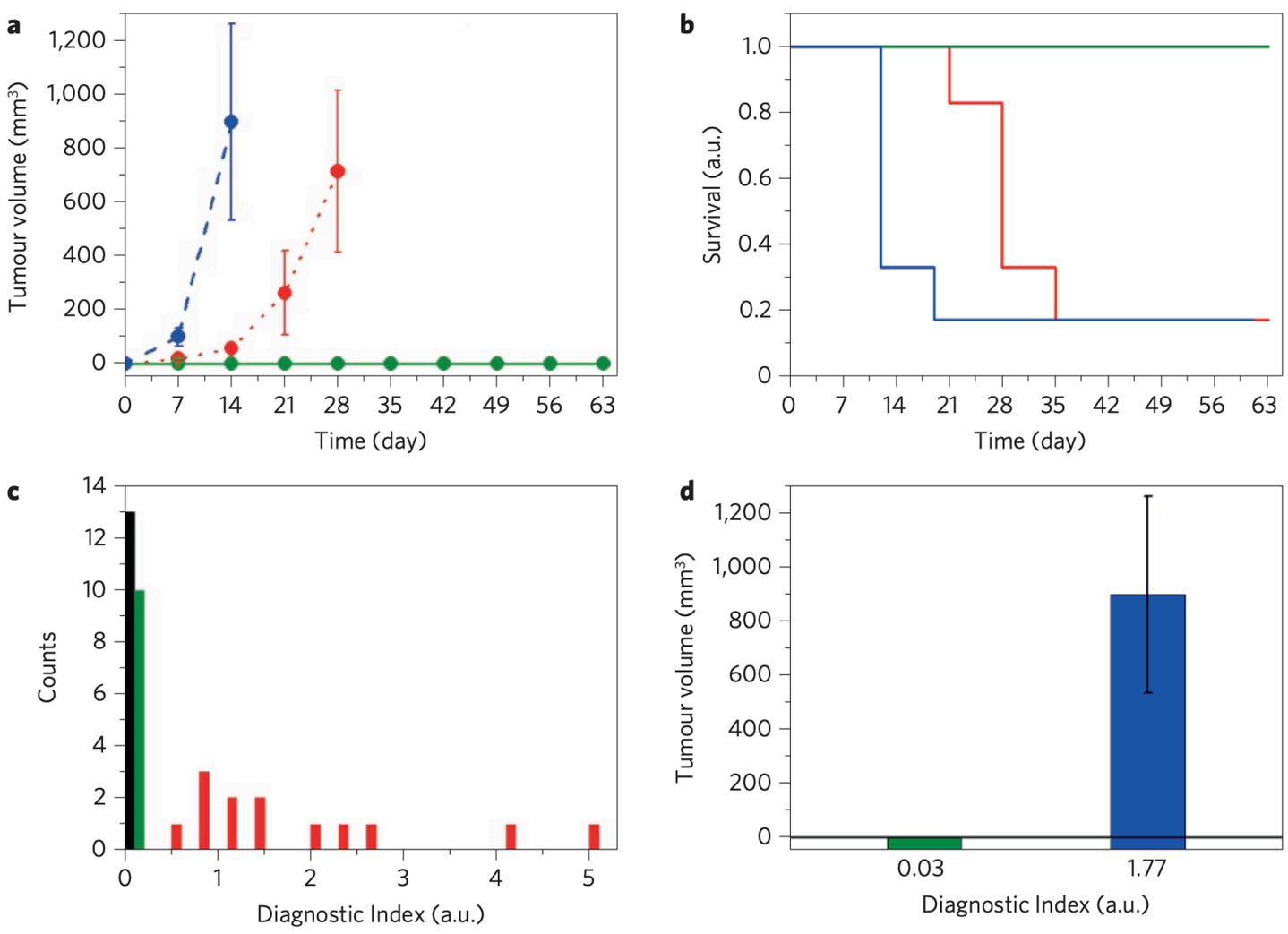
Plasmonic Nanobubble-Guided Surgery

PNB-guided surgery: Resectable MRDs

standard surgery

PNB-guided surgery of unresectable MRD

PNB-guided surgery of resectable MRD



100% survival rate on mouse model with resectable MRD

Lukianova-Hleb, E. et al. *Nat. Nano.* **2016**, *11*, 525.

Questions?

Wang, G. et. al. *ACS Nano*, **2016**, 2, 1788.