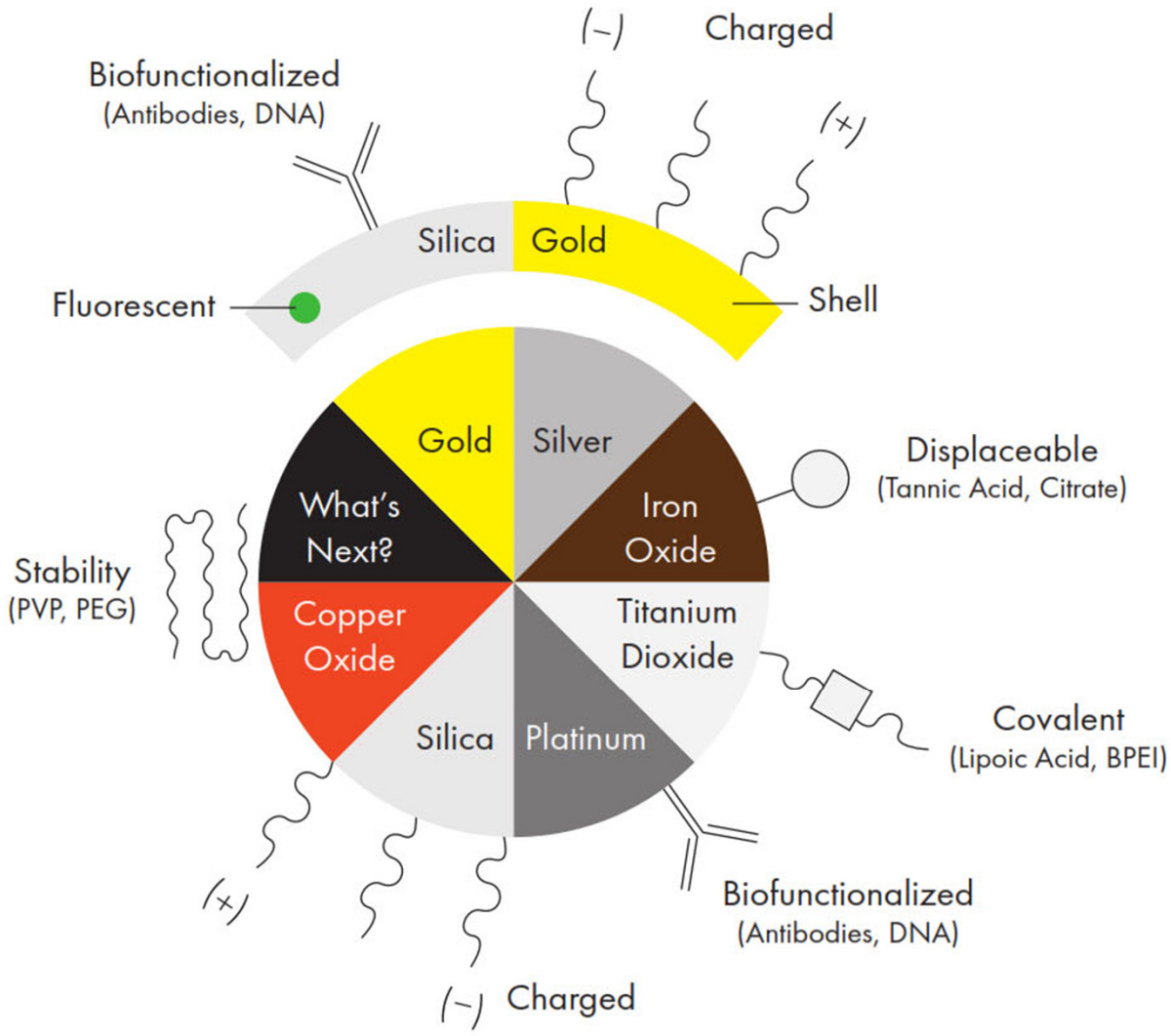
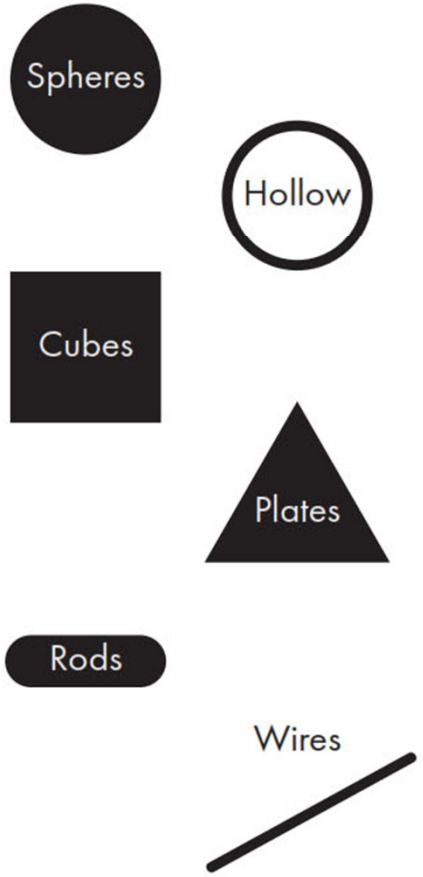
Plasmonic Nanoparticle Design for Commercial Diagnostic and Therapeutic Applications

Aaron E. Saunders

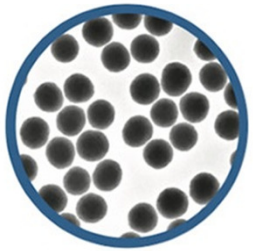
nanoComposix, Inc.
San Diego, California

Colloidal nanomaterial building blocks





nanoComposix



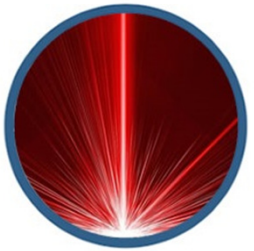
Bringing ***nano*** *from* ***concept*** *to* ***commercialization***

ANTIMICROBIAL

NANOSAFETY

NEXT GENERATION BIODIAGNOSTICS

PLASMONIC PIGMENTS



PHOTOTHERMAL THERAPY

Plasmonic Nanoparticles

Plasmonic Metal Nanoparticles

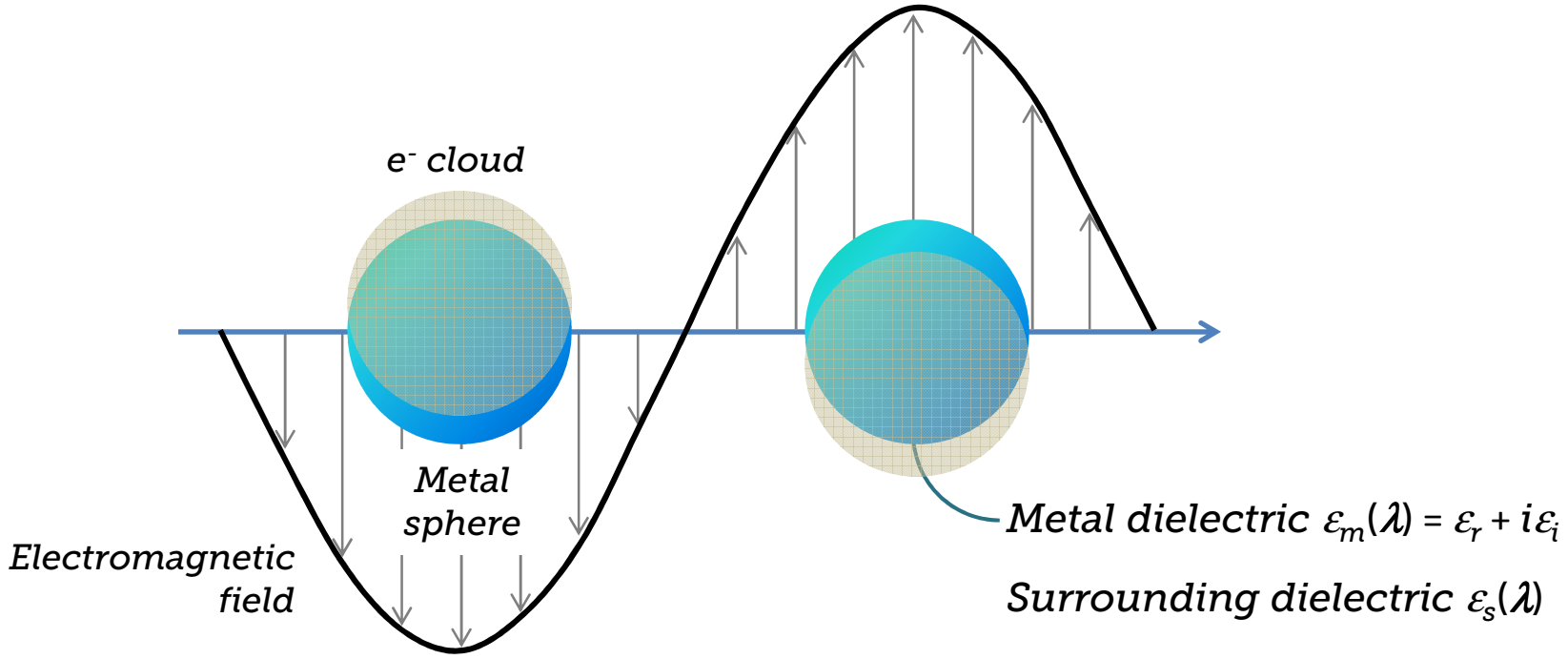
Gold particles in glass - Lycurgus Cup. Approximately 300 A.D.

Plasmonic Metal Nanoparticles

Colloidal gold. Approximately 1850-

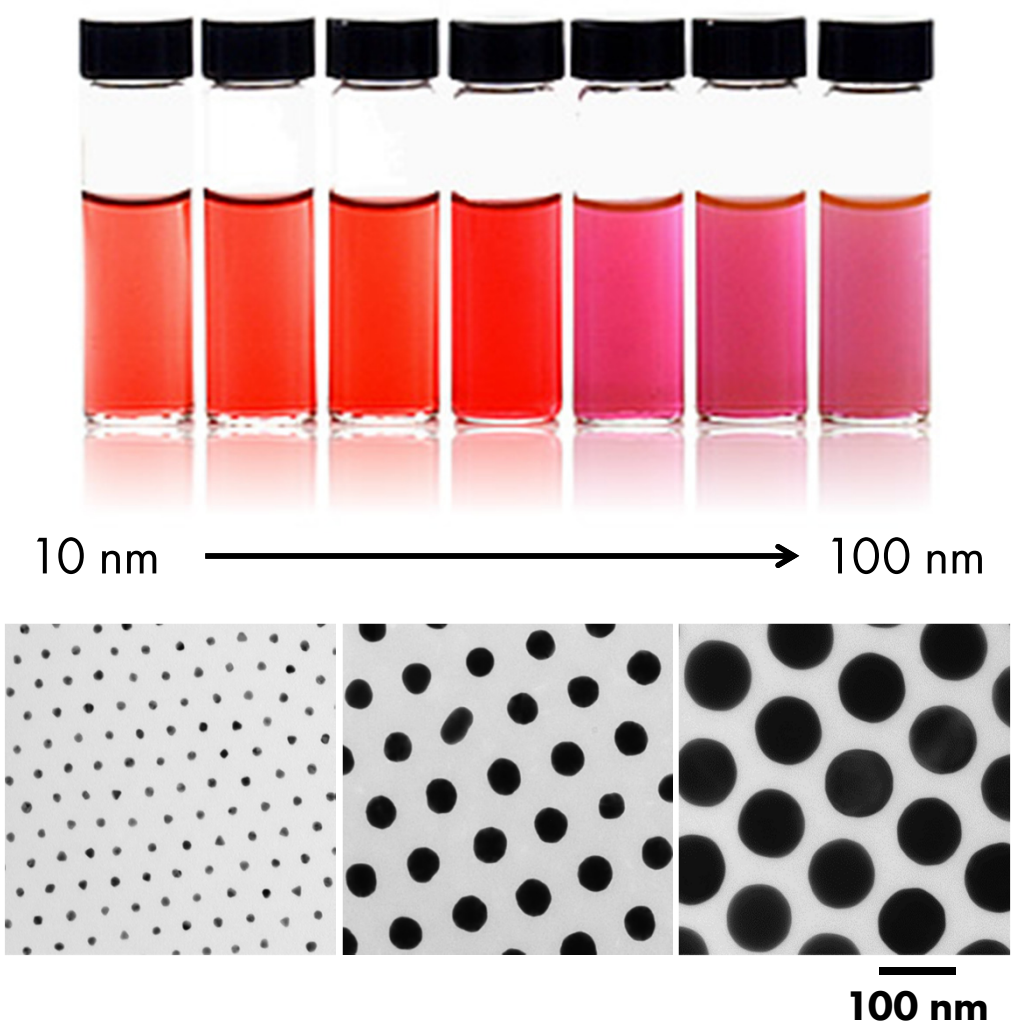
Surface Plasmon Resonance

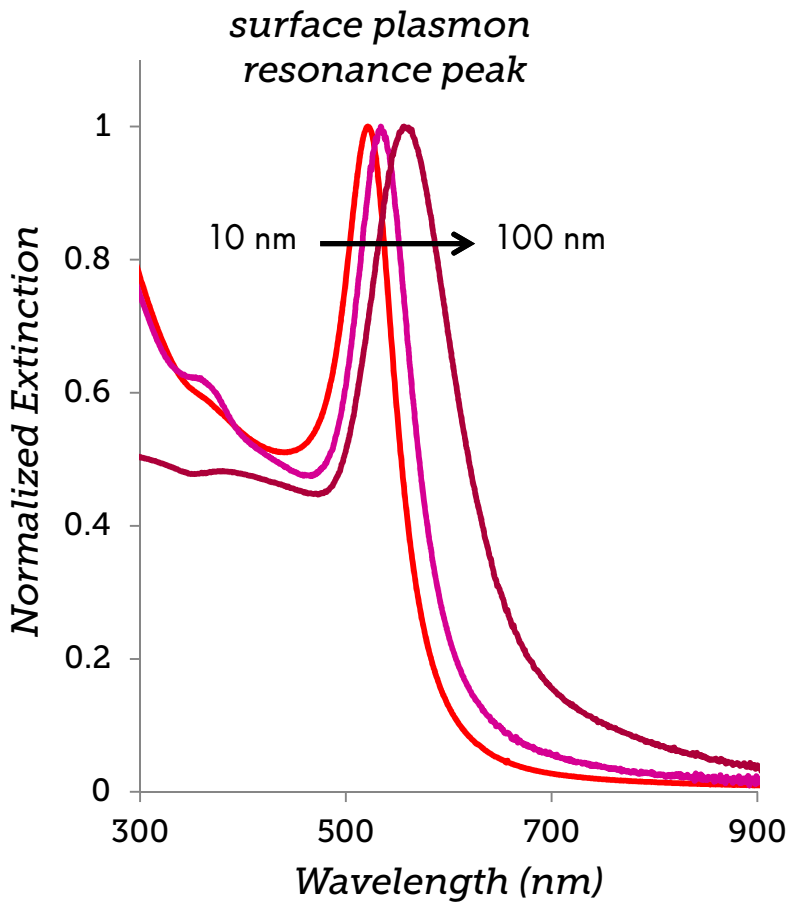
Oscillating electromagnetic field of incident light induces a coherent oscillation of free electrons in plasmonic metal nanoparticles



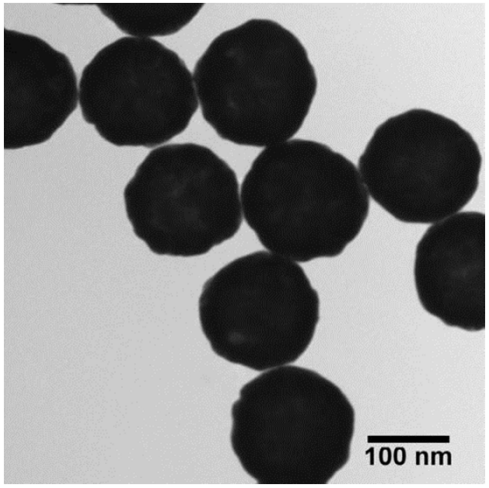
Extinction cross-section $\sigma_{ext} = \frac{24\pi^2 R^3 {\varepsilon_s}^{3/2}}{\lambda} \frac{\varepsilon_i}{(\varepsilon_r + 2\varepsilon_s)^2 + {\varepsilon_i}^2}$

Nanoparticle Morphology & Optical Response

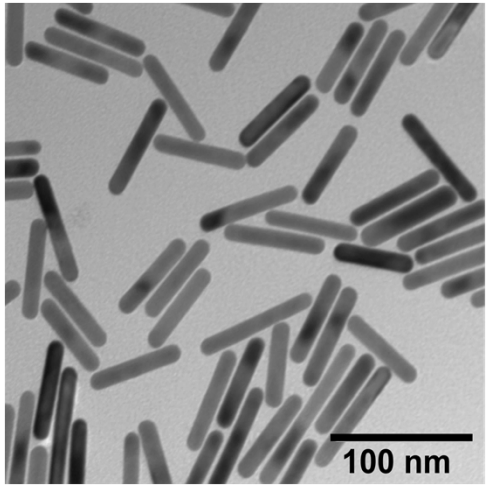




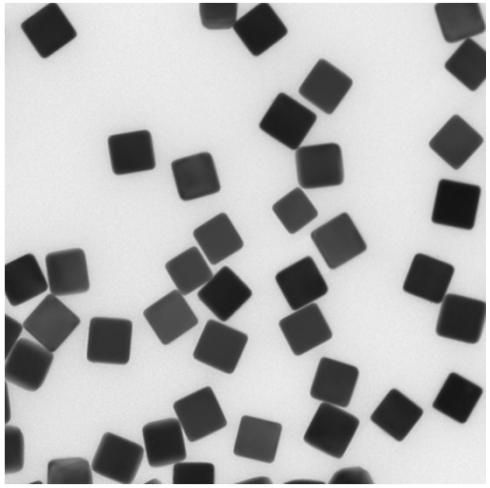
Nanoparticle Morphology



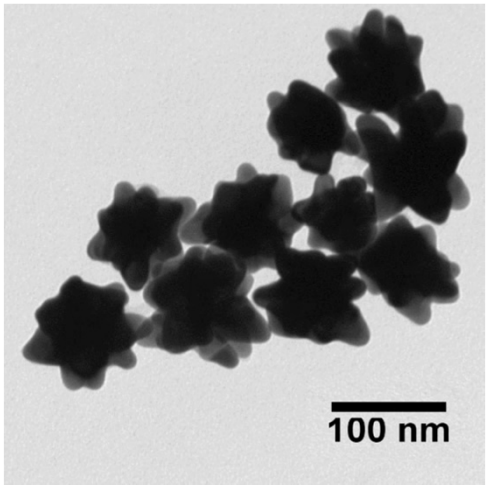
Gold nanoshells



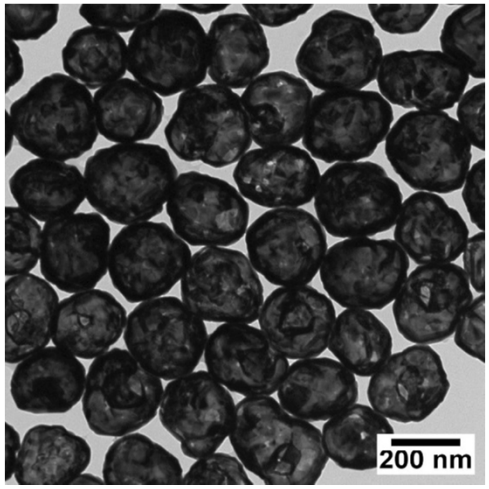
Gold nanorods



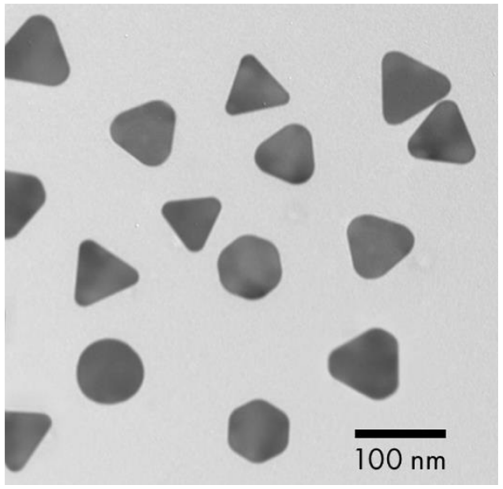
Silver cubes



Gold nanostars



Hollow gold nanoshells

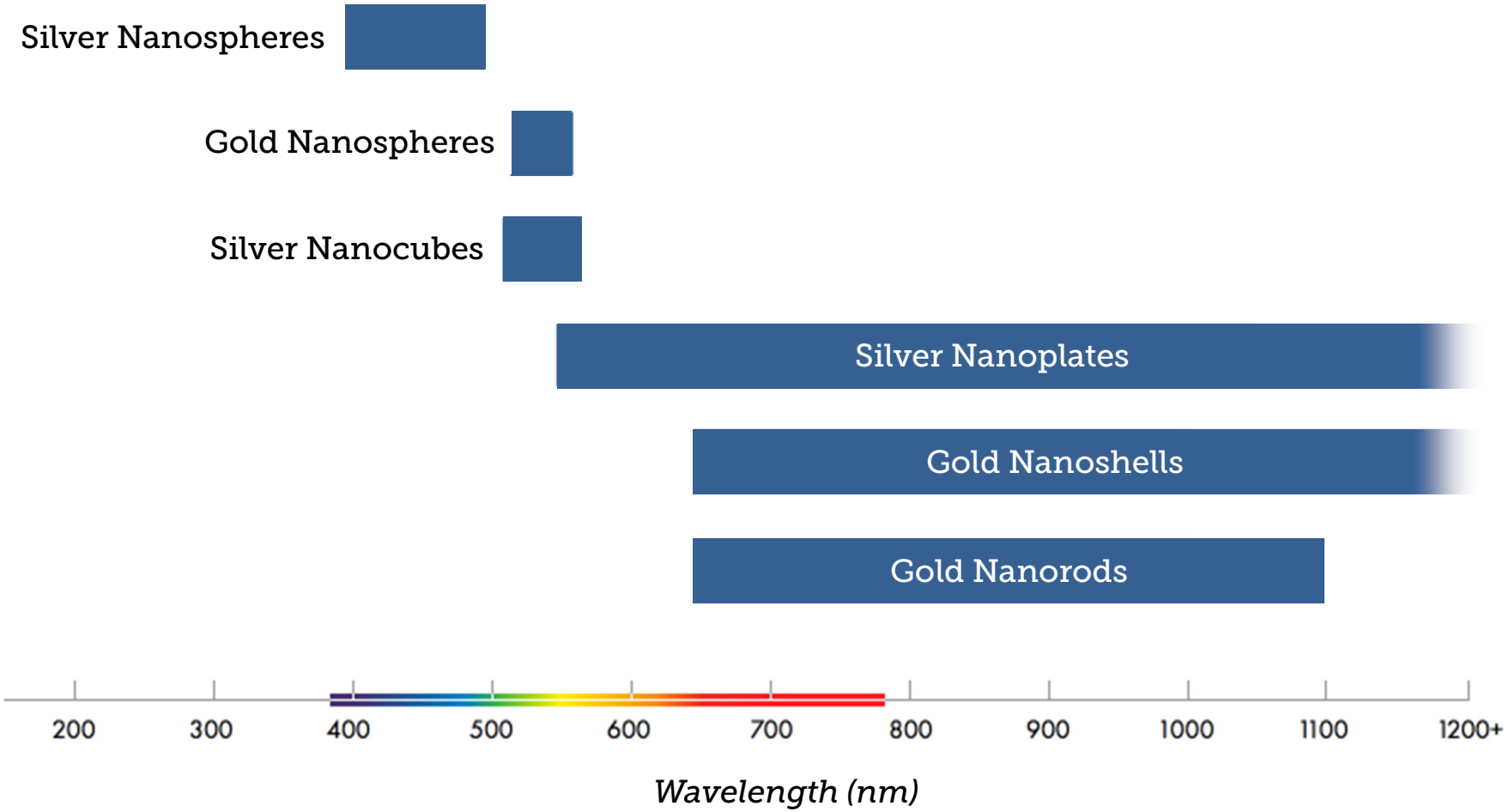


Silver nanoplates

Plasmonic Metal Nanoparticles

Optical response of metal nanoparticles is a function of the material, size, shape and local environment

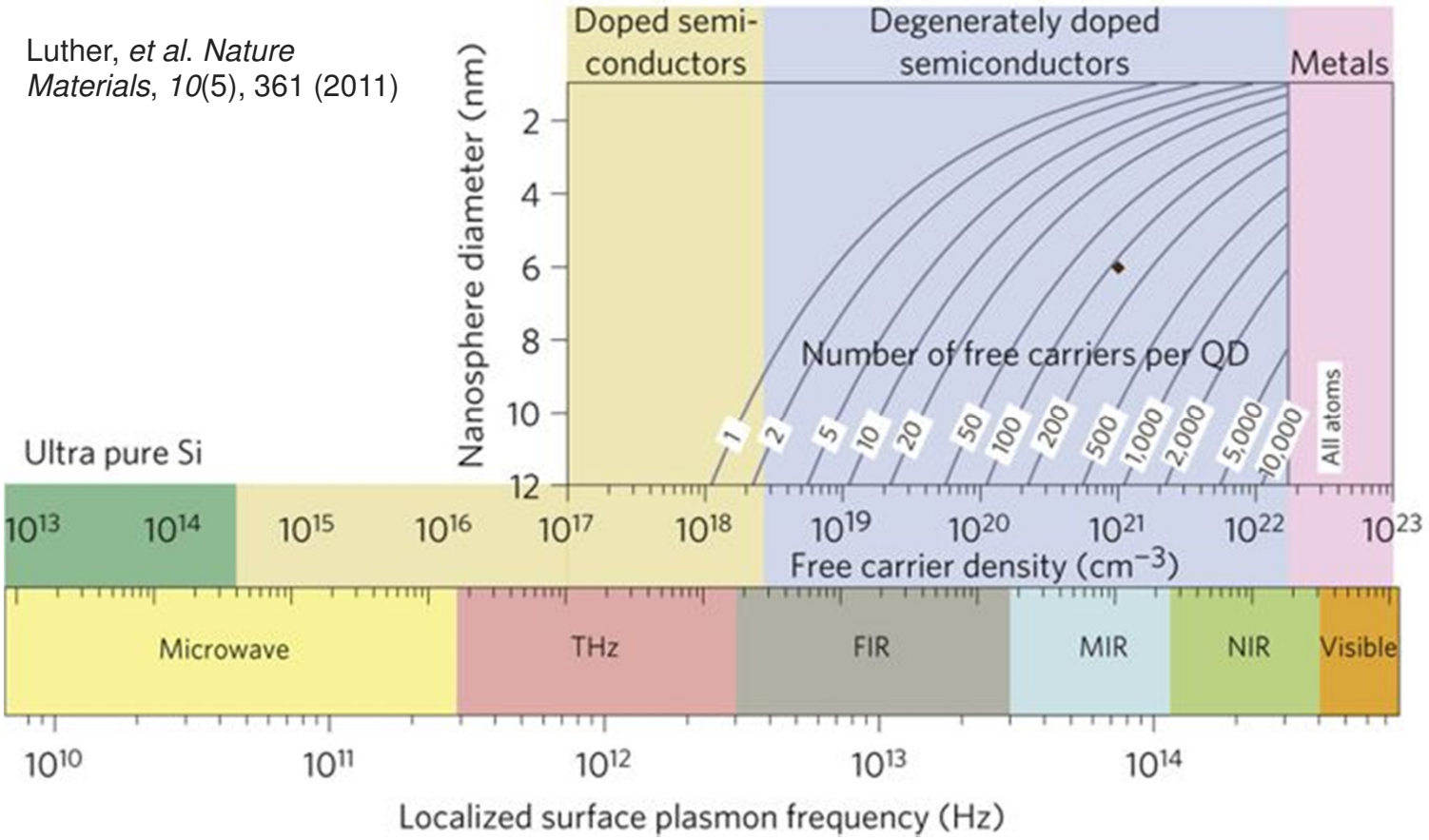
Nanoparticle Morphology & Optical Response



Tuning nanoparticle morphology and size allows the plasmon resonance to be tuned across the visible and near-IR.

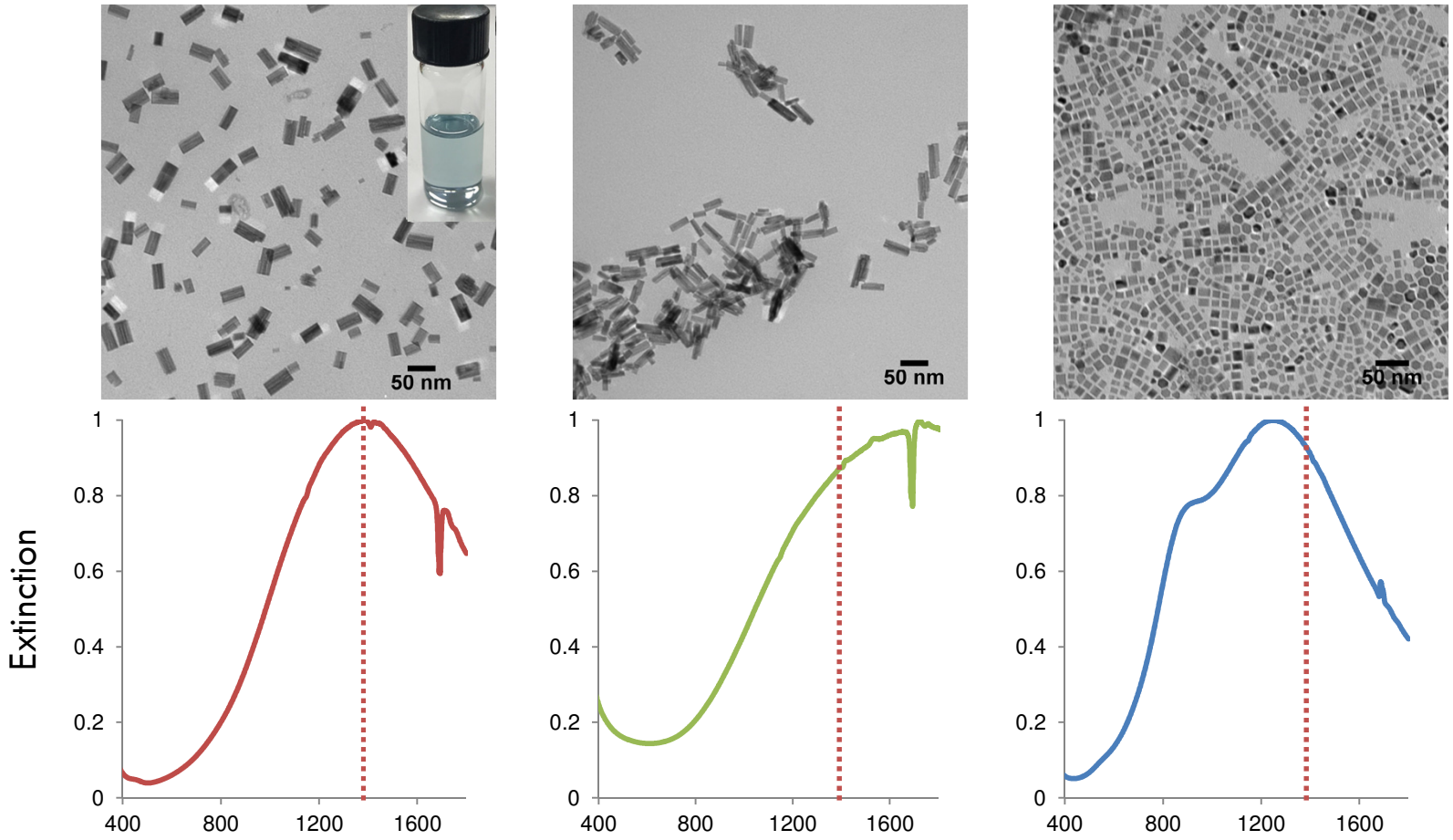
Plasmonic Semiconductor Nanoparticles

Luther, *et al. Nature Materials*, *10*(5), 361 (2011)



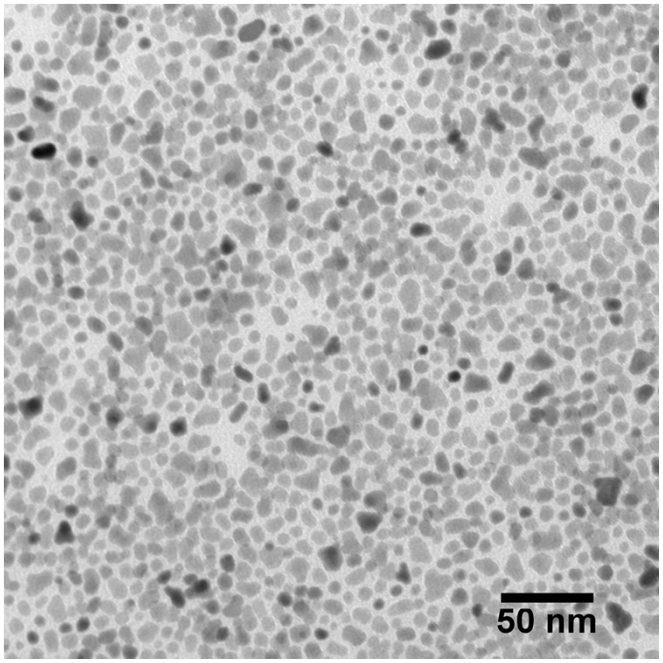
Free electrons can be added to semiconductor nanoparticles by dopant incorporation.

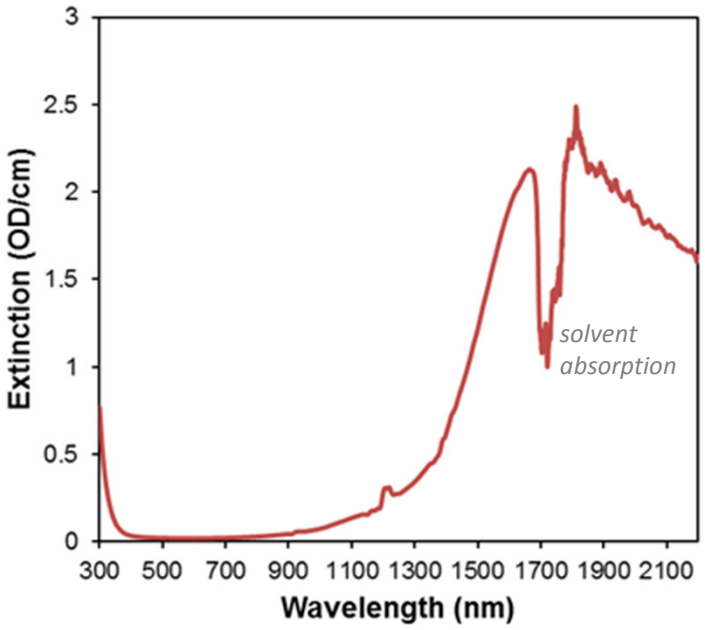
Cesium-doped Tungsten Oxide (WO_3:Cs)



Like metallic plasmonic nanoparticles, the optical properties of the WO_3 nanoparticles can be tuned by changing size and aspect ratio or morphology.

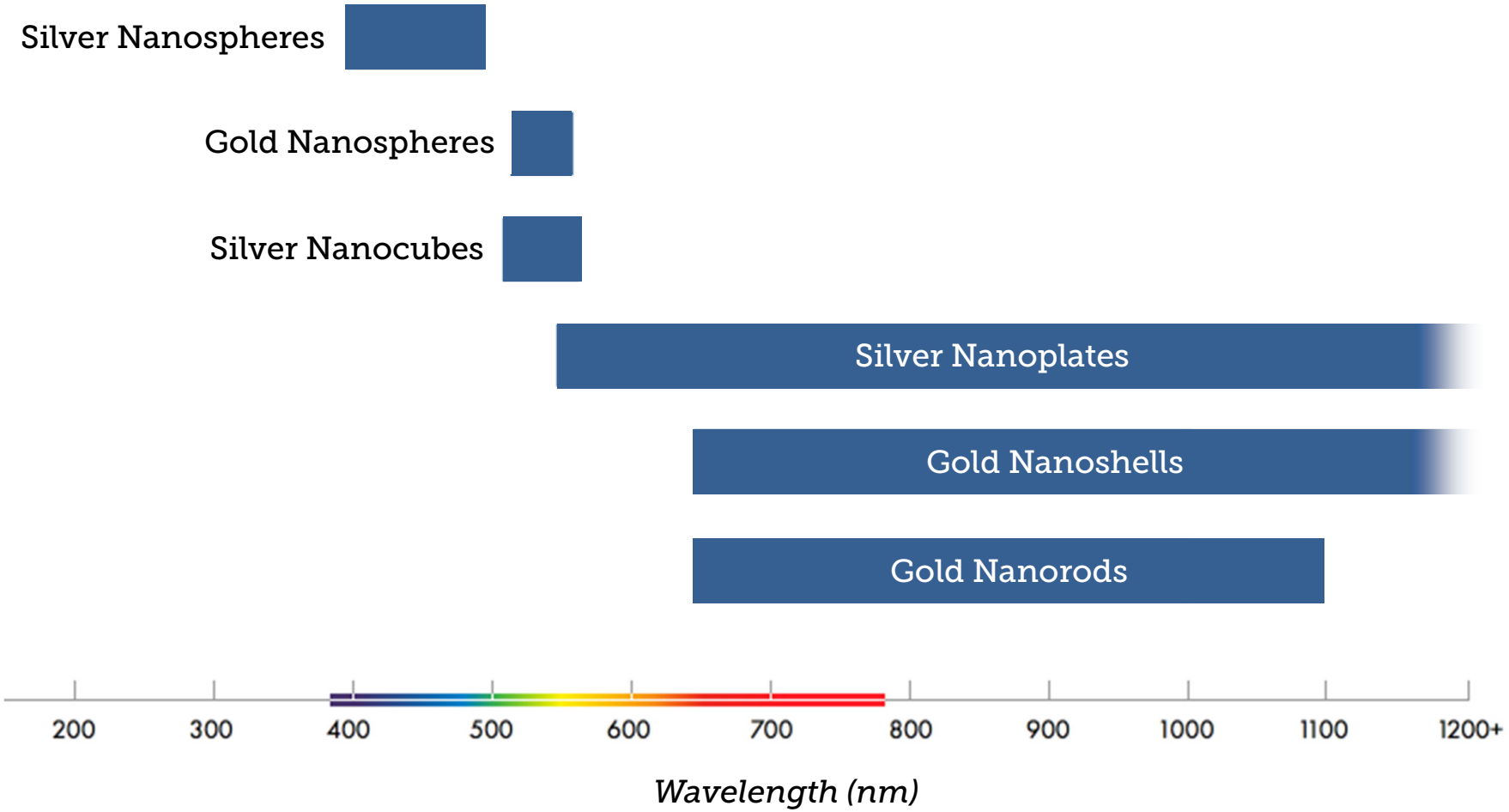
Indium-doped Tin Oxide (ITO)





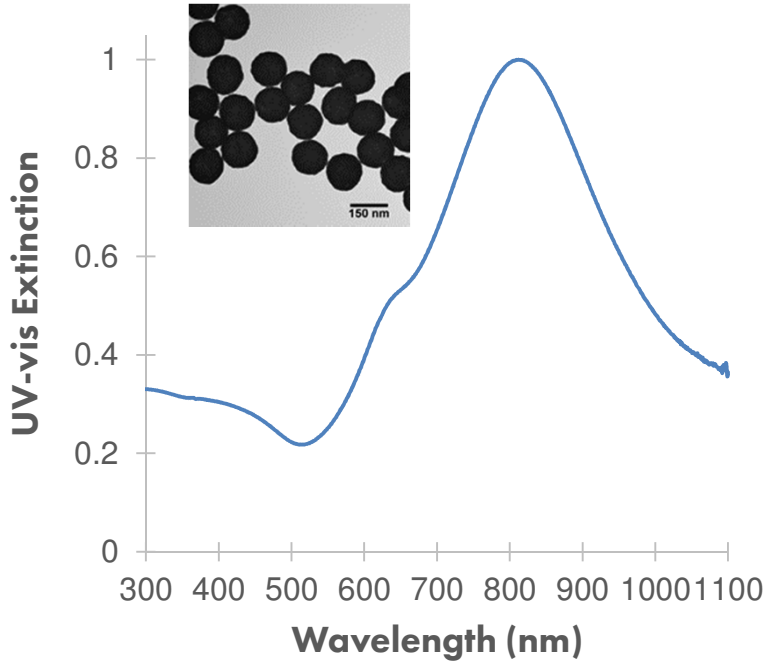
Colloidal indium-doped tin oxide nanoparticles can be fabricated with Sn doping levels between 3-30%. The particle are highly transparent in the visible, with a plasmon resonance in the NIR that can be tuned to a peak absorption between 1600-2000 nm, depending on Sn doping.

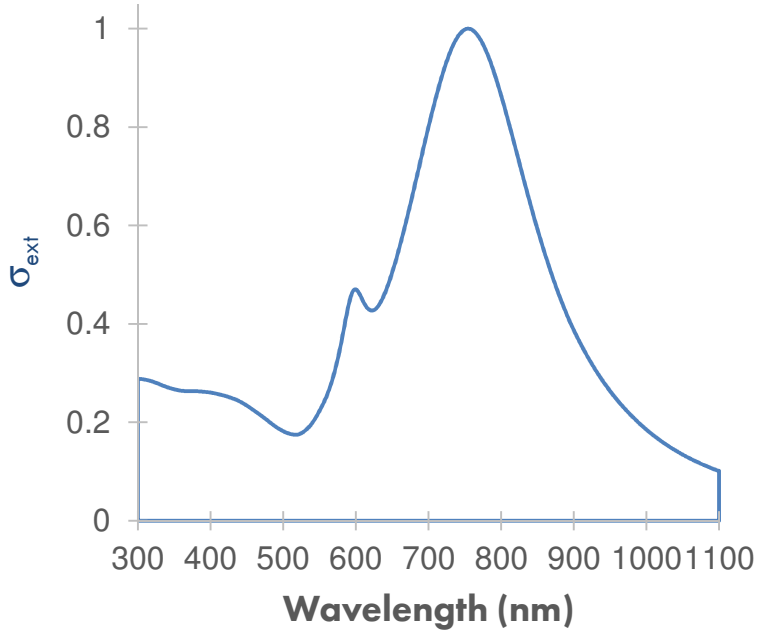
Nanoparticle Morphology & Optical Response



Tuning nanoparticle morphology and size allows the plasmon resonance to be tuned across the visible and near-IR.

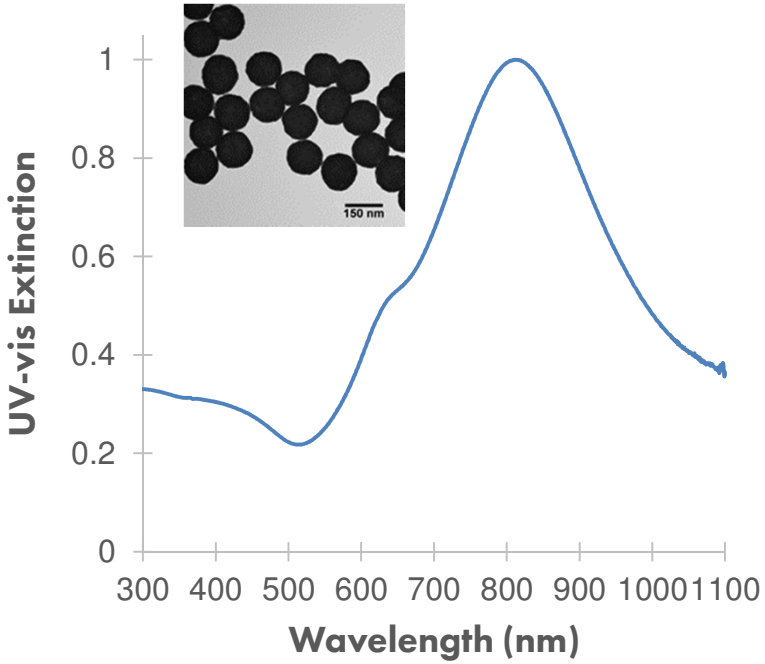
Nanoparticle Selection - Scattering/Absorption

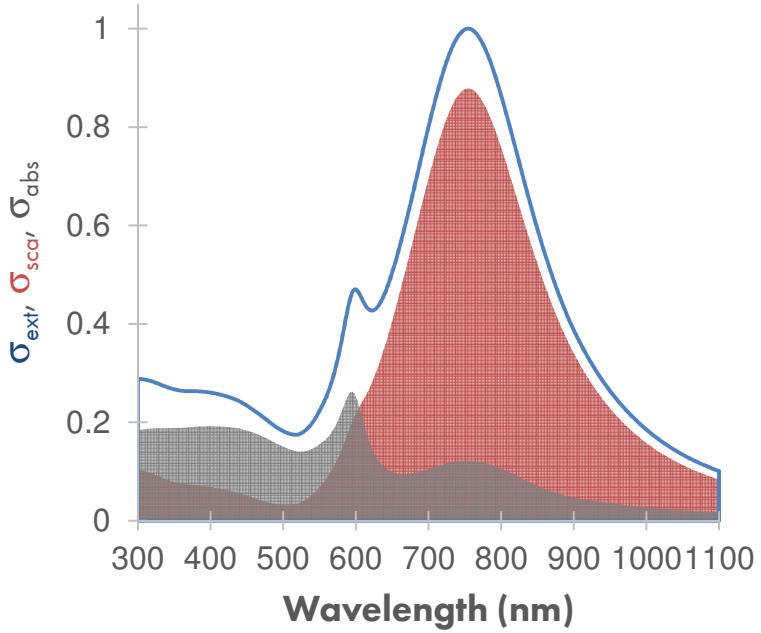




Nanoparticles can scatter and/or absorb light, depending on composition and morphology. UV-vis spectroscopy only measures total extinction, the sum of the scattering and absorption.

Nanoparticle Scattering/Absorption Split





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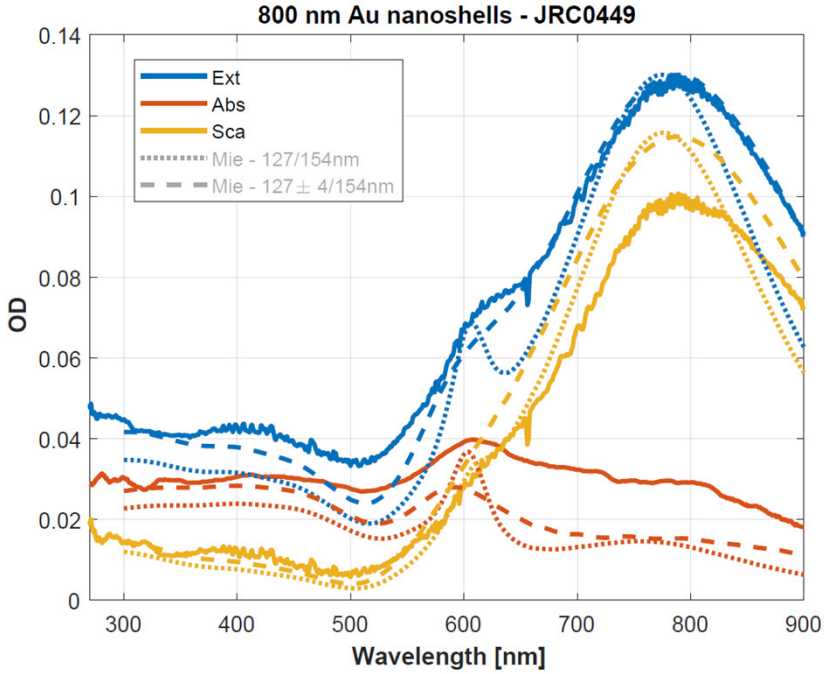

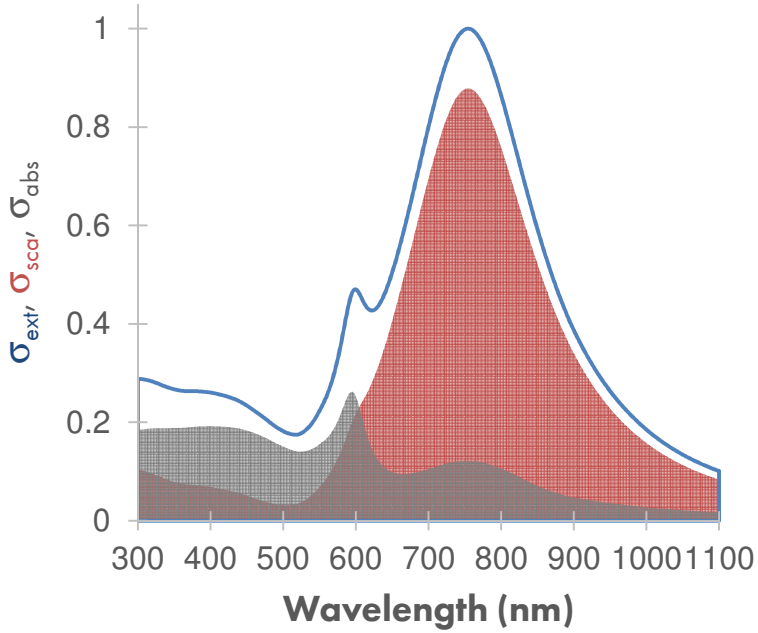

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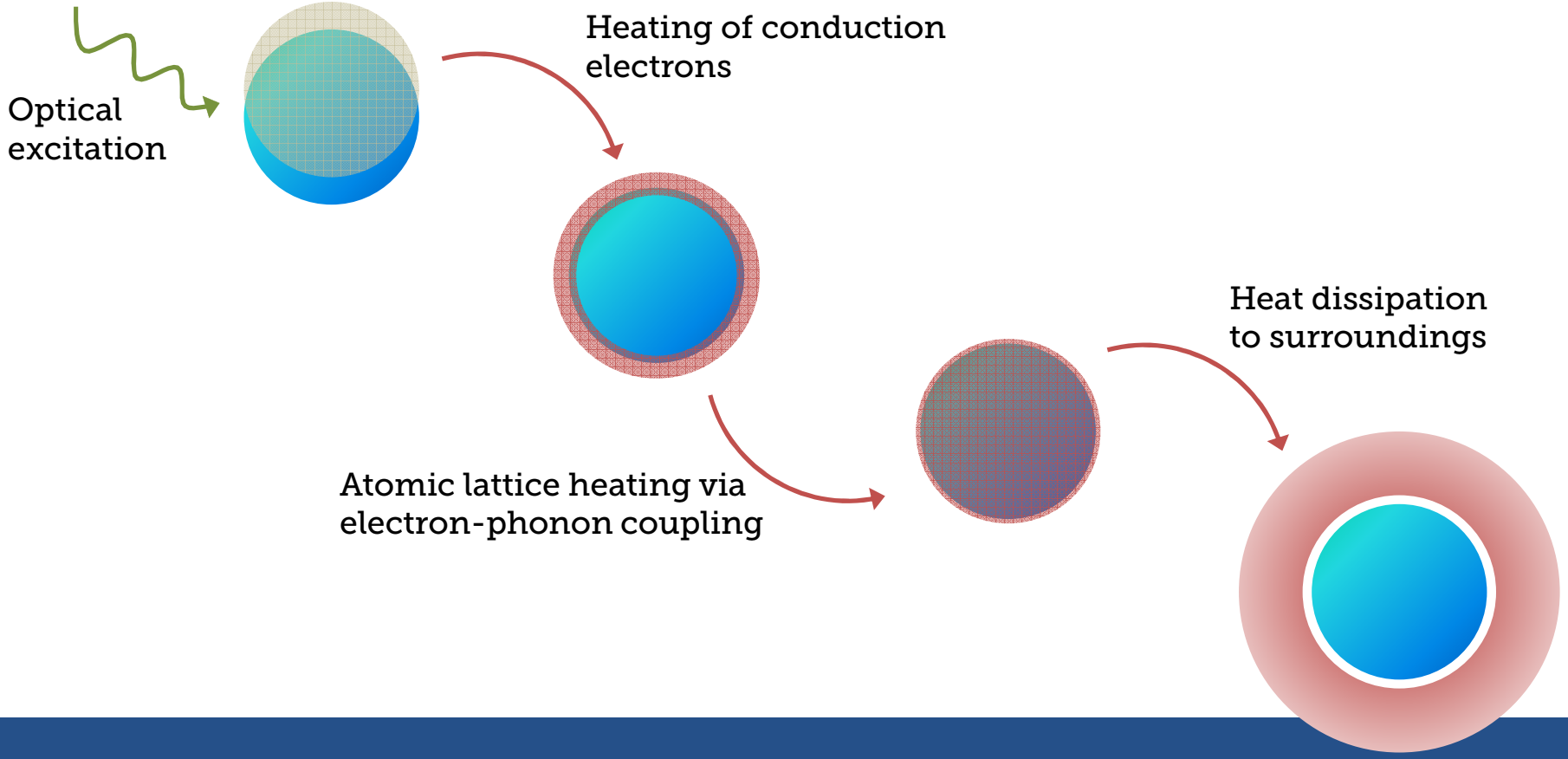
Photothermal Applications

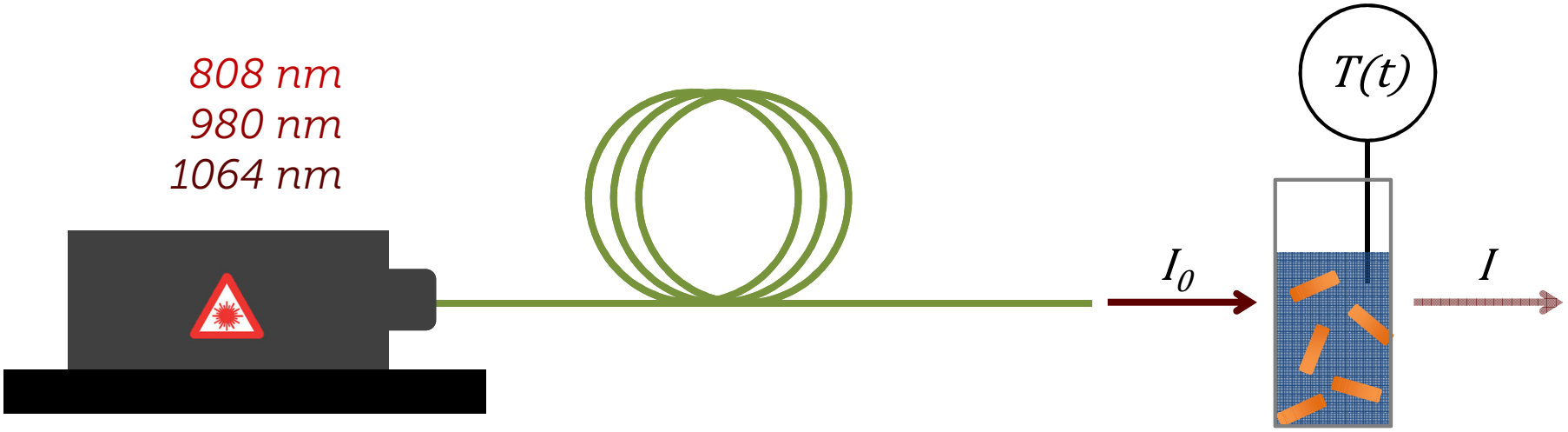
Photothermal Properties

The energy of absorbed photons is transferred to the nanoparticle through the optically excited electrons, and then released to the surrounding environment.



Photothermal Measurements

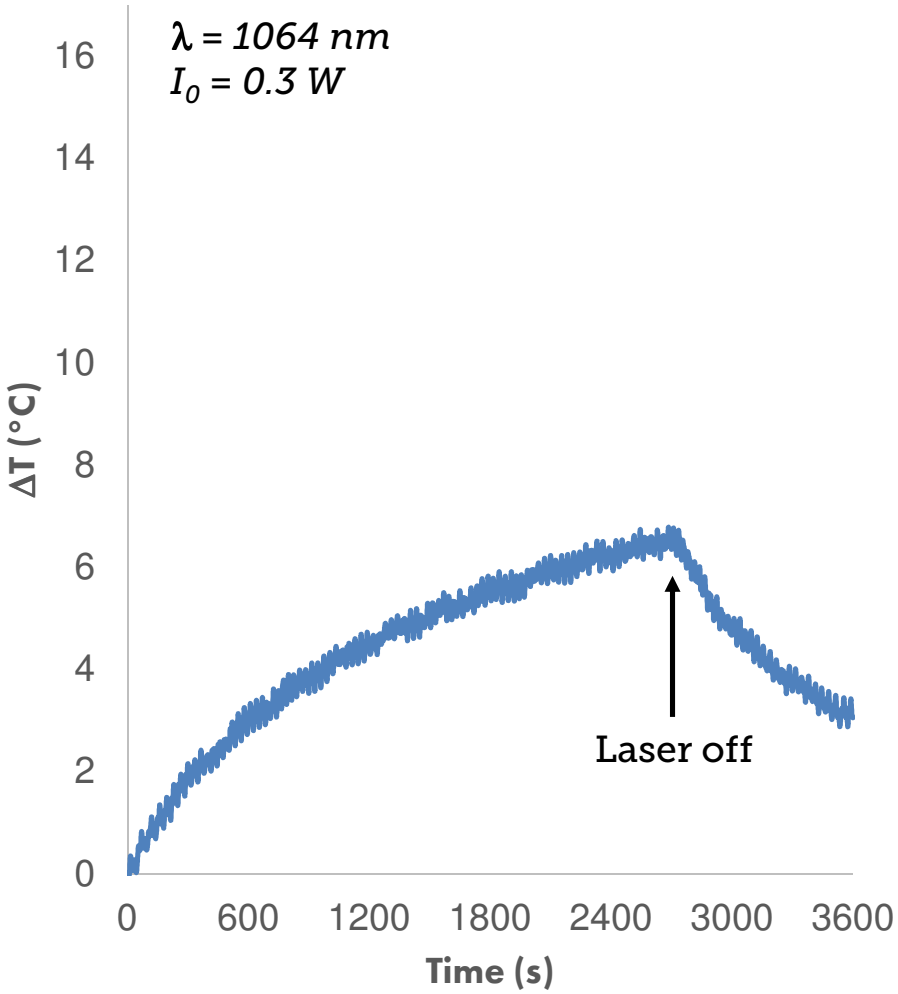
Bulk heating experiments are useful for comparing photothermal efficiency of different nanomaterials.



The temperature profile of a nanoparticle dispersion is measured during CW irradiation by a NIR laser.

Compare nanomaterials that all have the same extinction maximum.

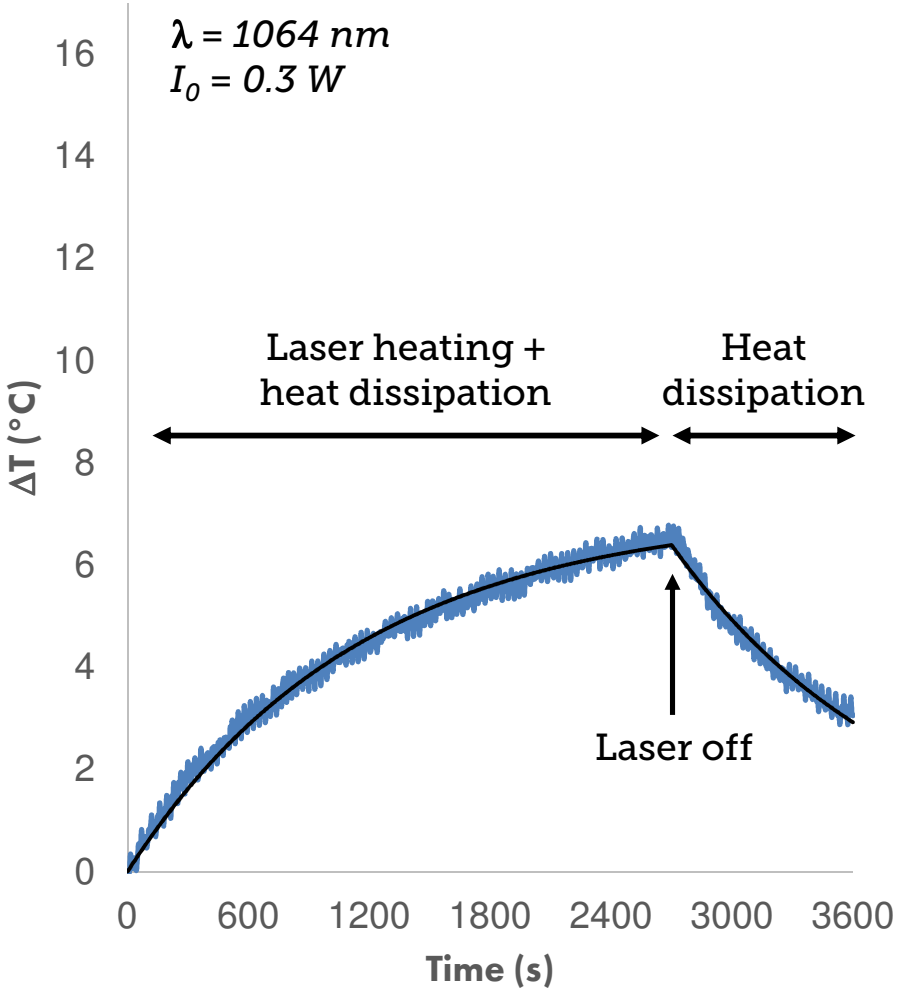
Photothermal Measurements



Water has a non-negliglble absorbance in the NIR and will heat under laser irradiation.

Contribution of water to the heating of nanoparticles dispersions must be taken into account.

Photothermal Measurements



An energy balance on the system can be solved to yield

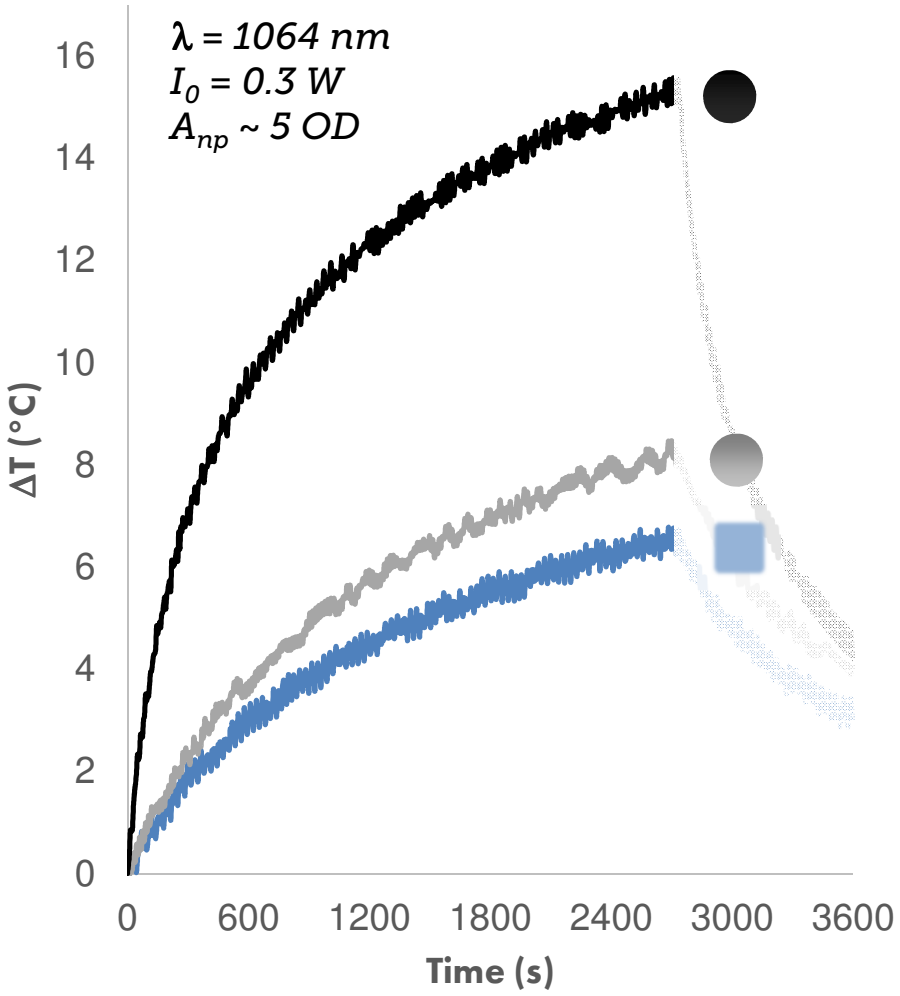
$$\Delta T(t) = \begin{cases} \frac{A'}{B'}\left(1 - e^{-B' \cdot t}\right) \\ (T_{max} - T_{amb})e^{-B' \cdot t} \end{cases}$$

where

$$A' = \frac{Q_{in,np} + Q_{in,w}}{\sum m_i C_{p,i}} = \frac{I_0\left(1 - 10^{-A_{np,1064}}\right)\eta + Q_{in,w}}{\sum m_i C_{p,i}}$$

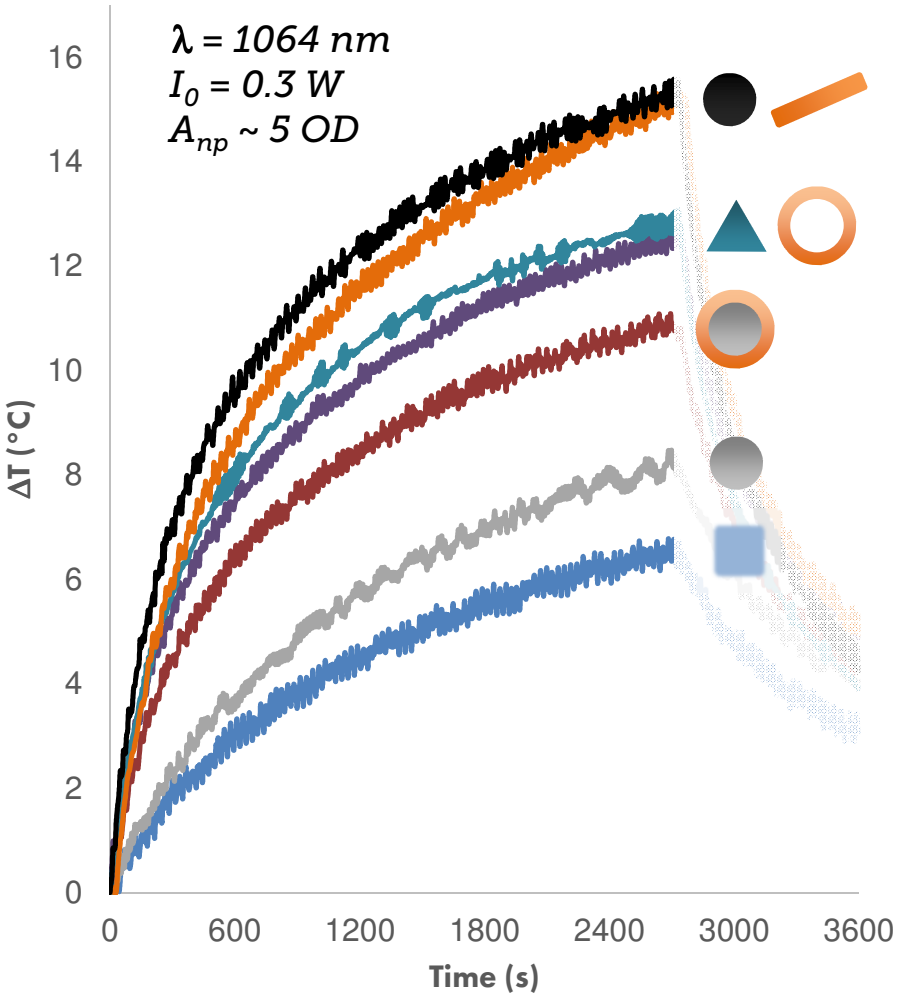
$$B' = \frac{hS}{\sum m_i C_{p,i}}$$

Photothermal Measurements



Measurements on colloidal systems that are primarily scattering (silica nanospheres) or absorbing (carbon black) bracket the expected response range from plasmonic nanoparticles

Photothermal Measurements

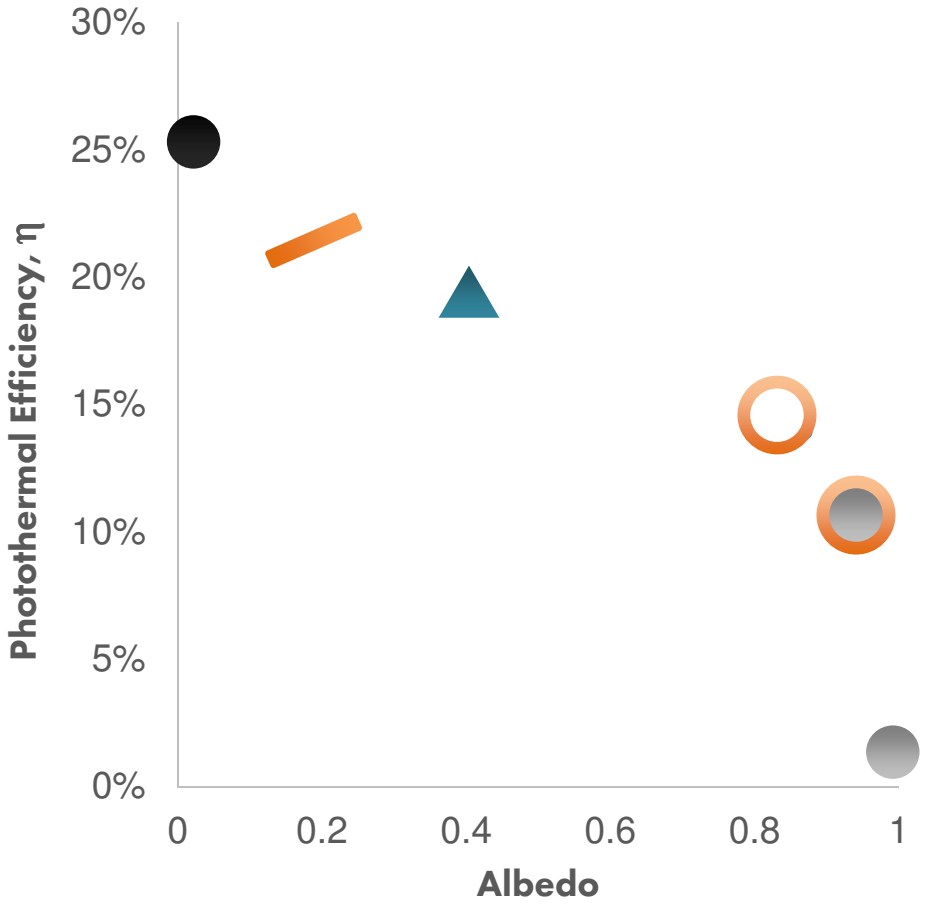


Measurements on plasmonic nanoparticles show particle-dependent heating profiles, with gold nanorods ( ) reaching the highest temperature, followed by silver nanoplates ( ), hollow gold nanoshells ( ), and silica-core gold nanoshells ( ).

From the energy balance modeling, we can calculate the photothermal efficiency η for each material as

$$\eta = \frac{hS(T_{max} - T_0) - Q_{in,w}}{I_0(1 - 10^{-A_{1064}})}$$

Photothermal Measurements



The nanoparticle albedo is the ratio of scattering to total extinction and varies from 0 (completely absorbing) to 1 (completely scattering)

$$Albedo = \frac{\sigma_{sca}}{\sigma_{ext}}$$

As albedo increases – the particles become more scattering – the photothermal efficiency decreases.

Commercial Photothermal Applications

Some of the first commercial photothermal nanoparticle uses have focused on cosmetic and dermatology applications.

sienna biopharmaceuticals

Silver nanoplate-based photothermal treatment of acne and hair removal. Topical application, currently finishing U.S. clinical trials.

SEBACIA

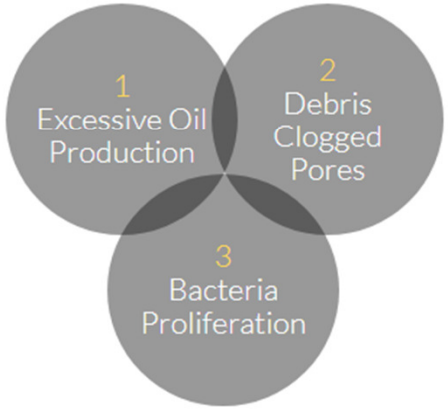
Gold nanoshell-based photothermal treatment of acne. Topical application, currently in clinical U.S. trials, approved products in EU.

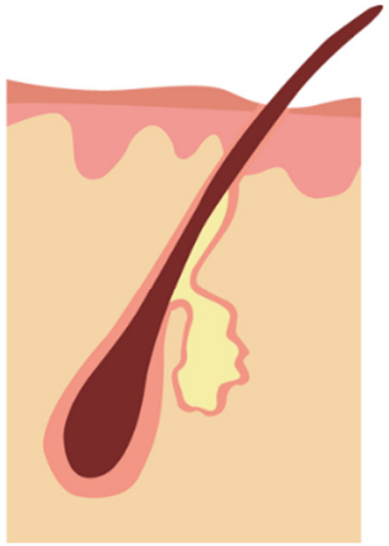
Commercial Photothermal Applications

SEBACIA

What Causes Acne?

Acne is caused by 3 main factors:

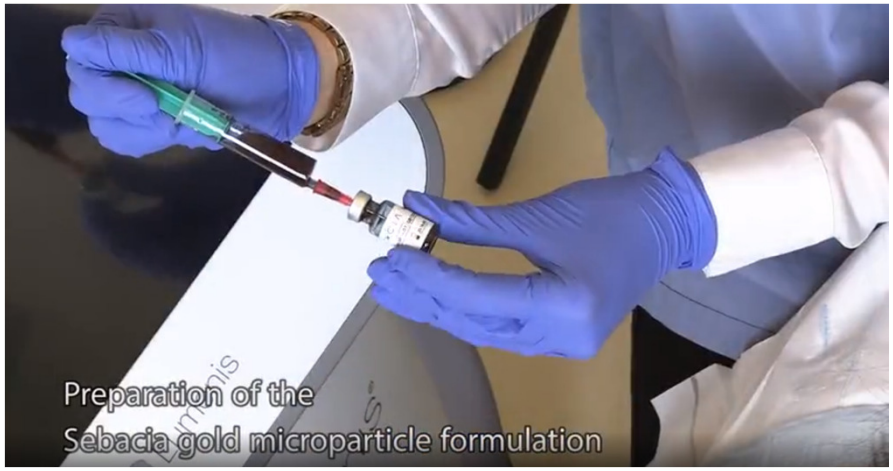




Normal

Acne

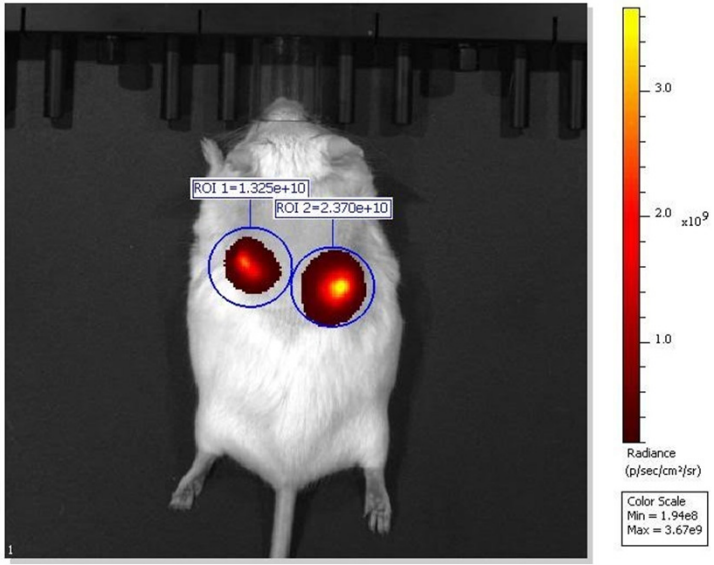
Commercial Photothermal Applications



Commercial Photothermal Applications

La Jolla NanoMedical

Gold nanorod based-photothermal treatment of skin cancer. Injectable, currently in animal trials.



La Jolla NanoMedical

Nanospectra Biosciences

Gold nanoshell-based photothermal treatment of prostate cancer. Injectable/intravenous administration, currently in clinical trials.

IV Bag of AuroShells

Nanospectra

Commercial Photothermal Applications

NANOSPECTRA

Diagnostic Applications

Lateral Flow Assays

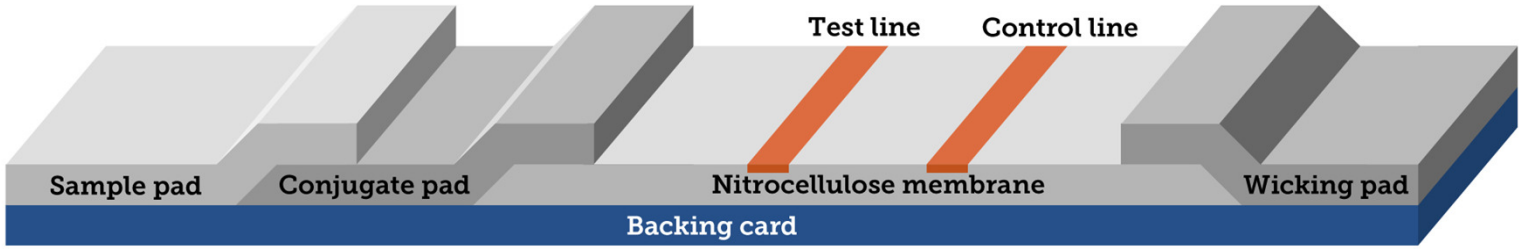
Lateral flow assays or strip tests, are simple devices intended to detect the presence (or absence) of a target analyte in a sample without the need for specialized and costly equipment.

Lateral Flow Assays

Lateral flow assays or strip tests, are simple devices intended to detect the presence (or absence) of a target analyte in a sample without the need for specialized and costly equipment.

Applications

- clinical/point-of-care testing
- veterinary diagnostics
- drug testing
- quality assurance



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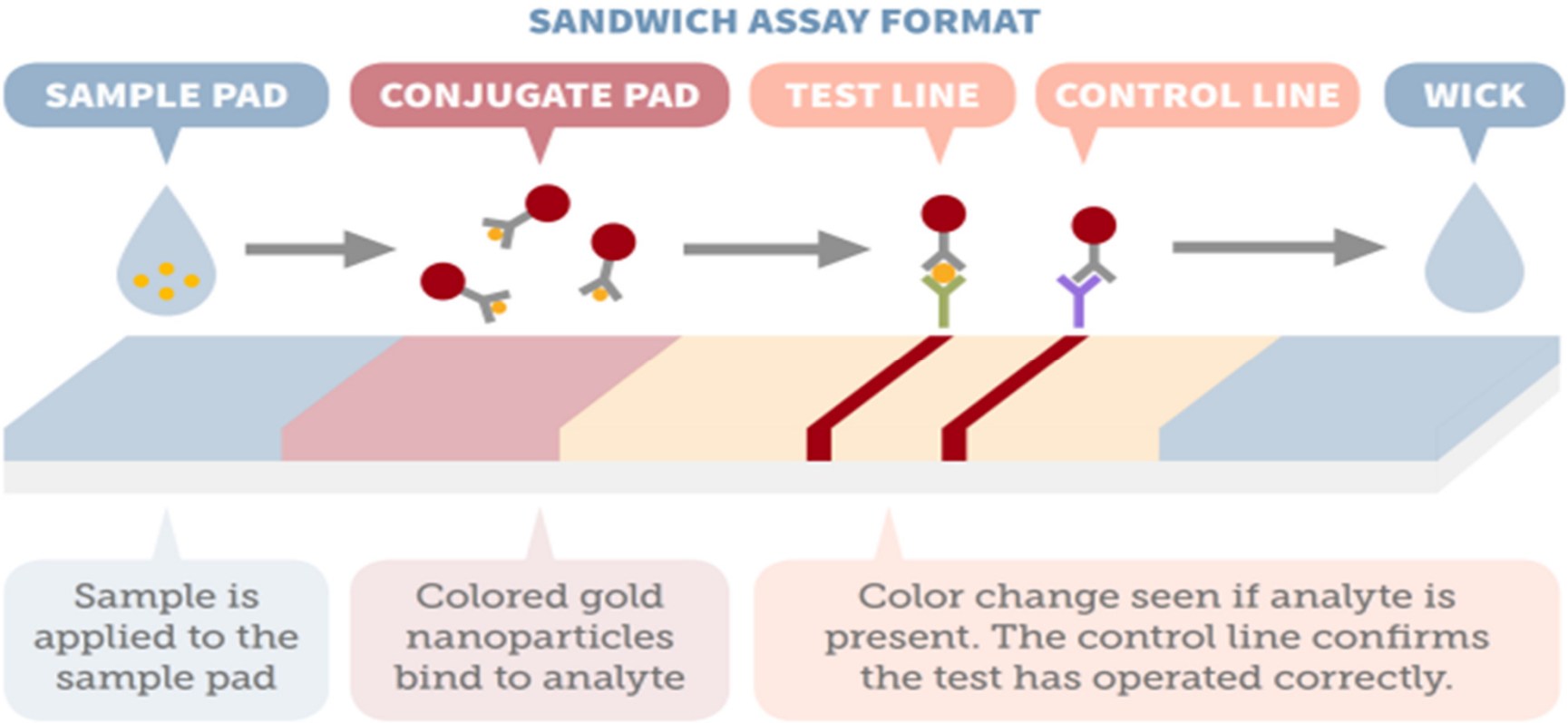
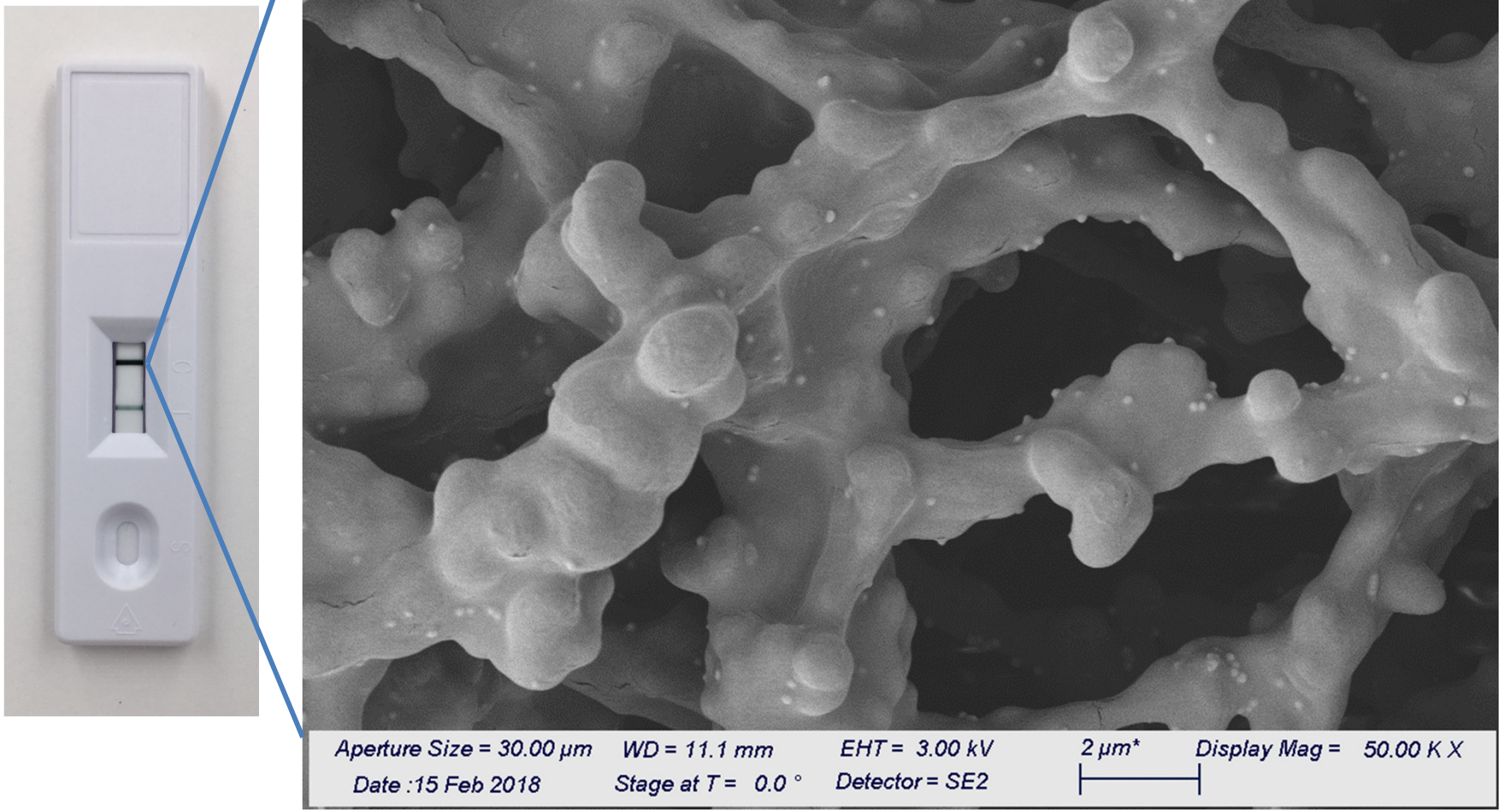
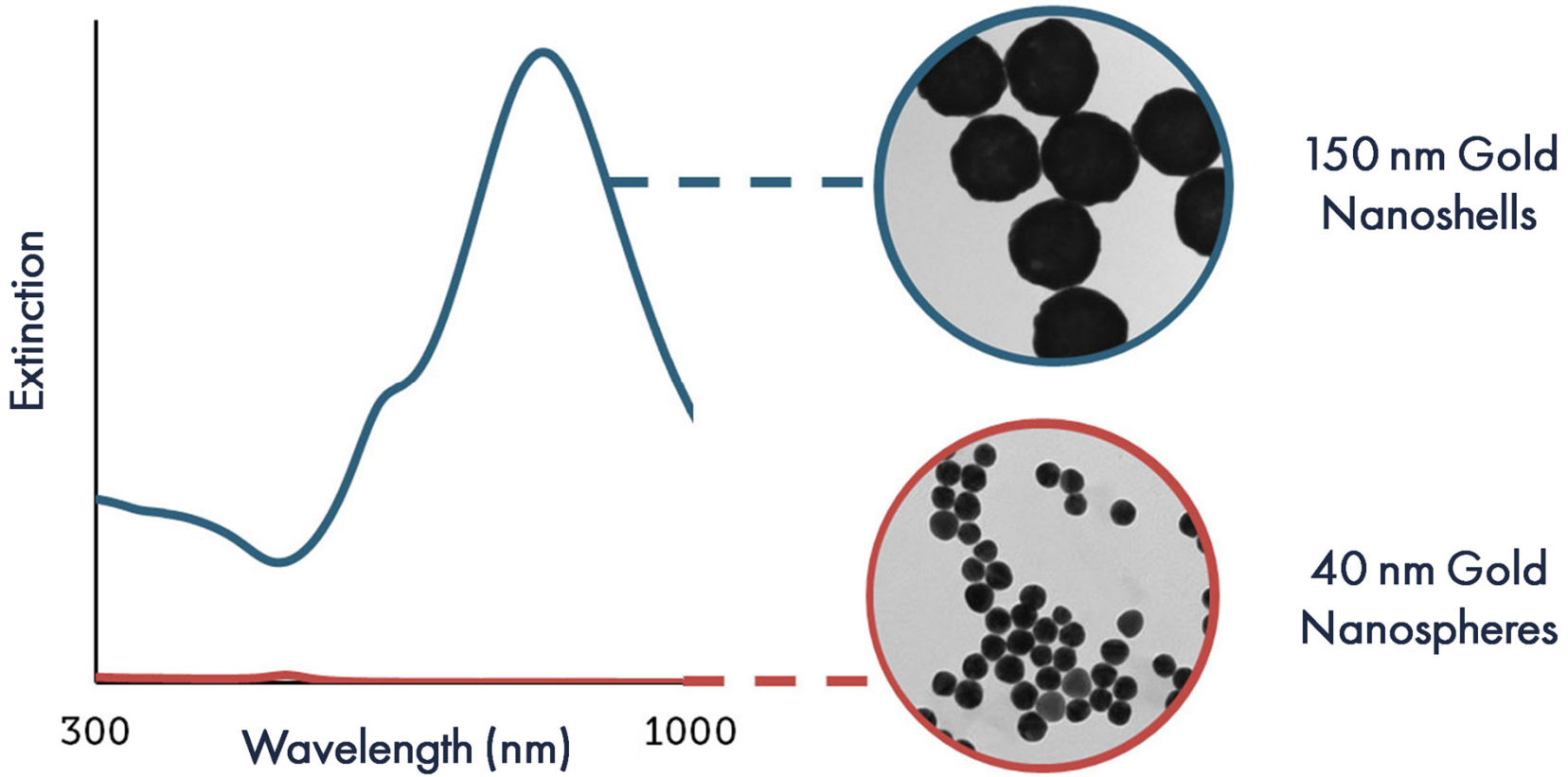


Nanoparticle binding on nitrocellulose

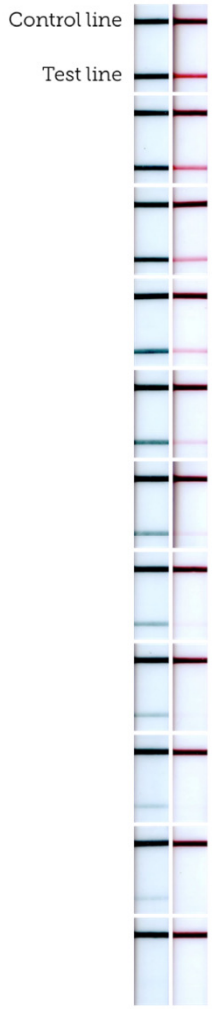


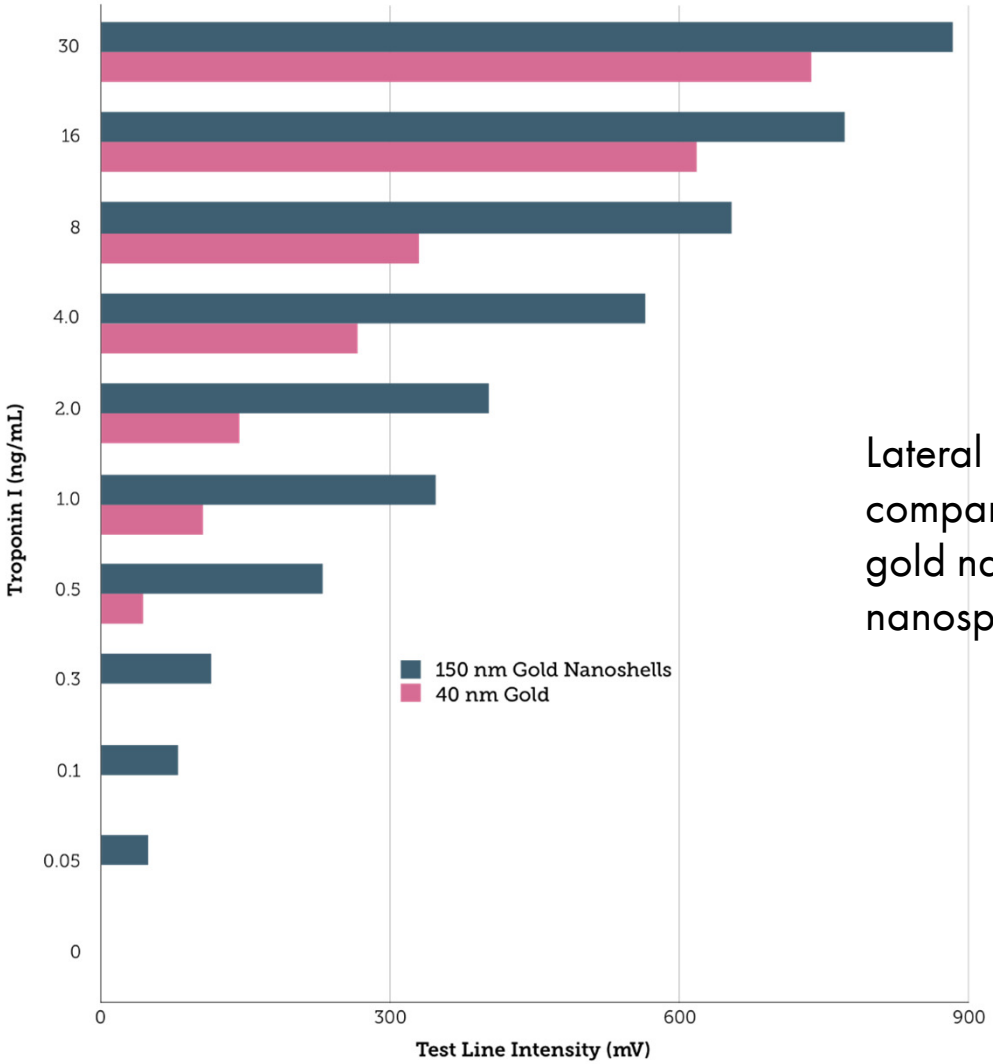
Maximizing signal per binding event



Comparison between per particle extinction of
40 nm gold nanospheres and 150 nm nanoshells

Maximizing signal per binding event

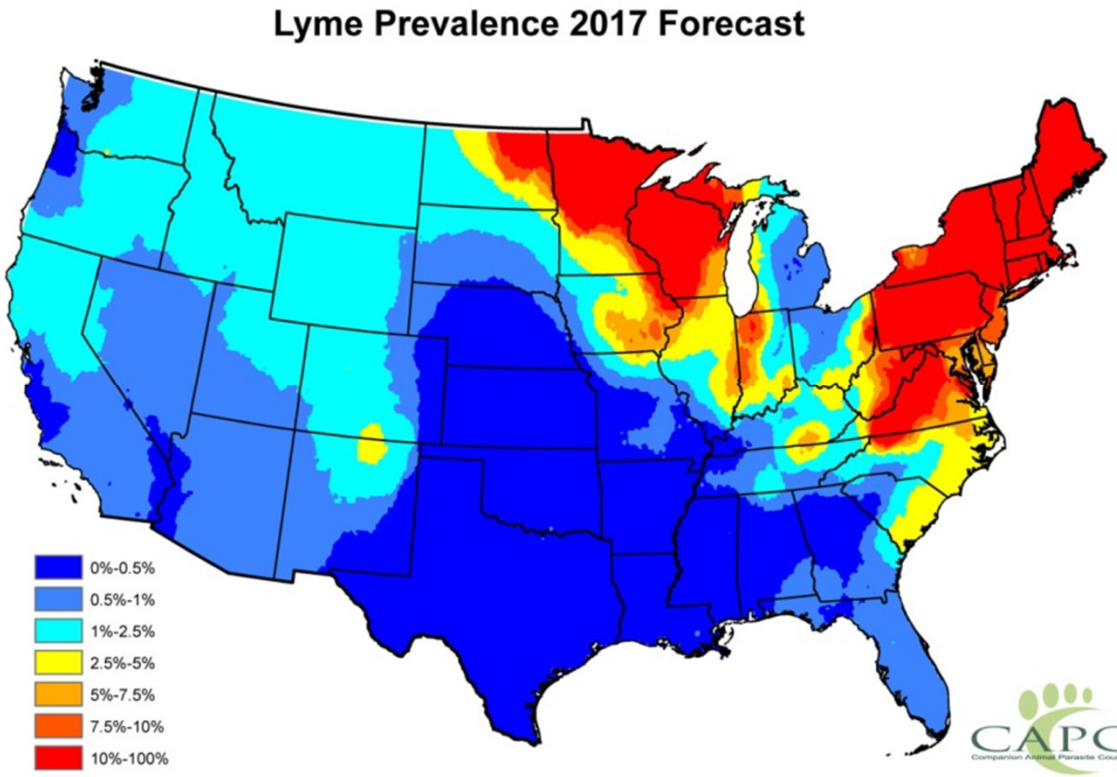




Lateral flow Troponin I sensitivity comparison between 150 nm gold nanoshells and 40 nm gold nanospheres reporter particles

Lyme Disease: An Increasing Threat

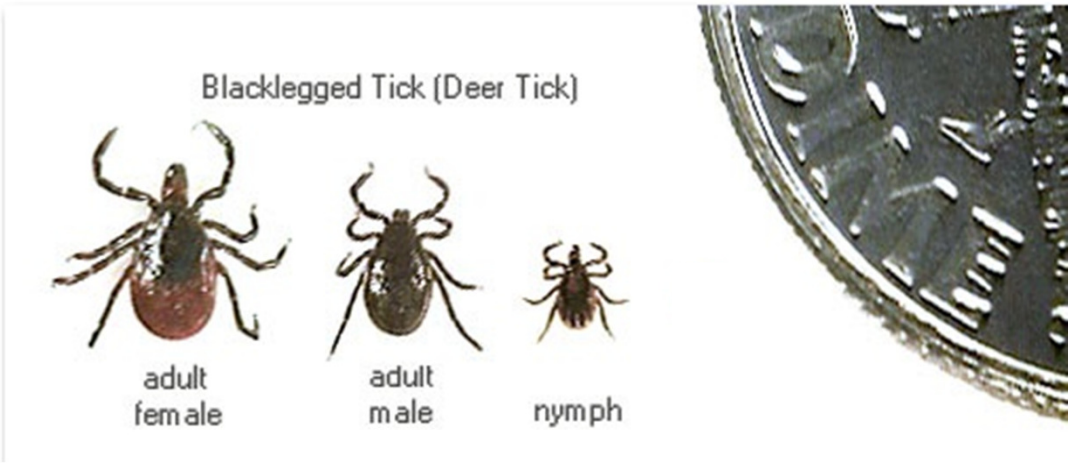
- Lyme disease is the most common tick-borne illness in North America.
- 30,000+ human, 600,000+ dog cases cases per year



Lyme Disease: An Increasing Threat

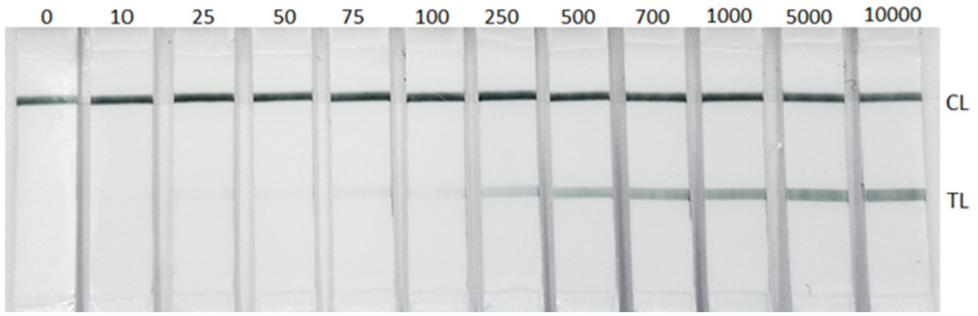
- Deer ticks are the primary disease vector
- Lyme disease in the U.S. is caused by bacterial spirochetes (*Borrelia burgdorferi*)

Ixodes scapularis (Blacklegged Deer Tick)
Critical Lyme Disease Vector.

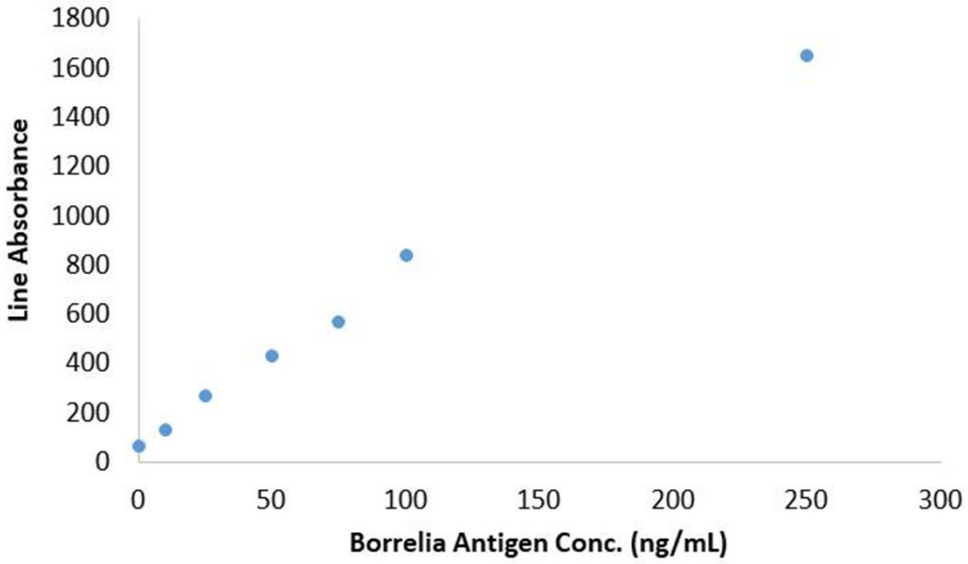


Borrelia assay sensitivity

A lateral flow assay was developed to detect the presence of *Borrelia*.



The visual limit of detection of the assay corresponds to approximately 60 bacteria

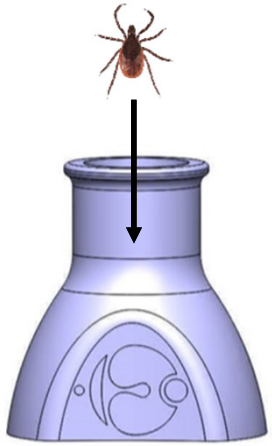


Typical *Borrelia* Infection Levels

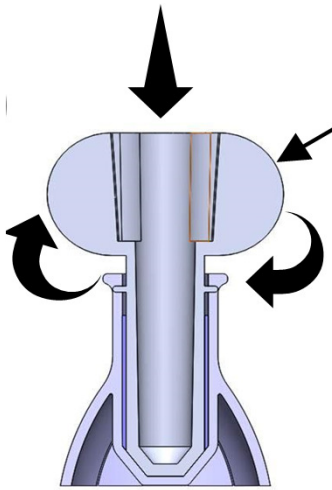
	# bacteria
Nymphs	300-500
Adults	up to 2400

Tick Disruption Device

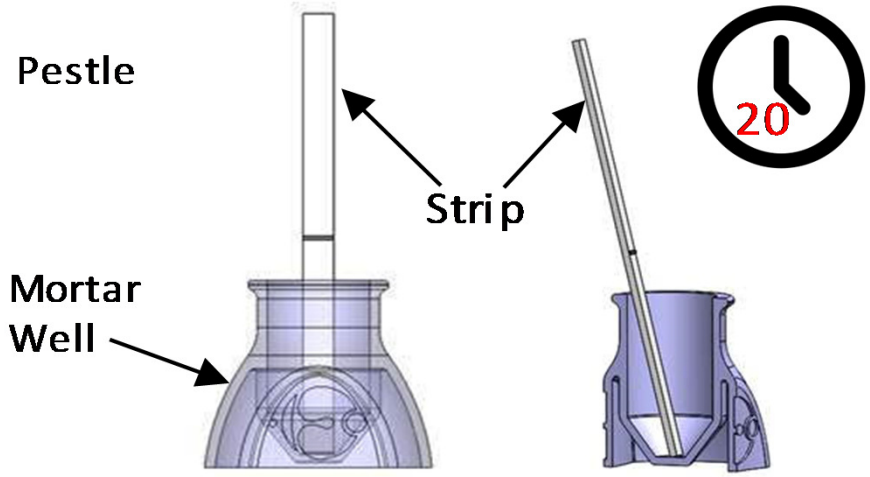
The Tick Disruption Device (TDD) was developed specifically to disrupt the tick sample and expose gut-residing *Borrelia* bacteria.



Insertion of tick into base

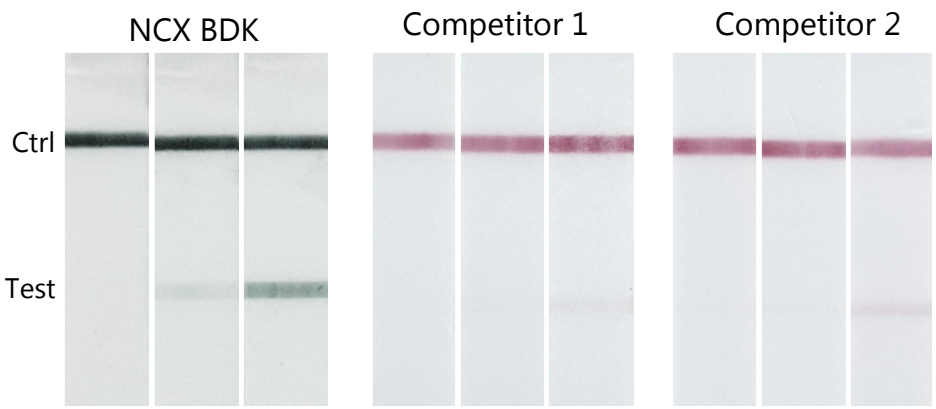


Disruption of Tick Specimen

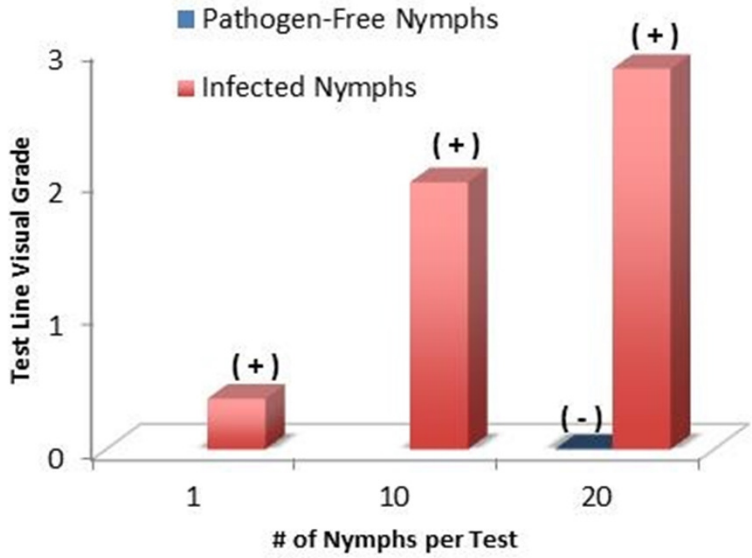


Insertion of LFA Strip into buffered sample.

Sensitivity and specificity



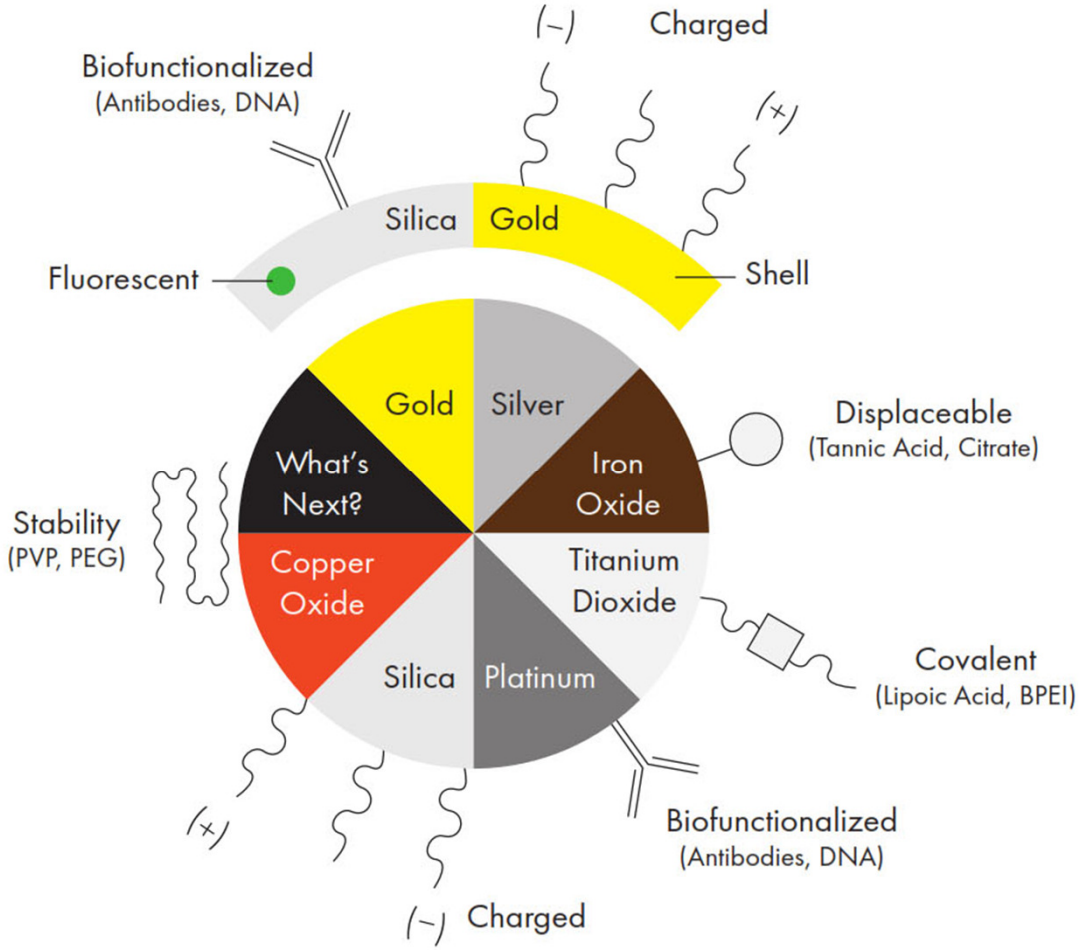
Left Strip = Negative; Center Strip = 100 ng/mL; Right Strip = 1,000 ng/mL



- BDK assay can detect *B. burgdorferi* in a single nymph subject
- Multiple non-infected nymph subjects do not cause non-specific binding

Safety & Regulatory – Path to manufacturing

Nanoparticle design contraints



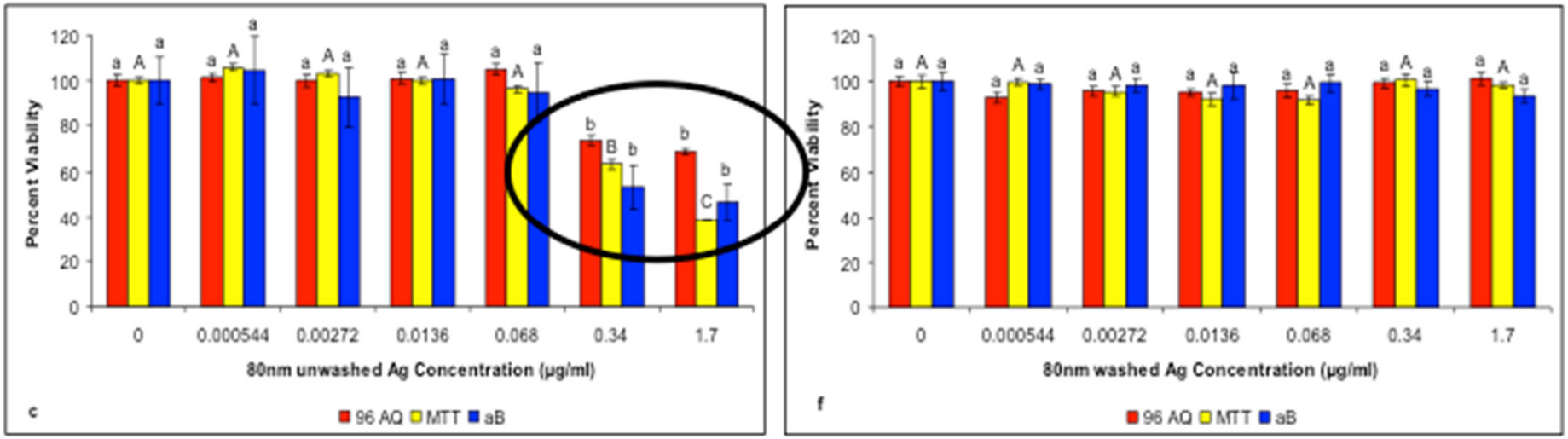
Will nanoparticles be used in a topical application or introduced into the body?

What environmental conditions (salt, pH, etc.) will the particles be exposed to?

Do the particles need to circulate and/or recognize biomarkers?

Nanoparticle Toxicity

Purification is vital - toxicity to cells can be caused by unremoved reactants and reaction byproducts.



Samberg, Monteiro-Riviere. *Environ Health Perspec* 118, 407-413 (2009)

Surface chemistry matters – positively charged particles are much more toxic to cells than those with negatively charged surfaces. Biocompatible coatings – such as polyethylene glycol – reduce toxicity further.

Regulatory oversight

The commercial pathway for drugs and medical devices is long and expensive. Showing that new materials meet regulatory standards can make up a significant portion of total cost.

- FDA – 21 CFR 210/211 (drugs) and 21 CFR 820 (devices)
- EU – Medical Device Directive 2017/745/EU
- ISO 13485:2016

Nanomaterials for therapeutic applications can be regulated as drugs, devices, or drug/device combinations. Each of these has different levels of regulatory scrutiny.

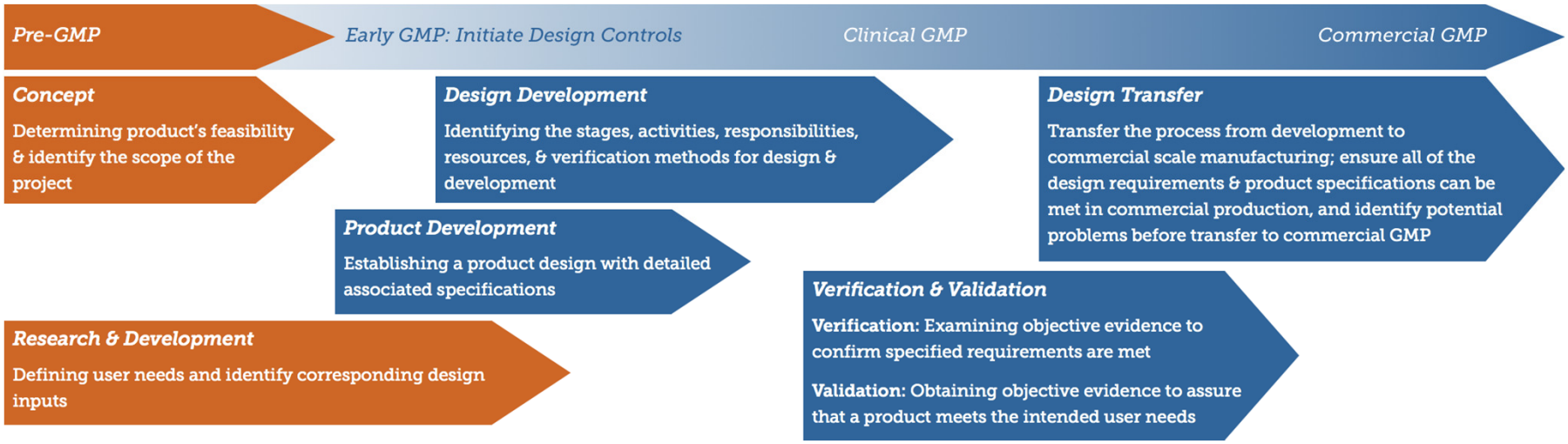
The overall risk class (Class I/II/III) also determines amount of regulation and testing required.

Current Good Manufacturing Practices

To meet FDA requirements, materials must be produced under more formal systems compared with R&D activities. A Quality Management System (QMS) is used to implement:

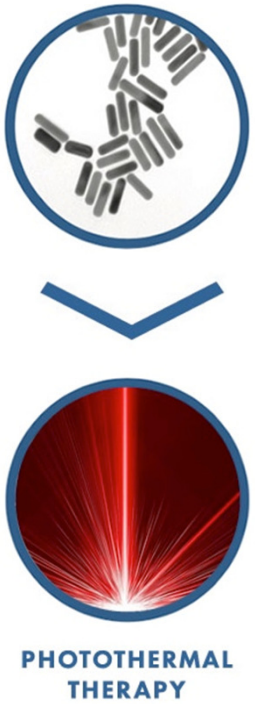
- Document control
- Design review
- Test protocols and reports
- Supplier qualification
- Manufacturing controls/records
- Control of monitoring and measuring equipment
- Product ID, traceability, and inspection status
- Equipment preventive maintenance
- Product labeling and packaging
- Sales order process, shipping, and distribution records
- Training process
- Analysis of data and corrective active and preventive action
- Internal and external audits
- Complaint handling
- Product development
- Design history file (DHF)
- Receiving and receiving inspection
- Purchasing controls
- Control of nonconforming material

Current Good Manufacturing Practices



Conclusions

- Tuning the overall optical response of nanoparticles is only part of the story – scattering and absorption components impact use
- New colloidal materials can improve efficiency of hyperthermia treatment, diagnostics
- Additional nanomaterial design constraints are imposed by use case, regulatory oversight. Meeting regulatory requirements is a significant portion of commercialization



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