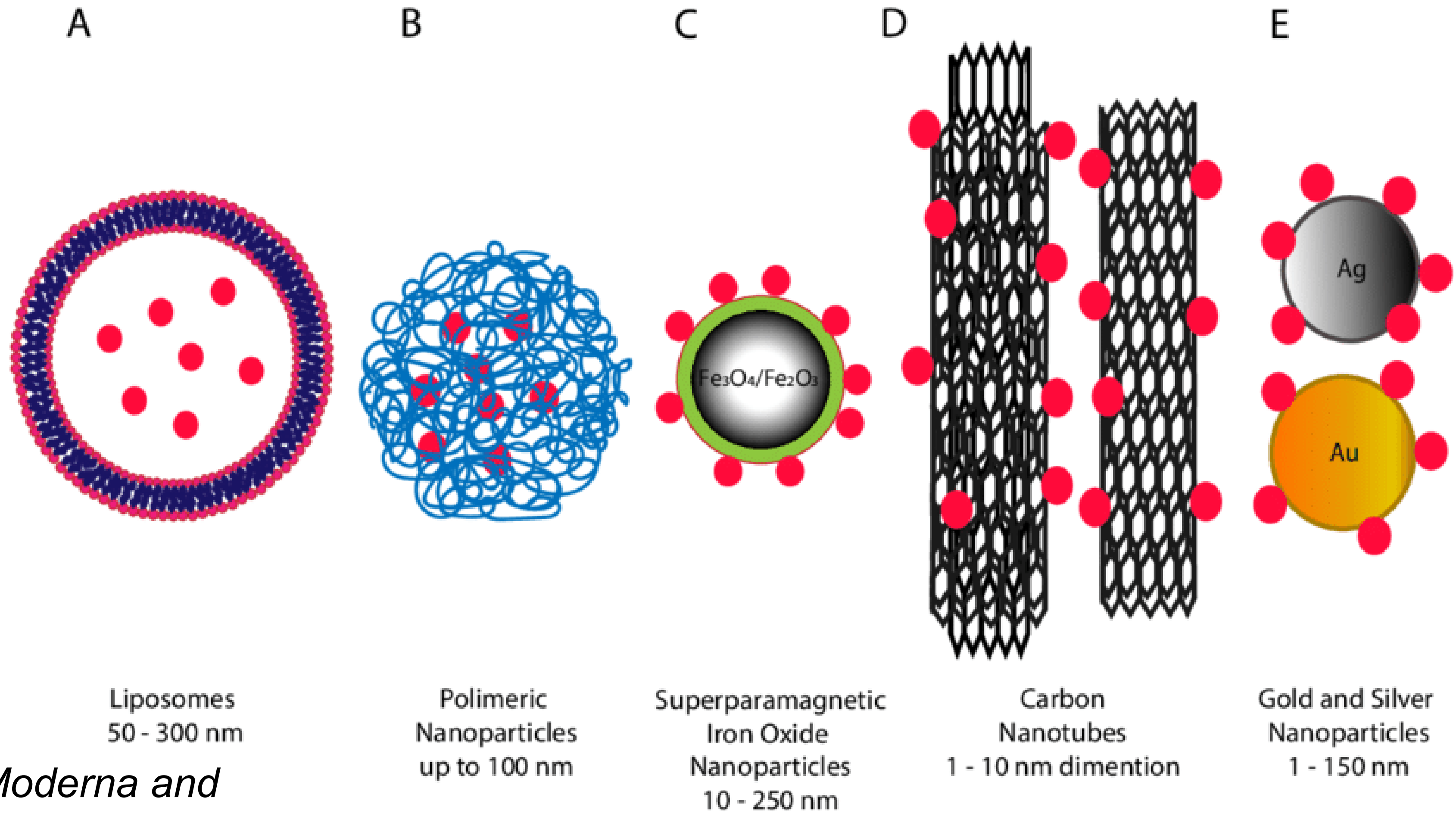
Nanoparticles

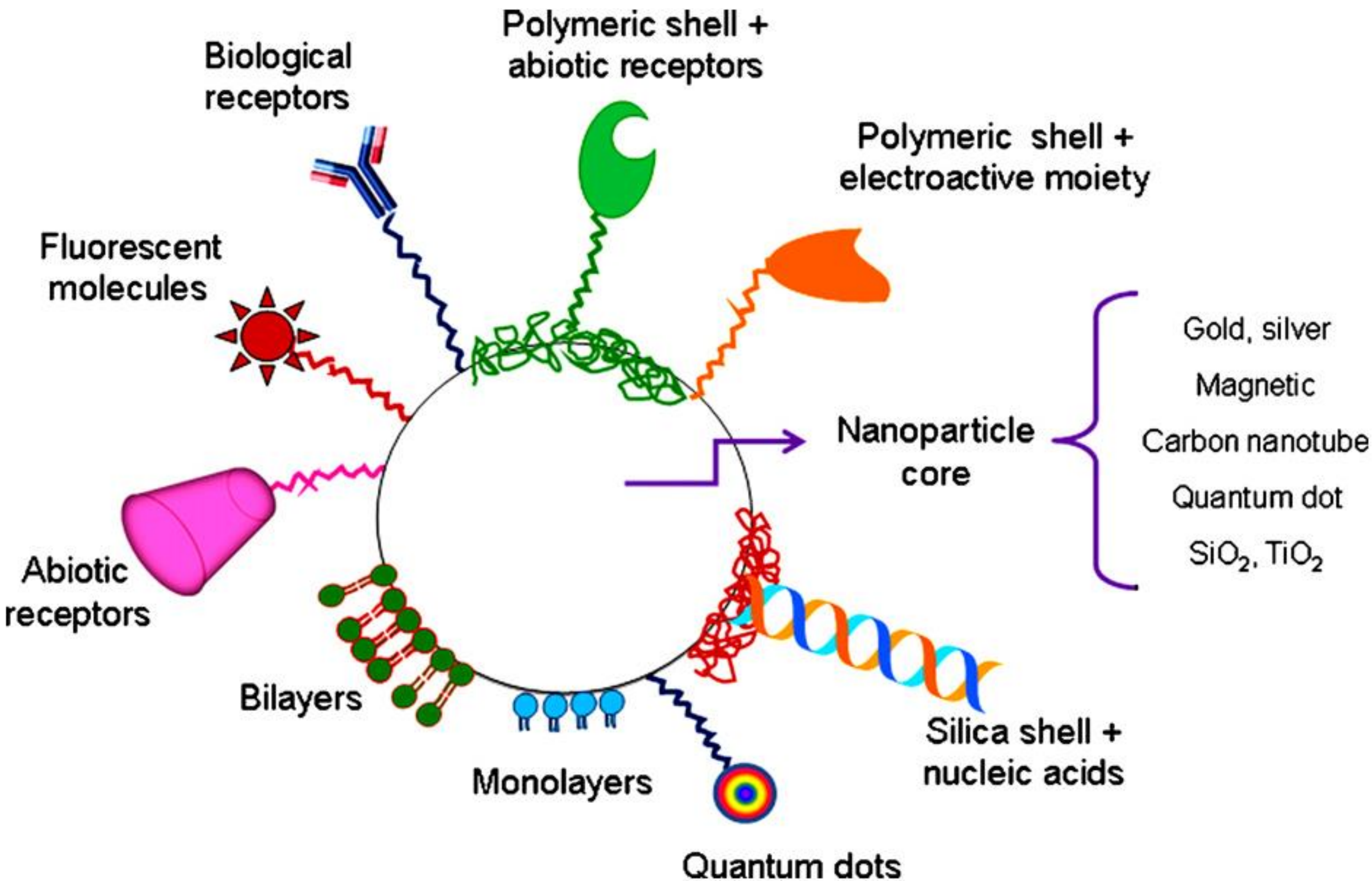
- Nanoparticles (NPs) are particles of inorganic or organic materials with linear dimensions between 1 nm (10^{-9} m, the billionth part of a meter, 10Å) and 500 nm (rarely >700 nm and in any case less than 1 μm).
- Since atoms have an average diameter of 1/3 nanometer, a 5-nm solid nanoparticle will consist of a few thousand atoms, while a 50-nm solid nanoparticle will consist of a few million atoms.
- NPs have a very high surface area/volume ratio.
- Their properties depend not only on their composition, but also on their **size** and **shape**. They can be spherical, cylindrical, star-shaped, hollow, *core-shell*,…

Nanoparticles for *drug delivery*



Moderna and Pfizer-BioNTech COVID-19 lipid nanoparticle mRNA vaccines

Nanoparticles as versatile platforms



Recent critical assessment of the impact of nanomedicine (before COVID!)

…..this sophistication, while well described in preclinical research, has had limited impact in the clinical management of cancer. Only 14 systemically administered cancer nanomedicines have been approved for clinical use worldwide, a majority of which are liposomal formulations of small-drug chemotherapies that were already approved in their free form

No actively targeted or stimulus-responsive cancer nanomedicine has yet been granted regulatory approval and, while some are among the >50 anticancer nanoformulations currently undergoing clinical trials, relatively simple liposomal and micellar formulations still predominate in this group.

Nature Materials, 2021

Recent comments on tumor extravasation

While traditionally thought to be highly favored by a leaky vasculature and the EPR effect, several observations in recent years challenge these assumptions.

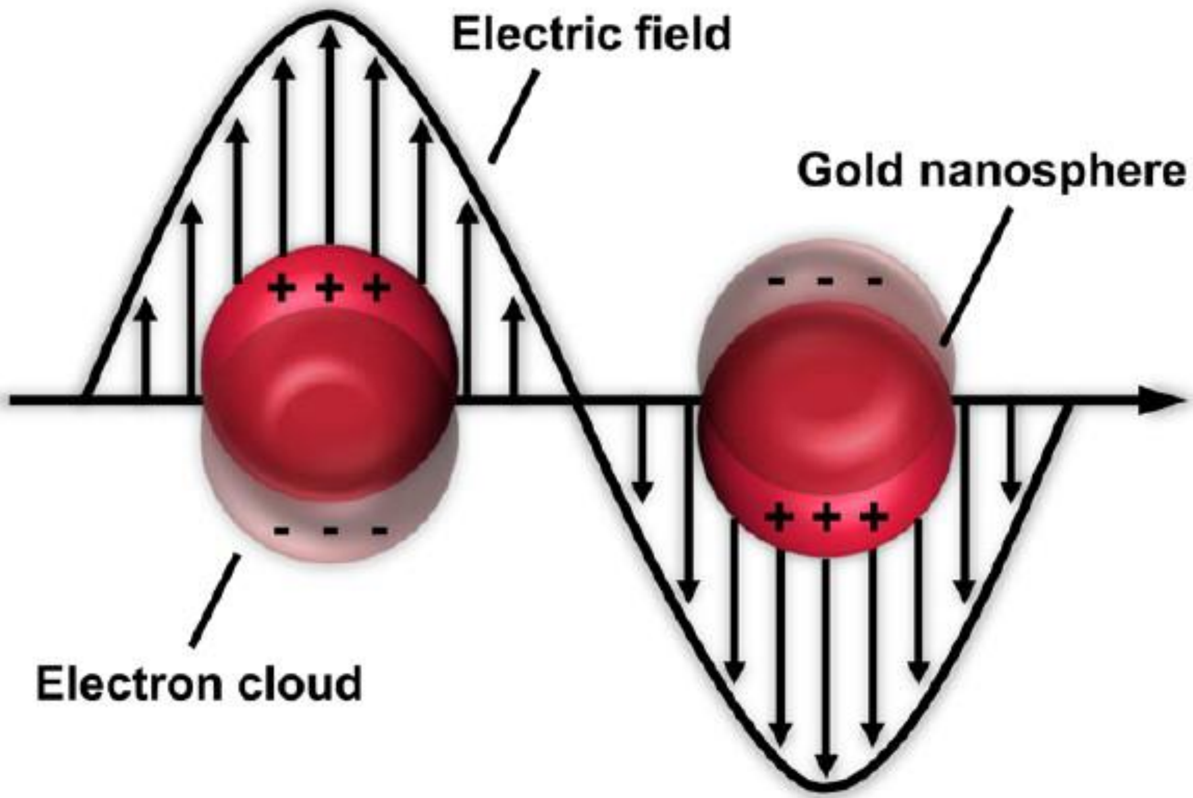
Several studies have questioned the EPR effect as a constant in tumor biology…..

….a meta-analysis of preclinical mouse and rat data revealed that only 0.7% of the nanoparticle (systemically) injected dose, on average, accumulated at the cancer site. This percentage is not yet settled, …..

Nature Materials, 2021

Nanoparticles and light

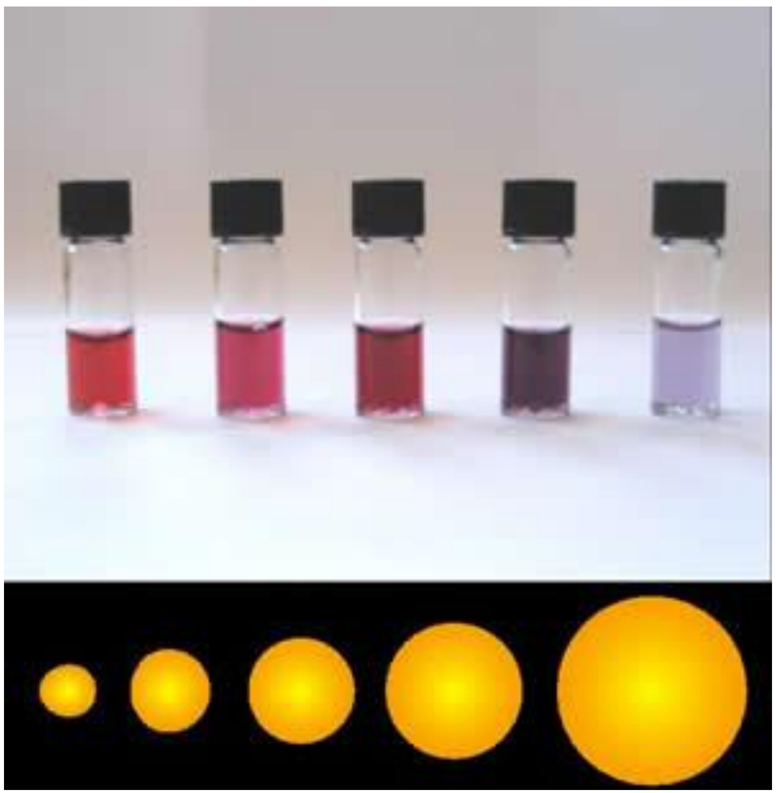
Localized Surface Plasmon Resonance (*LSPR*)



In NPs, the plasmonic resonance frequency depends on the **surface charge density** and thus, in addition to the **material**, also on the **size**, **shape**, and **medium** surrounding them (dielectric constant).

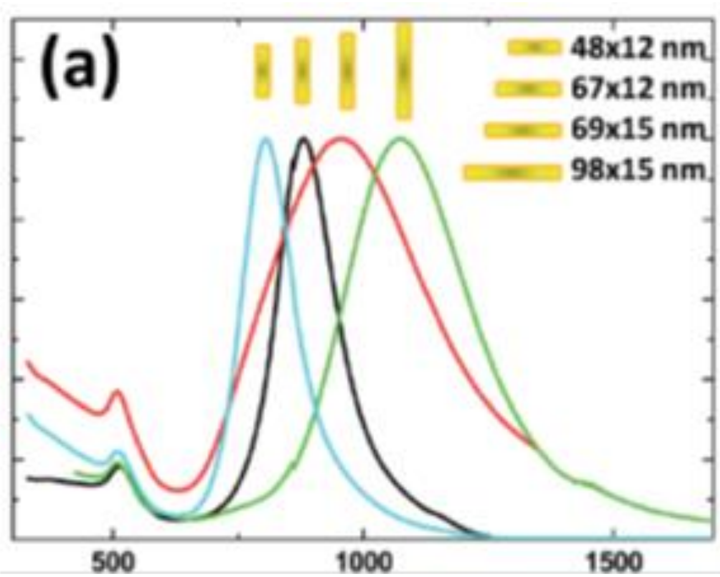
At the resonance frequency (LSPR) the absorption bands are **very intense**, even 5 orders of magnitude more than the best organic chromophores (a NP can be considered as equivalent up to 1 million molecules of an organic dye).

For example, the *absorption cross-section* of AuNPs (that corresponds to ε of molecules) in the NIR is $10^8 - 10^{10}$ M^{-1} cm^{-1}



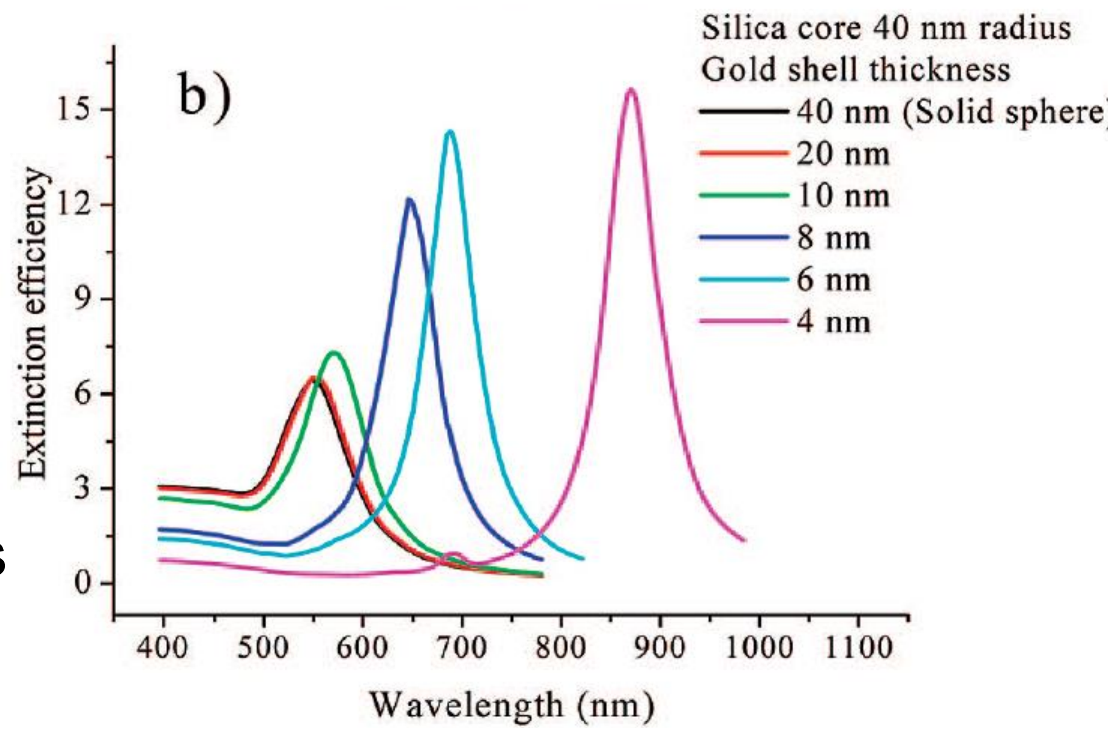
colloidal solutions

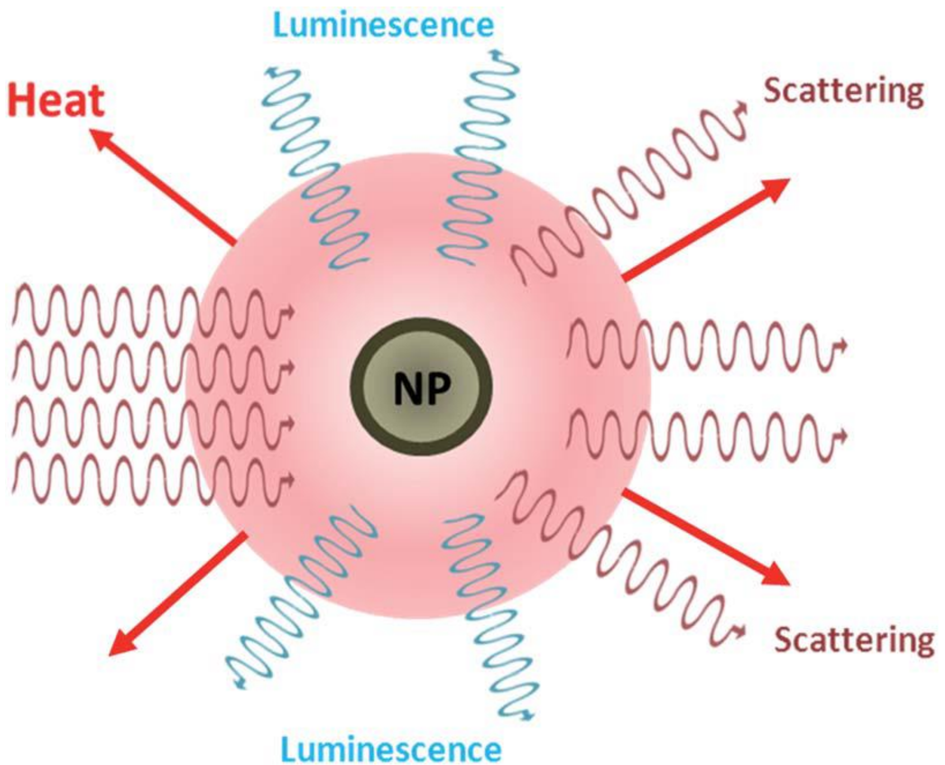
In spherical AuNPs, the absorption frequency (LSPR) decreases as NP size increases



Gold nano-rods

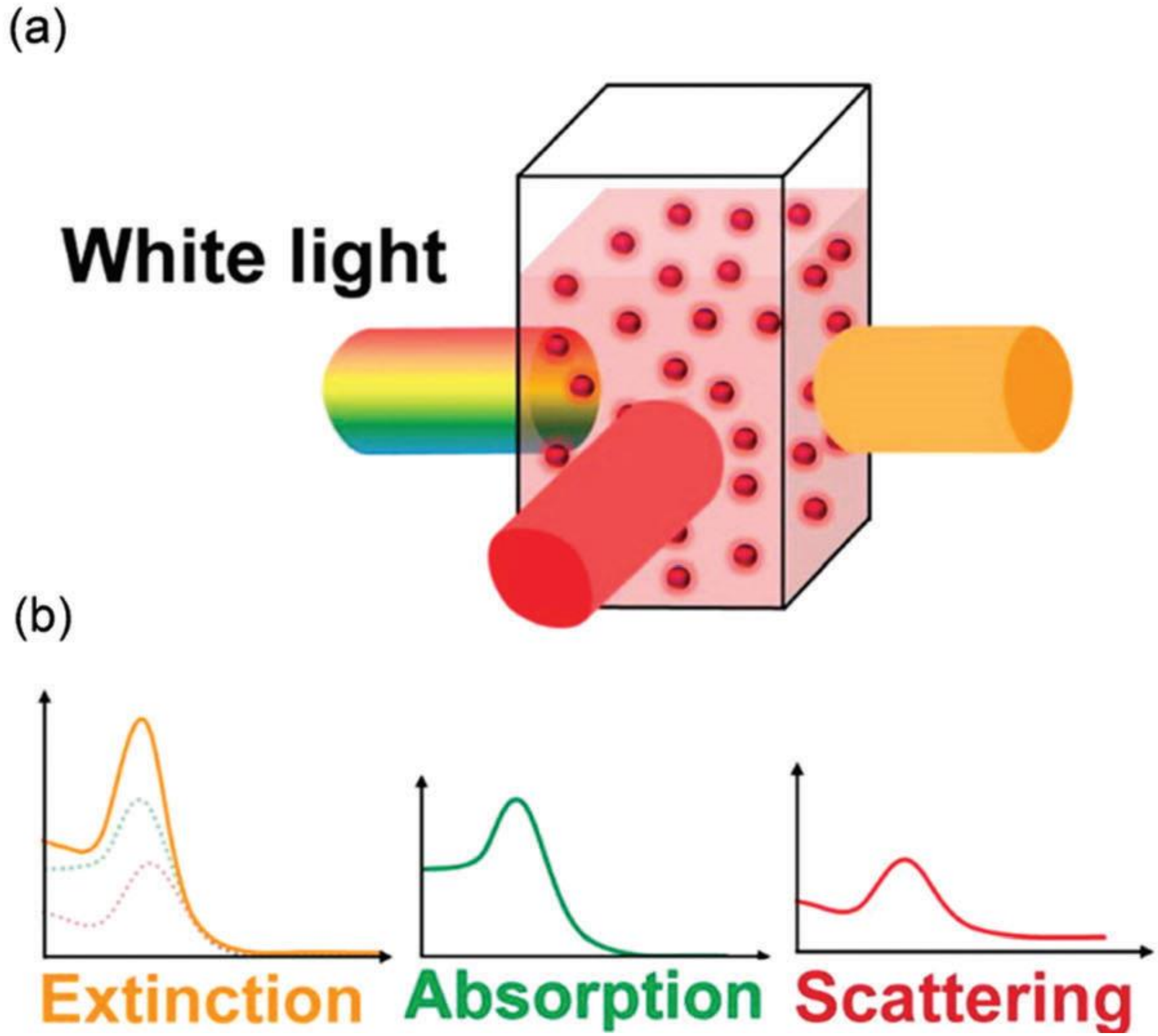
Silica-Au core-shell NP's



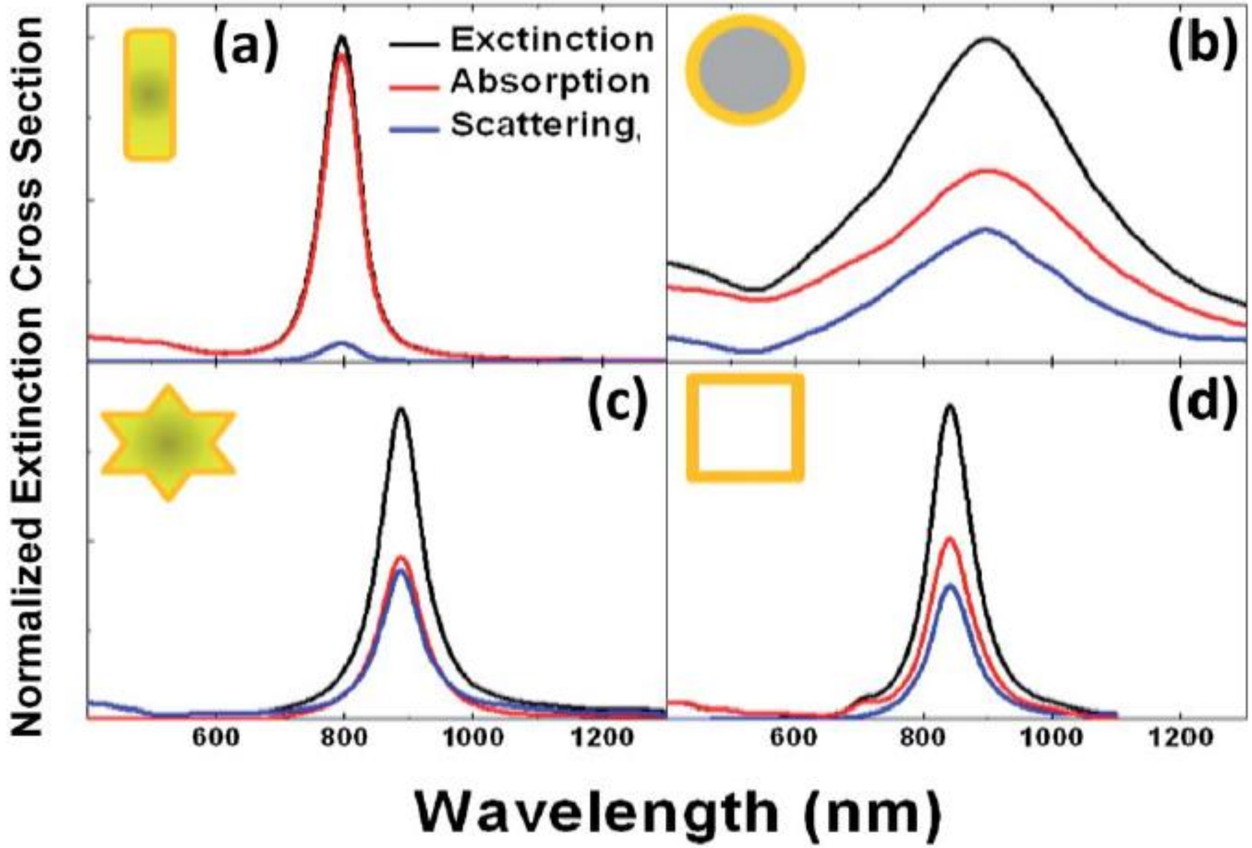


In addition to strong absorption, NPs are also **fluorescent** and **diffract** incident light (*scattering*)

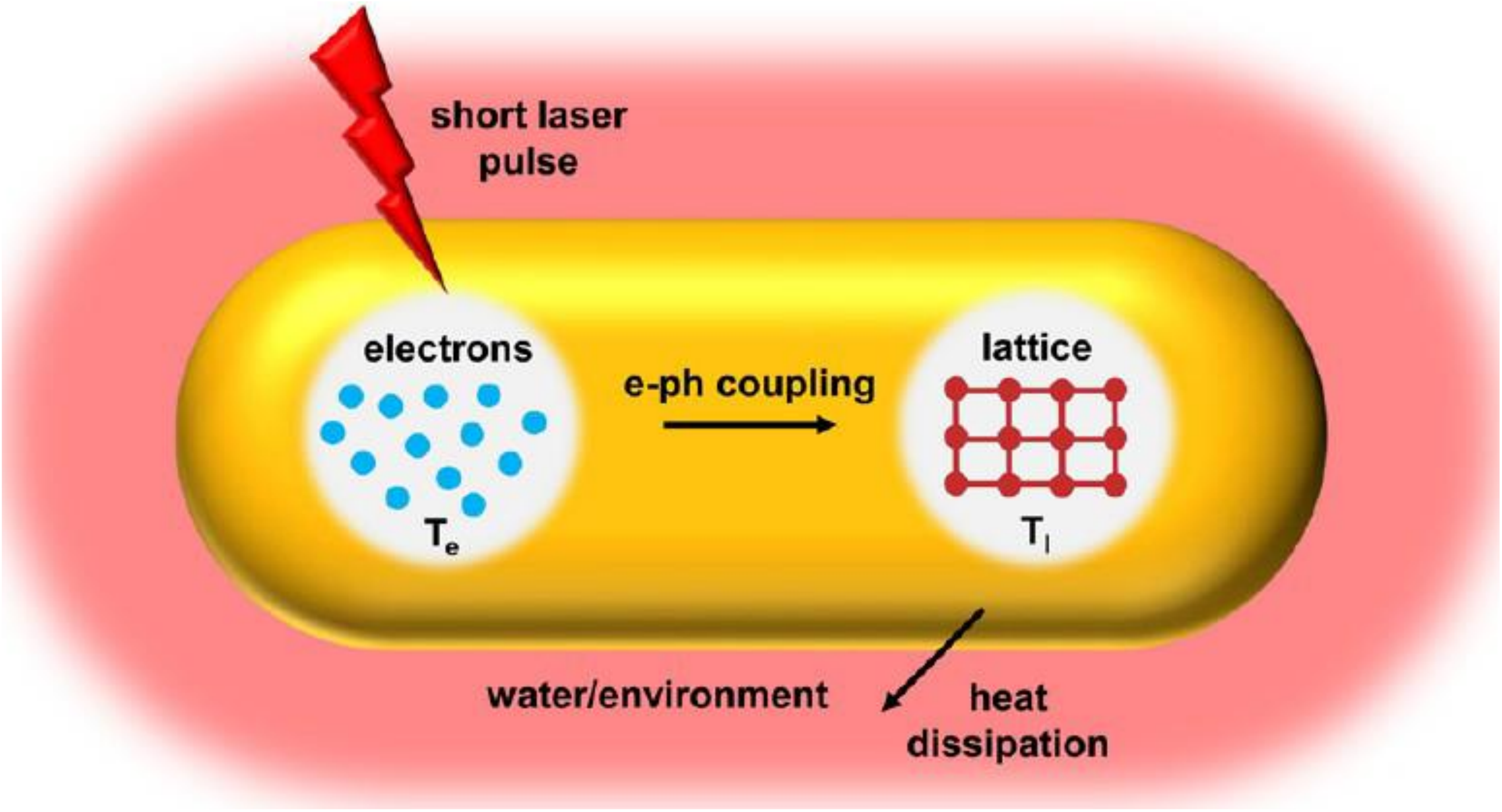
The total absorbance, chatacterized by an extinction cross-section, is the sum of absorption and scattering



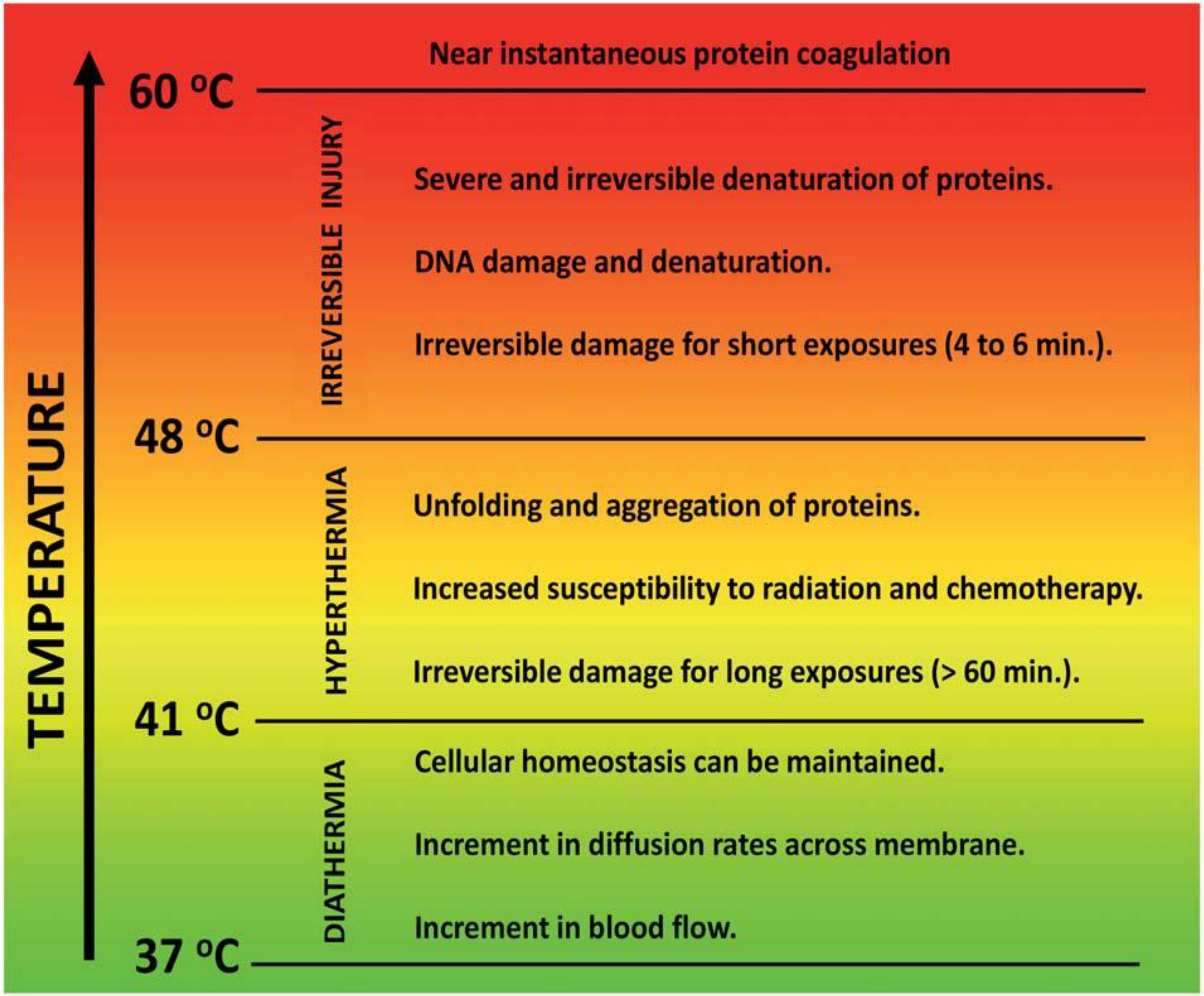
extinction cross-section



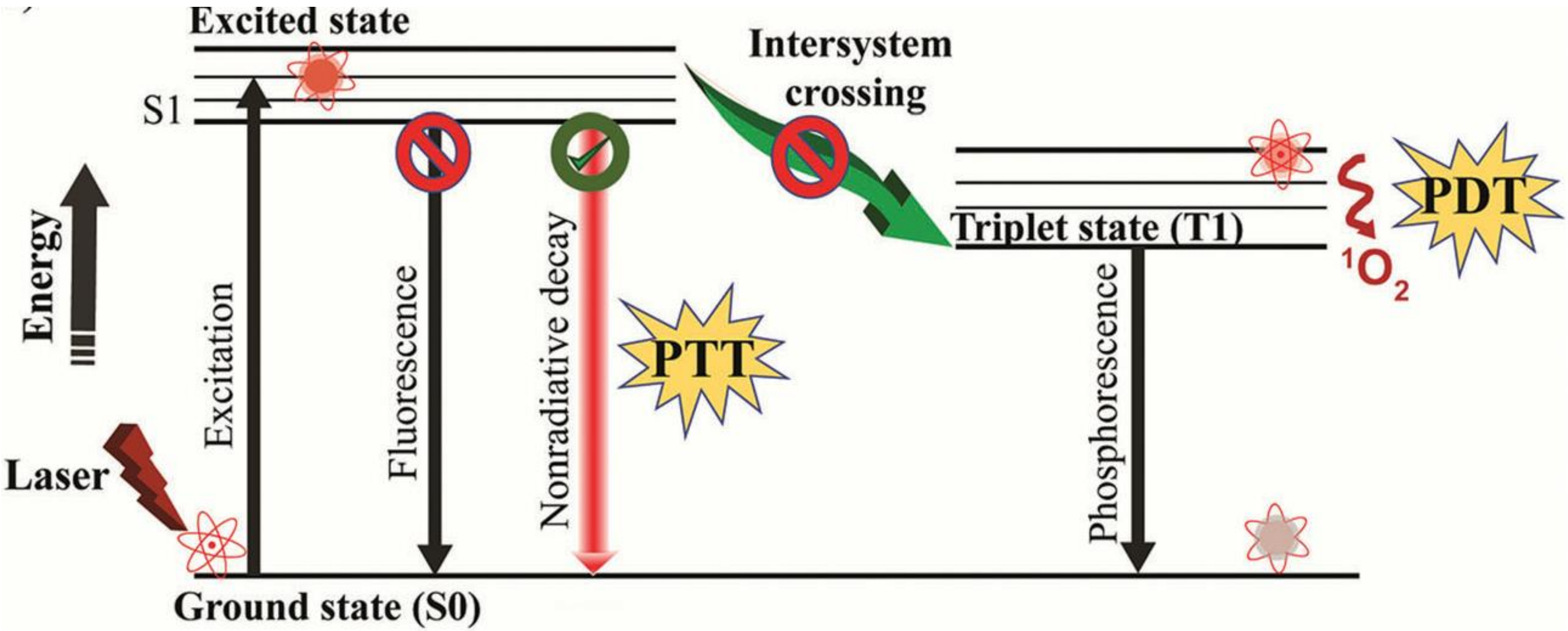
Photothermal Therapy (PTT)
(binary therapy)



The effect of increasing T on living matter

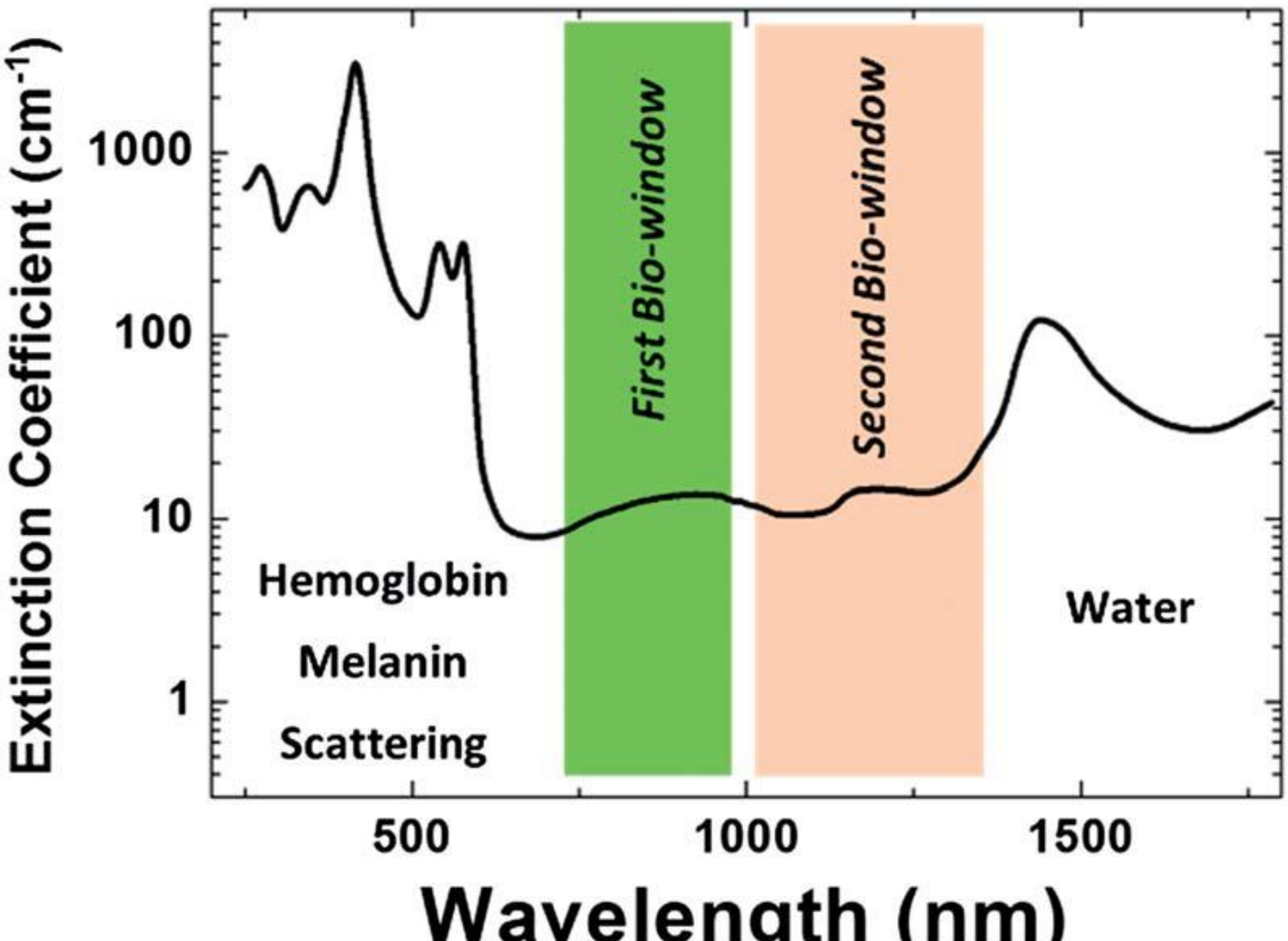


PTT vs PDT

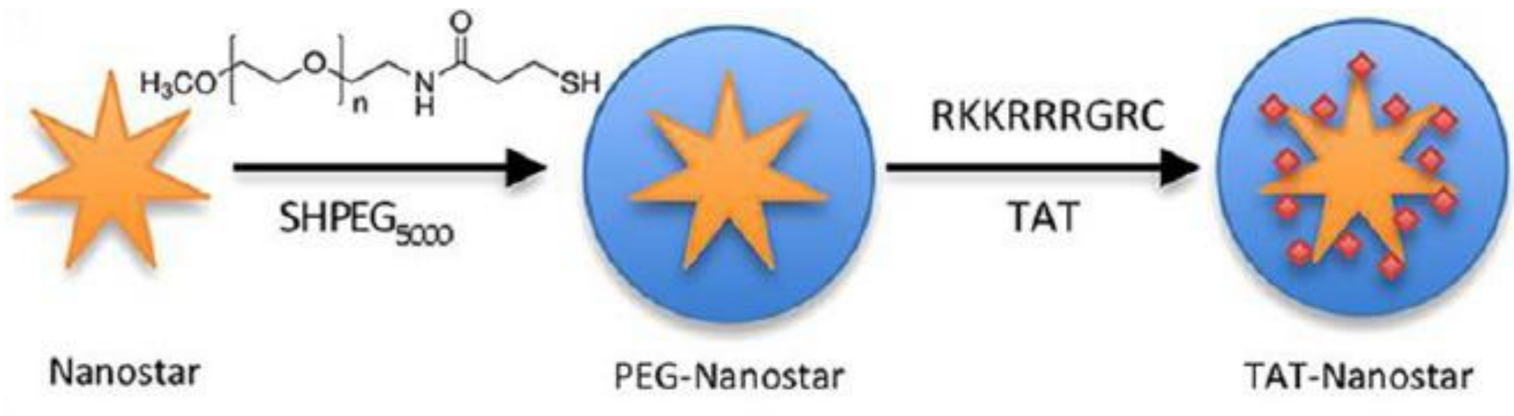

Excited state
S1
Intersystem crossing
Energy
Excitation
Fluorescence
Nonradiative decay
PTT
Triplet state (T1)
PDT
$^1O_2$
Phosphorescence
Laser
Ground state (S0)

Overall extinction spectrum of a human tissue

Overall extinction = absorbance + *scattering*



Targeted AuNP



TAT = cell-penetrating peptide

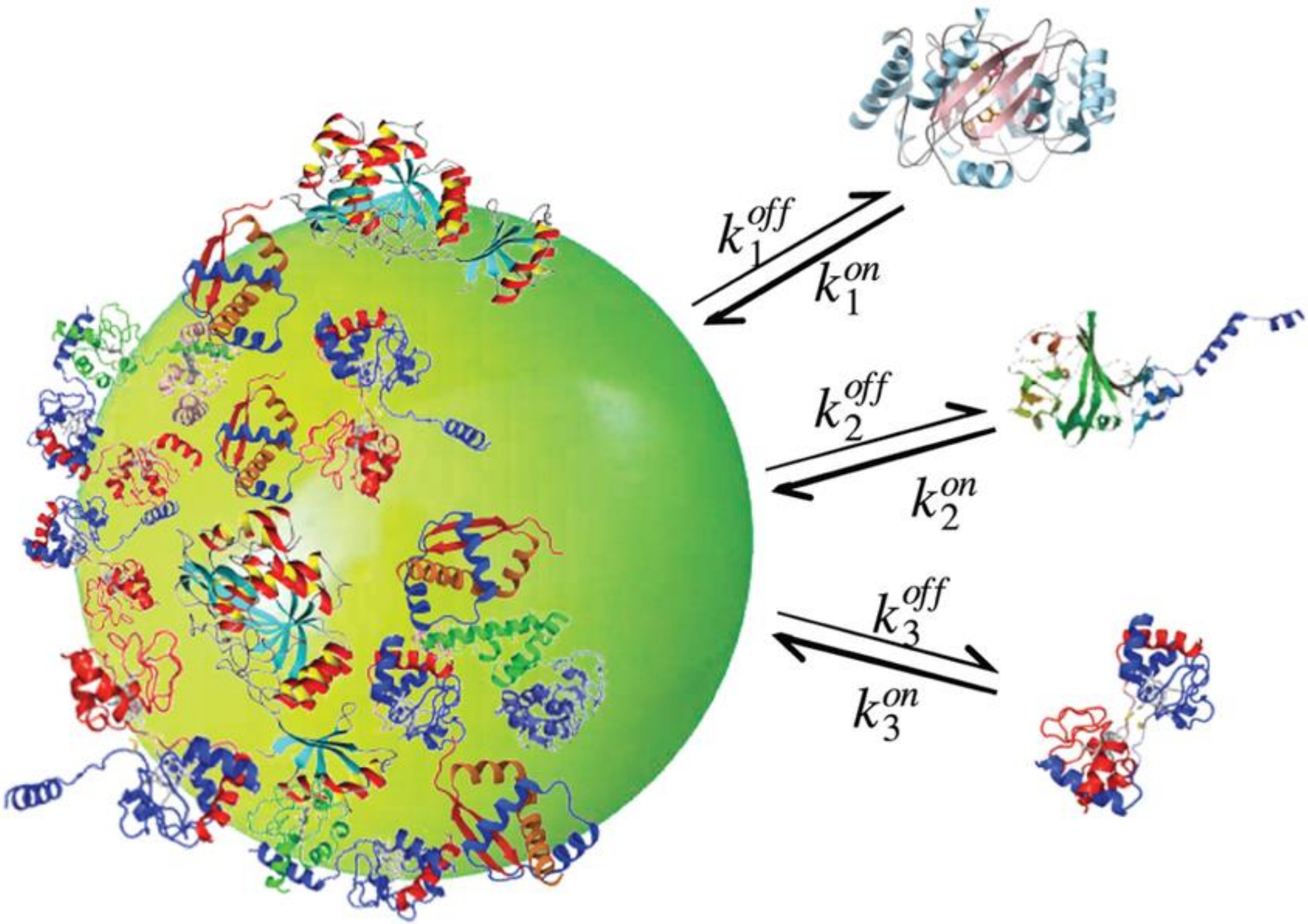
PEGylation increases the lifetime of a NP in the blood stream

The biodistribution of current NPs is highly unfavorable. Only a minor fraction (0.7%) of intravenously injected inorganic NPs ***with a cancer targeting coating*** *reach the tumor site and a tiny amount (0.0014%) actually enter cancer cells.*

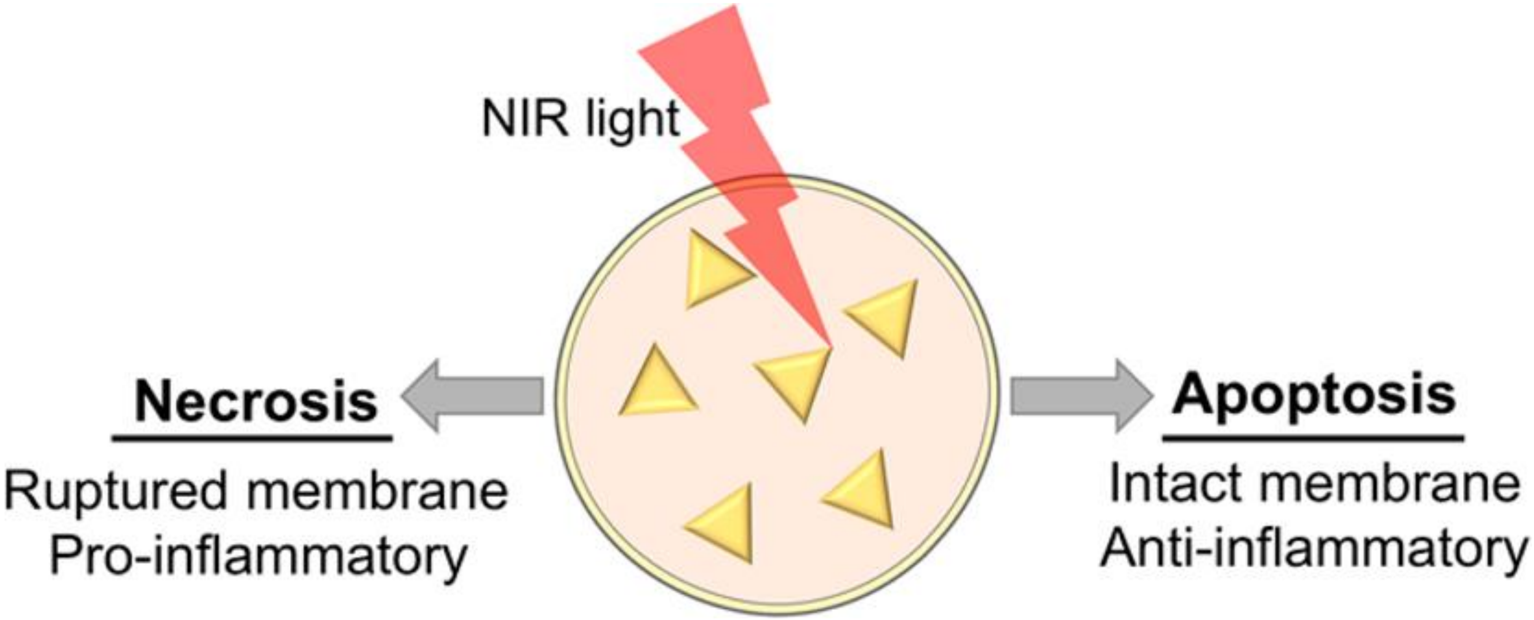
Nature Materials, 2021

The **reticular-endothelial system** (also called *mononuclear phagocyte system*), formed by monocytes, dendritic cells and macrophages (found in the liver, spleen and blood) rapifly sequesters particles larger than ca. 100 nm.
PEGylation of AuNPs decreases their capture by the reticulo-endothelial system.

Protein corona around nanoparticles



PTT-induced cell death



Eat-me signals

- The efficiency of PTT depends not only on characteristics of AuNPs (size, shape, wavelength of plasmon resonance, concentration, and nature of surface coating ligands), but also on **irradiation conditions**, such as irradiation time, laser power, type of laser (pulsed or continuous), and its wavelength, as well as the time between administration and irradiation.
- According to fairly recent estimates (2015), a single treatment for a patient with PEGylated Au-nanorods (commercial) would cost about 7500 $.

Piccole sfere d'oro contro il tumore della prostata

2019

Nanoparticelle biocompatibili che convertono la luce del laser in calore sono state utilizzate in 15 pazienti per bruciare il tessuto tumorale. I risultati dello studio pilota su Pnas

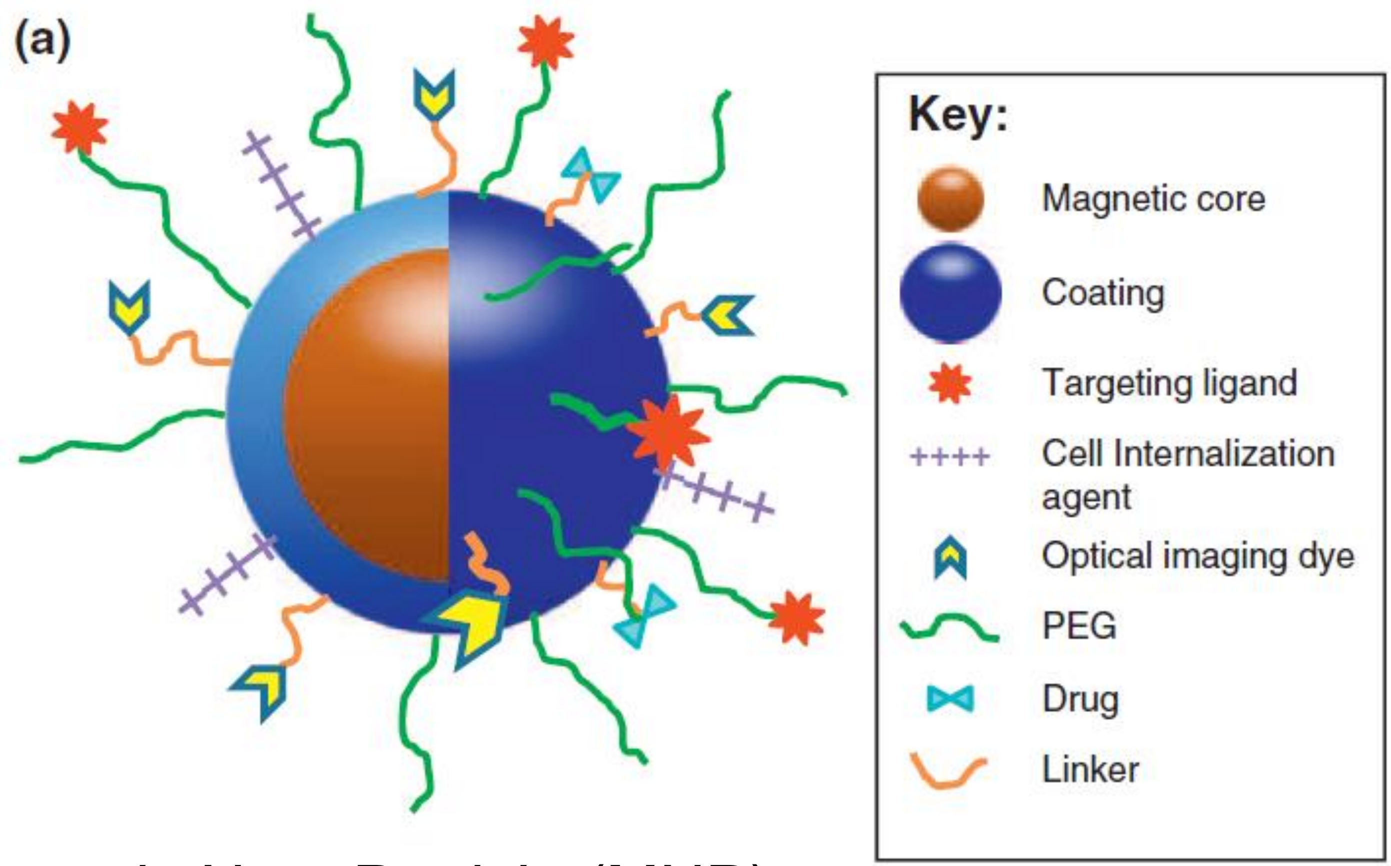
di TINA SIMONIELLO

04 settembre 2019

gold-silica nanoshells, ø ca.150 nm, laser NIR

“This treatment protocol appears to be feasible and safe in men with low- or intermediate-risk localized prostate cancer without serious complications or deleterious changes in genitourinary function.”

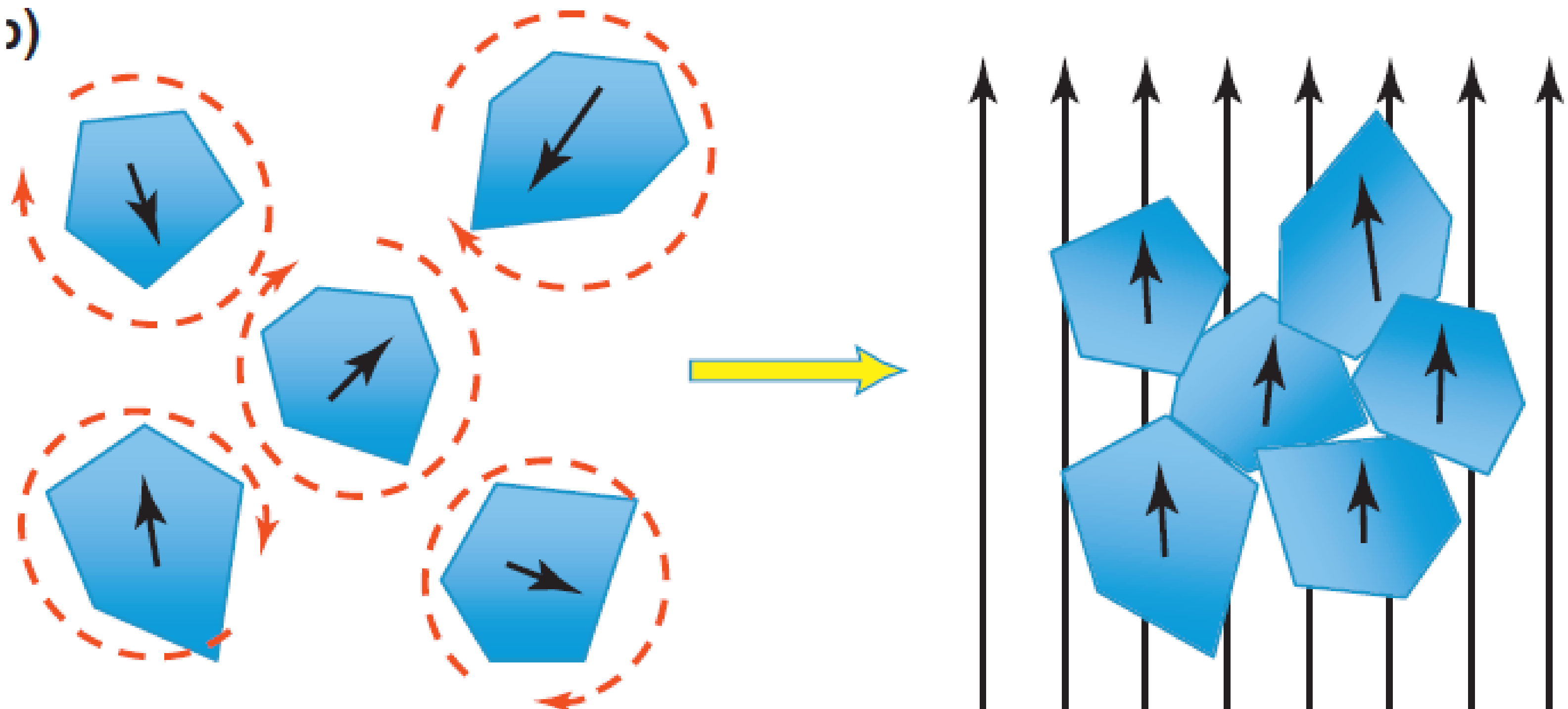
Magnetothermal Therapy



Magnetic NanoParticle (MNP)

The typical magnetic core is made by iron oxide

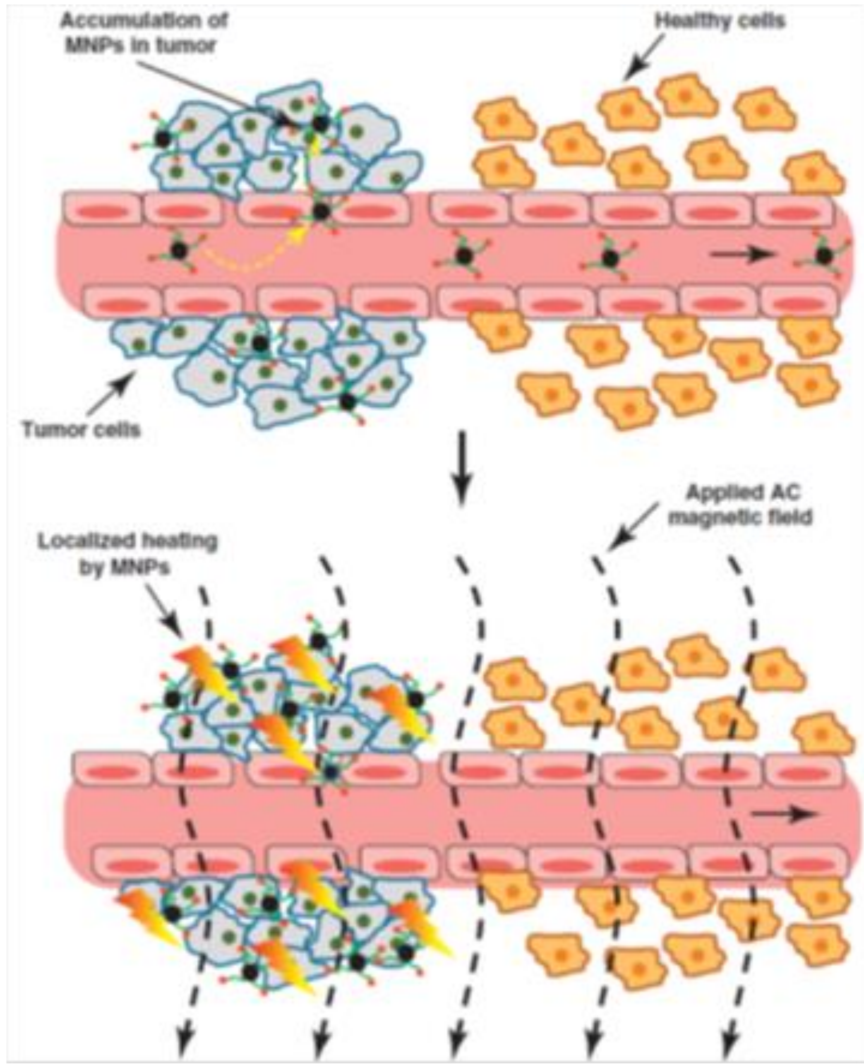
Super-paramagnetism



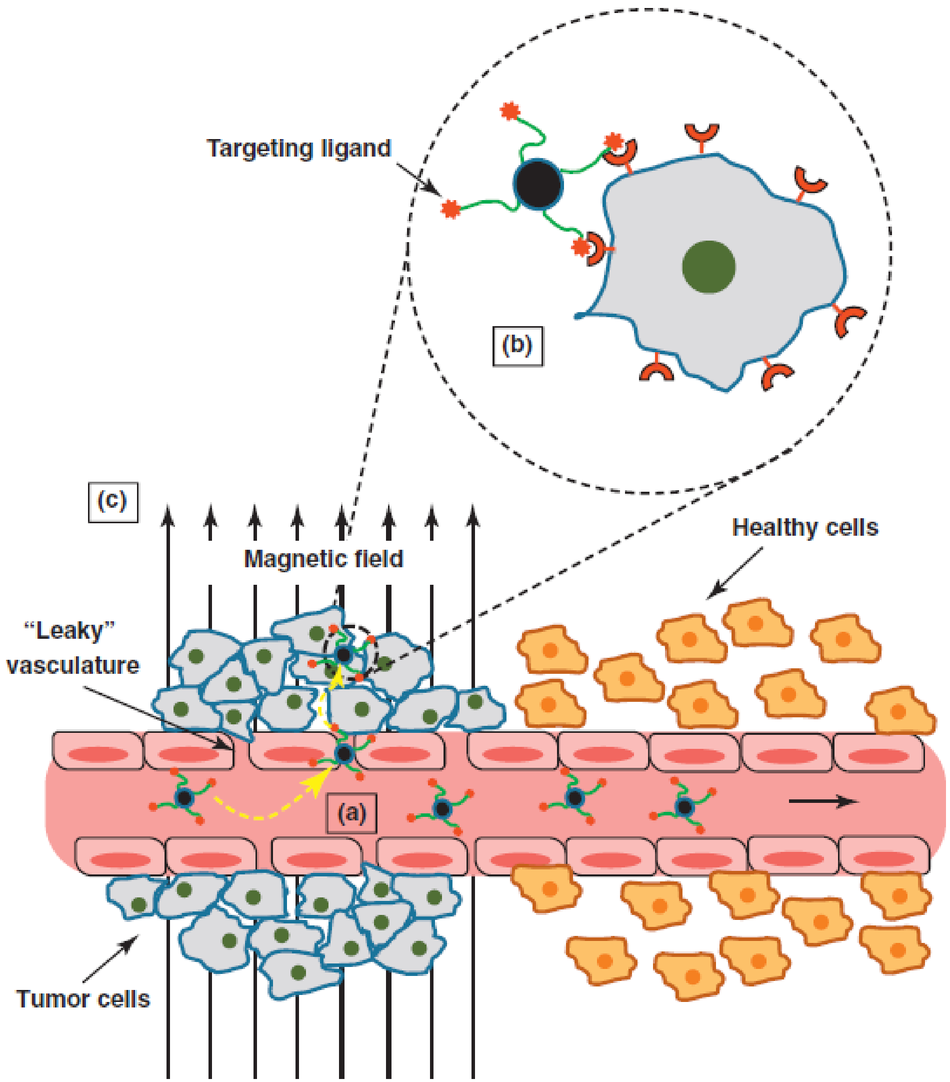
Superparamagnetic nanoparticle
Diameter < ~30 nm

Compared with a normal paramagnetic material, super-paramagnetic MNPs exhibit higher magnetic susceptibility.

Heating of magnetic NPs is achieved by *oscillating magnetic fields*

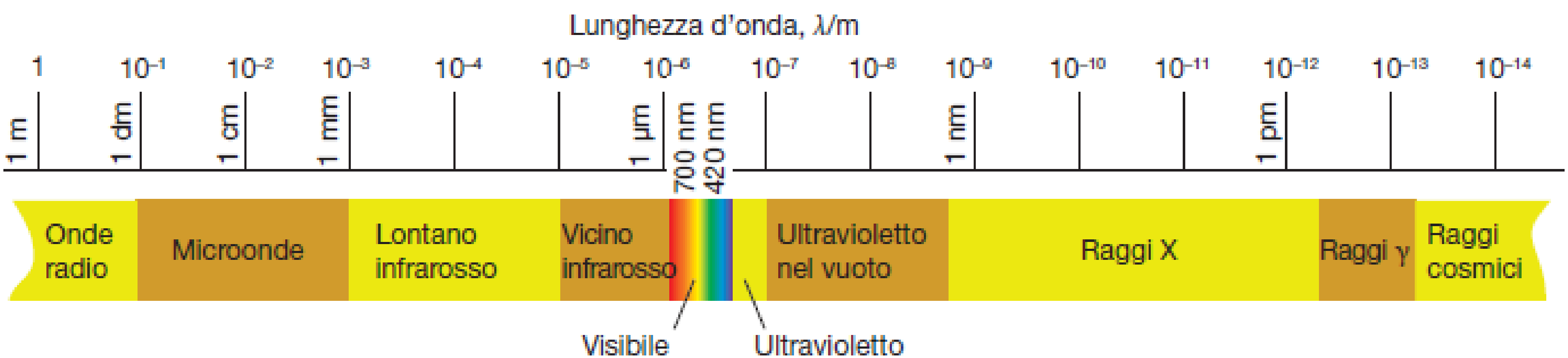


Active *magnetic targeting*



Radiosensibilization

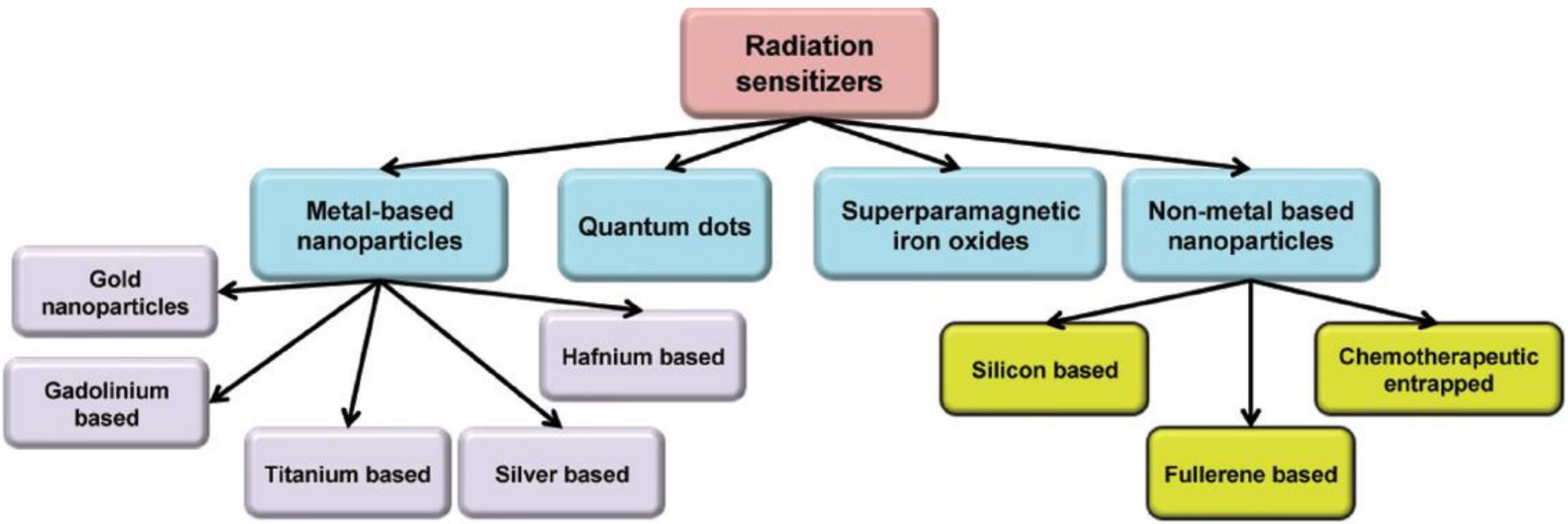
Cancer radiotherapy uses **ionizing radiation**, that is, radiation that has sufficient energy to rip electrons from atoms, generating ions and "aquated" electrons and, consequently, ROS (**indirect damage**).
The ionizing radiation can be made of charged particles (protons or carbon ions), but more often high-energy photons. i.e. γ-rays or X-rays.



Ideal radiosensitizer:

- Selectively enhances radiation activity in the tumor
- Be active even in hypoxic cells
- Should not depend on incorporation into DNA
- Should have a low toxicity

The most extensively investigated radiosensitizer are NPs



The **photoelectron cross section** of an atom depends ca. on Z^4

NP's have a large cross-section for γ o X radiations.