L1: Introduction to Nanomedicines

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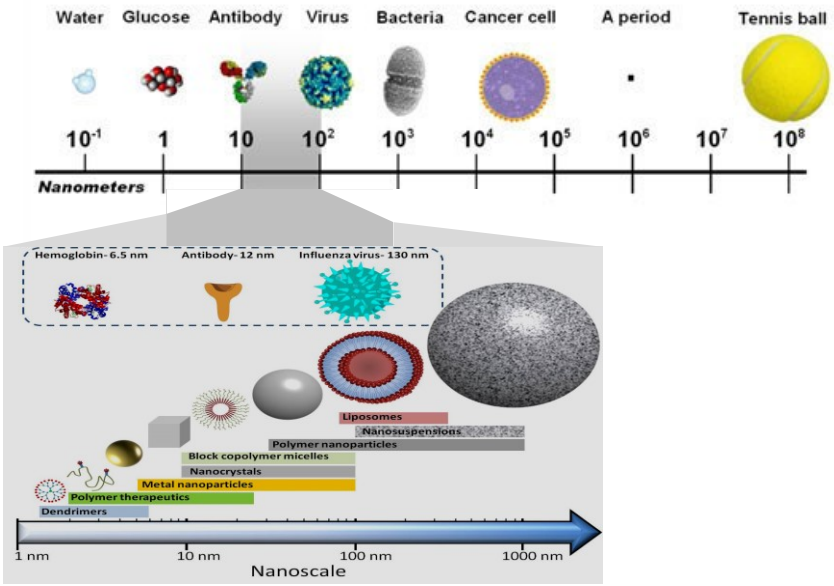
Lecture Series at the
Institute of Chemical Biology & Fundamental Medicine for Siberian Branch of Russian Academy of Sciences

Intended Learning Outcomes

To be aware of the wide range nanomedicines and to understand the principles underlying their different behaviours in the body, which are developed in more detail:

L2 as diagnostic contrast agents
L3-4 at epithelial barriers (gut, skin & lung RoAs)
L5-6 as reasons for success of biologics & nanoparticles
L7-8 for overcoming membrane barriers & targeting
L9-10 for overcoming drug-resistant infections
(Moscow: RNA targeting for different diseases)

Nano size scales & Nanomedicines



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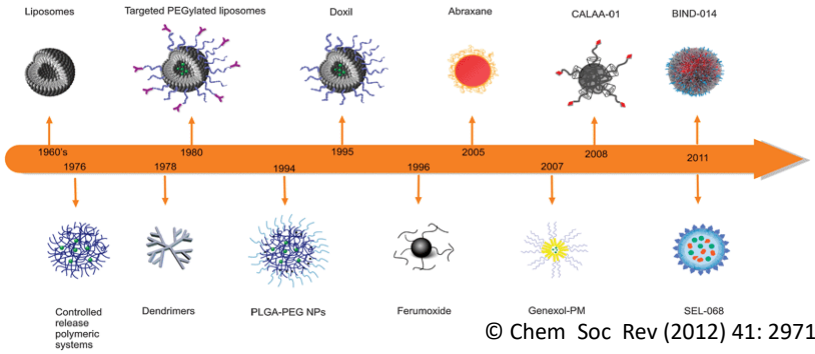
Nanomedicines: targeted therapeutics



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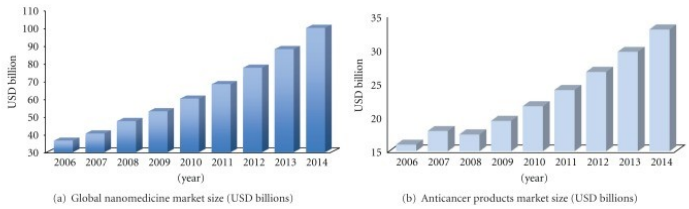

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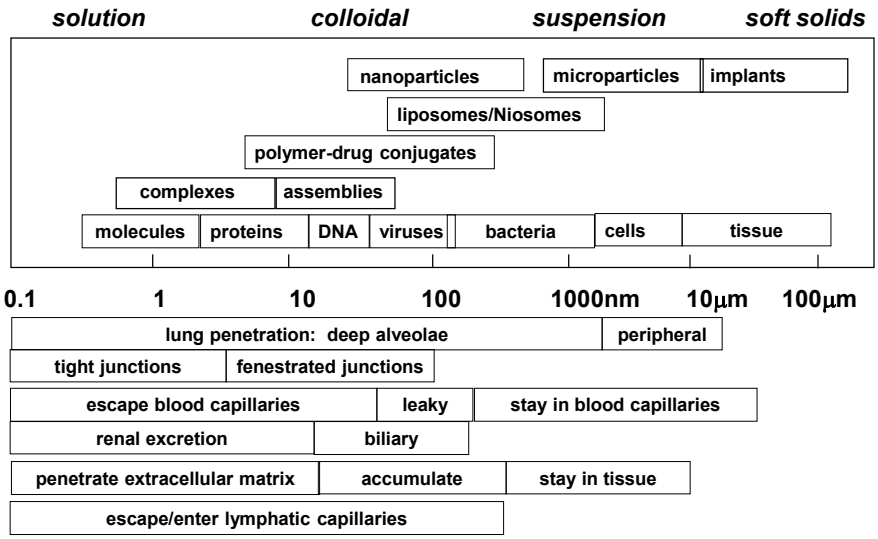
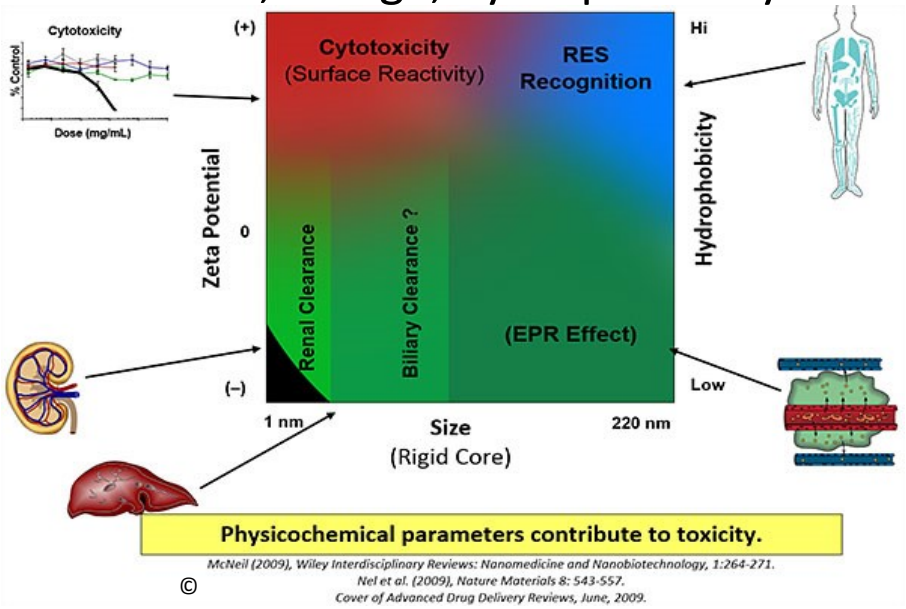
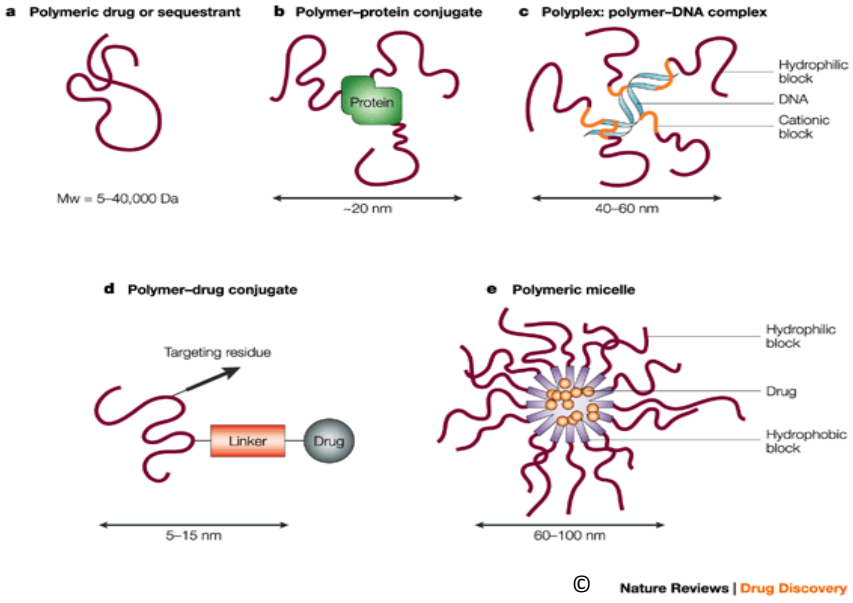
Why size is important – PK & biodistribution: particle sizes and delivery barriers



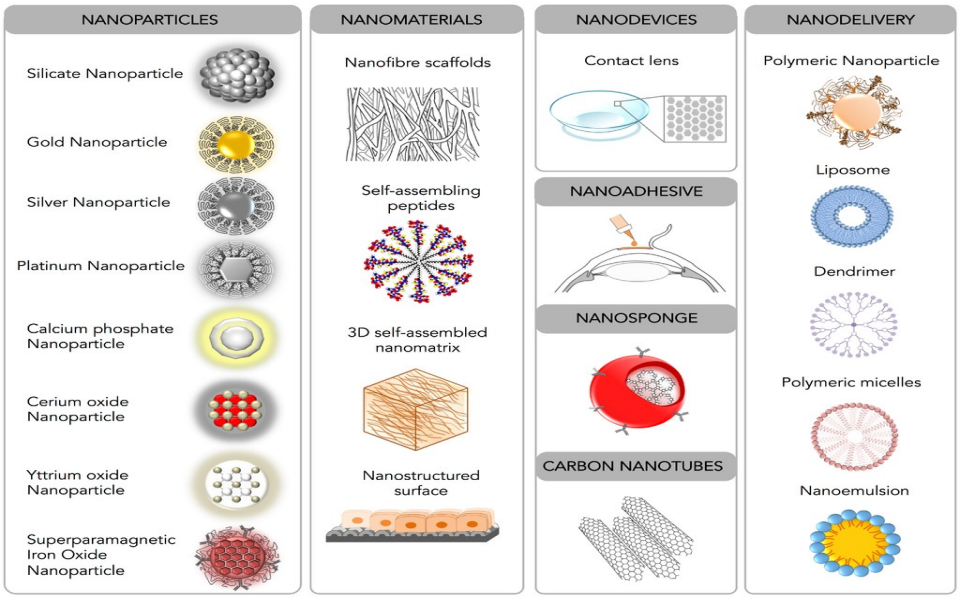
Fate of nanoparticles in the body: size, charge, hydrophobicity



Smaller scale nanomedicines



Larger scale nanomedicine



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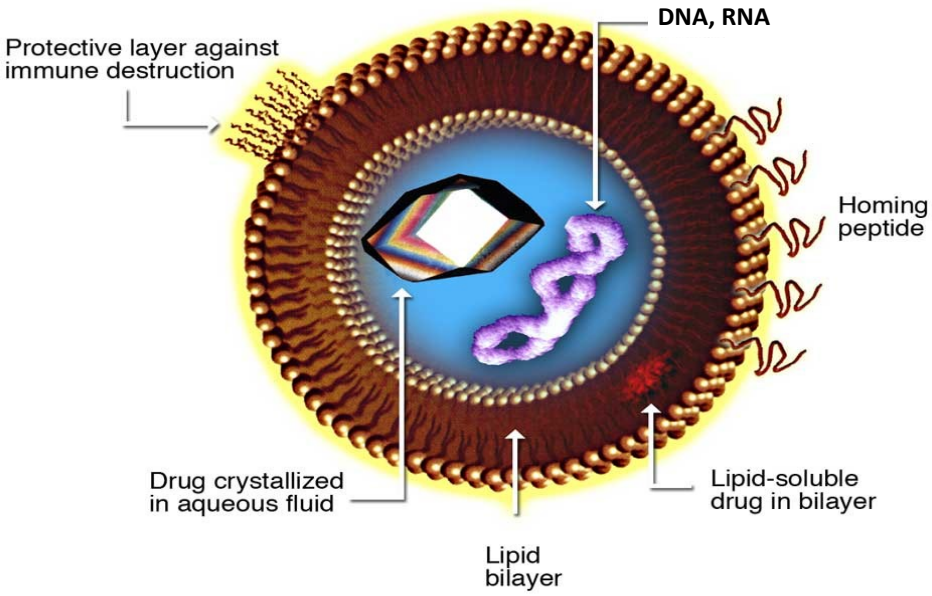
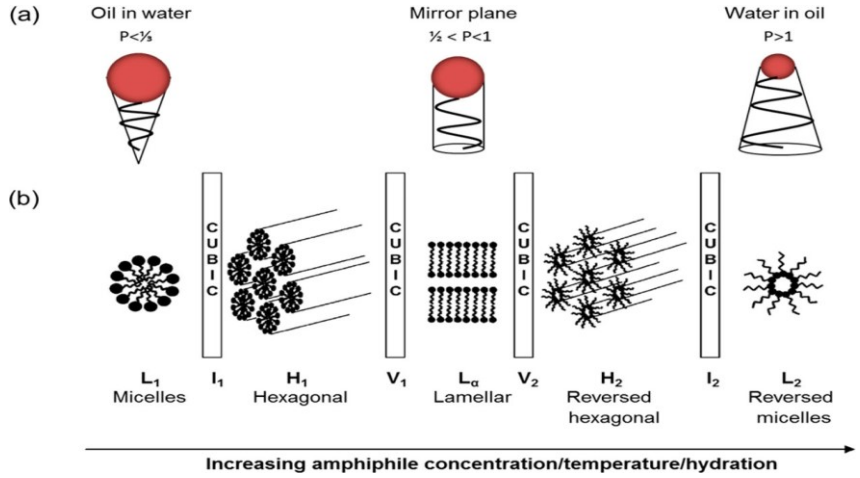
Liposome for Drug Delivery



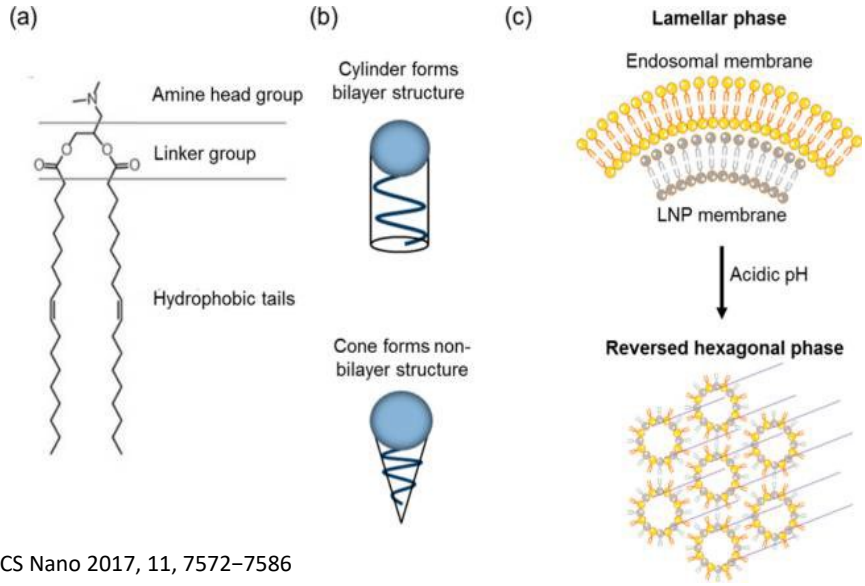
Lipid self-assembly structures

Critical packing parameter: P = V / (a.l)

[V = tail volume, l = tail length, a = area at interface]

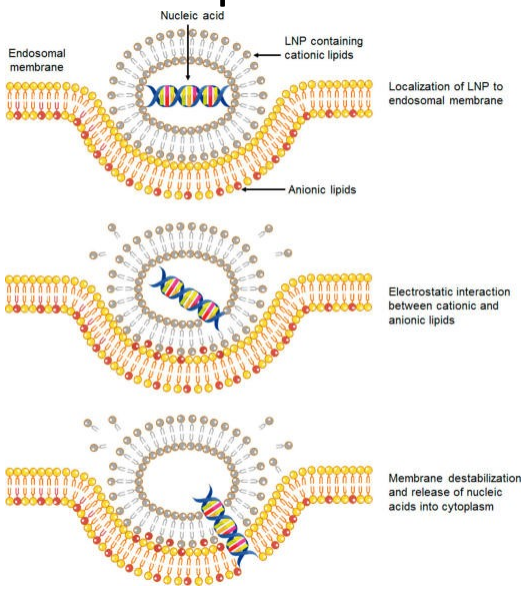


Ionizable cationic lipid liposome NPs (LNP)

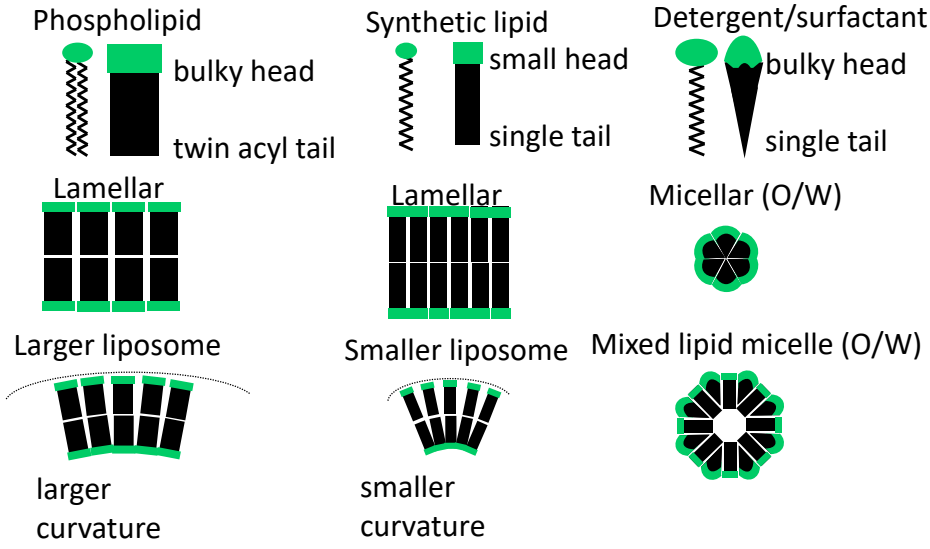


Ionizable cationic lipids

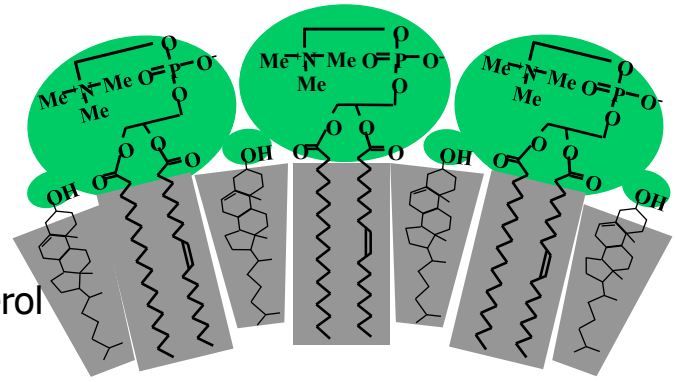
- Less toxic ionizable lipids
- Cationic lipids interact with endosome anionic lipids
- Endosome acidification increases ionization & interaction
- Endosomal escape



Amphiphile shape, assembly & curvature



Liposome: packing & stabilisation



Vesicle physical stability also increased by

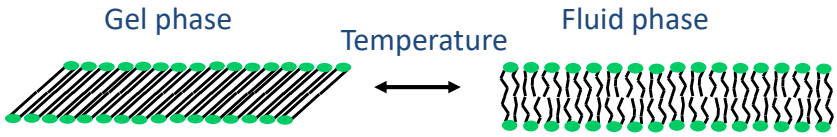
- high phase transition temperature lipids
- polymer-supported lipids (lipid membrane-coated particles)
- lipid-like polymer vesicles (polymersomes)

Liposome stabilisation against disruption by serum proteins

Serum high density lipoproteins (HDL) bind lipids, particularly from less rigid or unstable liposomes, leading to their disintegration, releasing drugs too soon.

Lipid compositions increasing physical rigidity and stability:

high gel-liquid transition temperature (T_c) lipids



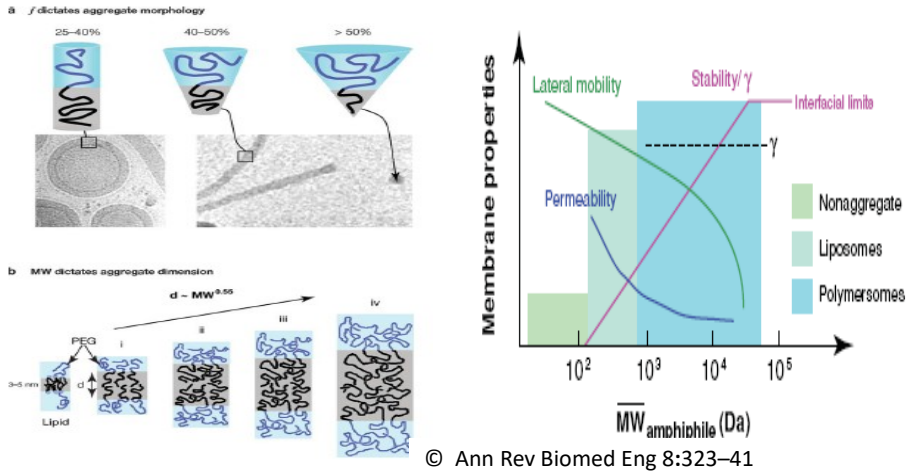
high cholesterol, high saturation, longer alkyl chains

dipalmityl phosphatidylcholine (DPPC): gel <33°C – fluid >42°C

sphingomyelin, ceramide

perfluoroalkylated phospholipids (*eg* lung aerosol delivery)

Polymersome: structure & stability



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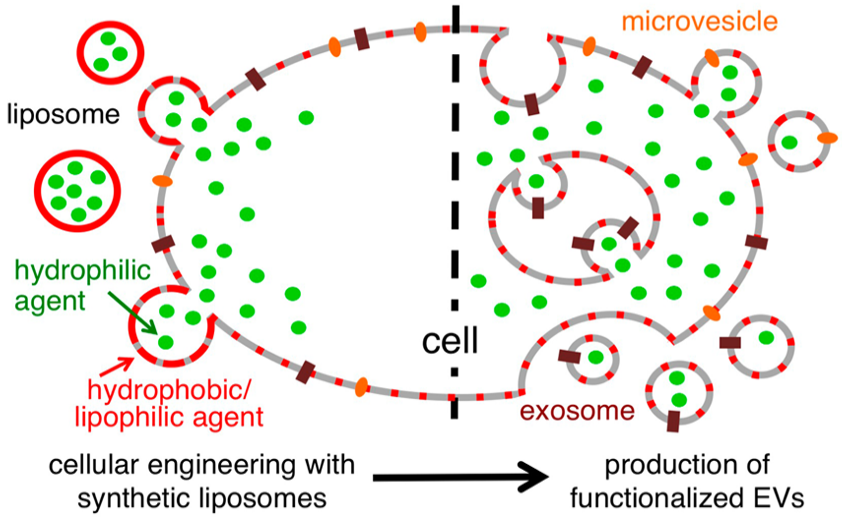
Hydrophilic fraction *(f)* → morphology, whereas MW → thickness.
Stability increases with membrane thickness to limit set by elasticity (γ).
Water permeation through polymerosome membranes considerably reduced compared with phospholipid liposome membranes.

Natural vesicles made from cells



L2: Near patient diagnostics & imaging

Intended Learning Outcomes

- To be aware of how nanotechnology is advancing near patient or point of care (POC) diagnostics (Dx) and body imaging technologies
- To understand how different types of nanoparticles & related nanostructures on surfaces make very small signals bright enough to see

Scope

The science, technology & practice of diagnostics and imaging are considerable – much greater than pharmaceuticals.

***In vitro* diagnostics:**

- **Consumer Dx**
- **Point of care Dx**
- **Drug monitoring**
- **Biomarkers**
- Bioimaging
- Laboratory analysers

***In vivo* diagnostics:**

- Implanted sensors
- Worn sensors
- **Portable imaging**
- **Whole body imaging**

What does Nano do for diagnostics?

- Diagnostics (Dx) often face challenges much greater than '*finding a needle in a hay stack*'
- Few analytes in the body are at sufficient levels to see directly, when lost in the large range of similar compounds or high levels of materials in the body

Nanoscience used to make capture and contrast agents, often using nanoparticle assemblies:

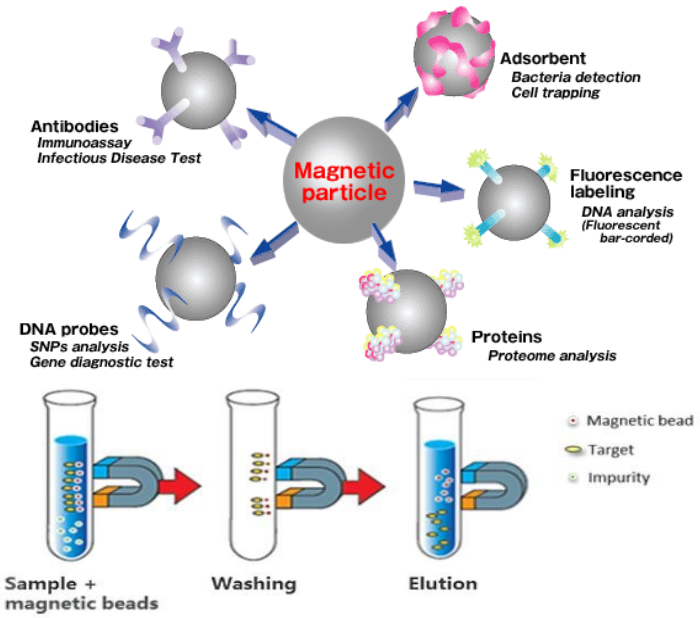
- Capture agents - grab the analyte, so sufficient to see or recover from a sample to measure
- Contrast agents - light up the analyte, so that remote measurements (*eg* imaging scanners) can see it

Dx NPs similar or more advanced than pharmaceutical NPs

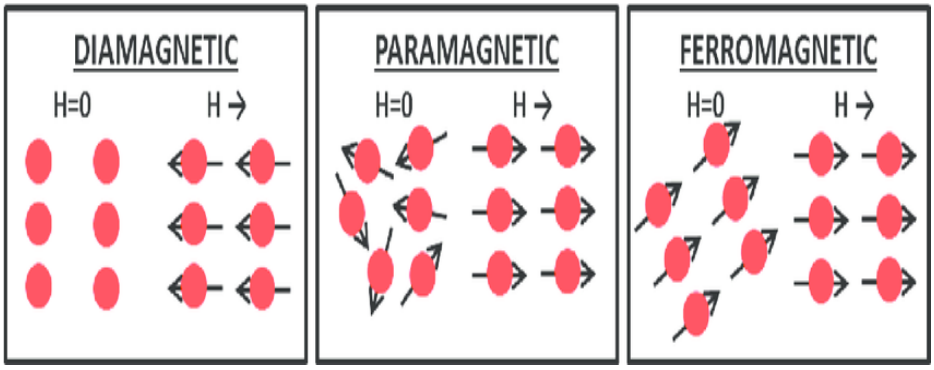
IVD: consumer, point of care Dx – some examples

- Magnetic nanoparticles
- Miniaturized NMR
- Gold nanoparticles
- Semiconductor nanoparticles – quantum dots
- Biosensors
- Surface plasmon resonance
- Nanosight
- Photoacoustic

Example: (para)magnetic particles



Magnetism

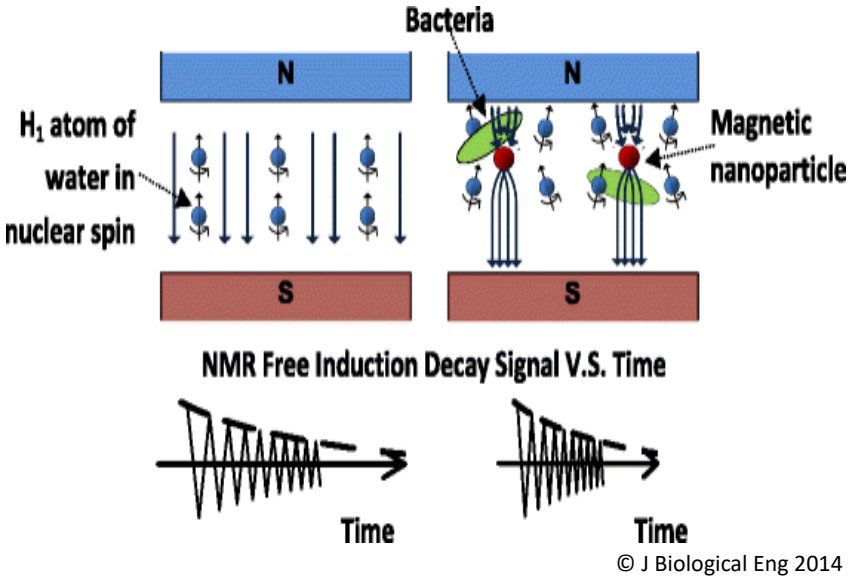


Weak repulsion with paired electron spins

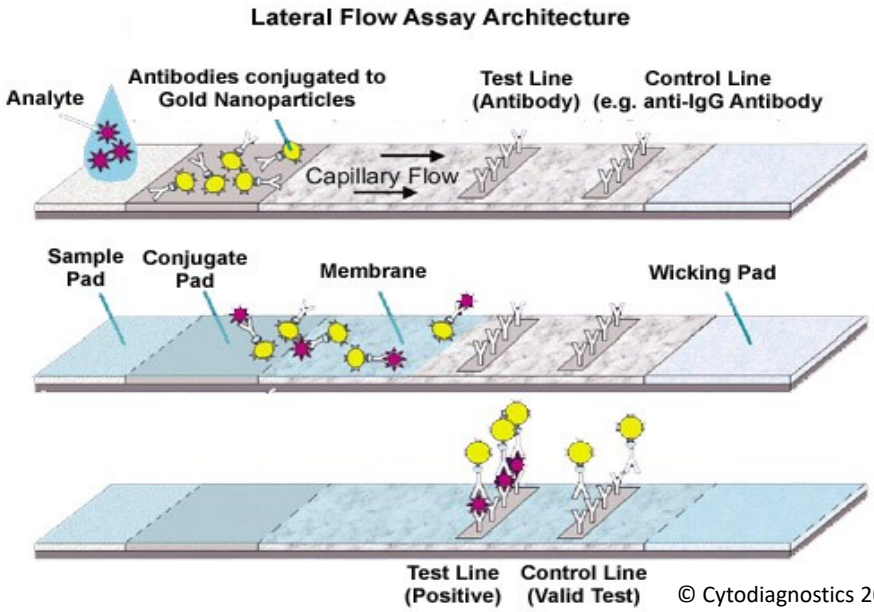
Alignment & attraction with unpaired electron spins

Strong attraction with well-ordered unpaired electron spins

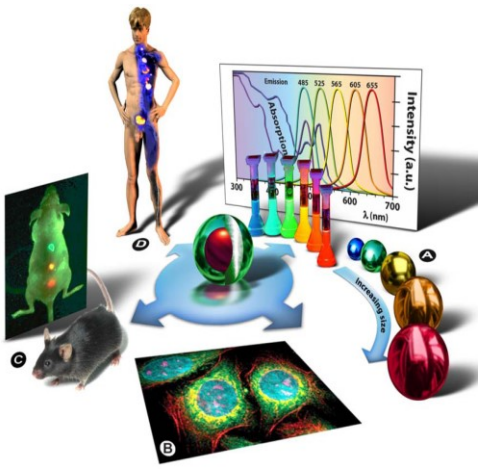
Miniaturised NMR using rare earth magnets with paramagnetic NPs



Gold / Au NPs

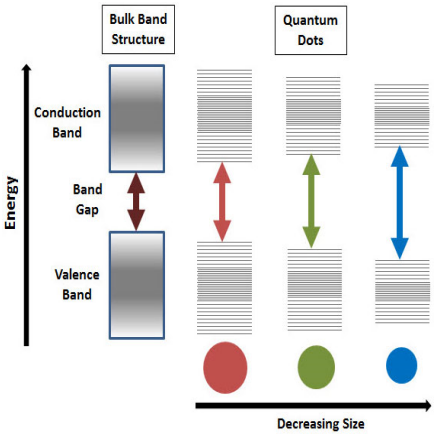


Semiconductor Nanaoparticles "quantum dots / QD"

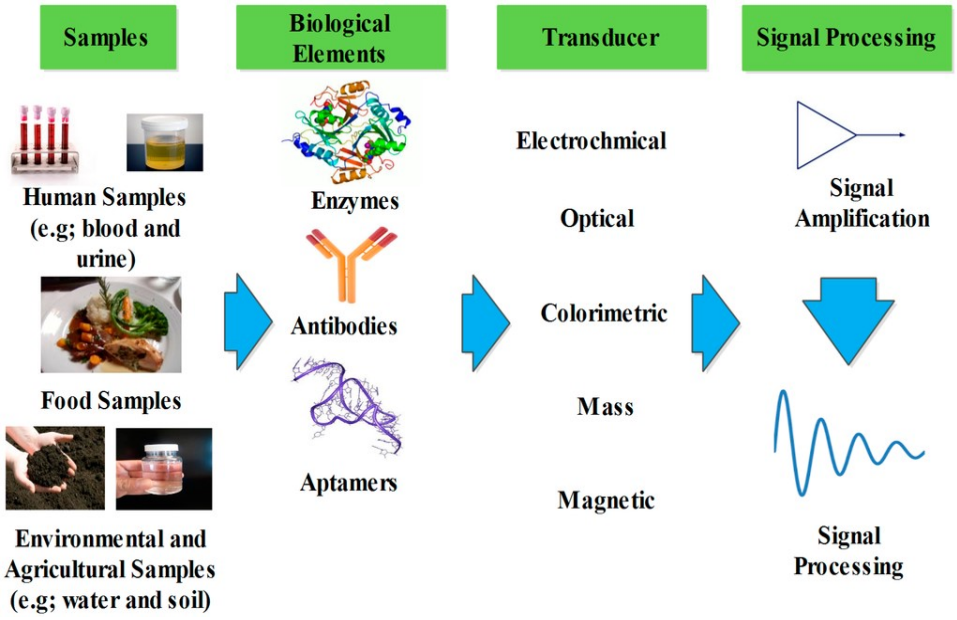


www.nanocotechnologies.com/

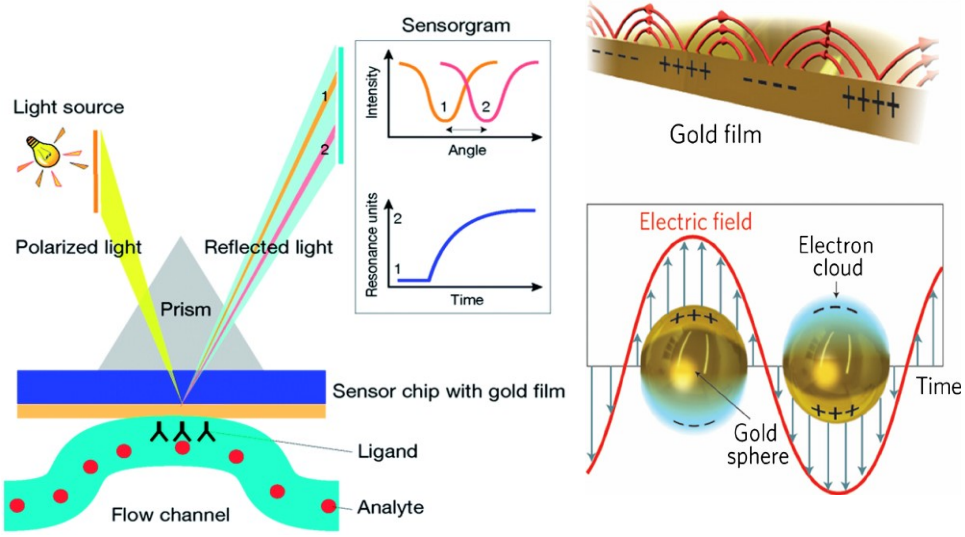
Quantum confinement effect



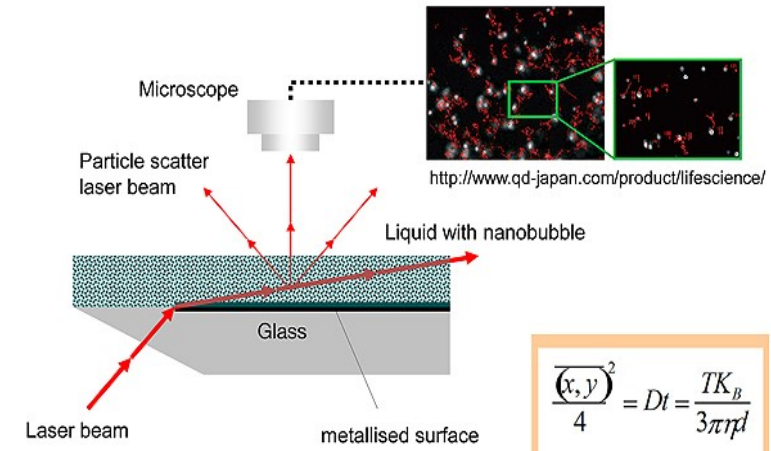
Example: biosensors



Example: surface plasmon resonance (SPR) sensor and NP sensors



Nanosight
(making nano visible to a simple camera)

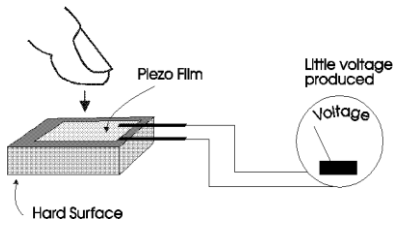


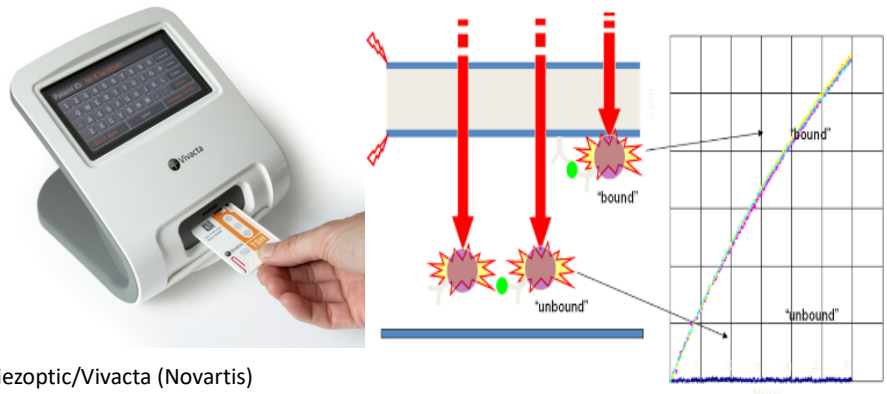
$$\frac{\overline{(x,y)}^2}{4} = Dt = \frac{TK_B}{3\pi\eta d}$$

η : solvent viscosity
K_B : Boltzmann's constant

© LM20 (NanoSight)

Photoacoustic sensor





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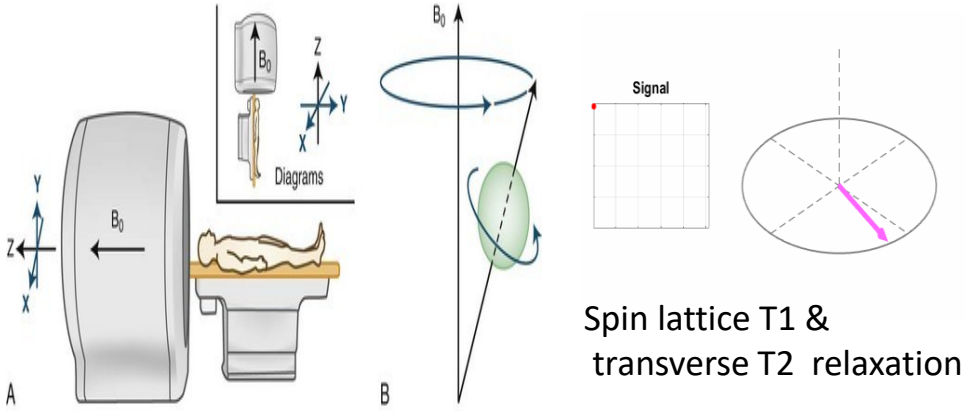
Diagnostic imaging & NPs

Imaging using nanoparticles as selective and highly-visible contrast agents:

- Magnetic resonance imaging (MRI)
- Positron emission tomography (PET)
- Photoacoustic
- Raman
- Fluorescence
- Multi-modal imaging (combining above)
- Theranostic : Dx → Rx targeted therapy

MRI scanner



Spin lattice T1 &
transverse T2 relaxation

Water dominates the relatively-low B magnetic field of the NMR in MRI unless paramagnetic image contrast NPs used, which change the relaxation time (T)

MRI image contrast: biodistribution strongly affected by size

T1 relaxation –bright (+ve) contrast

- Gd chelated to minimize its toxicity

T2 relaxation – dark (-ve) contrast

- iron oxide dextran NPs
- superparamagnetic NPs

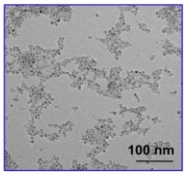
Dual - T1 $MnFe_2O_4$ & T2 $Gd_2O(CO_3)_2$

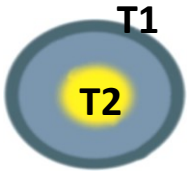
- minimizes artefacts

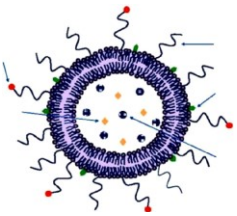
Liposomes

- versatility - T1 & T2
- targeting

dolinium chelate







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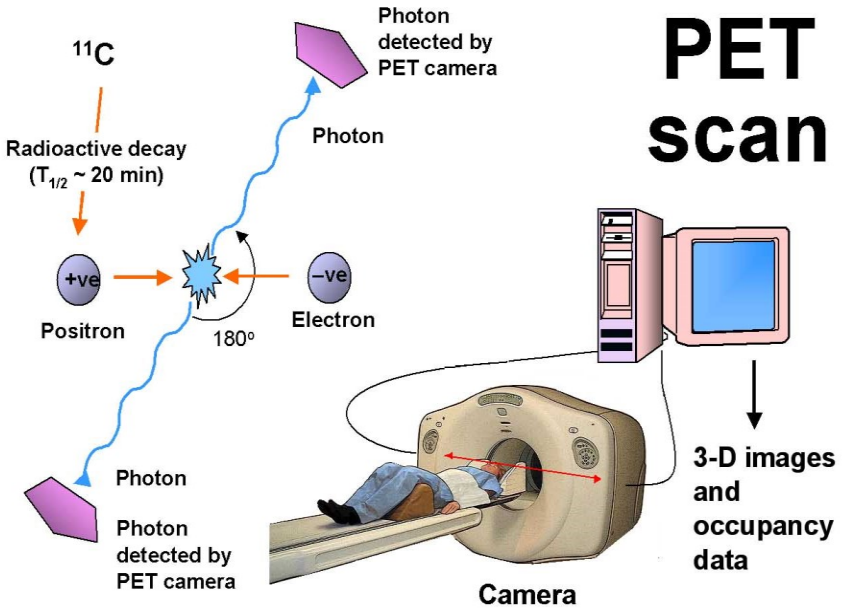
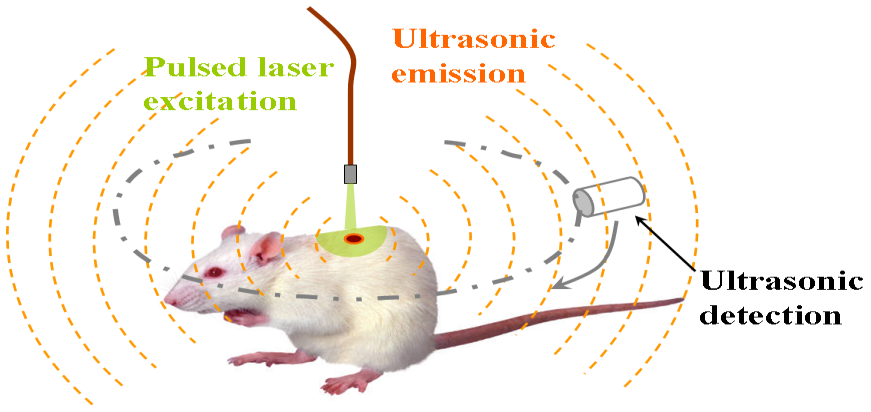
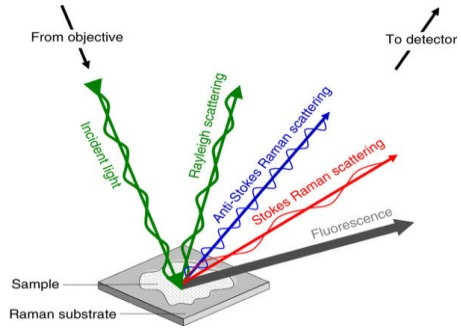
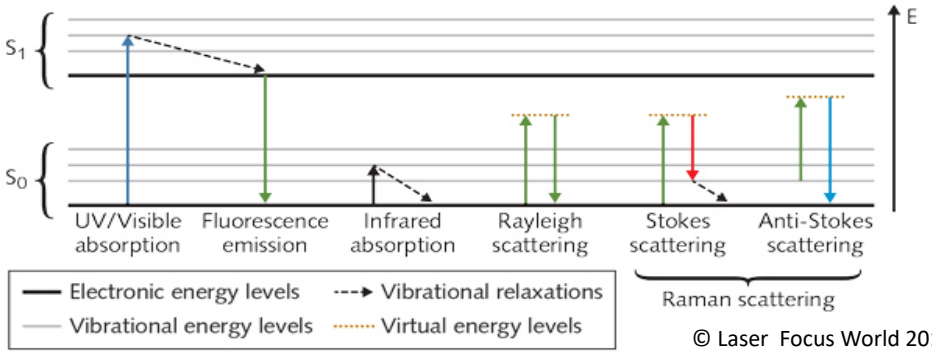


Photoacoustic scanning imaging

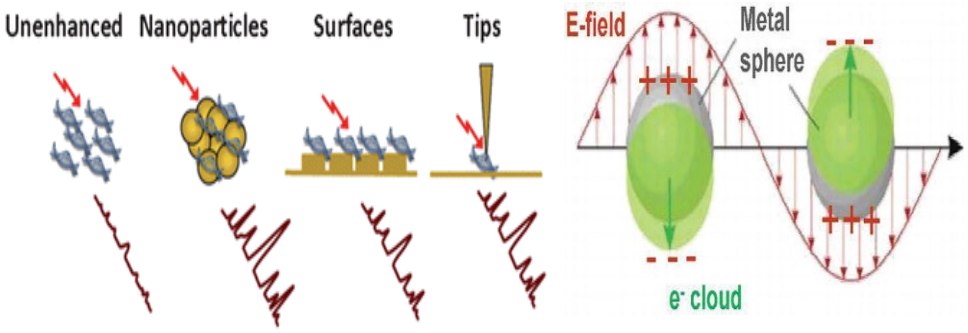


Raman & fluor scanning imaging



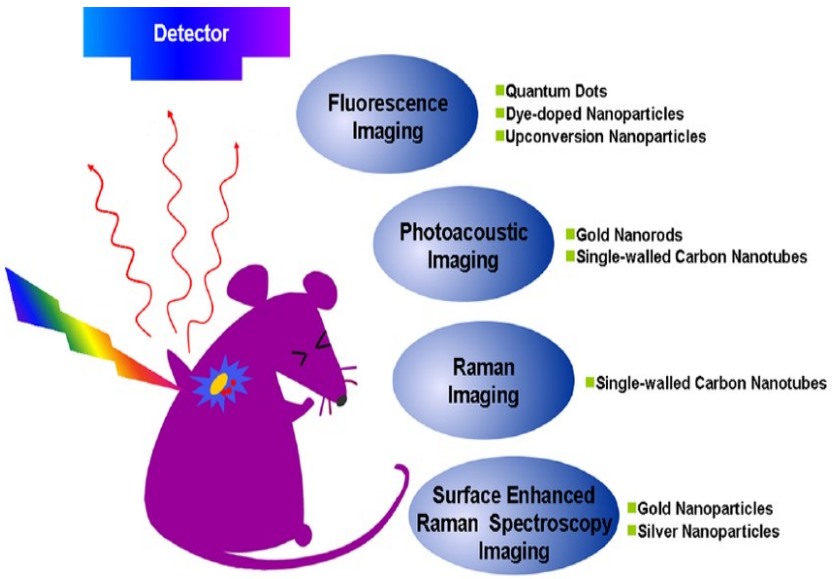


Surface enhanced Raman scattering (SERS)

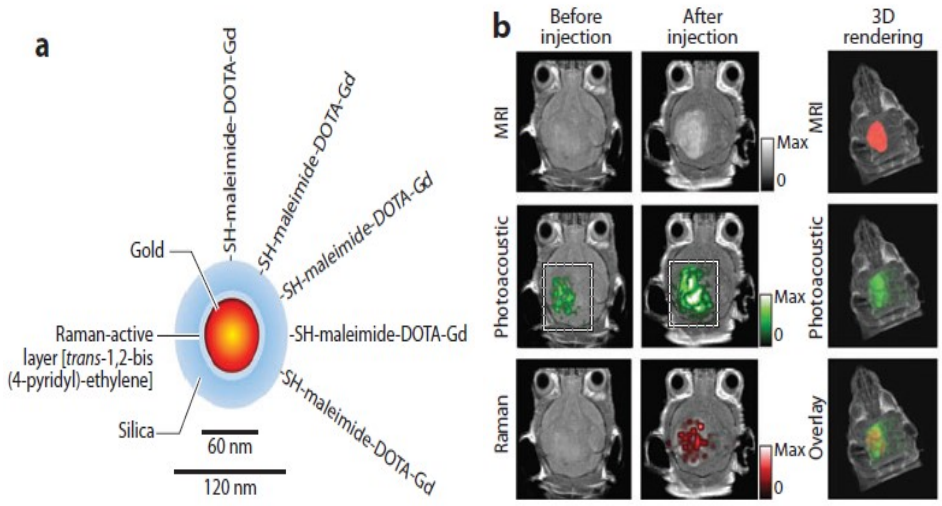


Raman scattering signals are weak but increased by orders of magnitude for molecules in plasmon resonance field between nanoparticles or on roughened surfaces or at probe tips

NPs in multimodal laser scanning imaging



Multiple modality imaging
eg brain tumor



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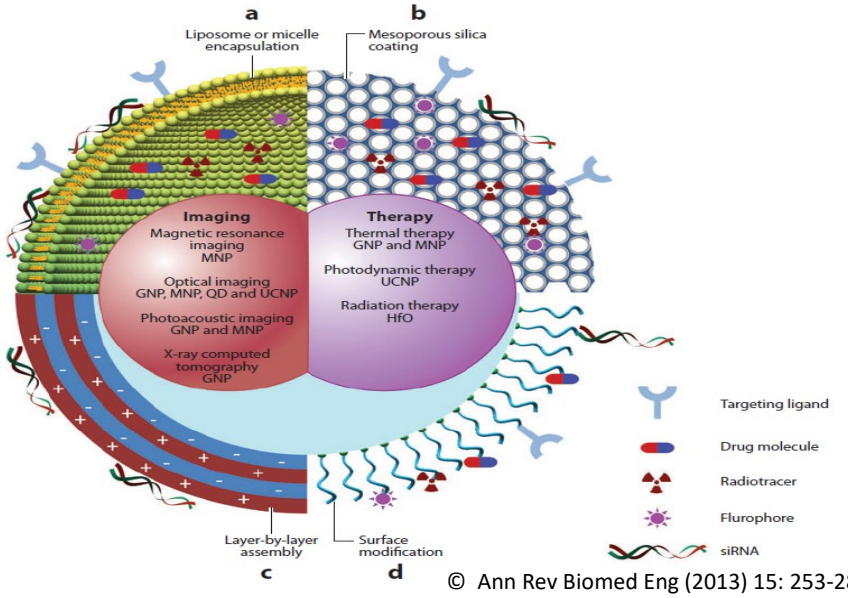
NP imaging / therapy modalities



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