

# Nanoparticulate Delivery Systems for Osteoarthritis Therapy

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Department of Biomedical Engineering

# OUTLINE

- What is Nanotechnology?
- Why Nano?
- Drug Delivery Systems
- NANO Drug Delivery Systems
- Literature Examples - **Osteoarthritis**

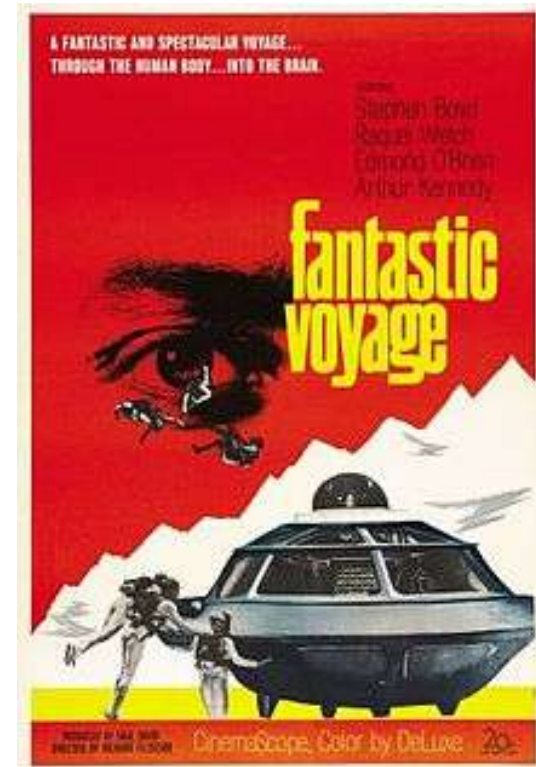
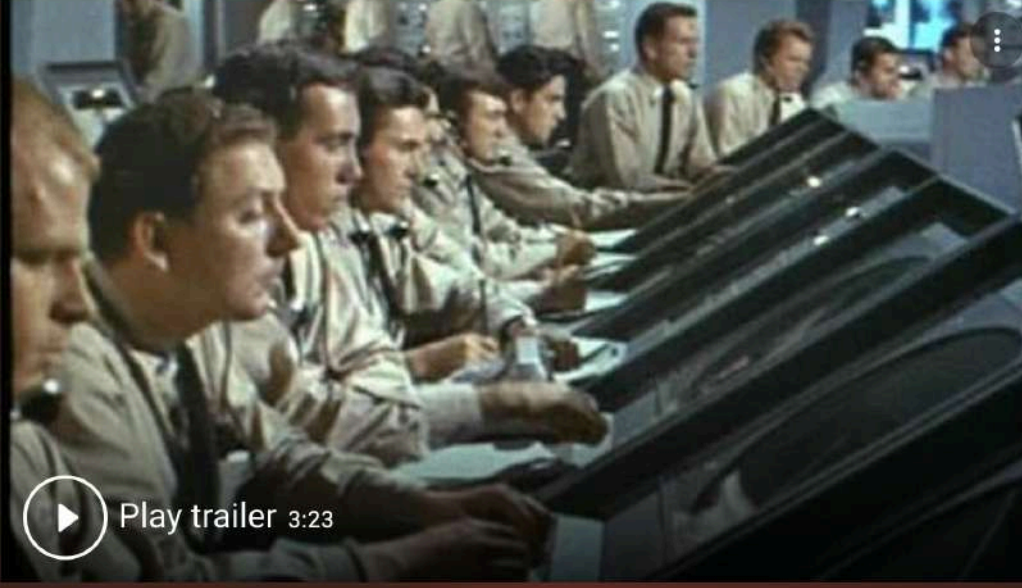
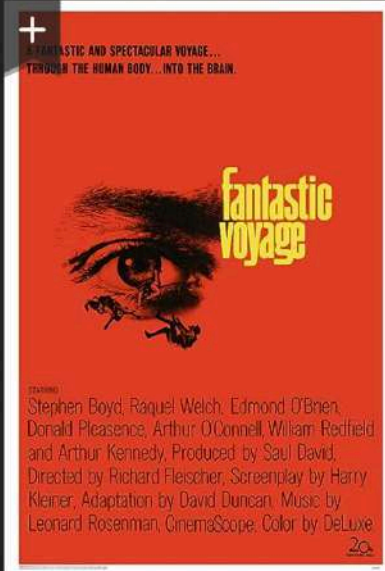
**Any sufficiently advanced  
technology is  
indistinguishable from  
magic.**

Arthur C. Clarke

Sir Arthur Charles Clarke CBE FRAS (16 December 1917 – 19 March 2008) was an English science-fiction writer, science writer, futurist, inventor, undersea explorer, and television series host.

# Fantastic Voyage

1966 · A · 1h 40m



A scientist is nearly assassinated. In order to save him, a submarine is shrunk to microscopic size and injected into his blood stream with a small crew. Problems arise almost as soon as they enter the bloodstream.

**Director:** [Richard Fleischer](#)

**Writers:** [Harry Kleiner](#) (screenplay), [David Duncan](#) (adaptation) | [2 more credits](#) »

**Stars:** [Stephen Boyd](#), [Raquel Welch](#), [Edmond O'Brien](#) | [See full cast & crew](#) »

# What is Nanotechnology?

# What is Nanotechnology?

One nanometer (nm) is **one billionth** or  $10^{-9}$  of a meter

by 1974, from **nano** + **technology**.

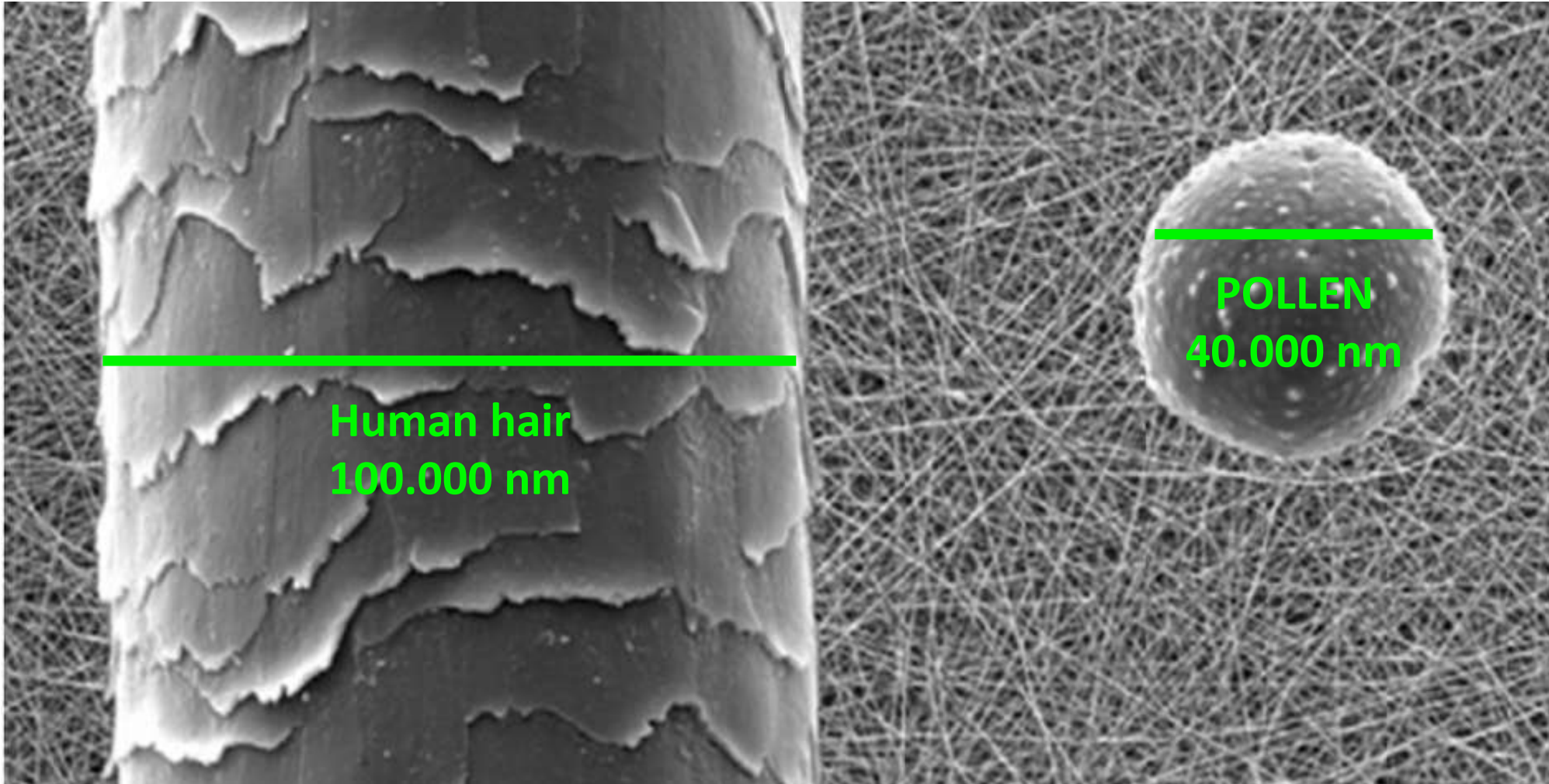


from Greek *nanos* "**a dwarf**."

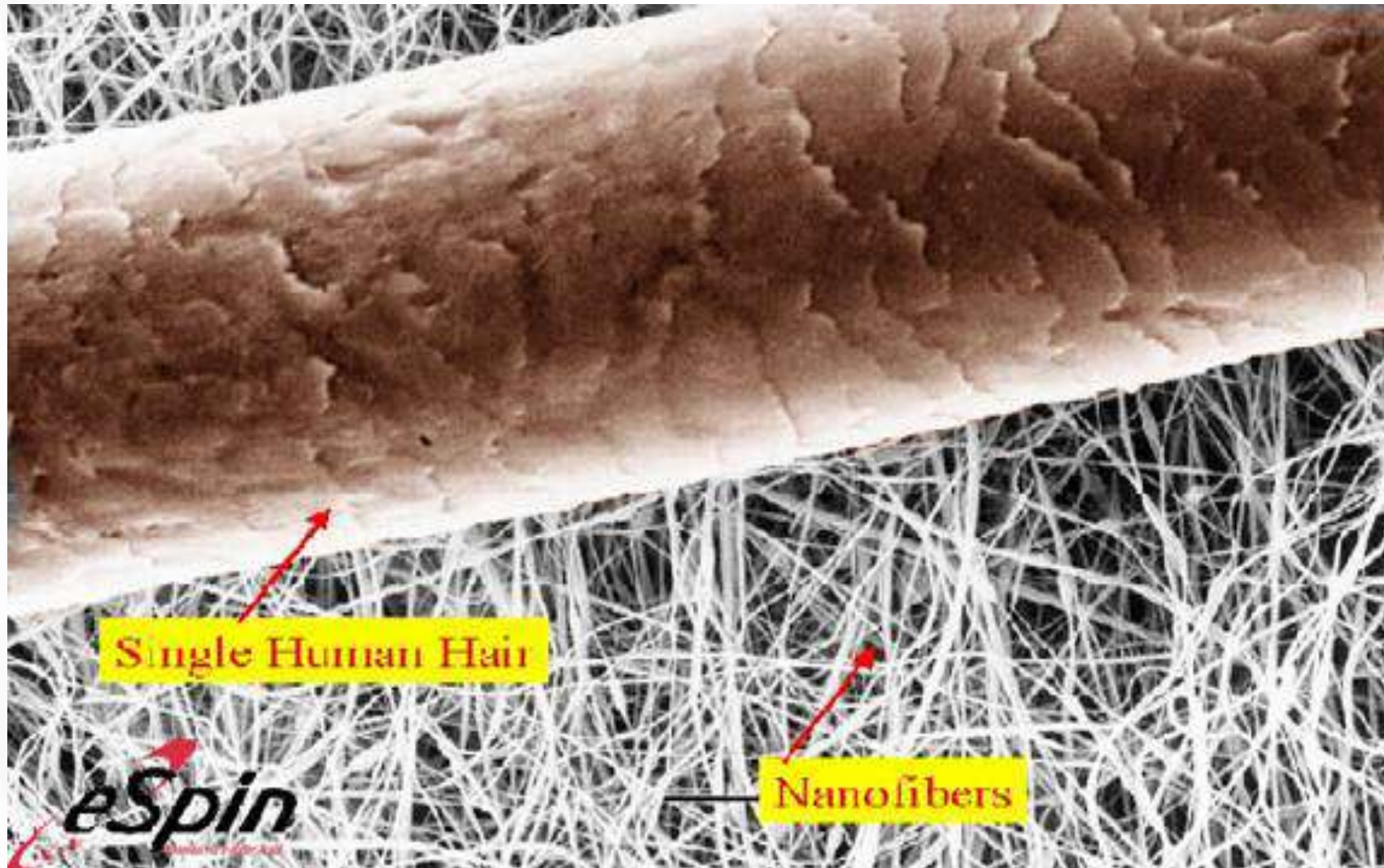
The practical application of  
scientific knowledge



# What is Nanotechnology?



# What is Nanotechnology?





# What is Nanotechnology?

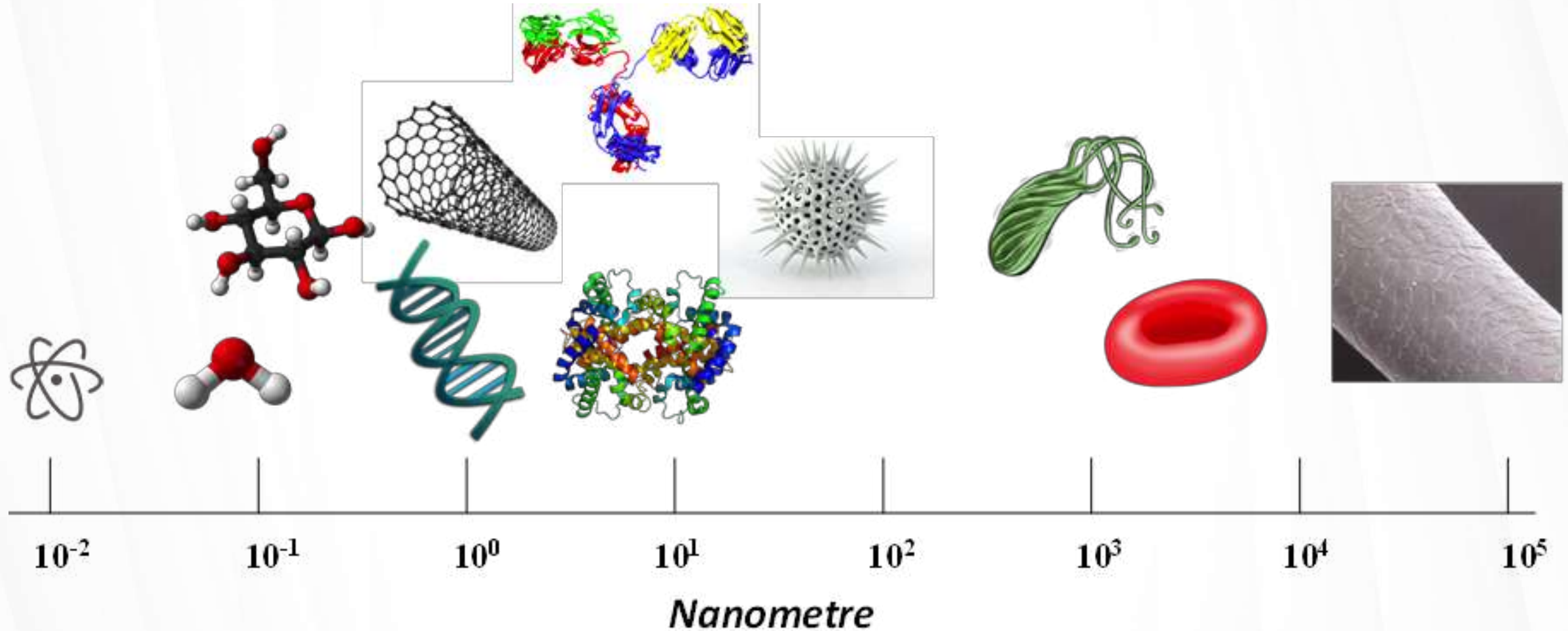
The ratio of the Earth to a football is equal to the ratio of the football to the buckyball.



**Nanometer** - One billionth ( $10^{-9}$ ) of a meter  
 $1 \text{ nm} = 10^{-9} \text{ m}$   
 $1 \text{ m} = 1.000.000.000 \text{ nm}$

- The size of Hydrogen atom 0.04 nm
- The size of Proteins ~ 1-20 nm
- Diameter of human hair ~ 100  $\mu\text{m}$

# What is Nanotechnology?



# Why “NANO”?

# Why Nanotechnology?

Surface Area / Volume Ratio

Quantum Size Effect



# Why Nanotechnology?

## Surface Area/Volume Ratio



Sugar cubes



Granulated sugar

Larger surface area /volume ratio  $\longrightarrow$  more reactive !

# Why Nanotechnology?

## Quantum Size Effect



Smaller particles can have different optical properties.

**Their colours** change because different sizes of particle **reflect and absorb** light differently.

Nanoparticles often **possess unexpected optical properties.**

# Why Nanotechnology?

## Quantum Size Effect

Medieval stained-glass was created **by trapping gold nanoparticles** in the 'glass matrix' to create **a red colour**.

Silver nanoparticles, meanwhile, gave it a deep yellow colour.  
Researchers have now taken divine inspiration from medieval stained-glass - because their colours haven't faded after hundreds of years being bombarded by UV radiation.



Medieval stained glass windows

Red stained glass >> gold nanoparticles that are only 20 nm  
Orange glass >> gold nanoparticles that are 80 nm

<https://www.dailymail.co.uk/sciencetech/article-2461418/How-medieval-stained-glass-creating-ultimate-SPACE-camera-Nanoparticles-used-church-windows-help-scientists-Mars-true-colours-extreme-UV-light.html>

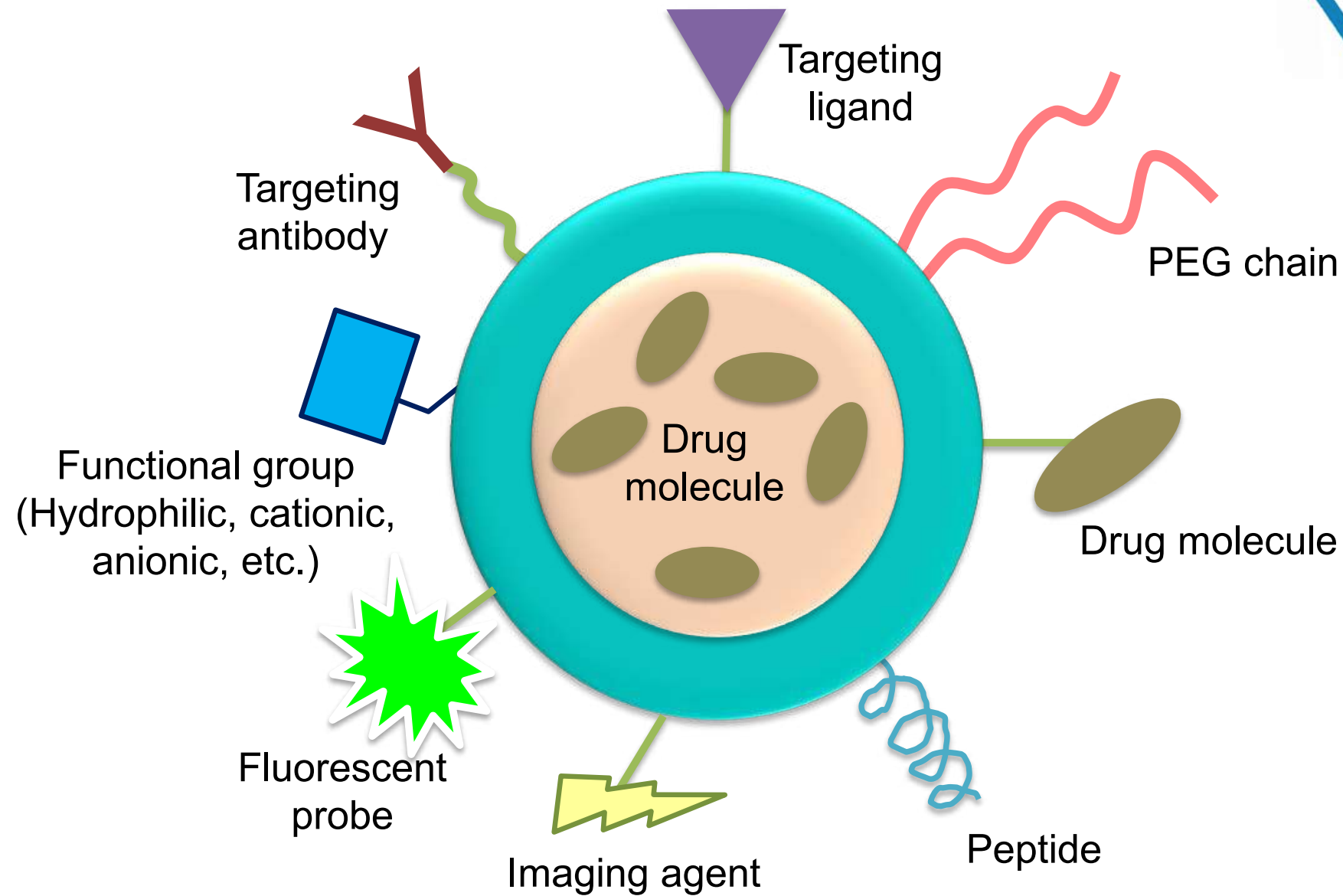
# Drug Delivery Systems





## Drug delivery systems (DDS)

- To **increase** the **efficiency** of drug molecules
- To **decrease** the **side effects**



# Osteoarthritis

Normal Knee



Knee Osteoarthritis



Osteoarthritis (OA), the most common **degenerative disorder** of the whole joint, affects more than half of people over 65, which is associated with significant **inflammation, cartilage degeneration, and joint pain.**

It occurs most frequently in the hands, hips, and knees.

Healthy



OA



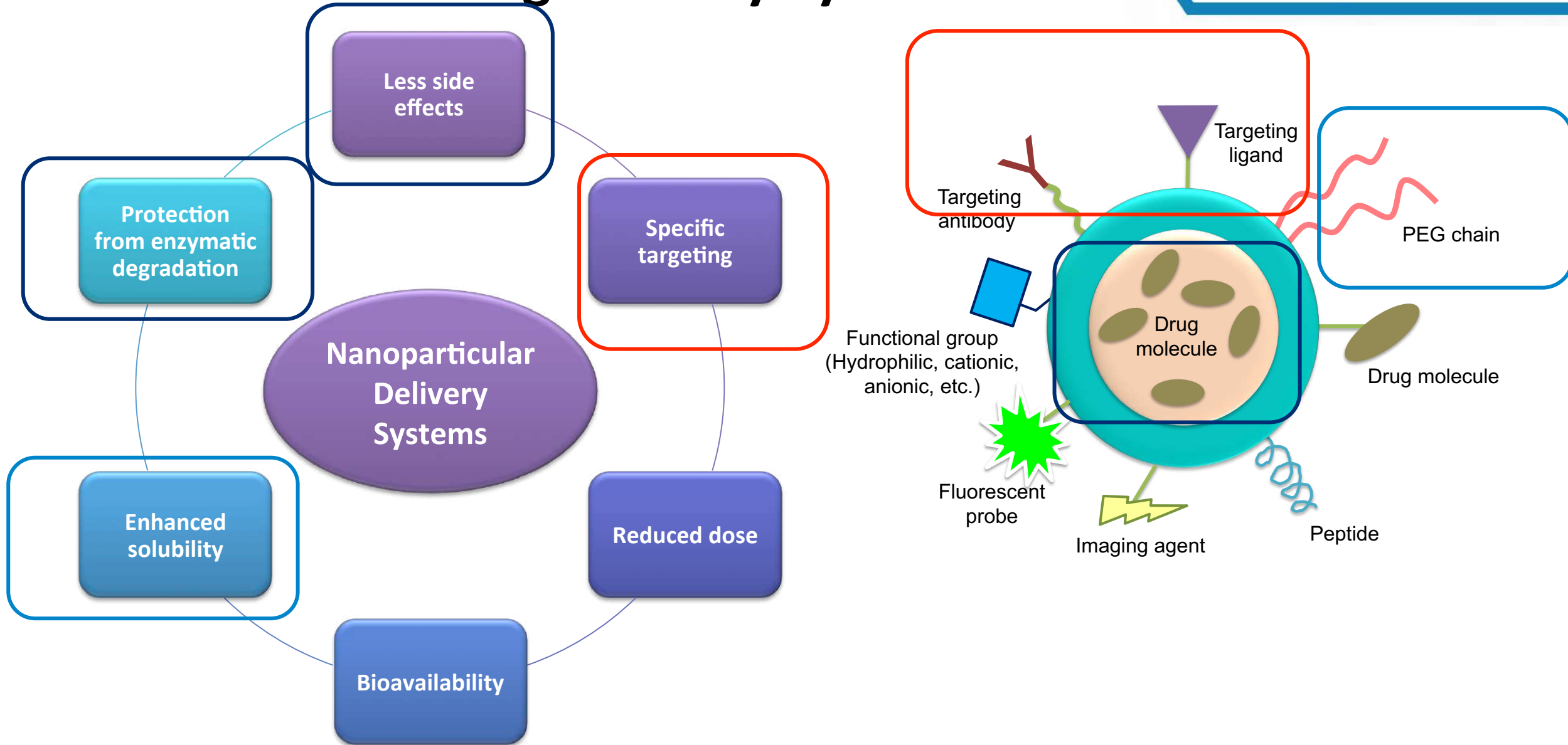
# Osteoarthritis – Traditional Drug Therapy

The **limitations** of traditional drug therapy for orthopedic disorders.

- ✗ Painful methods of administration
- ✗ Risk of systemic toxicity
- ✗ High rate of clearance
- ✗ Limited permeability of the synovial membrane and articular capsule of affected joints.



# Osteoarthritis – Drug Delivery Systems



# Osteoarthritis – Drug Delivery Systems

Prevention of dispersion or degradation of the drug by the body fluids leading to **enhanced drug circulation** or **retention time within the body**.

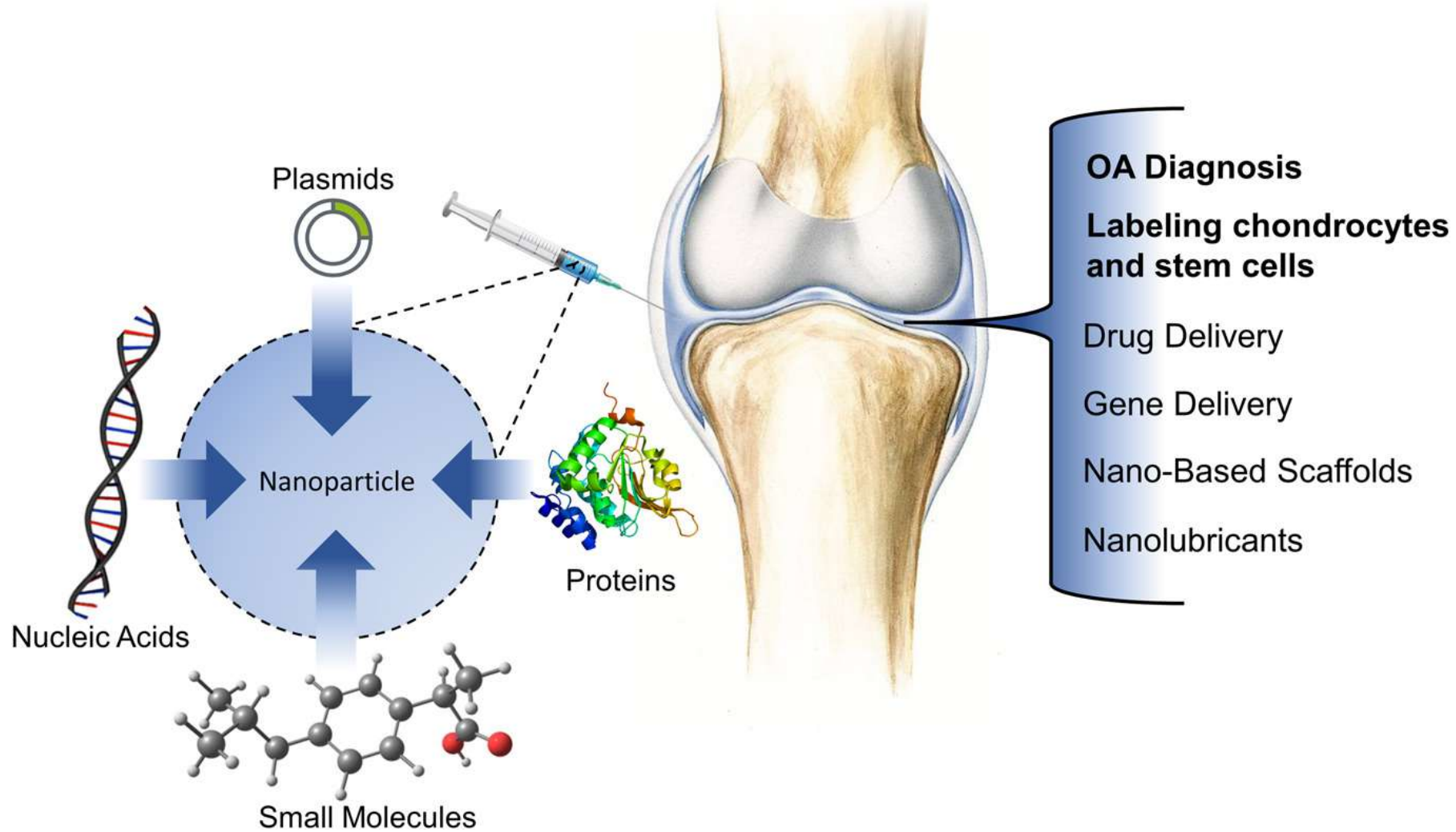
Can be designed with different physicochemical properties, such as size, shape, and surface charge to load drugs with a prolonged half-life in vivo. Capacity to transport a **large volume of drug** as well as increase **the solubility of hydrophobic** drugs

Capability of attaching **targeting molecules** via surface modification to achieve specific delivery

Drug delivery systems with **extended-release** properties, controlled and extended release of drug and increased retention times in joints while avoiding systemic side effects

Protect encapsulated therapeutics from **enzymatic degradation**

# Osteoarthritis

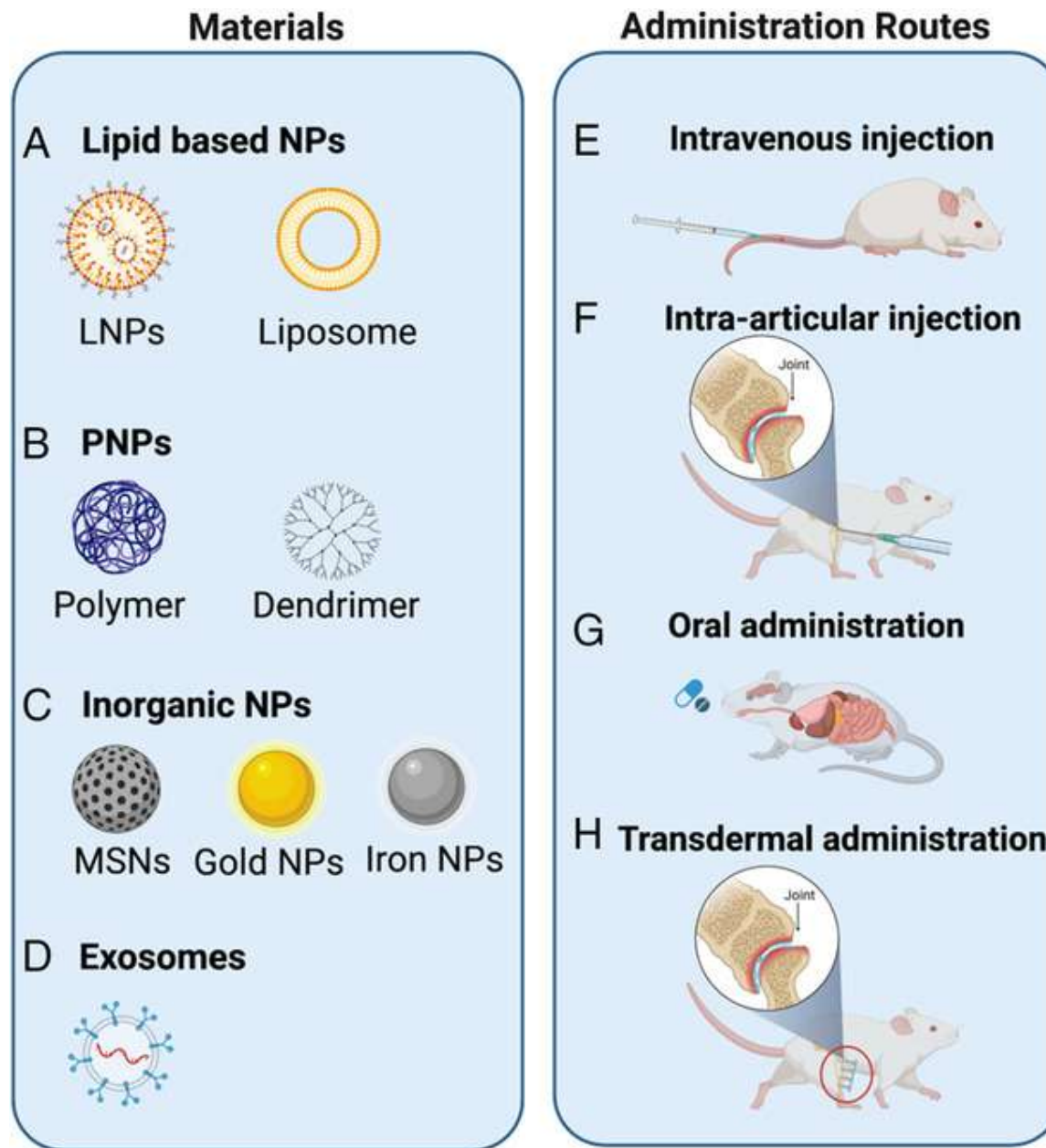


Rabiei, M., et al., (2021). *Journal of drug delivery science and technology*, 61, 102011.

Mao, L., et al. (2021). *Drug Delivery*, 28(1), 1861-1876.

CA21110 NetwOArk - Articular Cartilage Engineering  
Training School, İstinye University, İstanbul

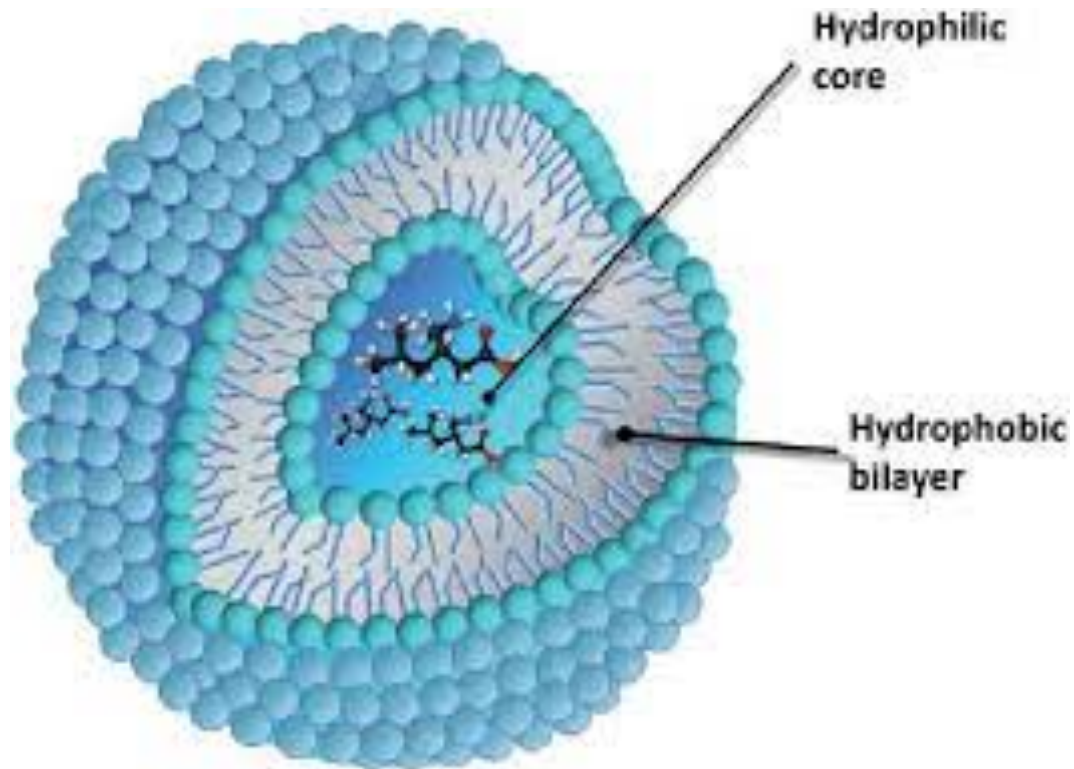
# Osteoarthritis



# NANO Drug Delivery Systems

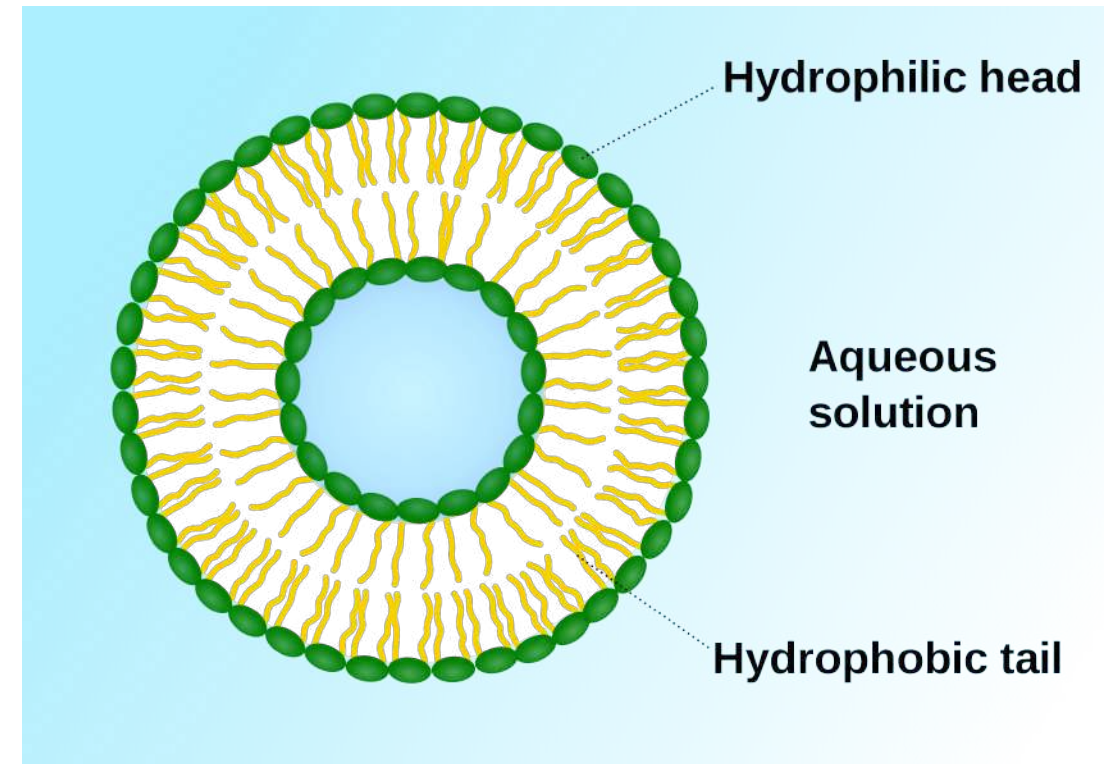


# Liposome



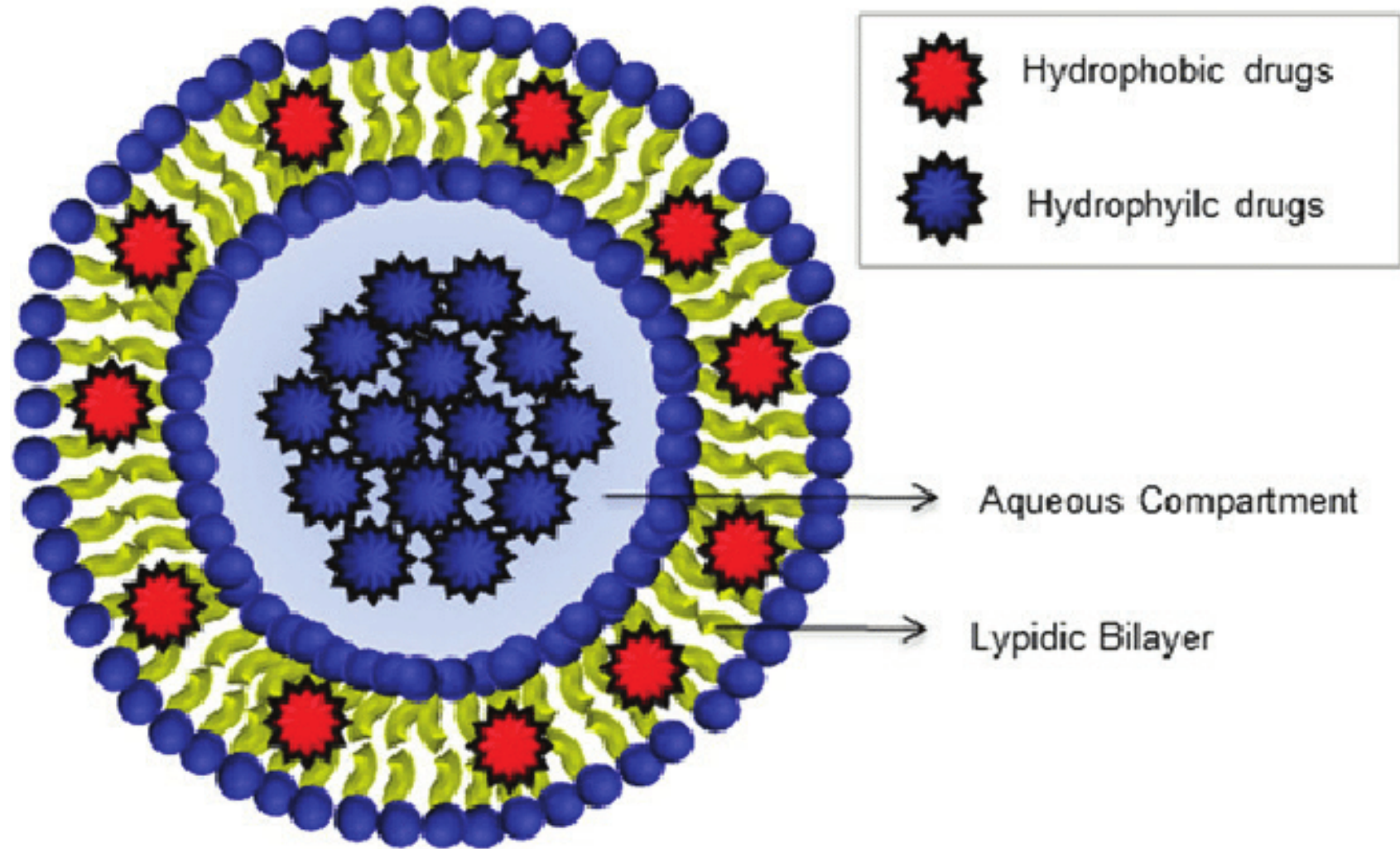
A liposome is a spherical vesicle having at least one lipid bilayer.

Liposomes are most often composed of phospholipids.



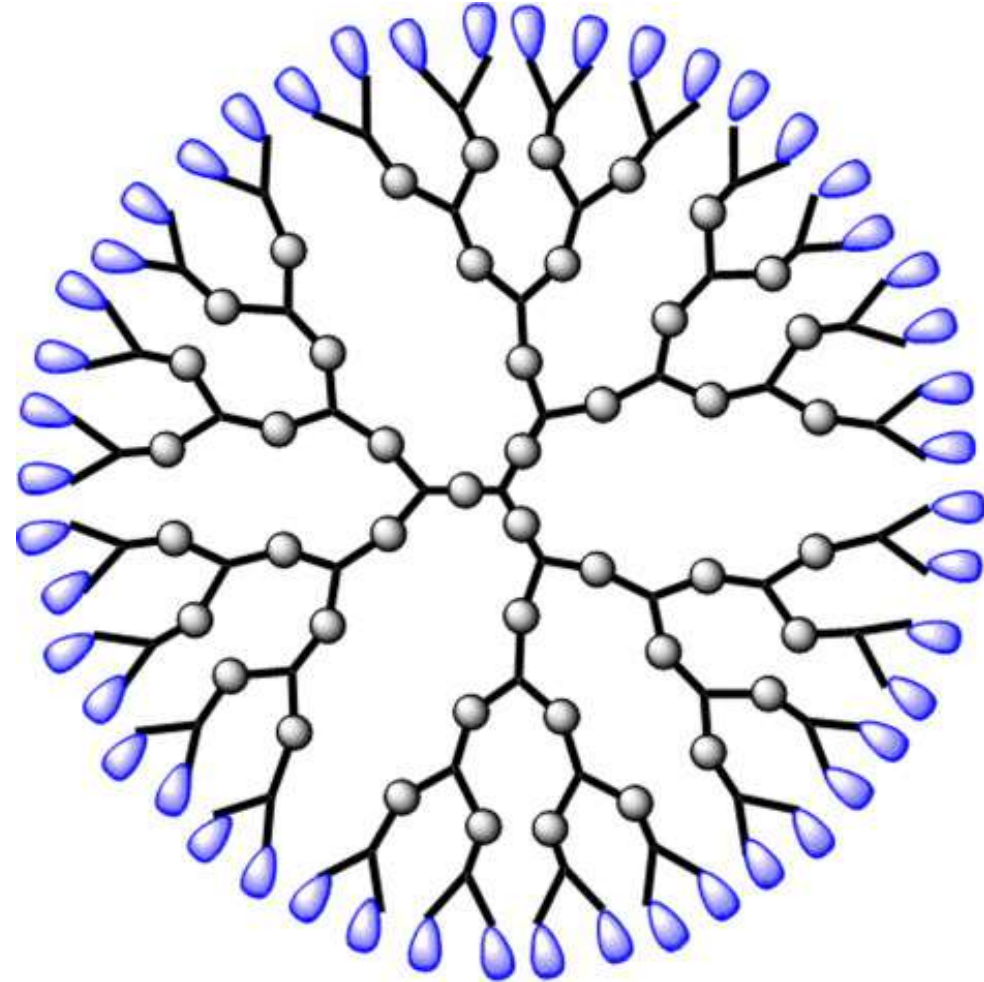
<https://www.openpr.com/news/3023870/liposome-drug-delivery-market-must-see-recent-development>

# Liposome



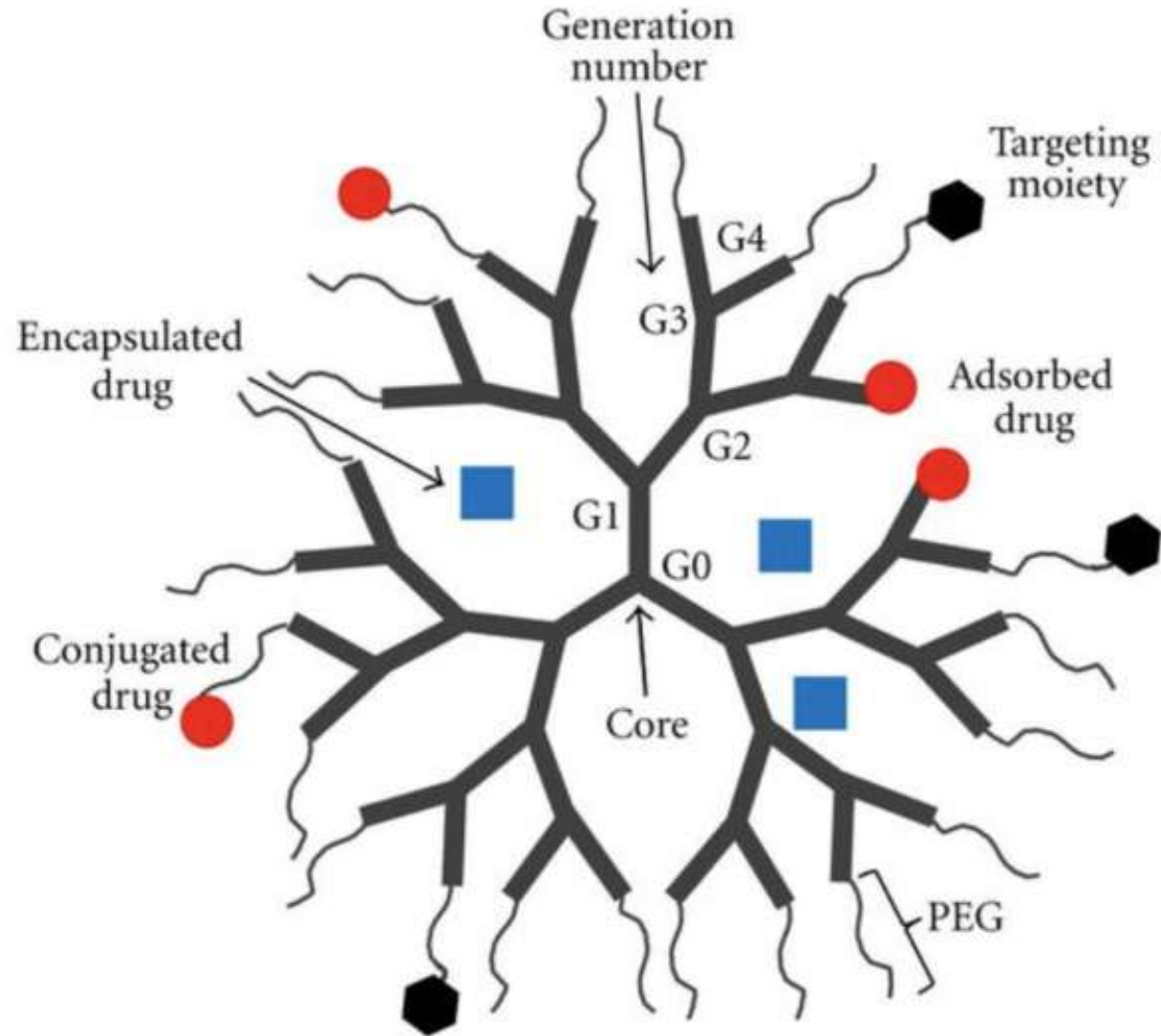
# Dendrimer

- A **well-defined polymer**, which is built in such a way that branches just keep growing out of branches and more branches grow out of those branches.
- Dendrimers are highly ordered, branched polymeric molecules.
- These are called ***dendrimers***, from the ancient Greek word for "tree".

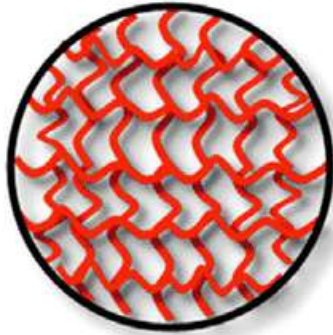




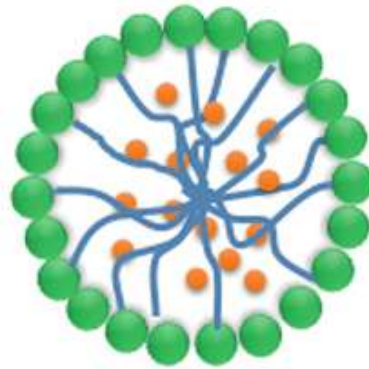
# Dendrimer



# Nanocarriers



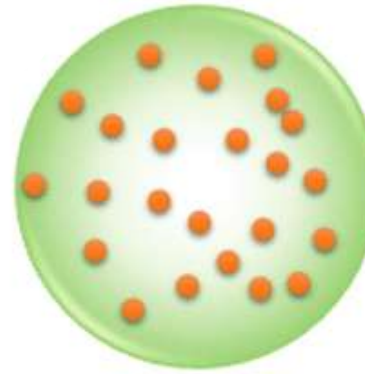
Hydrogel



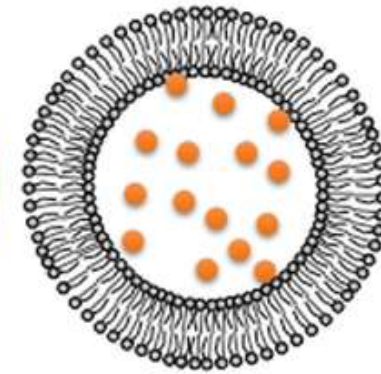
Micelle



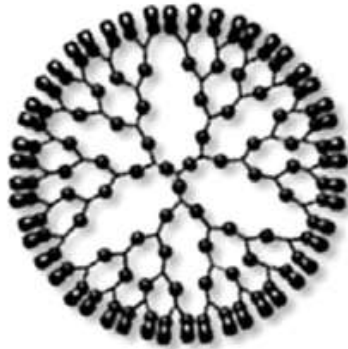
Nanocapsule



Nanosphere



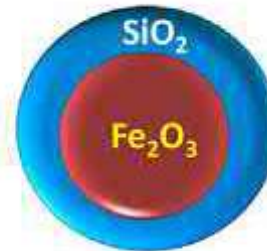
Liposome



Dendrimer



Quantum dot



SPION



Gold nanoparticles



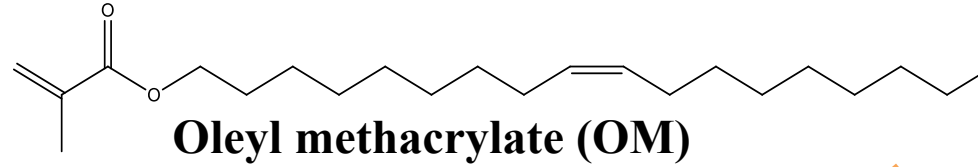
Mesoporous silica nanoparticles



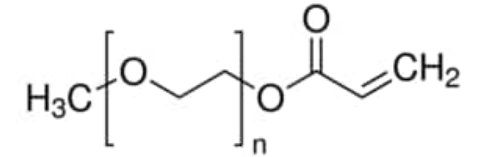
# Green Nanoparticles



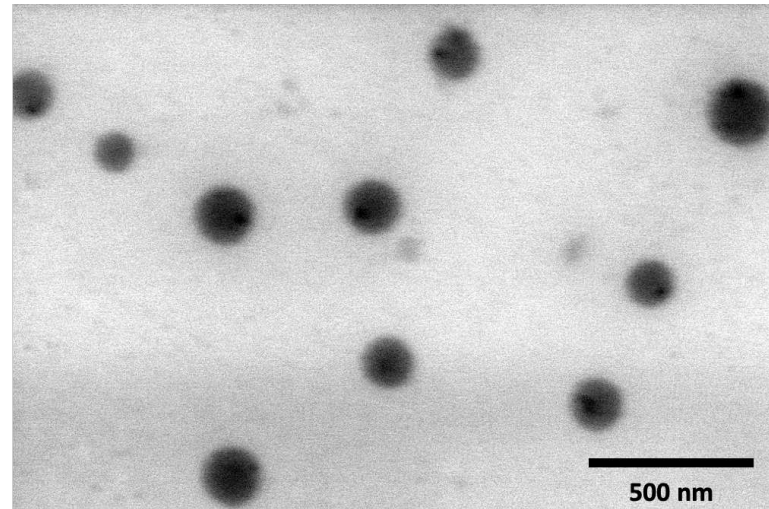
Olive oil



365 nm

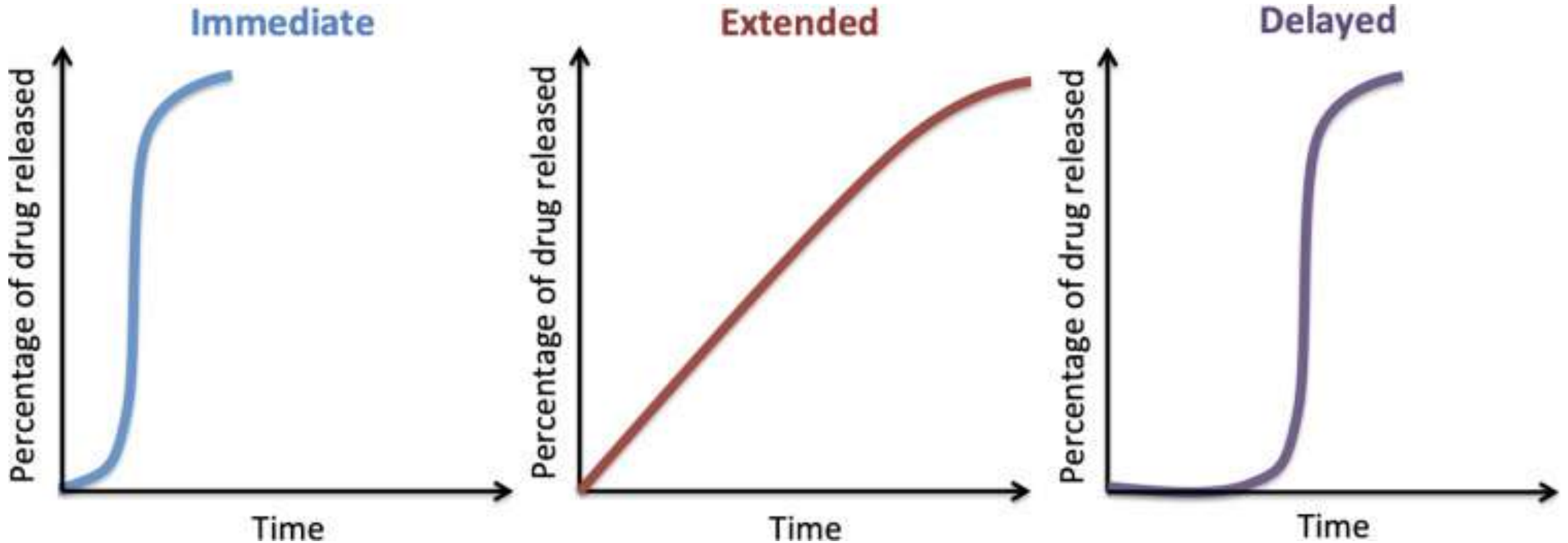


mPEG-acrylate



- **Immediate release** – drug is released immediately after administration.
- **Modified release**
  - **Delayed release:** Drug is released only at some point after the initial administration.
  - **Extended release:** Prolongs the release to reduce dosing frequency.
  - **Targeted release:** A dosage form that releases drug at or near the intended physiologic site of action.

# Drug Release Systems



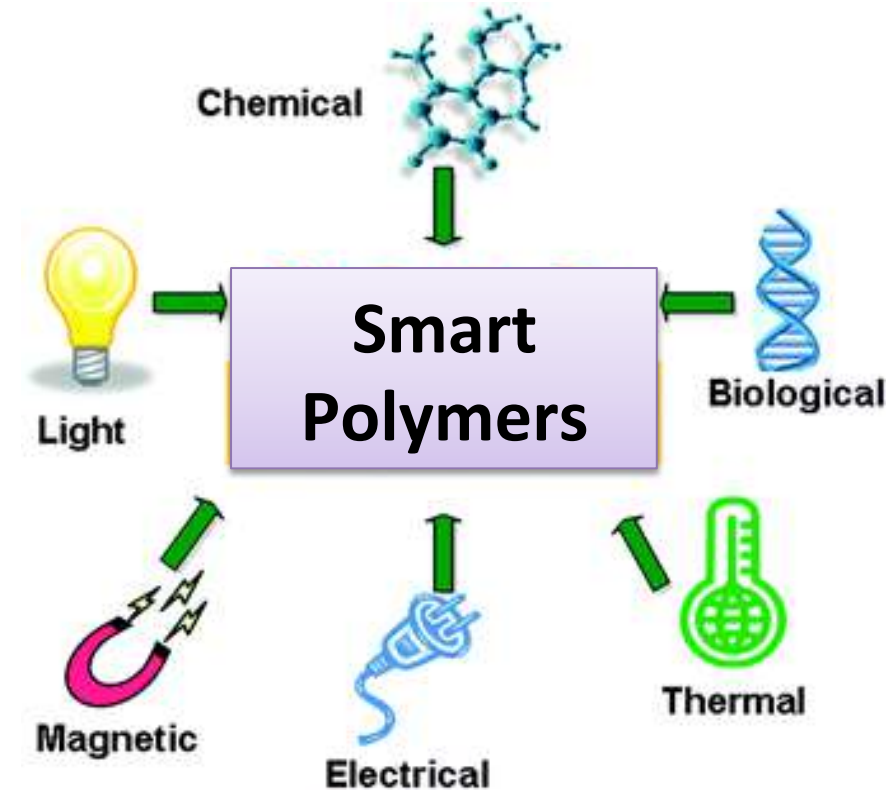
Awad, A., Trenfield, S. J., & Basit, A. W. (2021). Solid oral dosage forms. In *Remington* (pp. 333-358). Academic Press.

# Literature Examples

# Stimuli-Responsive Systems

**Stimuli-responsive systems** are smart systems that are able to respond to specific **environmental conditions**.

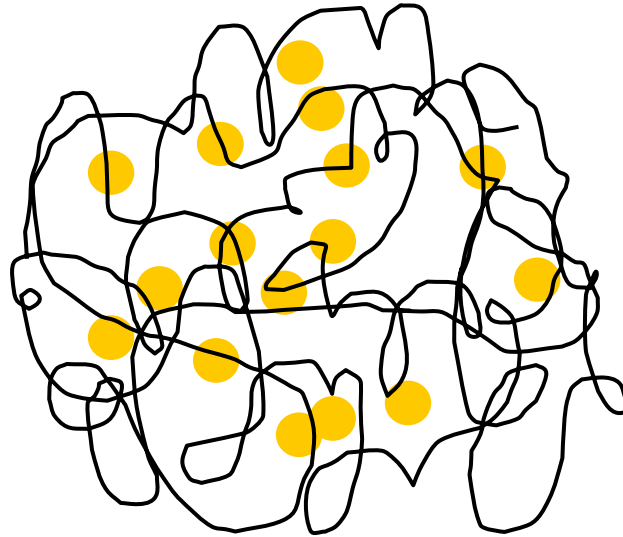
- Temperature,
- pH,
- Ionic and/or solvent composition of the media,
- Electric field,
- Magnetic field,
- Ultrasound,
- Photonic irradiation,
- Chemical composition of the media.





# Thermoresponsive Drug Delivery

## Drug delivery



$T < LCST$

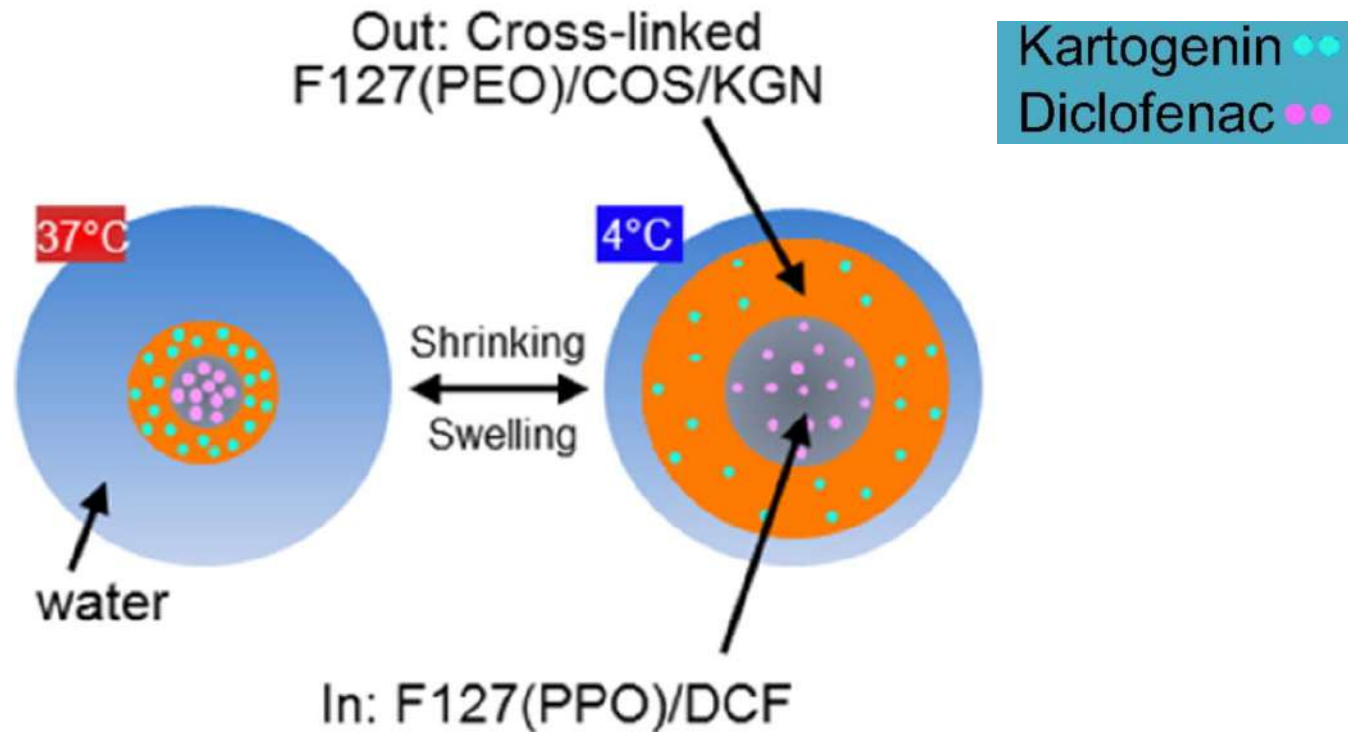
$T > LCST$

● Drug molecule

# Osteoarthritis - Dual drug delivery

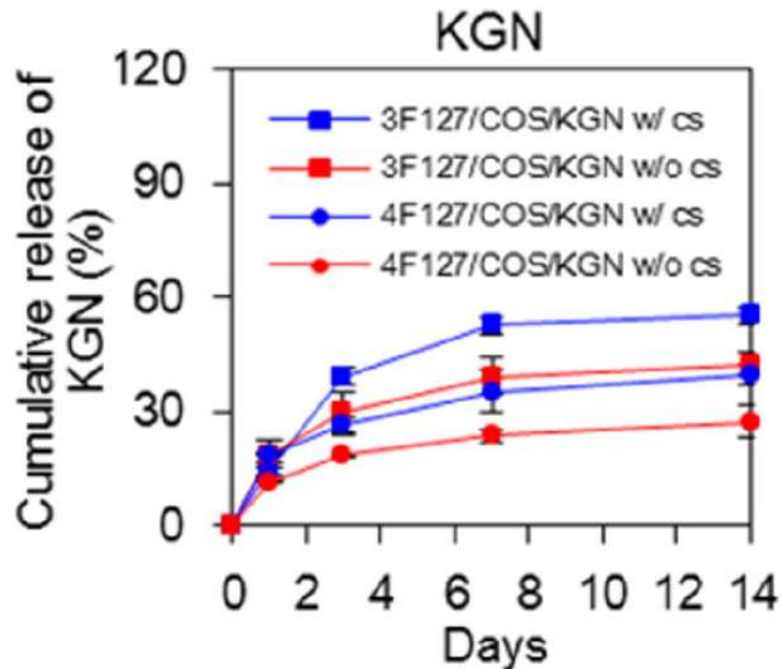
## Thermoresponsive drug delivery system

To achieve the dual drug release, kartogenin (KGN) was covalently cross-linked to the outer part of the nanosphere, and diclofenac (DCF) was loaded into the inner core of the nanosphere.

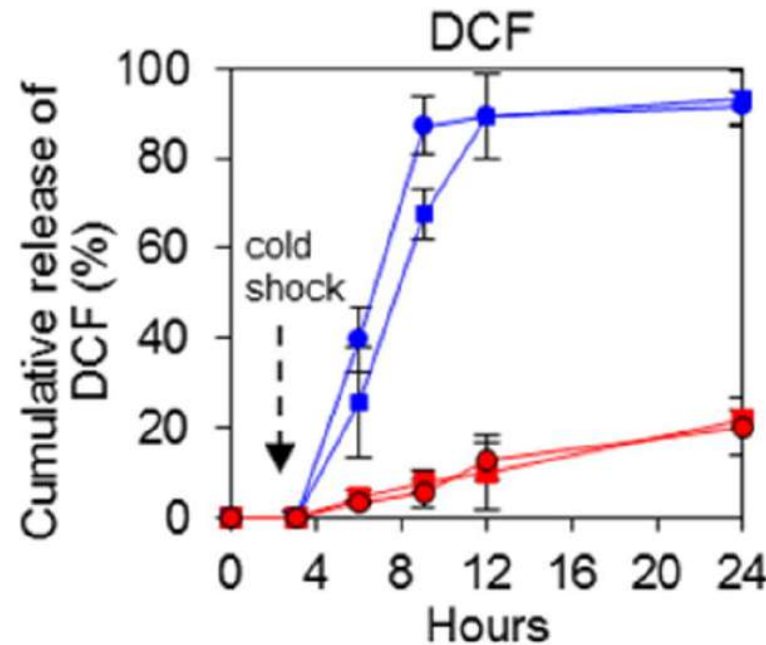


# Osteoarthritis - Dual drug delivery

## Thermoresponsive drug delivery system



Sustained release kinetics of crosslinked KGN



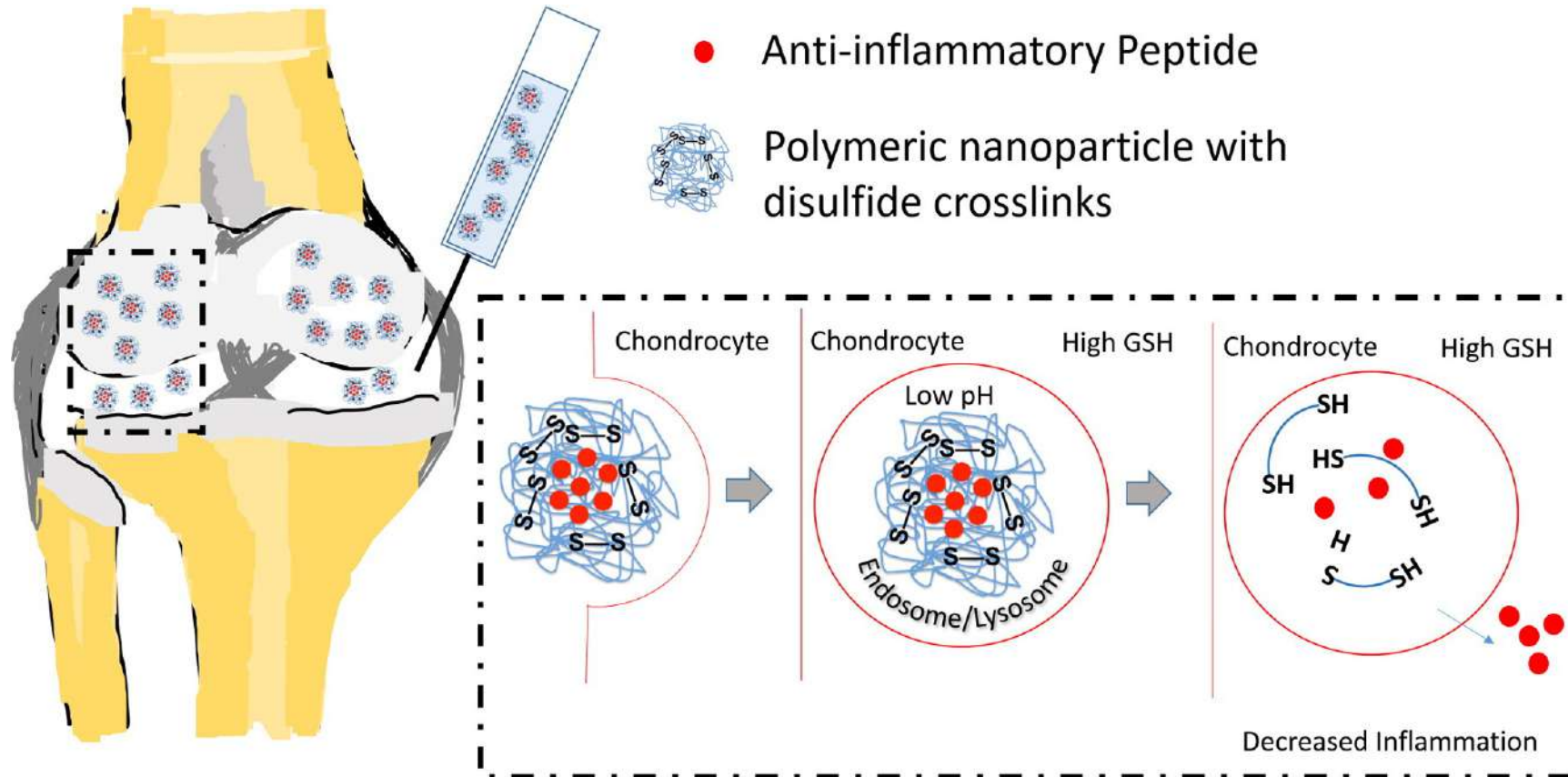
Immediate DCF-release kinetics after cold treatment

The nanospheres demonstrated **immediate release of DCF** and **sustained release of KGN**, which were independently controlled by temperature change.

The nanospheres demonstrated initial burst release of DCF and sustained release of KGN *in vitro*.

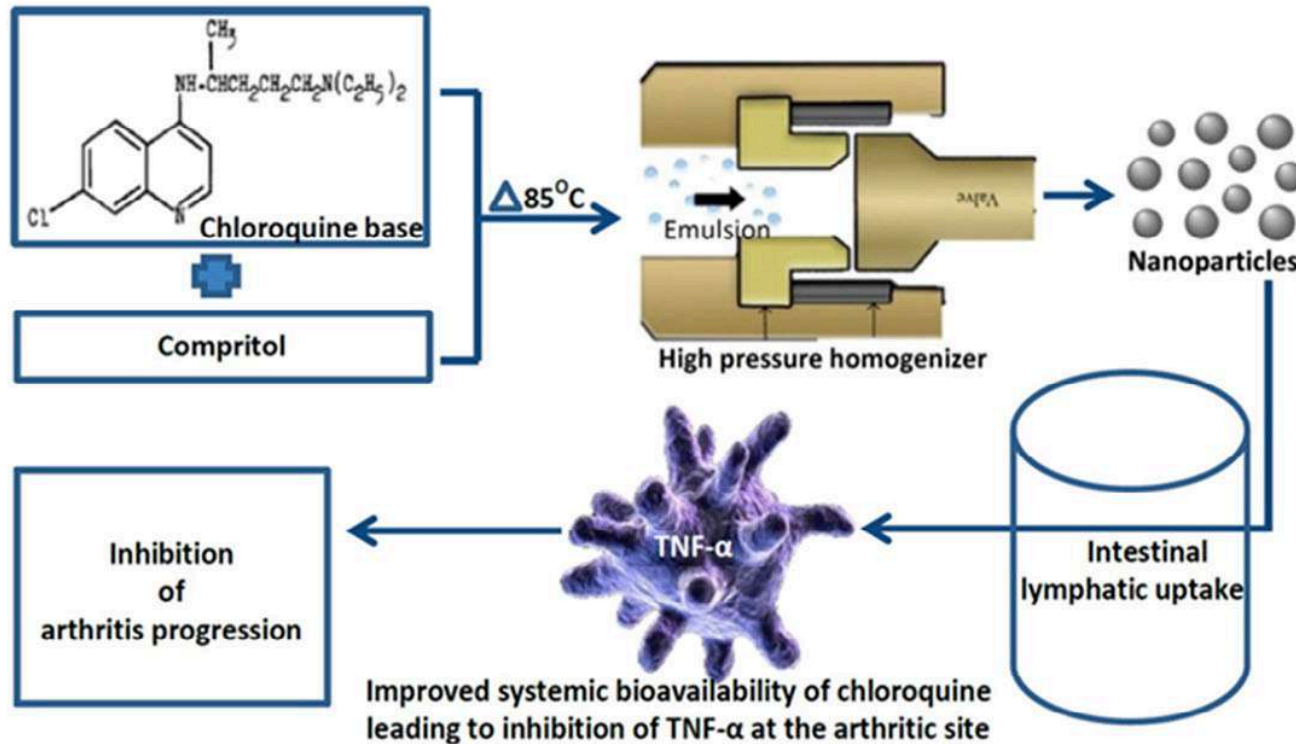
# Osteoarthritis - Controlled release

## Degradable drug delivery system



Intra-articular drug delivery systems with controlled release of anti-inflammatory peptides using degradable poly(N-isopropylacrylamide) (pNIPAM) nanoparticles could **prolong relief and minimize these side effects**.

# Osteoarthritis – Lipid Nanoparticles



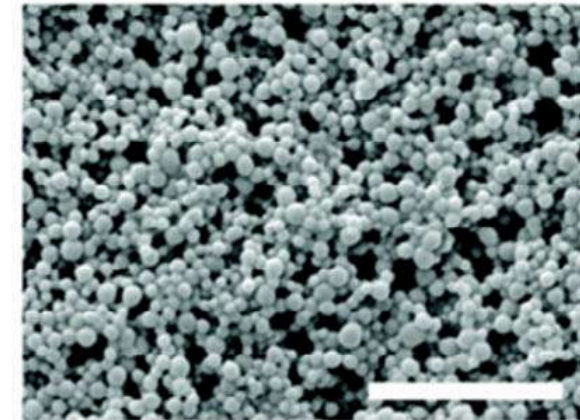
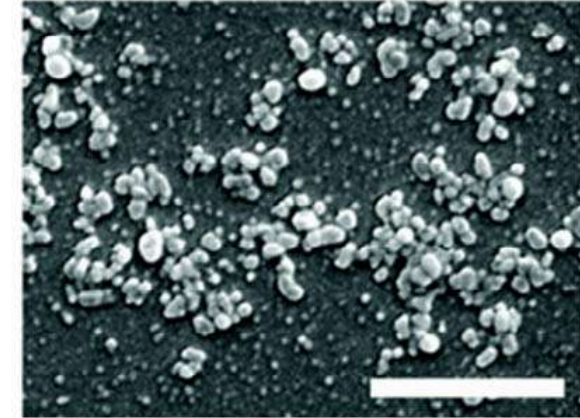
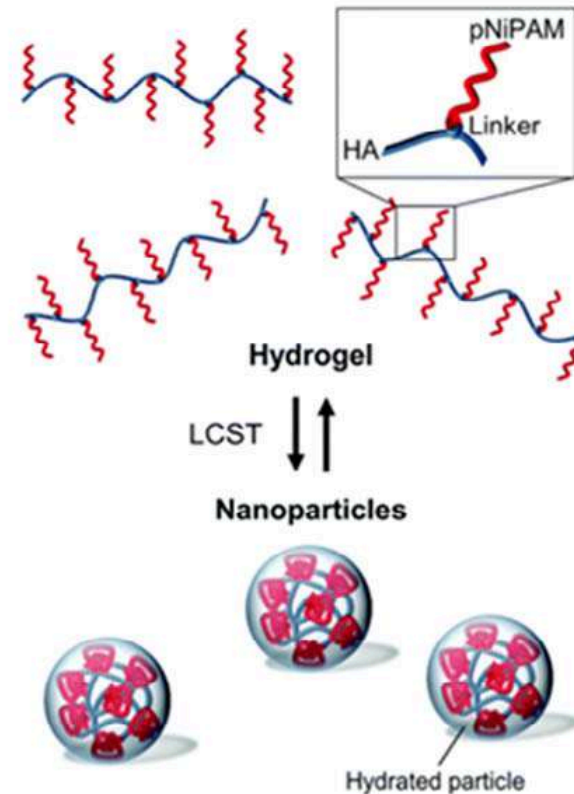
Lipid NPs with chloroquine and performed studies in rat OA models, and radiological **results revealed less bone damage and cartilage destruction in rats** treated with chloroquine-lipid NPs compared with free chloroquine.

The lipids Compritol and Chloroquine were mixed by an overhead stirrer and homogenized at high pressure and subsequently cooled to obtain **therapeutic chloroquine-lipid NPs**.



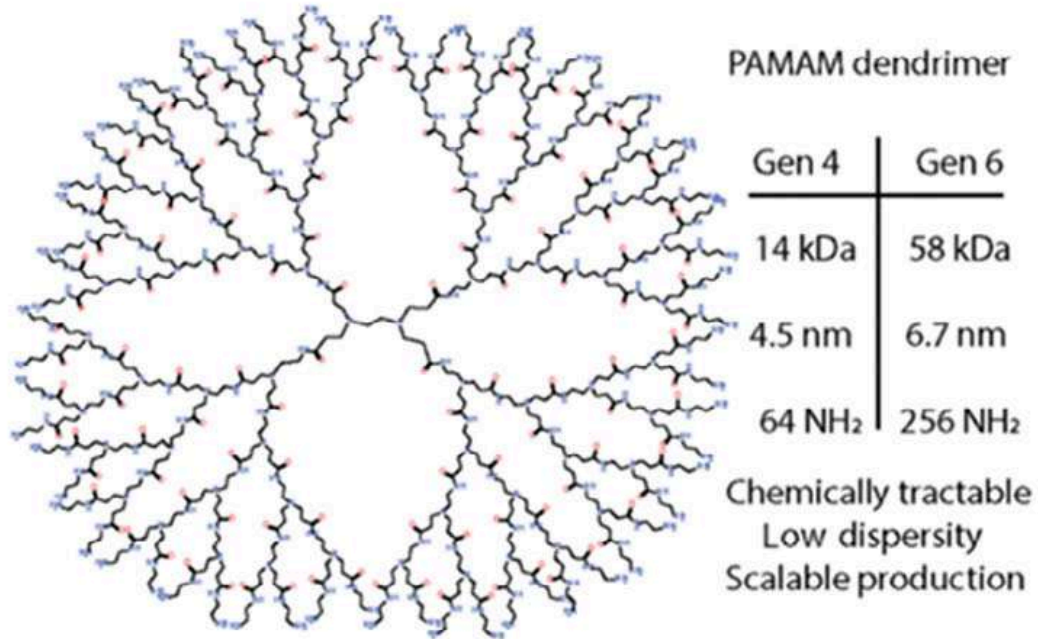
# Osteoarthritis - Thermoresponsive system

HA-pNiPAM **polymeric NPs** **spontaneously** form when **heated below the lower critical solubility temperature (LCST)** and SEM images of composition HA Nano.

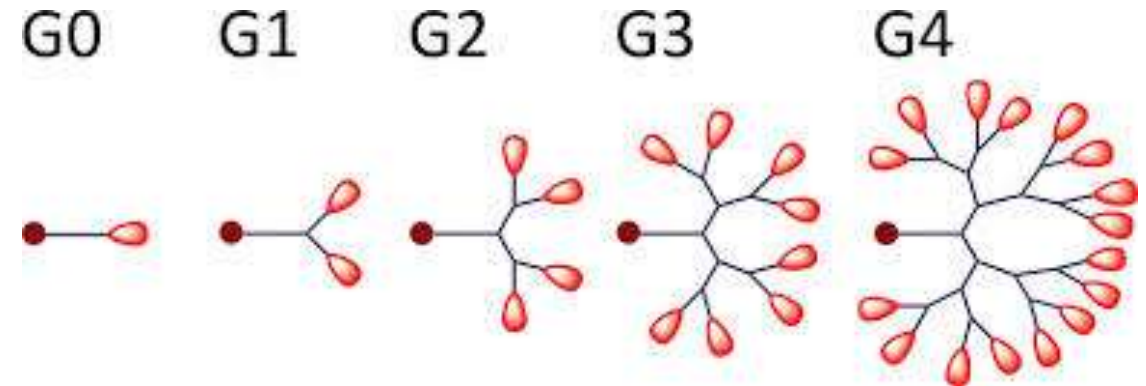


NPs were effective in **extending the residence time of intraarticular injection** materials and dexamethasone compared with conventional HA.

# Osteoarthritis - Dendrimer



Chemical structure of PAMAM dendrimers (Gen4 here) as cartilage-penetrating nanocarriers.



PEGylated dendrimer-IGF-1 conjugate

Geiger et al. designed a dendrimer nanocarrier ( 10 nm) based on polyamidoamine (PAMAM) and modified its amines with terminus PEG, using IGF-1 as cargo (Figure 3C), and found this system had **strong cartilage penetration in ex vivo bovine cartilage study**, and **in rats in vivo study**.



# THANK YOU

