Nanotechnology in drug delivery

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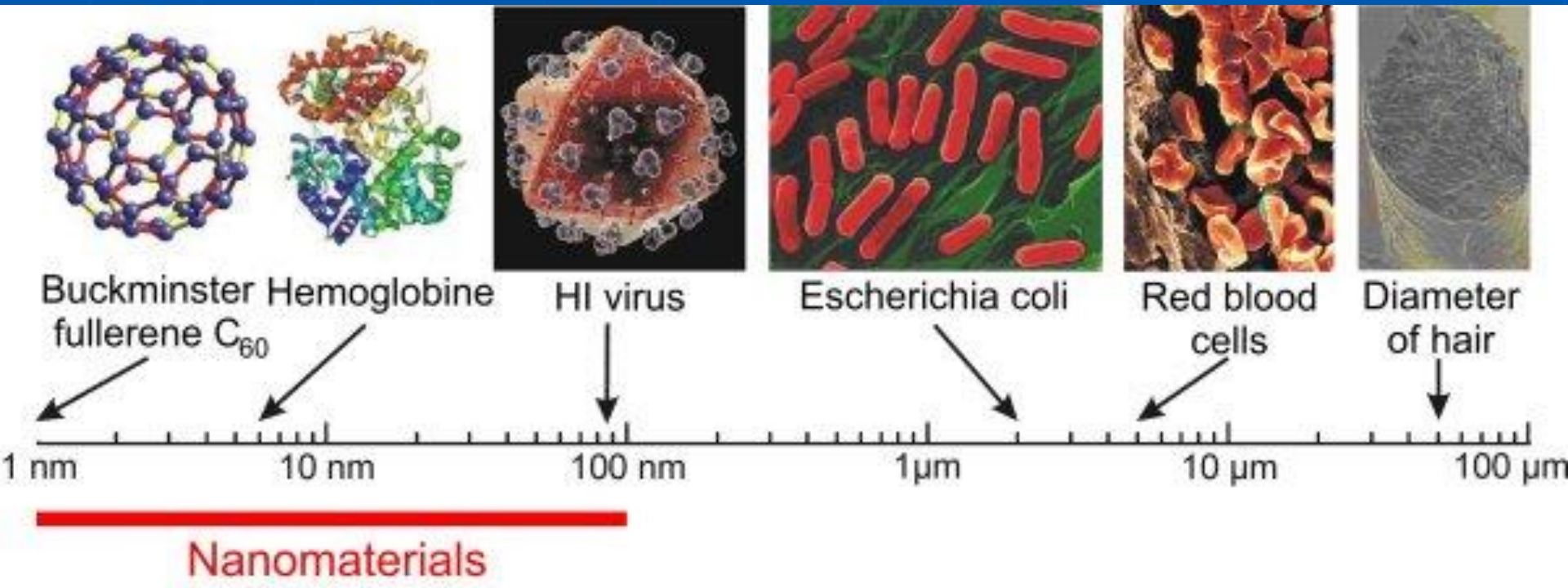
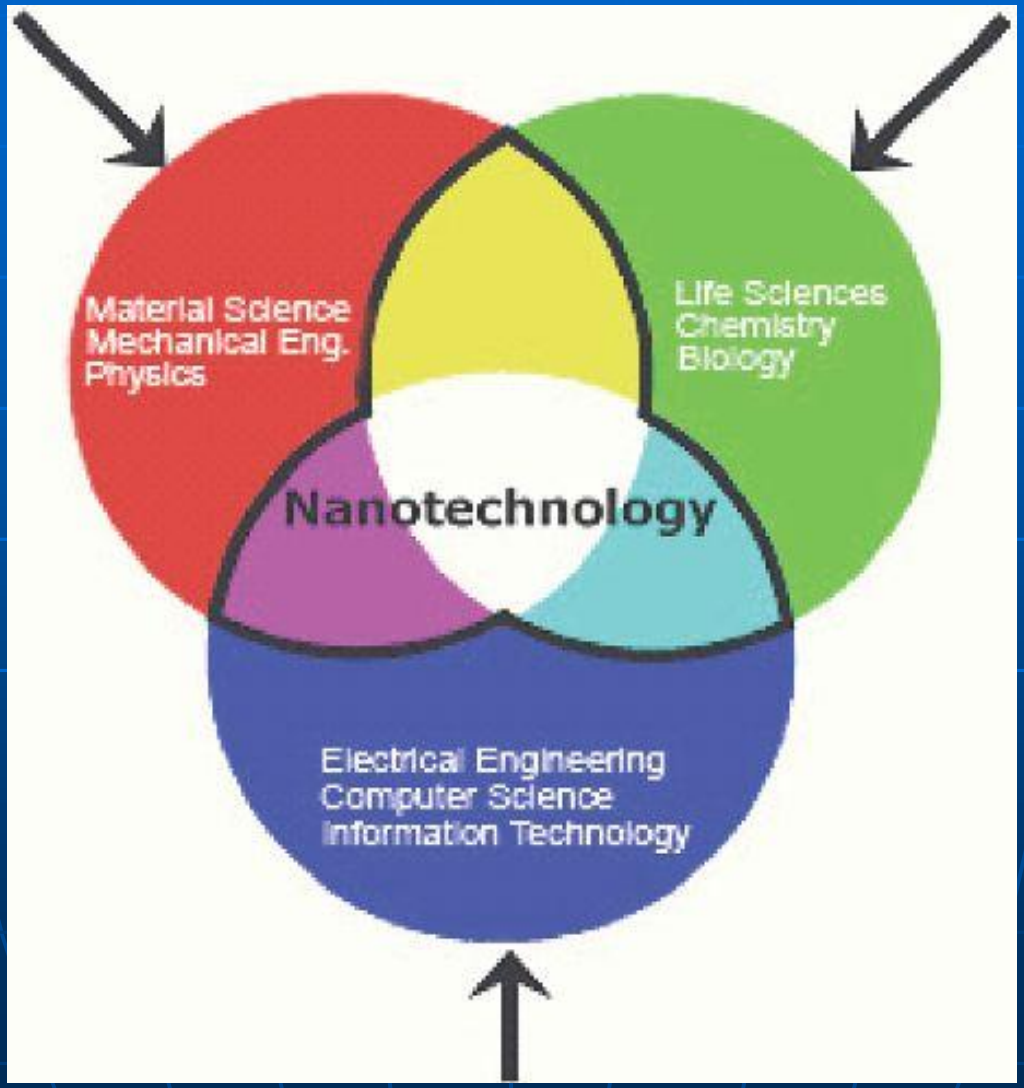
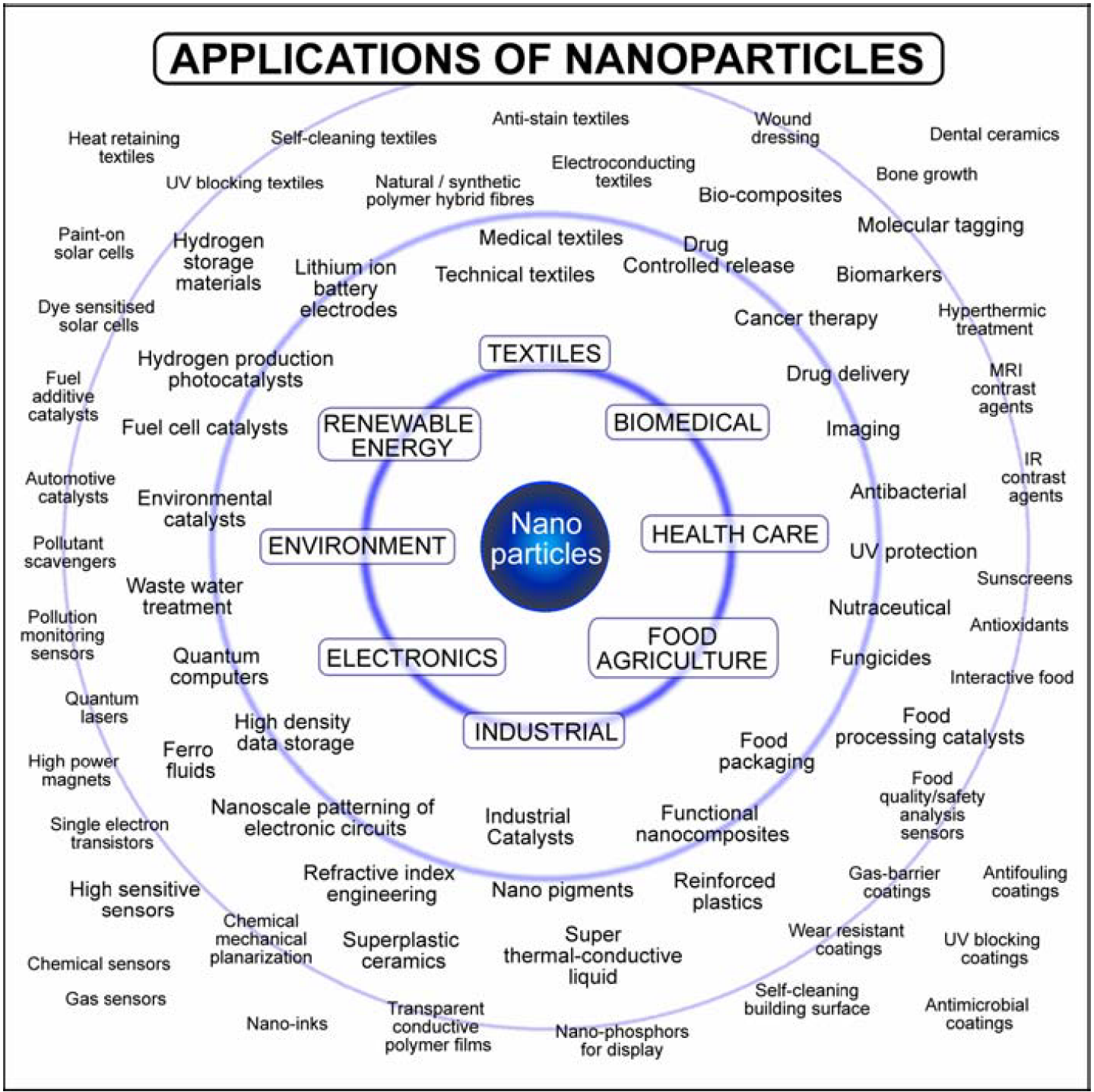
Nanotechnology

Nanotechnology, a multidisciplinary scientific undertaking, involves creation and utilization of materials, devices, or systems on the nanometer scale



Nanotechnology

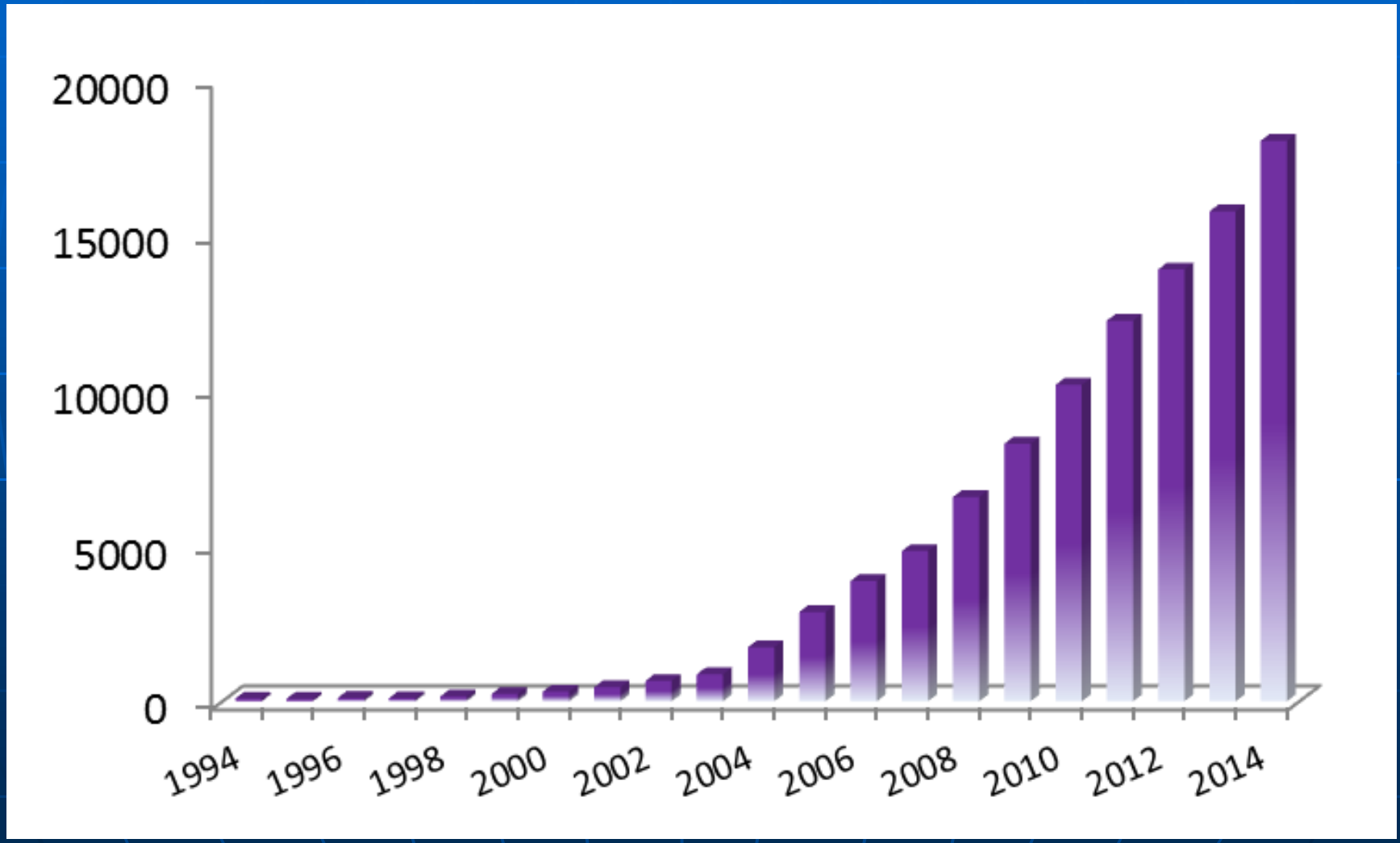



APPLICATIONS OF NANOPARTICLES
Nano particles
TEXTILES
BIOMEDICAL
HEALTH CARE
FOOD AGRICULTURE
INDUSTRIAL
ELECTRONICS
ENVIRONMENT
RENEWABLE ENERGY
Anti-stain textiles
Wound dressing
Dental ceramics
Heat retaining textiles
Self-cleaning textiles
Electroconducting textiles
Bone growth
UV blocking textiles
Natural / synthetic polymer hybrid fibres
Bio-composites
Molecular tagging
Paint-on solar cells
Hydrogen storage materials
Medical textiles
Drug Controlled release
Lithium ion battery electrodes
Technical textiles
Biomarkers
Dye sensitised solar cells
Cancer therapy
Hyperthermic treatment
Hydrogen production photocatalysts
Drug delivery
MRI contrast agents
Fuel additive catalysts
Fuel cell catalysts
Imaging
IR contrast agents
Automotive catalysts
Environmental catalysts
Antibacterial
Pollutant scavengers
UV protection
Sunscreens
Waste water treatment
Nutraceutical
Pollution monitoring sensors
Antioxidants
Quantum computers
Fungicides
Interactive food
Quantum lasers
High density data storage
Food processing catalysts
Ferro fluids
Food packaging
High power magnets
Food quality/safety analysis sensors
Nanoscale patterning of electronic circuits
Industrial Catalysts
Functional nanocomposites
Single electron transistors
Refractive index engineering
Nano pigments
Reinforced plastics
Gas-barrier coatings
Antifouling coatings
High sensitive sensors
Chemical mechanical planarization
Superplastic ceramics
Super thermal-conductive liquid
Wear resistant coatings
UV blocking coatings
Chemical sensors
Self-cleaning building surface
Gas sensors
Antimicrobial coatings
Nano-inks
Transparent conductive polymer films
Nano-phosphors for display

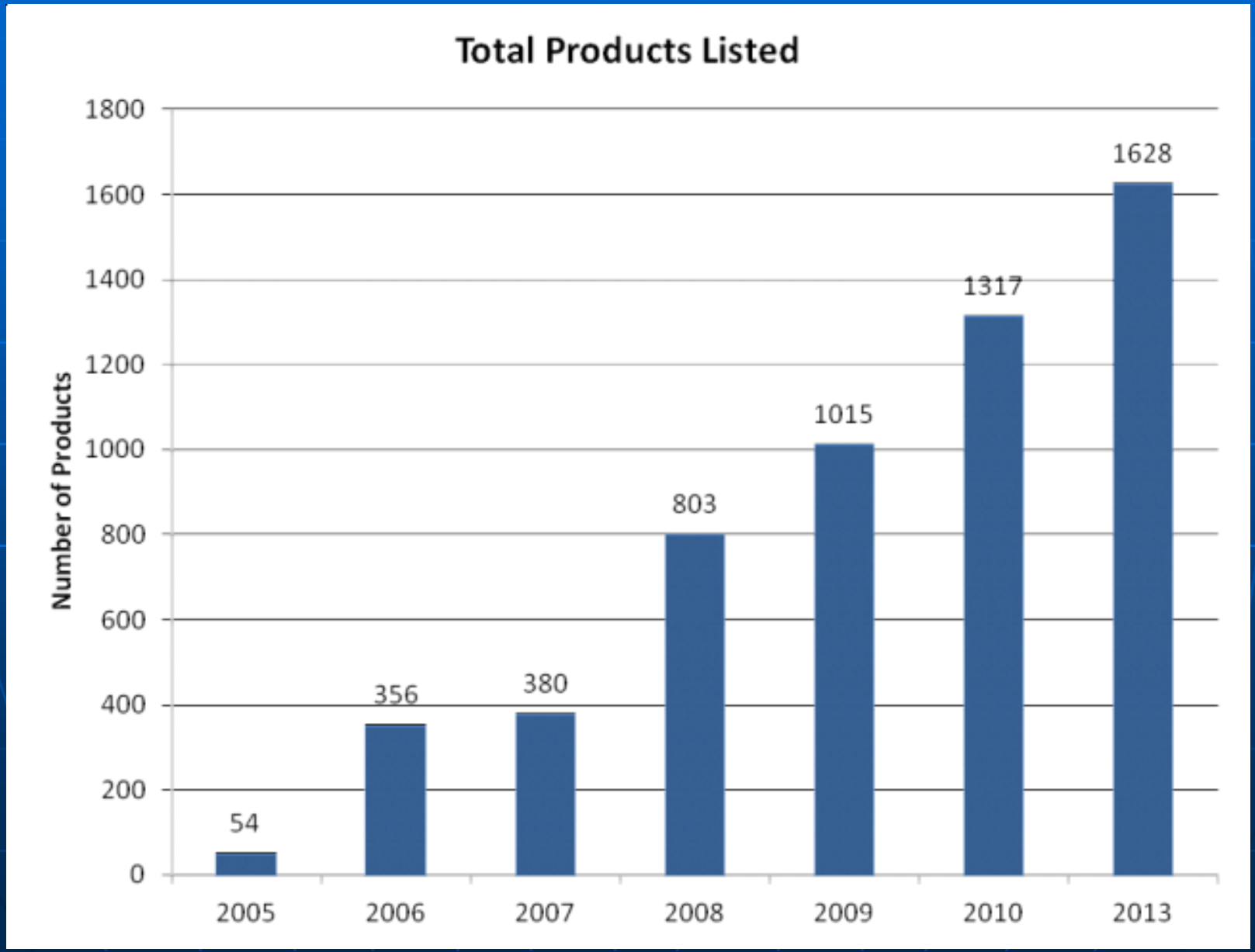
Nanotechnology applications

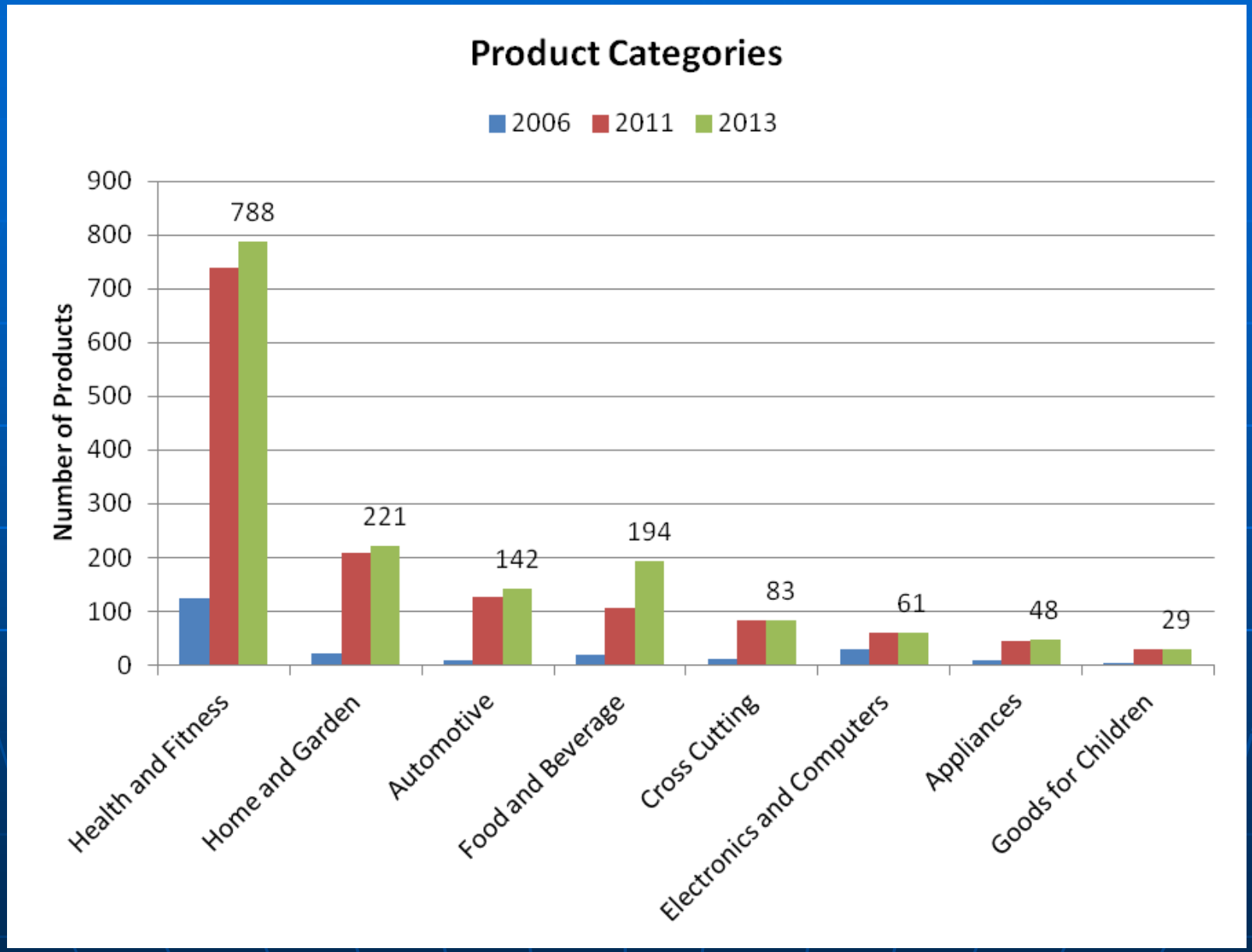
1. Medicine
    - 1.1 Diagnostics
    - 1.2 Drug delivery
    - 1.3 Tissue engineering
2. Environment
3. Energy
4. Information and communication
5. Heavy Industry
6. Consumer goods

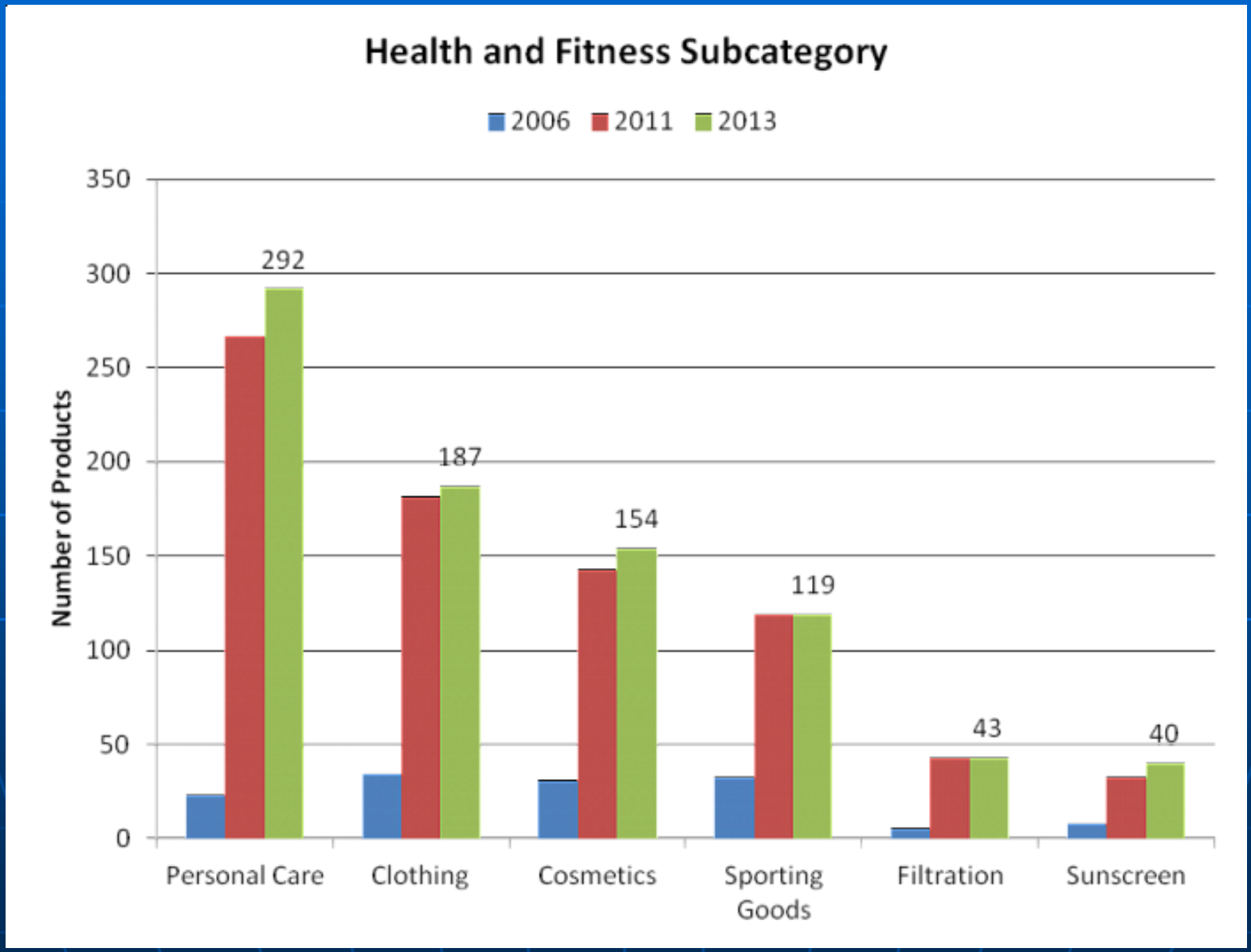
Number of scientific papers on nanotechnology topics

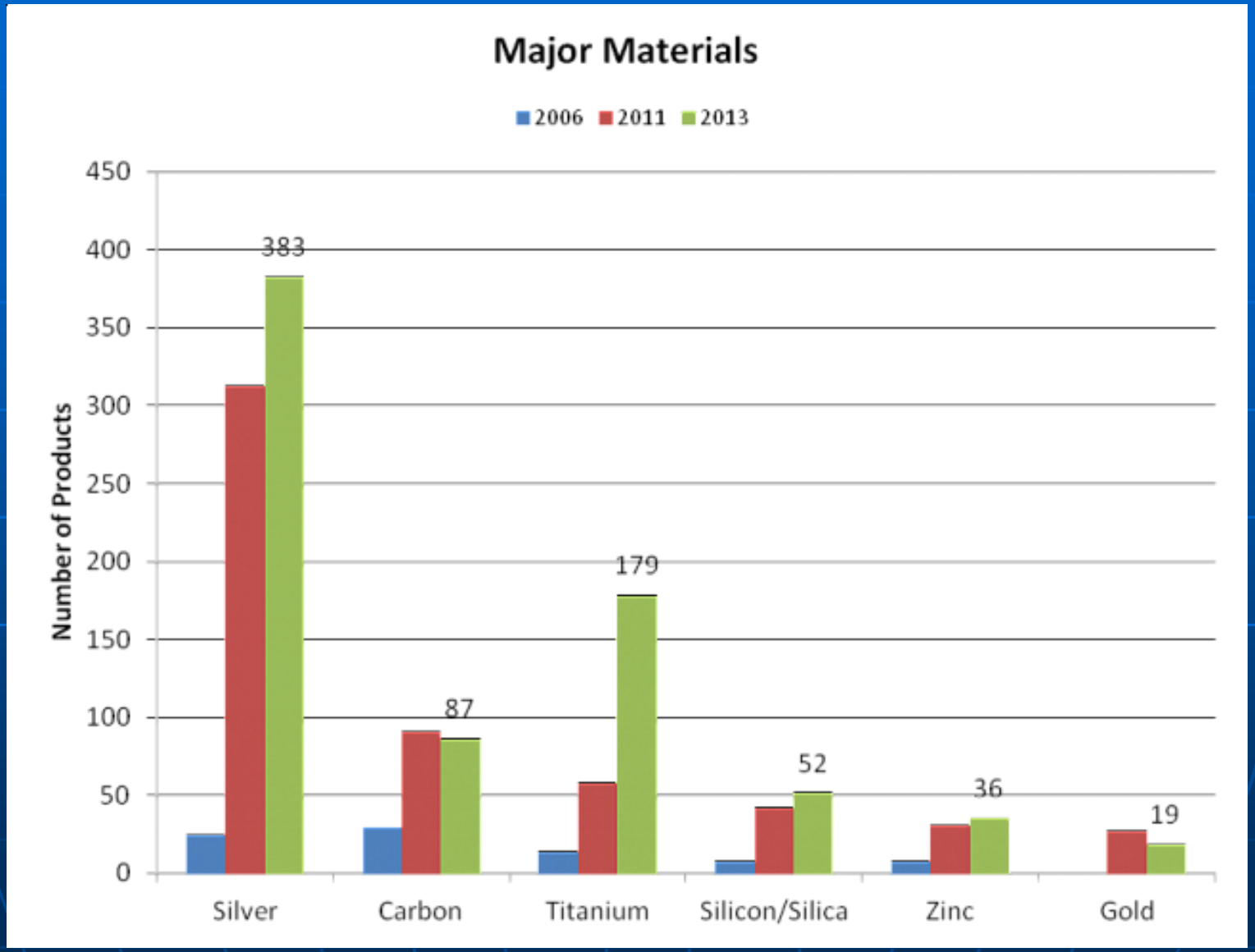


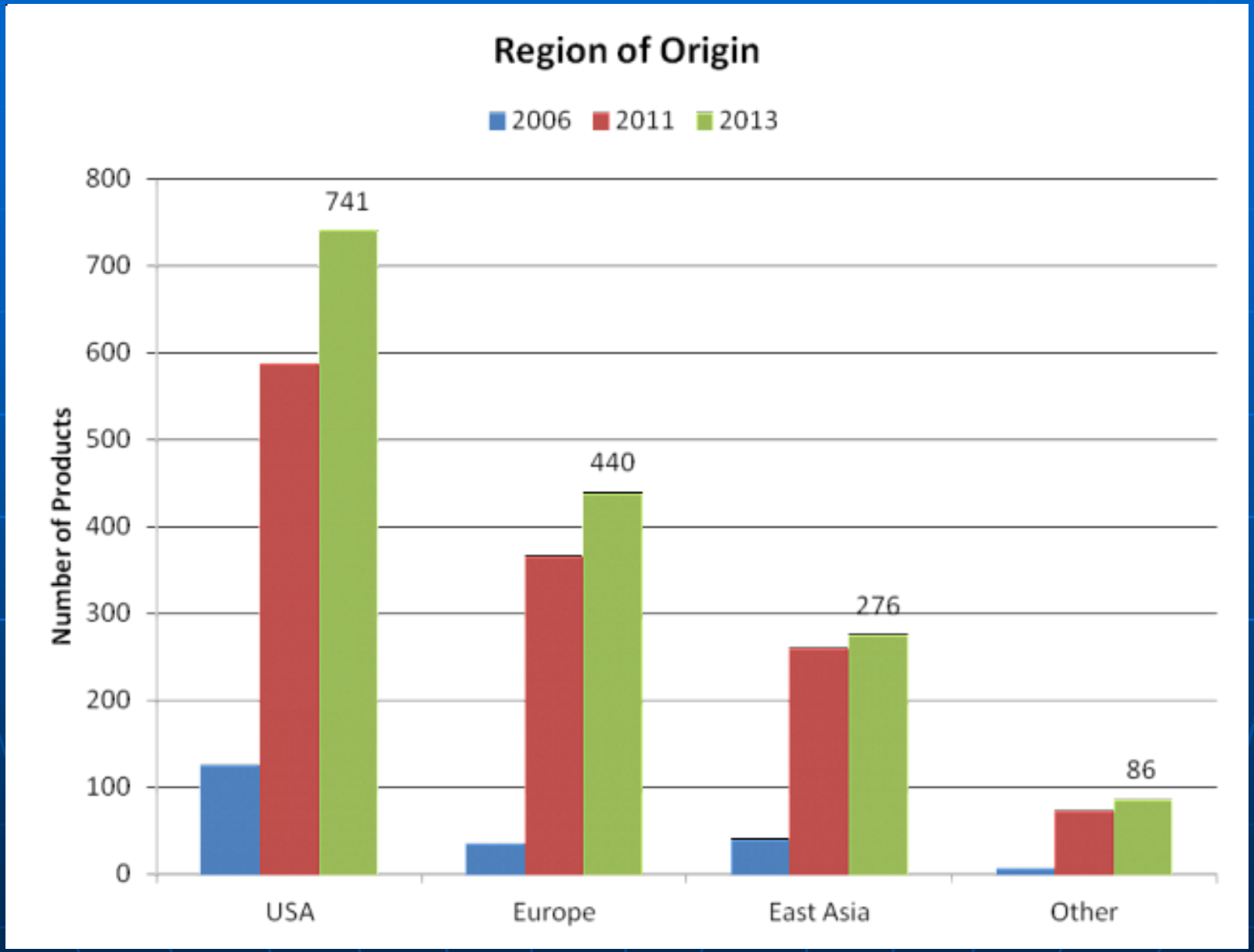
Nanotechnology applications




Product Categories
2006
2011
2013
Number of Products
900
800
700
600
500
400
300
200
100
0
788
221
142
194
83
61
48
29
Health and Fitness
Home and Garden
Automotive
Food and Beverage
Cross Cutting
Electronics and Computers
Appliances
Goods for Children


Health and Fitness Subcategory
2006
2011
2013
Number of Products
350
300
250
200
150
100
50
0
292
187
154
119
43
40
Personal Care
Clothing
Cosmetics
Sporting Goods
Filtration
Sunscreen


Major Materials
2006
2011
2013
Number of Products
450
400
350
300
250
200
150
100
50
0
383
87
179
52
36
19
Silver
Carbon
Titanium
Silicon/Silica
Zinc
Gold


Region of Origin
2006
2011
2013
800
700
600
500
400
300
200
100
0
Number of Products
741
440
276
86
USA
Europe
East Asia
Other

Molecular medicine

A science that seeks to comprehend disease causes and mechanisms at the molecular level, and to apply this basic research to the prevention, diagnosis and treatment of diseases and disorders.

Typical applications in molecular medicine include gene therapy, molecular structural analysis, genetic epidemiology, and molecular and clinical pharmacology.

Nanomedicine

Nanomedicine is defined as the application of nanotechnology in view of making medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical chemical and biological properties of materials at nanometre scale

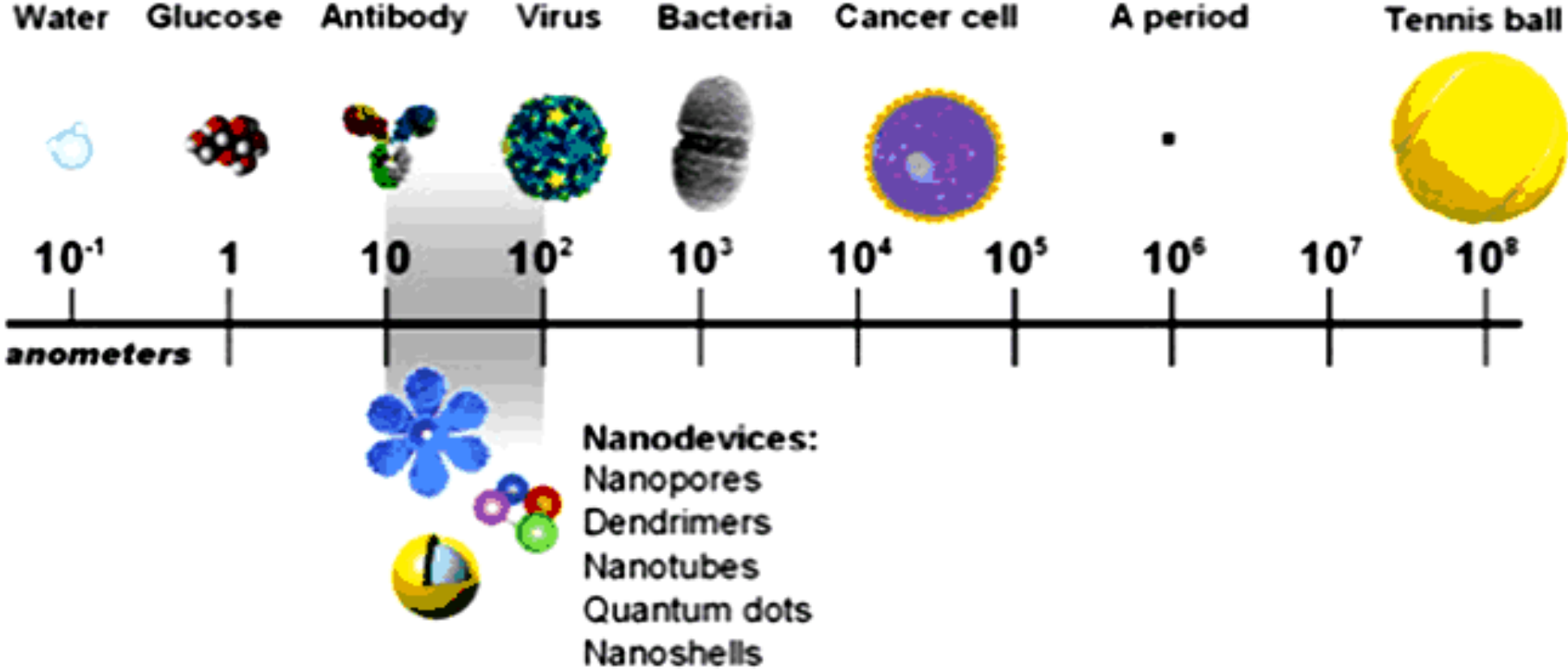
Nanotechnology

" Nanotechnology is the key to optimizing drug delivery"

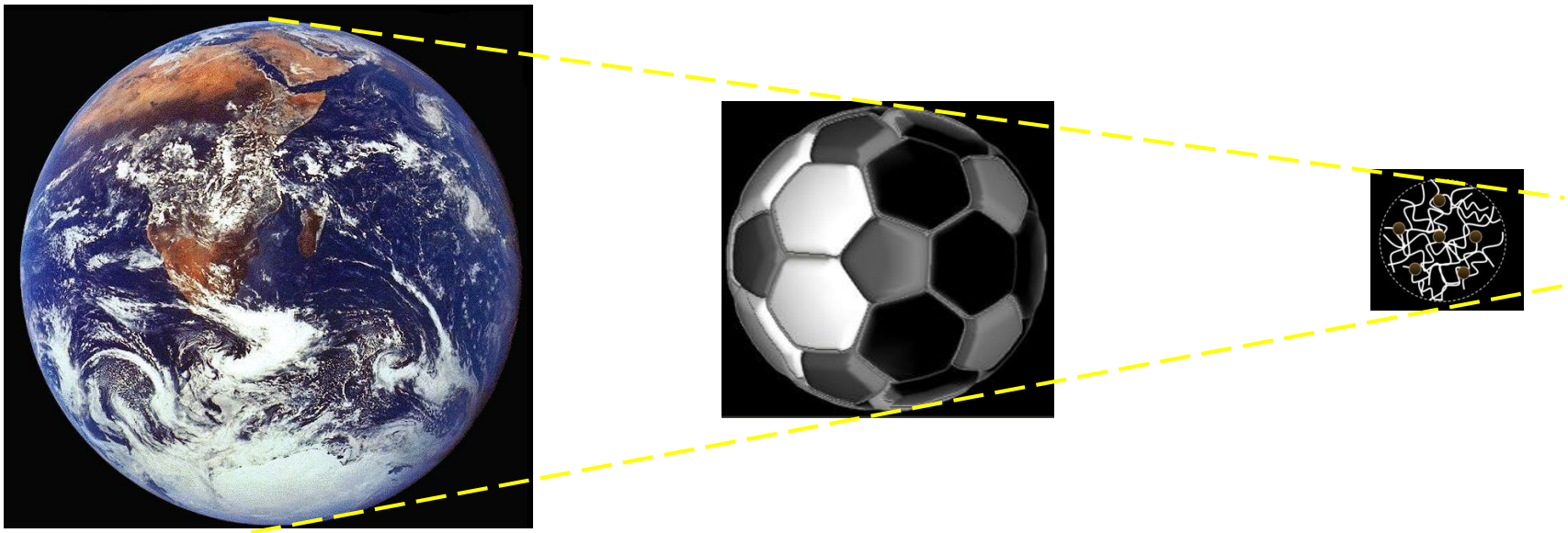
Dr. **Roger Aston**,
Director of Strategy at pSivida Limited in Australia.

Nanotechnology

How much does size matter?



Nanotechnology



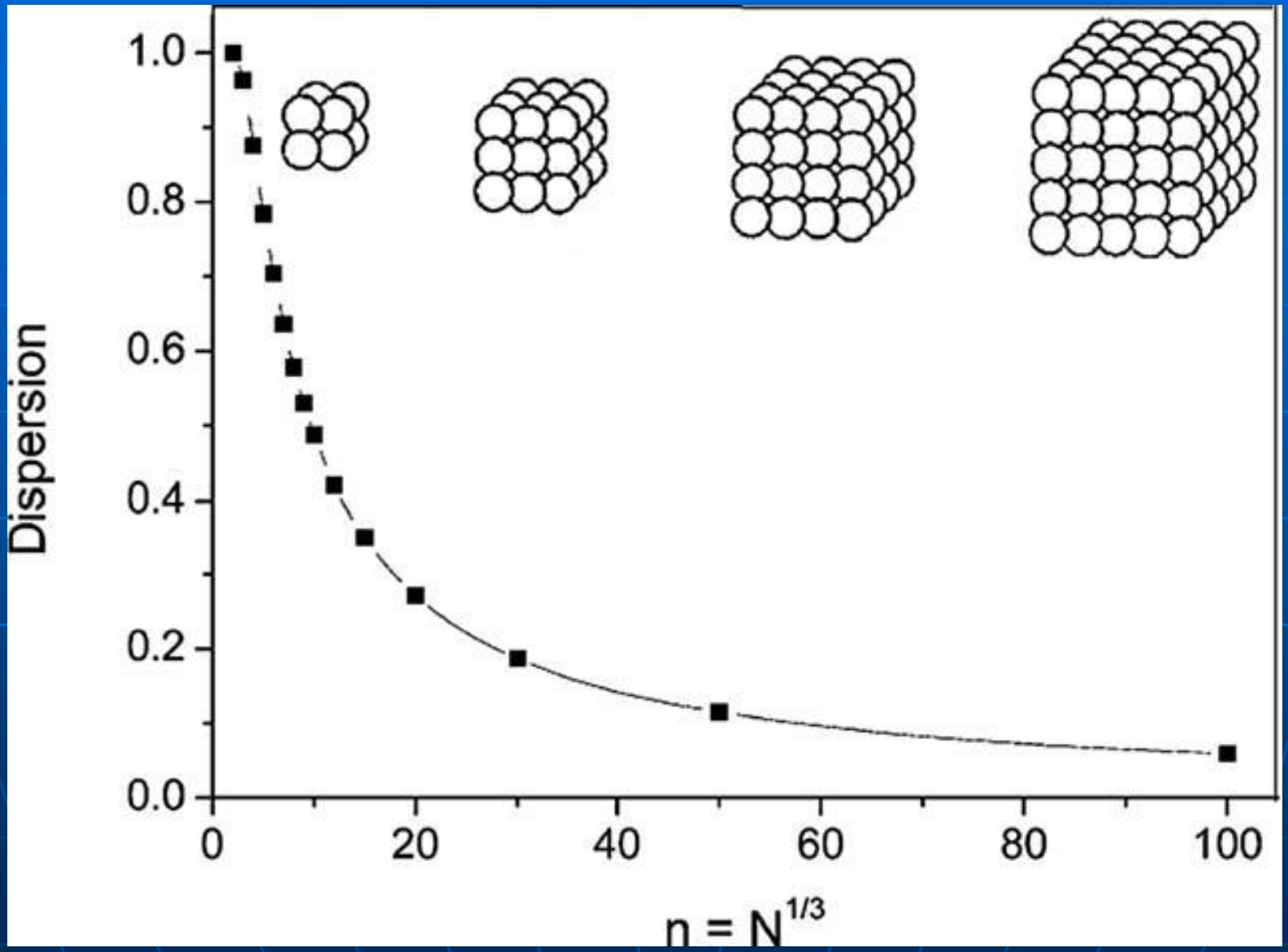
A size of the Earth relates to football as football relates to nanoparticle

Size effect on surface/volume ratio

Dispersion: fraction of atoms at the surface

- The dependence of the surface dispersion is illustrated for a cube of n atoms along an edge, with the total number of atoms in the cube described as $N=n^3$.
- A cube would therefore expose 6 surfaces and 12 edges, with the total number of surface atoms equal to 6n that has been corrected to eliminate double counting of corner atoms.
- For large numbers of atoms in a cube, these corrections become negligible and the dispersion could be scaled as follows:

$$F = \frac{6n^2 - 12n + 8}{n^3} = \frac{6}{N^{1/3}}\left(1 - \frac{2}{N^{1/3}} + \frac{8}{6N^{2/3}}\right) \approx \frac{6}{N^{1/3}}$$


Dispersion
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
n = N^1/3

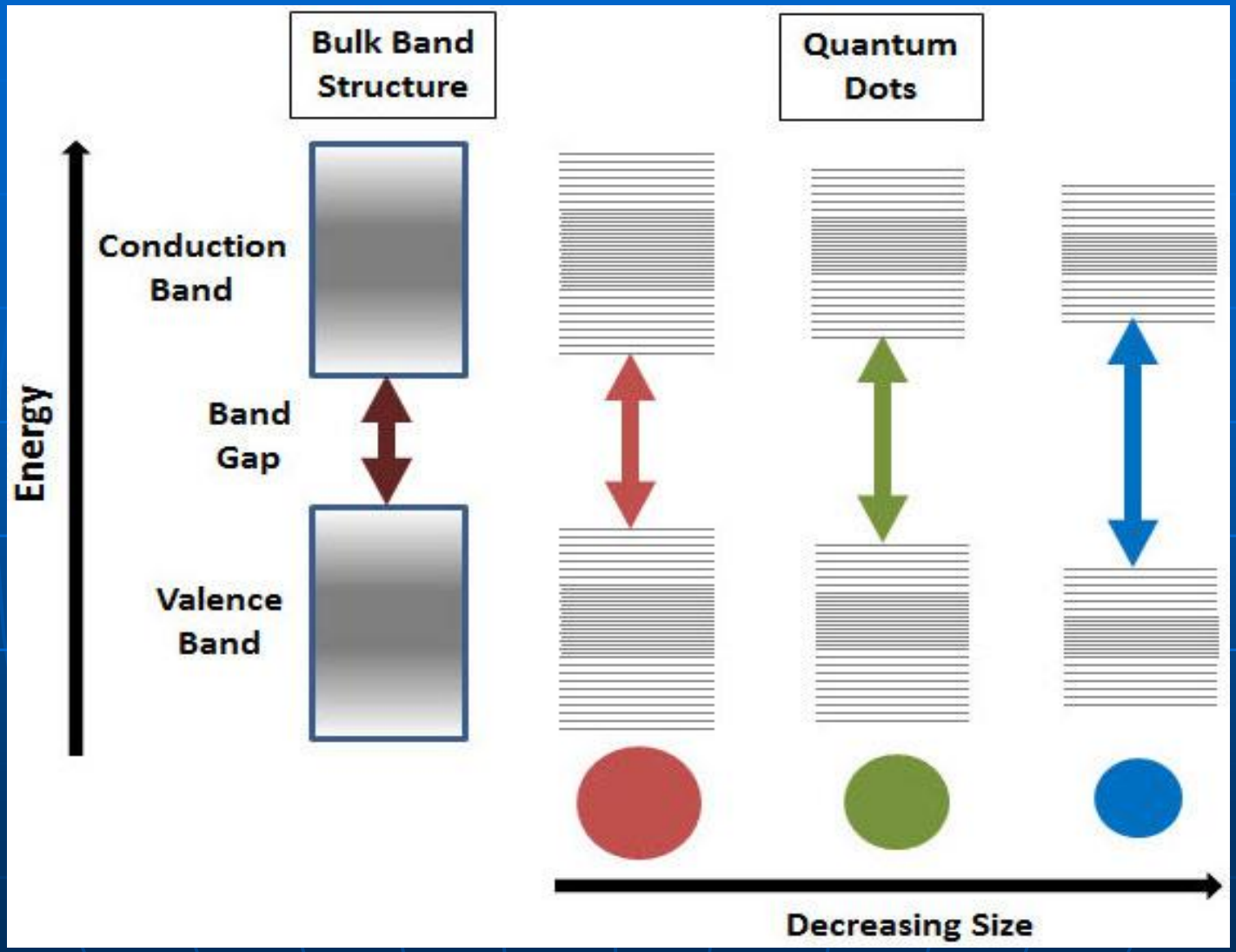
Quantum Effects

As with most orbital systems, electrons can be found at different (higher and lower) energy levels, and the average spacing of this energy level is known as the Kubo gap, . By considering the lowest unoccupied energy state of the electronic system of a bulk material, the Fermi energy, Ef, could be incorporated to describe the Kubo gap:

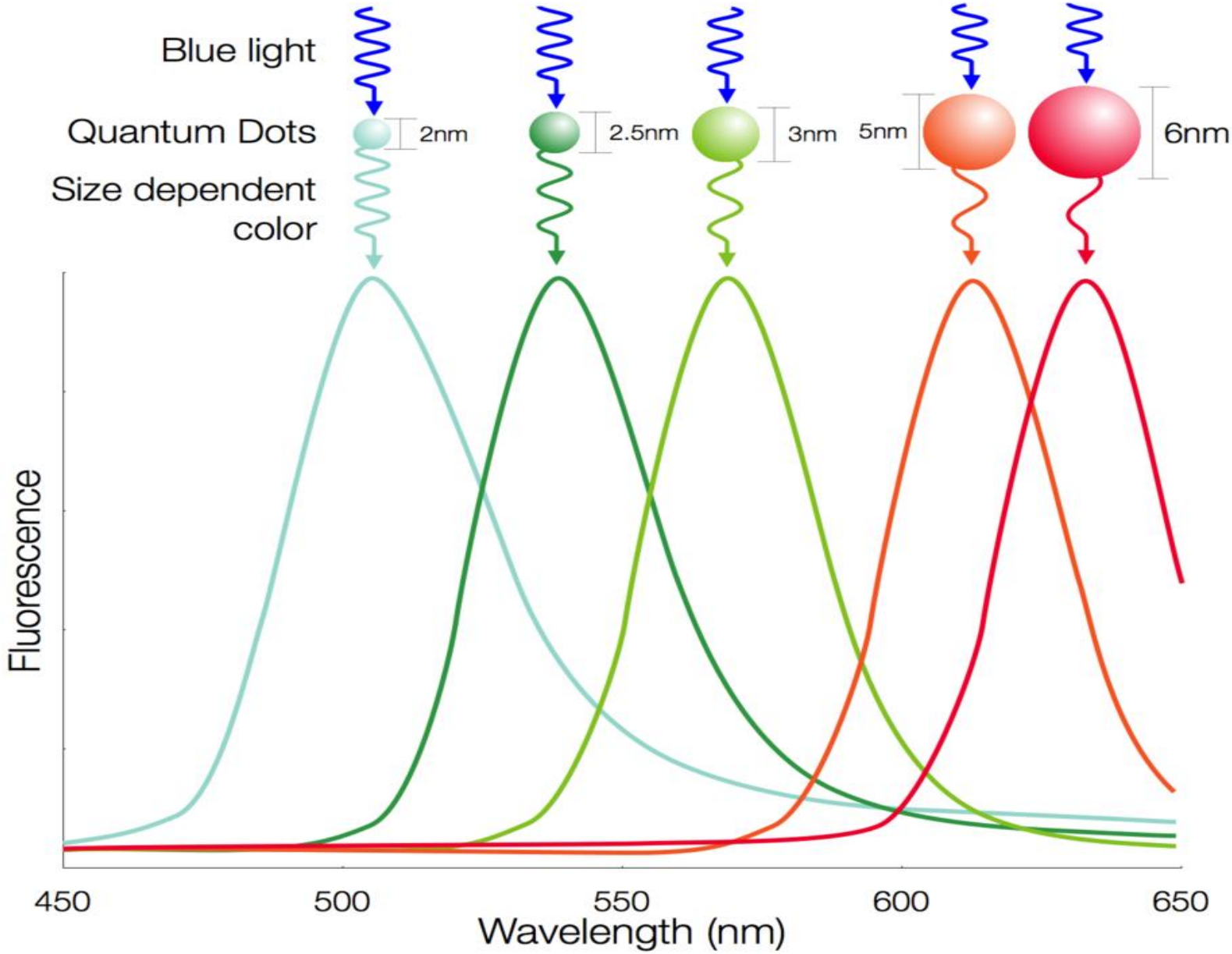
$$\delta = 4E_f/3n$$

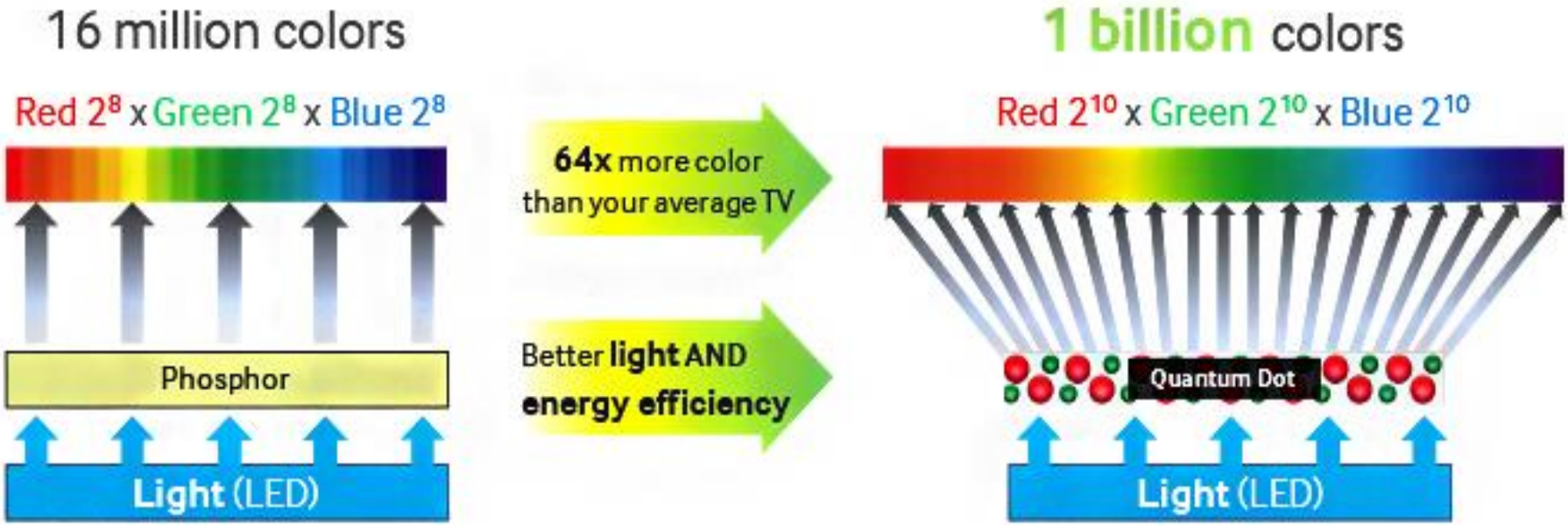
where n is representing the number of valence electrons in the nanosystems.

Due to their small size, the electrons in quantum dots are confined in a small space (quantum box), and when the radii of the semiconductor nanocrystal is smaller than the exciton Bohr radius (exciton Bohr radius is the average distance between the electron in the conduction band and the hole it leaves behind in the valence band), there is quantization of the energy levels according to Pauli's exclusion principle


Bulk Band Structure
Quantum Dots
Energy
Conduction Band
Band Gap
Valence Band
Decreasing Size

Quantum Dot Size and Color




16 million colors
Red 2^8 x Green 2^8 x Blue 2^8
Phosphor
Light (LED)
64x more color than your average TV
Better light AND energy efficiency
1 billion colors
Red 2^{10} x Green 2^{10} x Blue 2^{10}
Quantum Dot
Light (LED)

Nanotechnology in drug delivery

How did all begun?

-*controlled* drug delivery systems (DDS)

1950s, „Spansules”

-*silicon rubber implants* Judah Folkman at Harvard Medical School 1960s

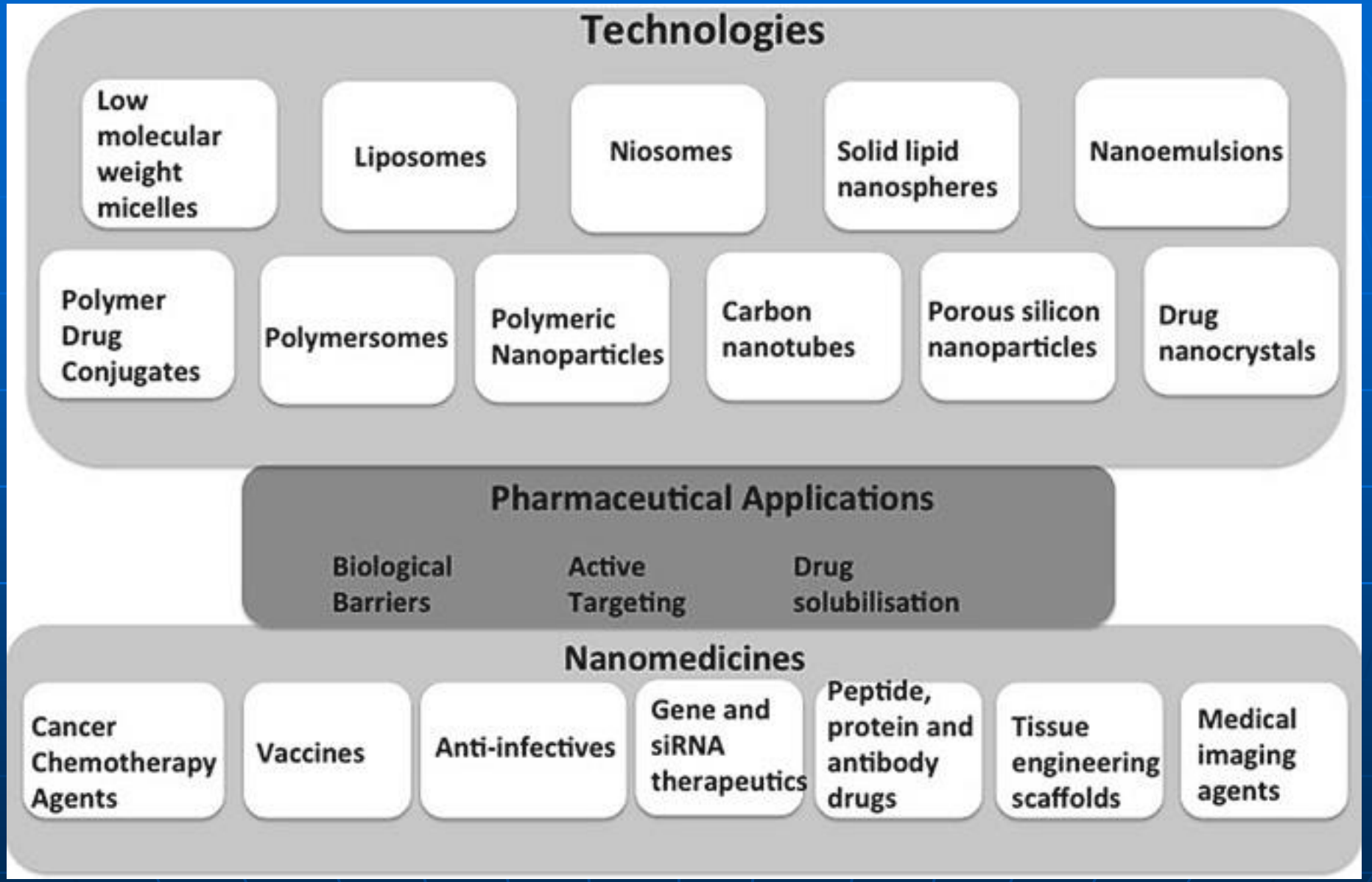
-first company based on DDS concept Alza Corp, 1968

-1970-1980, expand of DDS system

- -contraceptive drug-loaded poly(ethylene-co-vinylacetate EVA)
- -drug-loaded skin patch for topical application
- -glaucoma drug-loaded poly(EVA) sandwich wafer for insertion into the eye
- -drug-loaded, degradable microparticles composed of poly[lactic-co-glycolic]acid (PLGA)

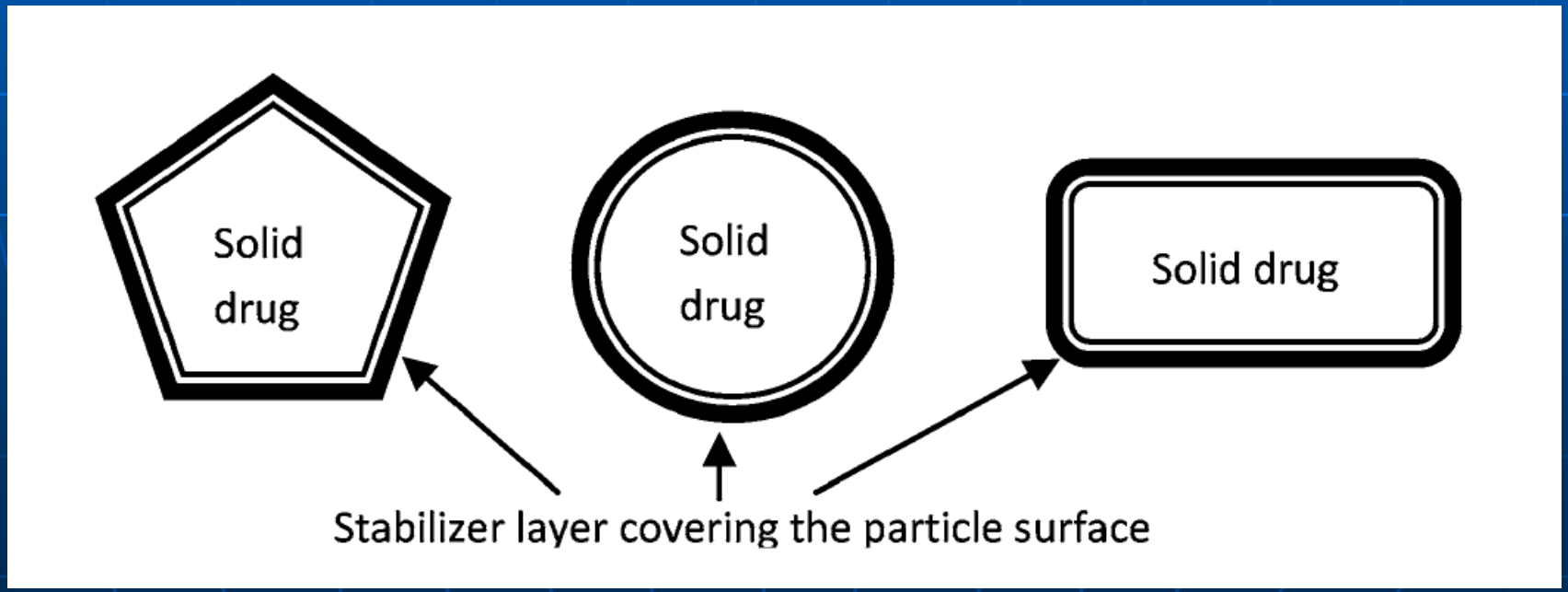
1990s rapidly expanding nanotechnology

- -1995, the liposome- doxorubicin product called “Doxil ® ” first nanocarrier-drug DDS approved for clinical use


Technologies
Low molecular weight micelles
Liposomes
Niosomes
Solid lipid nanospheres
Nanoemulsions
Polymer Drug Conjugates
Polymersomes
Polymeric Nanoparticles
Carbon nanotubes
Porous silicon nanoparticles
Drug nanocrystals
Pharmaceutical Applications
Biological Barriers
Active Targeting
Drug solubilisation
Nanomedicines
Cancer Chemotherapy Agents
Vaccines
Anti-infectives
Gene and siRNA therapeutics
Peptide, protein and antibody drugs
Tissue engineering scaffolds
Medical imaging agents

Drug Nanocrystals

Drug nanocrystals are crystals in the nanometer size range (1–1,000 nm). They contain 100 % drug without any matrix material.
Stabilizing agents, such as surfactants or polymers, are located on the surface of the nanocrystals



Drug Nanocrystals

Stabilization of Drug Nanocrystals

The most crucial problem with nanosized particles is the low stability of the particles; particles tend to aggregate back to larger structures.

Stabilization can be based on two different mechanisms:

-steric stabilization

-electrostatic stabilization (charge stabilization)

or combination, both steric and electrostatic stabilization

Drug Nanocrystals

Electrostatic stabilization

If pure electrostatic stabilization is utilized, the zeta potential (ζ) of the nanocrystals should be either less than −30 mV or more than +30 mV.

Typical electrostatic stabilizers:

-ionic surfactants

-polyelectrolites (charged polymers)

Steric stabilization

Typical Steric stabilizers:

-nonionic surfactants

-polymers

Drug Nanocrystals

Nanocrystal Synthesis

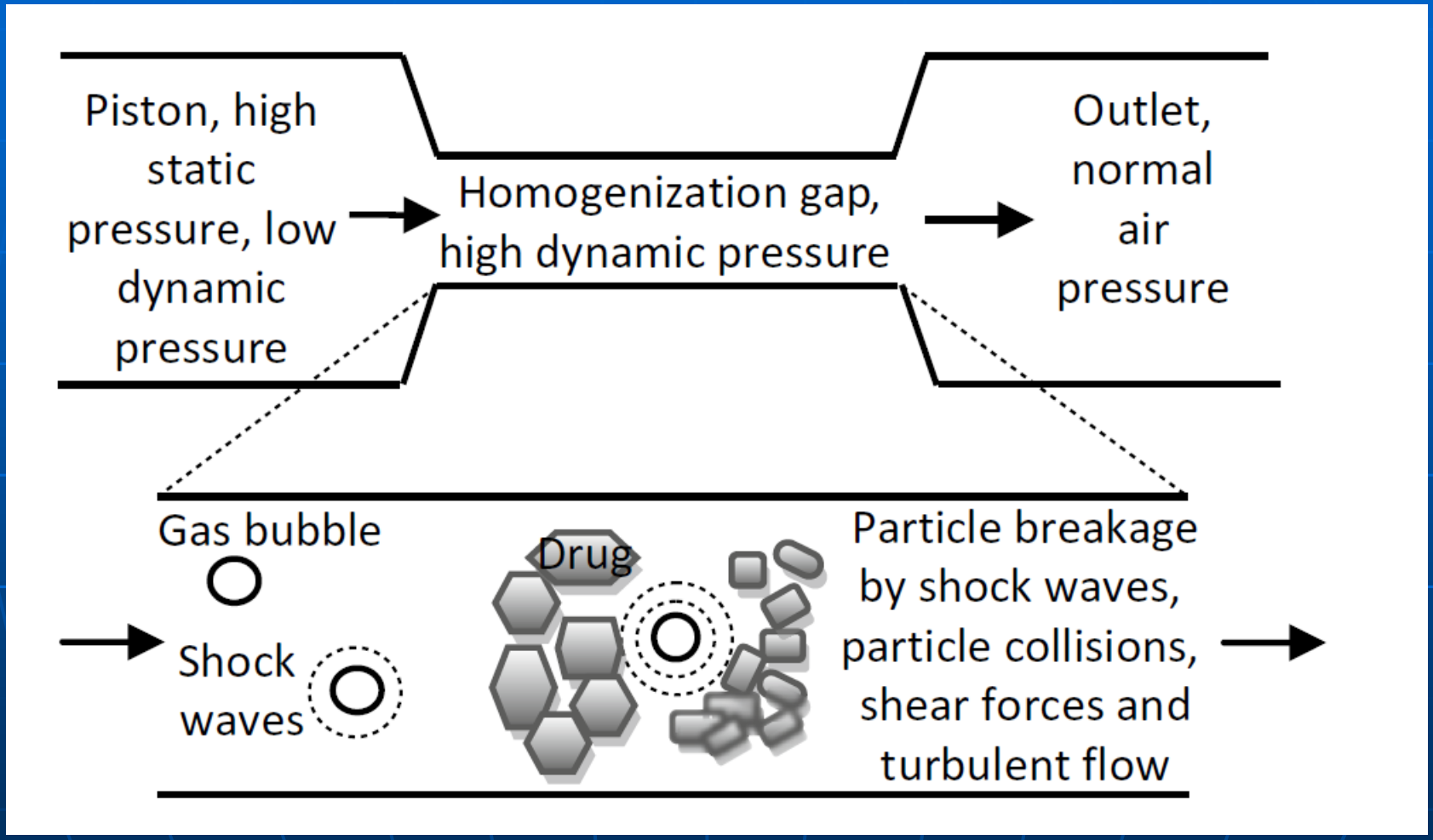
Two main classes:

-bottom-up techniques

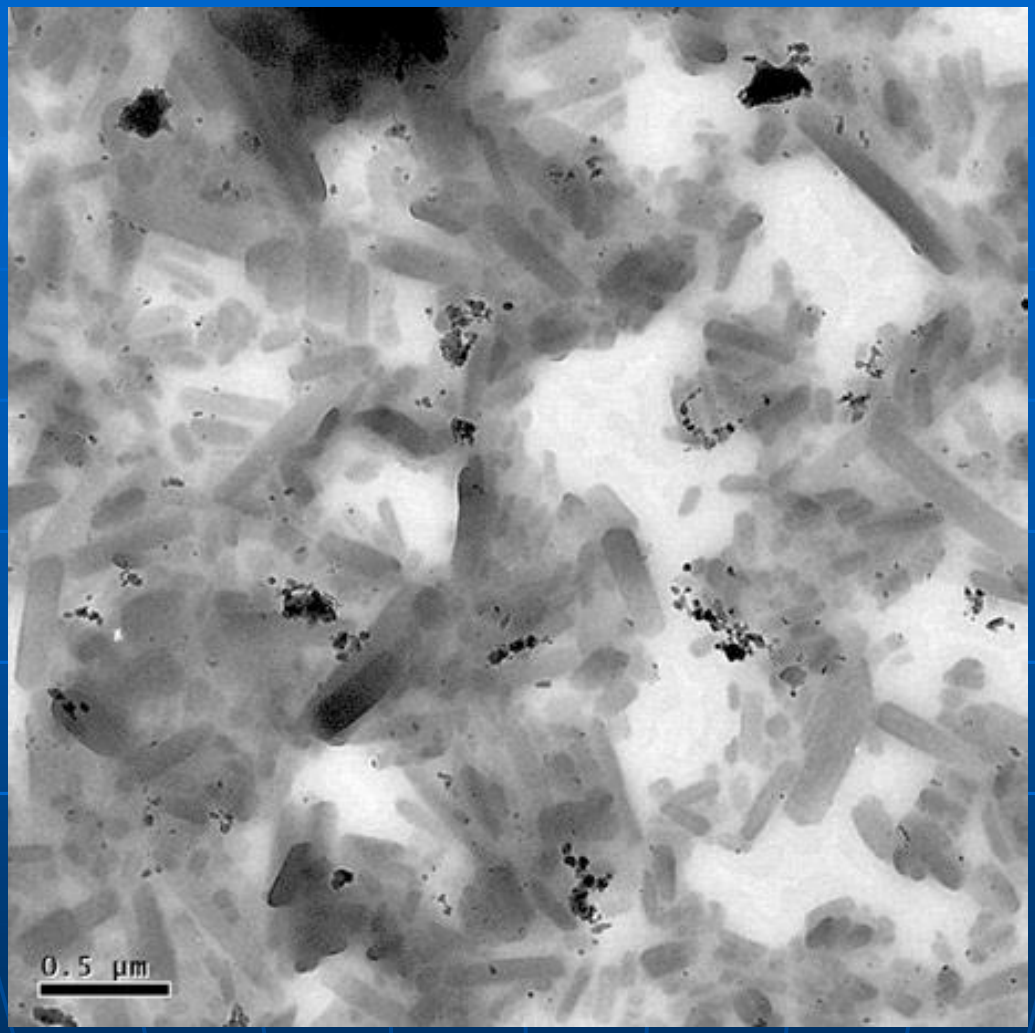
-top-down techniques

In bottom-up techniques the nanocrystals are formulated by building larger structures from smaller ones, e.g., precipitation from a solution

In top-down methods the starting point is with larger entities and during the process their particle size is diminished, for example, by milling or by high-pressure homogenization


Piston, high static pressure, low dynamic pressure
Homogenization gap, high dynamic pressure
Outlet, normal air pressure
Gas bubble
Shock waves
Drug
Particle breakage by shock waves, particle collisions, shear forces and turbulent flow

top-down techniques



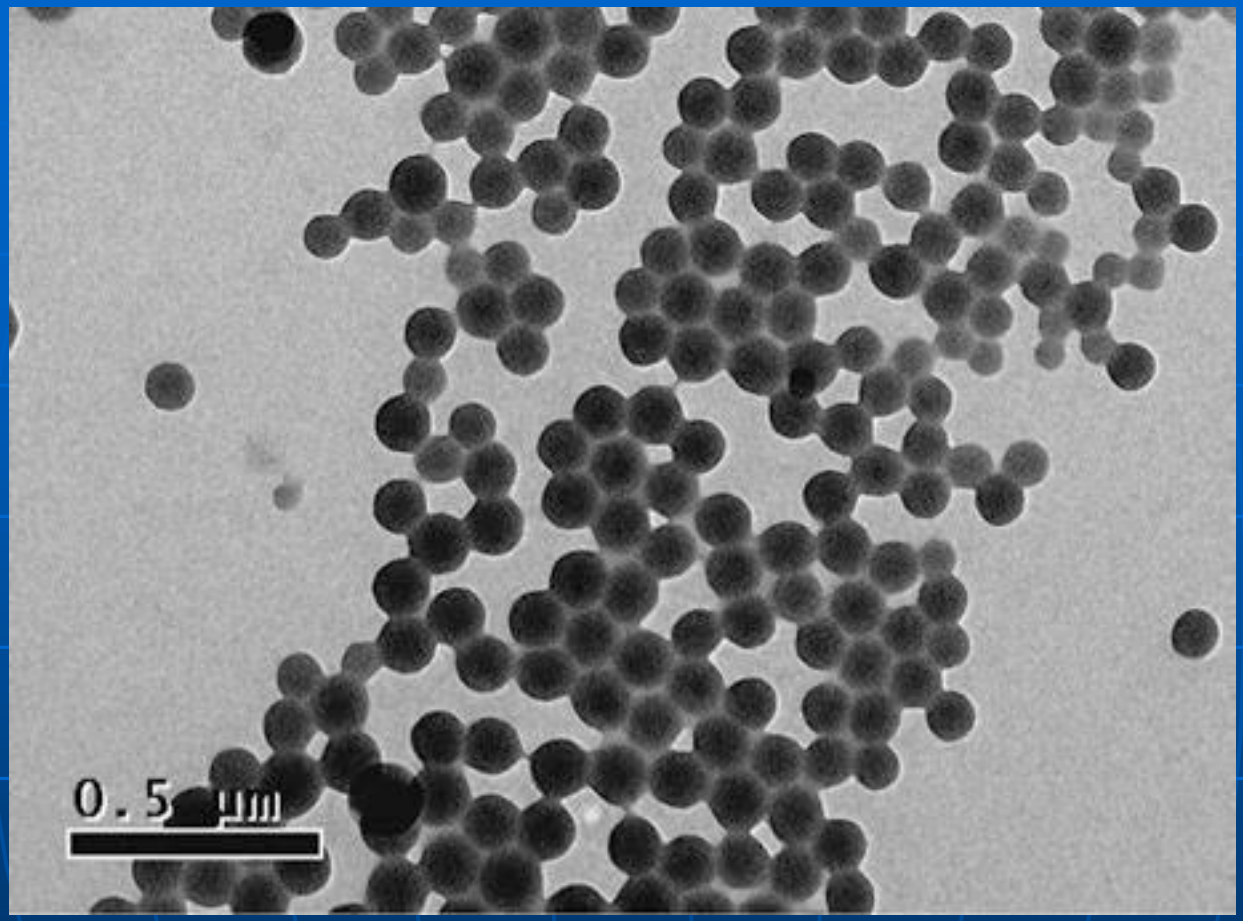
TEM figure of itraconazole nanocrystals prepared by nanomilling. Ethylene oxide/propylene oxide block copolymer (Pluronic F127) was used as a stabilizer and the total milling time was 30 min.

bottom-up techniques

Antisolvent precipitation method

- The drug solution is mixed with the antisolvent and precipitation occurs immediately
- The solvent (S) is miscible with the antisolvent (AS), but the drug has low solubility in the antisolvent

bottom-up techniques

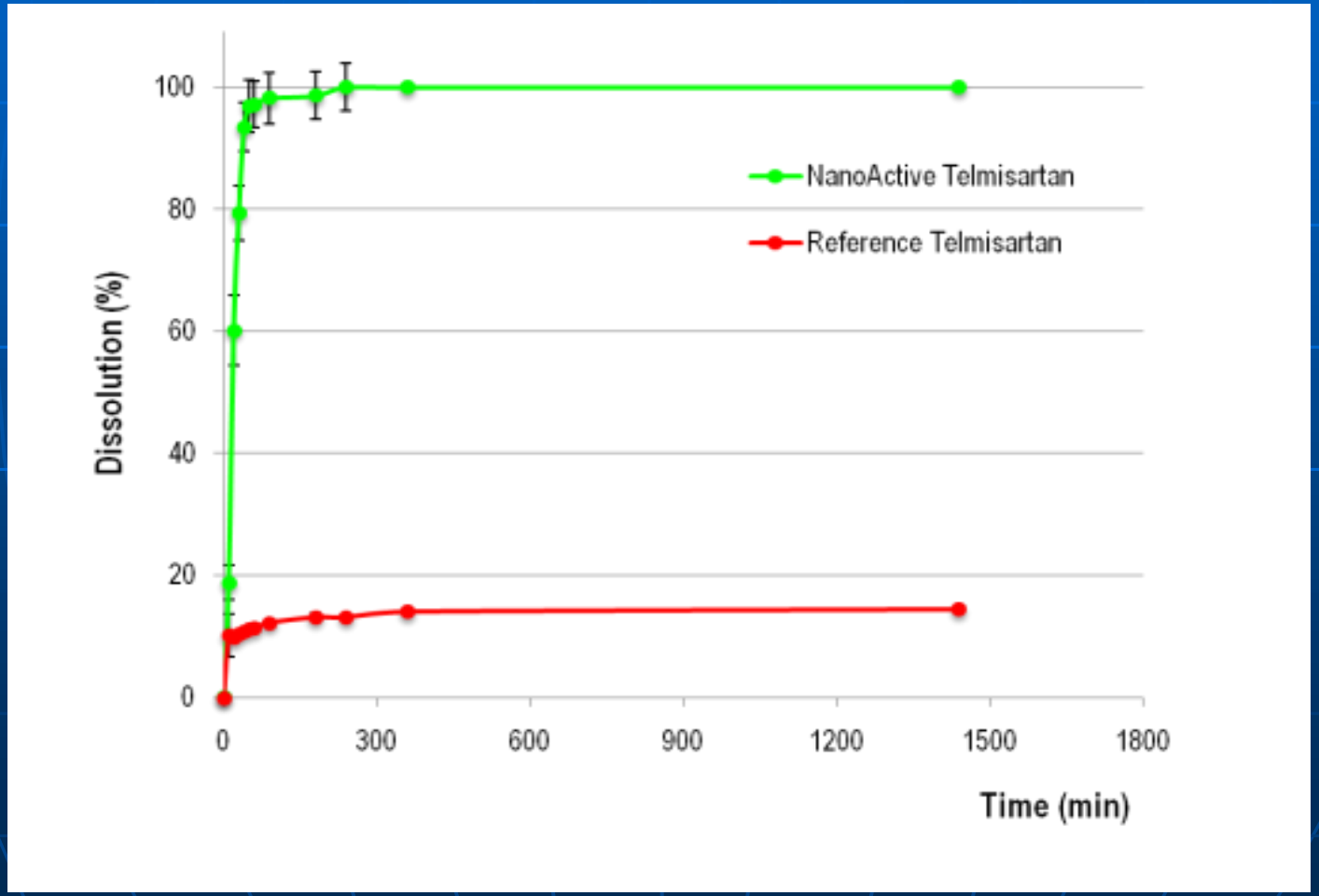


Transmission electron micrograph (TEM) of itraconazole nanocrystals prepared by antisolvent technology with hydrophobic HFBII as a stabilizer. Particle size is below 100 nm and the size distribution is very narrow, which is typical for bottom-up techniques

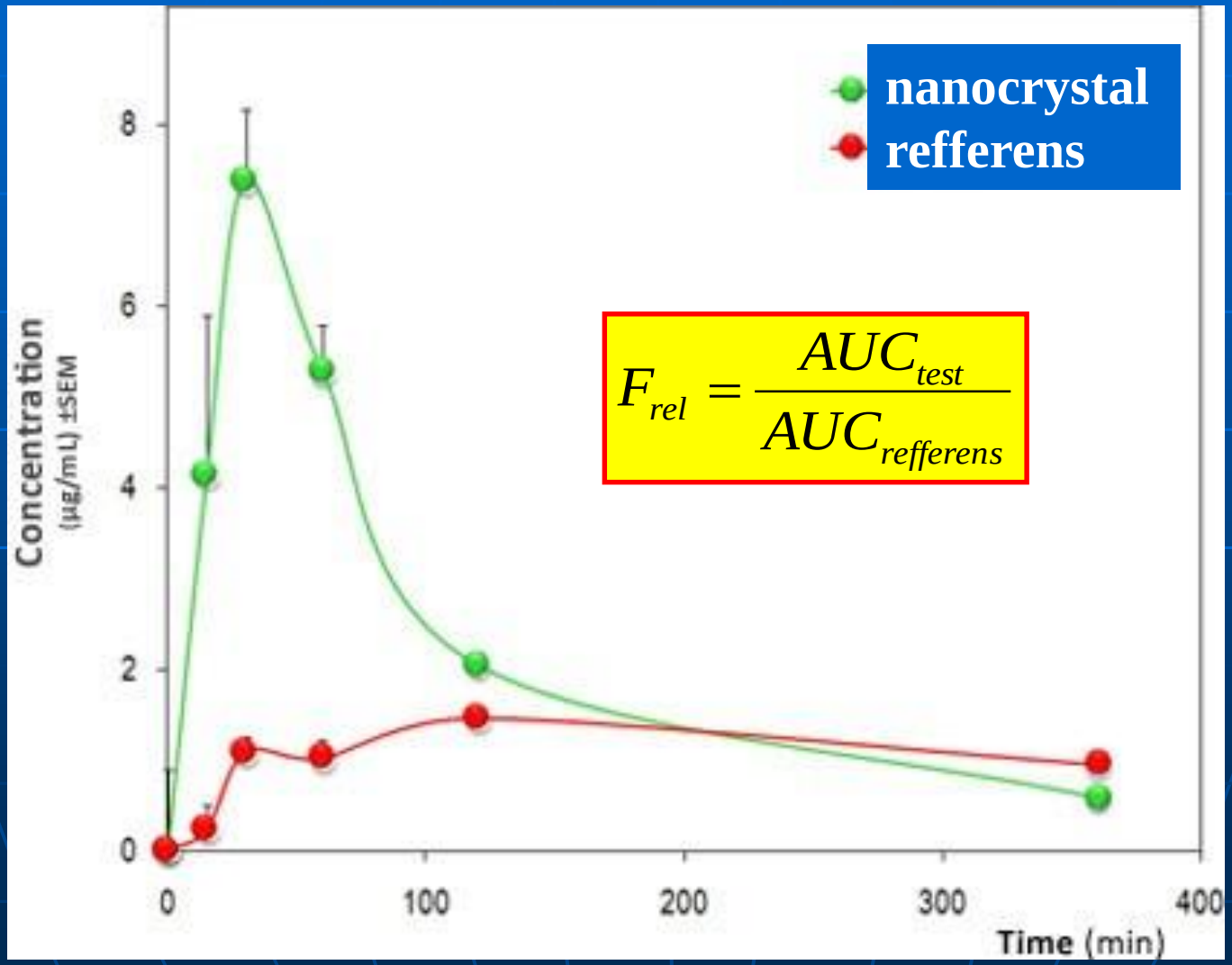
- **Combination Technologies** :Nanoedge® Technology (Microprecipitation™ and High Shear Forces (NANOEDGE™)
- **Nanopure® Technology**

Drug Nanocrystals

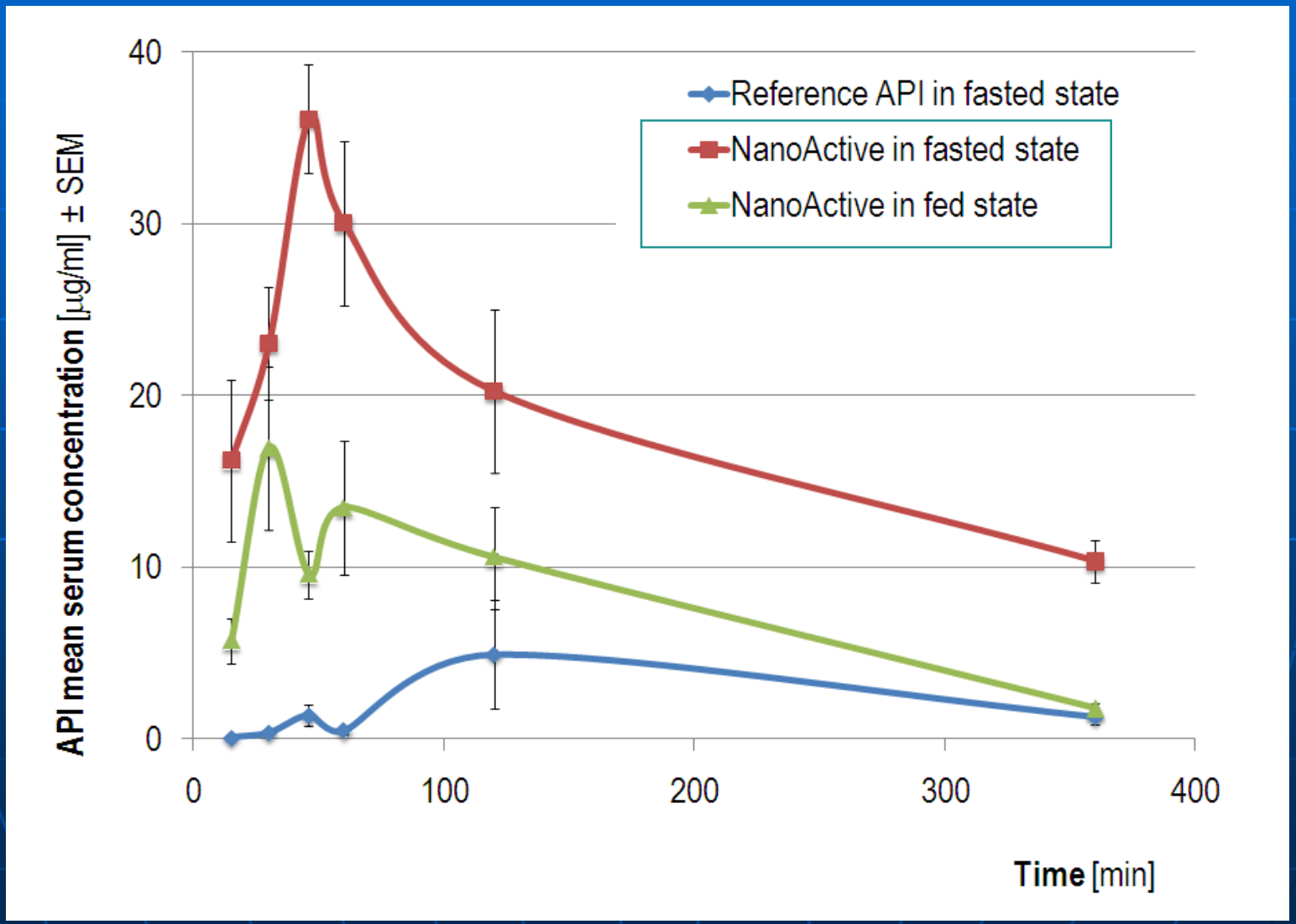
Benefits of Drug Nanocrystals

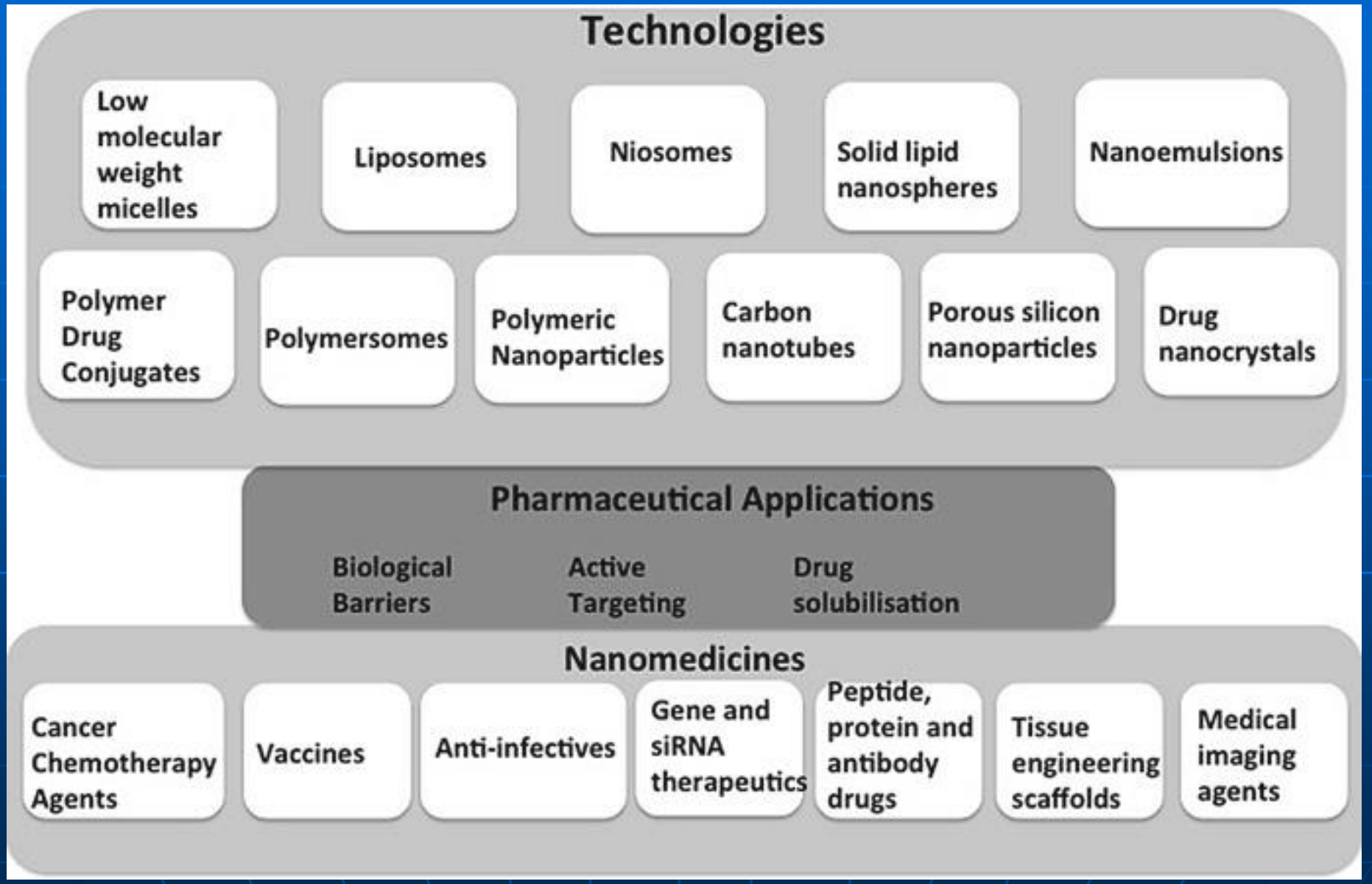


Enhanced bioavailability



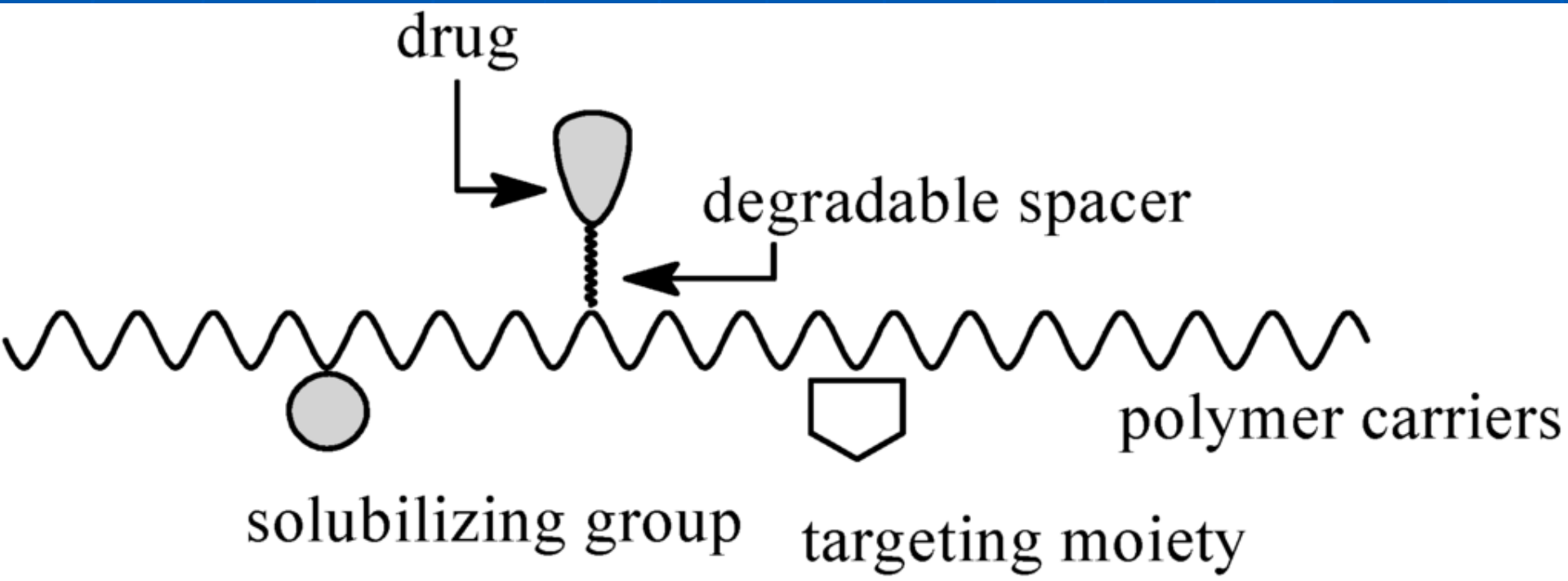
Enhanced bioavailability




Technologies
Low molecular weight micelles
Liposomes
Niosomes
Solid lipid nanospheres
Nanoemulsions
Polymer Drug Conjugates
Polymersomes
Polymeric Nanoparticles
Carbon nanotubes
Porous silicon nanoparticles
Drug nanocrystals
Pharmaceutical Applications
Biological Barriers
Active Targeting
Drug solubilisation
Nanomedicines
Cancer Chemotherapy Agents
Vaccines
Anti-infectives
Gene and siRNA therapeutics
Peptide, protein and antibody drugs
Tissue engineering scaffolds
Medical imaging agents

Polymer-Drug Conjugates

Polymer-drug conjugates are nanosized drug delivery systems, which comprise several drug molecules *covalently* attached to the polymer via a biodegradable linker

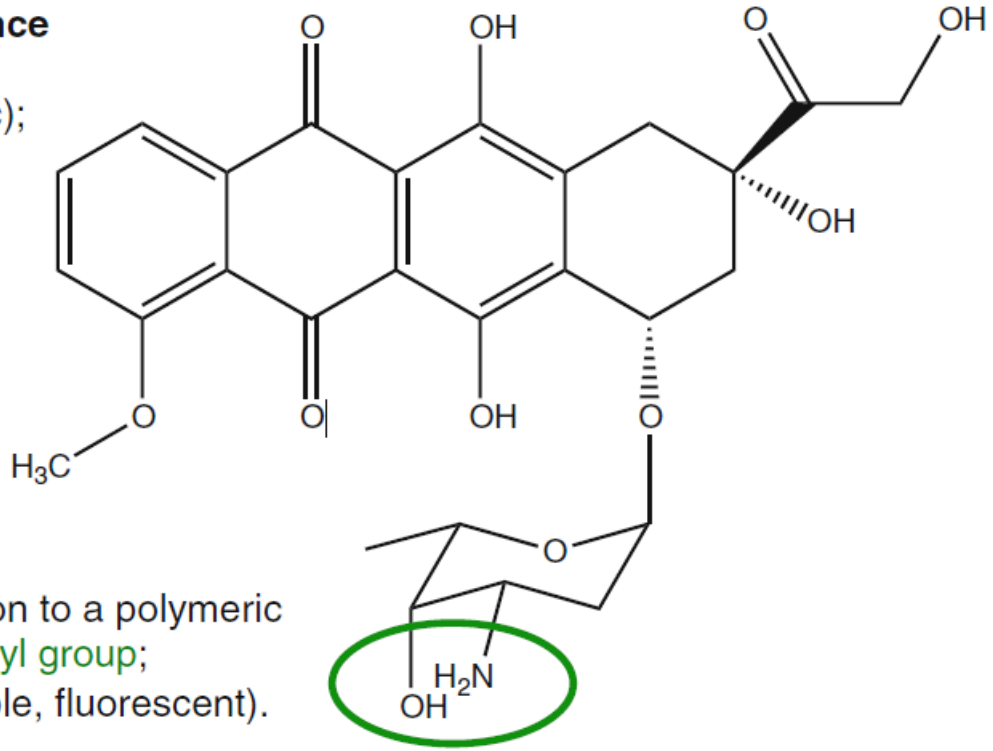


Benefits of Polymer-drug conjugates :

– *Prolonged circulation time of the drug.*
– *Restricted body distribution .*
– *Selective drug release.*

Therapeutic applications and performance

- Used in cancer treatment;
- Non-selective (doxorubicin is cardiotoxic);
- Potent.



Chemical features

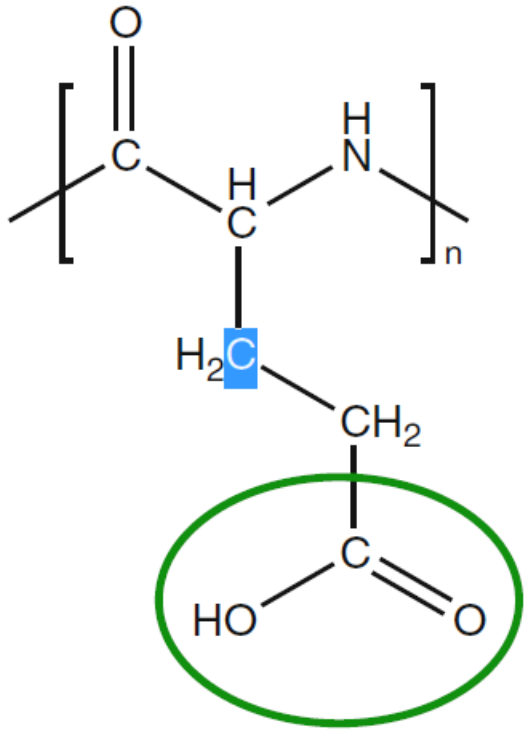
- Functional group(s) that allow conjugation to a polymeric carrier: primary amino group and hydroxyl group;
- Detectable for characterization (UV visible, fluorescent).

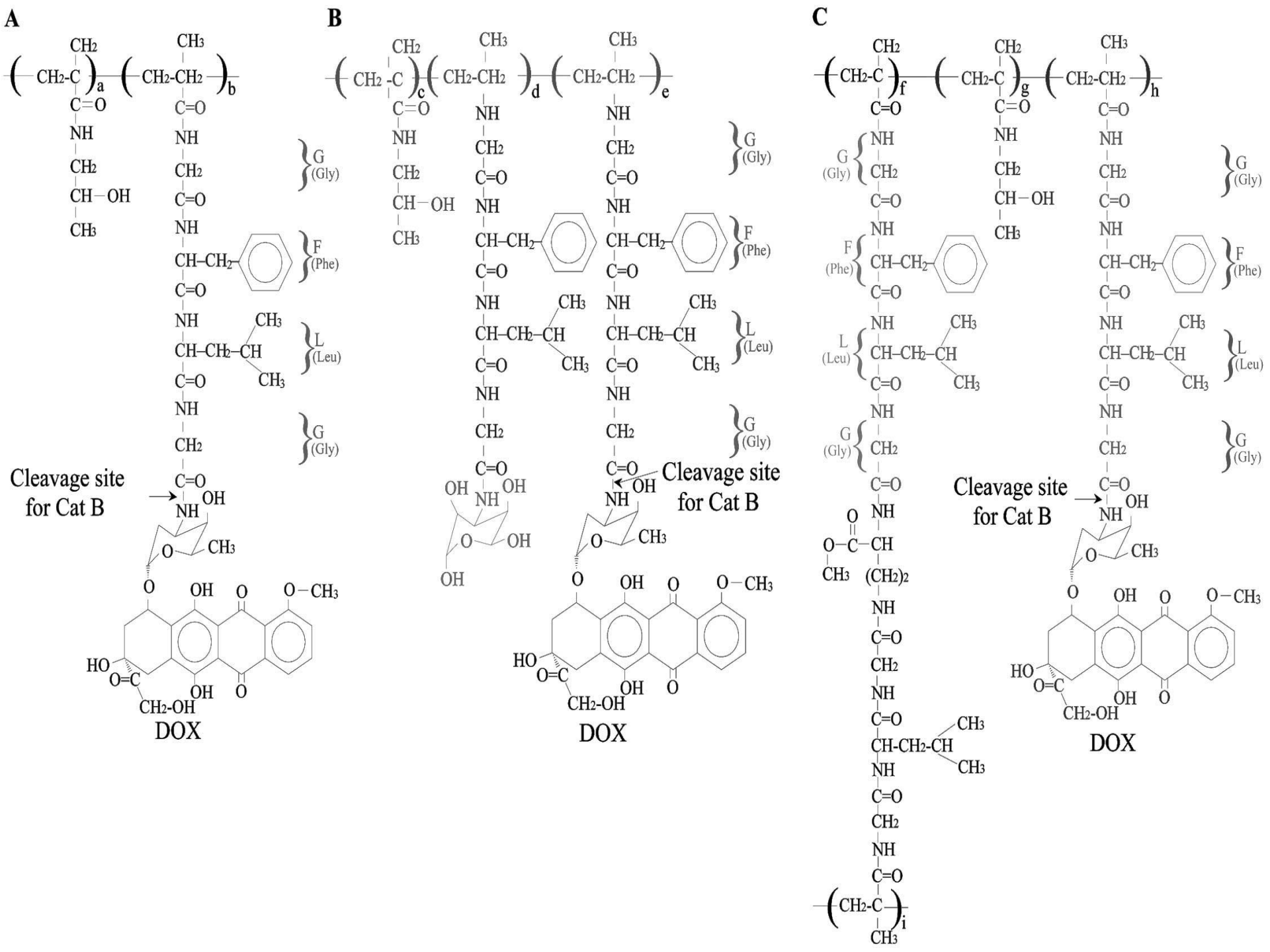
polyglutamic acid (PGA)

Physico-chemical characteristics
- Solubility in water;
- High molecular weight;

Biological behaviour
- Biodegradability: breaks down into smaller fragments in the body;
- Non toxic;
- Non immunogenic.

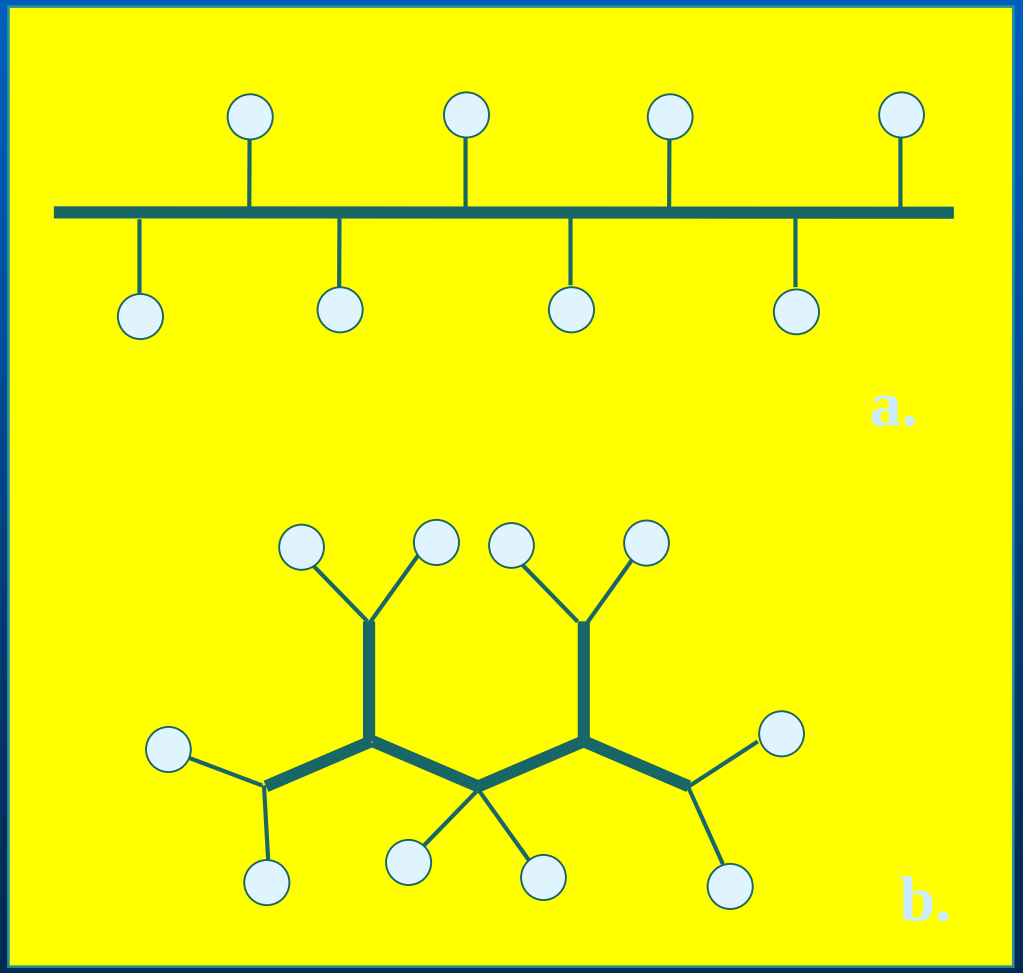
Chemical structure
Conjugation sites: one carboxyl group per monomer (high loading capacity).




A
B
C
Cleavage site for Cat B
DOX
G (Gly)
F (Phe)
L (Leu)

a.) Linear

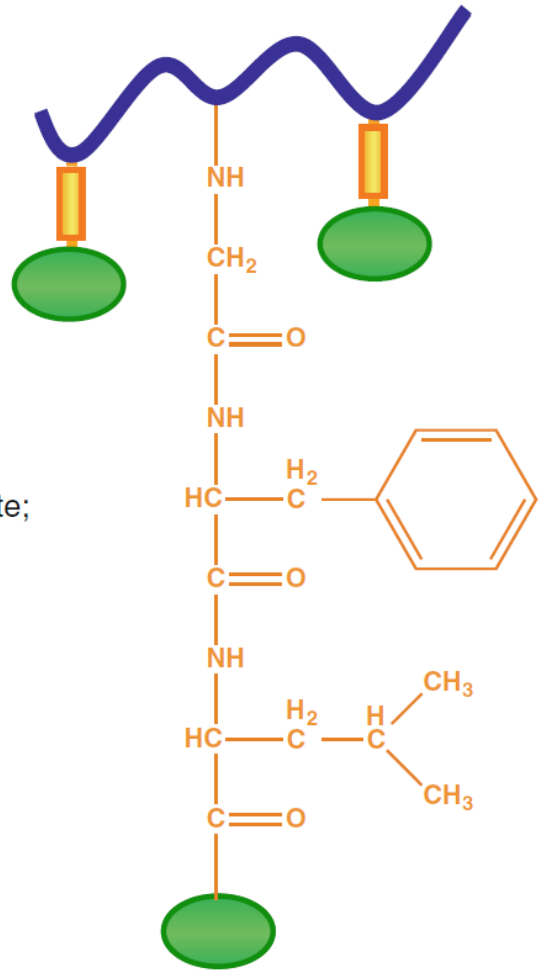
b.) Branched



Polymer

Linker

Drug

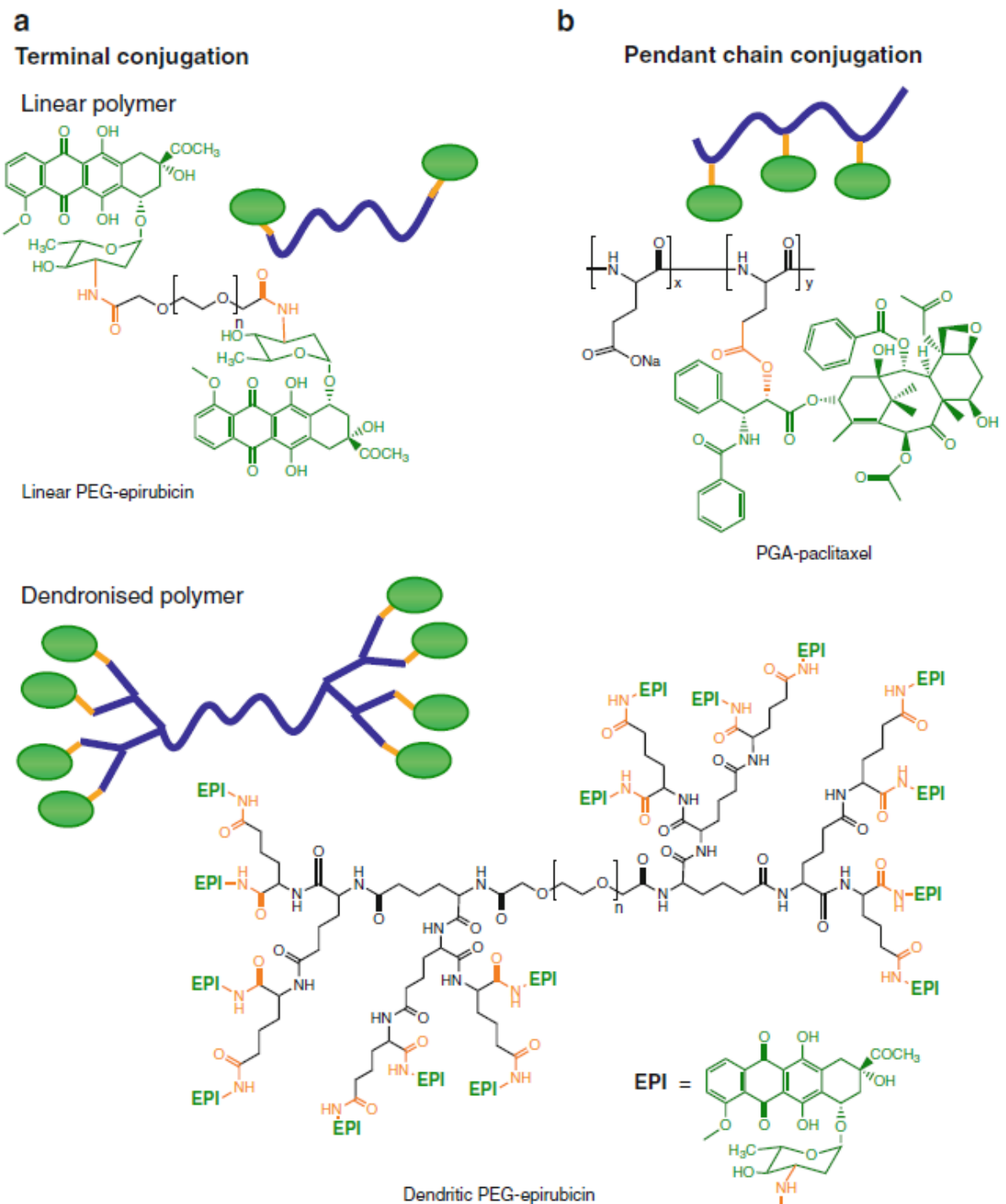


Biological behaviour:

- Degradable at the target site;
- Stable in blood.

Types of conjugation according to the position of the conjugation site within the polymer chain. The drug can be attached to the polymer through:

(**a**) its terminal groups;
(**b**) its side chains

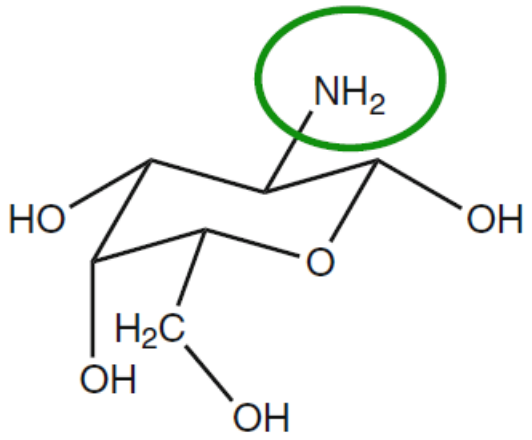


Targeting group is an optional component in a polymer-drug conjugate designed

galactosamine

Biological behaviour:
Tissue-specific (binds selectively to the hepatocyte galactose receptor, liver-specific);

Chemical features
Functional group that allows conjugation to a polymeric carrier (primary amino group).



Galactosamine is an amino sugar able to bind selectively to the hepatocyte galactose receptor, a liver-specifi c receptor
(Ashwell and Harford 1982).

Galactosamine was covalently bound to an HPMA copolymer-doxorubicin conjugate designed for the treatment of liver cancer (Seymour et al. 1991)

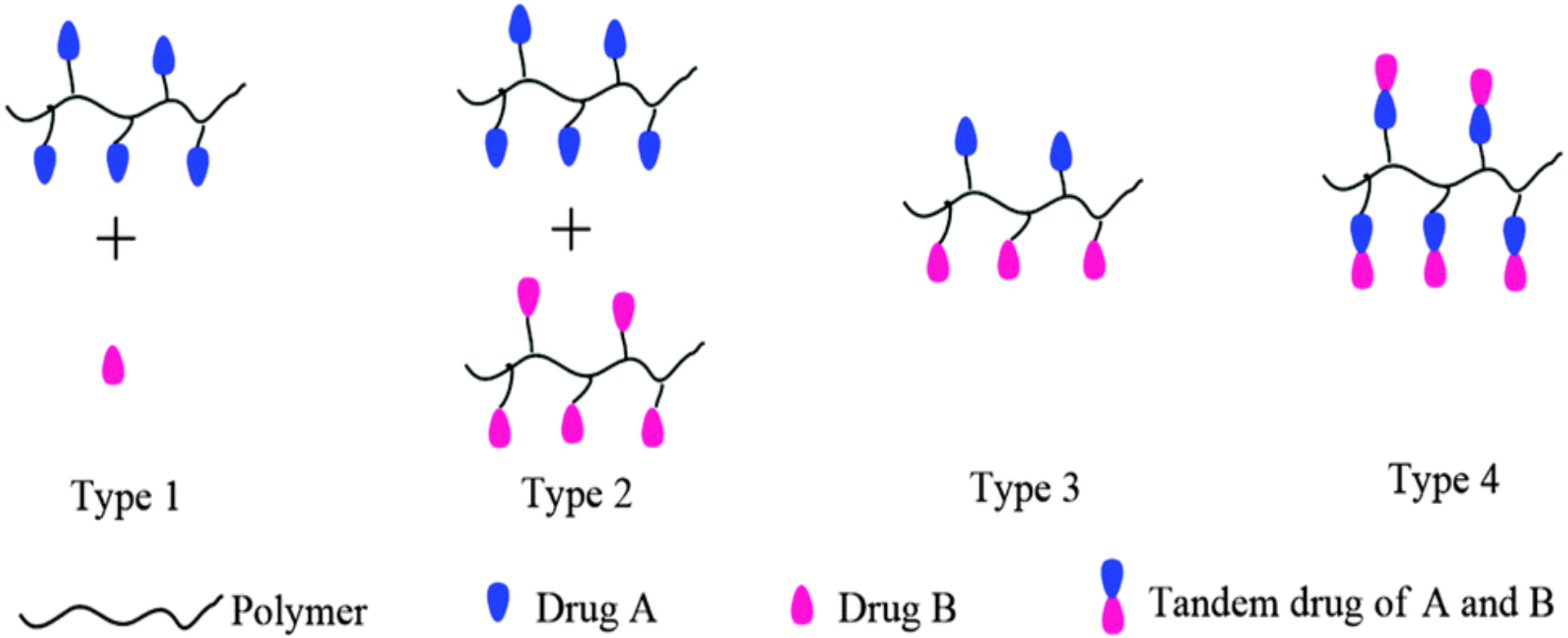
N-(2-hydroxypropyl)methacrylamide

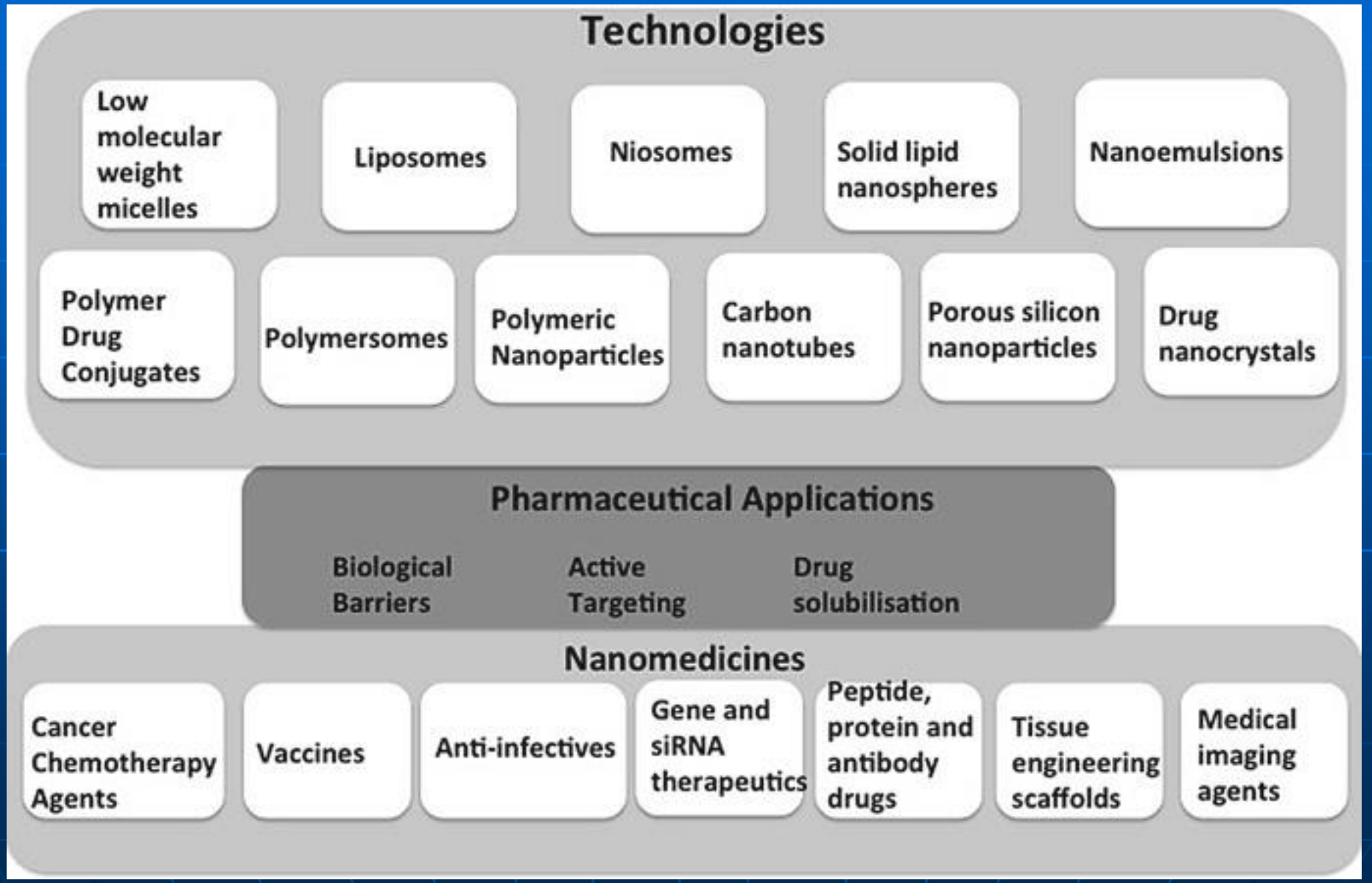
Combination Therapy

Many diseases (e.g. cancer and HIV) are treated with cocktails of drugs rather thanwith a single therapeutic agent. The overall aim of this type of therapeutic regimen(combination therapy) is to maximise efficancy while decreasing toxicity.

Conjugate	Type of combination	Reference
HPMA copolymer-doxorubicin-aminoglutethimide	Chemotherapy; Endocrine therapy	Vicent et al. (2005), Greco et al. (2007)
PEG-NO-epirubicin	Chemotherapy; cardioprotective agent.	Pasut et al. (2009), Santucci et al. (2006)
HPMA copolymer-TNP470-alendronate	Antiangiogenic agent; bisphosphonate drug.	Segal et al. (2009)
HPMA copolymer-paclitaxel-alendronate	Chemotherapy; biphosphonate drug.	Miller et al. (2011)
HPMA copolymer-doxorubicin-dexamethasone	Chemotherapy; anti-inflammatory and anti-proliferative agent	Kostkova et al. (2011)
PEG-paclitaxel-alendronate	Chemotherapy; biphosphonate drug.	Clementi et al. (2011)

Combination Therapy




Technologies
Low molecular weight micelles
Liposomes
Niosomes
Solid lipid nanospheres
Nanoemulsions
Polymer Drug Conjugates
Polymersomes
Polymeric Nanoparticles
Carbon nanotubes
Porous silicon nanoparticles
Drug nanocrystals
Pharmaceutical Applications
Biological Barriers
Active Targeting
Drug solubilisation
Nanomedicines
Cancer Chemotherapy Agents
Vaccines
Anti-infectives
Gene and siRNA therapeutics
Peptide, protein and antibody drugs
Tissue engineering scaffolds
Medical imaging agents

Nanoemulsions

Nanoemulsions are nano-sized oil-in-water or water-in-oil emulsions with a number of applications in biomedicine. Nanoemulsions are highly versatile systems, in terms of composition and physicochemical properties, which can be tailor-made using simple and mild technologies to associate a great variety of drugs and fulfil the requirements for a wide range of pharmaceutical applications.

Emulsions are mixtures of two immiscible phases, wherein an emulsifier (surfactant) is added in the continuous or external phase to stabilise the dispersed droplets (internal phase).

Emulsions are classified as:

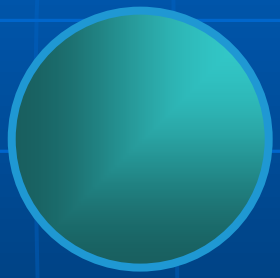
-oil-in-water (O/W),

-water-in-oil (W/O),

Emulsions can be further classified depending on droplet size into:

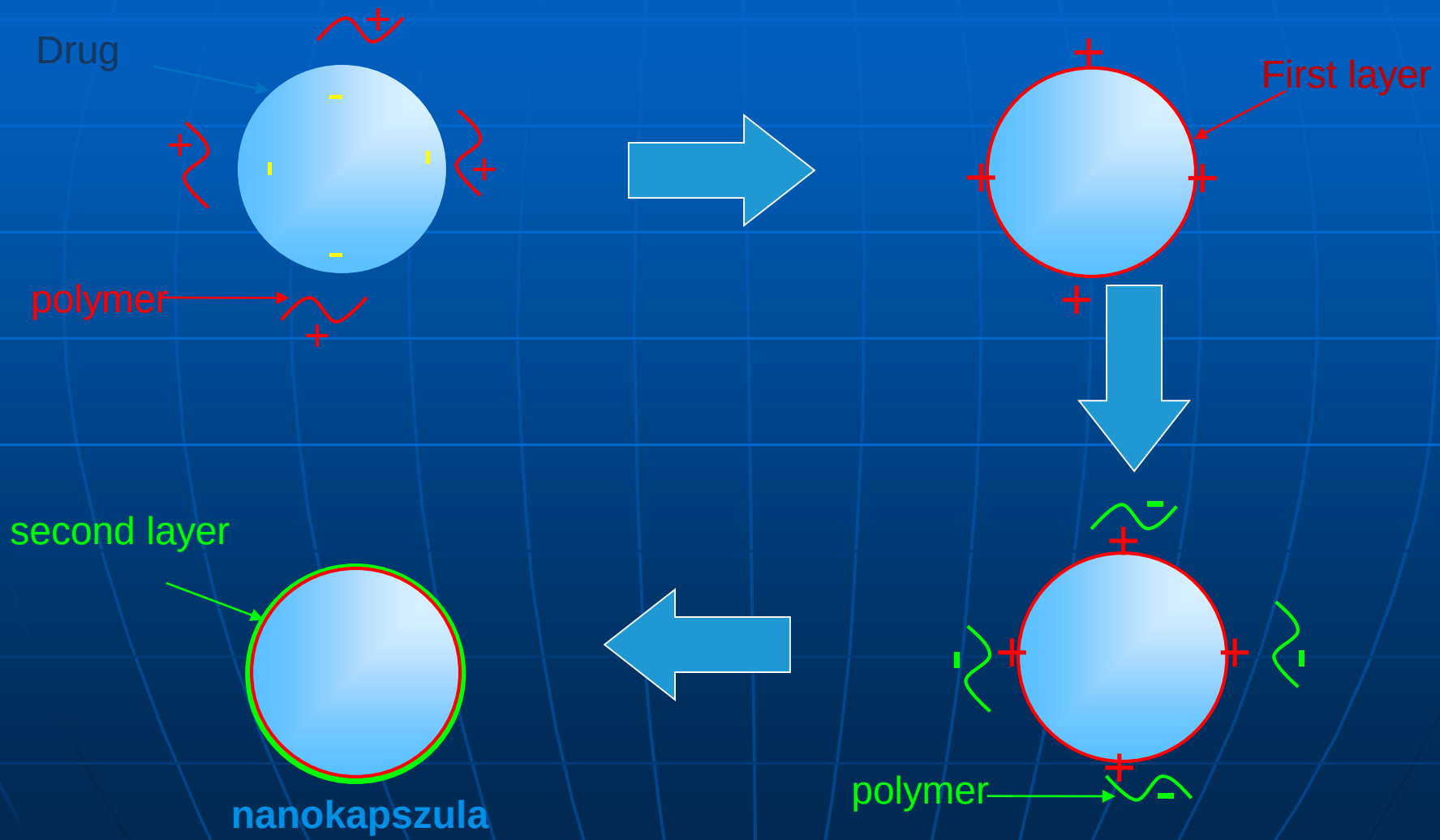
- coarse emulsions
- microemulsons (thermodynimically satble emulsions)
- nanoemulsions. (10–300 nm) (thermodynimically unsatble emulsions)

Polymer-coated nanoemulsions, otherwise known as nanocapsules

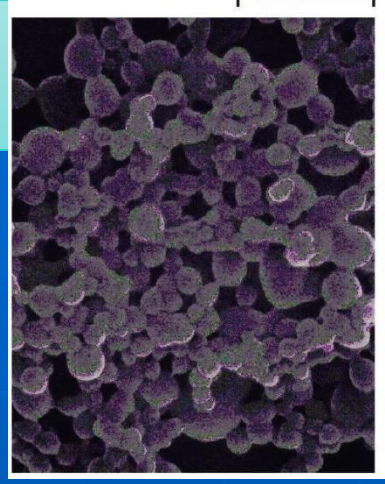


Nanocapsules

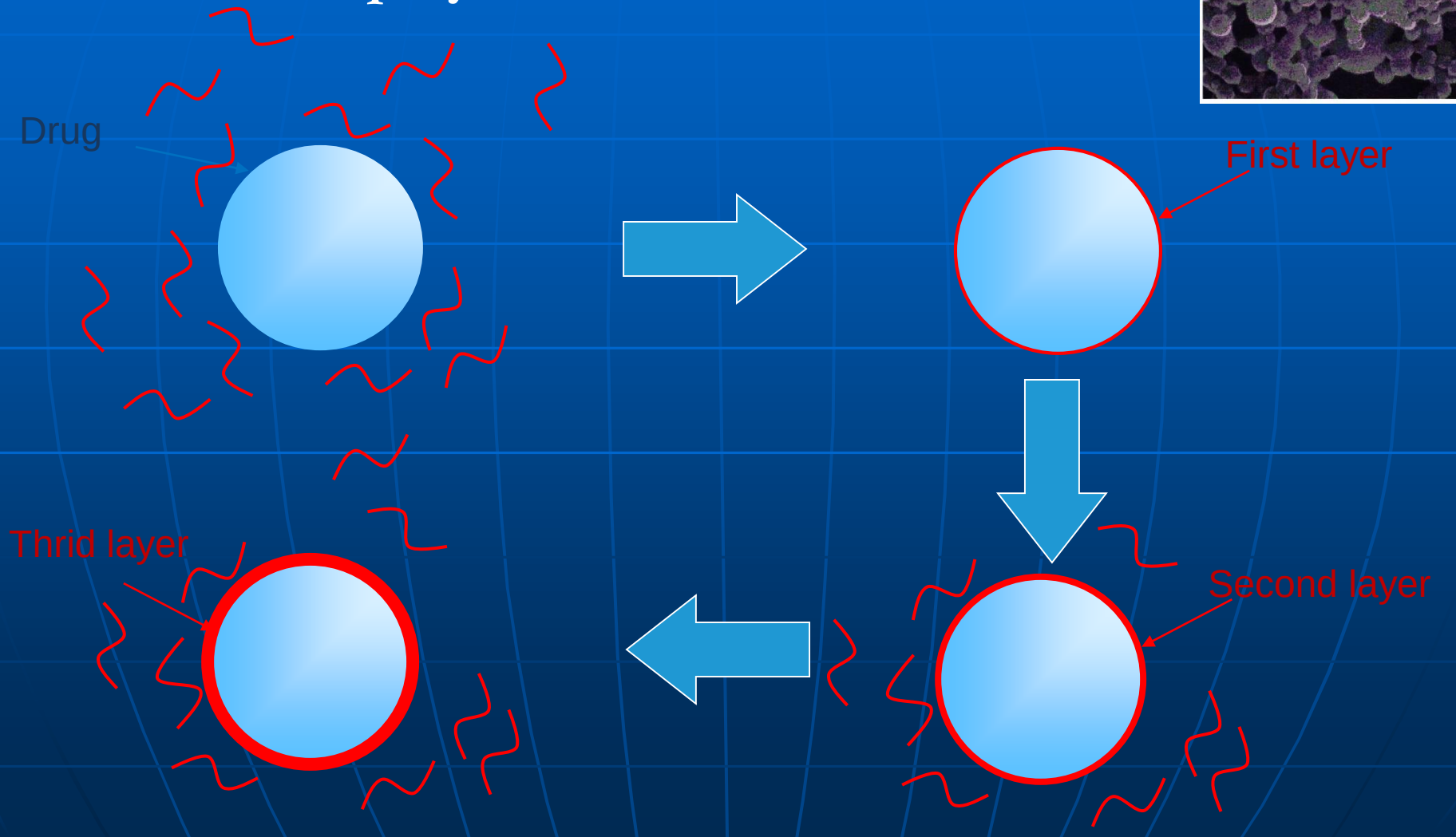
- Electrostatic interactions



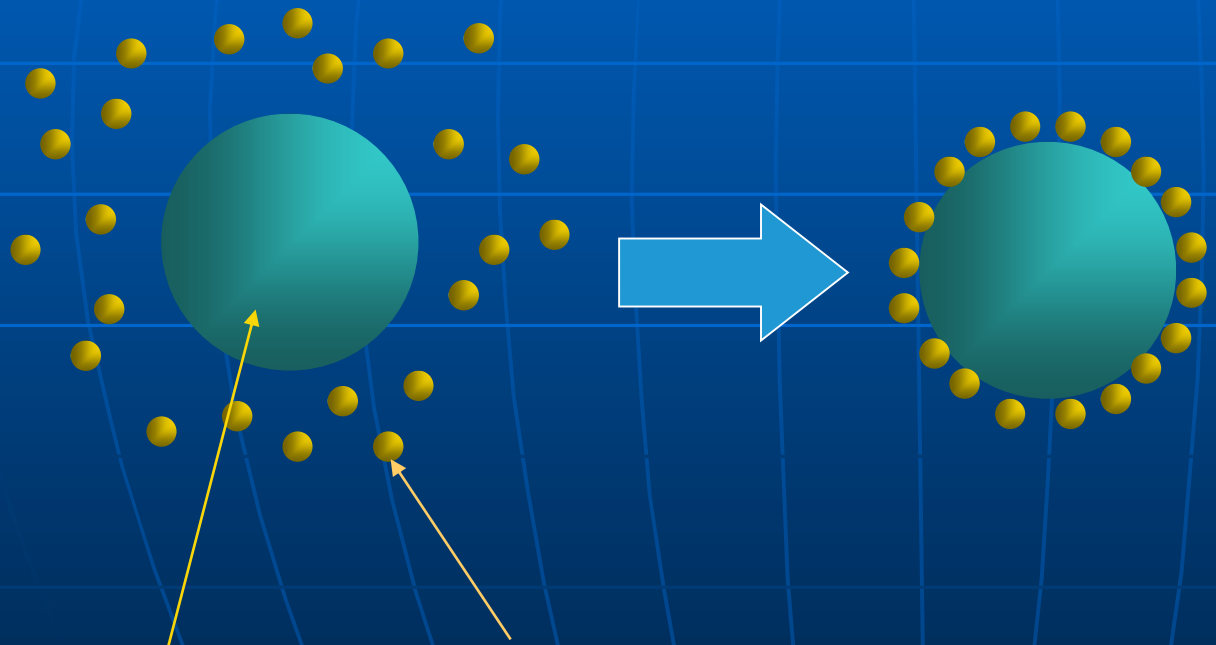
Nanocapsules



- Surface polymerization



Pickering emulsions



Pickering emulsions