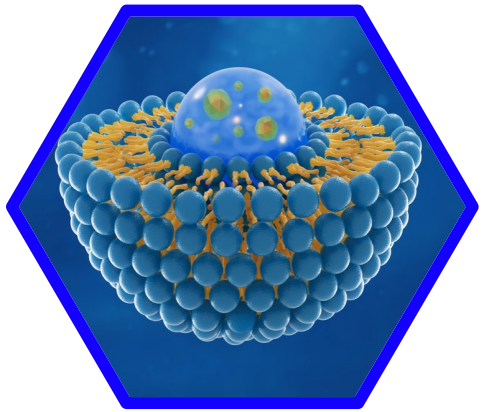
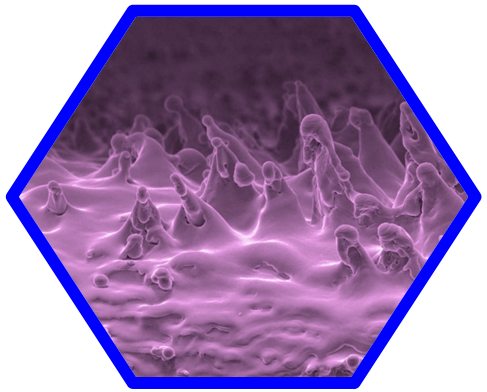




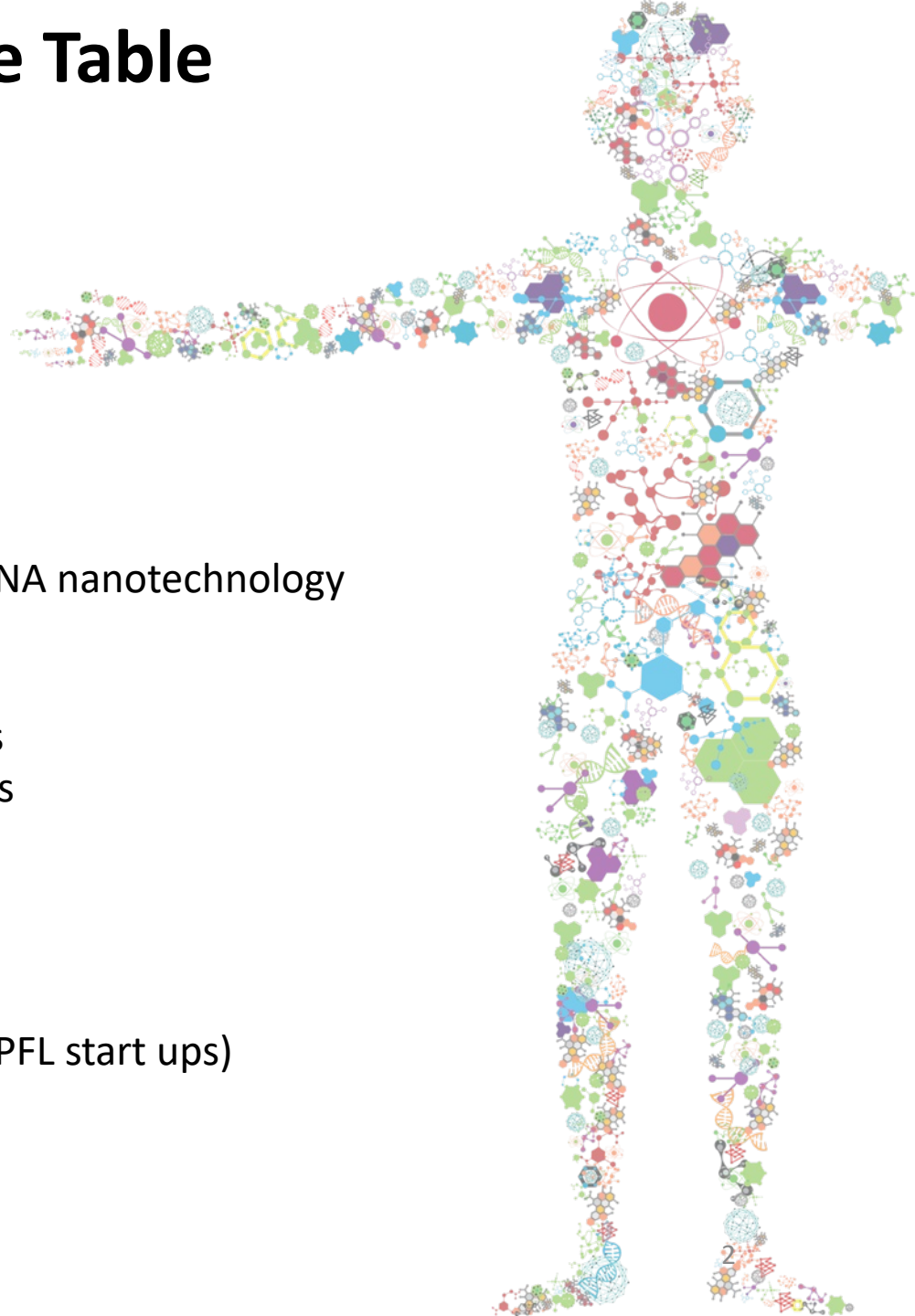
Biomaterials for MX

MSE – 471

Prof. Maartje M.C. Bastings

Course 4: Polymers, Particles and Surfaces

Course Content & Time Table



BLOCK 1: Introduction and materials overview

11-9	Lecture 1.	Intro to biomaterials and biology
18-9	Lecture 2.	Naturally derived biomaterials
25-9	Lecture 3.	Implants and metals
2-10	**Lecture 4.**	**Polymers, Particles, and Surfaces**

BLOCK 2: Interactions and specific applications

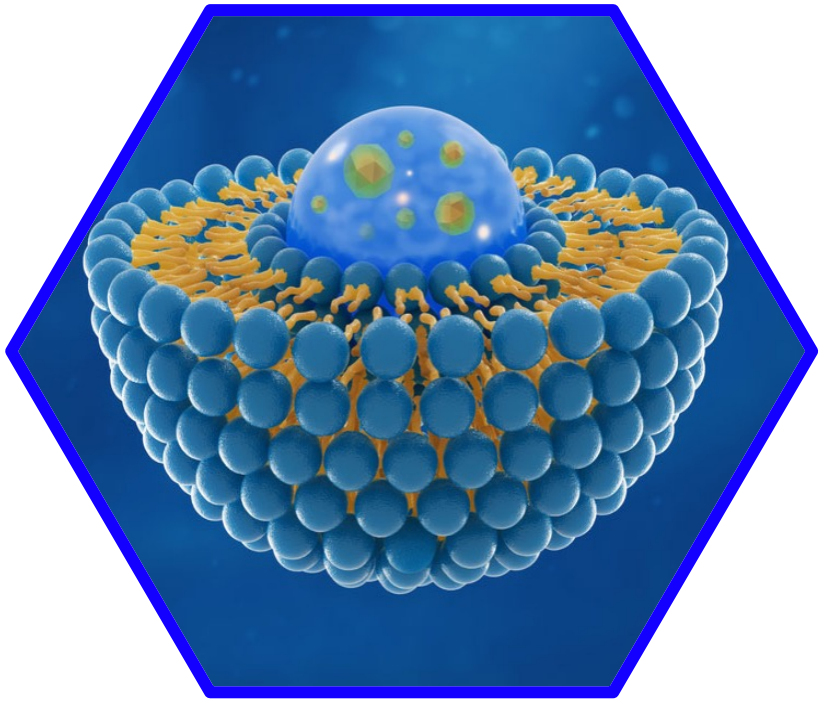
9-10	Lecture 5.	Materials for drug delivery and targeting: DNA nanotechnology
16-10	Lecture 6.	Materials for cell adhesion: scaffolds
---	*Break*	
30-10	Lecture 7.	Materials for immune engineering: vaccines
6-11	Lecture 8.	Materials for tissue engineering: heartvalves

BLOCK 3: Measurements, regulation and translation

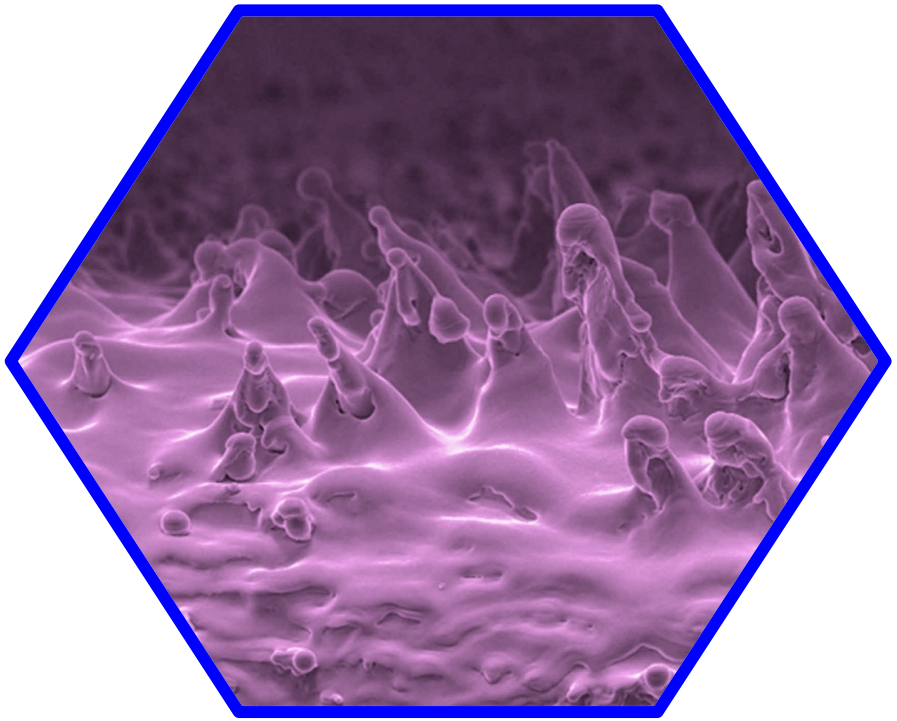
13-11	Lecture 9.	Characterization and performance
20-11	Lecture 10.	Sensors and diagnostic devices
27-11	Lecture 11.	Translation to industry, patents, spin-offs (EPFL start ups)
4-12	Lecture 12.	Regulatory aspects and trials (EPFL TTO)
11-12	Lecture 13.	Revision and conclusion
18-12	Open discussion and hand in of lab papers	

Today's focus

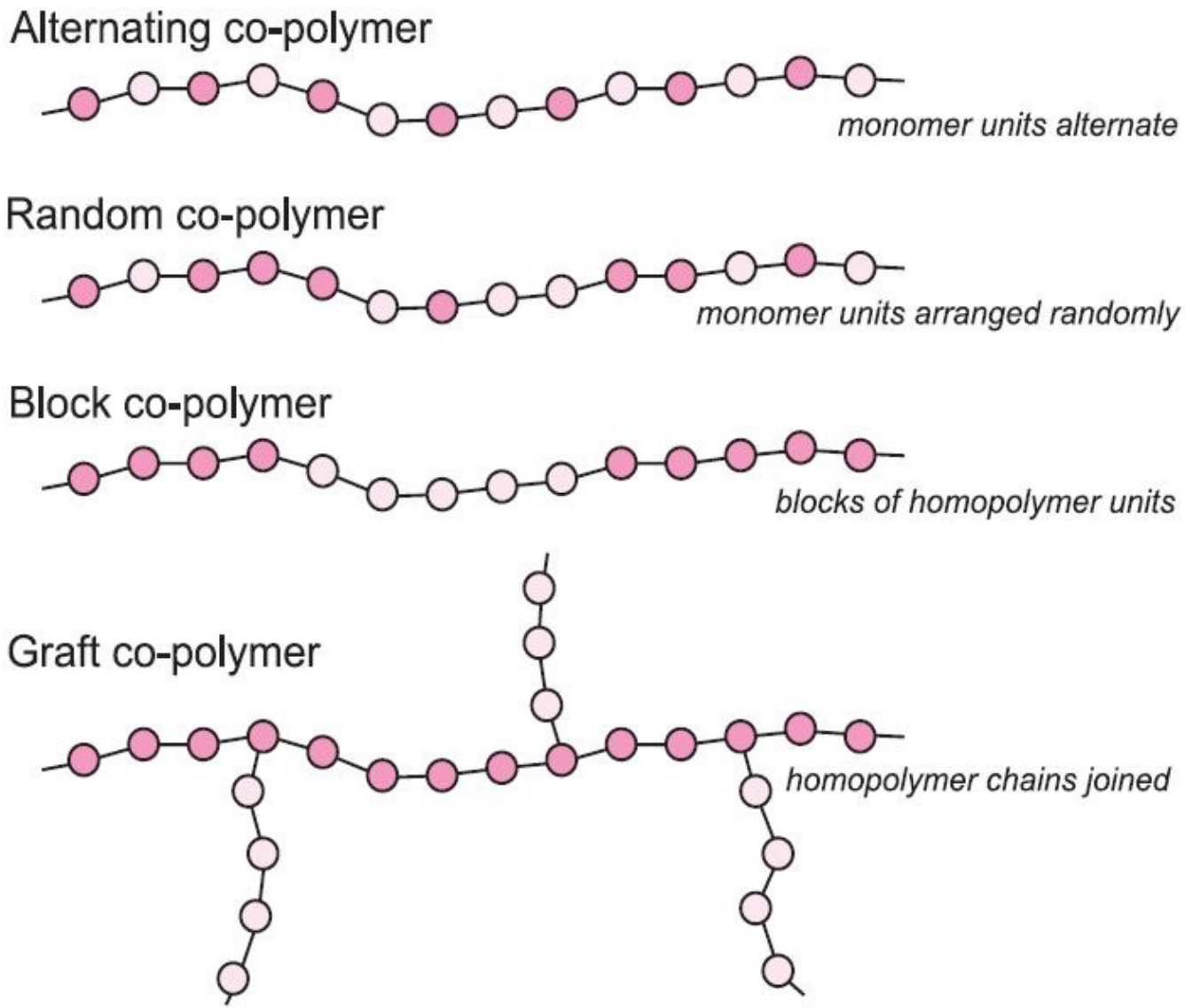
Polymers & Particles



Surfaces

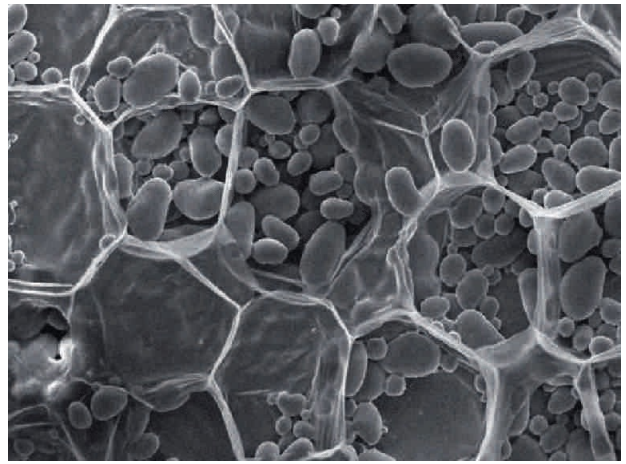


Polymers



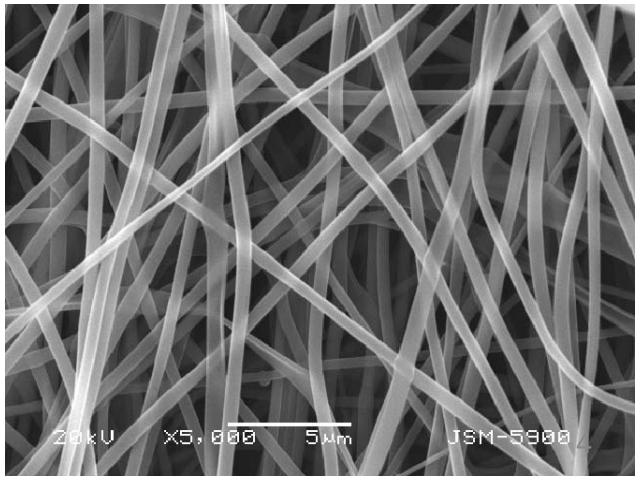
Natural

e.g. Cellulose, Collagen etc.

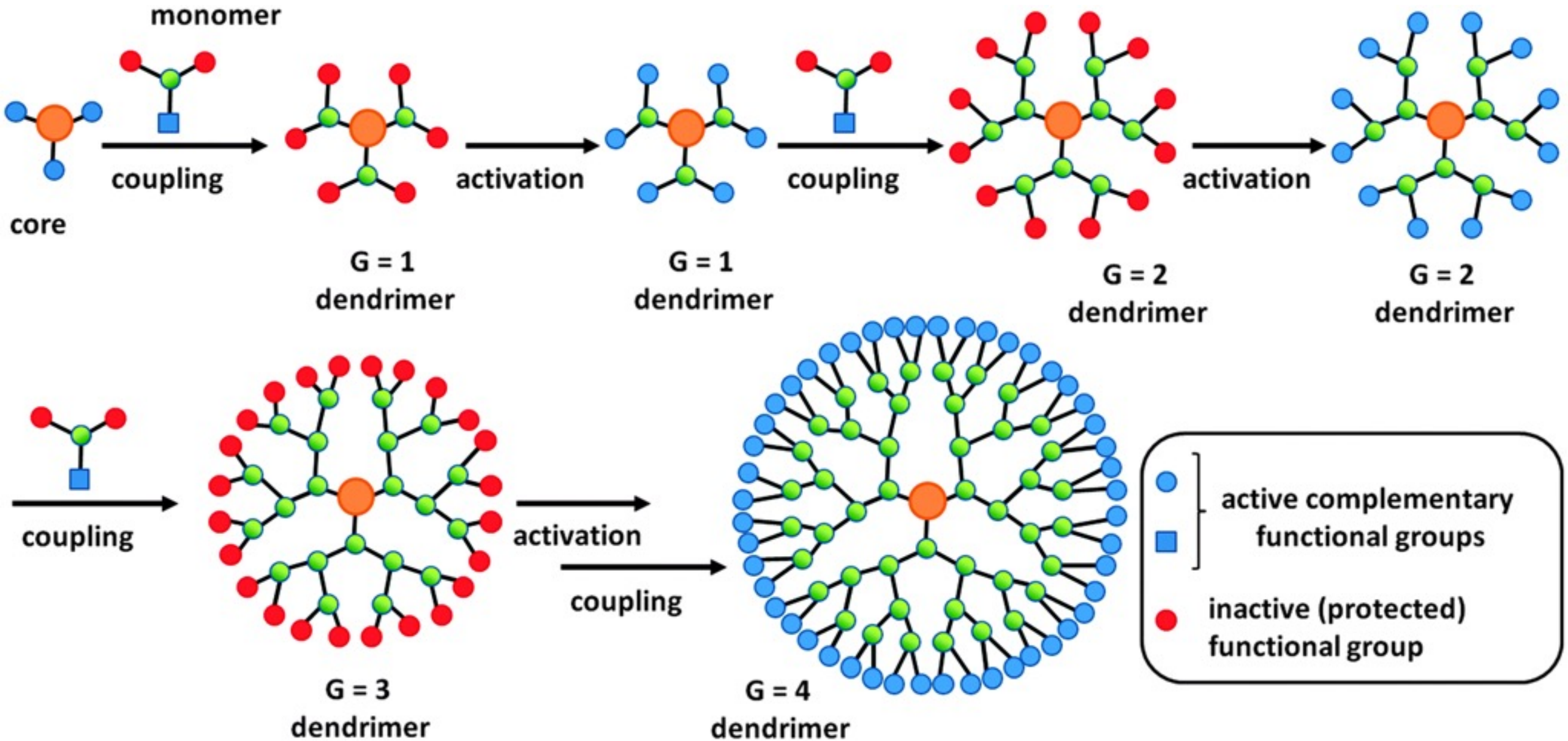


Synthetic

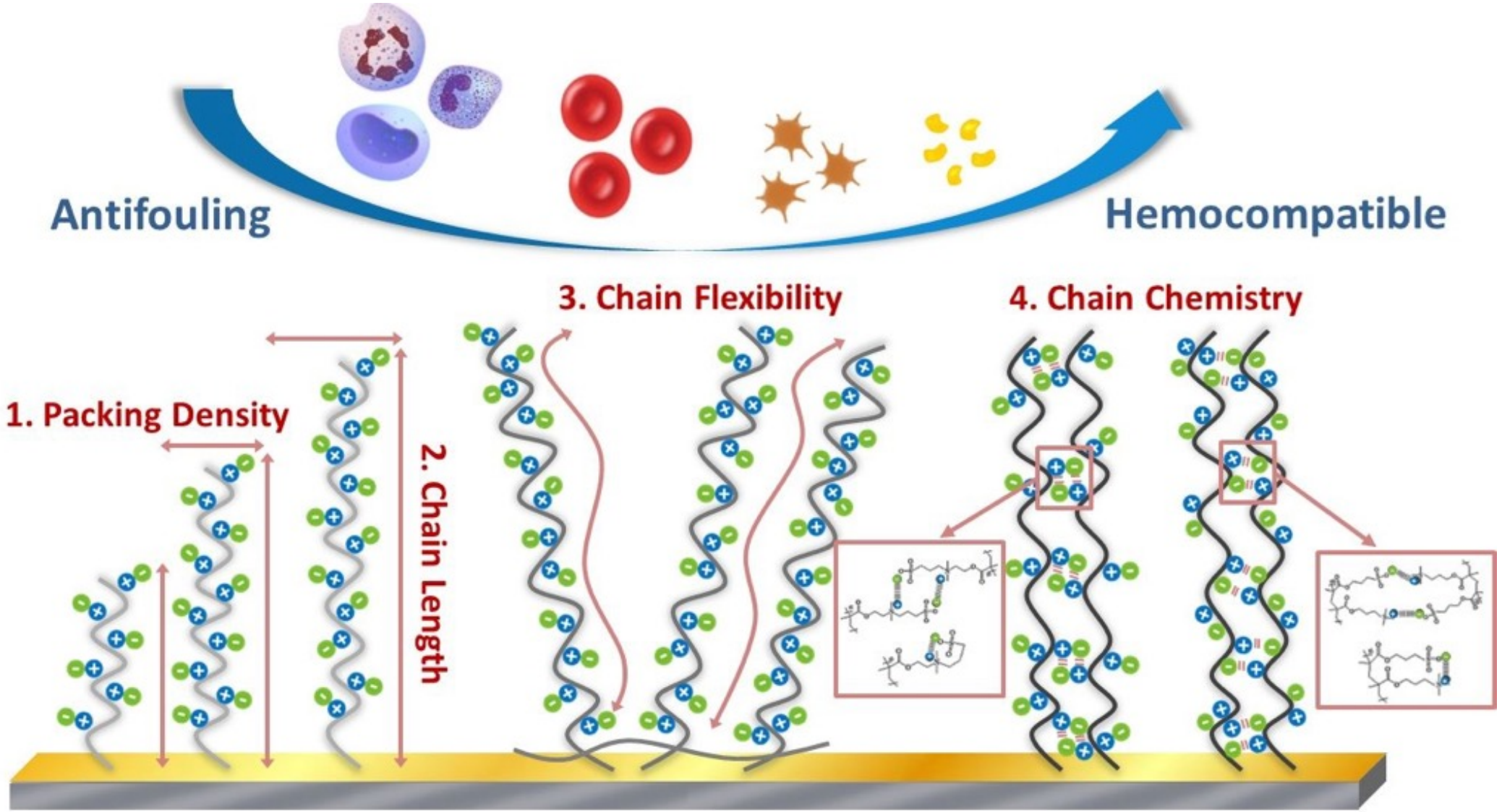
e.g. PEG, PS, PMMA etc.



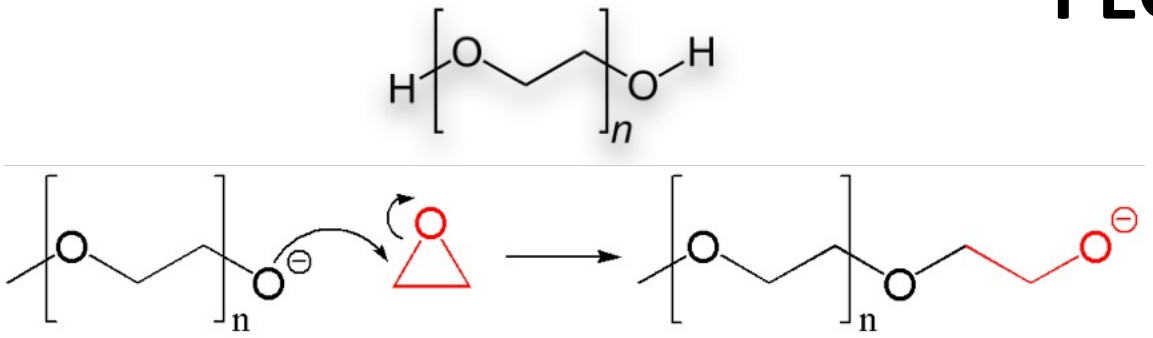
Dendrimers


monomer
coupling
core
G = 1
dendrimer
activation
G = 1
dendrimer
coupling
G = 2
dendrimer
activation
G = 2
dendrimer
coupling
G = 3
dendrimer
activation
coupling
G = 4
dendrimer
active complementary
functional groups
inactive (protected)
functional group

Polymer coatings

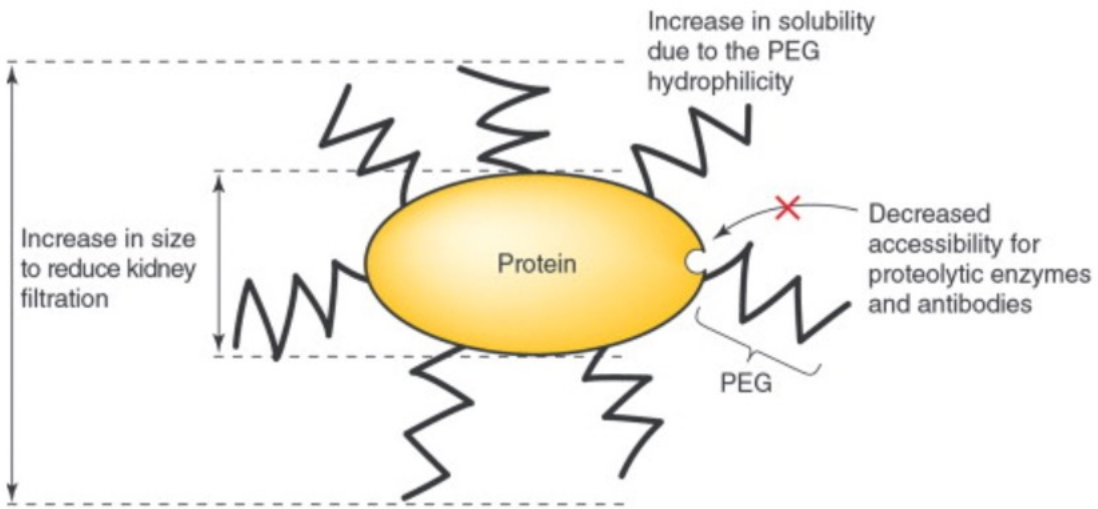


PEG

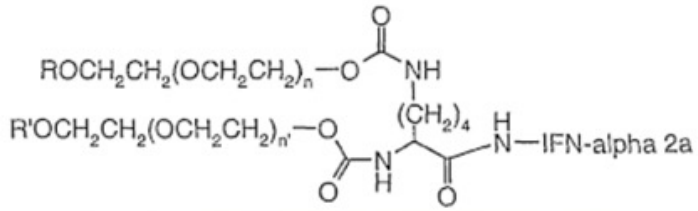


Antifouling
Increase circulation lifetime
Increase size
Reduce immunogenicity (?)

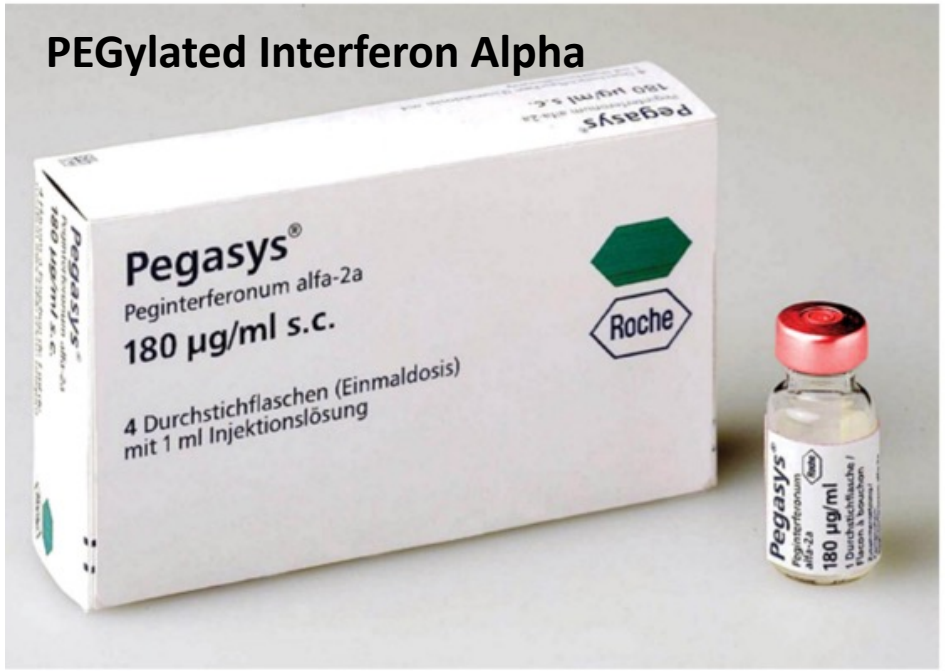
Bioeliminable:
E.g. 'PEGylation' of drugs



Drug Discovery Today
Volume 10, Issue 21, 1 November 2005, Pages 1451–1458

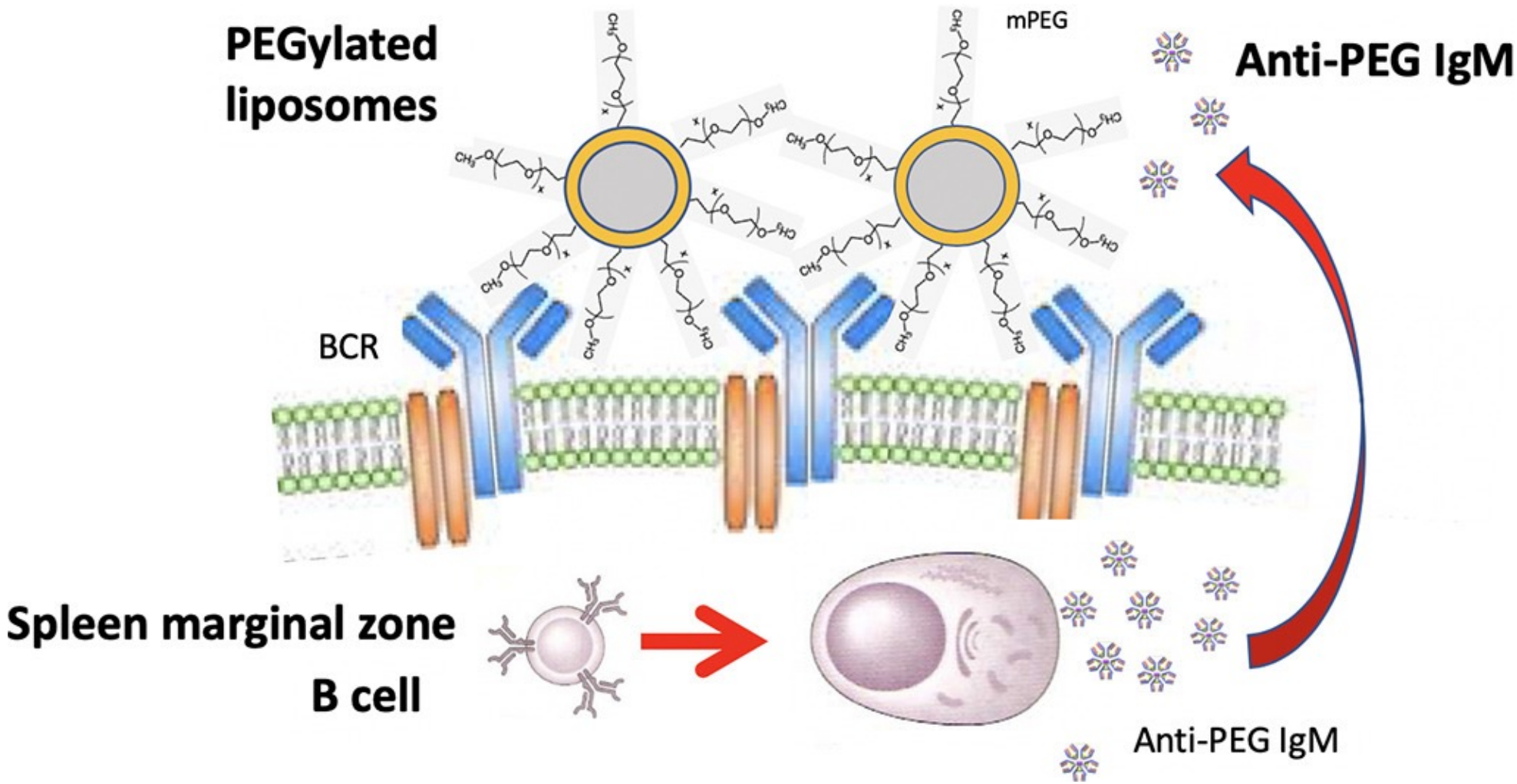


PEGylated Interferon Alpha



Treatment of hepatitis C and hepatitis B

PEG – current issues



Hydrogels

Hydrogels are 3D networks of cross-linked polymers

90+ % is water
Crosslinks can be covalent or non-covalent
Swelling occurs until in **equilibrium** with osmotic pressure

> a (neutral) hydrogel experiences a thermodynamic force of mixing and a contractive force that become balanced once a hydrogel reaches its equilibrium swelling state

Pore size is dependent on the average molecular weight of polymer chain segments between adjacent crosslinks and acts as a selective barrier with regard to the permeability of substances

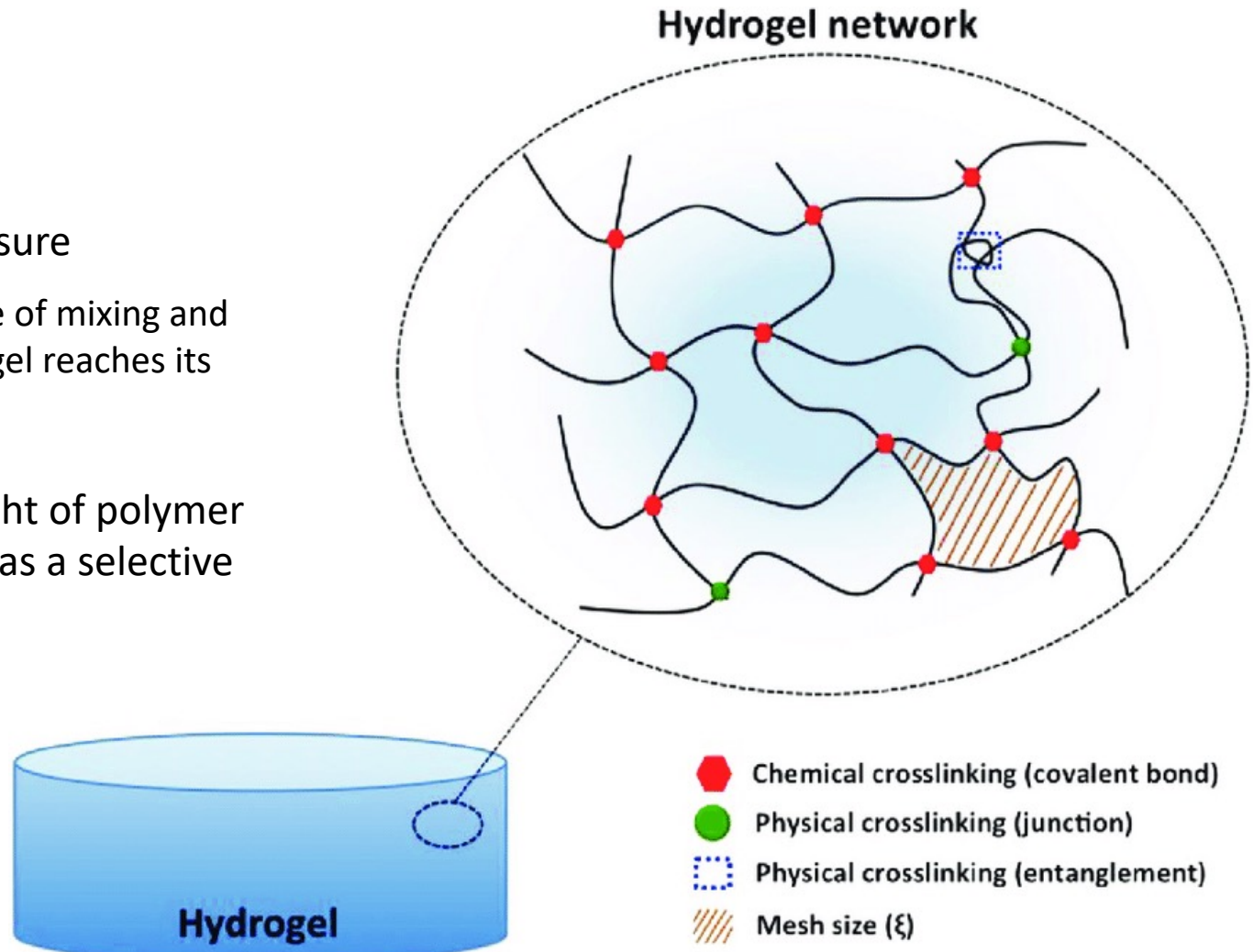
$$G = N_p kT = \frac{\rho RT}{\overline{M}_c}$$

E = 2G(1+*v*)

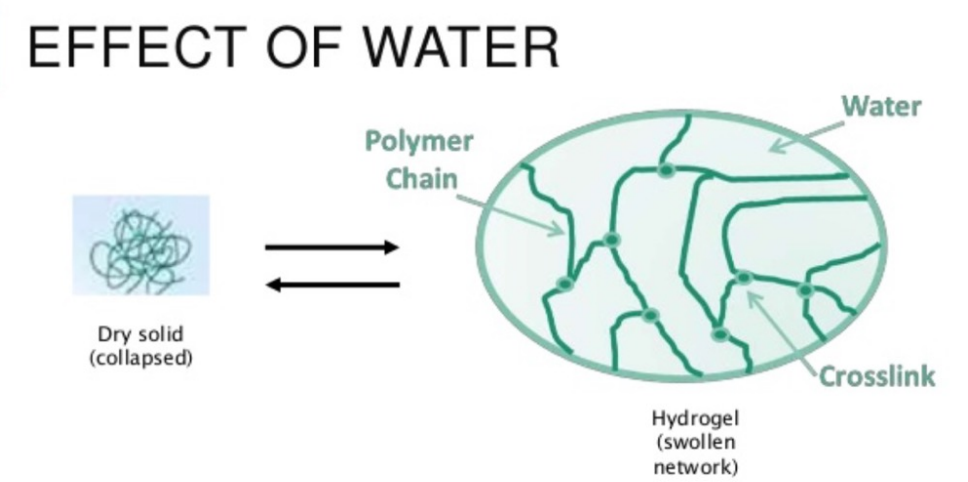
N_p is the number of polymer chains per unit volume

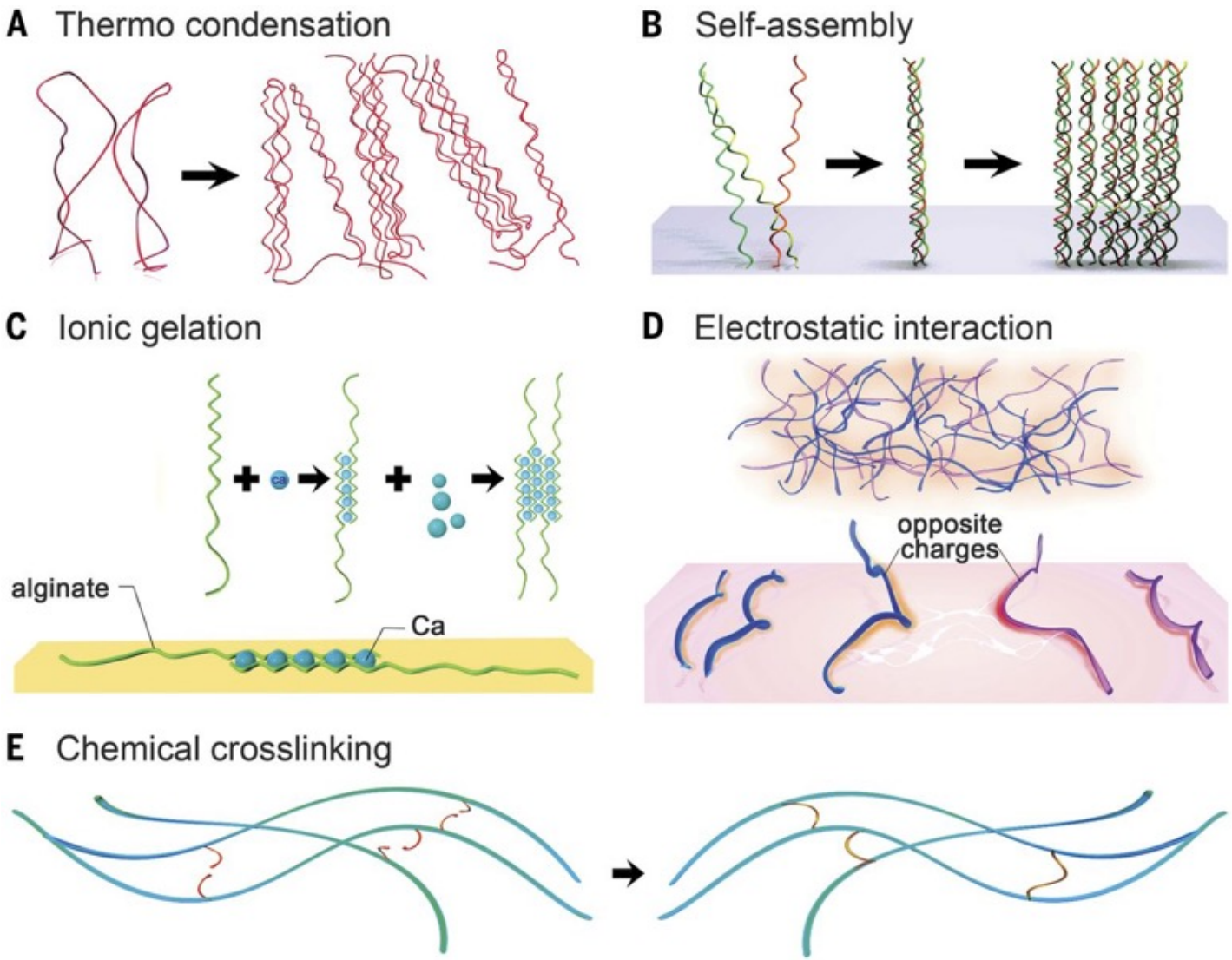
Mc = average molecular weight between cross-links

v = Poissons ratio



Hydrogels: Cross linking



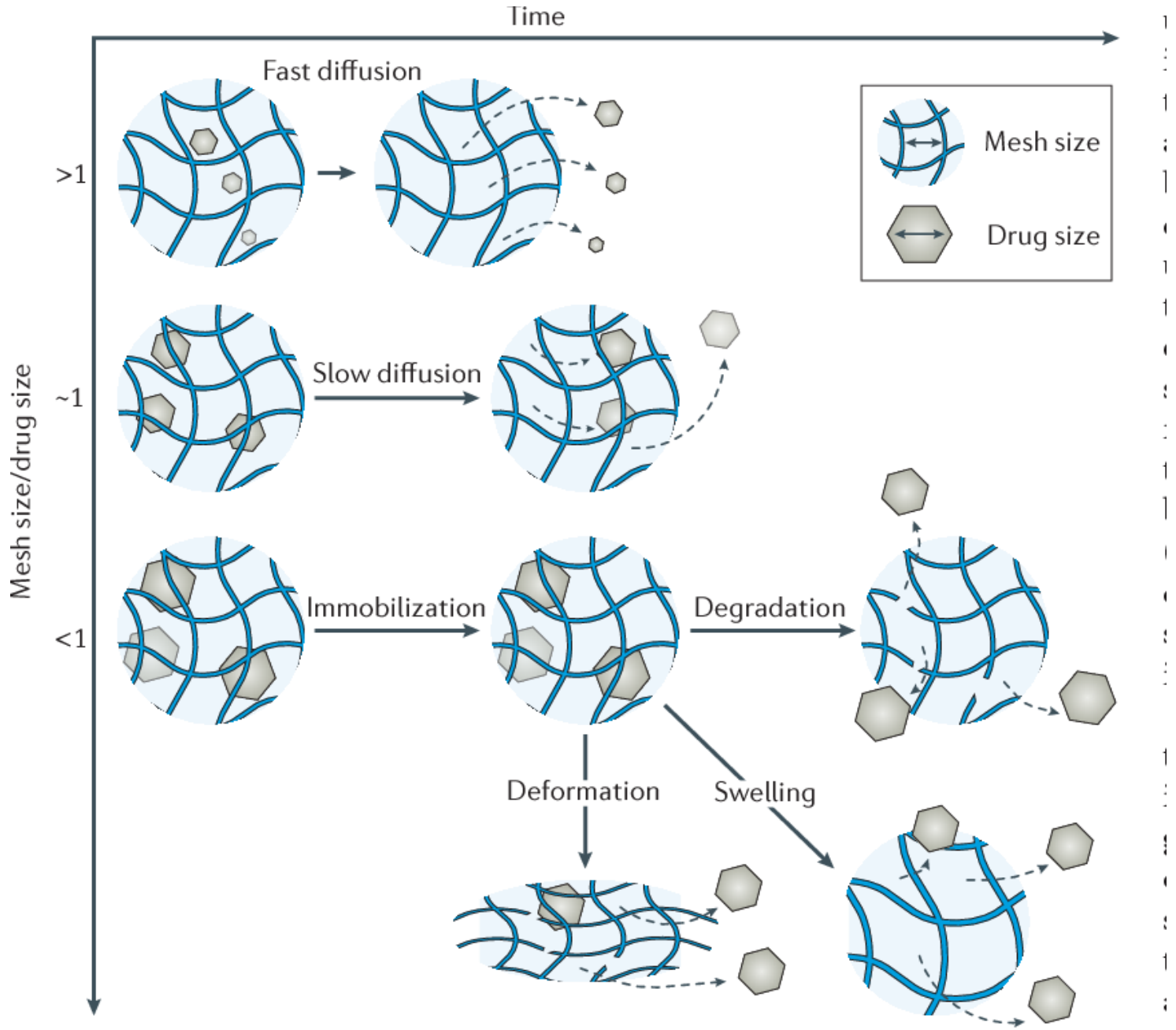


Importance of pore size

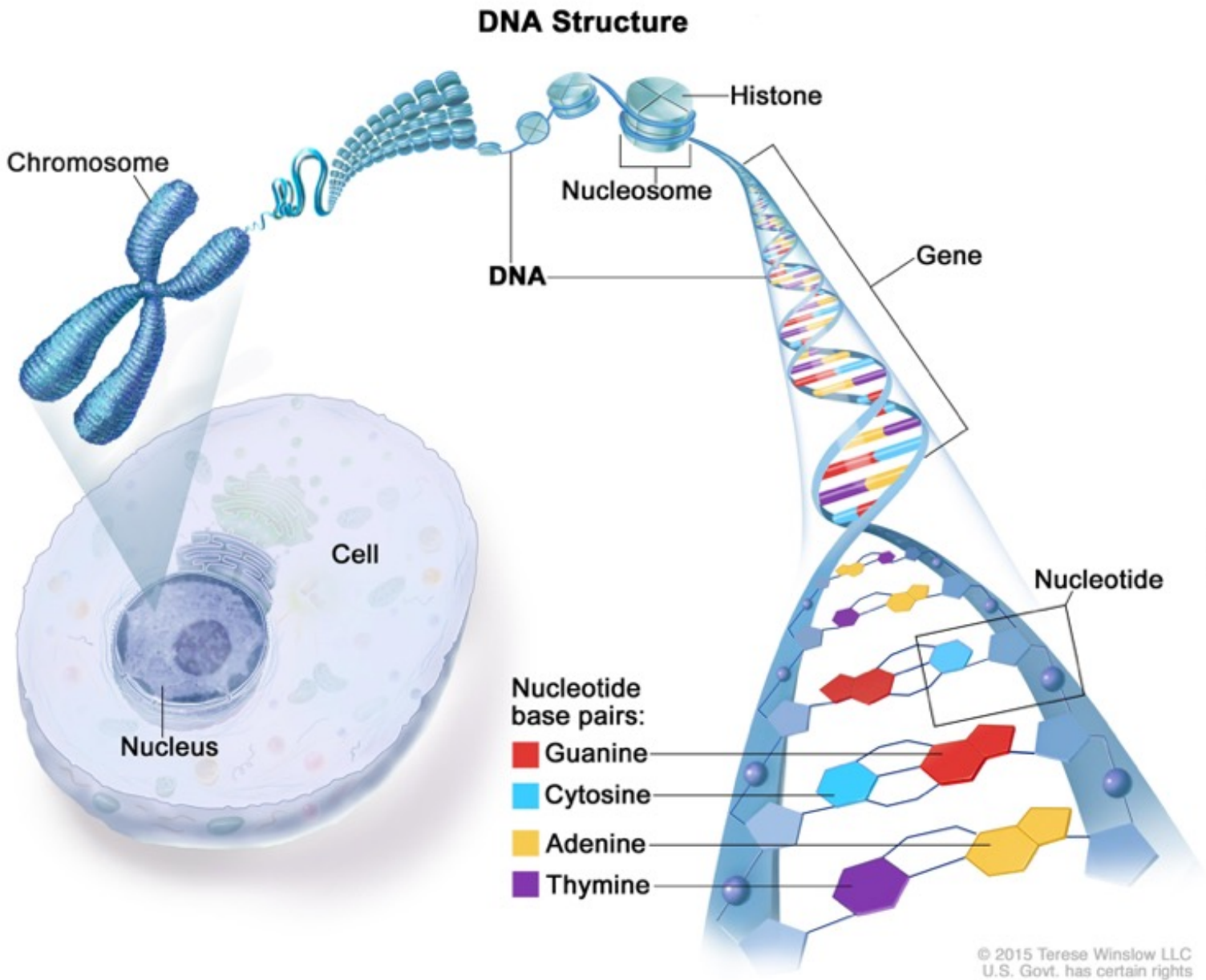
Function and performance of a hydrogel depend on

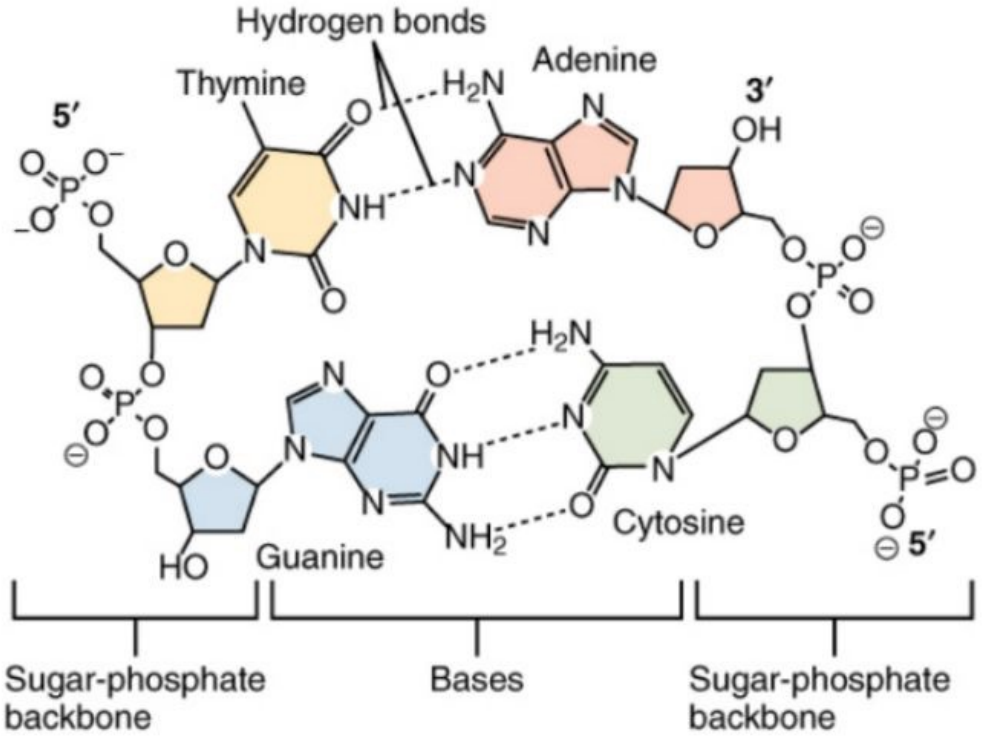
1) the polymer structure
    i. Hydrophobic ?
    ii. Crosslinks ?
    iii. Degradation ?
2) the gel properties
    i. Mesh size
    ii. Elasticity
3) the drug & incorporation method
    i. Size
    ii. Covalent?
    iii. Physical ?

TIME!



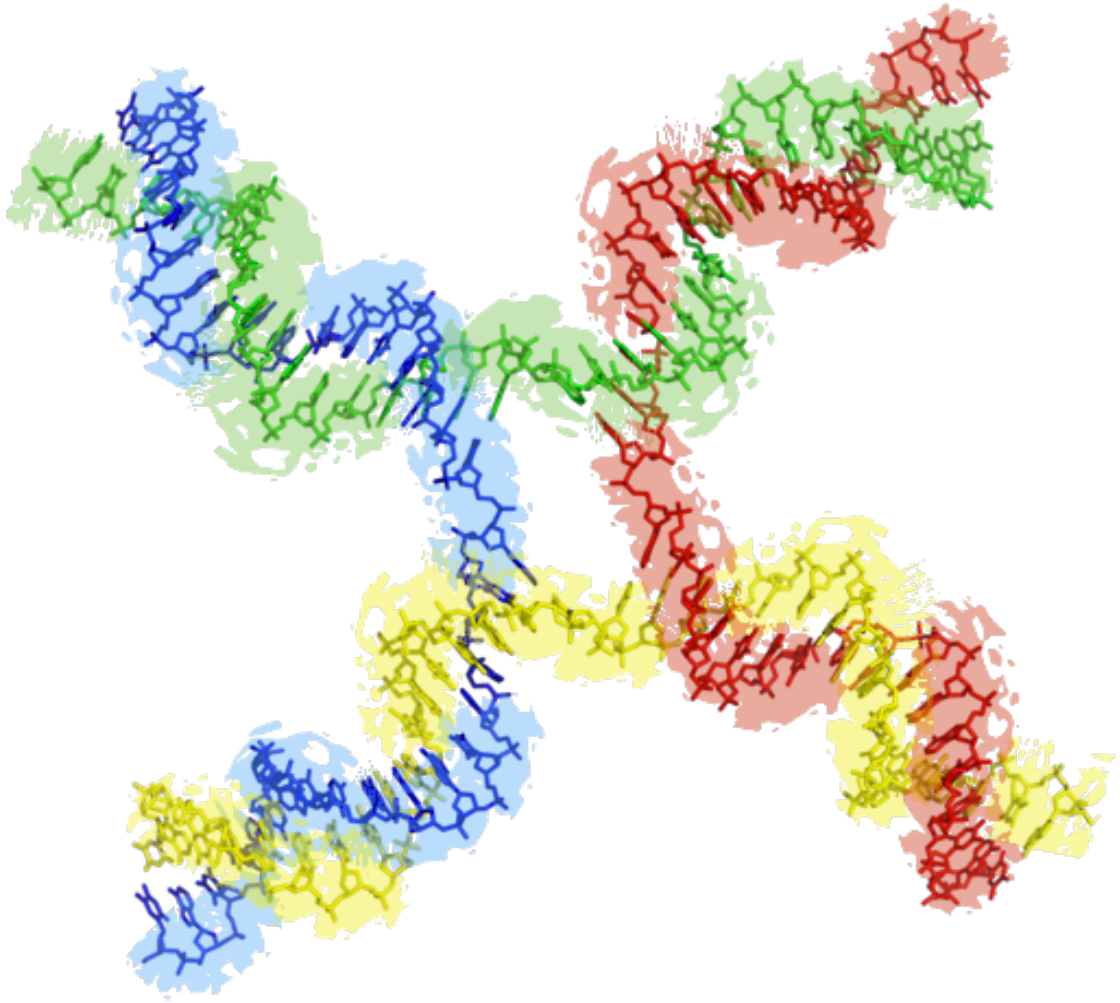
Programmable polymers

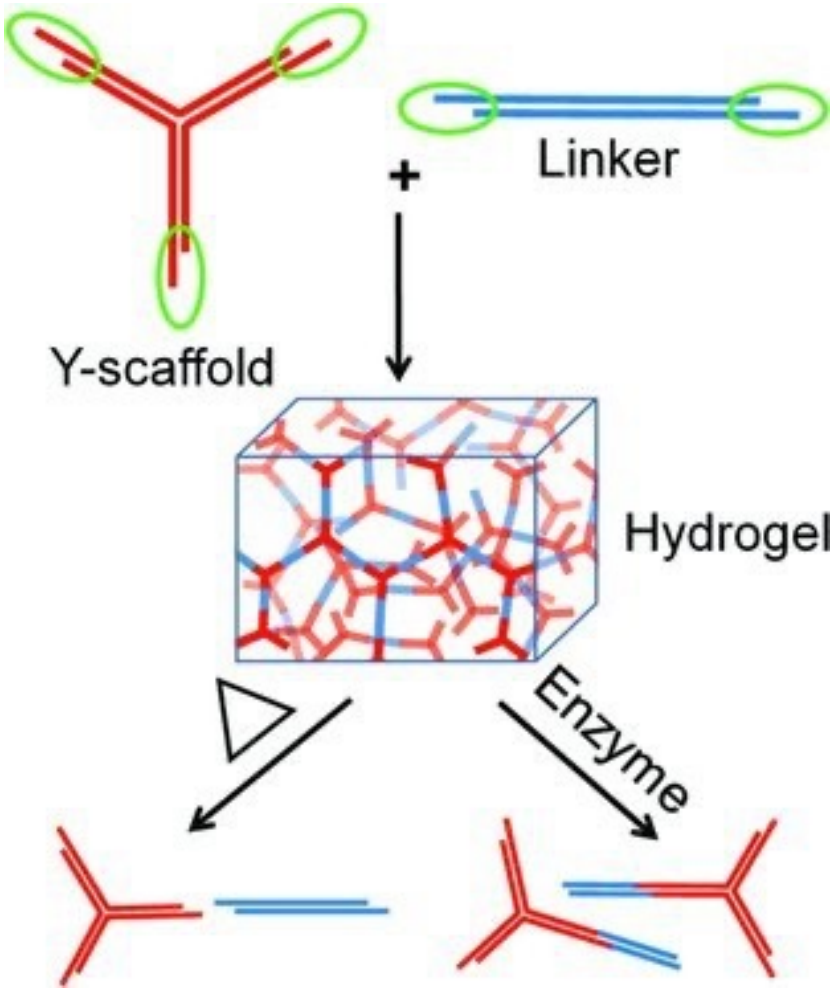




Reprogramming DNA interactions

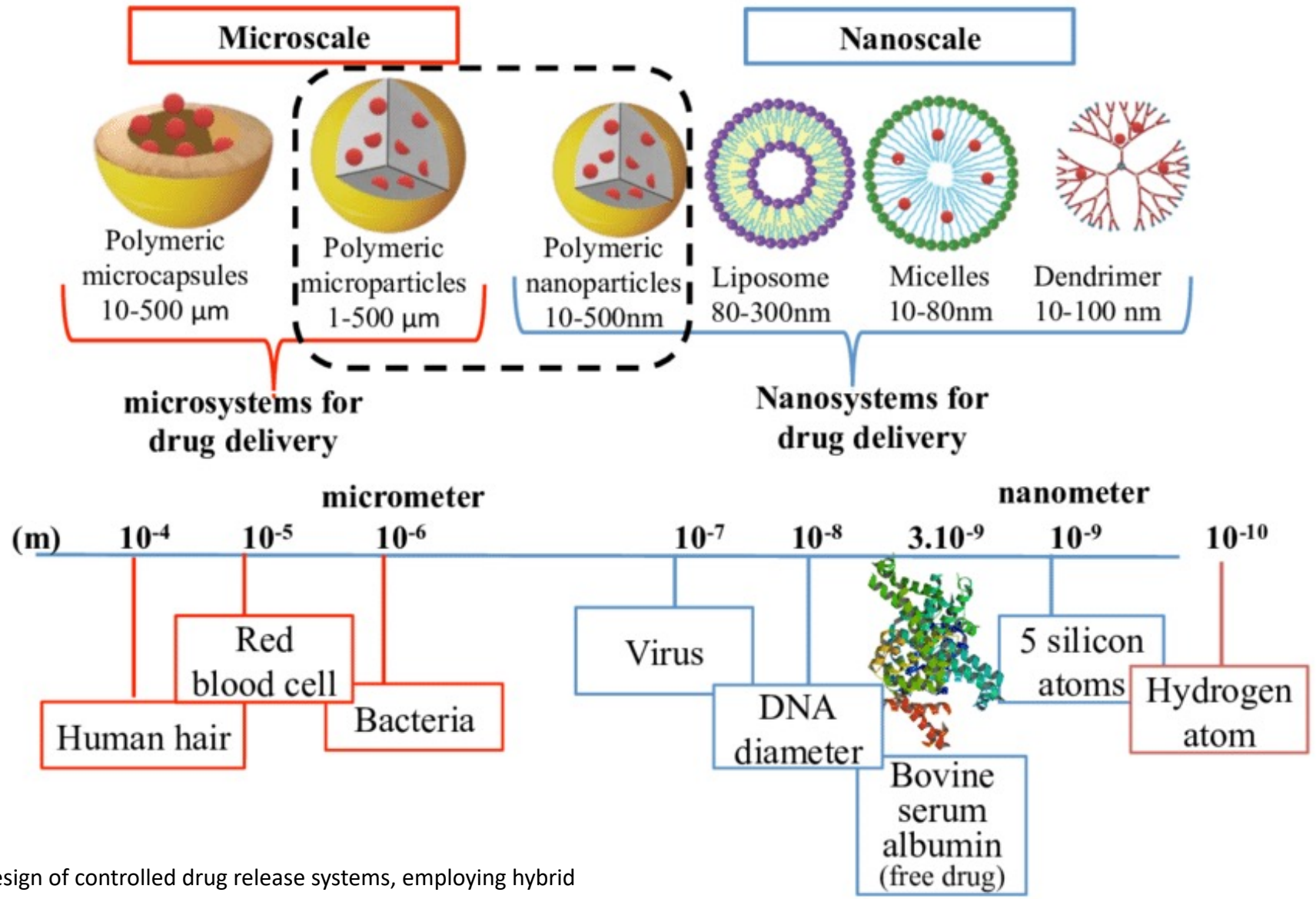
Short synthetic DNA strands can make new architectures!





Seeman, N (1982). "Nucleic acid junctions and lattices". *J. of Theor. Biol*. **99** (2): 237–47

Nanoparticles vs Microparticles



Novel approaches for effective design of controlled drug release systems, employing hybrid semi-parametric mathematical systems-

Nanoparticles: Overview

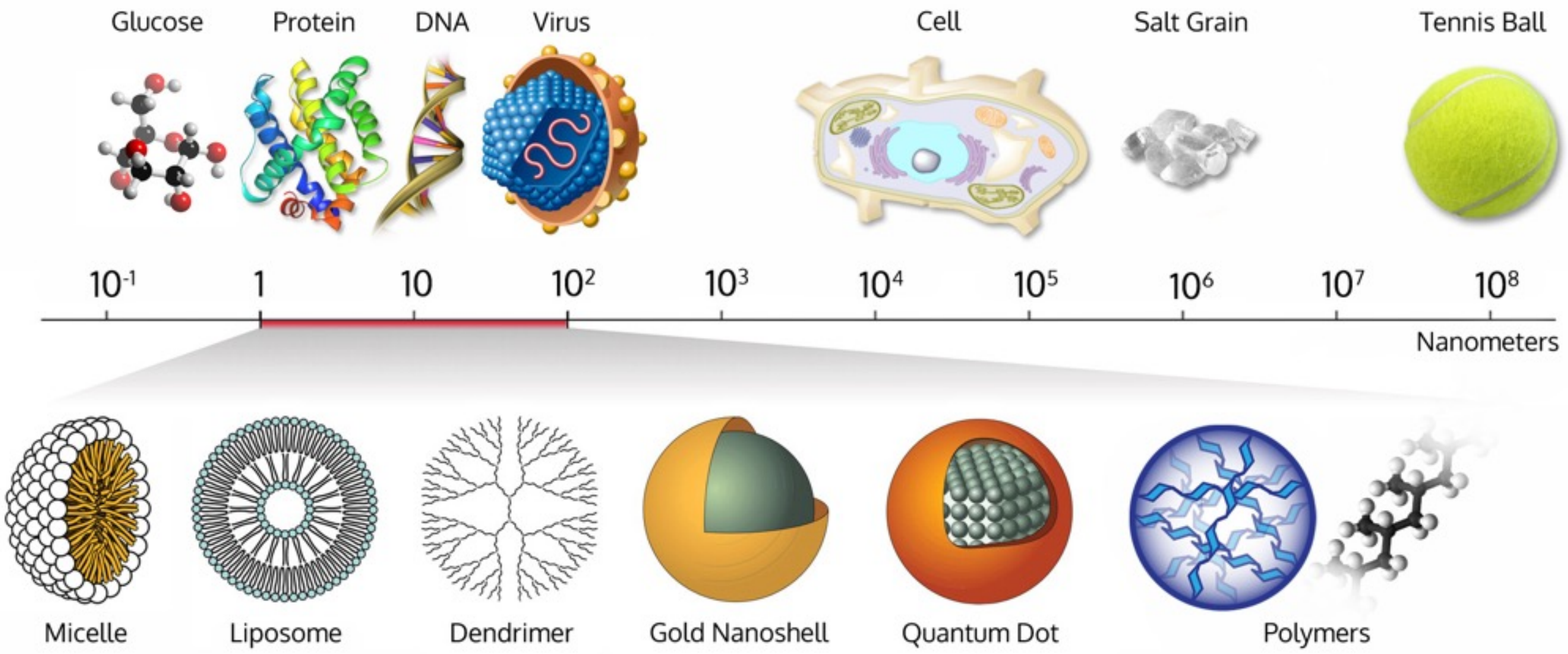
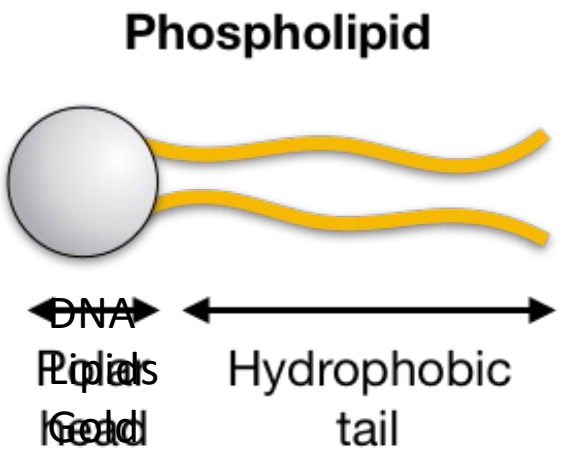
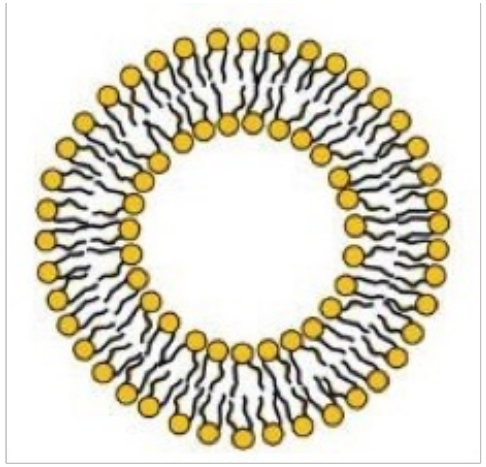


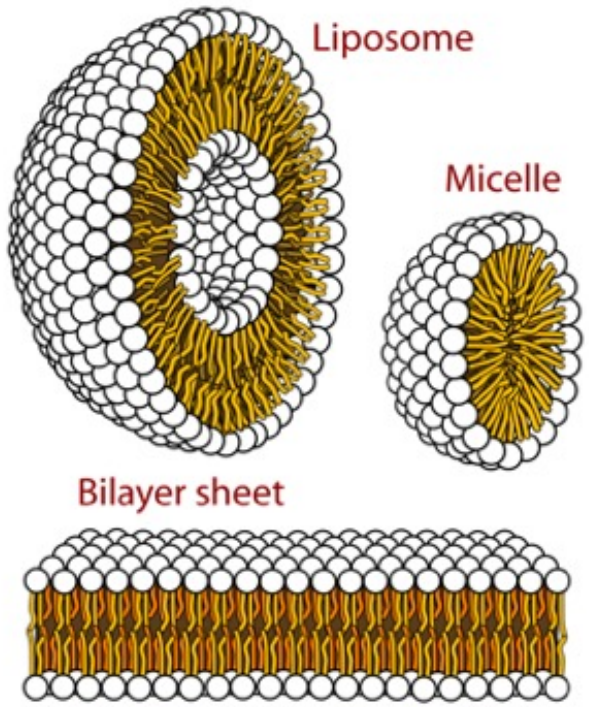
image: http://www.wichlab.com/research/

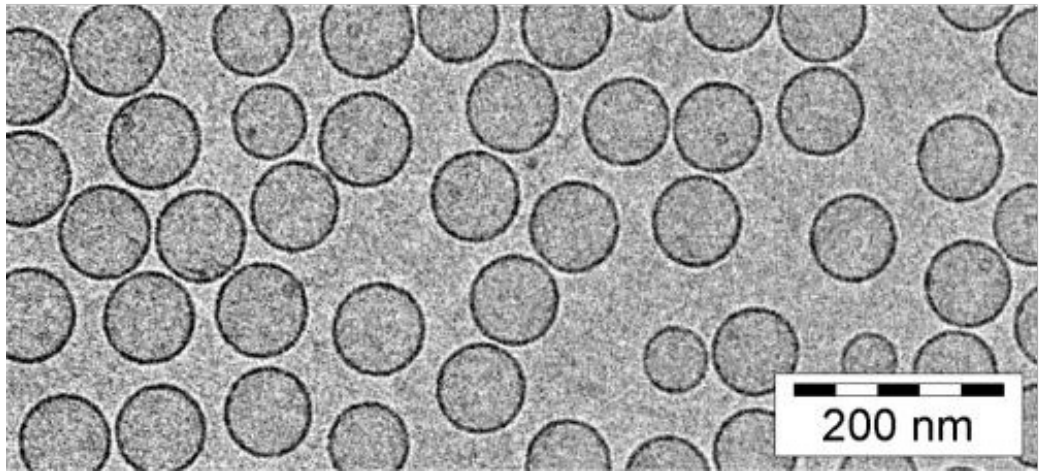
Nanoparticles: Lipid Based

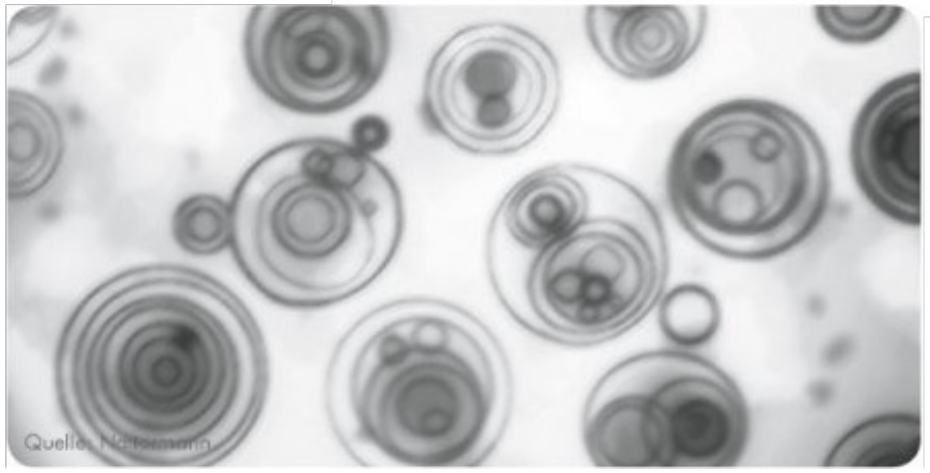




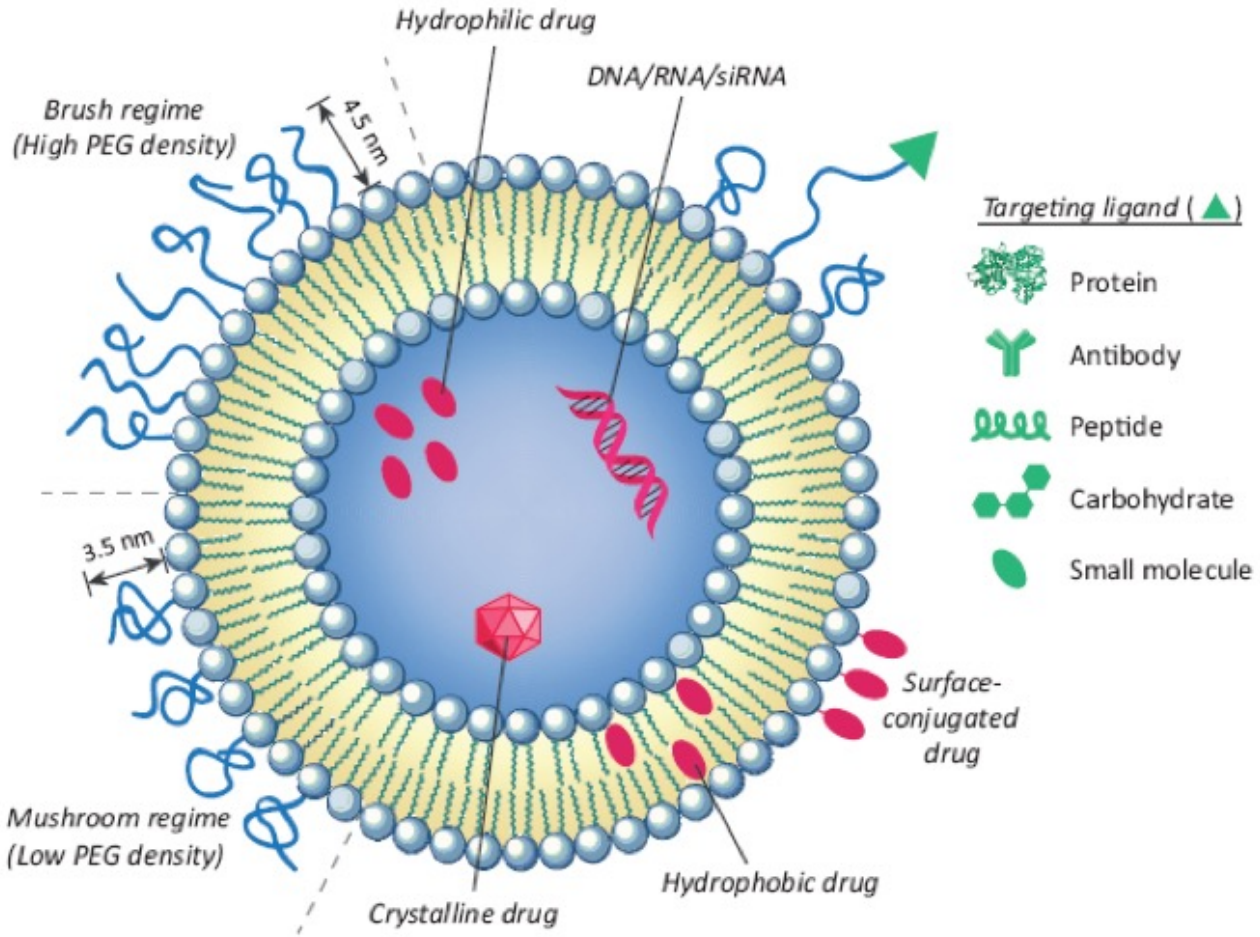
Liposome
Sizes: 10 nm - submicrometer







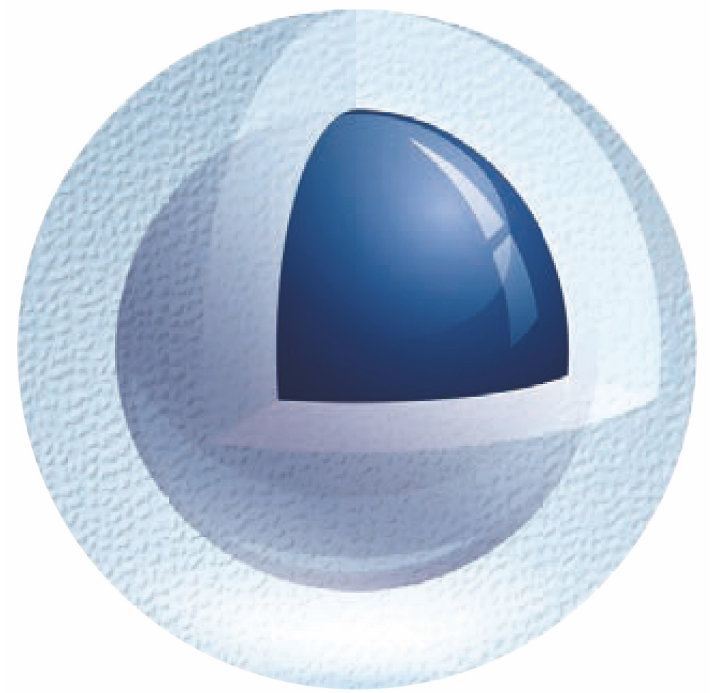
Nanoparticles: Lipid Based

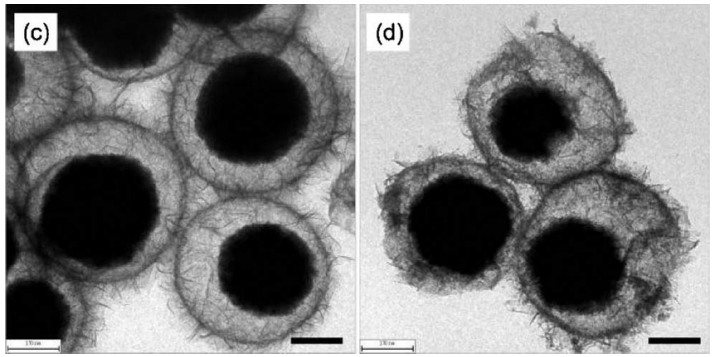


Mulder et al, NMR Biomed. 2006;19:142–164

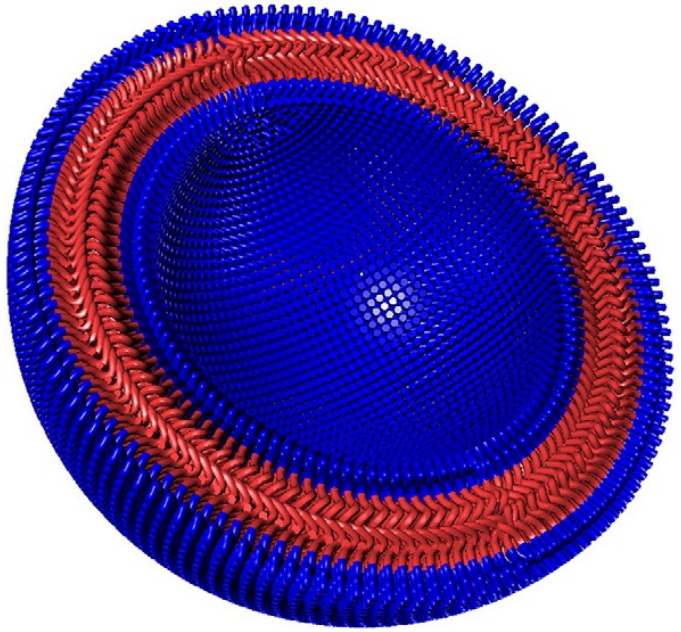
Microparticles - Overview

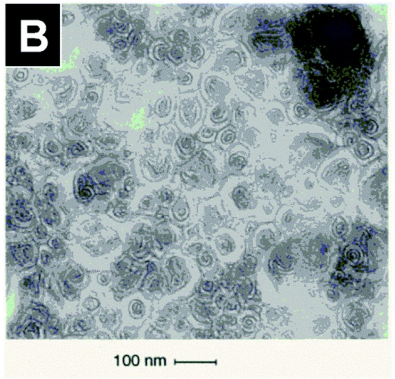
Core shell

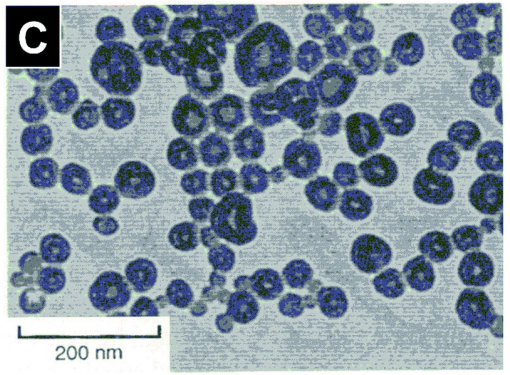




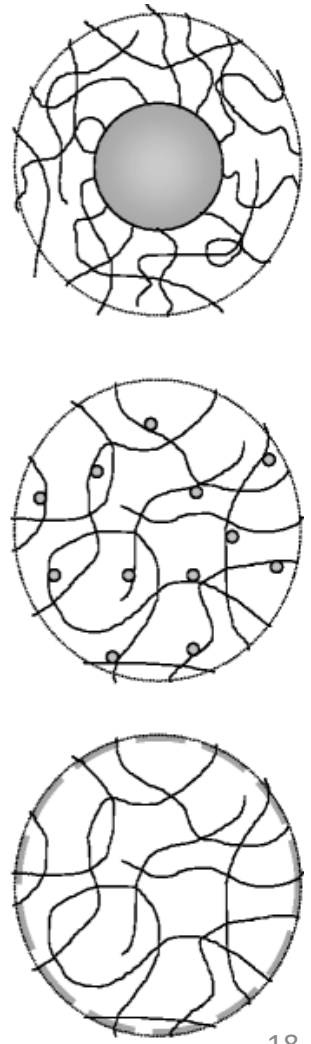
Polymersomes







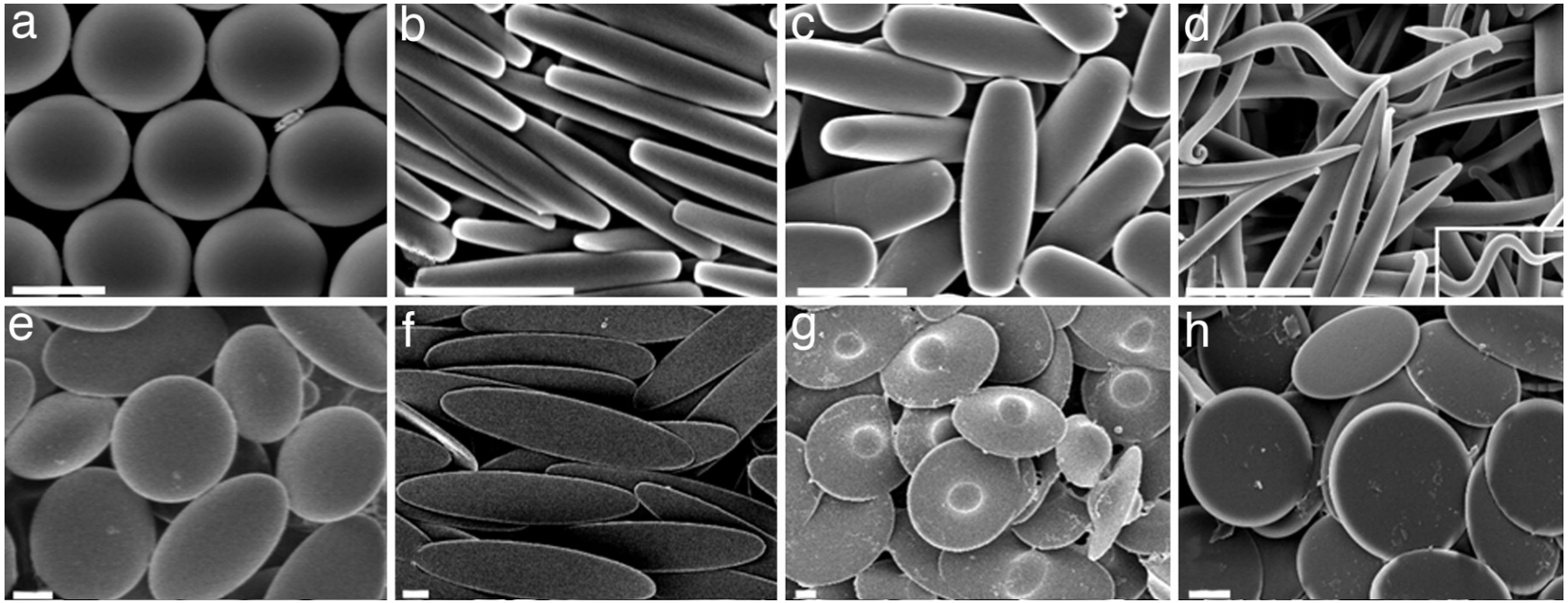
Microgels

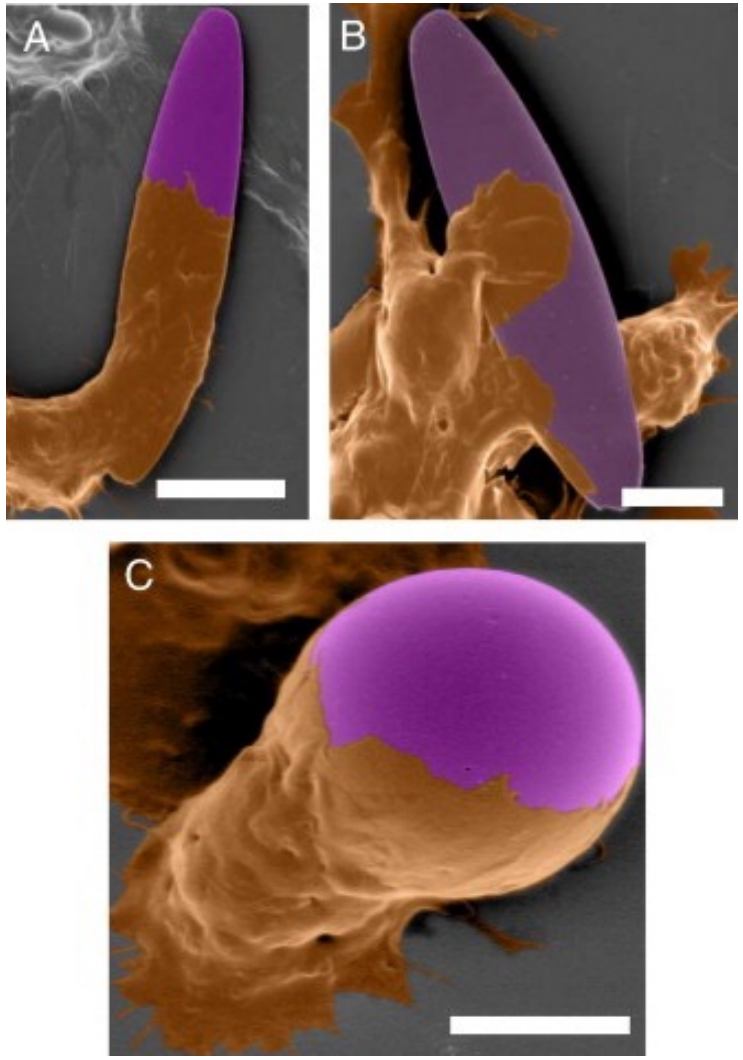


Microparticles – Effect of Shape

Functional behavior of polymeric particles in these fields is strongly influenced by their shape.

size from 100 nm to 30 um.

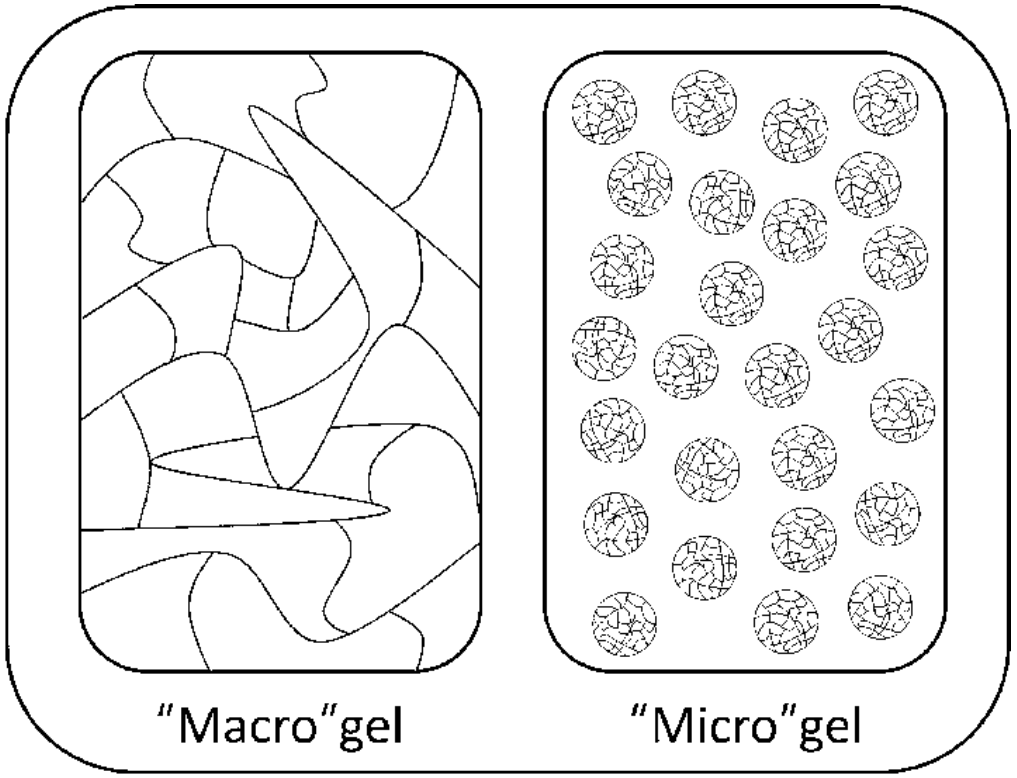




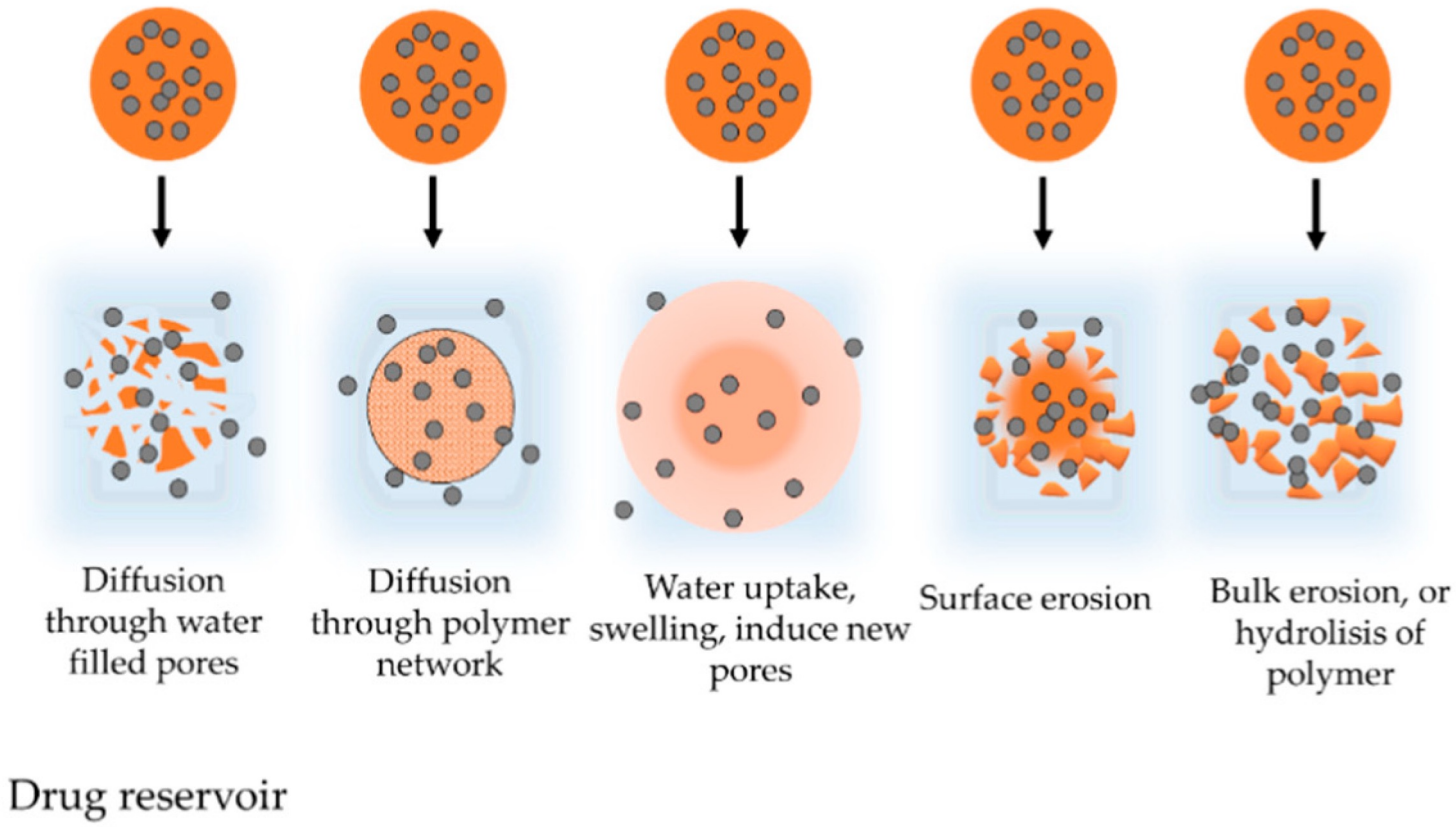
https://doi.org/10.1016/j.jconrel.2007.03.022 www.pnas.org/cgi/doi/10.1073/pnas.07053261041

Julie A. Champion, Samir Mitragotri

Microparticles – Microgels



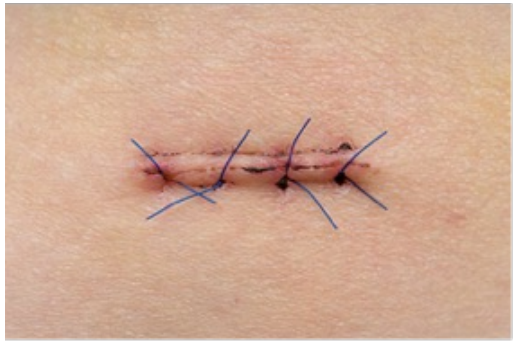
Small versions of a bulk hydrogel

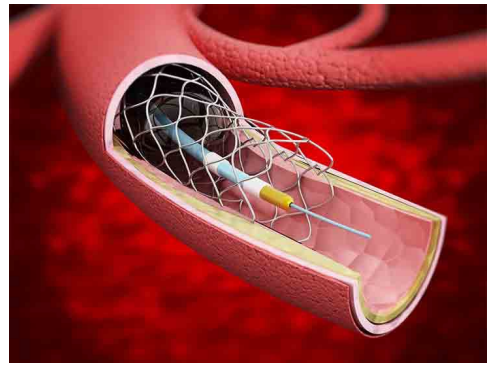


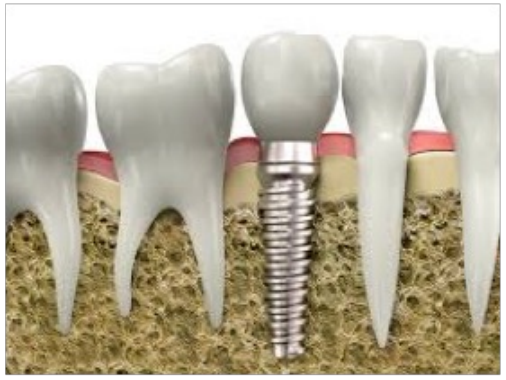
Sci. Pharm. **2019**, *87*(3), 20;
https://doi.org/10.3390/scipharm87030020

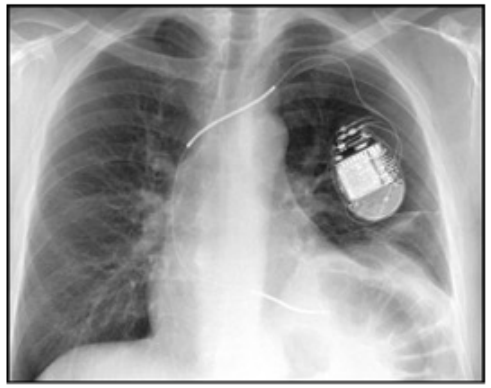
break

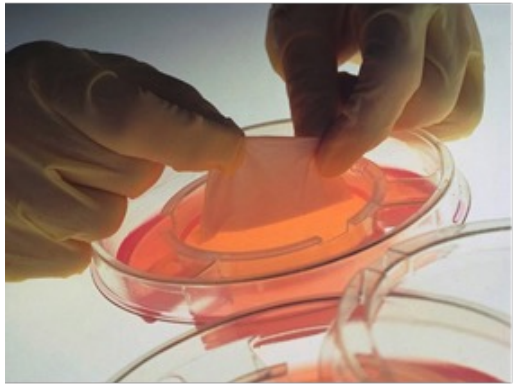
Surfaces are everywhere!

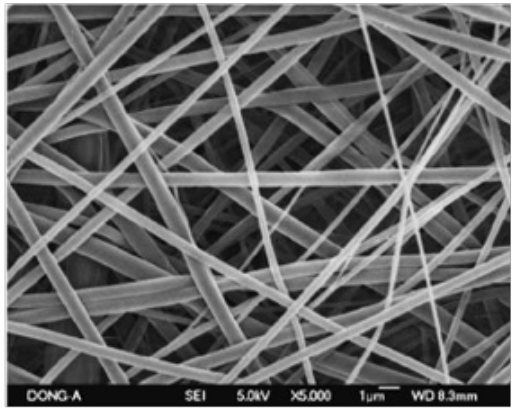












Time defines surface (and material!) robustness

Biomaterial use is time dependent!

Biocompatibility is the ability of a material

to ***perform with an appropriate host response***

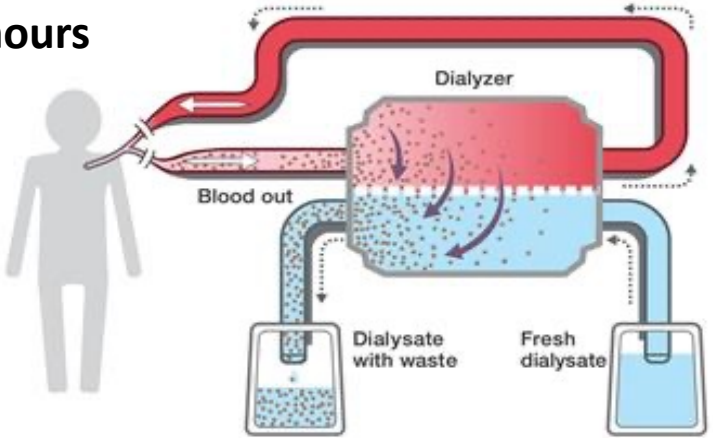
in a ***specific application during a certain time***

Physical / mechanical properties
- Strength
- (visco)-elasticity
- Pore size

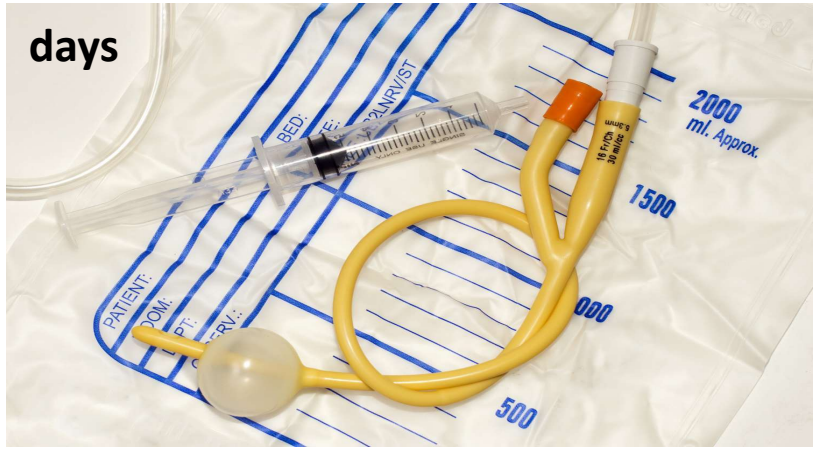
Chemical properties
- Degradability
- Toxicity
- Water content

Biological properties
- Cell adhesion
- Release of active components

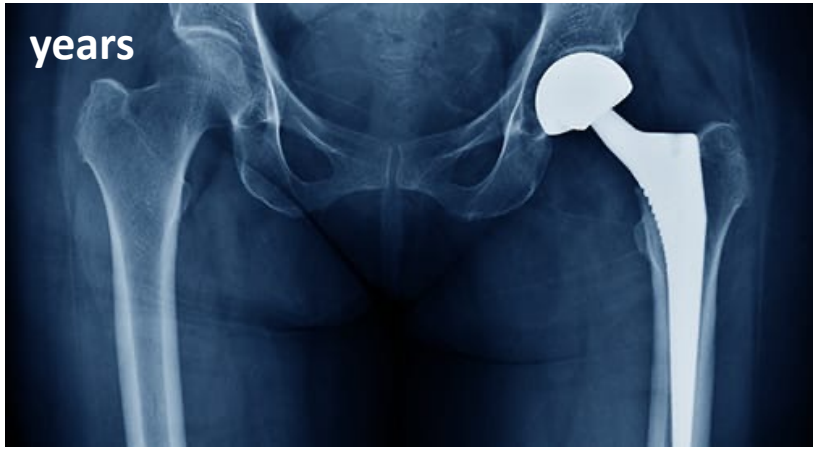
hours



days



years



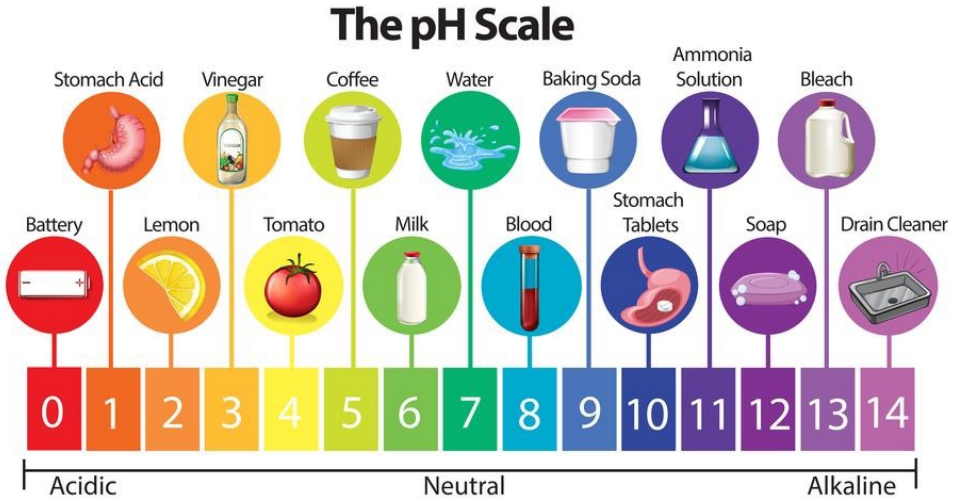
SURFACES

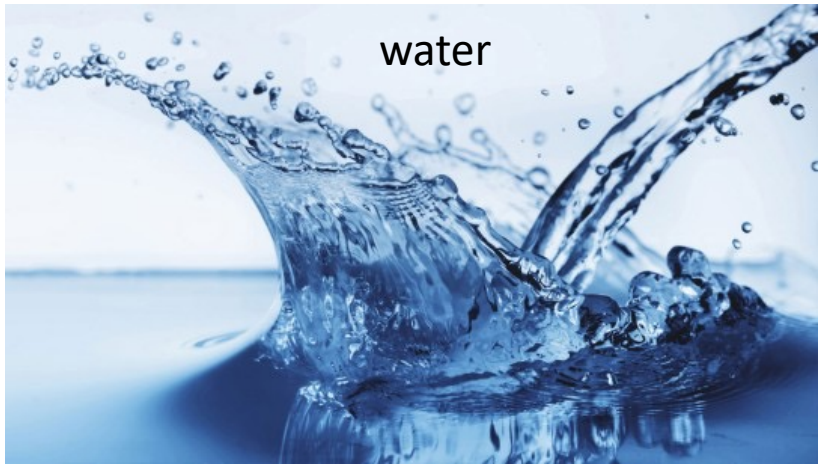
What challenges do biomaterial surfaces face?

SURFACES

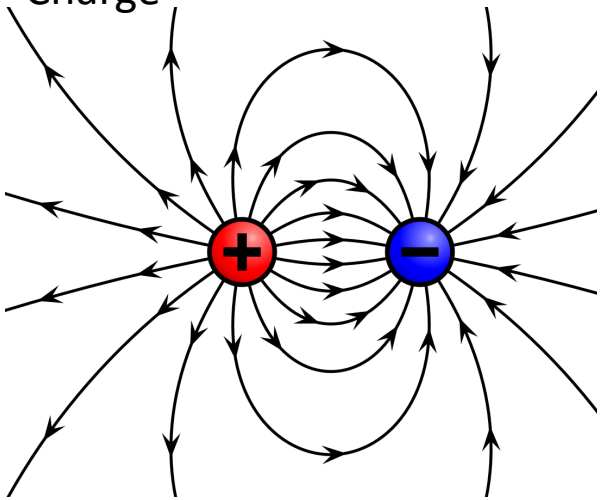
What challenges do biomaterial surfaces face?

UV

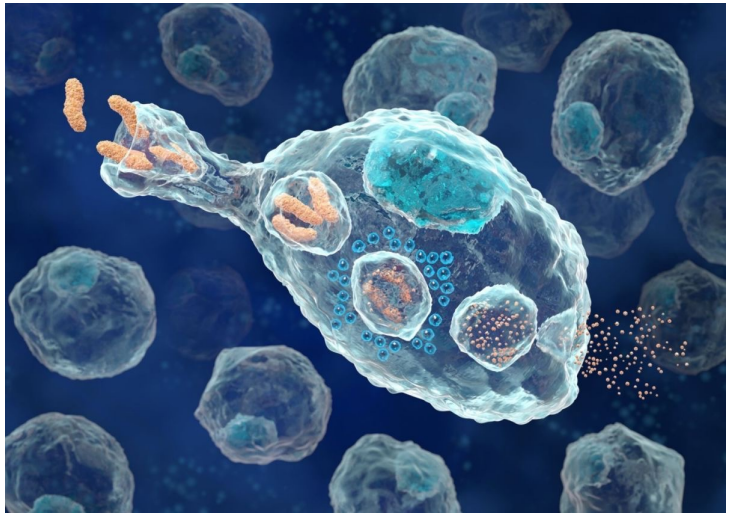




Charge

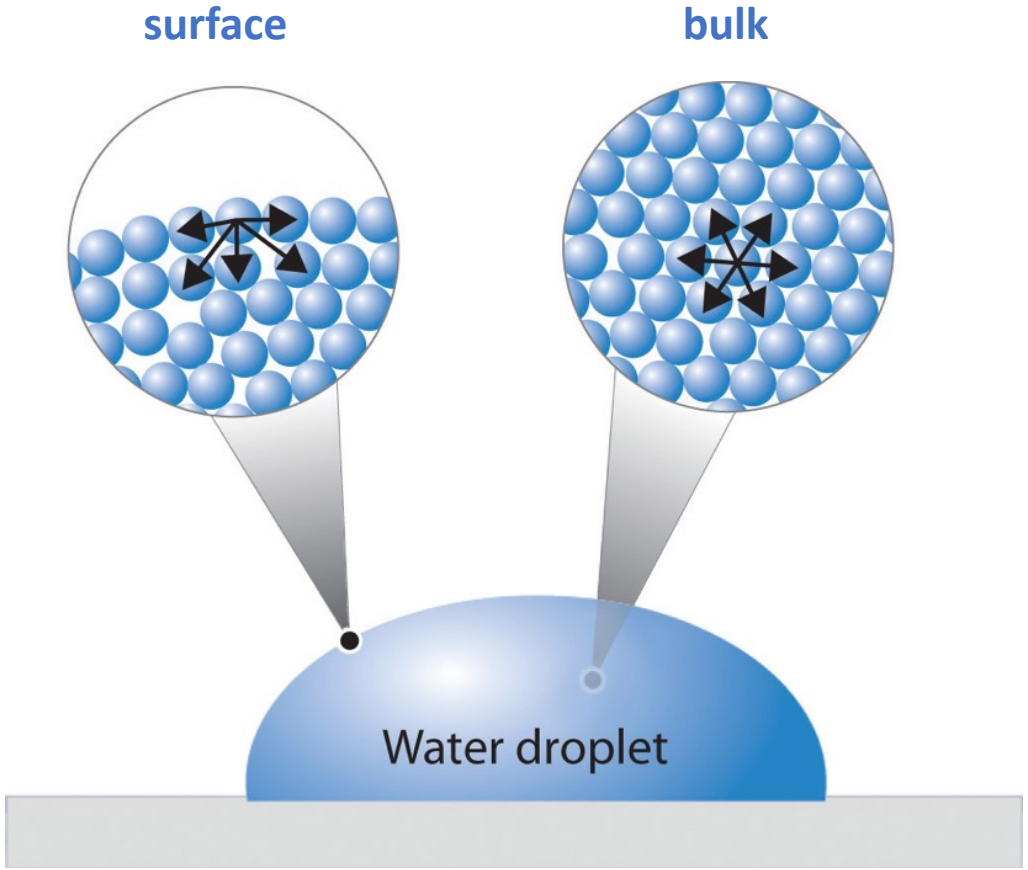


Immune cells



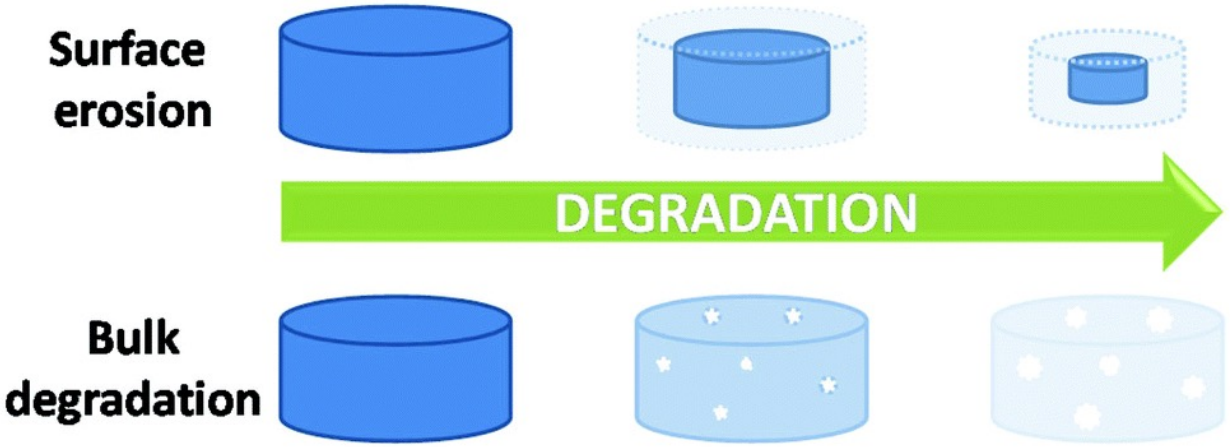
Challenges and Characteristics

1. Surfaces have unique **reactivity** (—> catalysis)
2. The surface is inevitably different than the bulk
3. The mass that makes up the surface is very small
4. Surfaces easily **contaminate**
5. Surface molecules can exhibit considerable **mobility**



Example:

Why is erosion vs degradation an important engineering parameter?

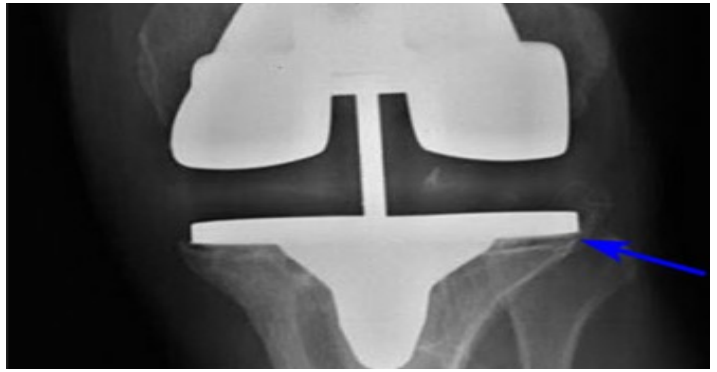


quantum physicist Wolfgang Pauli used to say:
'God made solids, but surfaces were the work of devil'.

Location is important:

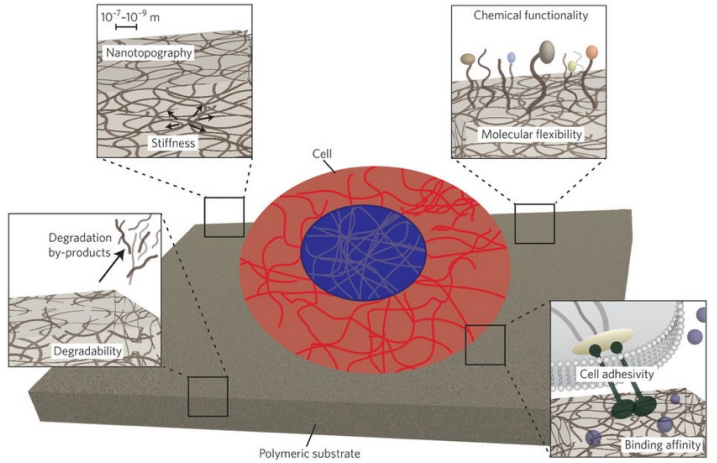
Biomaterials inside the body
main role: replacement of specific tissue

main problems: immune system, uncontrolled protein adhesion, foreign body response, corrosion, mechanical failure

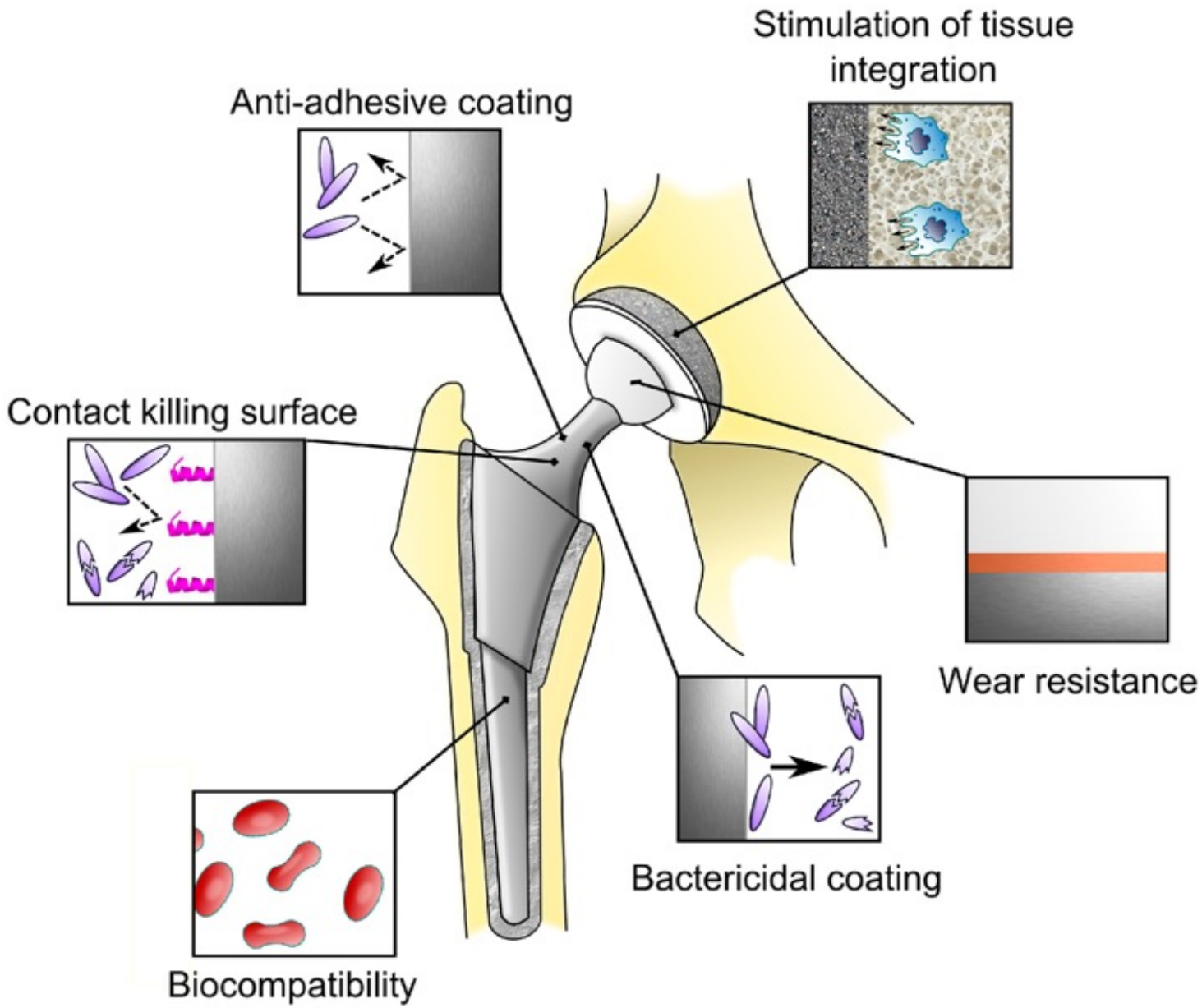


Biomaterials outside the body
main role: guiding of new tissue formation

main problem: contaminations, UV, temperature, dust



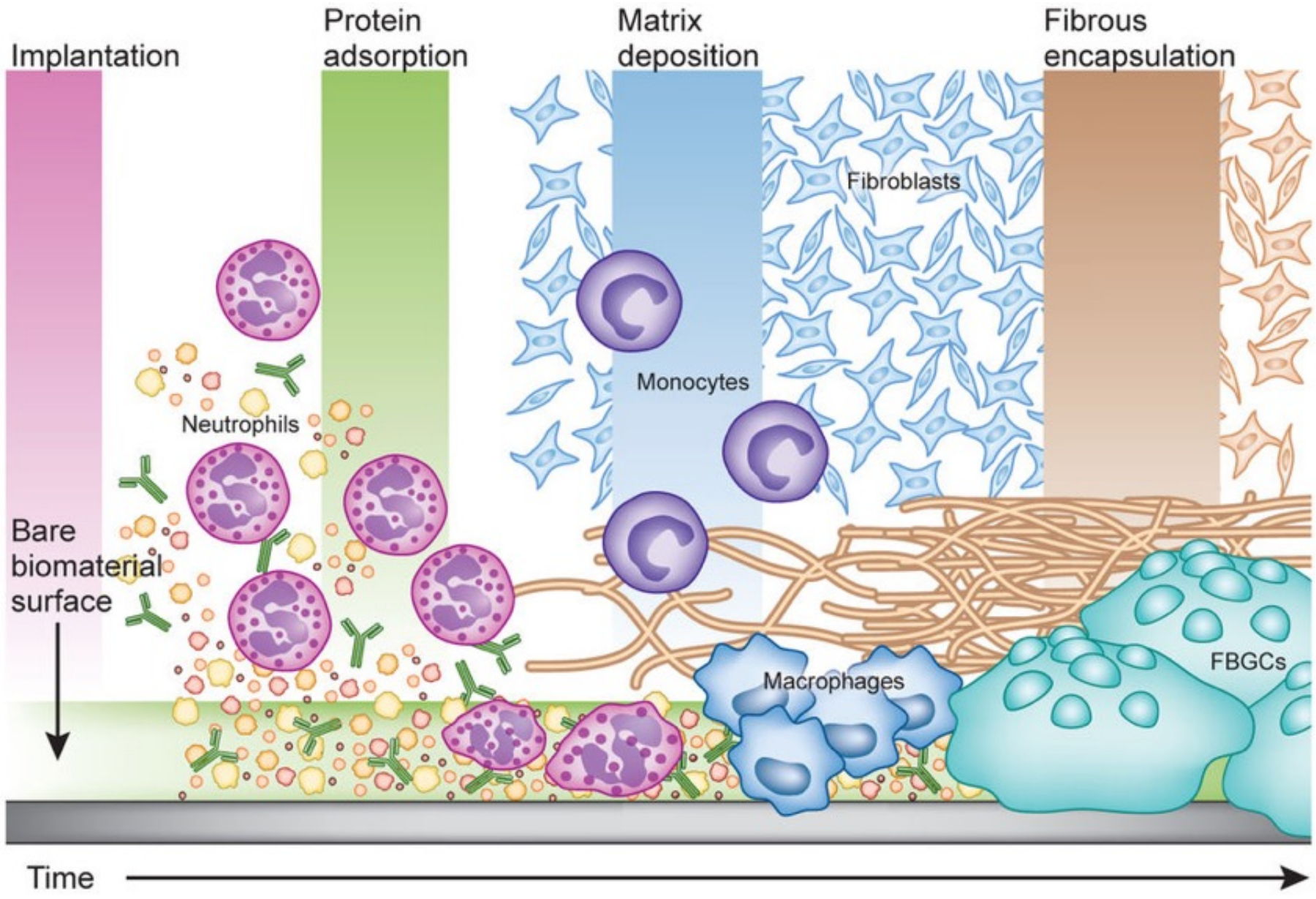
Surfaces inside the body



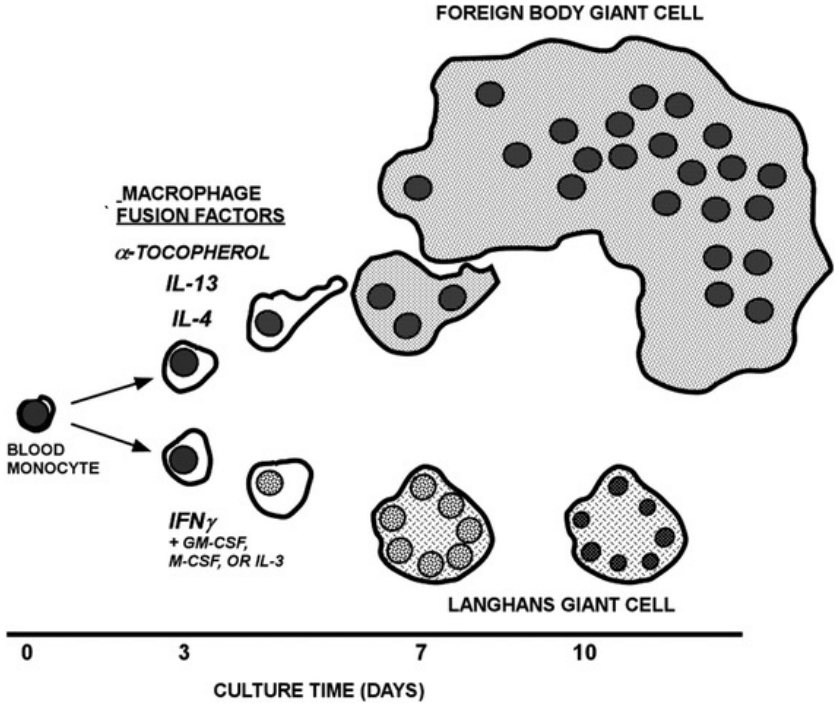
Foreign Body Response

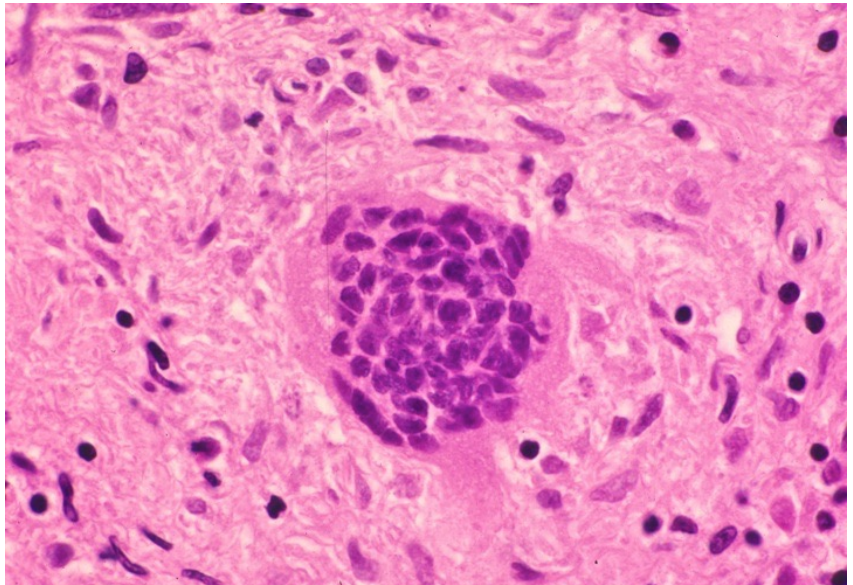
Proteins:

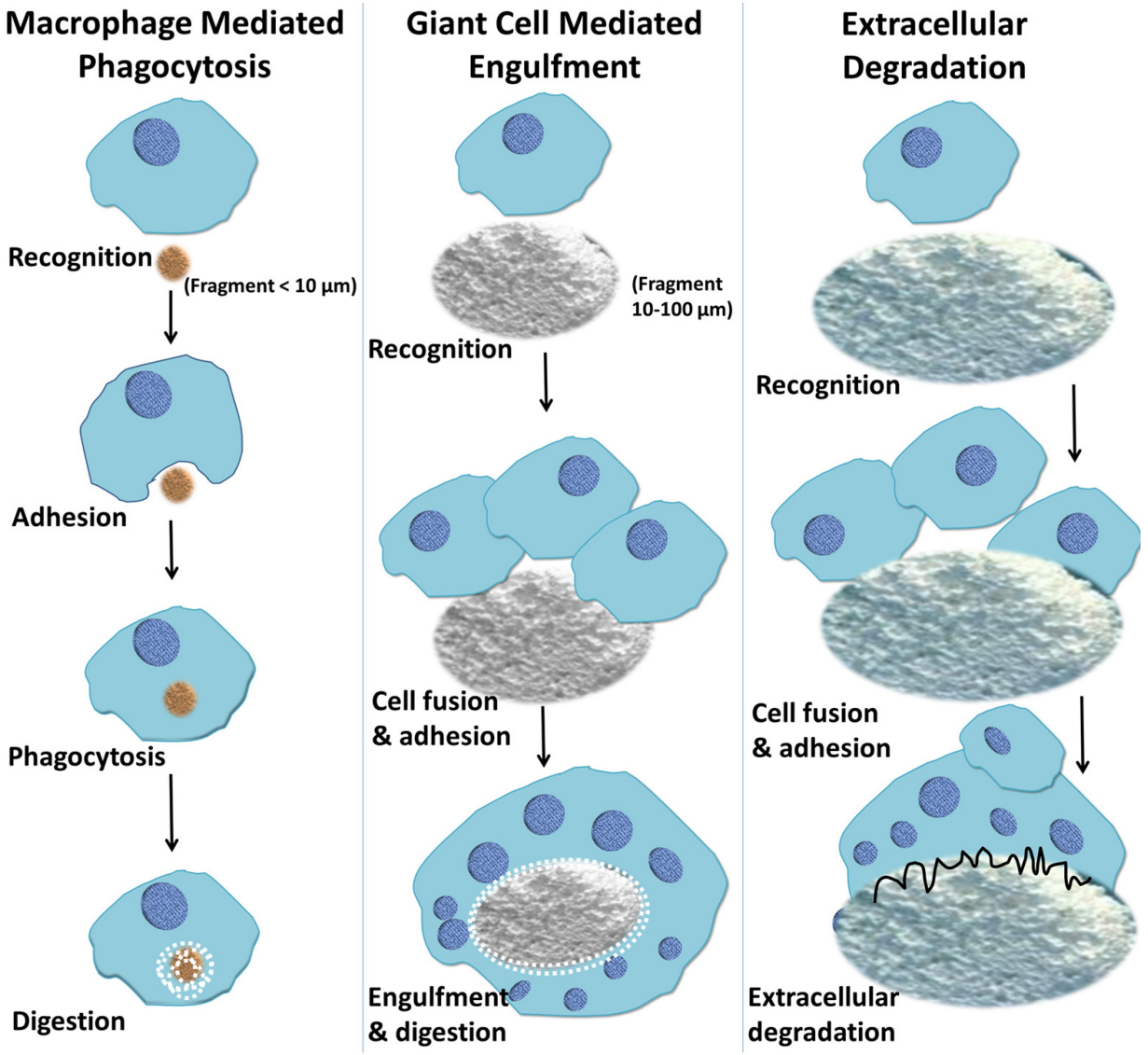
- Modulate cell adhesion
- **Trigger the biological cascade resulting in foreign body response**
- Central to diagnostic assays /sensor device design
- Initiate other bioadhesion: e.g., marine fouling, bacterial adhesion



Fibrous encapsulation - FBGC

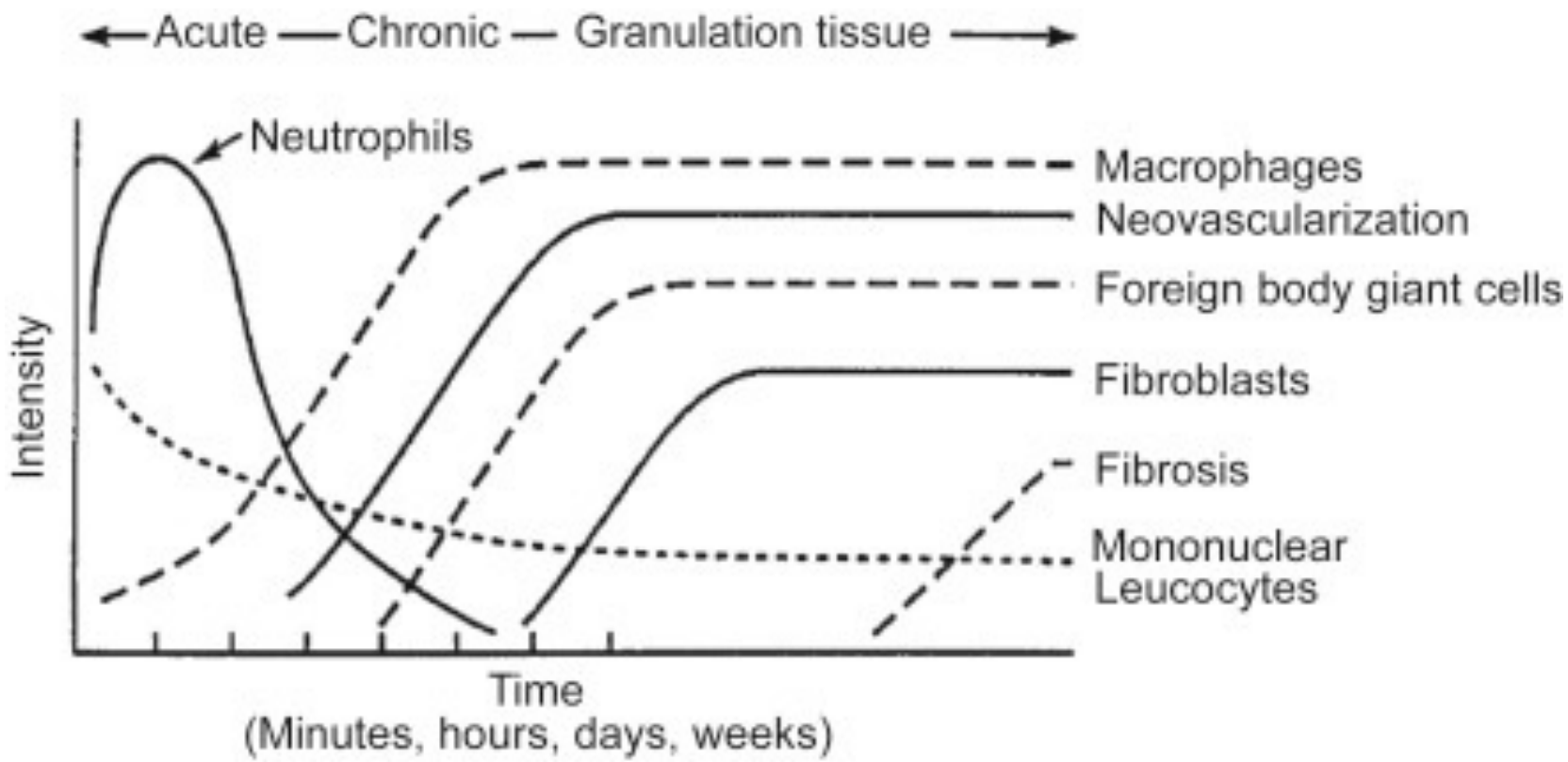






Materials 2015, 8, 5671-5701; doi:10.3390/ma8095269

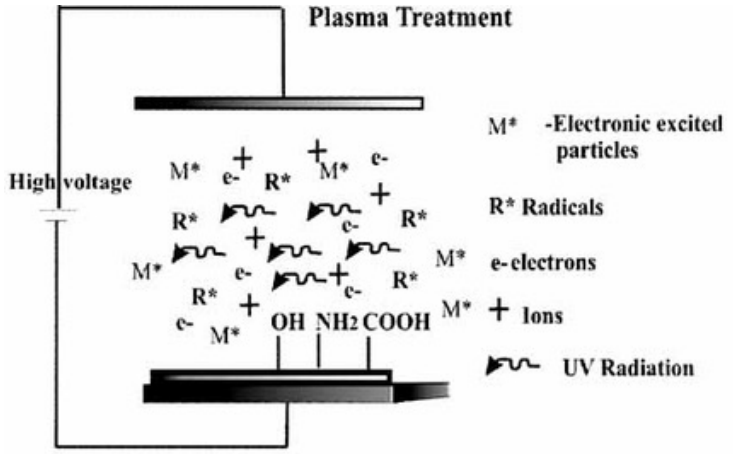
Implications of Time



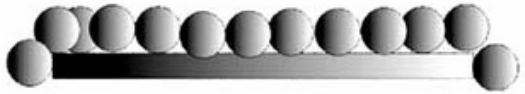
Surface Modifications and Characterization

Why?

1. Clean a surface
2. Reduce/eliminate protein adsorption
3. Reduce/eliminate cell adhesion
4. Reduce bacterial adhesion
5. Reduce thrombogenicity
6. Promote cell attachment/adhesion
7. Alter transport properties
8. Increase lubricity
9. Increase hardness
10. Enhance corrosion/degradation resistance

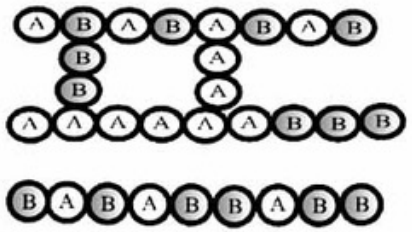


High energy radiation



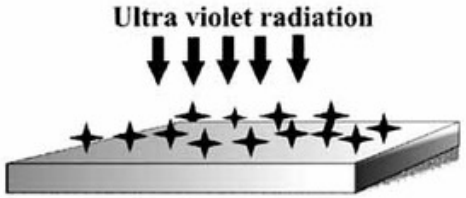
Polymer coating

Chemical modification



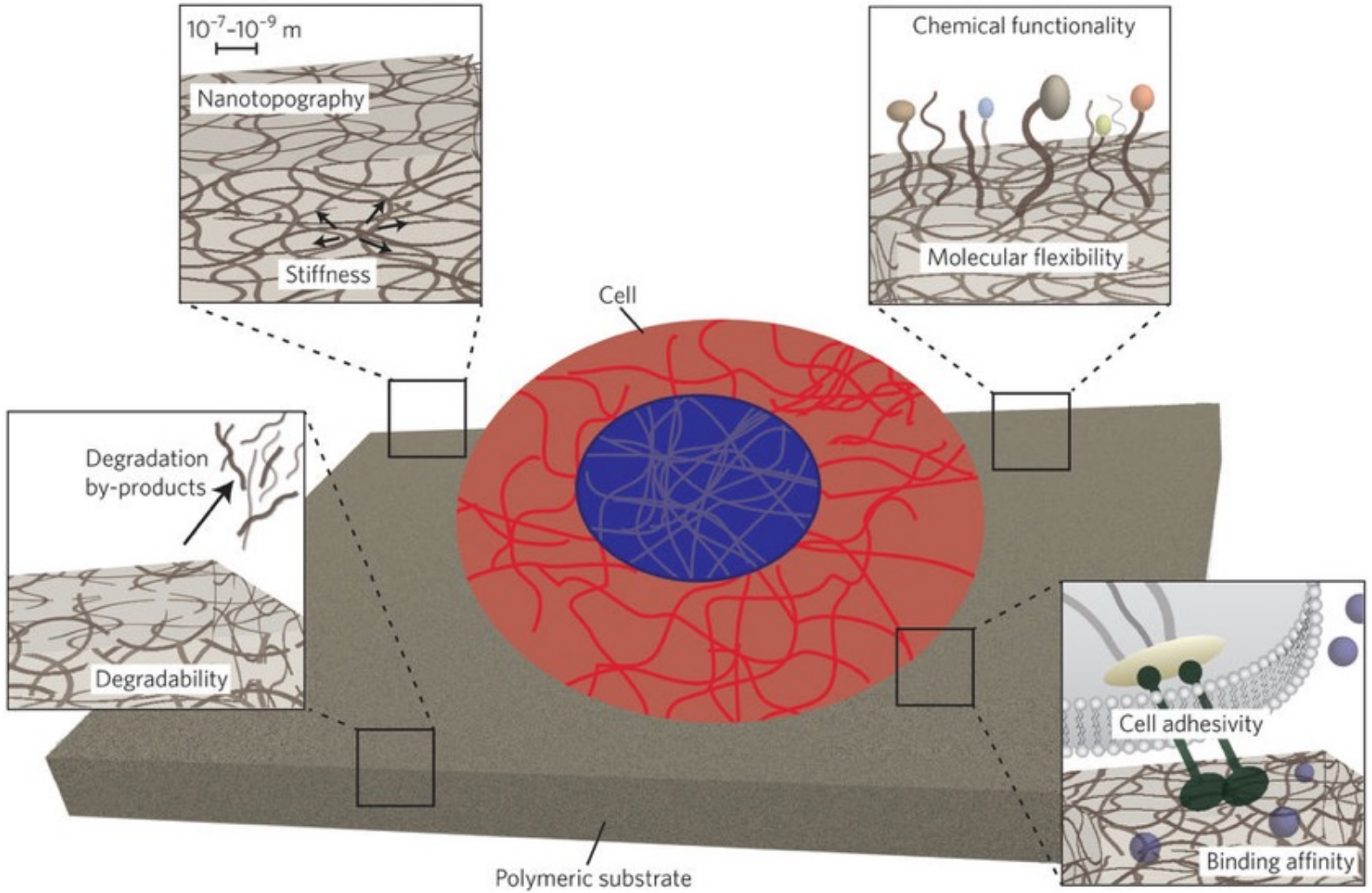
Polymer composite /blend

Incorporation of ECM proteins

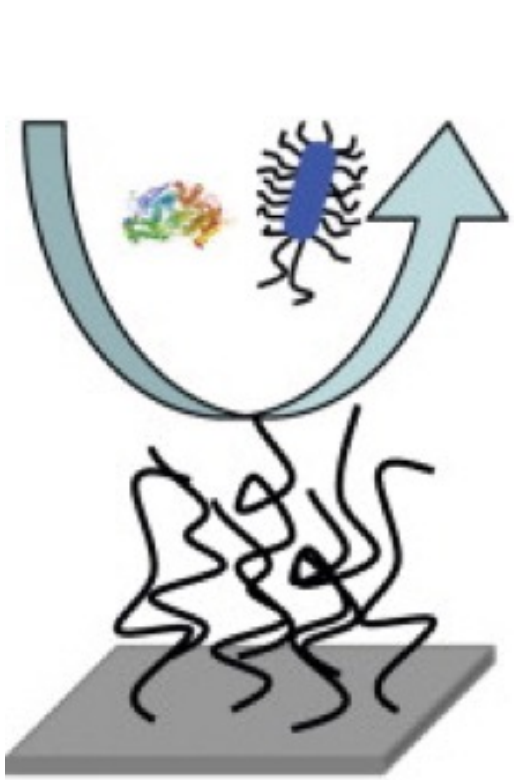


Photochemical modifications

Surfaces outside the body

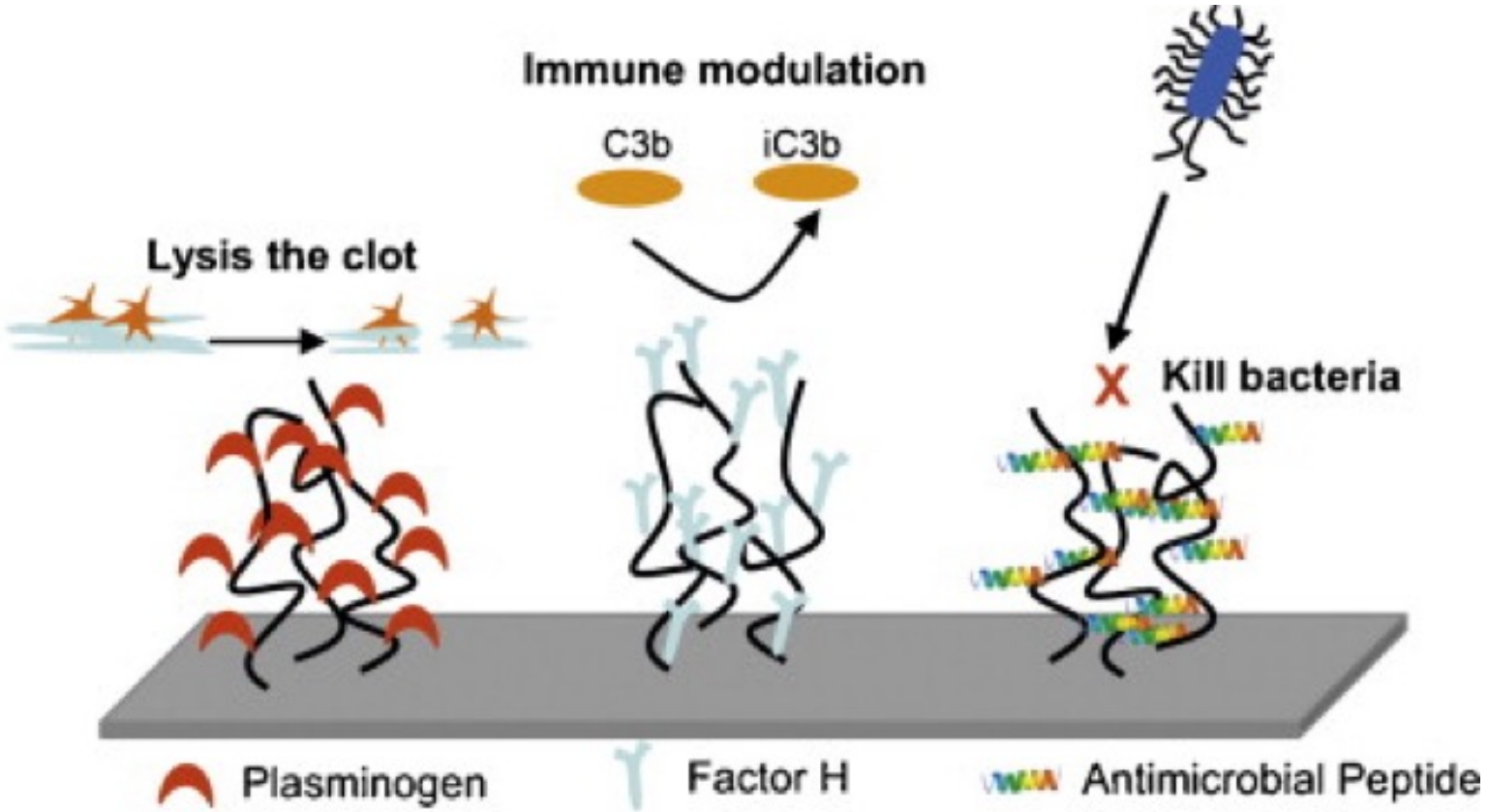


Passive versus Active Surfaces



Passive surface

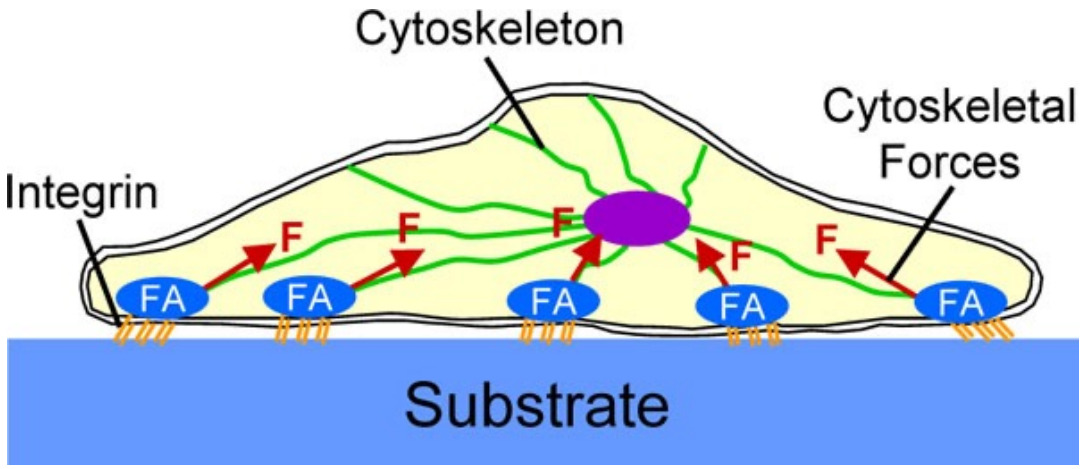
Anti fouling

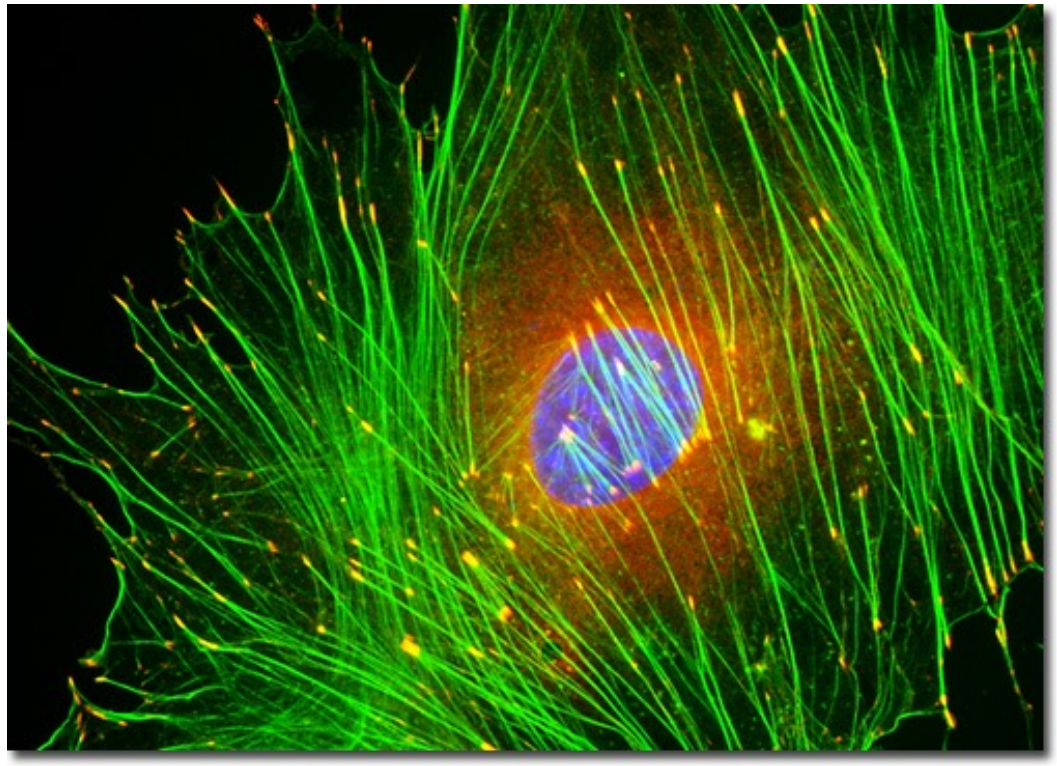


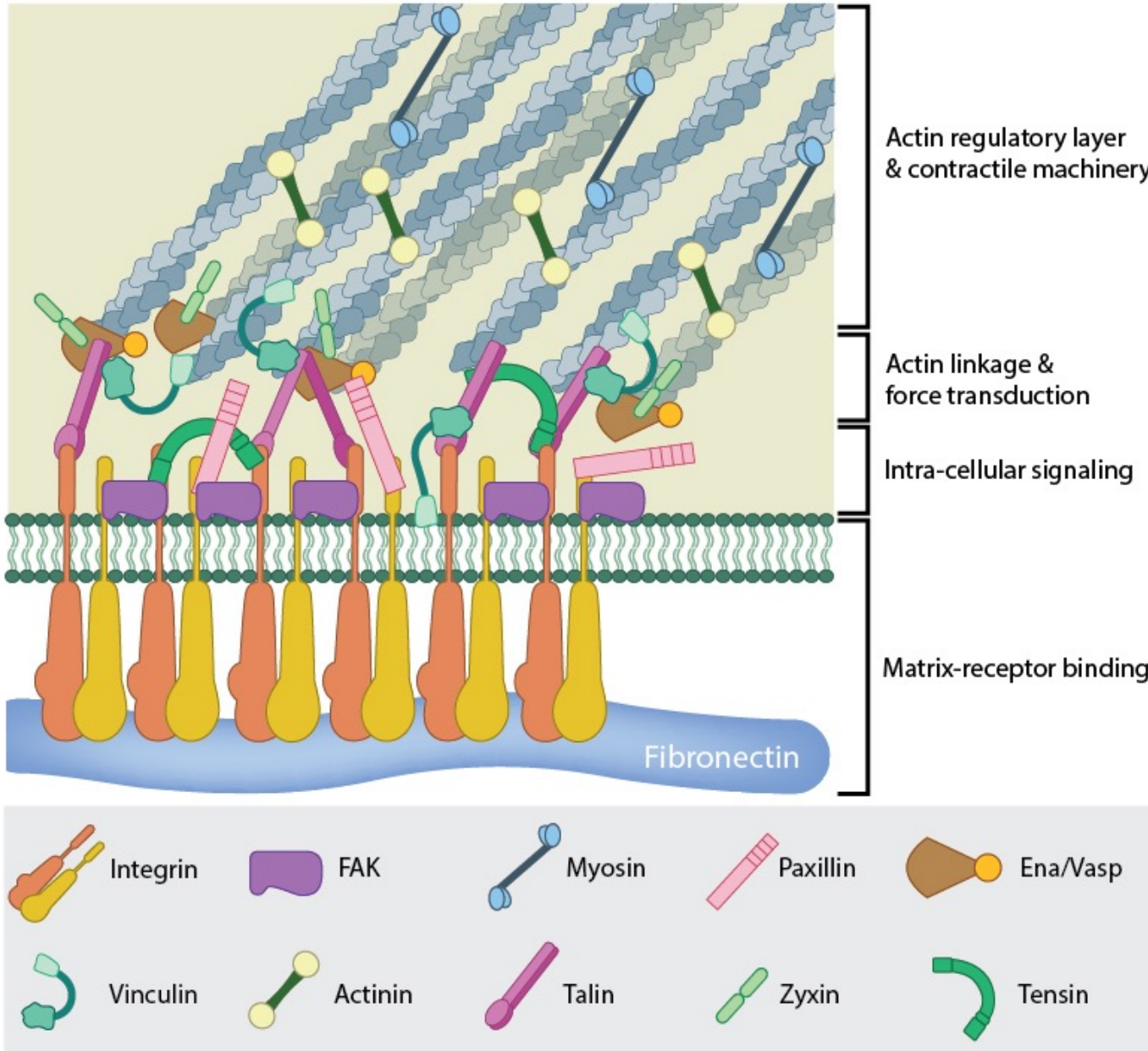
Bioactive surface

Controlled interactions

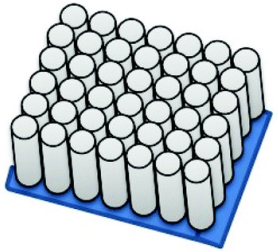
Cell adhesion: Focal Adhesions



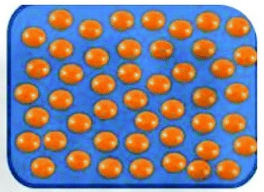




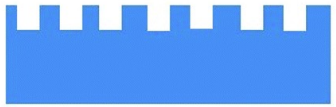
Nanotopology



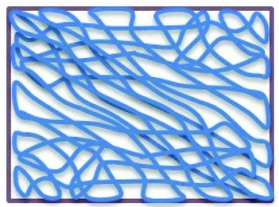
Nanotubes
(Anodization)



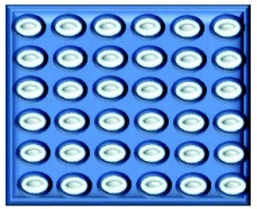
Nanocolloids
(Colloidal Lithography)



Nanopits
(Replica Moulding,
Electron Beam
Lithography,
Nanoimprinting)

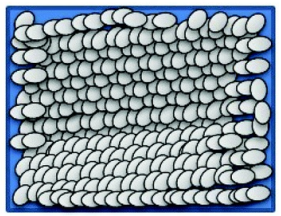


Nanofibers
(Electrospinning)

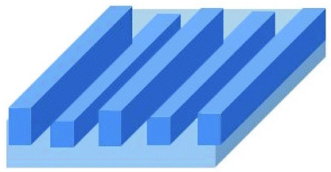


Nanodots
(Phase Separation,
Electron Beam
Lithography)

Nanopillars
(Replica Moulding,
Anodization, Colloidal
Lithography)



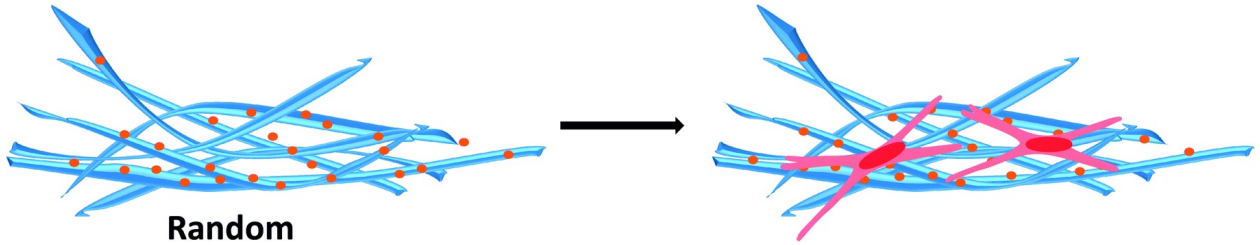
Random Roughness
(Reactive Ion Etching)



Nanogrooves
(Electron Beam Lithography,
Nanoimprinting, Replica
Moulding)

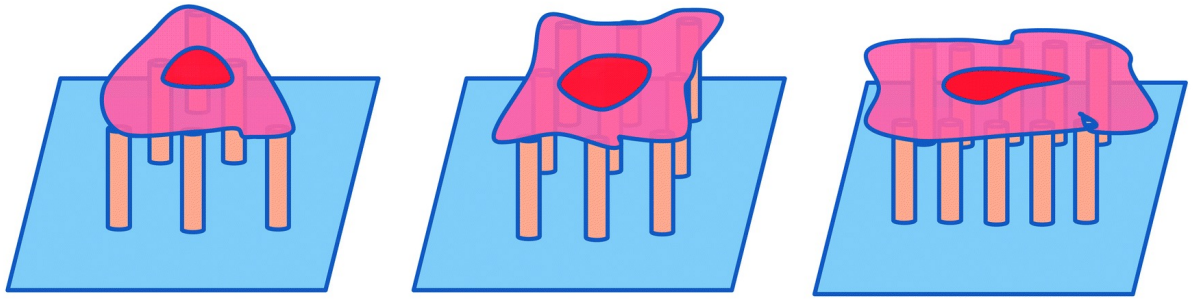
(a) Stem cell interaction with nano-structure scaffolds

Oriented



Random

(b) Nanopatterned surface to mediate stem cell



Triangle

Square

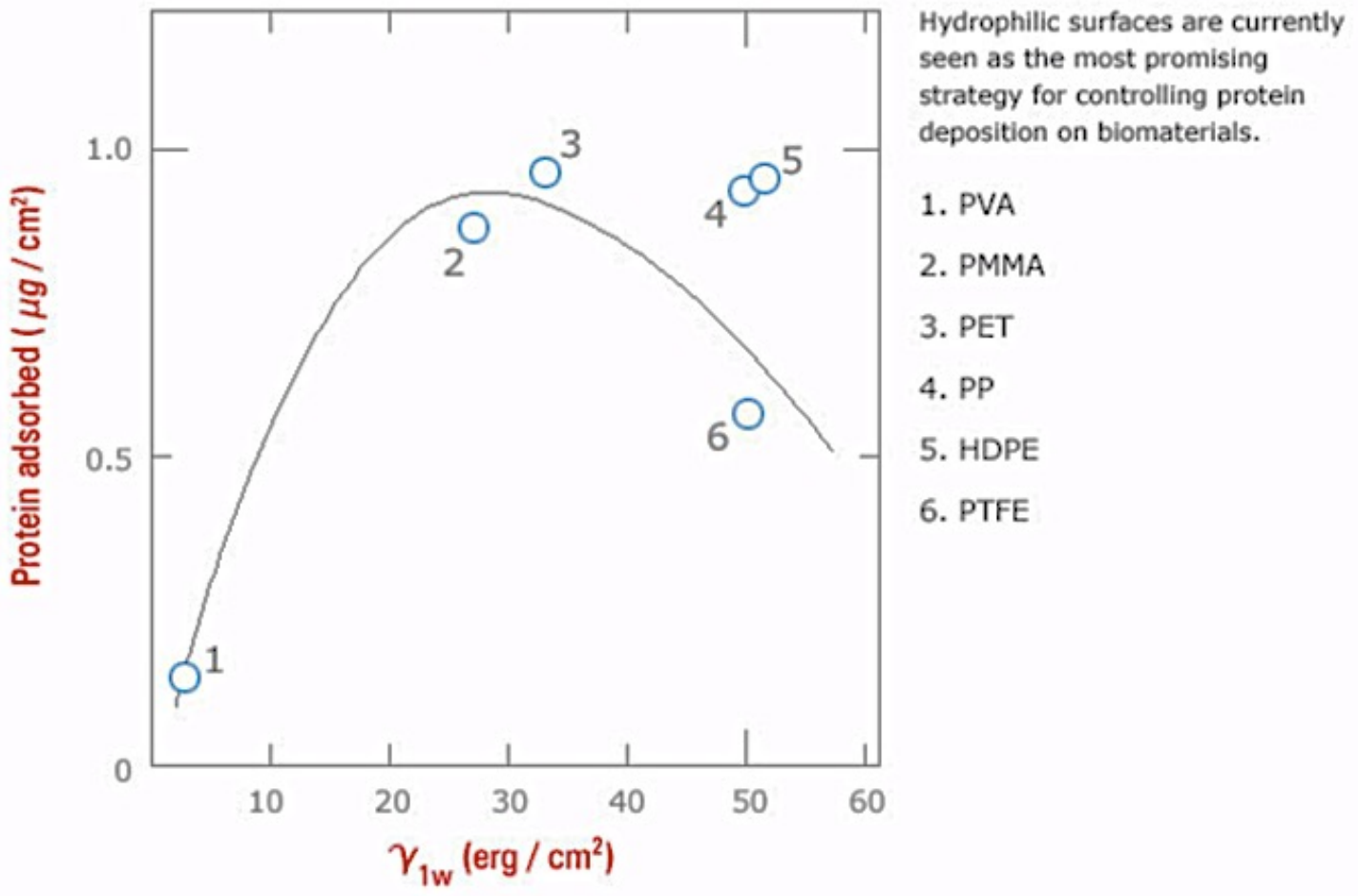
Rectangle

Nanoscale, 2017, **9**, 18129-18152

RSC Adv., 2018, **8**, 17656-17676

Preparation of non-fouling surfaces

to prevent non-specific protein/cell or bacterial adhesion to reduce thrombogenicity



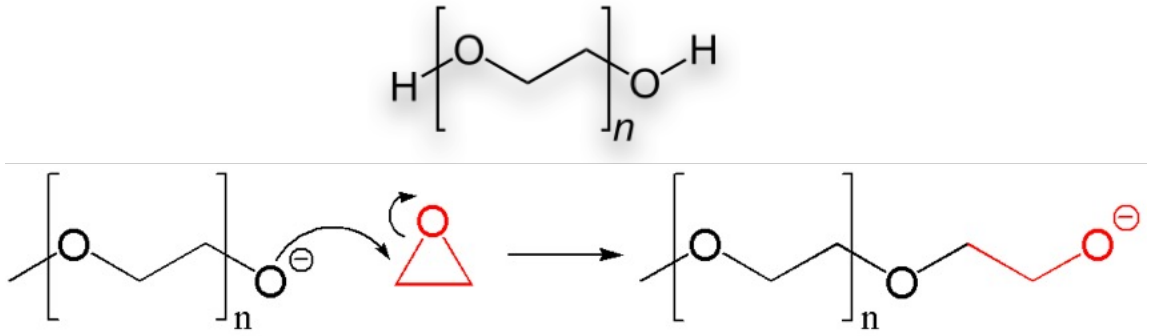
(after Y. Ikada et al., *Polymers as Biomaterials*, Plenum Press, NY 1984)

Surfaces should be hydrophilic or very hydrophobic.

PEG vs SLIPS

Hydrophilic versus hydrophobic

PEG

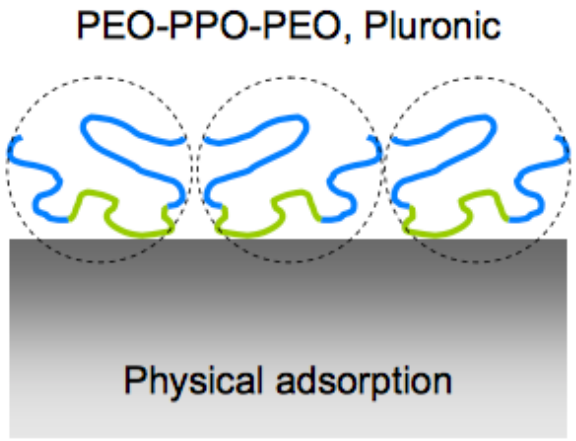


Antifouling

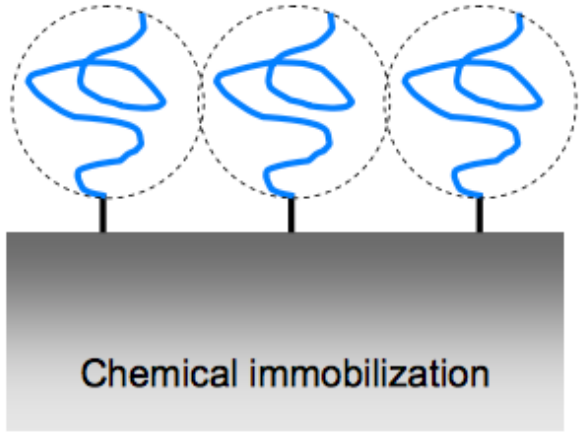
Increase circulation lifetime

Increase size

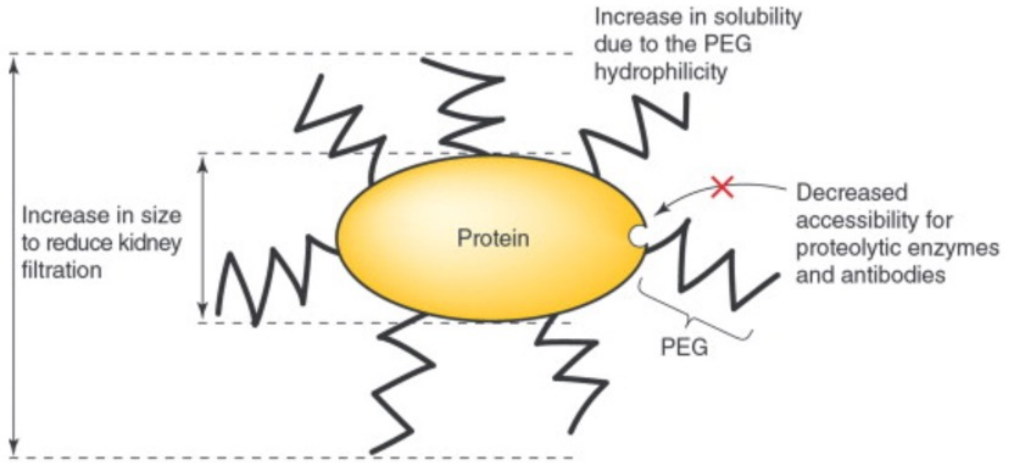
Reduce immunogenicity (?)



Short-time use
Ex. Drug delivery



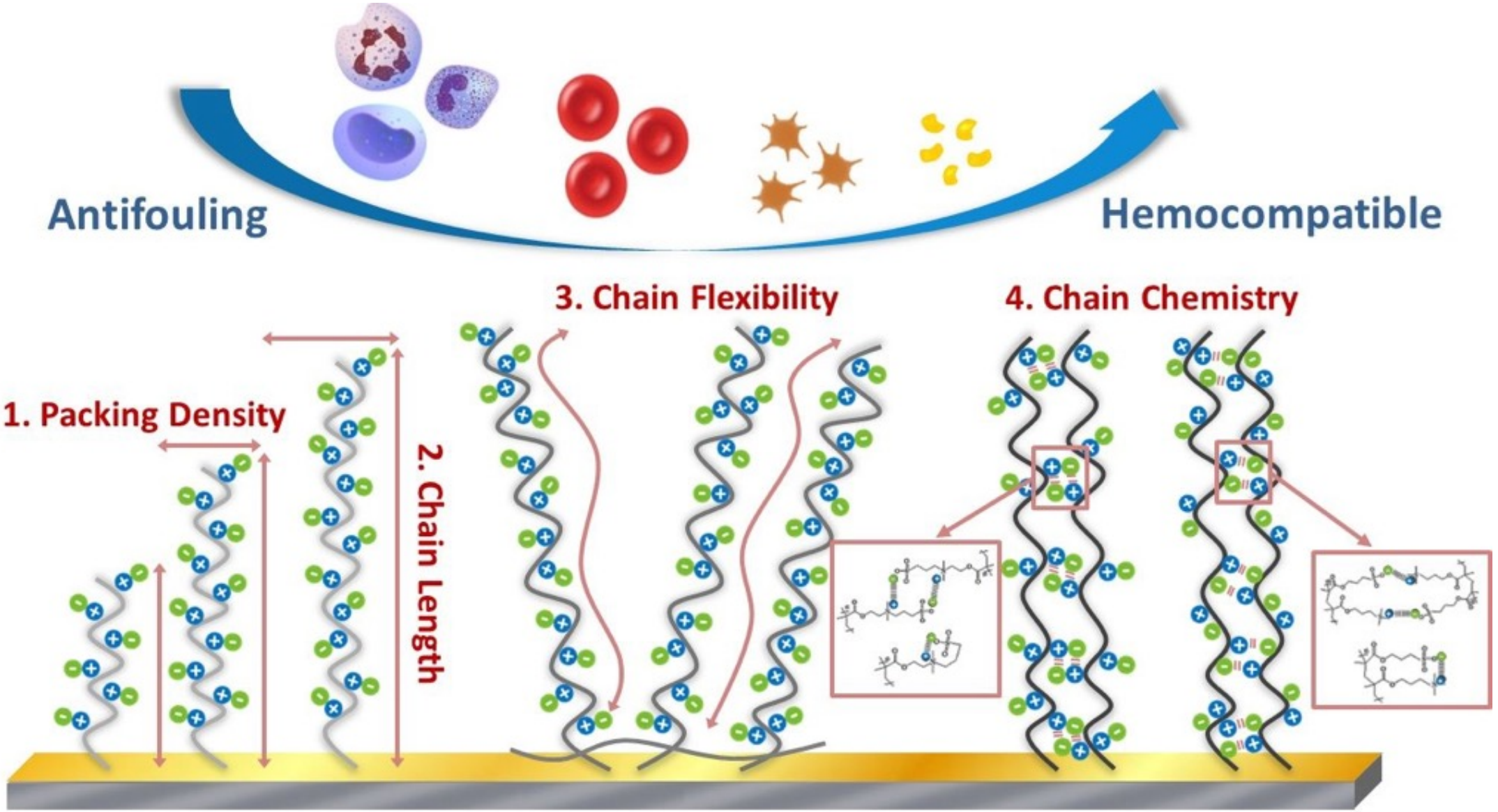
Long-time use



Drug Discovery Today
Volume 10, Issue 21, 1 November 2005, Pages 1451–1458

Example of “gold standard”
Surface modification with PEO derivative.

Polymer coating



SLIPS: omniphobic surfaces

Slippery Liquid Infused Porous Surfaces

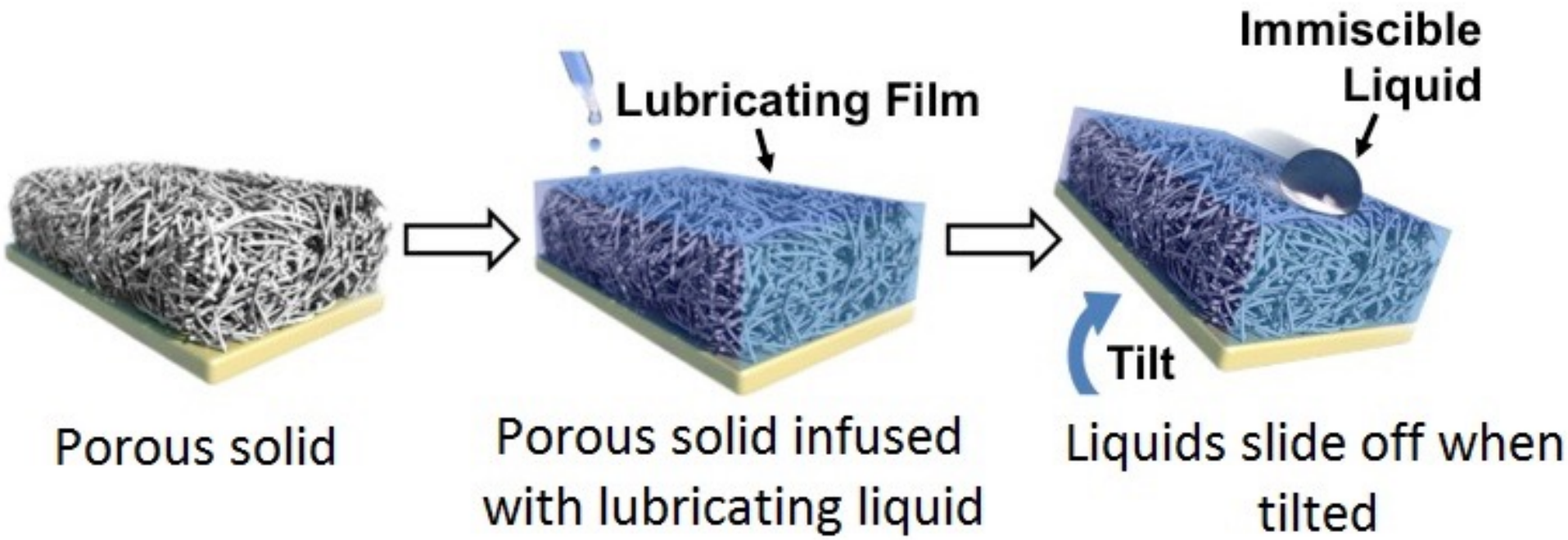
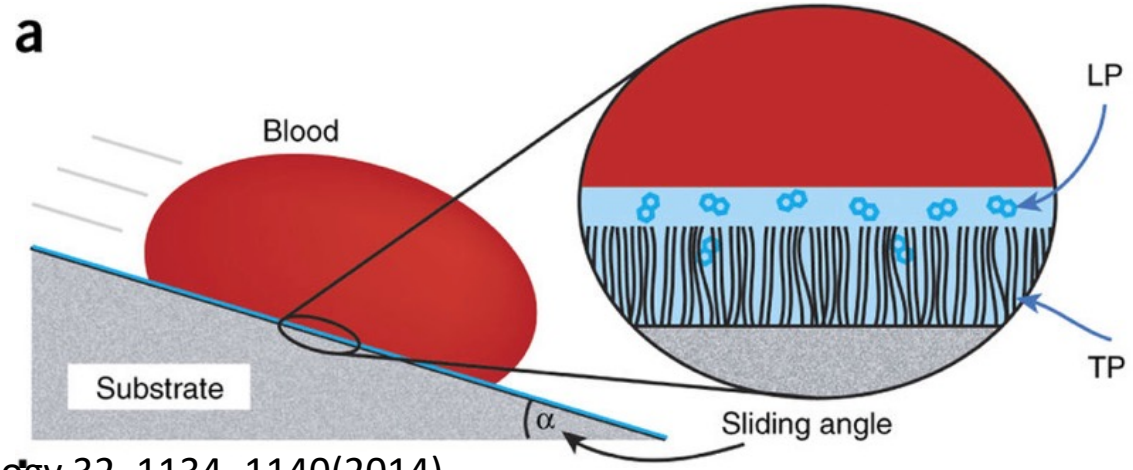


Image credit :www.seas.harvard.edu



These slippery surfaces repel almost any fouling challenge a surface may face—whether from bacteria, ice, water, oil, dust, or other contaminants.

Nature Biotechnology 32, 1134–1140(2014)

The Gecko Test

Conclusion

Polymers provide enormous engineering opportunities: Chemists and bioengineers need to work hand-in-hand

We need to understand both the **chemical engineering potential** as well as the **fundamental biological processes** that result from cell interactions cell in order to design the best nano / micro material platform

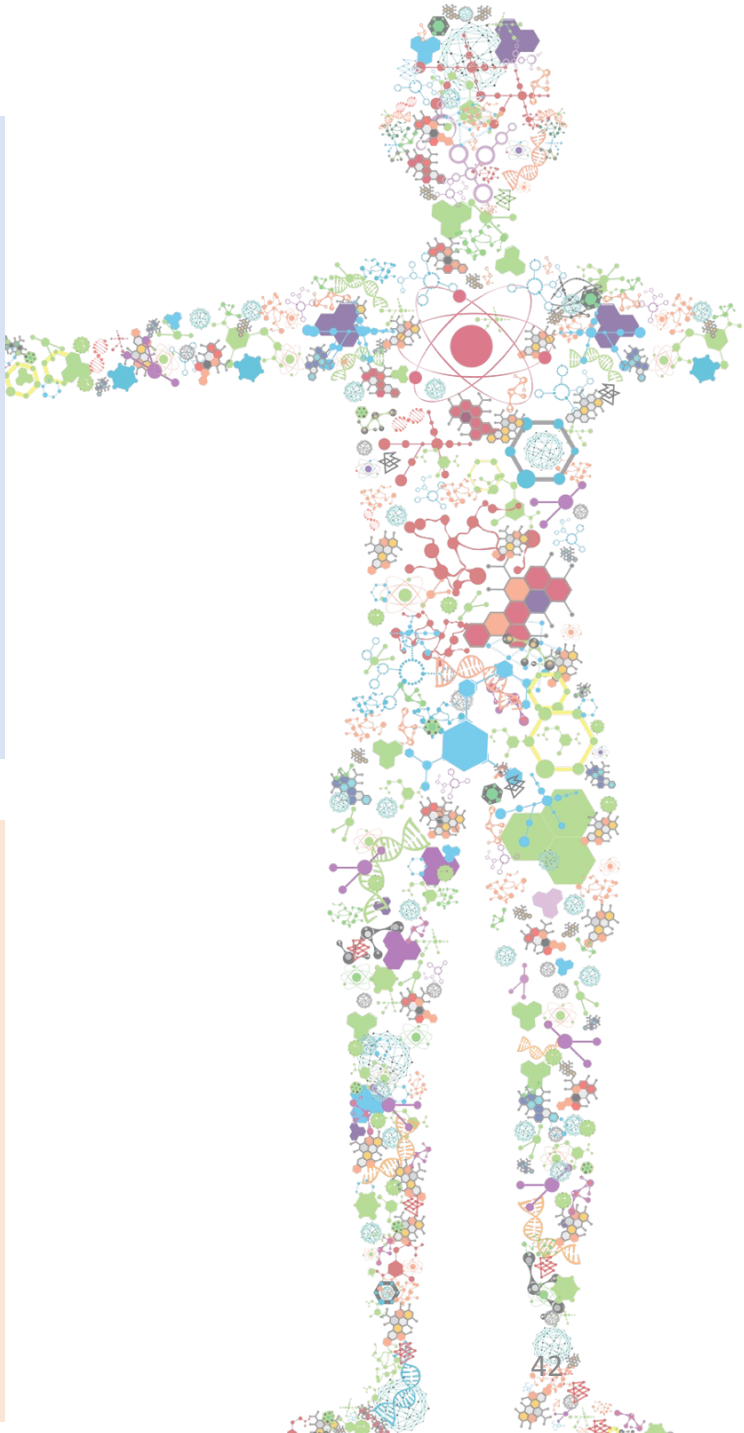
The size and shape of particles influence their interaction with cells
The choice of material and chemistry defines functional behavior and stability

Atoms and molecules that reside at the **surface** of a biomaterial have **special reactivity and direct biological responses**, good and bad

An engineered biomaterial **surface** will never look the way it was designed when used **in contact** with biological material

The intended biomaterial function is compromised by the host's **foreign-body response**

Nothing is perfect: defect in a coating is an initiation side for side reactions / failure!



Test Questions

Name 5 stimuli that can be used the degrade a hydrogel

Design and sketch a nanoparticle that can deliver a protein drug in a tumor, and releases this drug upon temperature change. Highlight what material and architecture you choose.

When would you use nanoparticles versus microparticles?

Draw a schematic of a hip implant and indicate the various surfaces with their properties / effects on prosthesis function

What is a foreign body response? Do all biomaterials trigger it?

What is anti-fouling? Name 2 strategies to achieve this behavior at a biomaterials surface. Will biomaterials that are anti-fouling trigger a foreign body response?