AWP 2-4 – Polymer Chemistry

Polymers in Life Science – C) Nanomedicine

University of Potsdam

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Summer term 2025

A fraction of the slides copied or adapted with curtesy of Dr. Anja Träger (FSU Jena)

Overview

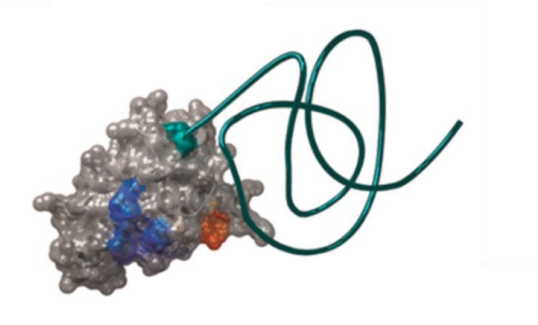
- History and definition of nanomedicine
- Purpose & Requirements
- Excurse: Block copolymers
- Physiological barriers
- Stealth effect & PEGylation
- Passive & active targeting
- The cell & cellular uptake

Learning objectives

- Understand the necessity for nanomedicine and be able to explain how its basic principles work
- Know some nanomedicines in clinical use
- Understand how the barriers within the human body make drug delivery a difficult task
- Understand the concepts of the stealth effect and the EPR effect. Be able to discuss targeted drug delivery
- Be able to discuss different ways how to marry a drug with a drug delivery system
- Understand the basic principles behind cellular delivery of compounds

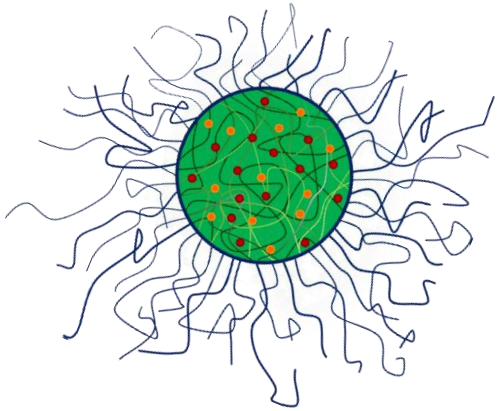
Categories of polymers in drug delviery

Polymer-Drug conjugates



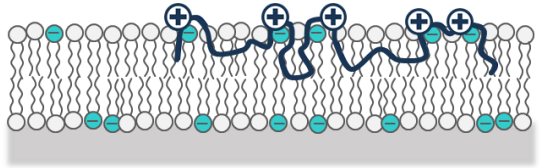
- Attachment of drug to polymer
- Improved pharmacokinetics, solubility, …
- Often for modification of proteins/enzymes
- Cleavable linker function possible

Drug Delivery Systems



- Immobilization of drug in a nanocontainer (micelle, nanoparticle, vesicle, ..)
- Release at specific time and/or place
- Increasing availability of water non-soluble drugs

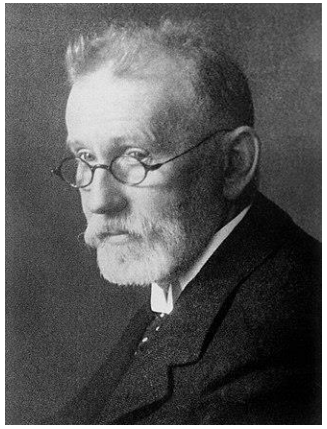
Polymer as drug



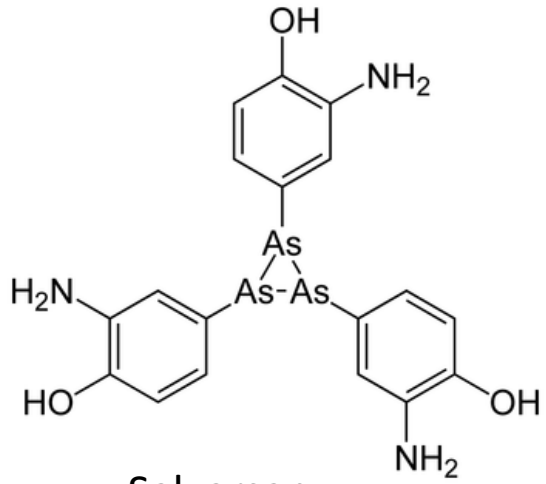
- Macromolecular pharmaceutical
- See last Antimicrobial polymers

The magic bullet

- Concept of „magic bullet“ that hits only the desired goal
- „Wir müssen chemisch zielen lernen“
- Development of a drug that targets pathogens or unhealthy cells without harming the body
- He developed the concept of antimicrobial and the first examples: salvarsan (a treatment for syphilis)
- Described the concept of a „Lastwagens“ (Carrier): a compound that transports drugs to the right place in the body



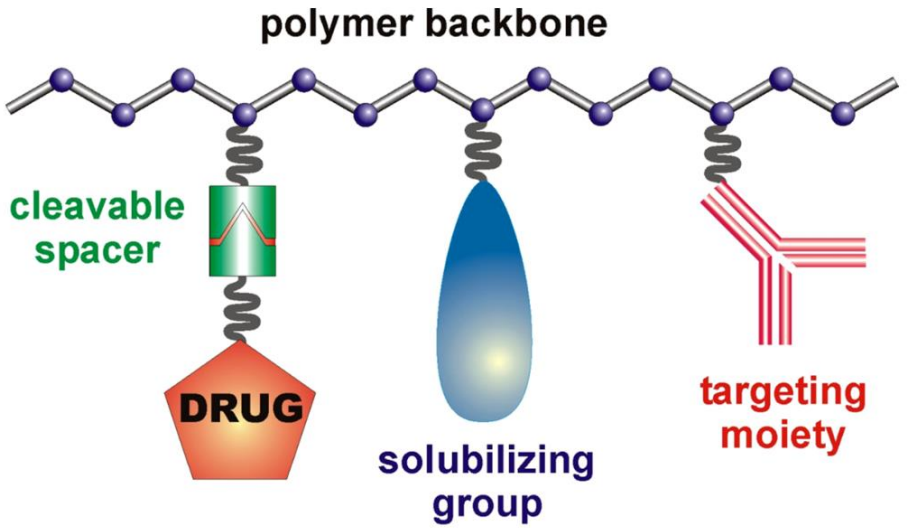
Paul Ehrlich
(Nobel Price for Medicine 1908)

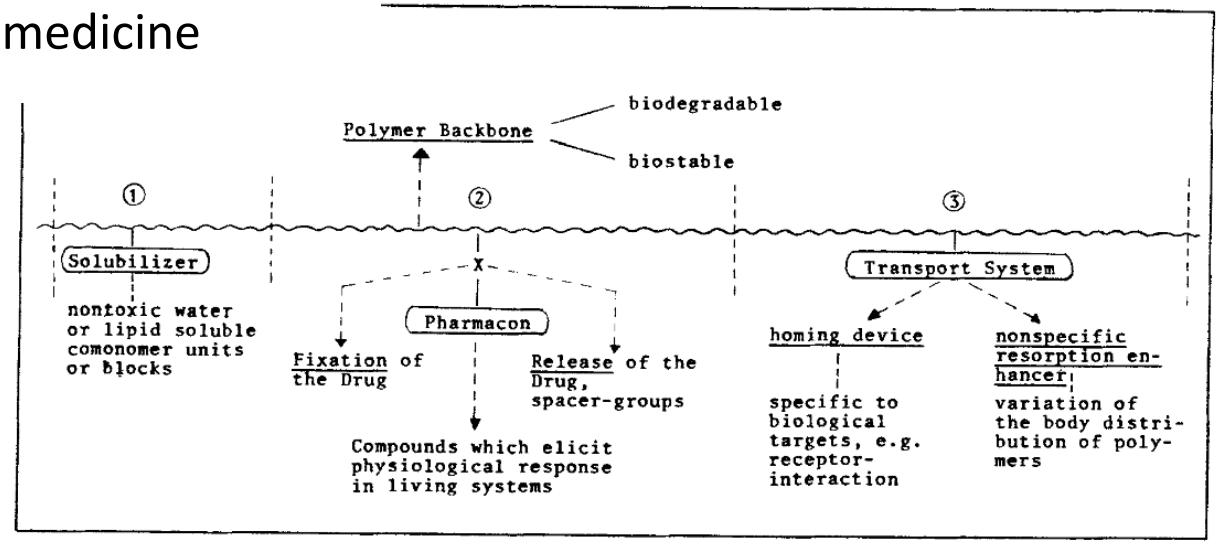


Salvarsan

Pharmacologically active polymers

- Helmut Ringsdorf applied the concept to polymers in 1975
- The idea: a polymer connected to a drug
  - Increased solubility
  - Transport to the desired place in the body
  - Release of drug
- = the birth of nanomedicine



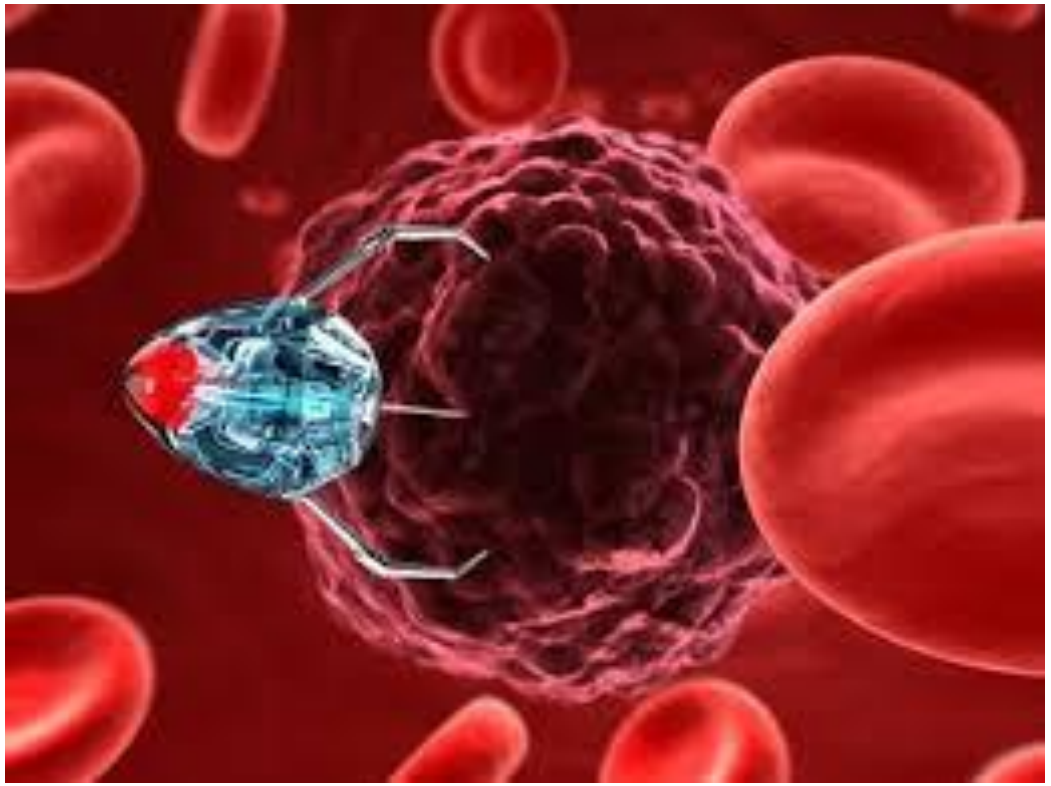


Ringsdorf

Helmut Ringsdorf

Ringsdorf, H. Structure and properties of pharmacologically active polymers.
J. Polym. Sci. Polym. Symp.1975,51, 135–153.

Nanomedicine

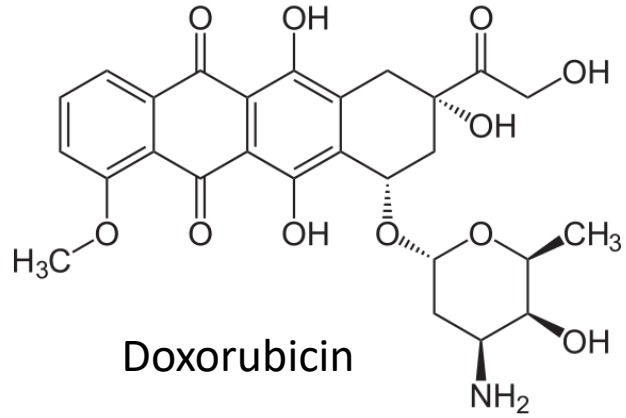


- **Nanomedicine** is the medical application of nanotechnology
- Functionalities can be added to nanomaterials
- The **size** of nanomaterials **is similar to** that of most **biological molecules** and structures; therefore, nanomaterials can be useful for both *in vivo* and *in vitro*
- Examples:
  - diagnostic devices
  - contrast agents
  - analytical tools
  - physical therapy applications
  - drug delivery vehicles

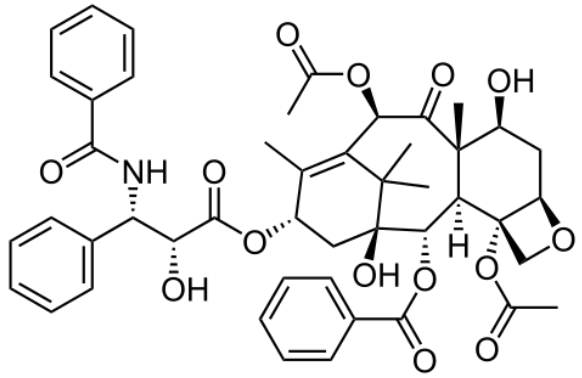
Approved nanomedicines

Doxil®	Johnson & Johnson	FDA (1995), EMA (1996)	doxorubicin (adriamycin)	metastatic ovarian cancer, HIV-associated Kaposi's sarcoma (KS) [72]
Lipodox®	Sun Pharma Global FZE	FDA (2013)	doxorubicin hydrochloride	metastatic ovarian cancer, HIV-associated KS [73]
DaunoXome®	Galen Ltd.	FDA, EMA (1996)	daunorubicin	cancers and HIV-associated KS [74]
Onivyde®	Merrimack Pharmaceuticals	FDA (2015)	irinotecan	metastatic pancreatic cancer [75]
DepoCyt®	Pacira Pharmaceuticals	EMA (2002), FDA (2007)	cytarabine	lymphomatous meningitis [76]
Myocet®	Teva Pharmaceutical Industries Ltd.	EMA (2000)	doxorubicin hydrochloride	breast cancer [77,78]
Caelyx®	Janssen Pharmaceuticals	EMA (1996)	doxorubicin	breast cancer, ovarian cancer, HIV-associated KS [79,80]
Mepact®	Takeda France SAS	EMA (2009)	mifamurtide	osteogenic sarcoma [81]
Marqibo®	Talon Therapeutics	FDA (2012)	vincristine	Philadelphia chromosome-negative chronic myelogenous leukemia in adult patients [82,83]
Onpattro®	Alnylam	FDA & EMA (2018)	patisiran	hereditary transthyretin (TTR) mediated amyloidosis [84,85]
Lipusu®		FDA (2016)	paclitaxel	breast cancer, non-small-cell lung cancer (NSCLC) [86]
Pfizer-BioNTech Vaccine	Pfizer Pharmaceuticals	FDA (2020)	mRNA vaccine	prevents COVID-19 infection [95,96]
Moderna COVID-19 Vaccine	ModernaTX Inc.	FDA (2020)	mRNA vaccine	prevents COVID-19 infection [96,97]

Σ < 100



Doxorubicin

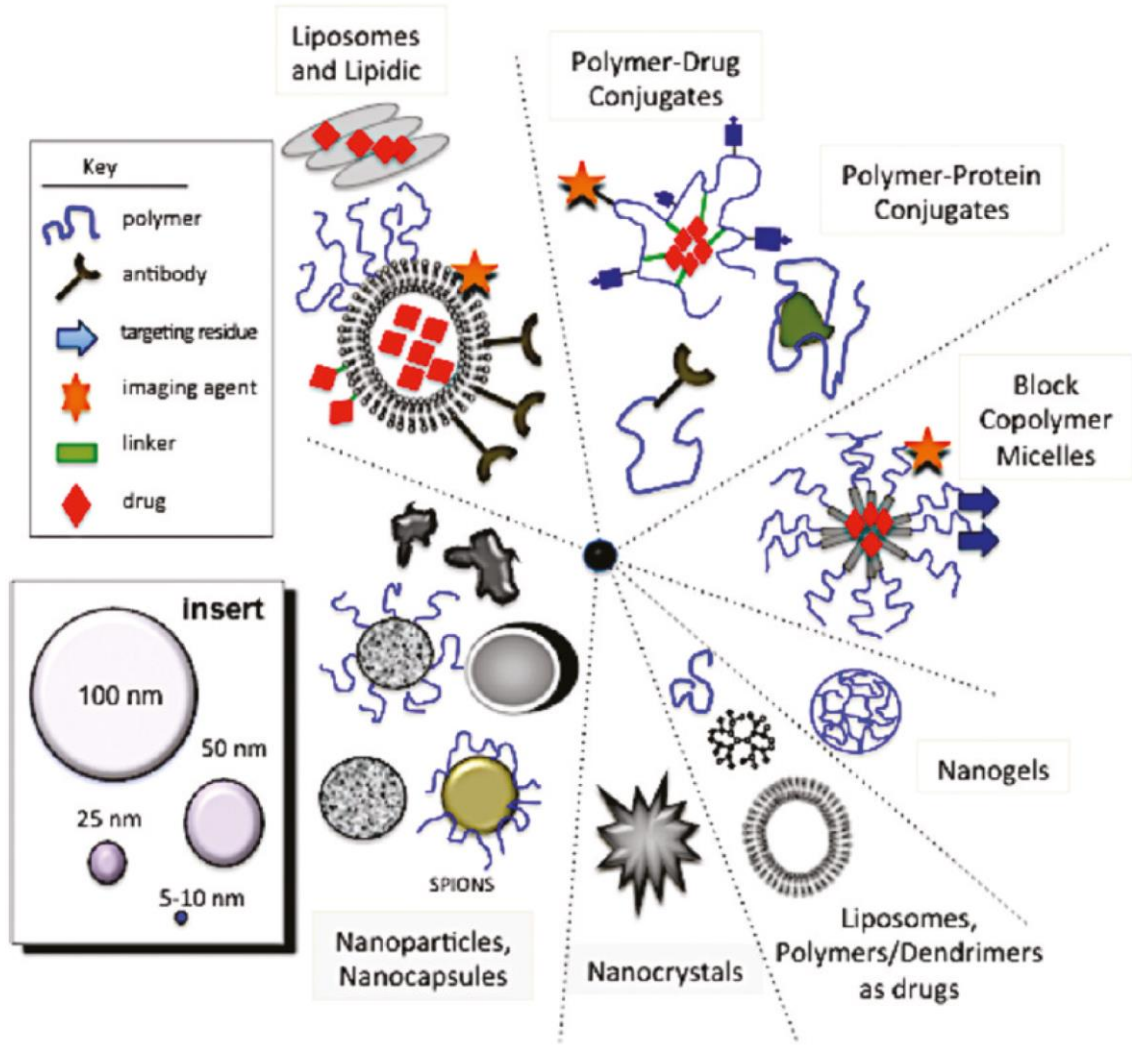


Paclitaxel

Halwani, A.A. Development of Pharmaceutical Nanomedicines: From the Bench to the Market. *Pharmaceutics* **2022**, *14*, 106. https://doi.org/10.3390/pharmaceutics14010106

Polymers in drug delivery

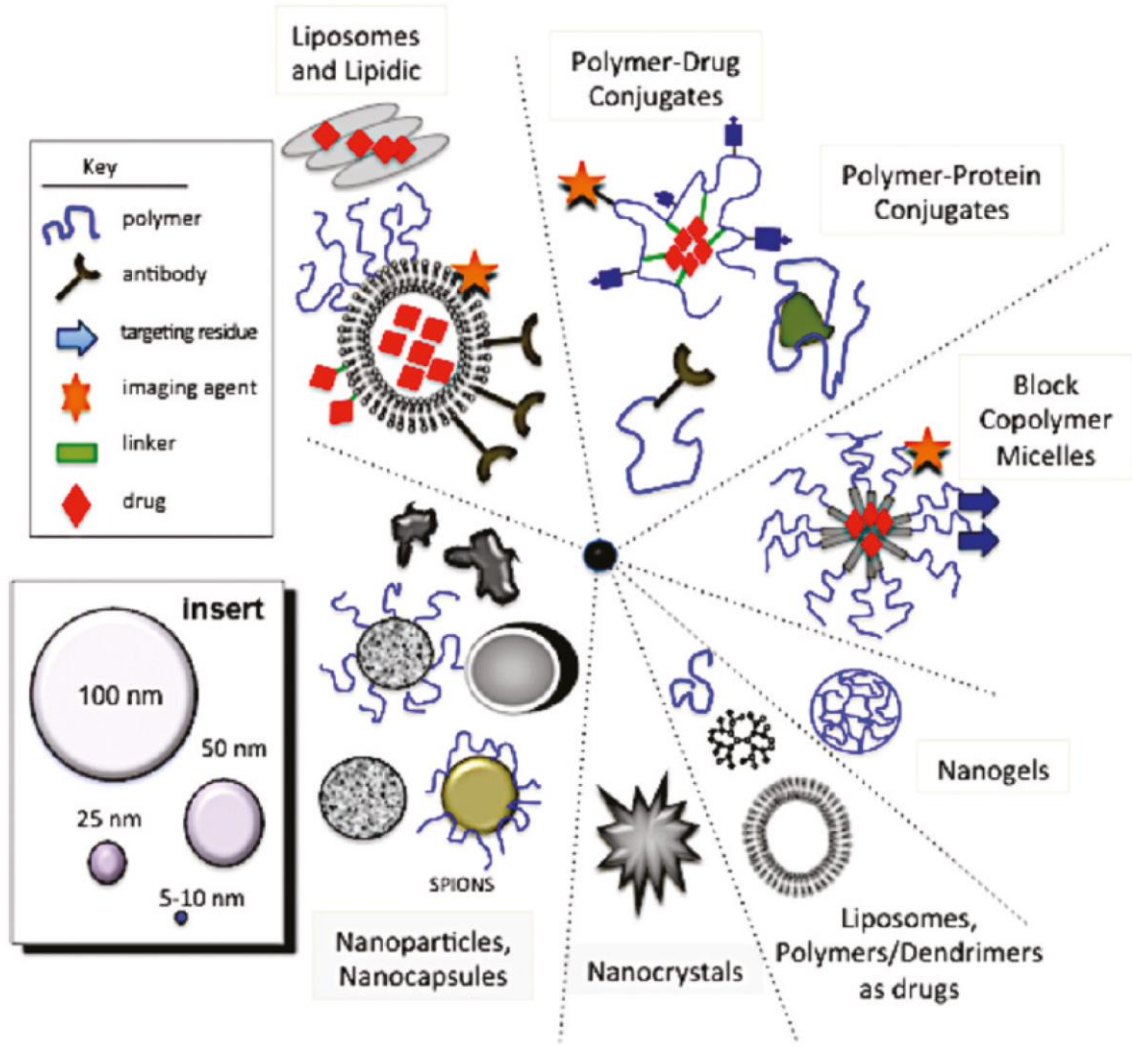
- Potential Advantages of nanomedicines
  - Improved pharmacokinetics
    - Longer circulation
    - Slower excretion
  - Increased solubility
  - (accumulation in certain areas of the body)
  - (cell specific uptake)
  - Reduced (unspecific) toxicity



R. Duncan, R. Gaspar, *Mol. Pharm.* ***2011, 8, 2101-2141.***

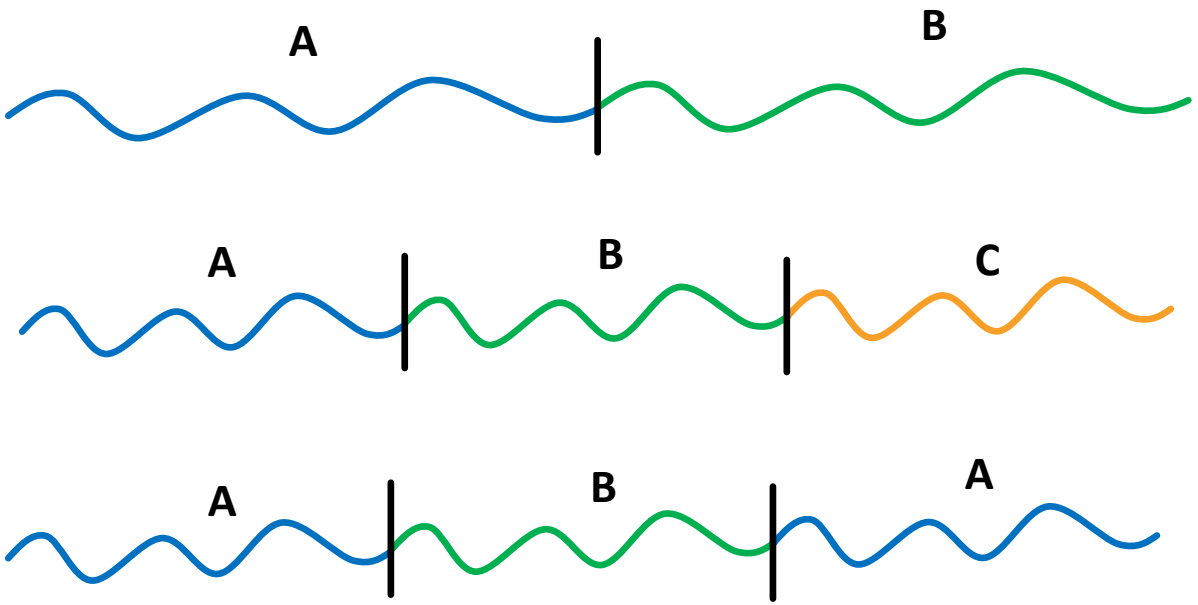
Polymers in drug delivery

- Requirements for polymers in nanomedicine
  - Degradation products nontoxic
  - Good water soluble (some part at least)
  - Synthesis reproducible
  - Defined polymers (Đ)
    - → structure property relationship
  - Stability (in storage)



Excurse: Blockcopolymere (BCP)

- Minimum 2 monomers in minimum 2 Segments (blocks)



Diblock Copolymer

Triblock Terpolymer (ABC Triblock copolymer)

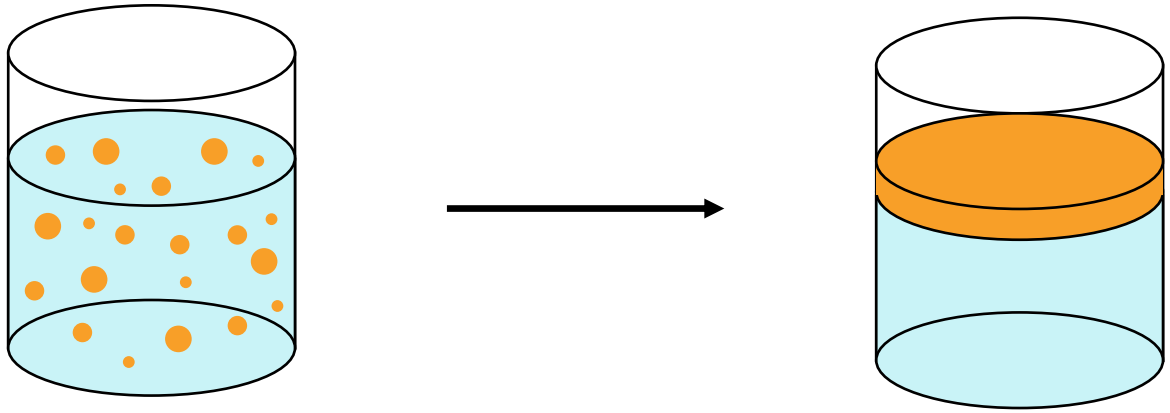
Triblock Dipolymer (ABA Triblock copolymer)

…

Multiblock copolymers

BCP in solution

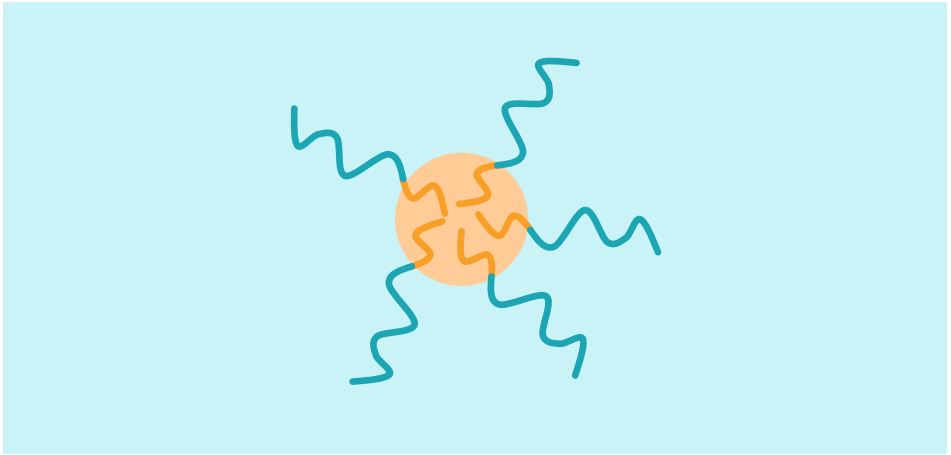
- Hydrophobic effect
  - E.g. oil in water



Phase separation leads to minimal interface

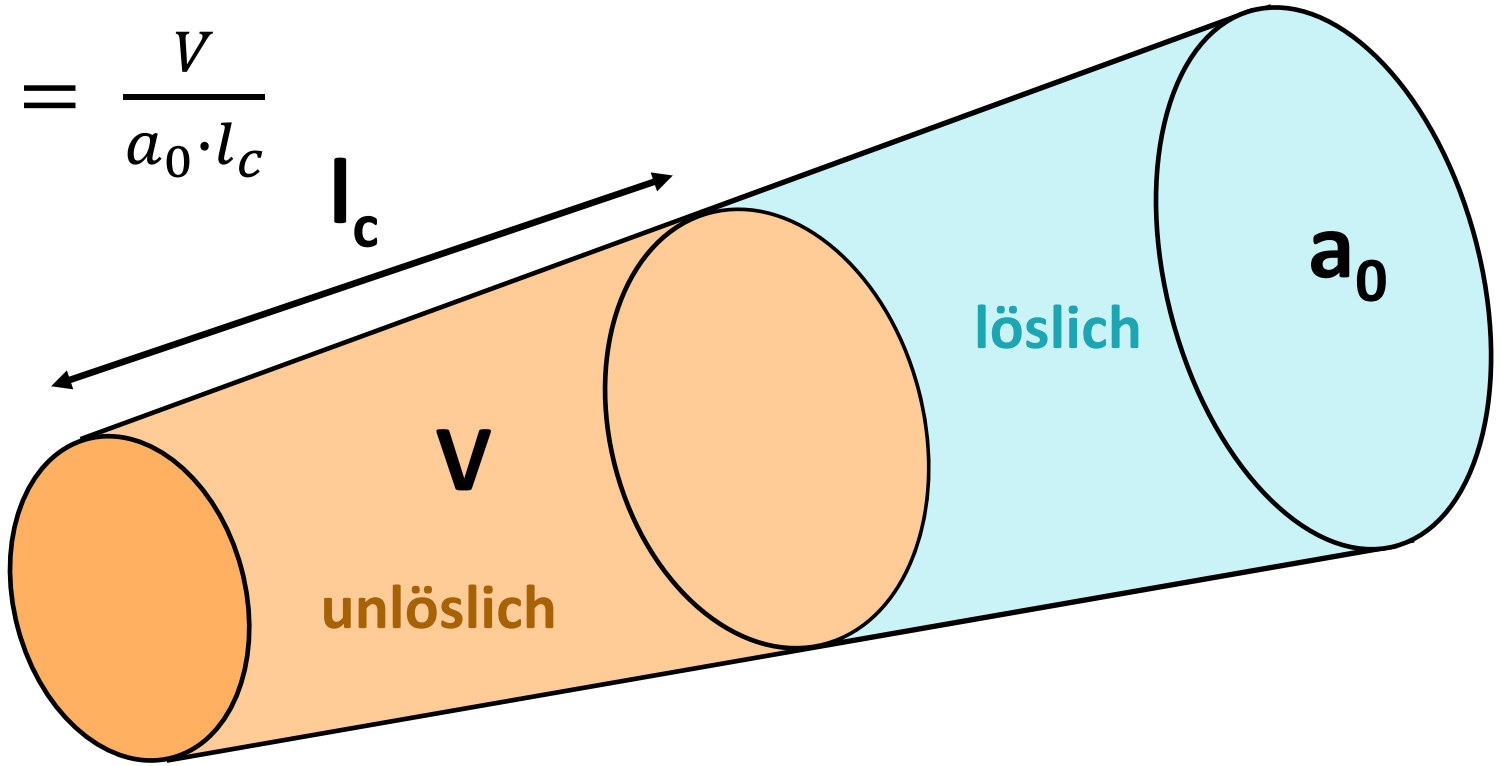
- Amphiphilic BCP: Block 1 – soluble

  Block 2 – insoluble
  - But: 2 phases are covalently connected
  - Self-assembly to micelles to minimize inte



Self-assembly

- Shape is dependent on the volume ratio of blocks
- This determined the curvature of the interface
- Packing parameter $p = \frac{V}{a_0 \cdot l_c}$



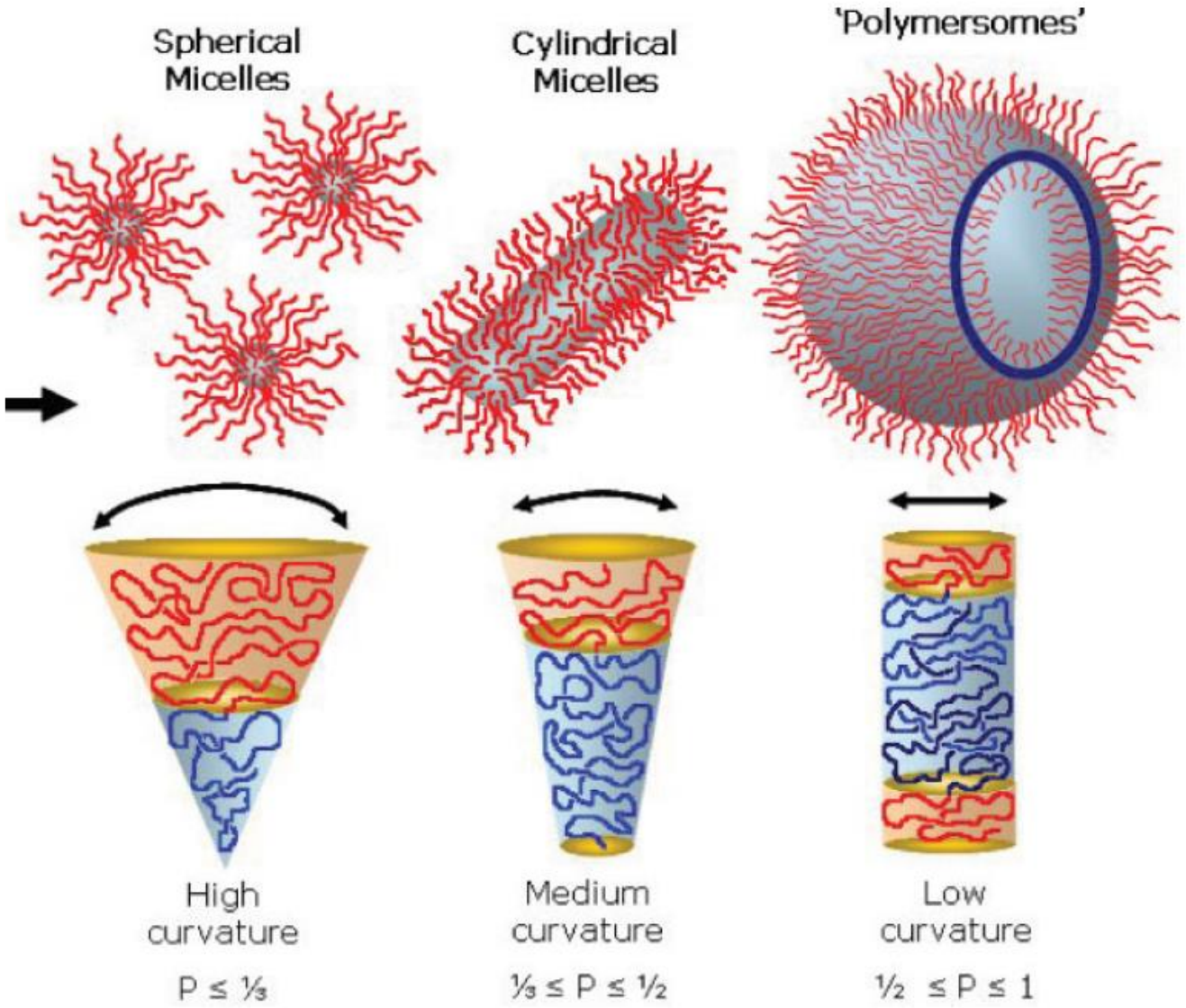
V = volume of hydrophoben block

l_c = length of hydrophobic segment

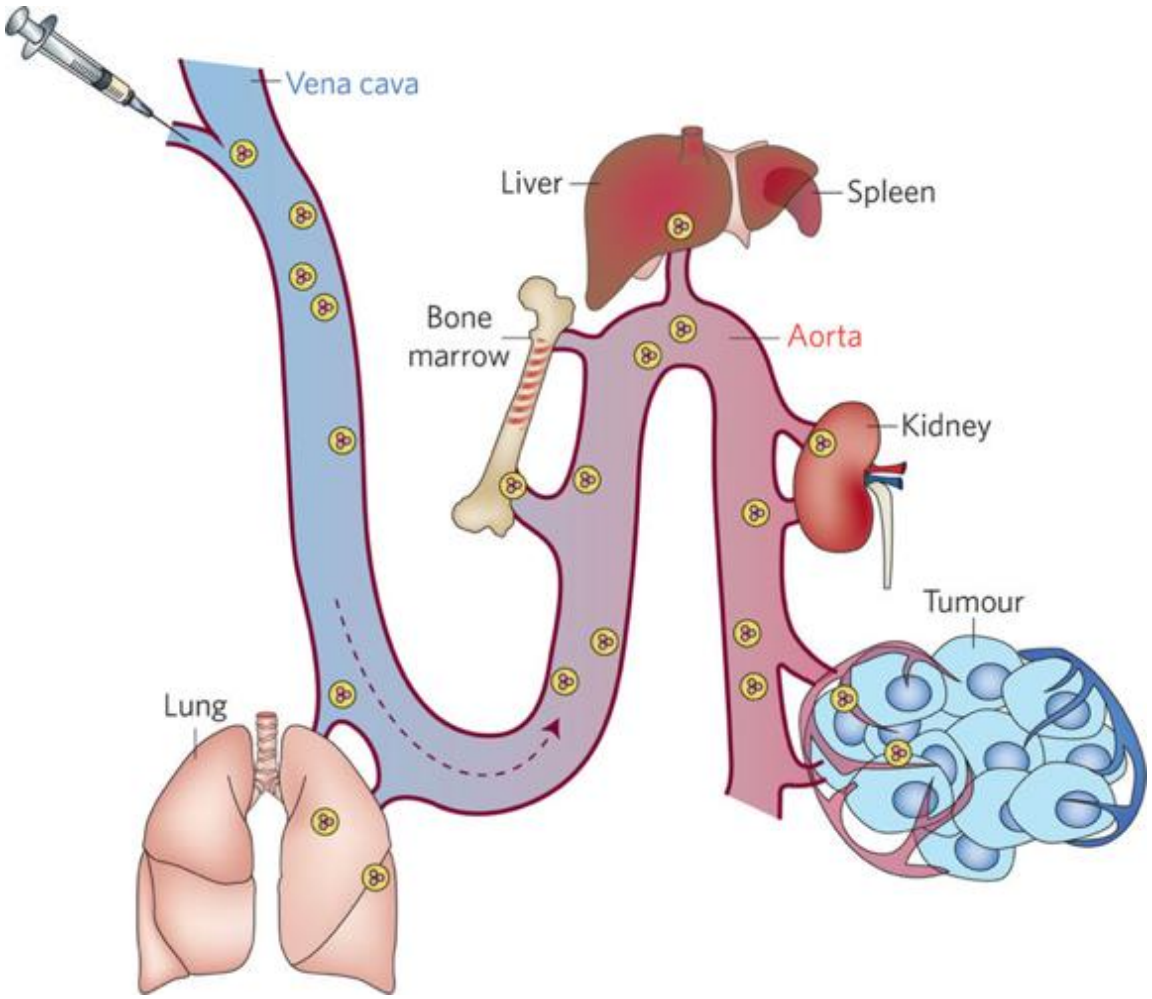
a_0 = areas of head group

BCP assembly in solution

- Curvature determines structure
- Depends also on solvent and type of polymer
- Assembly <u>above</u> critical micellar concentration (CMC)



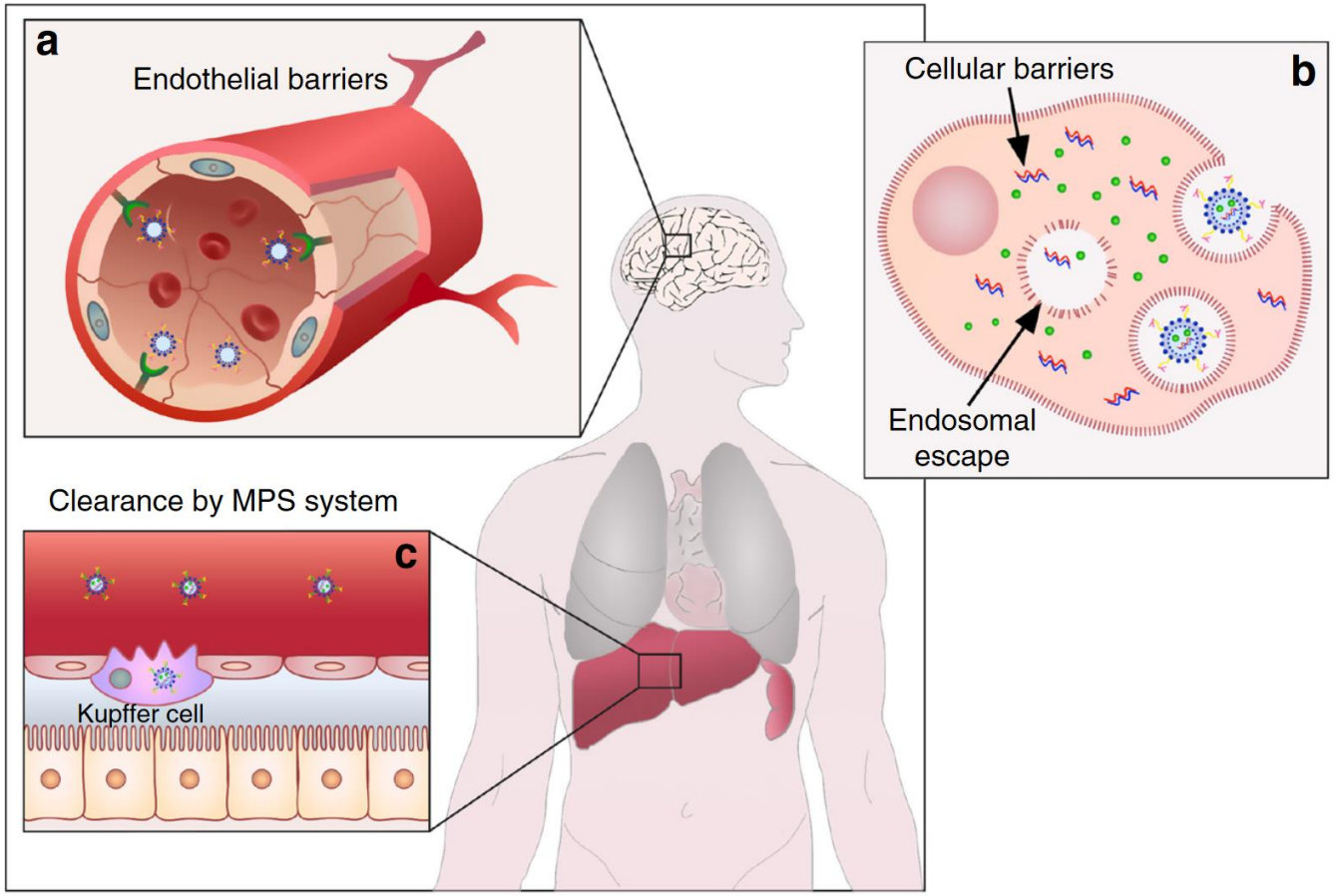
Physiological barriers for nanomedicines



- Aggregation with blood components
- Immune reaction
- Unwanted clearance
- Disassembly / drug release at low concentration
- Assembly in non-targeted organs /cells
- Does not reach target (blood brain barrier)
- Low accumulation in targeted cells / organ
- Uncontrolled degradation

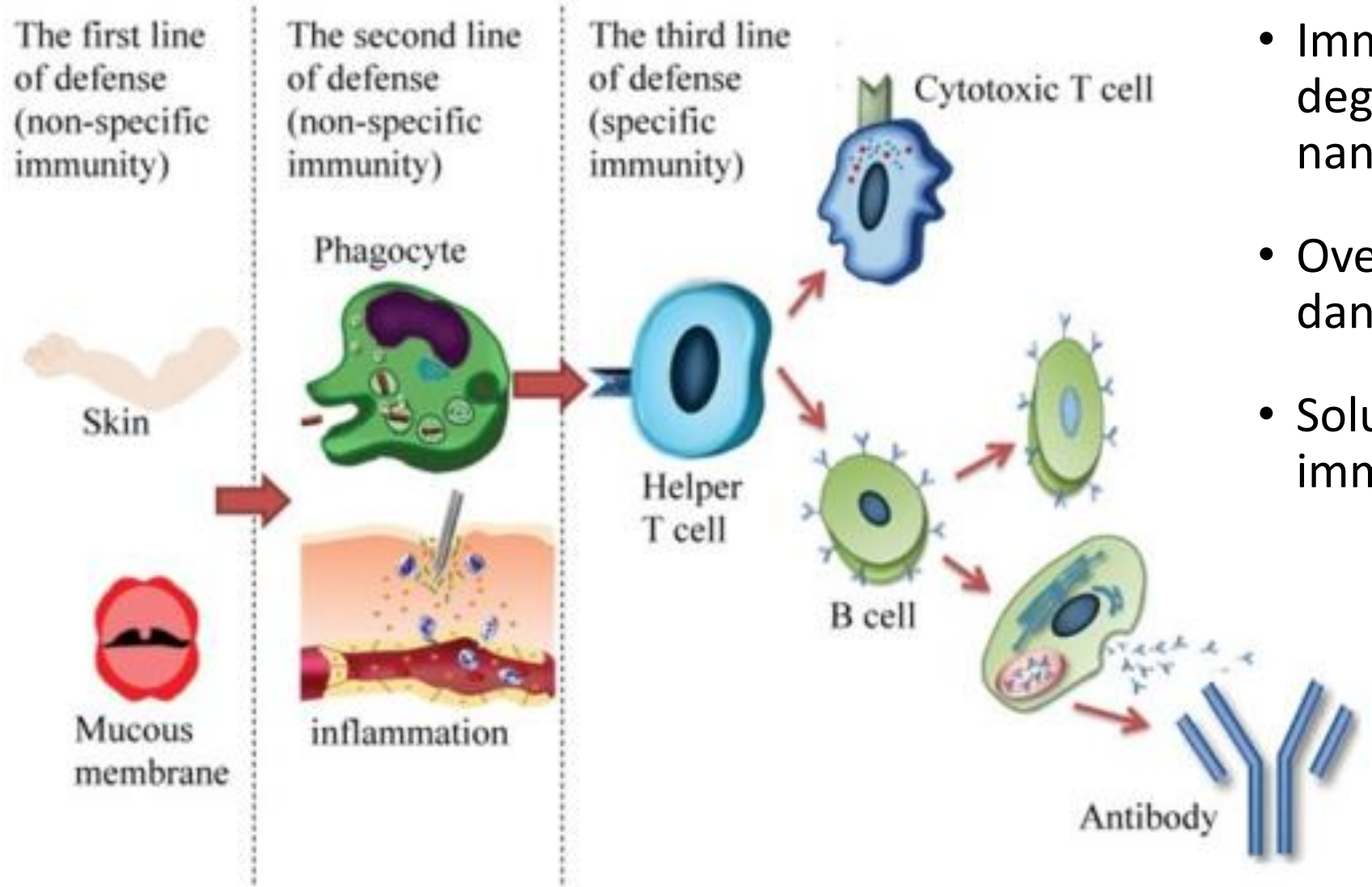
Nanotransporters

- Requirements
  - Transport to target site
  - Overcoming barriers
  - No/little unspecific interactions
  - Release of drug at target
  - Biodegradation/excretion (without toxic side products)



Rosenblum, D., Joshi, N., Tao, W. *et al.* Progress and challenges towards targeted delivery of cancer therapeutics. *Nat Commun* **9,** 1410 (2018

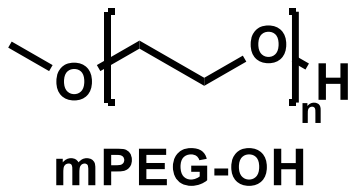
Our ultimate line of defence...



- Immune reactions can degrade/excrete nanomedicines
- Over reaction can also be dangerous for the patient
- Solution: hide from immunity!

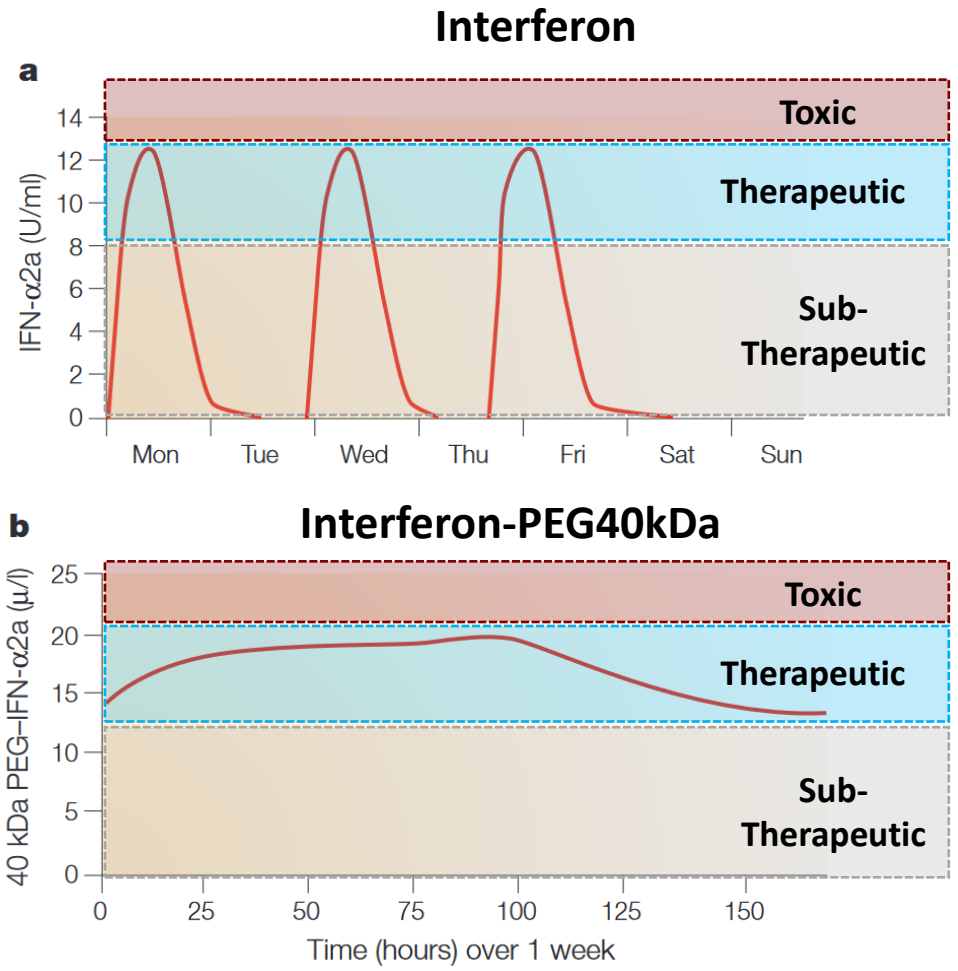
https://openi.nlm.nih.gov/imgs/512/257/4152211/PMC4152211_504fig1.png

Stealth Effect - PEGylation



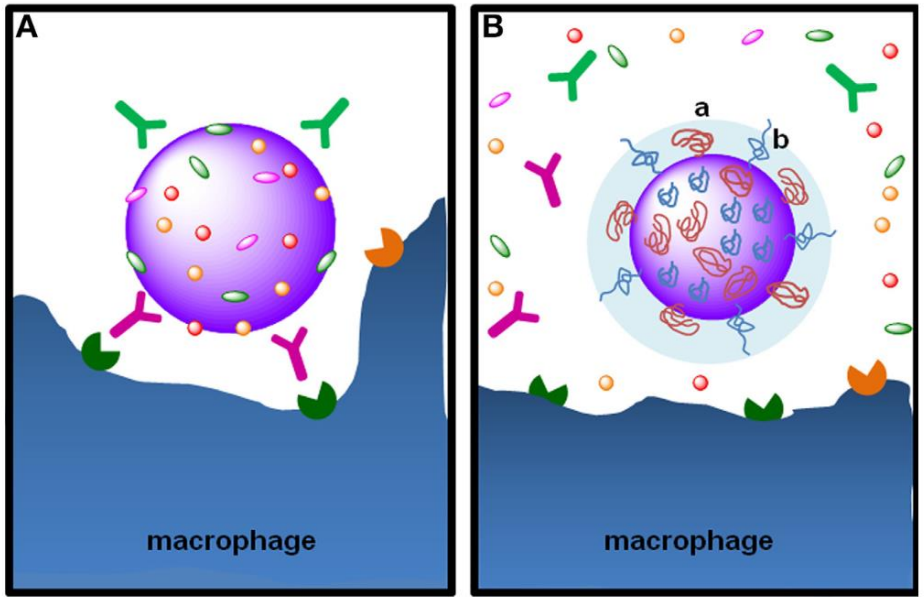
mPEG-OH

- Poly(ethylene glycole)
  - Hydrophilic polymers (but also nicely organo soluble)
  - Conjugation via end-functions
  - Relatively non-toxic
  - Approved for use in humans
  - Increases solubility of substrates
  - **Reduced unspecific interaction with proteins/tissue**
  - **Increased circulation times**



PEGylation (II)

- The interface of foreign objects is coated in antibodies and immune factors (opsonisation)
- These molecules marc the object for the immune systems (e.g. macrophages)
- PEG forms a strongly hydrated layer around nanomedicine
- Visibility of the immune system is decreased(Stealth)
- Prerequisite for specific targeting via ligands!



Conniot J, Silva JM, Fernandes JG, et al. Cancer immunotherapy: nanodelivery approaches for immune cell targeting and tracking. *Front Chem*. 2014, 2:105.

PEGylation (III)

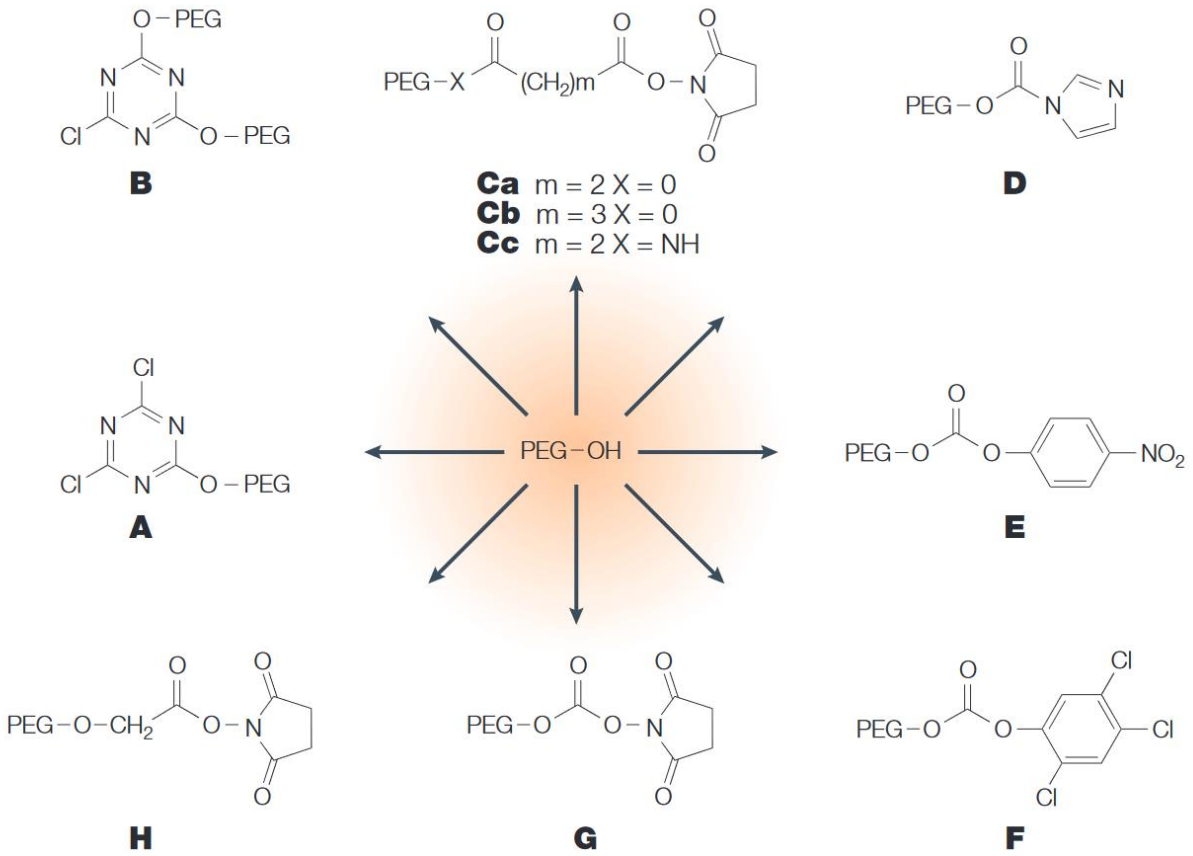
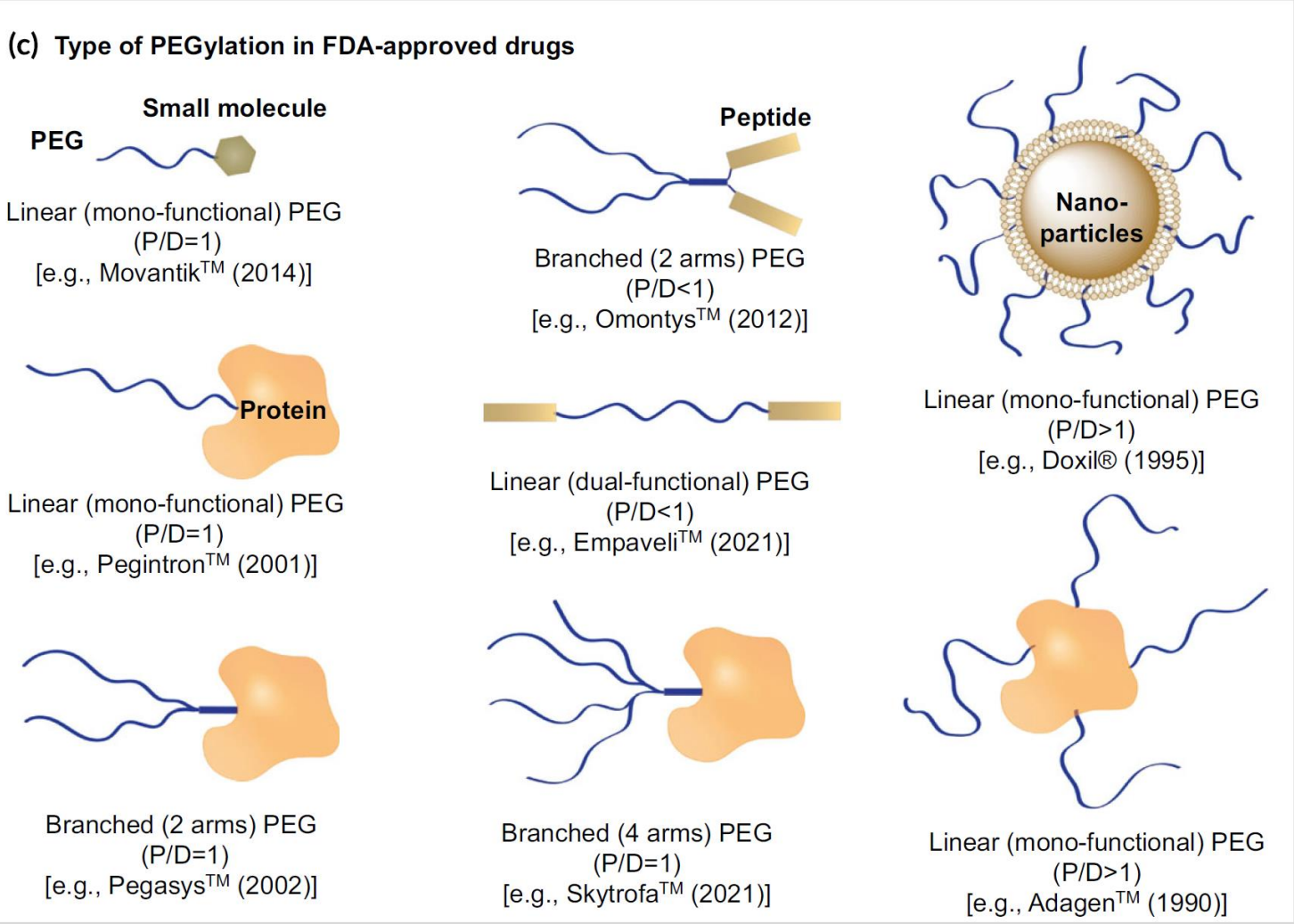
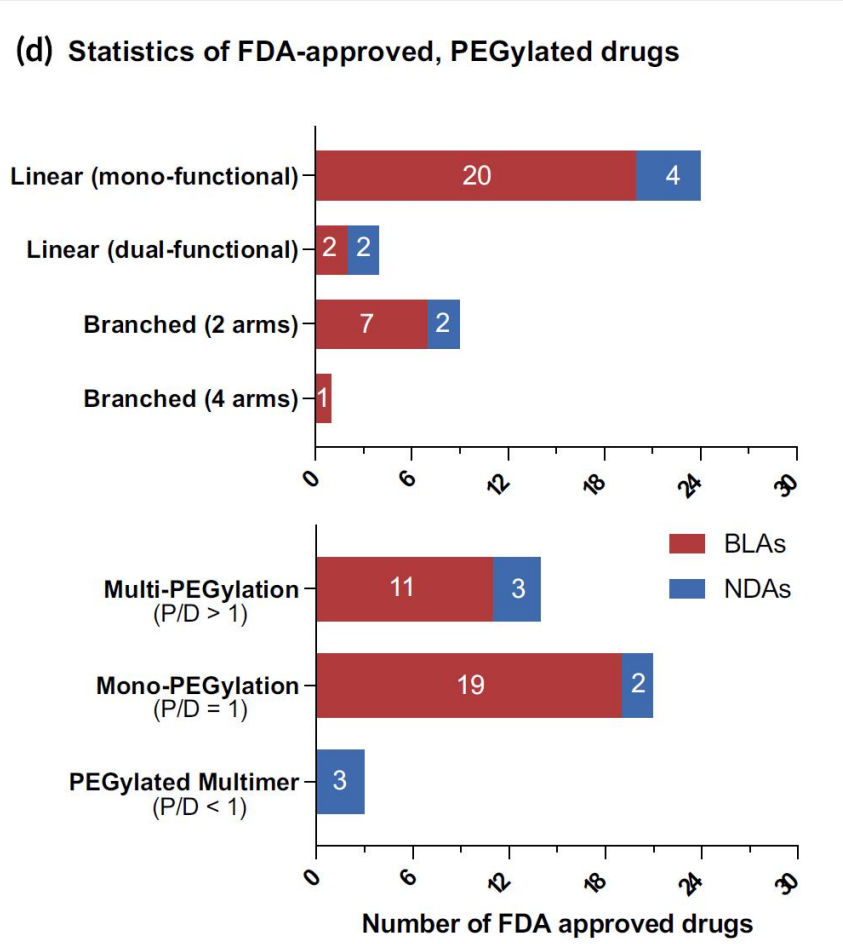


Figure 2 | **Method for the activation of PEG molecules. A** | Cyanuric chloride method. **B** | A variation on the cyanuric chloride method. **Ca** | Polyethylene glycol (PEG)–succinimidyl succinate method. **Cb** | Substitution of the succinate residue by glutarate. **Cc** | Substitution of the aliphatic ester in **Ca** by an amide bond. **D** | Imidazoyl formate method. **E** and **F** | Variations using phenylcarbonates of PEG. **G** | Succinimidyl carbonates of PEG. **H** | Succinimidyl active ester of PEG.

- Problems of early methods:
  - Contamination with PEG-diol
  - Uncontrolled number of polymers attached
  - Instable attachment
- First approval 1990: Adagen
  - PEGylated bovine Adenosin-Deaminase

PEG conjugates

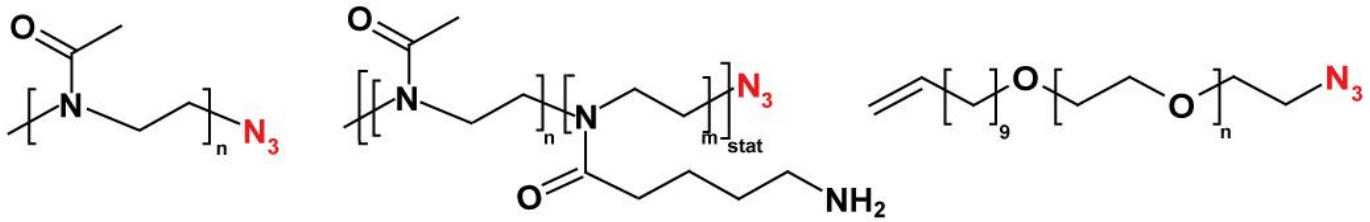




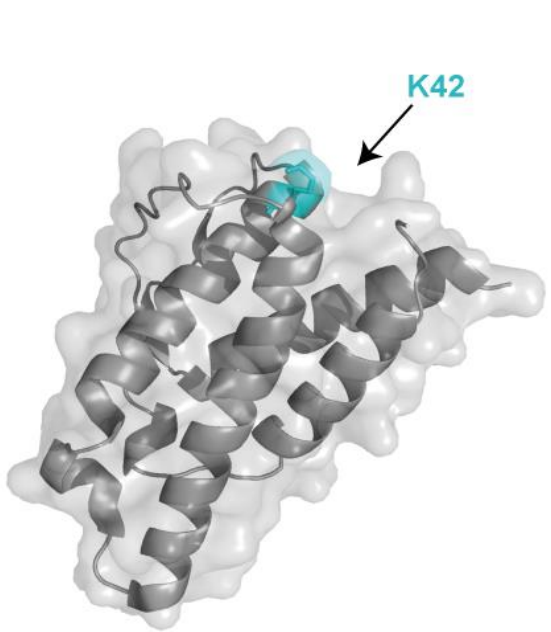
Gao Y, Joshi M, Zhao Z, Mitragotri S. PEGylated therapeutics in the clinic. Bioeng Transl Med. 2023 Sep 22;9(1):e10600. doi: 10.1002/btm2.10600. PMID: 38193121; PMCID: PMC10771556.

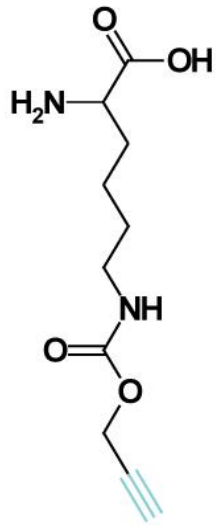
Site-specific PEGylation/POxylation

- Coupling reaction should be orthogonal to biological functions

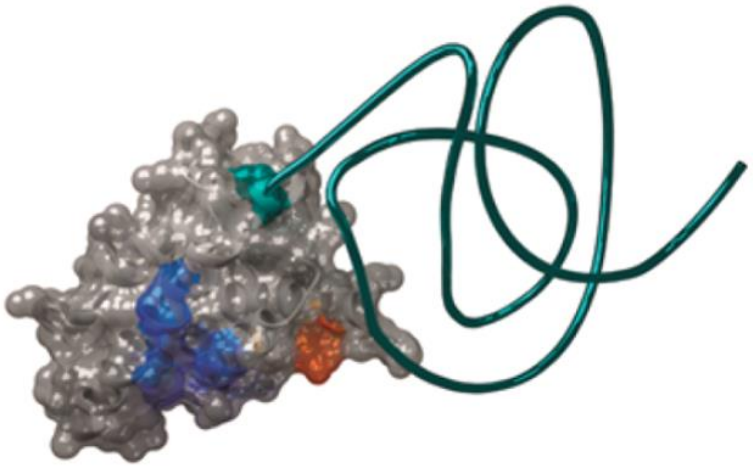


1. $P(MeOx)_n$-N_3 2. $P(MeOx_n$-*stat*-$AmOx_m)$-N_3 3. PEG_n-N_3

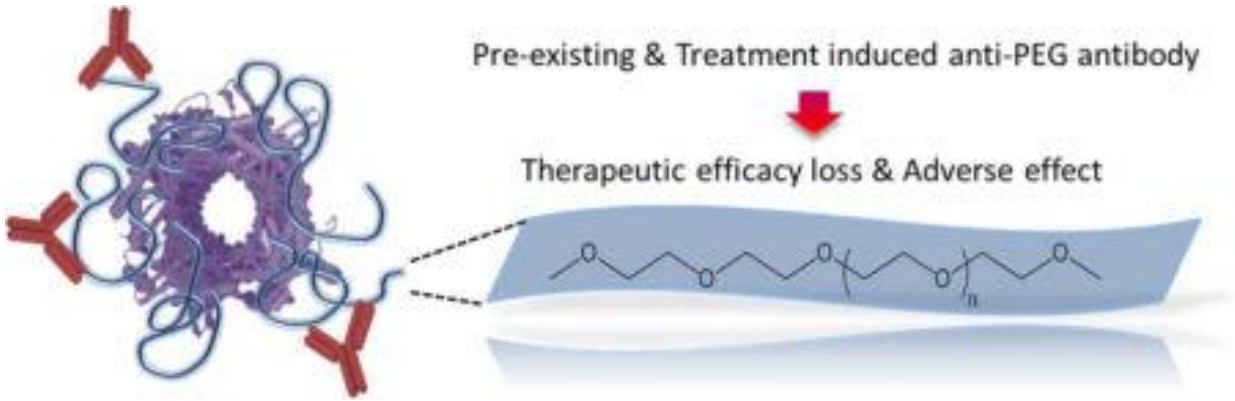




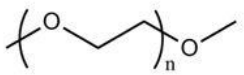
4. Propargyl-L-lysine (Plk)



PEG Antibodies

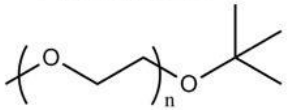


Methoxy-PEG

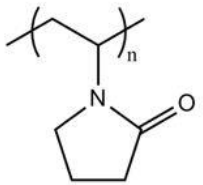


Hydroxyl-PEG

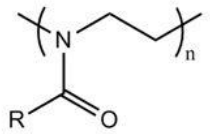
t-butoxy-PEG



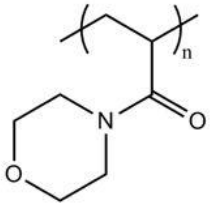
Poly(N-vinylpyrrolidone)



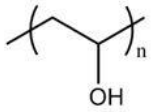
Polyoxazoline



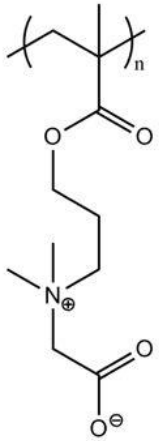
Poly(N-acryloyl morpholine)



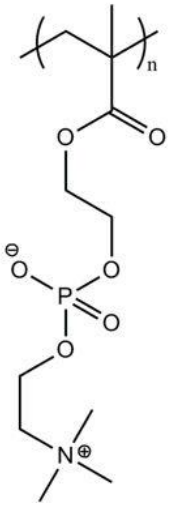
Poly(vinyl alcohol)



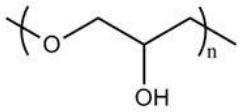
Poly(carboxybetaine)



Poly(2-methacryloyloxyethyl phosphorylcholine)



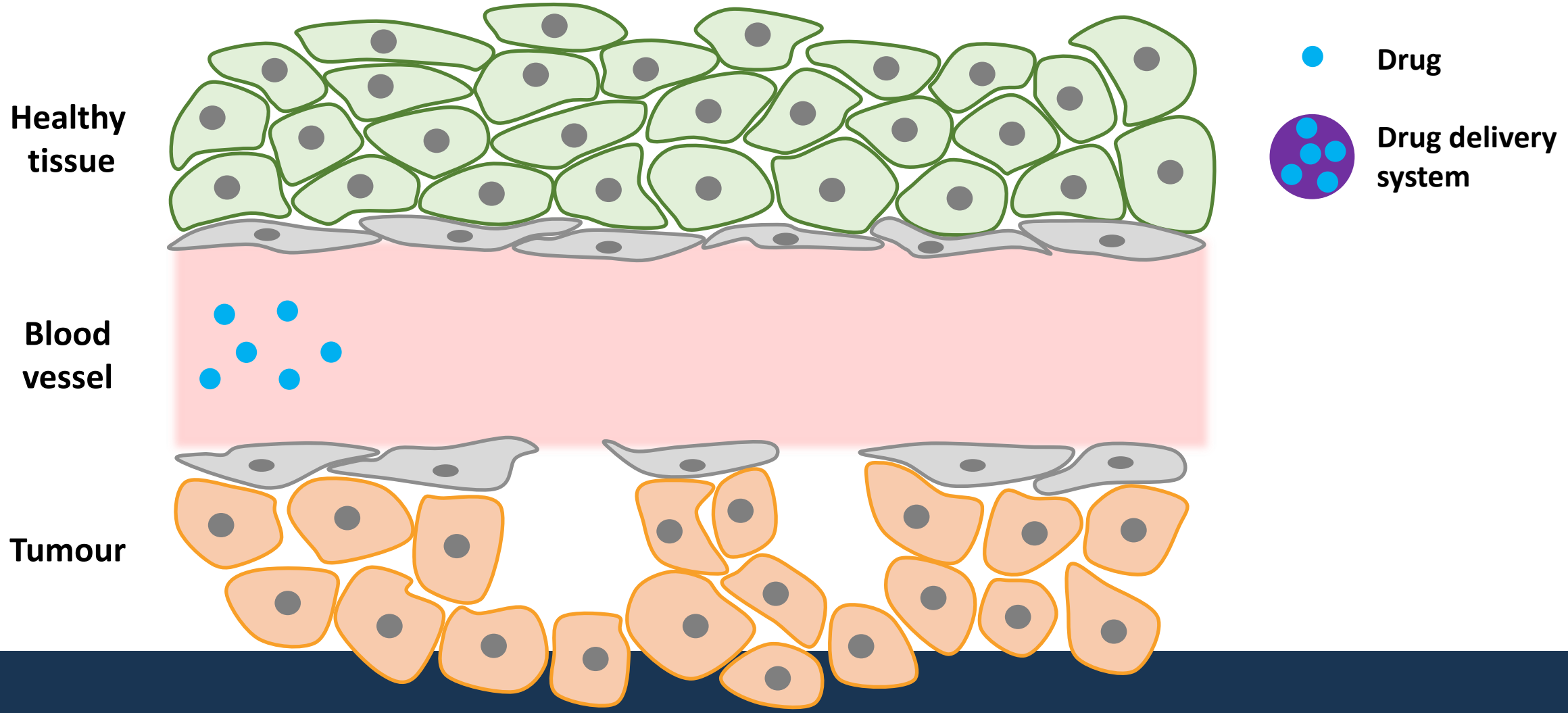
Polyglycerol



doi:10.1016/j.jconrel.2016.06.040

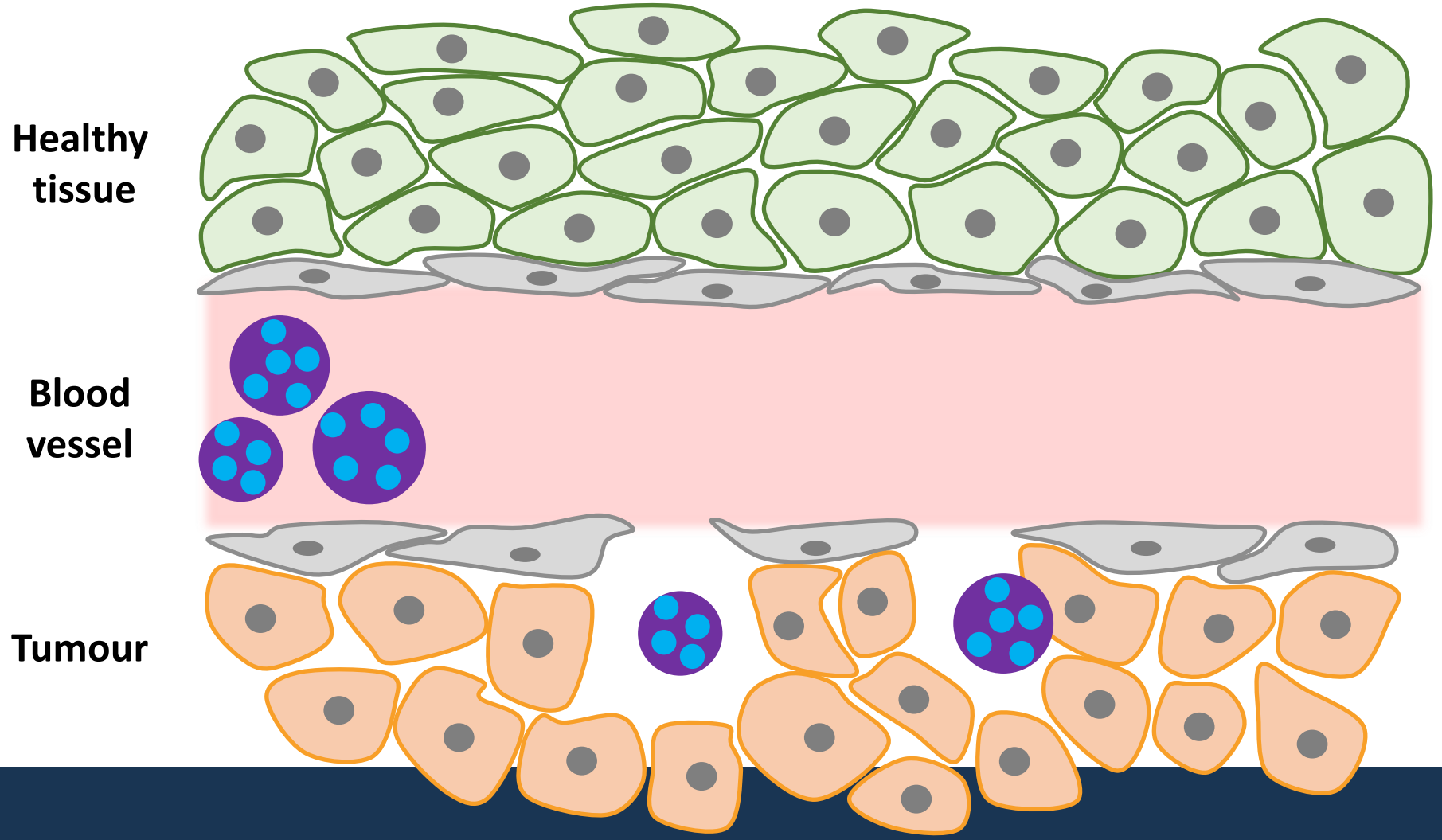
Krebstherapie: EPR-Effect

- **E**nhanced **P**ermeability and **R**etention **Effect** (Hiroshi Maeda 1986)
- Passive targeting of tumour tissue by prolonged circulation



Krebstherapie: EPR-Effect

- **E**nhanced **P**ermeability and **R**etention **Effect** (Hiroshi Maeda 1986)
- Passive targeting of tumour tissue by prolonged circulation



Drug

Drug delivery system

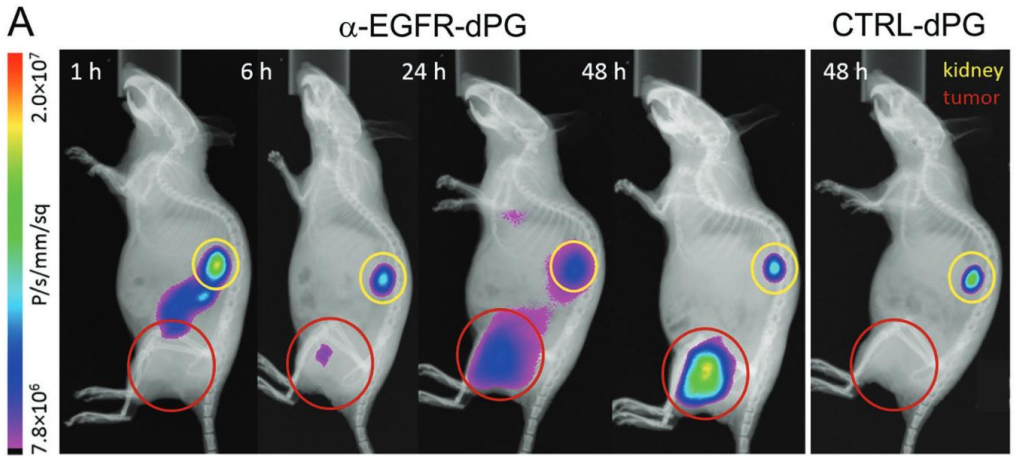
<10 nm – Excretion

>200 nm – no diffusion into the tissue

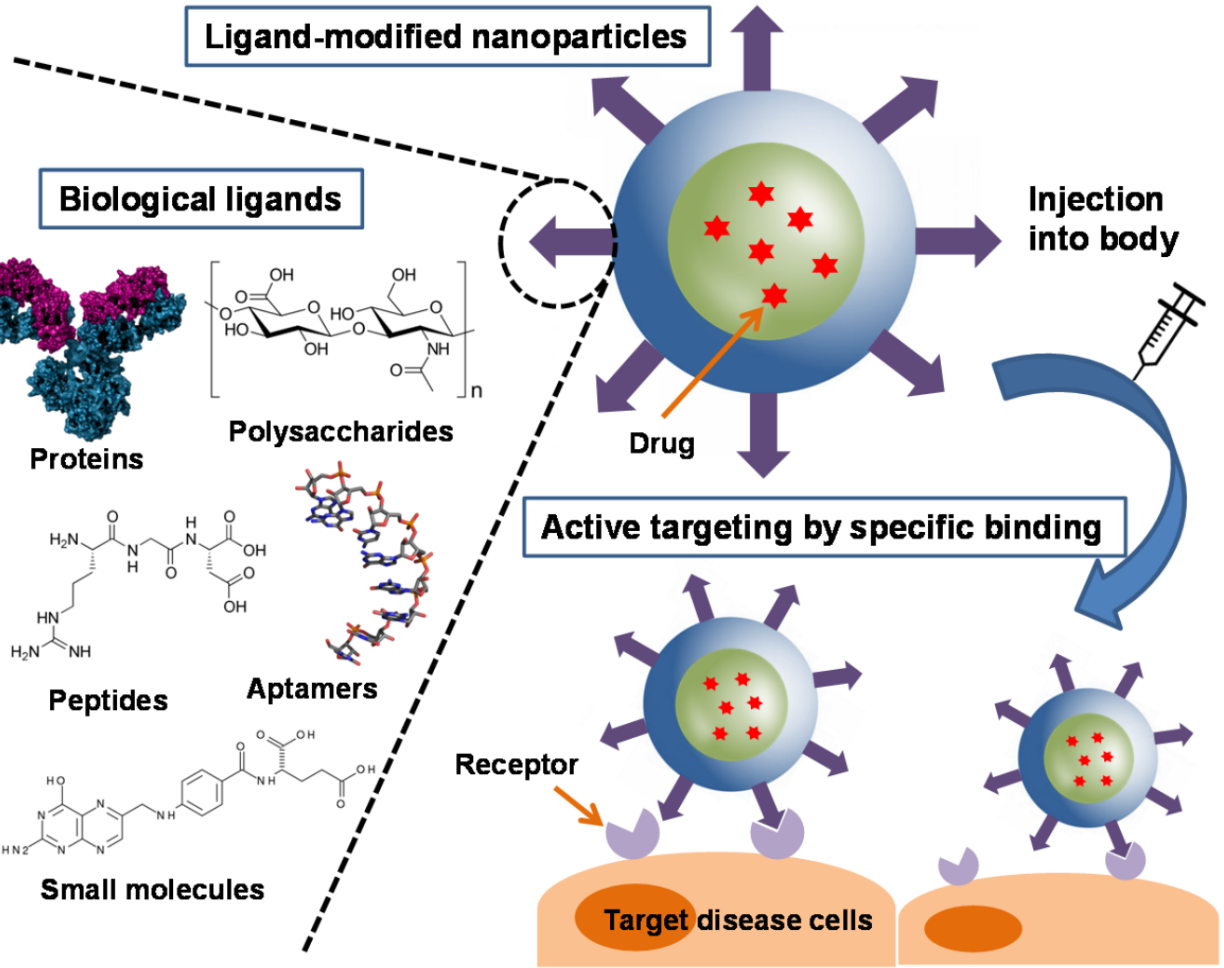
Long circulation times necessary (stealth!)

Aktive (Tumour)-Targeting

- Specific ligands
- Binds to specific cell/tissue type
- Only works in the absence of unspecific interaction

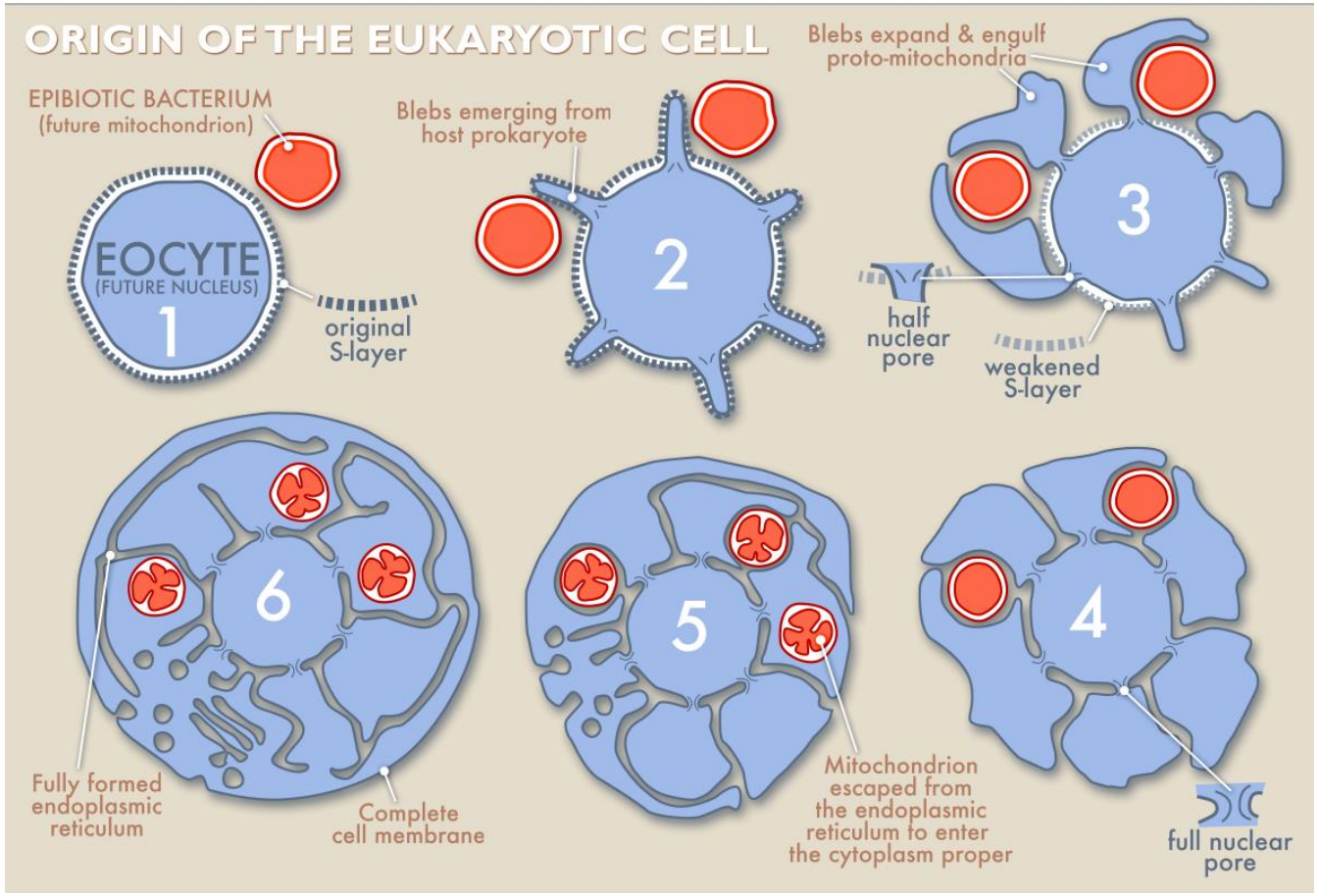


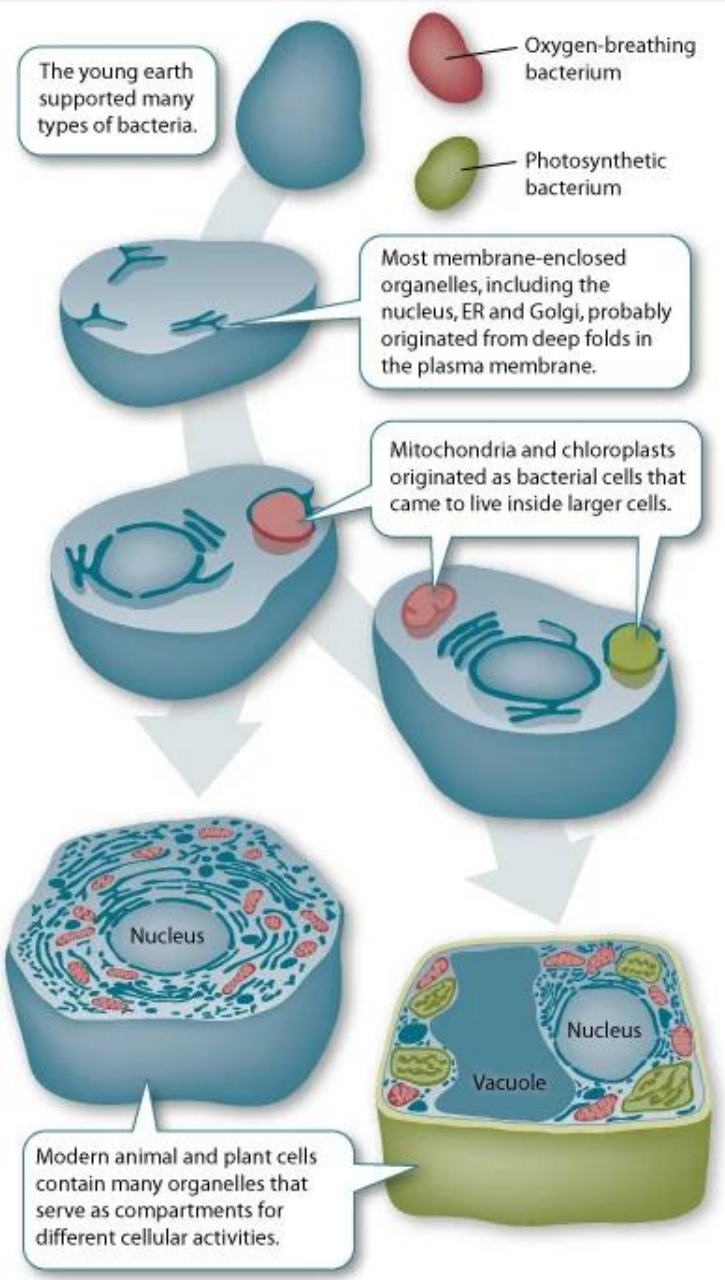
Pant, K., Neuber, C., Zarschler, K., Wodtke, J., Meister, S., Haag, R., Pietzsch, J., Stephan, H., Active Targeting of Dendritic Polyglycerols for Diagnostic Cancer Imaging. *Small* 2020, 16, 1905013.



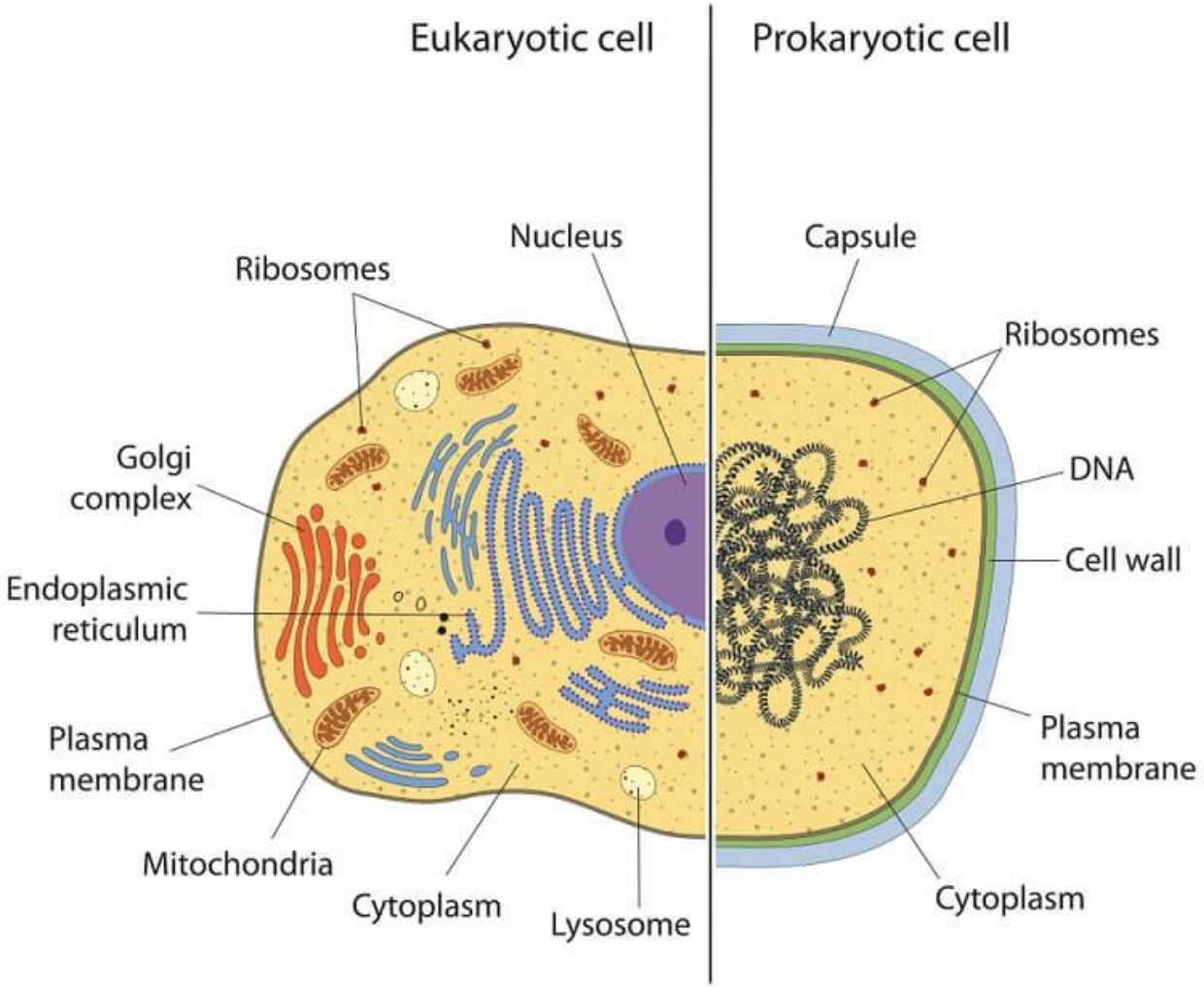
Yoo J, Park C, Yi G, Lee D, Koo H. Active Targeting Strategies Using Biological Ligands for Nanoparticle Drug Delivery Systems. *Cancers (Basel)*. 2019;11(5):640

Where to deliver: the cell

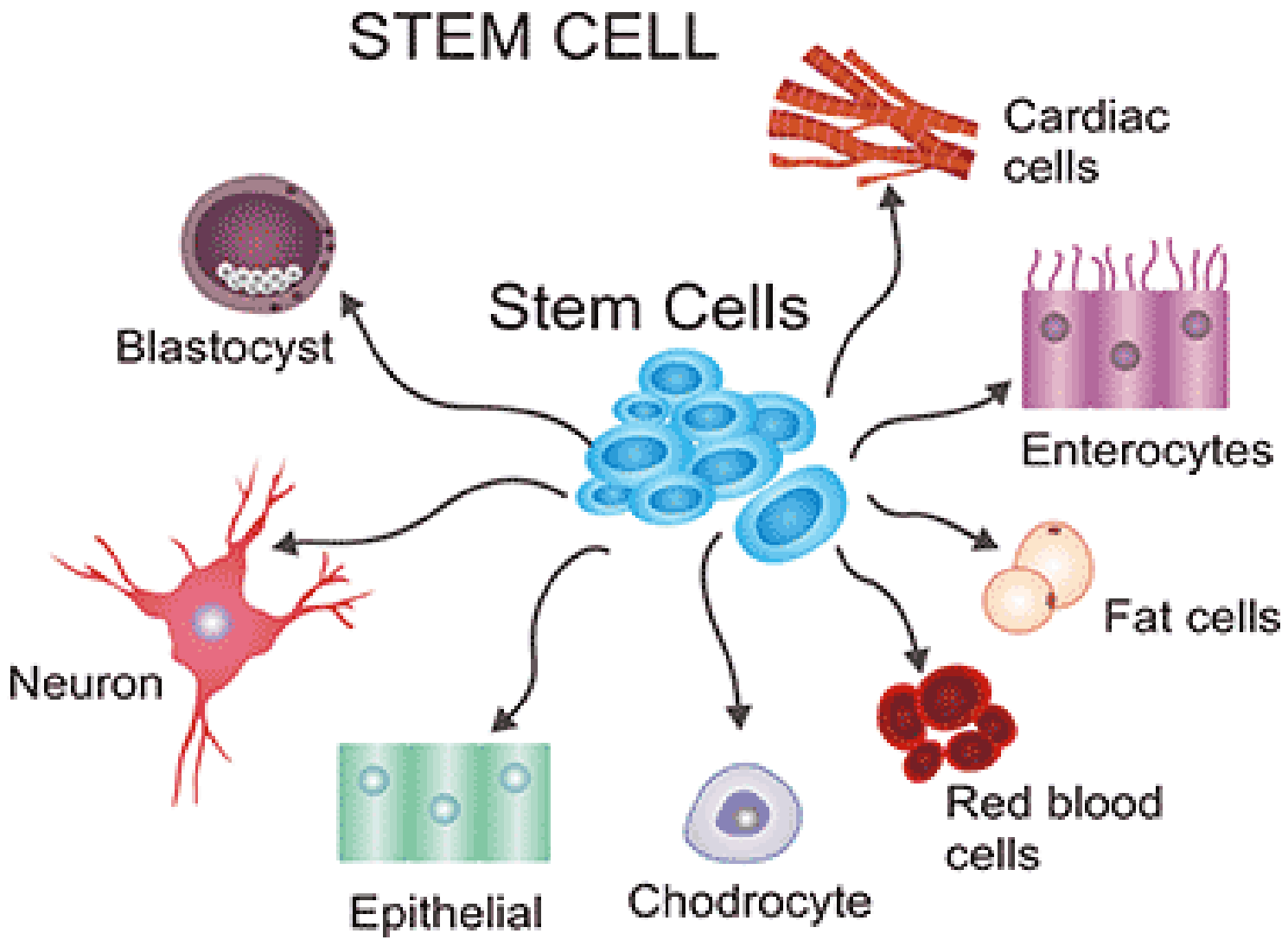




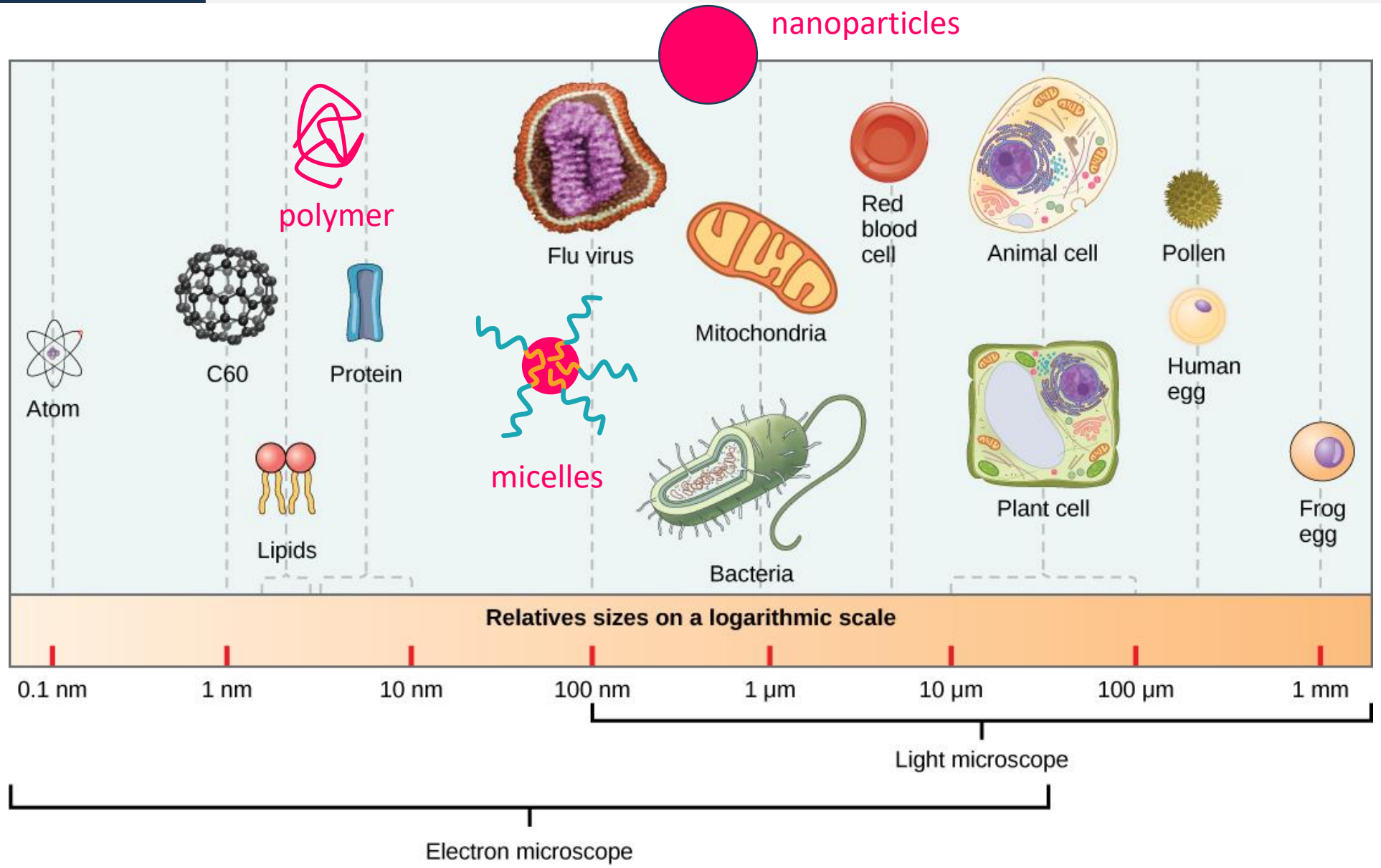
Eukaryotic vs. prokaryotic cell



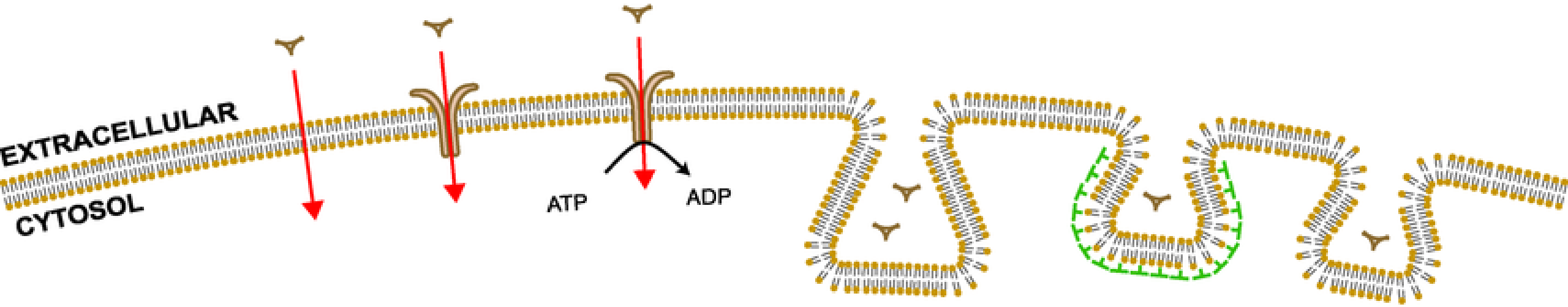
Differentiation of cells



Size of cells



Cellular Entry

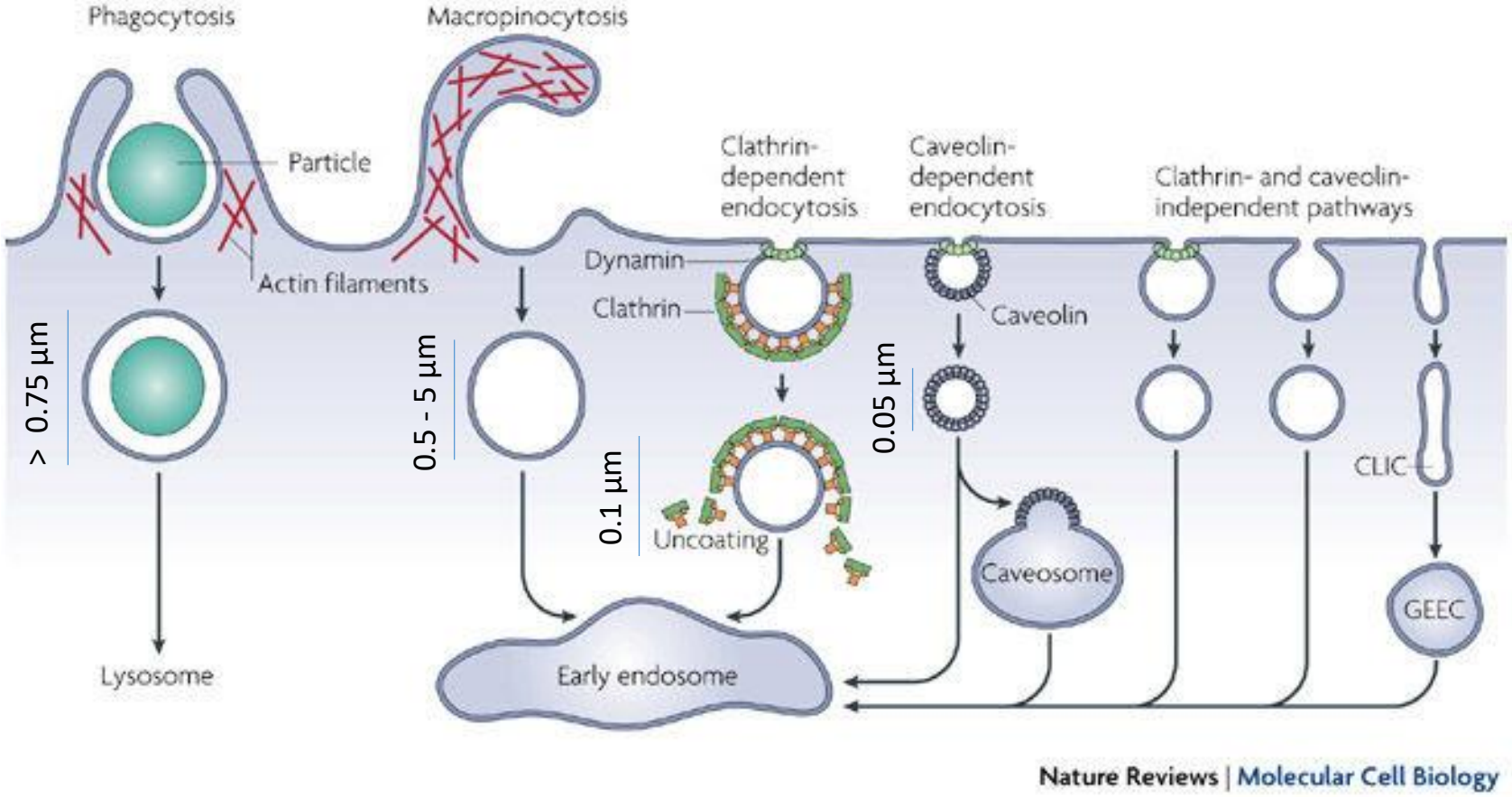


PASSIVE DIFFUSION	FACILITATED DIFFUSION	ACTIVE TRANSPORT	MACROPINOCYTOSIS	CLATHRIN DEPENDENT ENDOCYTOSIS	CAVEOLIN DEPENDENT ENDOCYTOSIS
	- transporter specific inhibitors	- low temperature - transporter specific inhibitors	+ phorbol esters + diacylglycerols - amiloride, EIPA	- chlorpromazine - K^+ depletion - MDC	- filipin - nystatin

DOI: 10.1039/B922209J

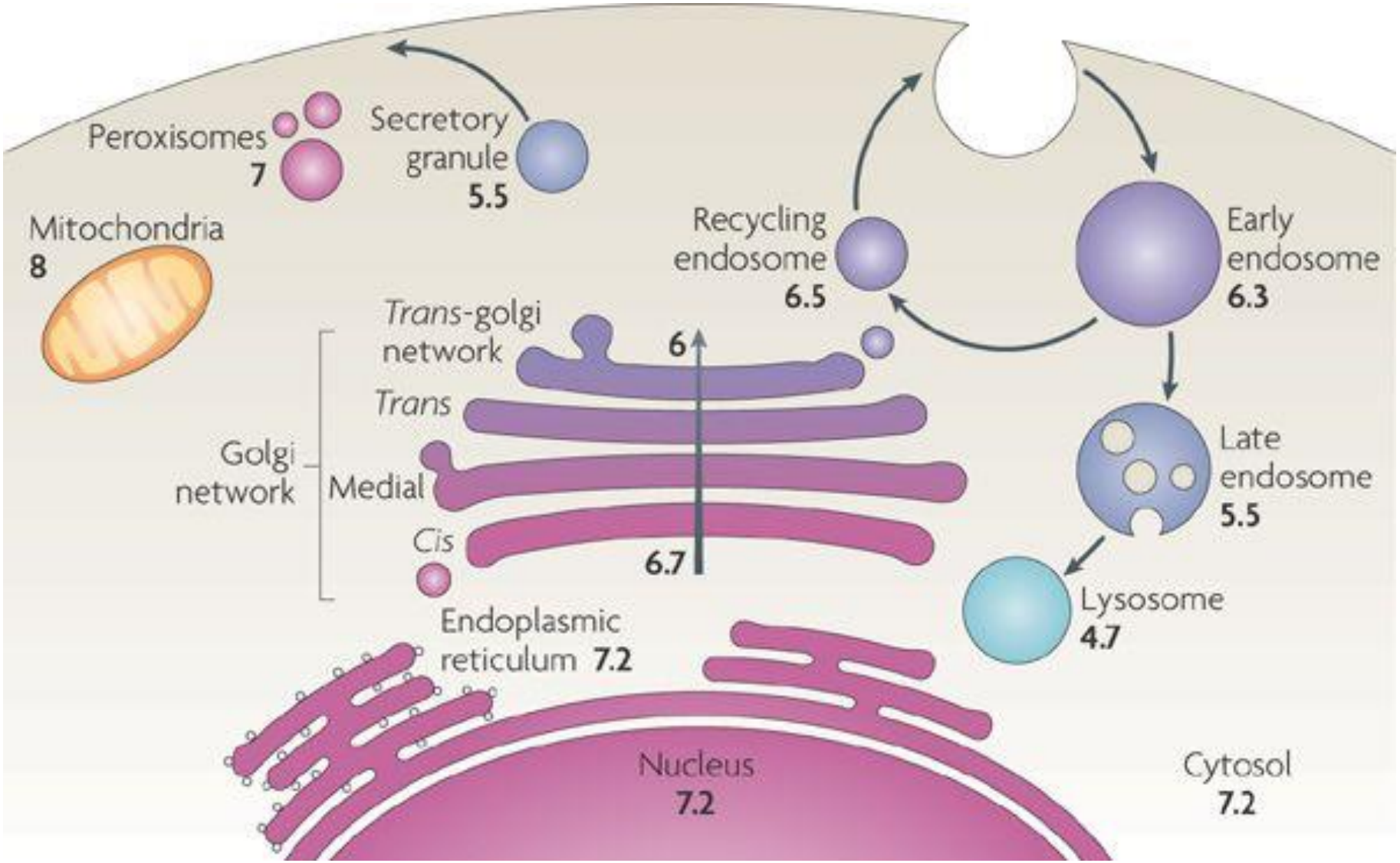
Endocytosis Pathways

- S. Mayor, R. E. Pagano, *Nature Reviews Molecular Cell Biology* **2007**, *8*, 603.



CLIC - clathrin- and dynaminindependent carriers
GEEC - glycosyl phosphatidylinositol-anchored protein enriched early endosomal compartments

Cellular vesicular trafficking



The pH of individual cellular organelles and compartments in a prototypical mammalian cell. The values were collected from various sources. The mitochondrial pH refers to the matrix, that is, the space contained by the inner mitochondrial membrane. Early endosomes refer to the sorting endosomal compartment. The pH of the multivesicular late endosome refers to the bulk luminal fluid; the pH of the fluid contained by the internal vesicles might differ.

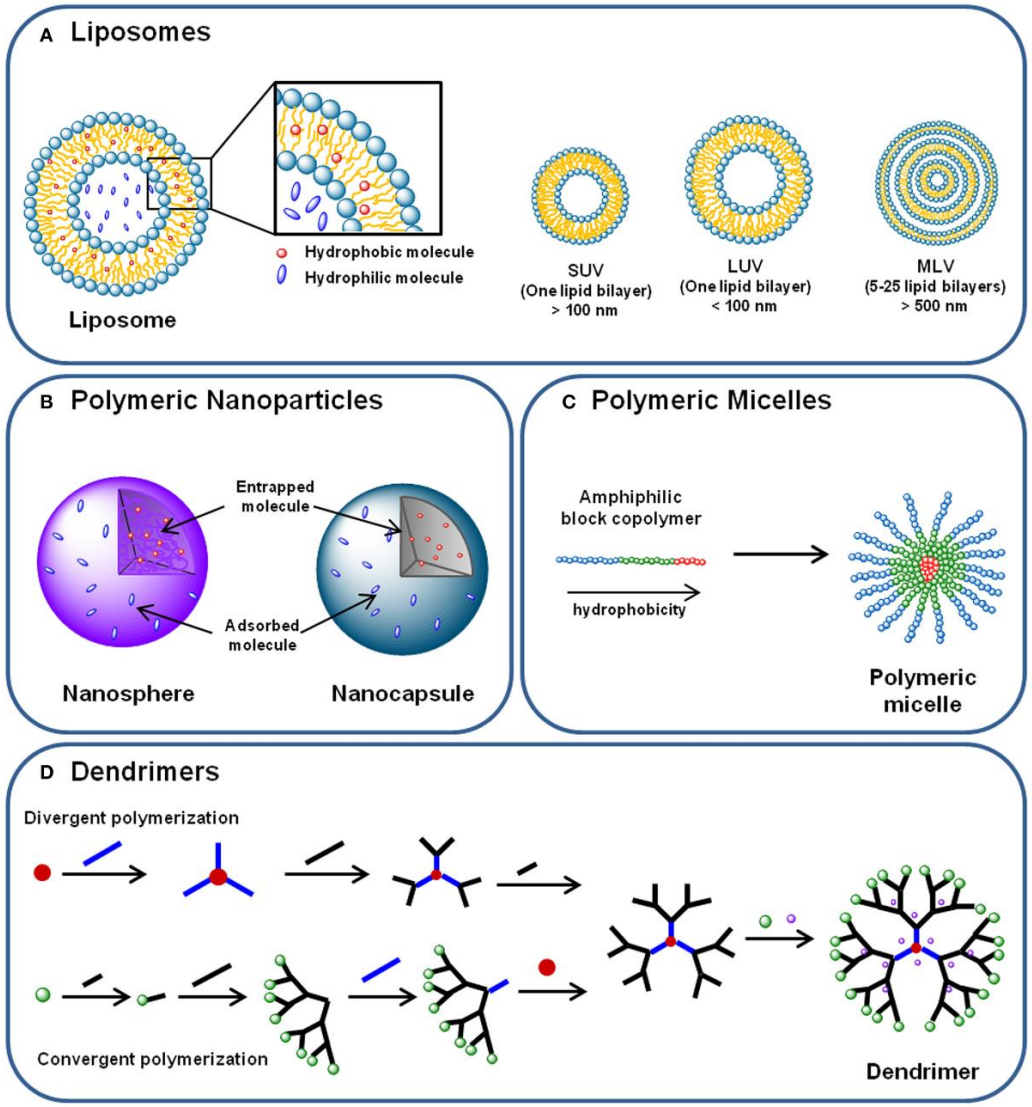
doi: 10.1038/nrm2820

Examples for Nanotransporters

Drug attachment:

- Covalent (but cleavable)
- non-covalent (e.g. by incorporation into hydrophobic domain)

- Reproducible synthesis (e.g. by self-assembly)
- Functionalization of the interface essential (e.g. PEGylation)



Conniot J, Silva JM, Fernandes JG, et al. Cancer immunotherapy: nanodelivery approaches for immune cell targeting and tracking. *Front Chem*. 2014, 2:105.

Take home message

- Drug delivery is a concept to improve the **pharmaceutical properties** (pharmacokinetics, solubility, toxicity, availability, …) of drugs by using a **transporter** (e.g. micelles, nanoparticle, …)
- There are different ways to construct such vehicles, **interface** modification is essential to modulate interaction with biology (proteins, cells, tissue, immune system)
- Polymers can also directly be attached to drugs (e.g. **PEGylation**)
- The **stealth effect** can be used to shield from unspecific interactions and is essential for targeted drug delivery of passive targeting via the **EPR-effect**