MUNI PHARM

Department of Natural Drugs

Supramolecular Pharmacy

10. Nanoparticles for drug delivery

Ondřej Jurček

Nanochemistry, nanotechnology, nanoparticles

- Chemistry of multi-nanometer scale molecules (dimensions of 2-200 nm)
- ***Nanotechnology*** a field of applied science and technology based on the control, manipulation, and fabrication of matter on the size scale approaching that of atoms and molecules
- Nanotechnology is highly multidisciplinary and draws on techniques and knowledge from applied physics, materials science, interface and colloid science, device physics, chemical and biological engineering and of course supramolecular chemistry
- ***Nanoparticles (NPs)*** very small usually approximately spherical fragments of material of radius in the approximate range 2–100 nm
- Nanoparticles can be made of any material and includes crystalline or amorphous solid particles
- NPs = nanocrystals, quantum dots (semiconductor particles having often fluorescence), nanoclusters (1-10 nm NPs)
- NPs are usually monodispersed (size distribution <15 %)
- NPs are often used as suspension in some kind of solvent (colloid)
- Solid usually does not separate as a precipitate (size, stabilization by coating – prevents aggregation, increases solubility)

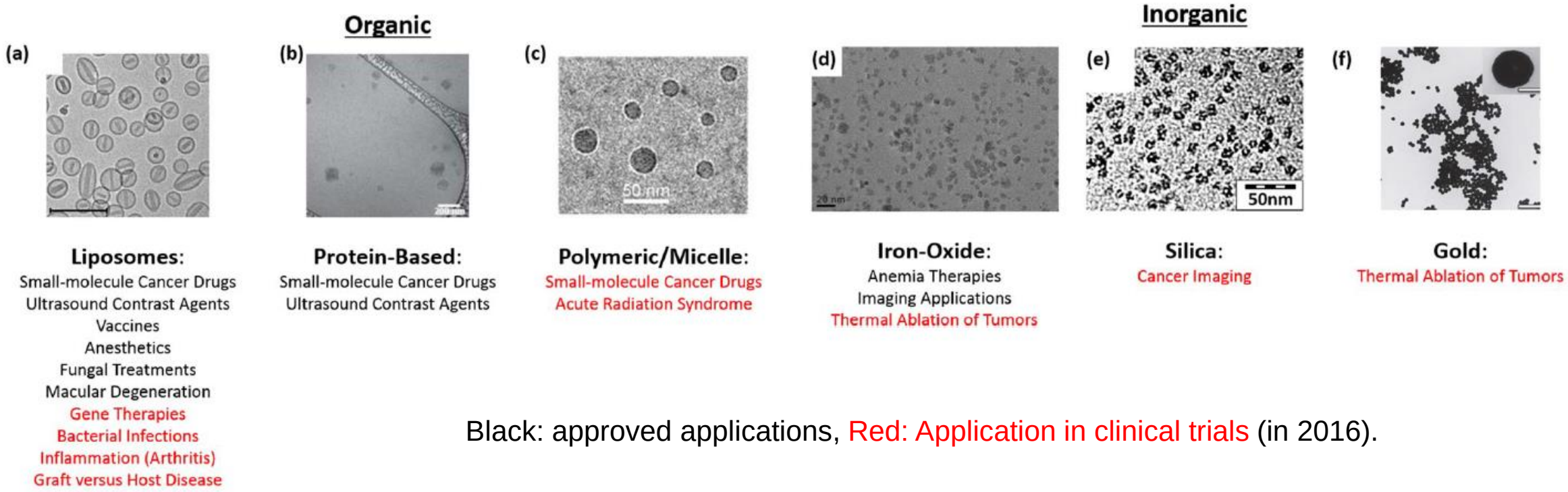
Nanoparticles (NPs) in drug delivery (nanocarriers)

- Oral, local, topical, and systemic nano-/microparticle delivery systems have been approved by FDA or EMA
- Intravenously administered NPs are the most studied preclinically and clinically
- Systemic delivery provides direct access to nearly all parts of the body
- ***Organic*** (including polymeric micelles and vesicles, liposomes, dendrimers, and hydrogels) and ***inorganic*** (including quantum dots, gold and mesoporous silica NPs)
- Organic materials: (a) NPs for gene therapy applications or (b) NPs for delivery of small molecule drugs for cancer treatment
- Organic NPs provide enhanced drug protection, controlled release, extended circulation, improved targeting to diseased tissues/cells
- Inorganic NPs provide the same and stimuli responsive functions due to surface plasmon resonance (thermal heating or imaging) or magnetic responsiveness (MRI, magnetic targeting)
- Introducing new or improving the old therapies

Anselmo et al. *Bioengineering & Translational Medicine* 2016, 1, 10-29.

Clinically relevant NPs and their applications

- Nanoparticles have been developed to overcome the limitations of free therapeutics and navigate biological barriers — systemic, microenvironmental, and cellular — that are heterogeneous across patient populations and diseases
- Personalized delivery – precision medicine



Black: approved applications, Red: Application in clinical trials (in 2016).

Anselmo et al. *Bioengineering & Translational Medicine* 2016, 1, 10-29.

Organized efforts towards precision medicine

- US National Science and Technology Council (NSTC) launched the National Nanotechnology Initiative (NNI) in 2000
- The number of nanomedicines available to patients is drastically below projections for the field
- Gap comes from a lack of understanding of the differences in physiology and pathology between animal model species and humans
- Heterogeneity amongst patients can also limit the success of nanomedicines
- Few are recommended as first-line treatment options, and many show improvements in only a small subset of patients
- Moreover, growth, structure and physiology of diseased tissue alter NP distribution and functionality
- Complex systems: nanocarrier-mediated combination therapies — to alter multiple pathways, maximize the therapeutic efficacy against specific macromolecules, target particular phases of the cell cycle or overcome mechanisms of drug resistance

Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

Organized efforts towards precision medicine

- New focus on generating NPs to overcome biological barriers specific to patient subsets or disease states can be attributed, in part, to the increasing prevalence of precision, or personalized medicine and the creation of the Precision Medicine Initiative (PMI) in 2015
- Precision medicine is to utilize patient information — such as genetic profile, environmental exposures or comorbidities — to develop an individualized treatment plan
- Minimizes the impact of patient heterogeneity and allows for more accurate patient stratification, improved drug specificity and optimized dosing or combinatorial strategies

Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

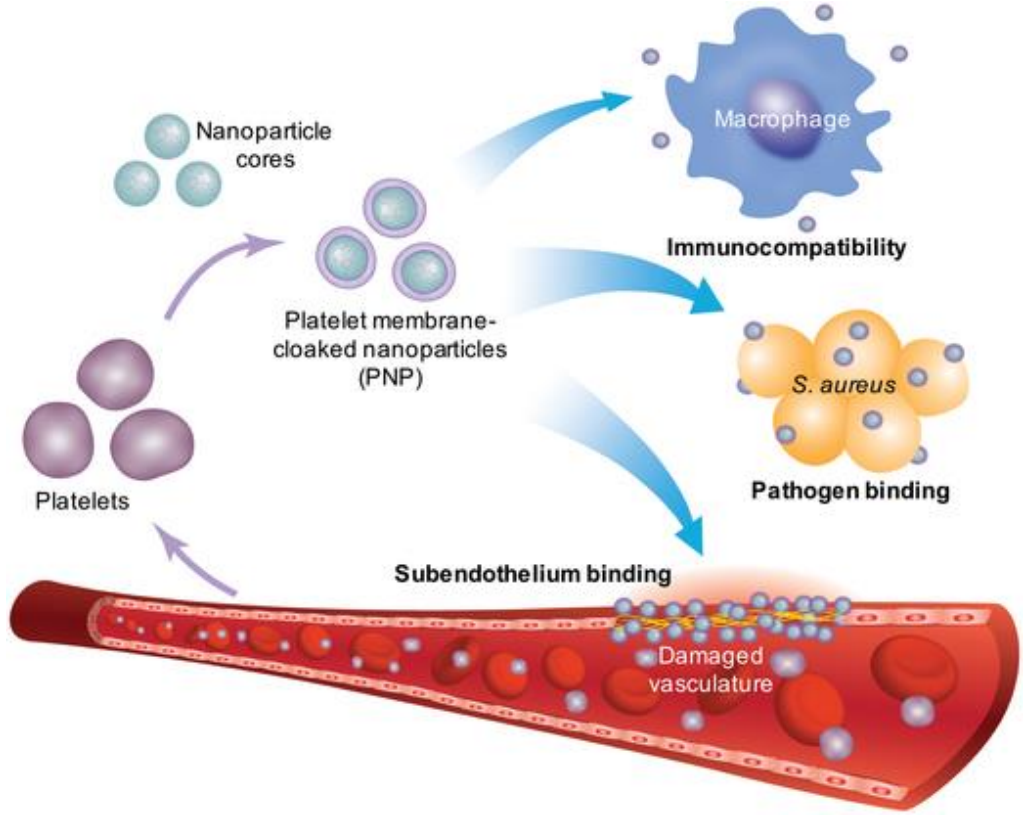
Biological barriers to precision medicine applications

- Biodistribution and drug delivery are difficult to achieve as NPs face both physical and biological barriers: shear forces, protein adsorption and rapid clearance
- These are often altered in disease states and can be even more difficult to overcome with a generalized, one-size-fits-all approach, but also patient specific
- Systemic delivery – ***circulation, stability, and clearance***
- While in ***circulation*** excretion, blood flow, coronas and phagocytic cells can reduce NP stability and delivery
- NPs with a diameter less than 10 nm have generally been shown to be rapidly eliminated by the kidneys, whereas NPs larger than 200 nm risk activating the complement system*
- To avoid rapid excretion based on surface properties, many NP formulations incorporate PEG as a stealth coating
- PEGylation improves the circulation time by altering the NP size and solubility while shielding the NP surface from enzymes and antibodies that may induce degradation, secretion and clearance

* Plasma proteins that induce inflammation and aid in the clearance of foreign bodies or damaged cells by enhancing antibody and phagocytic cell activity

Biological barriers to precision medicine applications

- Platelet (thrombocyte) membrane cloaking
- NP ***stability*** is greatly affected by how its composition material interacts with the environment
- Lipid-based and polymer-based NPs are the most susceptible to instability and aggregation both in circulation and in storage
- The balance between stabilization and effective intracellular delivery — which typically requires carrier degradation — must be considered



Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

NPs interaction with blood vessels and blood components

- In the bloodstream, NPs experience varying flow rates that induce shear stress which can lead to their damage, prevent their movement into surrounding tissues
- Larger microparticles have higher probability of localizing to vessel walls, non-spherical NPs (ellipsoids, disc, and rod-like) show better margination than spherical
- Non-specific adherence of serum proteins and lipids forms a corona on the surface of NPs
- This corona will dictate the distribution of the NP, and can compromise stability of both the NP and its cargo
- For example, coronas containing apolipoprotein E (ApoE) act as targeting moieties for low-density lipoprotein receptors, which leads to NP delivery to hepatocytes and, in some instances, across the blood–brain barrier (BBB)

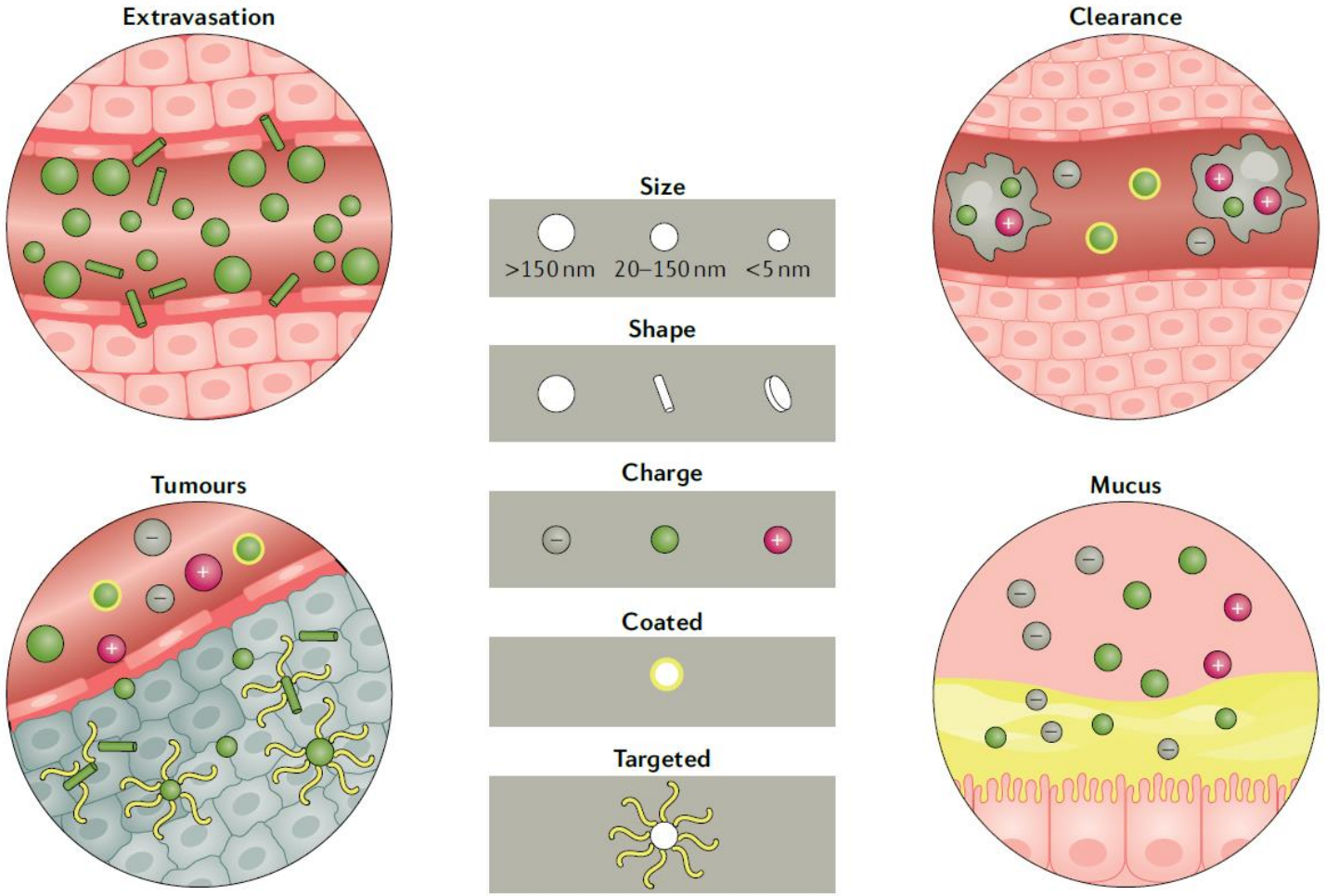
Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

NPs interaction with blood vessels and blood components

- ***Clearance*** usually results from the interaction with the mononuclear phagocytic system (MPS) or reticuloendothelial system (RES)
- Systems feature phagocytes (predominantly macrophages), monocytes and dendritic cells, which take up NPs and accumulate in the spleen and liver
- Stiffer NPs are often cleared more rapidly
- Cationic NPs are generally most rapidly cleared, followed by anionic NPs, whereas neutral and slightly negative NPs have the longest half-lives in circulation (PEGylation or cell membrane coating prevents clearance)
- Spherical NPs induce a stronger immune response overall. Uptake by phagocytic cells has been related to the NP curvature and aspect ratio: triangular and rod-shaped NPs show more uptake than star-shaped or spherical NPs, and rod-shaped NPs induce more inflammation in macrophages

Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

NPs interaction with blood vessels and blood components



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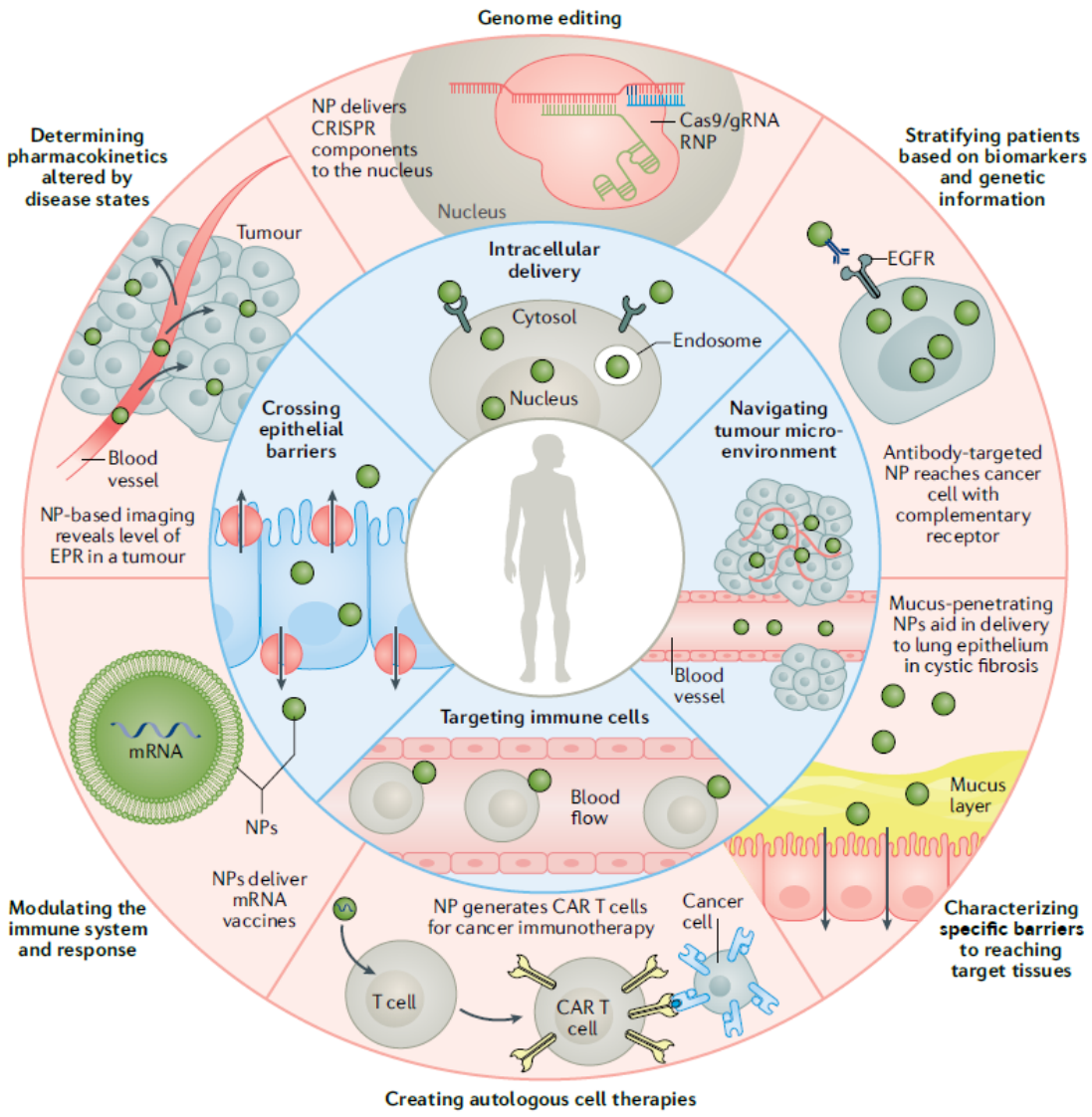
Biological barriers to precision medicine applications

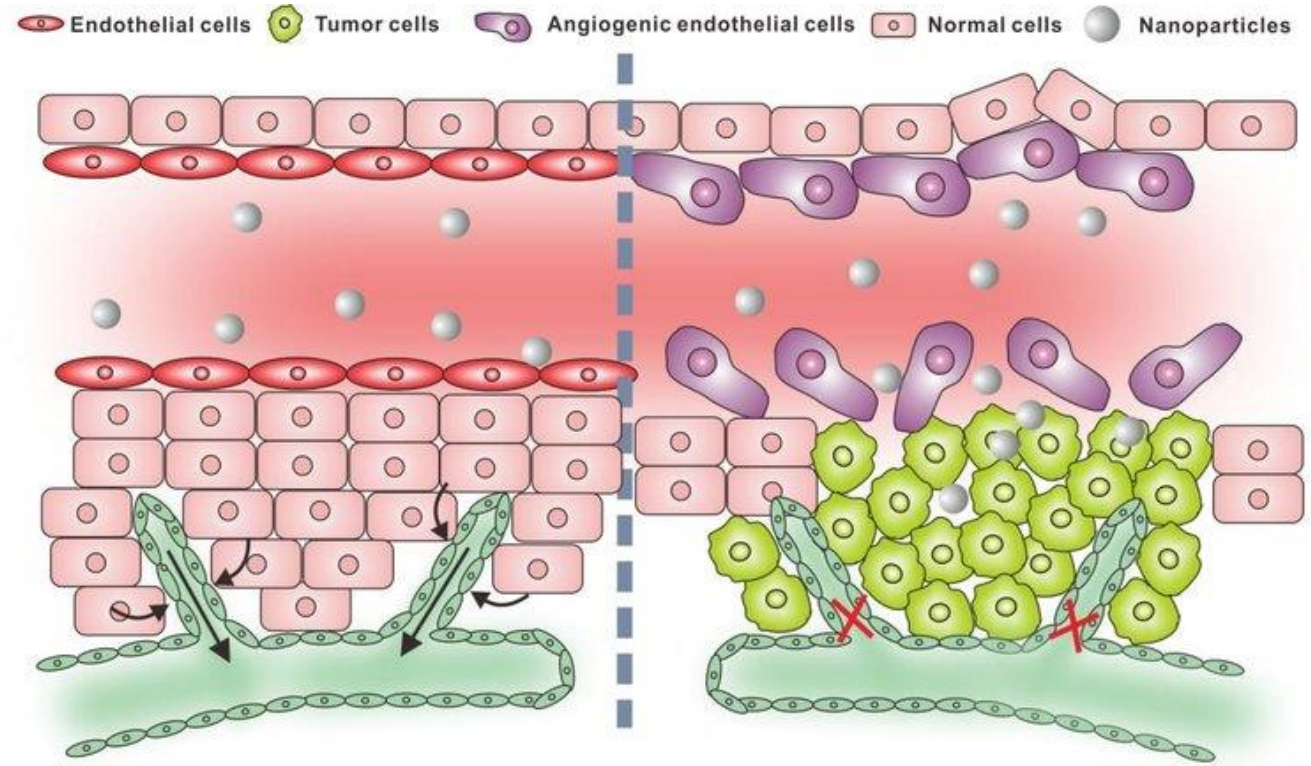


CAR, chimeric antigen receptor;
EGFR, epidermal growth factor receptor;
EPR, enhanced permeation and retention;
gRNA, guide RNA;
RNP, ribonucleoprotein.

Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

Enhanced permeability and retention (EPR) effect

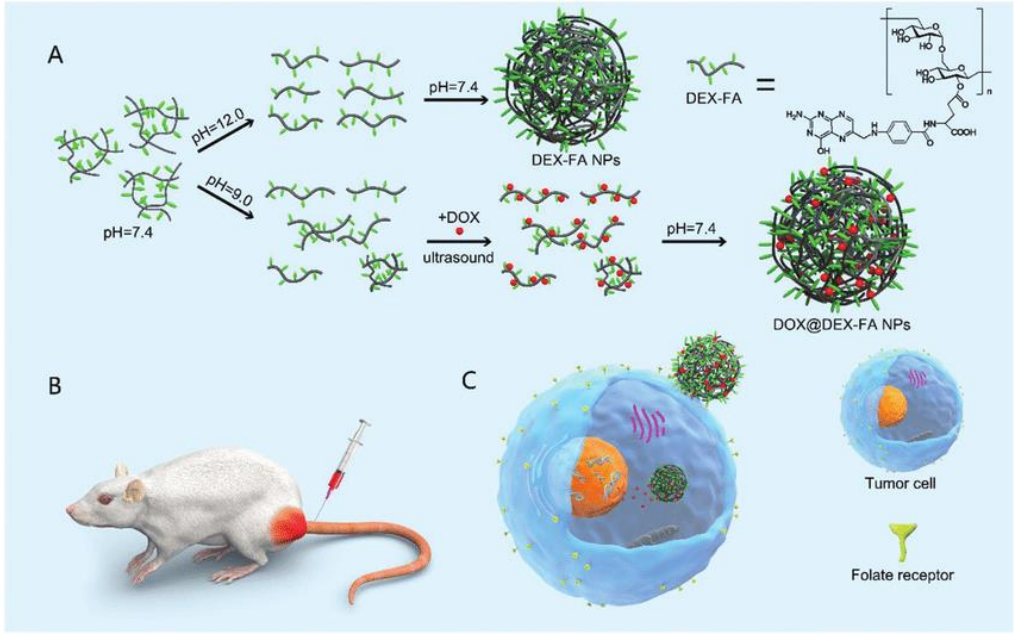
- high–molecular weight nontargeted drugs and prodrugs accumulate in tissues that offer increased vascular permeability, such as in sites of inflammation or cancer



Xie et al. *Curr. Cancer Drug Target* **2019**, *19*(4), 257.

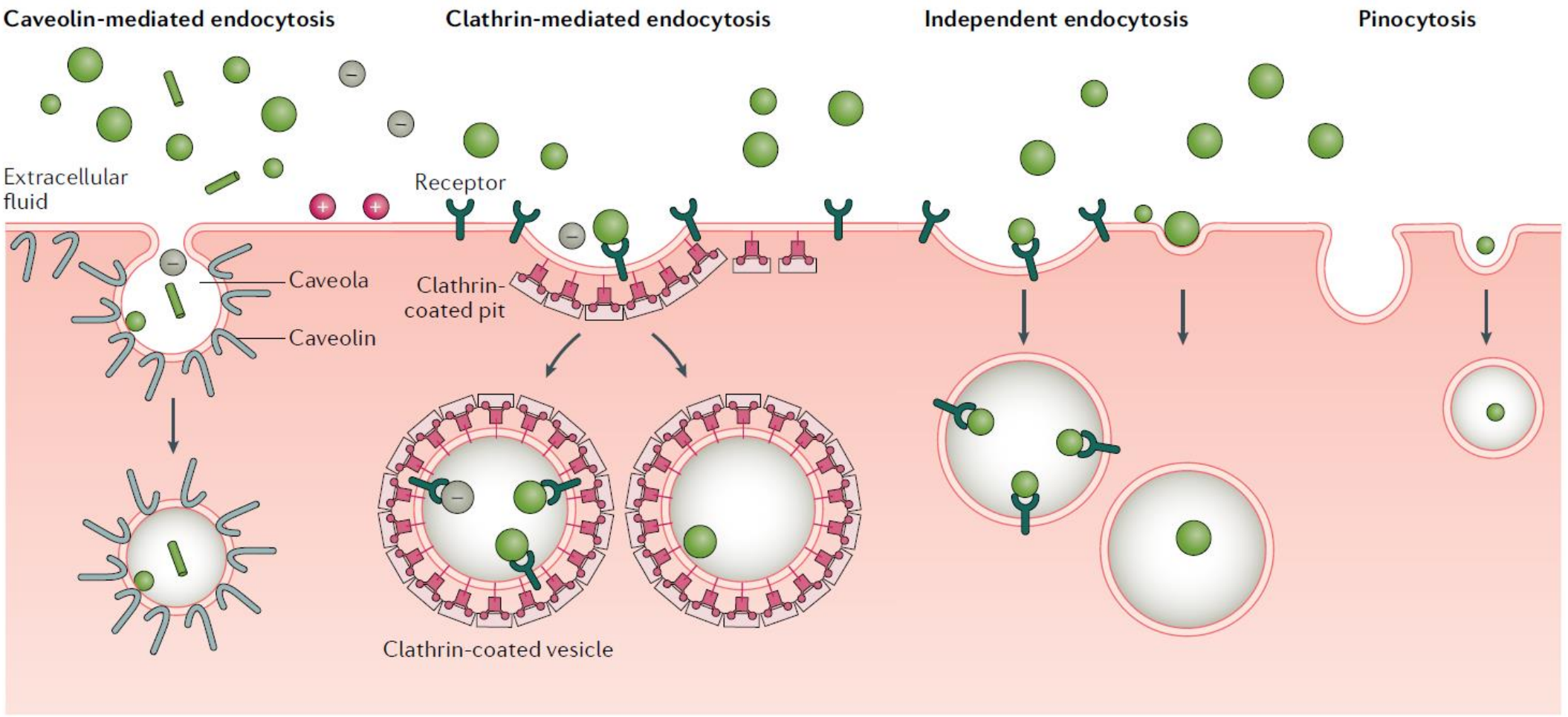
Nanoparticle targeting

- Many NP platforms have added targeting moieties to their surface to direct their delivery
- Targeting moieties: antibodies, glucose, transferrin, folate, transporters and integrin ligands
- Use interactions with molecules on the target cell's surface, such as ligand–receptor, enzyme–substrate or antibody–antigen mediated interactions.
- Targeted NPs must be engineered with a targeting moiety density that allows for these cell surface interactions
- Ratio of receptors to ligands and the number of interactions needed to overcome the initial energy barrier to NP uptake



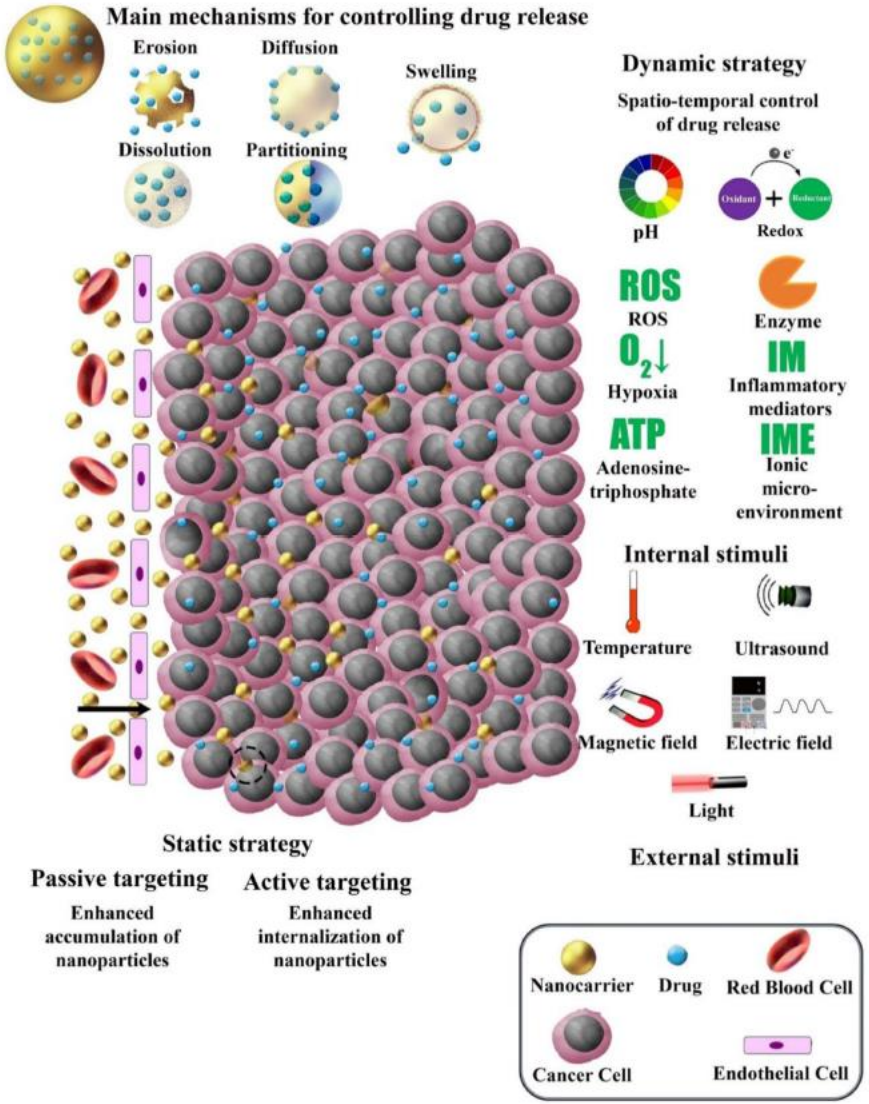
Mitchell et al. *Nature Reviews* 2021, 20, 101–124.
Tang et al. *Nanoscale* 2018, 10, 17265-17274.

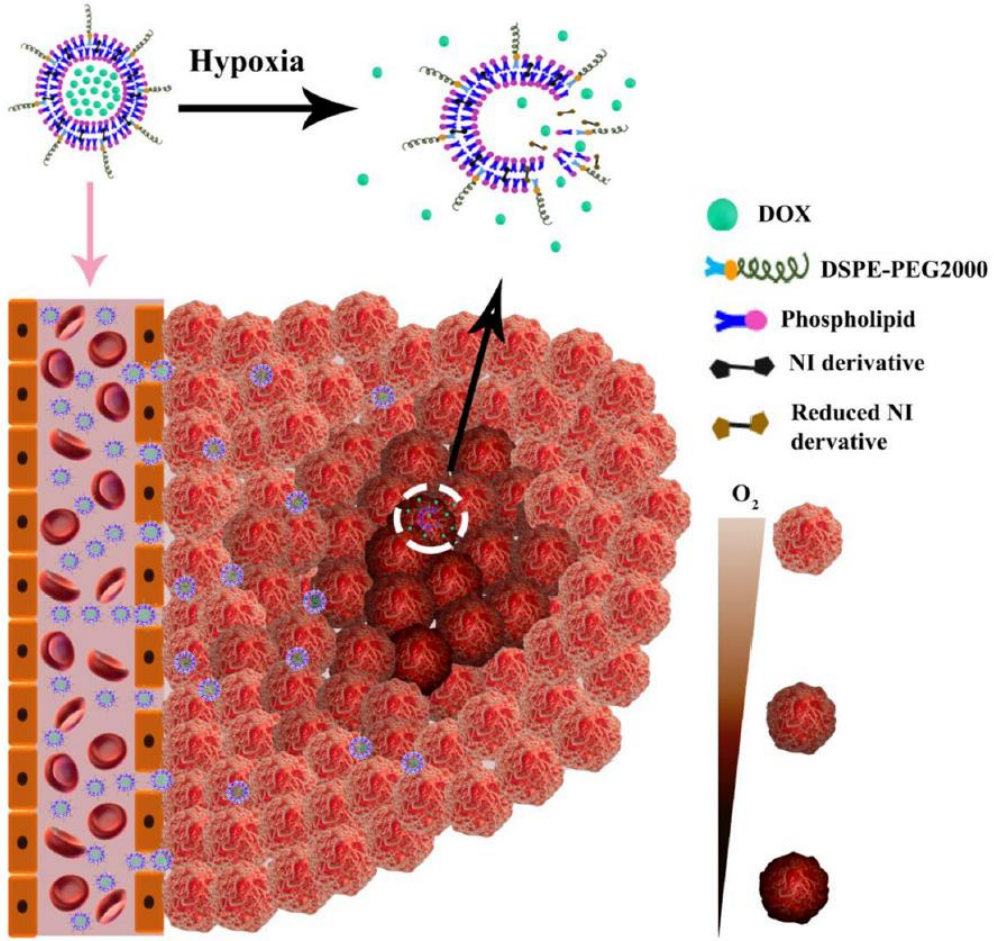
Common uptake pathways that determine NP fate



Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

Mode of action



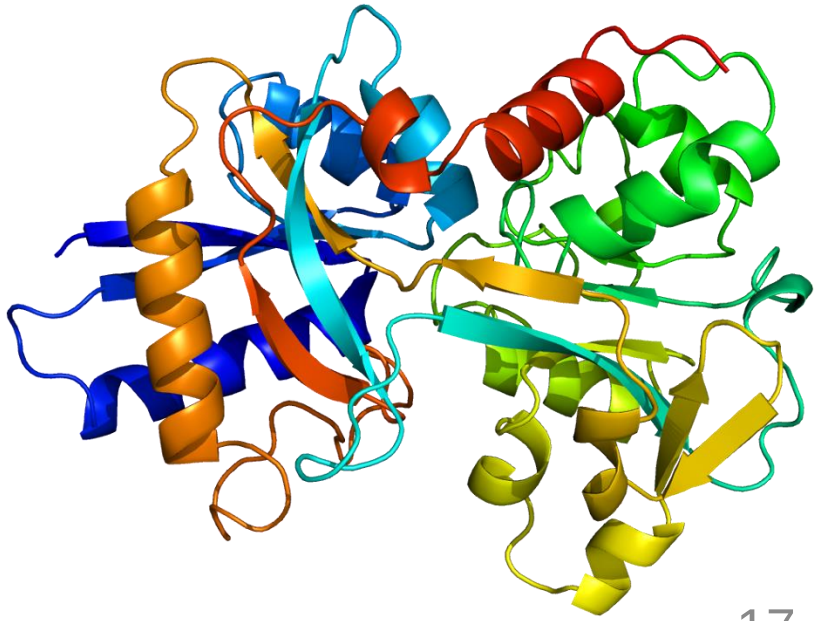


FDA/EMA approved (1995/1996) doxil (caelyx) – doxorubicin
Ovarian cancer (secondary to platinum based therapies)

Kashkooli et al. *Journal of Controlled Release* 2020, 327, 316–349.

Oral drug delivery

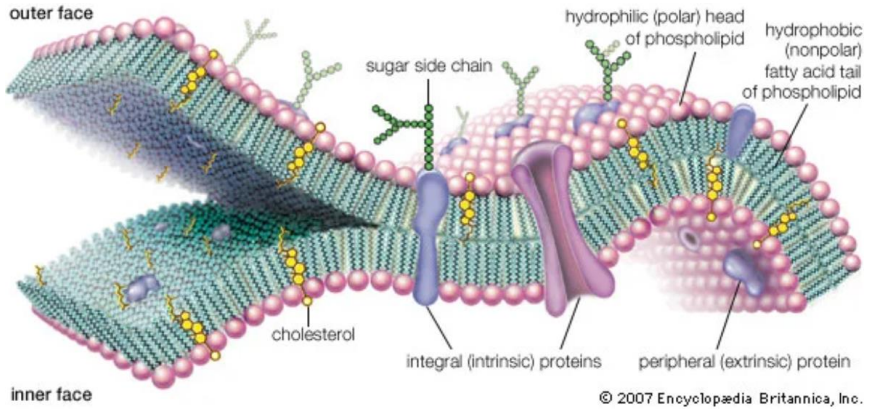
- Gastrointestinal tract presents numerous barriers for NPs
- Average optimal reported size for NP transcytosis in gastrointestinal applications seems to be around 100 nm
- Rod-shaped NPs generally outperform spherical particles
- Even when NPs are internalized by intestinal epithelial cells, only a small percentage undergo exocytosis
- Transferrin pathway can be exploited for transepithelial movement in the intestine
- Problem is nevertheless with formation of coronas
- Barriers are made heterogeneous by pathologies, such as inflammatory diseases, that may increase epithelial permeability and alter mucus production, pH and the gastrointestinal microbiome



Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

Order in liquids

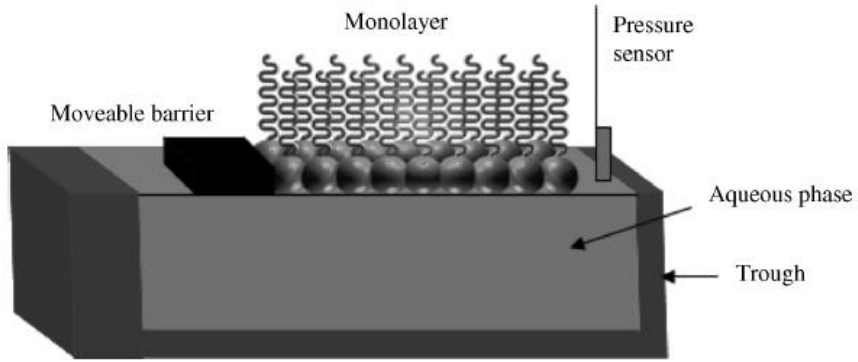
- Biological cell membranes are made of bulky phospholipids that are forced to order themselves in water by combination of hydrophobic effects and interactions between the solvent and the hydrophilic head group, forming capsule-like vesicles – cells
- Cell membrane must exist in the liquid phase to allow rapid biochemical transport and solution chemistry
- Solid-like long-term structure is needed to preserve membrane potentials, control cellular signaling and protect sensitive intracellular enzymes
- Cell membrane must also be sufficiently ordered to anchor transmembrane proteins such as ATPases
- Fluid mosaic model



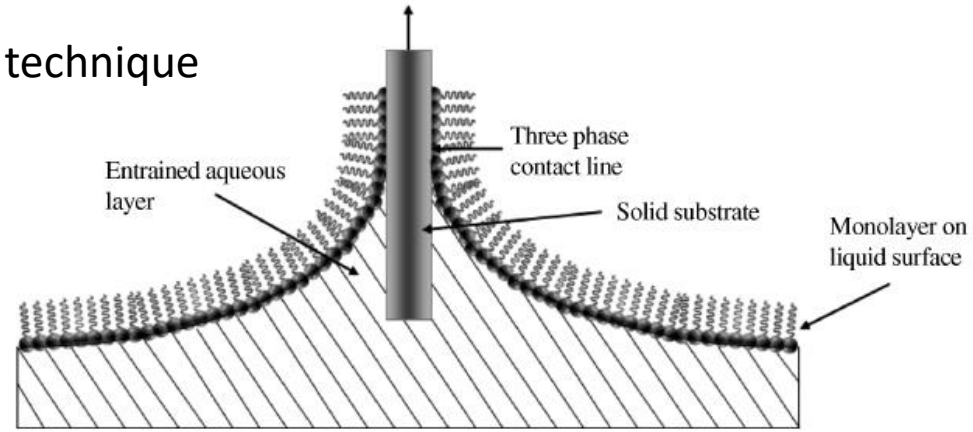
Surfactants, micelles, vesicles

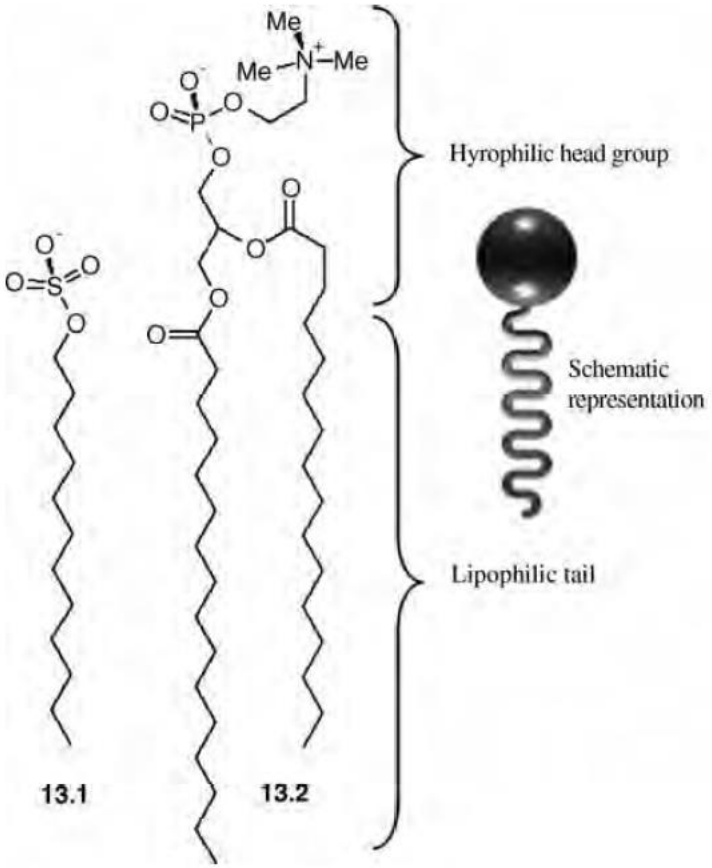
- Surfactant is a molecule that has two different moieties – polar, hydrophilic and non-polar lipophilic – they are amphiphiles
- Daily components – part of soap, washing liquid

Langmuir through



Langmuir-Blodgett technique

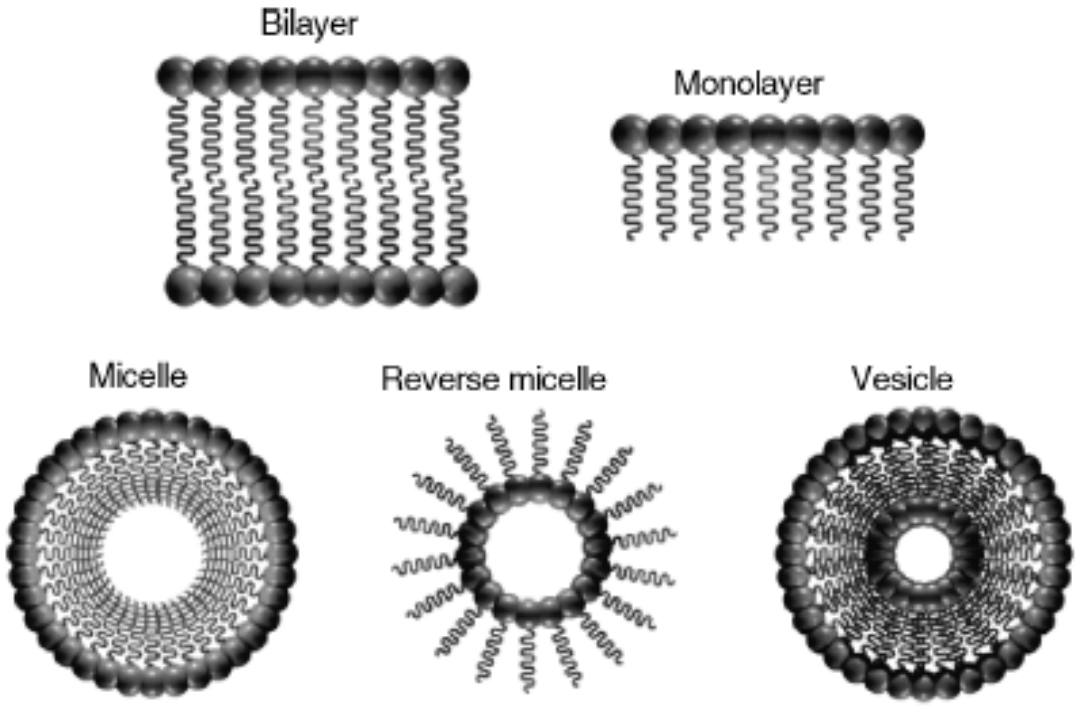


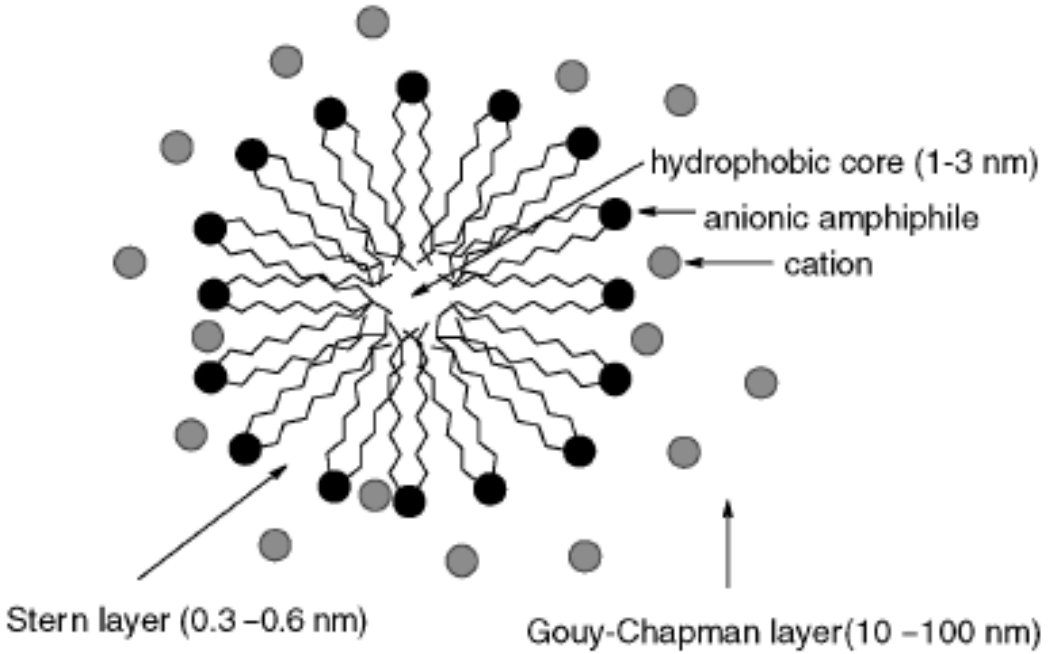


- anionic (phospholipids, soaps)
- cationic (quaternary ammonium salts)
- amphoteric (zwitterionic betaines)
- nonionic (fatty acids).

Ordered surfactant structures

- The mode of behavior depends on concentration and structure of surfactant
- Critical micelle concentration - CMC (T, mol dm^{-3})

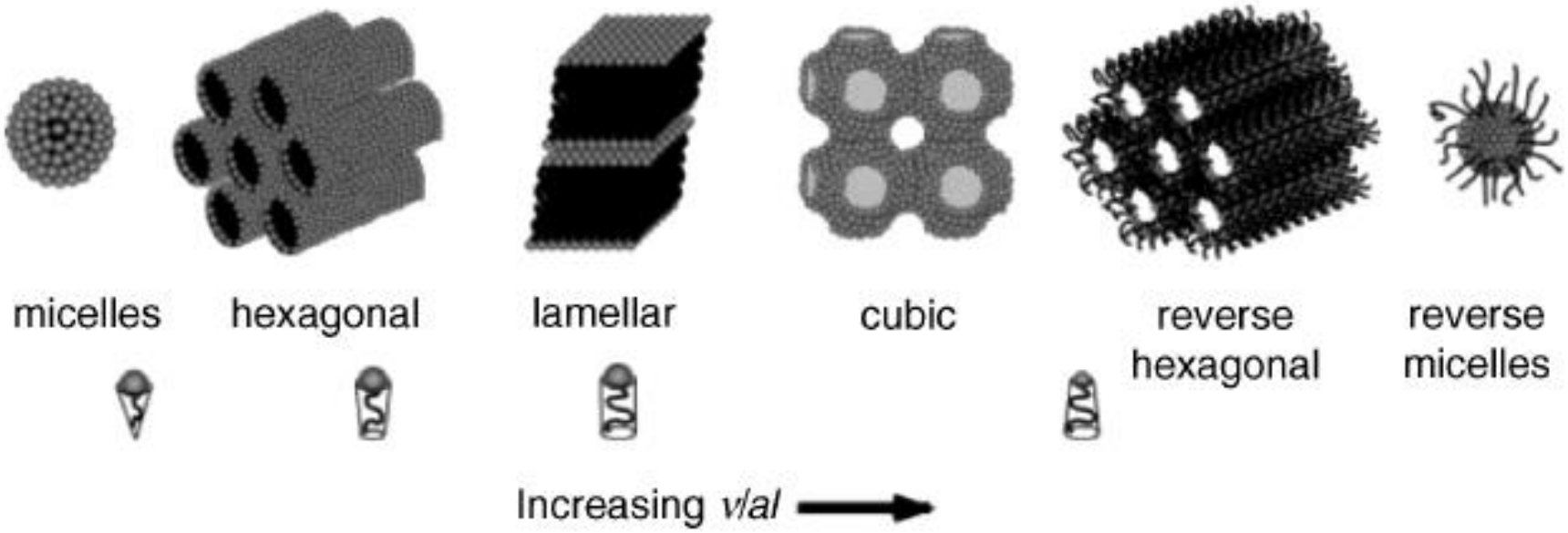




Jonathan W. Steed, Jerry L. Atwood for Supramolecular Chemistry, ISBN: 978-1-119-58251-9.

Changes of micelles

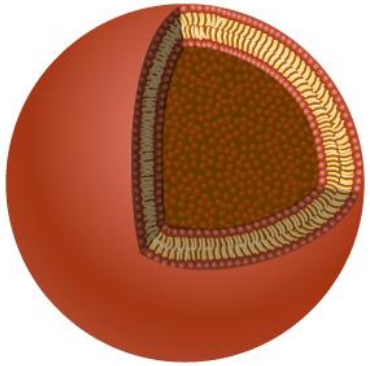
- Micelles go through several changes based on their concentration and size of the surfactant

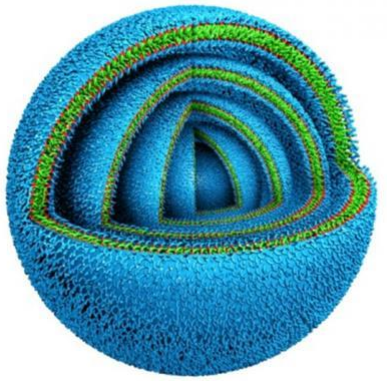


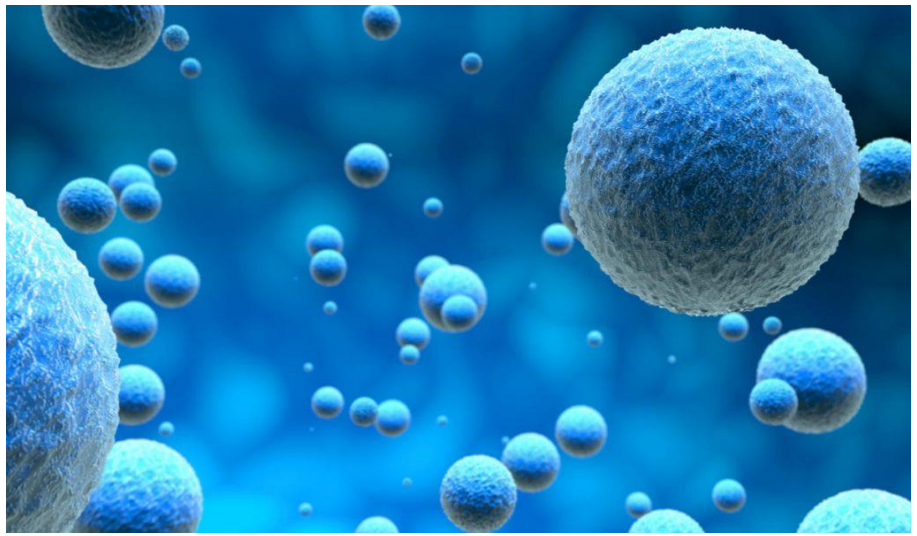
Jonathan W. Steed, Jerry L. Atwood for Supramolecular Chemistry, ISBN: 978-1-119-58251-9.

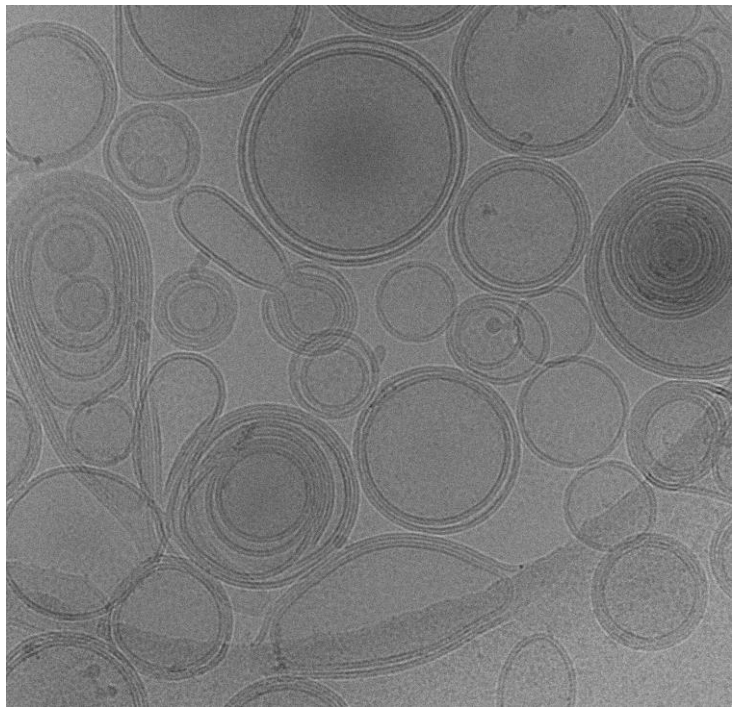
Bilayers and vesicles

- Sheet like micelles – vesicles
- Cells are formed of phospholipid bilayers
- Source of the origin of the first biological cells?
- Protocells



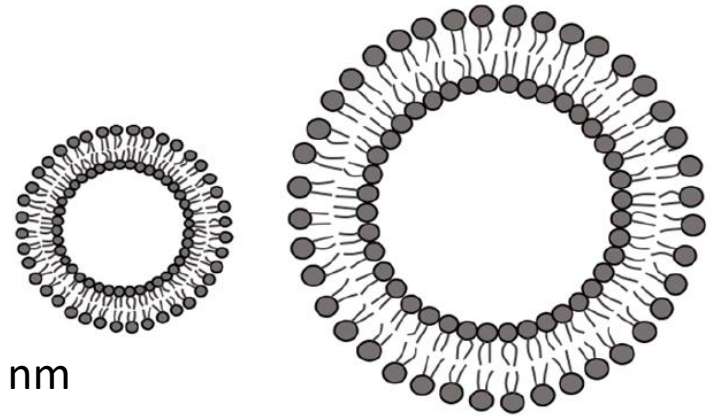






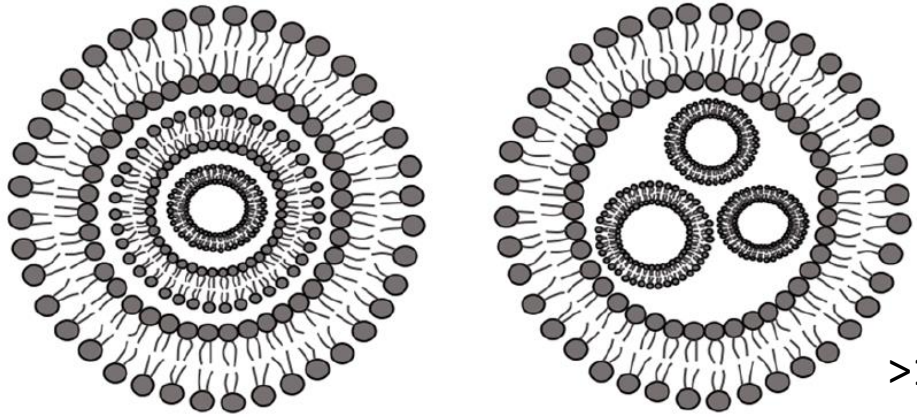
TEM: 79 000 x – ca 200 nm

Liposomes



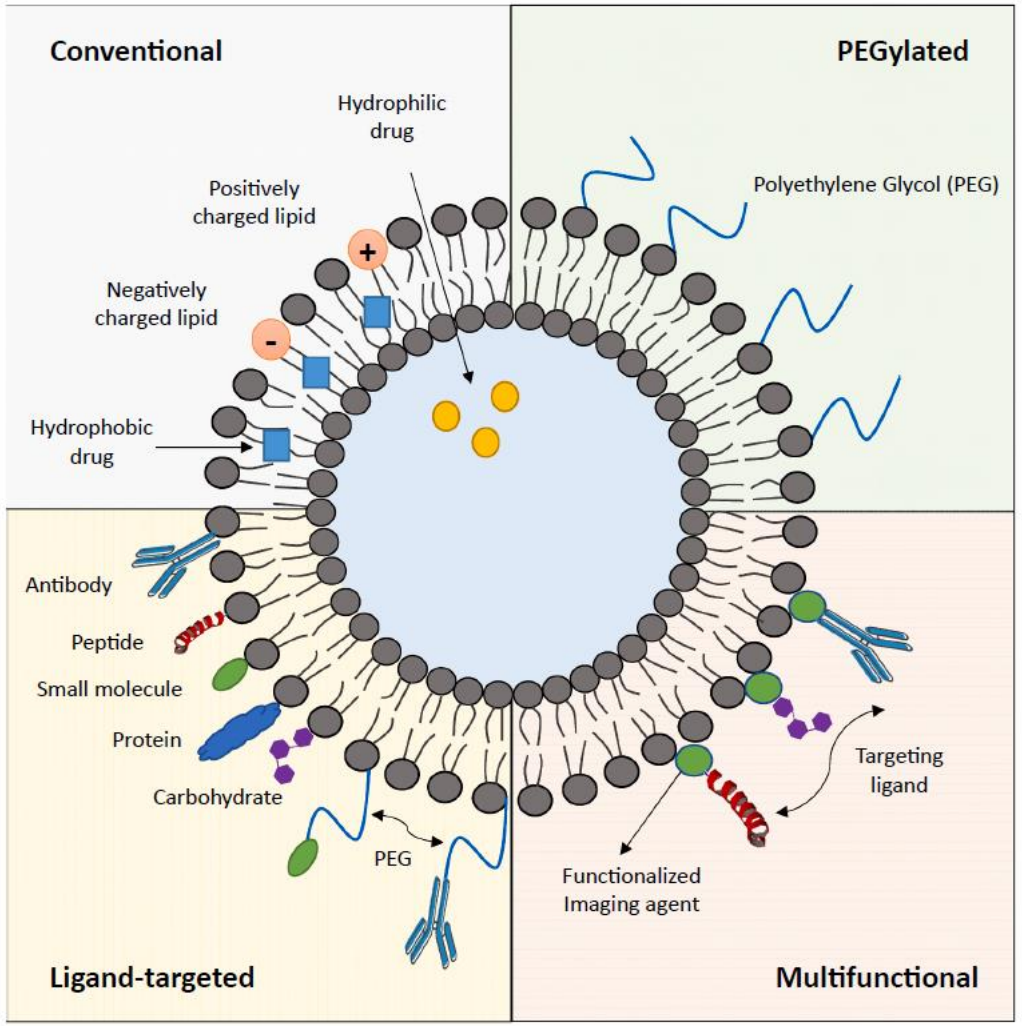
20-100 nm >100 nm

SUV LUV



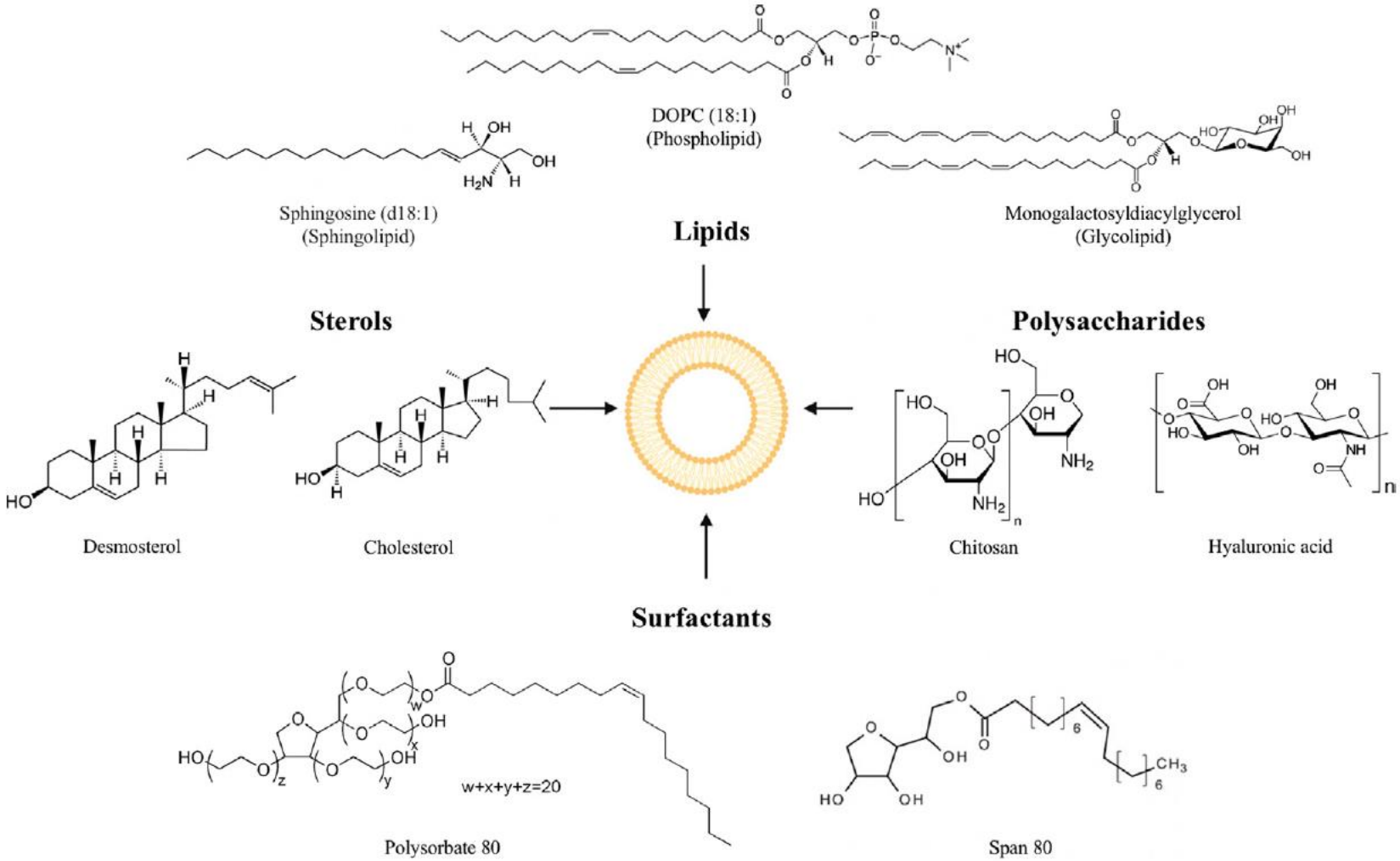
>500 nm >1000 nm

MLV MVV



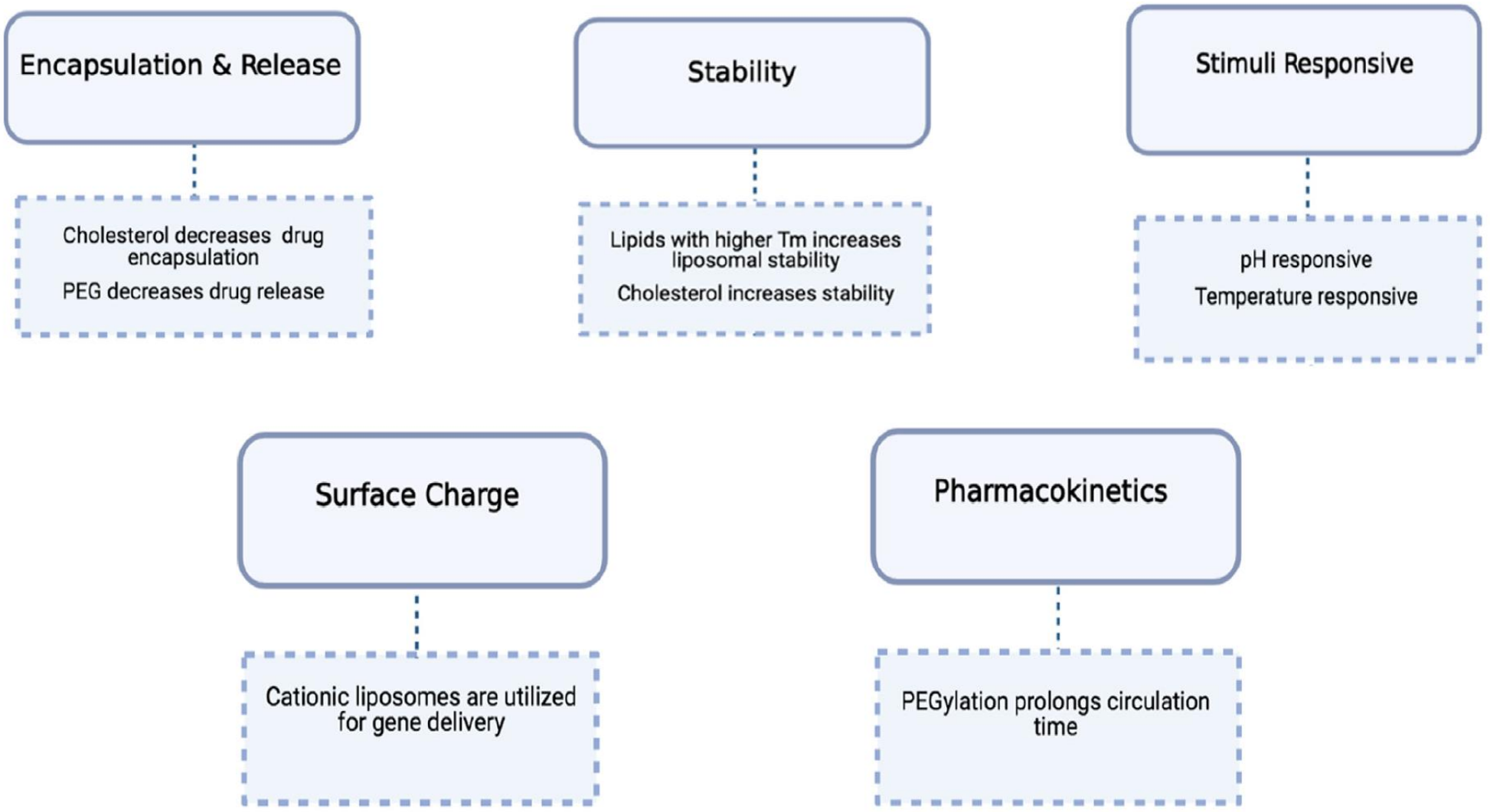
Guimarães et al. *International Journal of Pharmaceutics* 2021, 601, 120571.

Building units



Large et al. *Advanced Drug Delivery Reviews* 2021, 176, 113851.

Tuning their properties



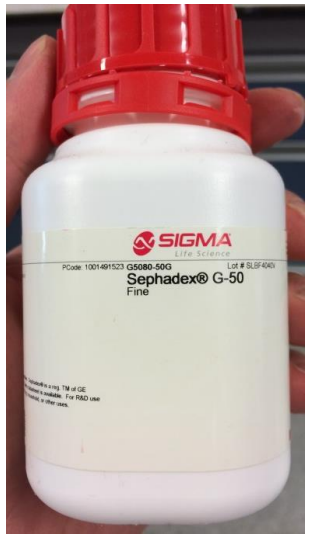
Large et al. *Advanced Drug Delivery Reviews* 2021, 176, 113851.

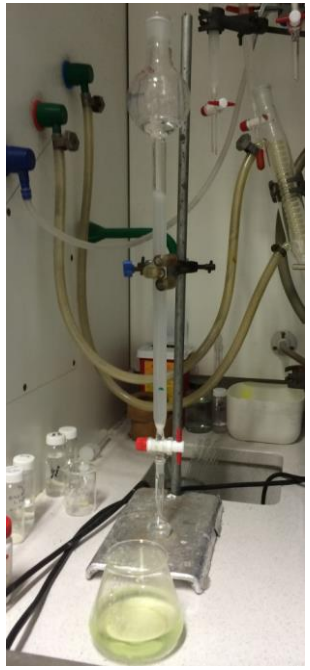
Vesicle preparation – thin film hydration

1. Mix POPC and cholesterol
2. Evaporate solvents
3. Re-dissolve in aqueous soln. of drug
4. Stir for 1 h (vesicle formation)
5. Freeze-thawing (breaking down multilamellar vesicles) or sonication
6. Sizing (formation of vesicles smaller than 200 nm, extruder)
7. Size exclusion separation (removal of small vesicles and free dye)

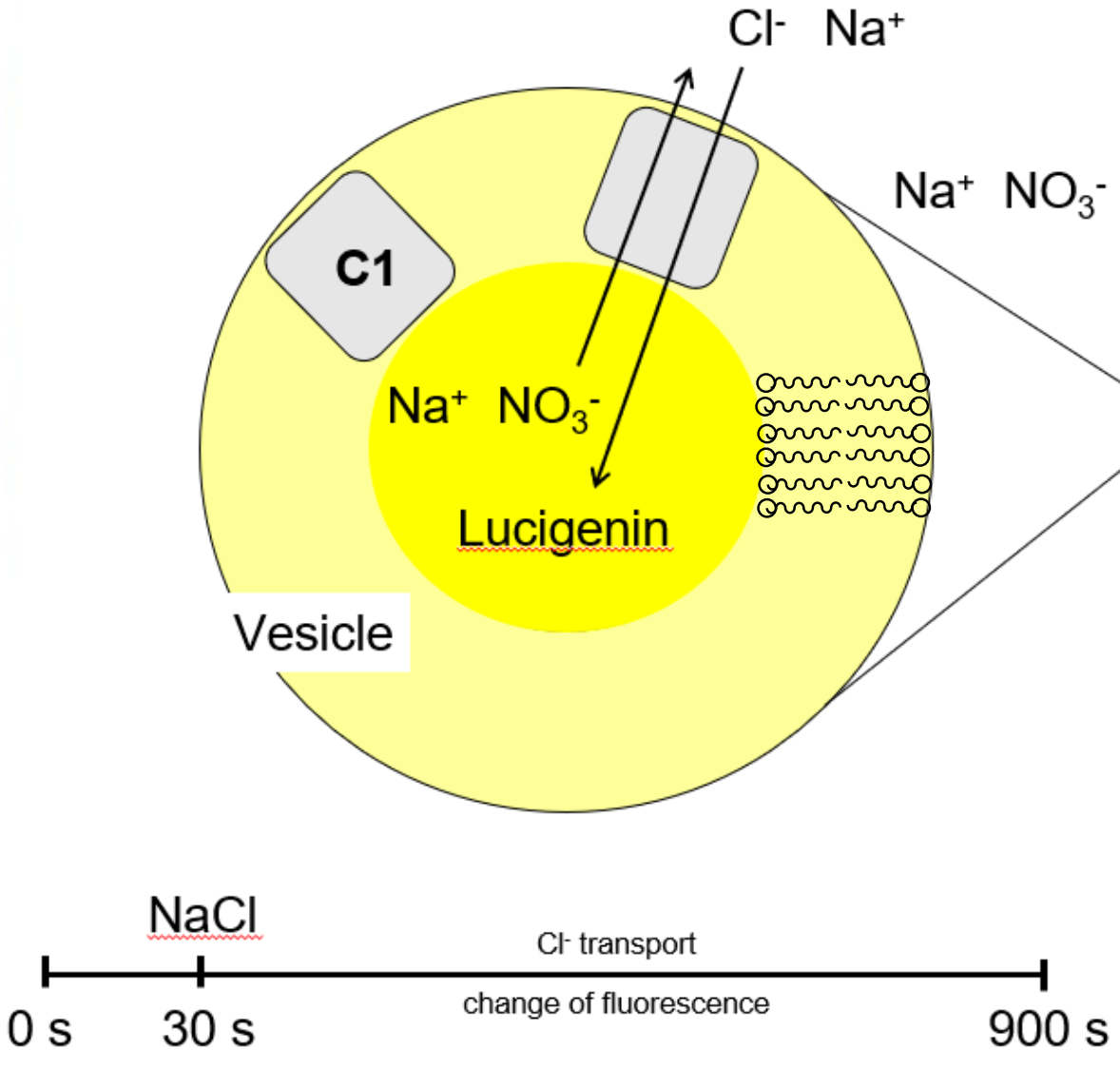
6.

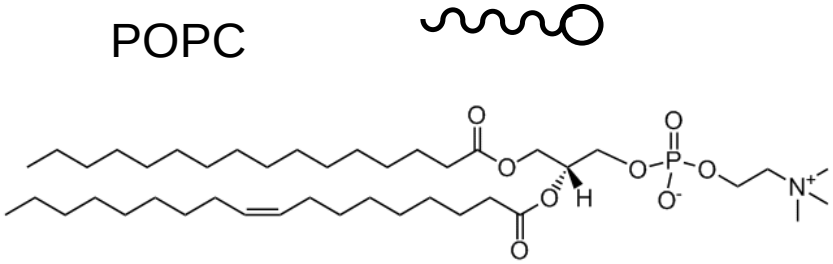
7.

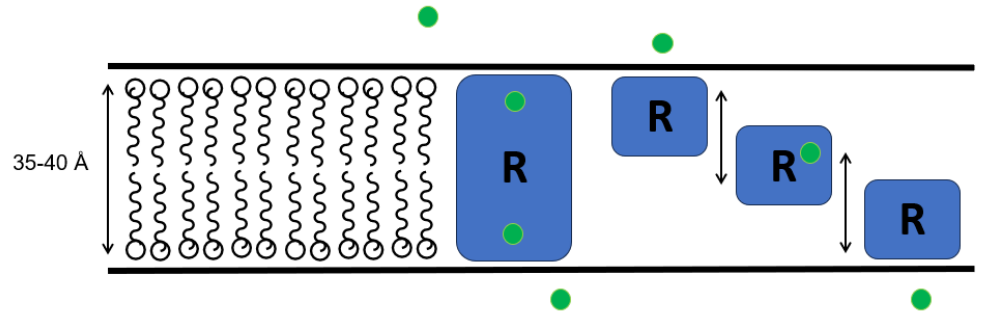


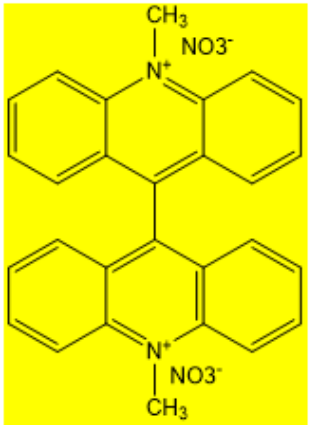


Anion (chloride) transport study









Lucigenin

Vesicle preparation

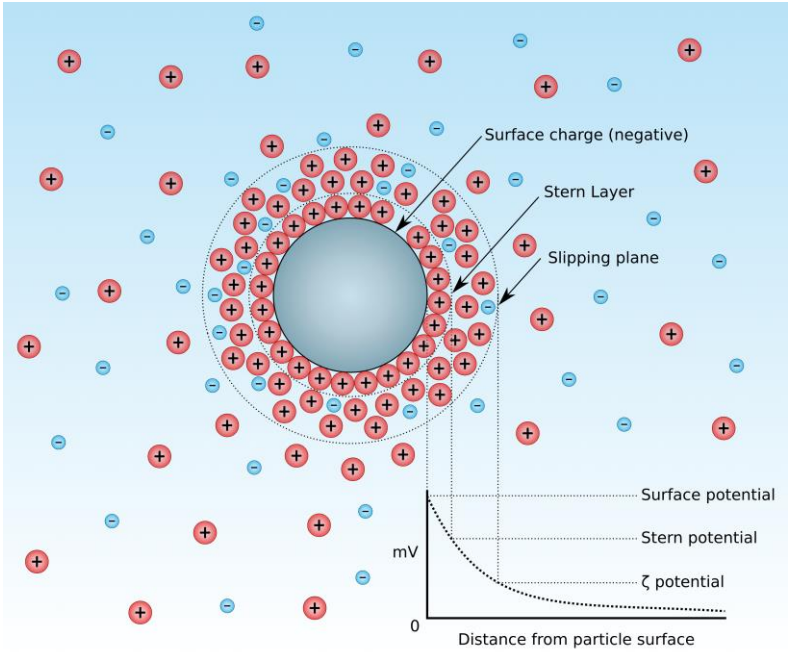
- Reverse-phase evaporation – LUV, MLV – protein encapsulation
- Injection – LUV – many variations, injection of lipids in low boiling solvent
- Detergent removal – LUV – surfactant with high CMC
- Dehydration-rehydration – LUV – without organic solvent
- Etc.

    - Freeze-thaw - solution can be sonicated at room temperature, frozen in liquid nitrogen and left at room temperature to melt. As the liposomal solution thaws, vesicles fuse forming LUVs. Up to 10 freeze-thaw cycles may be used to achieve the intended results.

Large et al. *Advanced Drug Delivery Reviews* 2021, 176, 113851.

Vesicle characterization

- Zeta potential = overal net charge of the particles - net charge of liposomes is influenced by key parameters, such as lipid composition, the head group of lipids and associated ligands



Properties	Analytical techniques
Size	Dynamic light scattering (DLS), Nanoparticle tracking analysis (NTA), Nuclear magnetic resonance (NMR), Field-flow fractionation (FFF), Size exclusion chromatography (SEC). Microscopy techniques: Transmission electron microscopy (TEM), Cryogenic-TEM (Cryo-TEM) and Atomic force microscopy (AFM).
Zeta potential	Laser Doppler electrophoresis (LDE) and Capillary electrophoresis.
Shape	Microscopy techniques: TEM, Cryo-TEM and AFM.
Lamellarity	Cryo-TEM, ^{31}P NMR, Small-angle X-ray scattering (SAXS) and trapped volume determination techniques.
Phase behavior	Differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA), fluorescence probe polarization, NMR, Electron paramagnetic resonance, Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD).
Encapsulation Efficiency	Ultraviolet–visible (UV–Vis) and Fluorescence spectroscopy, enzyme or Protein-based assays, High-performance liquid chromatography (HPLC), Ultra-performance liquid chromatography (UPLC), Liquid chromatography–mass spectrometry (LC–MS), Gas chromatography–mass spectrometry (GC–MS), Electron spin resonance (ESR) and ^{1}H NMR.
Drug release	Spectrophotometry methods, HPLC and UPLC.

Guimarães et al. *International Journal of Pharmaceutics* 2021, 601, 120571.

Lipid-based NPs - liposomes

- Lipid-based NPs are the most common class of FDA-approved nanomedicines
- Many advantages including formulation simplicity, self- assembly, biocompatibility, high bioavailability, ability to carry large payloads and a range of physicochemical properties that can be controlled to modulate their biological characteristics
- Unique physiological functions, such as pH response, prolonged blood circulation, and reduced systemic toxicity
- Liposomes are typically composed of phospholipids, which can form unilamellar and multilamellar vesicular structures, usually spherical
- Liposomes can carry and deliver hydrophilic, hydrophobic and lipophilic drugs, and they can even entrap hydrophilic and lipophilic compounds in the same system
- *In vitro* and *in vivo* stability are altered by NP size, surface charge, lipid composition, number of lamellae and surface modifications (with ligands or polymers)
- Shelf-stability of liposomes can be increased by freeze-drying

a) Large et al. *Advanced Drug Delivery Reviews* 2021, 176, 113851; b) Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

Lipid-based NPs – lipid nanoparticles (LNPs)

- Lipid nanoparticles (LNPs) - liposome-like structures widely used for the delivery of nucleic acids (form micellar structures within the particle core)
  - Composition: cationic or ionizable lipids that complex with negatively charged genetic material and aid endosomal escape, phospholipids for particle structure, cholesterol for stability and membrane fusion, and PEGylated lipids to improve stability and circulation
  - Important in personalized genetic therapy applications for their efficacy of their nucleic acid delivery along with their simple synthesis, small size and serum stability
  - Ionizable LNPs are an ideal platform for the delivery of these nucleic acid therapies as they have a near-neutral charge at physiological pH but become charged in acidic endosomal compartments, promoting endosomal escape for intracellular delivery
  - Limited by low drug loading and biodistribution that results in high uptake to the liver and spleen

Mitchell et al. *Nature Reviews* 2021, 20, 101–124.

Technological challenges in use of NPs

- Scale-up synthesis – it is essential to have consistent and highly reproducible formulation prior to the clinical trials
- Performance optimization
- Performance prediction – correlation between animal and human model is essential
- Sterilization – provide compromise between stability and sterilization

Name	Particle type/drug	Approved application/indication	Approval (year)
New approvals since 2016			
VYXEOS CPX-351 (Jazz Pharmaceuticals)	Liposomal formulation of cytarabine:daunorubicin (5:1M ratio)	Acute myeloid leukemia	FDA (2017) EMA (2018)
ONPATTRO Patisiran ALN-TTR02 (Alnylam Pharmaceuticals)	Lipid nanoparticle RNAi for the knockdown of disease-causing TTR protein	Transthyretin (TTR)-mediated amyloidosis	FDA (2018) EMA (2018)
NBTXR3 Hensify (Nanobiotix)	Hafnium oxide nanoparticles stimulated with external radiation to enhance tumor cell death via electron production	Locally advanced squamous cell carcinoma	CE Mark (2019)
Cancer nanoparticle medicines			
Doxil Caelyx (Janssen)	Liposomal doxorubicin (PEGylated)	Ovarian cancer (secondary to platinum based therapies) HIV-associated Kaposi's sarcoma (secondary to chemotherapy) Multiple myeloma (secondary)	FDA (1995) EMA (1996)
DaunoXome (Galen)	Liposomal daunorubicin (non-PEGylated)	HIV-associated Kaposi's sarcoma (primary)	FDA (1996)
Myocet (Teva UK)	Liposomal doxorubicin (non-PEGylated)	Treatment of metastatic breast cancer (primary)	EMA (2000)
Abraxane (Celgene)	Albumin-particle bound paclitaxel	Advanced non-small cell lung cancer (surgery or radiation is not an option) Metastatic breast cancer (secondary) Metastatic pancreatic cancer (primary)	FDA (2005) EMA (2008)
Marqibo (Spectrum)	Liposomal vincristine (non-PEGylated)	Philadelphia chromosome-negative acute lymphoblastic leukemia (tertiary)	FDA (2012)
MEPACT (Millennium)	Liposomal mifamurtide (non-PEGylated)	Treatment for osteosarcoma (primary following surgery)	EMA (2009)
Onivyde MM-398 (Merrimack)	Liposomal irinotecan (PEGylated)	Metastatic pancreatic cancer (secondary)	FDA (2015)
Iron-replacement nanoparticle therapies			
CosmoFer INFeD Ferrisat (Pharmacosmos)	Iron dextran colloid	Iron deficient anemia	FDA (1992) Some of Europe
DexFerrum DexIron (American Regent)	Iron dextran colloid	Iron deficient anemia	FDA (1996)
Ferrlecit (Sanofi)	Iron gluconate colloid	Iron replacement for anemia treatment in patients with chronic kidney disease	FDA (1999)
Venofer (American Regent)	Iron sucrose colloid	Iron replacement for anemia treatment in patients with chronic kidney disease	FDA (2000)
Feraheme (AMAG) Rienso (Takeda) Ferumoxytol	Iron polyglucose sorbitol carboxymethylether colloid	Iron deficiency in patients with chronic kidney disease	FDA (2009)

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Name	Particle type/drug	Approved application/indication	Approval (year)
Injectafer Ferinject (Vifor)	Iron carboxymaltose colloid	Iron deficient anemia	FDA (2013)
Monofer (Pharmacosmos)	10% iron isomaltoside 1,000 colloid	Treating iron deficiency and anemia when oral methods do not work or when iron delivery is required immediately	Some of Europe
Diafer (Pharmacosmos)	5% iron isomaltoside 1,000 colloid	Iron deficient anemia	Some of Europe
Nano/microparticle imaging agents			
Definity (Lantheus Medical Imaging)	Perflutren lipid microspheres	Ultrasound contrast agent	FDA (2001)
Feridex I.V. (AMAG) Endorem	Iron dextran colloid	Imaging of liver lesions	FDA (1996) Discontinued (2008)
Optison (GE Healthcare)	Human serum albumin stabilized perflutren microspheres	Ultrasound contrast agent	FDA (1997) EMA (1998)
SonoVue (Bracco Imaging)	Phospholipid stabilized microbubble	Ultrasound contrast agent	EMA (2001)

Name	Particle type/drug	Approved application/indication	Approval (year)
Resovist (Bayer Schering Pharma) Cliavist	Iron carboxydextran colloid	Imaging of liver lesions	Some of Europe Discontinued (2009)
Ferumoxtran-10 Combidex Sinerem (AMAG)	Iron dextran colloid	Imaging lymph node metastases	Only available in Holland
Nanoparticle vaccines			
Epaxal (Crucell)	Liposome with hepatitis A virus	Hepatitis A vaccine	Some of Europe (discontinued)
Inflexal V (Crucell)	Liposome with trivalent-influenza	Influenza vaccine	Some of Europe (discontinued)
Particle anesthetics			
Diprivan	Liposomal propofol	Induction and maintenance of sedation or anesthesia	FDA (1989)
Nanoparticles for fungal treatments			
AmBisome (Gilead Sciences)	Liposomal amphotericin B	Cryptococcal meningitis in HIV-infected patients Aspergillus, Candida and/or Cryptococcus species infections (secondary) Visceral leishmaniasis parasite in immunocompromised patients	FDA (1997) Most of Europe
Nanoparticles for macular degeneration			
Visudyne (Bausch and Lomb)	Liposomal verteporfin	Treatment of subfoveal choroidal neovascularization from age-related macular degeneration, pathologic, or ocular histoplasmosis	FDA (2000) EMA (2000)

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Marketed liposomes

Name	Company	Liposomal Composition (molar ratio)	Drug Encapsulated	Drug Type	Route of Administration	Clinical Approval Year
Abelcet	Leadiant Biosciences, Inc.	DMPC : DMPG (2.3 : 1)	Amphotericin B	Antifungal	I.V.	1995
Ambisome	Fujisawa Healthcare, Inc. and Gilead Sciences, Inc.	HSPC : DSPG : Cholesterol : Amphotericin B (5 : 2 : 2.5 : 1)	Amphotericin B	Antifungal	I.V.	1997
Amphocil	Zeneca Pharmaceuticals	Cholesteryl sulphate : Amphotericin B (1 : 1)	Amphotericin B	Antifungal	I.V.	1993
Amphotec	Sequus Pharmaceuticals Inc.	Cholesteryl sulphate : Amphotericin B (1 : 1)	Amphotericin B	Antifungal	I.V.	1996
Arikayce	Insmed, Inc. of Bridgewater, NJ.	DPPC and Cholesterol : Amphotericin B (0.6–0.79 : 1 wt ratio)	Amikacin	Antibacterial	Oral Inhalation	2018
DaunoXome	Galen US, Inc.	DSPC : Cholesterol (2 : 1)	Daunorubicin	Chemotherapeutic	I.V.	1996
DepoDur	Pacira Pharmaceuticals, Inc.	DOPC : DPPG : Cholesterol : Tricaprylin and Triolein (507 : 11 : 76 : 6 : 1)	Morphine sulfate	Narcotic Analgesic	Epidural	2004
Doxil	Johnson & Johnson	HSPC : Cholesterol : DSPE-PEG2000 (11.2 : 7.8 : 1)	Doxorubicin	Chemotherapeutic	I.V.	1995
Epaxal	Johnson & Johnson	DOPC : DOPE (3 : 1)	Hepatitis A virus antigen, strain RG-SB	Vaccine	I.M.	1993
Exparel	Pacira Pharmaceuticals, Inc.	DEPC : DPPG : Cholesterol : Tricaprylin (7.6 : 1 : 10 : 3.5)	Bupivacaine	Anesthetic	I.V.	2011
Evacet	Liposome Company Inc.	(Hydro Soy PC, cholesterol and DSPE-PEG) : Doxorubicin (8 : 1)	Doxorubicin	Chemotherapeutic	I.V.	1995
Inflexal V	Johnson & Johnson	70% Lecithin, 20% Cephalin and 10% Phospholipids (DOPC : DOPE, 3 : 1)	Influenza virus antigen, strains A and B	Vaccine	I.M.	1997
Lipodox	Sun Pharmaceutical Industries Ltd.	DSPC : Cholesterol : DSPE-PEG2000 (10.9 : 7.3 : 1)	Doxorubicin	Chemotherapeutic	I.V.	1995
Marqibo	Acrotech Biopharma, LLC	Sphingomyelin : Cholesterol (1.5 : 1)	Vincristine	Chemotherapeutic	I.V.	2012
Mepact	Takeda Pharmaceutical Limited	DOPS : POPC (1 : 2.3)	Mifamurtide	Immunomodulator/ Antitumor	I.V.	2004
Myocet	Zeneus Pharma Ltd.	EPG : Cholesterol (1.2 : 1)	Doxorubicin	Chemotherapeutic	I.V.	2000
Onivyde	Merrimack Pharmaceuticals, Inc.	DSPC : MPEG-2000 : DSPE (200 : 133.3 : 1)	Irinotecan	Chemotherapeutic	I.V.	2015
Visudyne	Novartis International AG	Verteporfin : DMPC and EPG (1 : 8)	Verteporfin	Photosensitizer	I.V.	2000

Large et al. *Advanced Drug Delivery Reviews* 2021, 176, 113851.

In the next class…

Nanoparticles for drug delivery 2

Thank you for your attention!