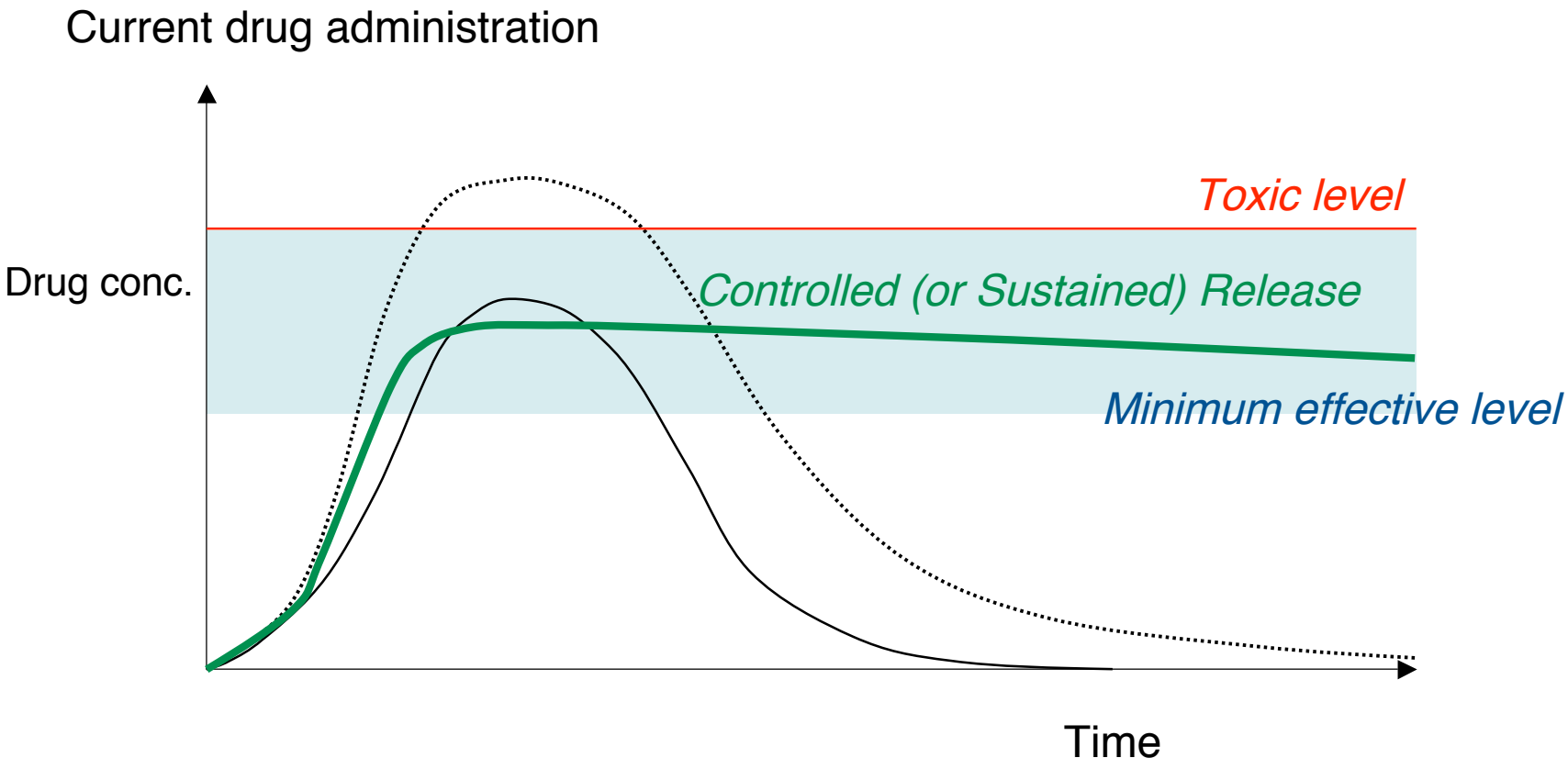
Lecture 18:

Drug Delivery: Controlled Release
Chemically-controlled Devices

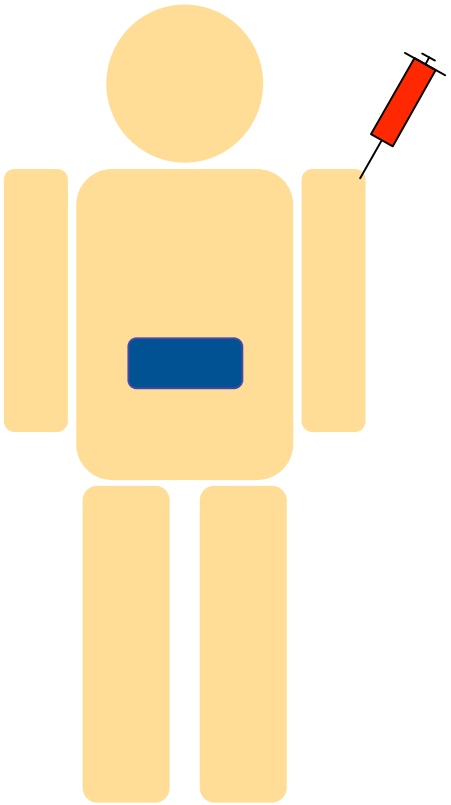
3.051J/20.340J Materials for Biomedical Applications,
Spring 2006

Drug Delivery System (DDS)

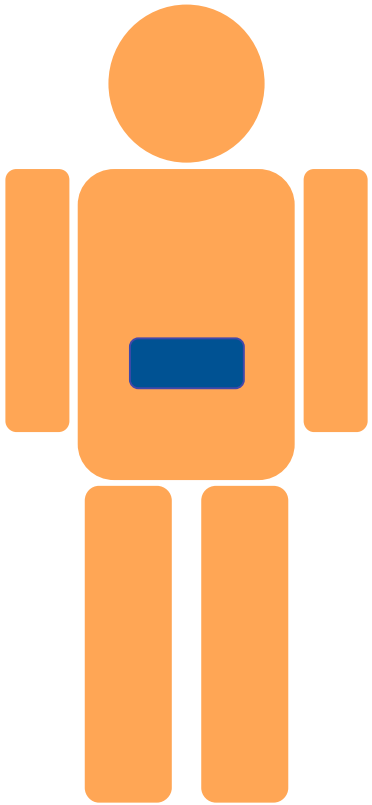
Controlling delivery rate and ***Site-specific delivery of drugs***



Even though controlled release can be achieved…

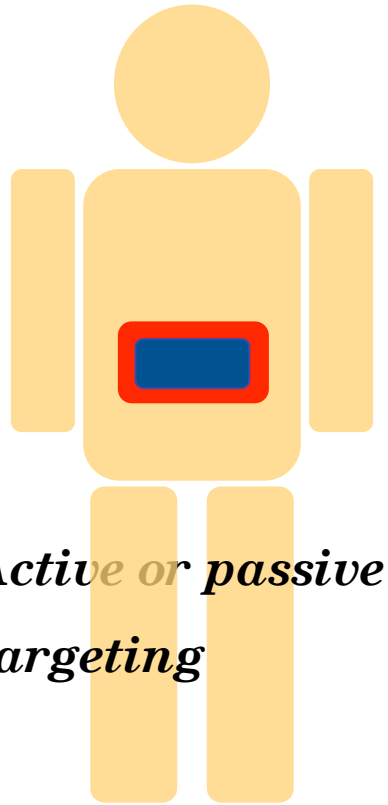


Spread over body



might cause side effect.

Site-specific delivery



Active or passive targeting

Table Controlled Release DDS

Diffusion-controlled DDS

Reservoir and monolithic systems

Water penetration-controlled DDS

Osmotic and swelling-controlled systems

Chemically-controlled DDS

Biodegradable reservoir and monolithic systems

Biodegradable polymer backbones with pendant drugs

Responsive DDS

Physically- and chemically-responsive systems

Mechanical, magnetic- or ultrasound-responsive systems

Biochemically-responsive; self-regulated systems

Particulate DDS

Microparticulates

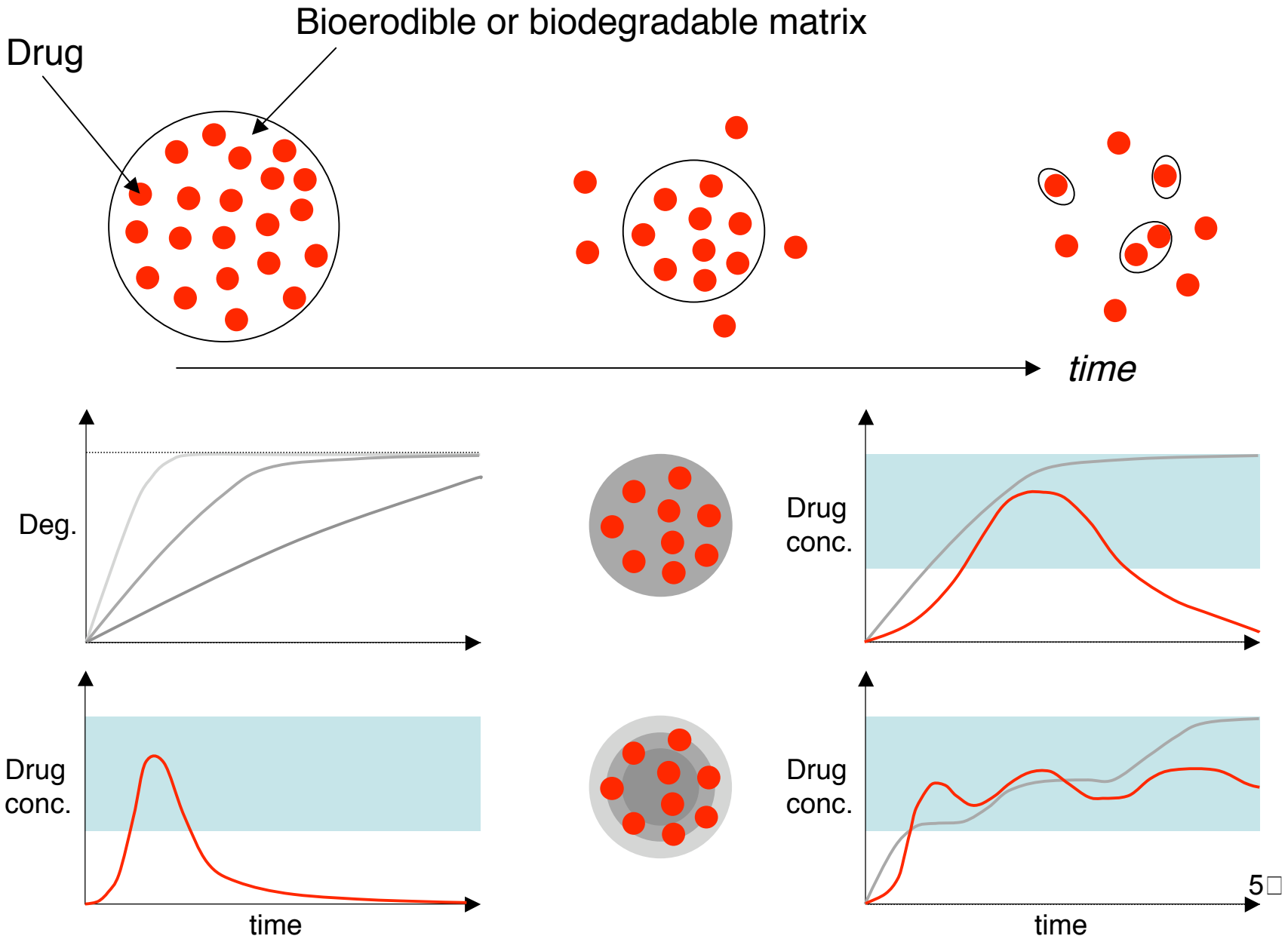
Polymer-drug conjugates

Polymeric micelle systems

Liposome systems

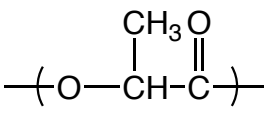
Ratner, et al. Biomaterials Science

Chemically-controlled DDS

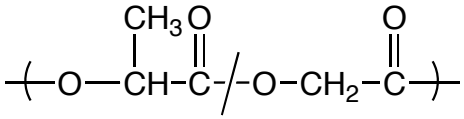


Four major classes of matrix in DDS

Poly(lactic acid) and its copolymers with poly(glycolic acid)



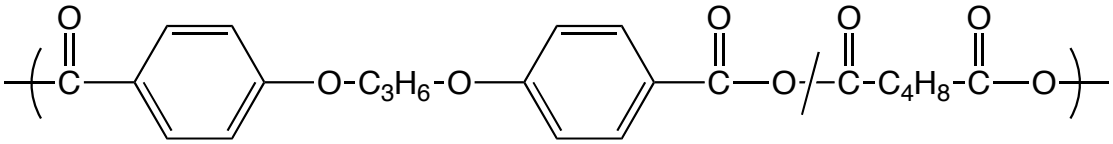
PLA



P(LA-*co*-GA)

Safe degraded products
Acid-induce inflammatory

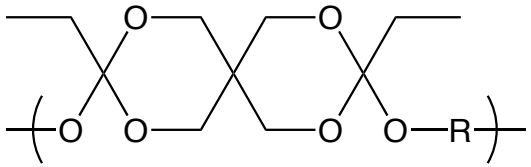
Polyanhydrides



Poly(bis-(*p*-carboxyphenoxy)propane-*co*-sebacic anhydride)

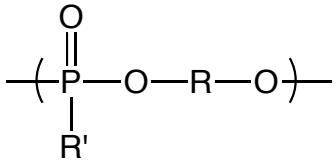
First degradation rate
Hydrolytic instability

Polyorthoesters



Well studied by 21st century
Good property R: PLGA

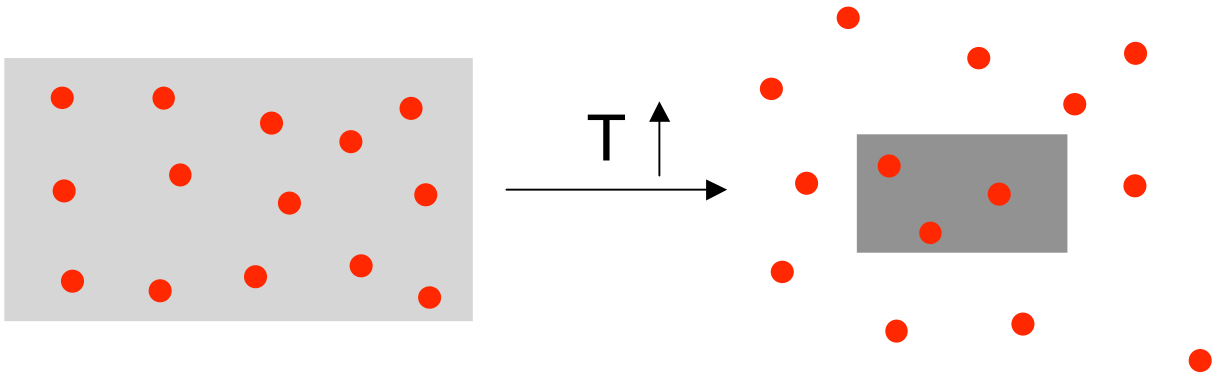
Polyphosphoesters

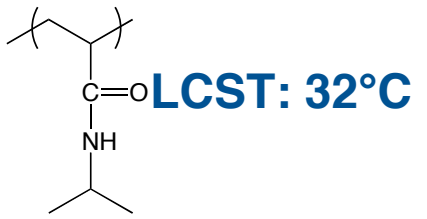


First degradation rate
Hydrolytic instability, high cost

Environmentally responsive systems

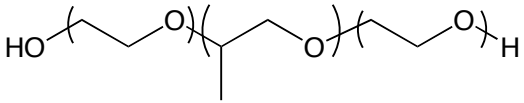
1. Temperature responsive systems





LCST: 32°C

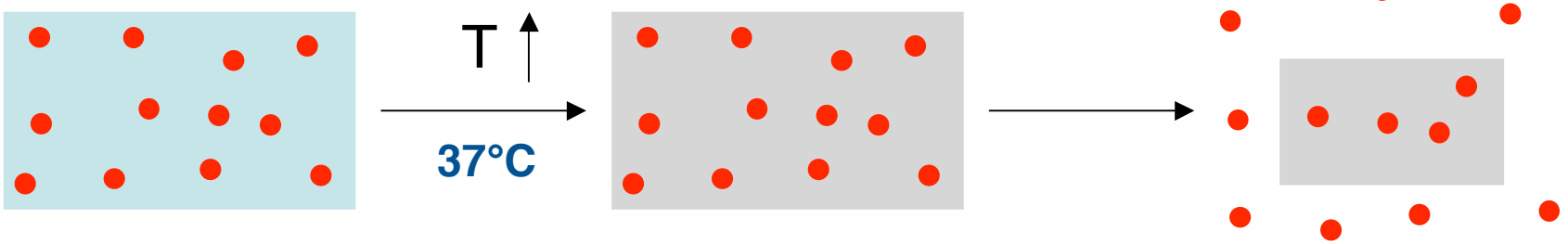
Poly(*N*-isopropyl acrylamide)

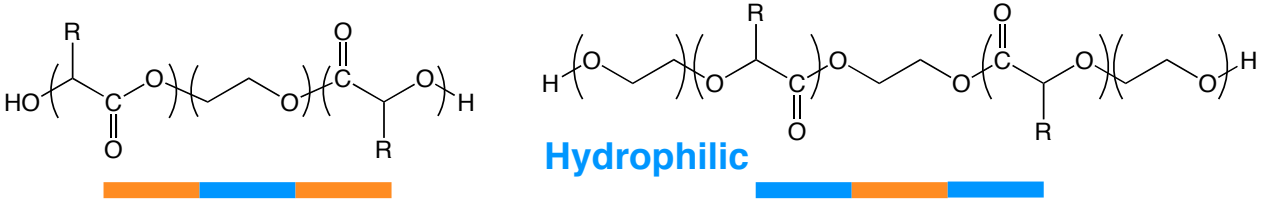


Pluronics®

37°C

Polymer-drug solution *Gelation* *Bioerosion*



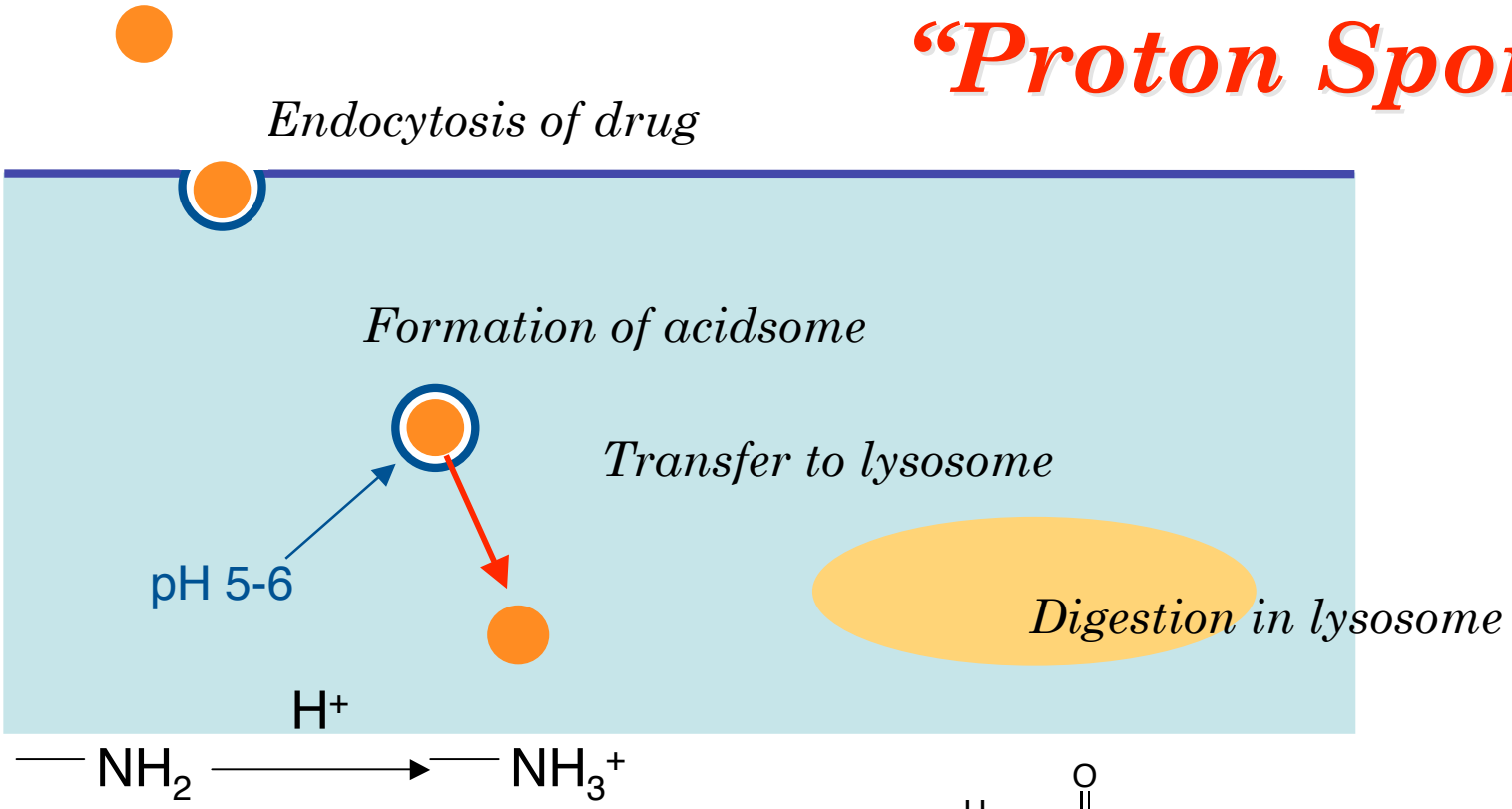


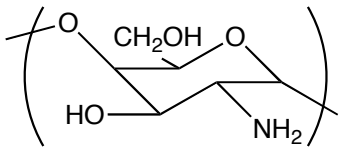
R: -H, -CH_3

Environmentally responsive systems

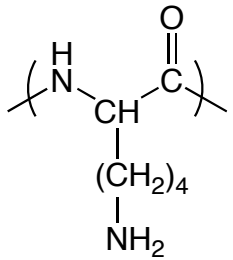
2. pH responsive systems

“Proton Sponge”





Chitosan



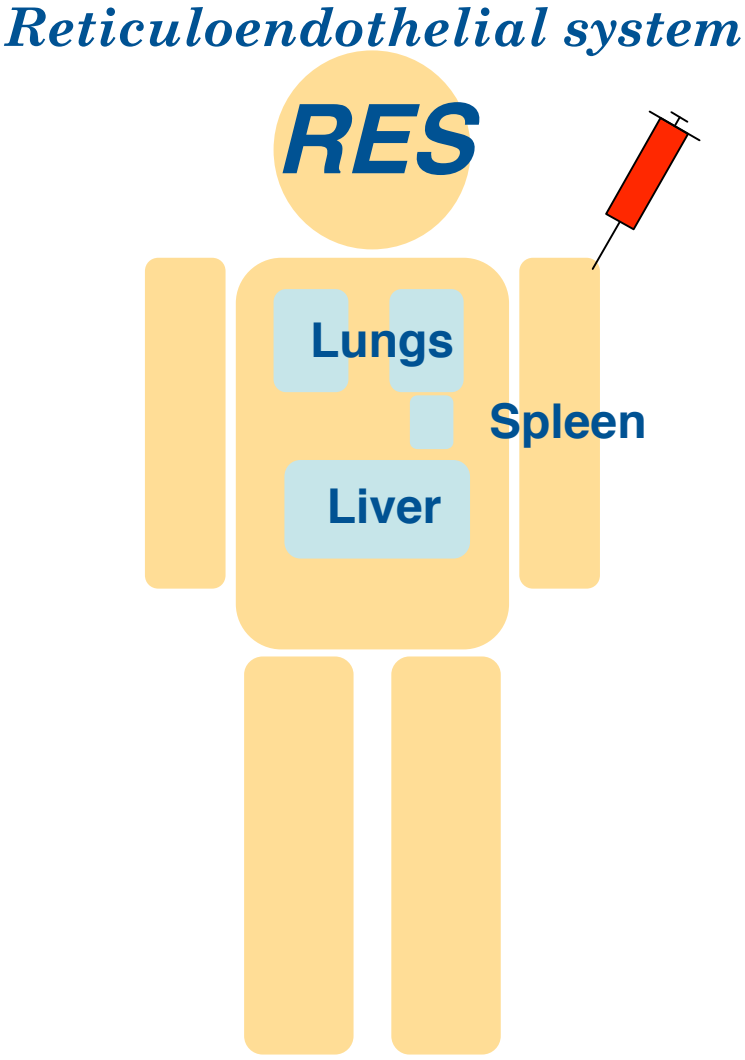
Poly(*L*-lysine)

Second key point in DDS

1. Controlling release rate
2. **Site-specific delivery**

Particulate system

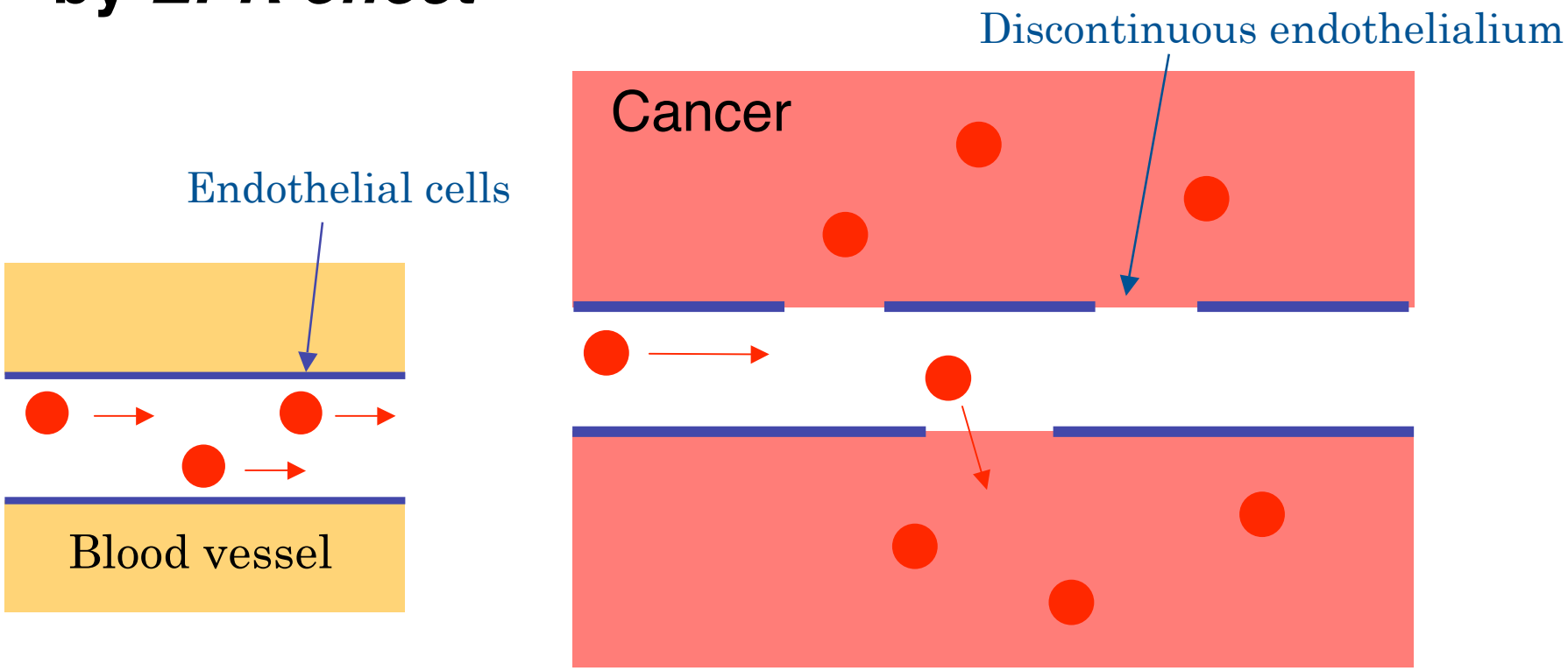
Passive targeting
Active targeting



Particulate should be between 10 to 200 nm.

Passive targeting of particulate

by *EPR effect*

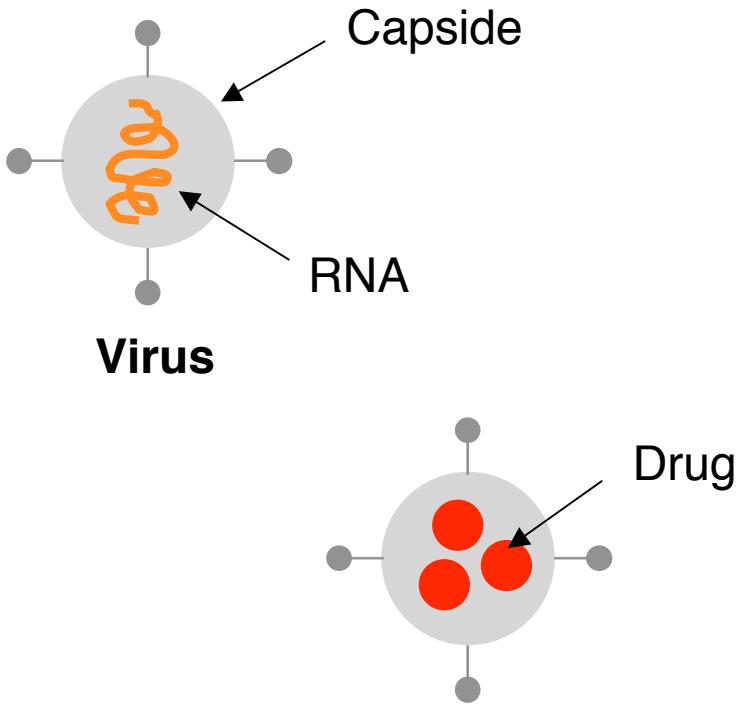


Enhanced permeability and retention (EPR) effect

Disorganization of tumor vasculature
Poor lymphatic drainage

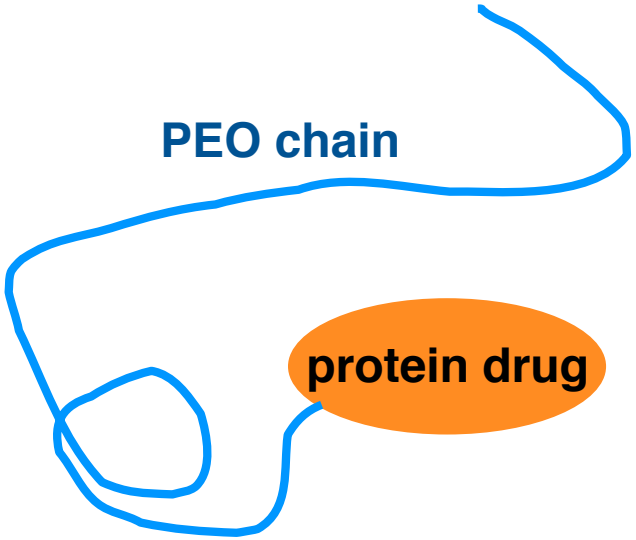
Micro (nano) capsules and spheres 1

Capside vehicle



Immunogenic response

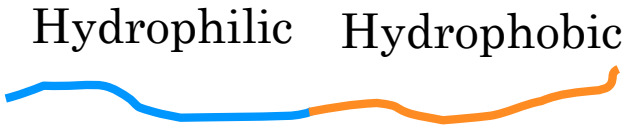
PEO-protein conjugates



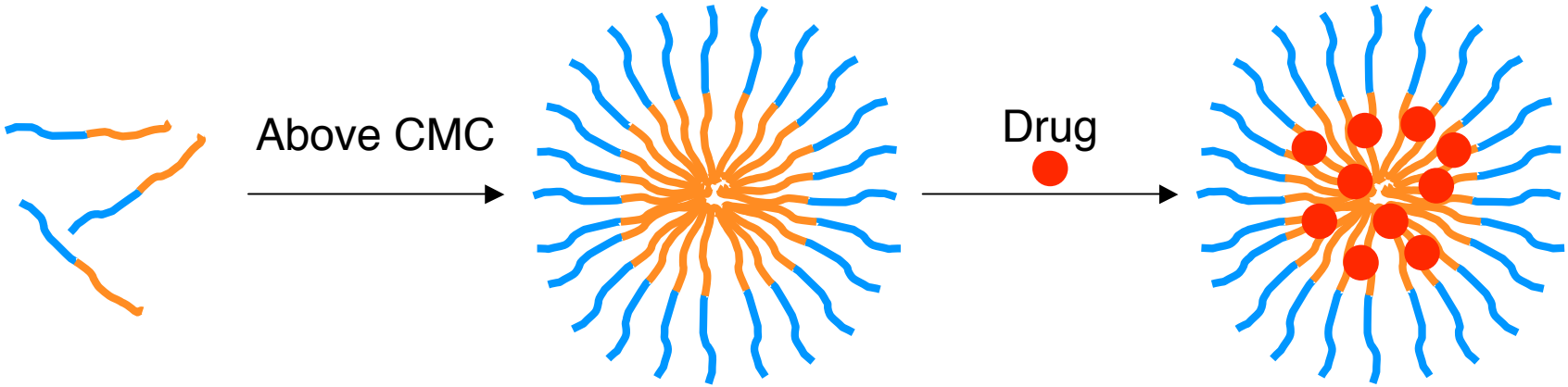
Prolong circulation
Lowering activity

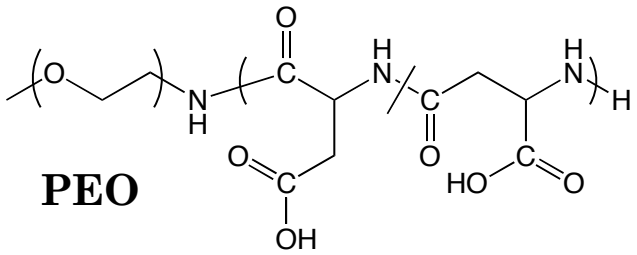
Micro (nano) capsules and spheres 2

Polymeric micelles



Amiphilic block copolymer



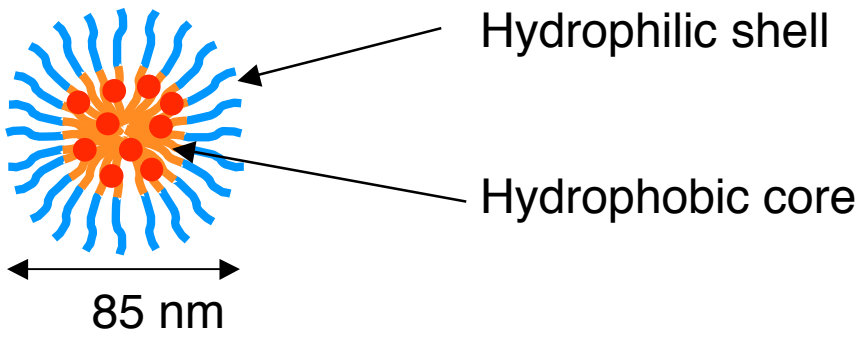


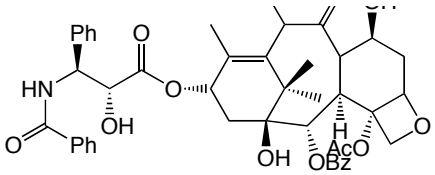
PEO

Poly(aspartic acid)

Yokoyama et al. *Cancer Res*, **1991**, *51*, 3229.

Paclitaxel incorporating micellar nanoparticle





Paclitaxel(Taxol®)
or PTX

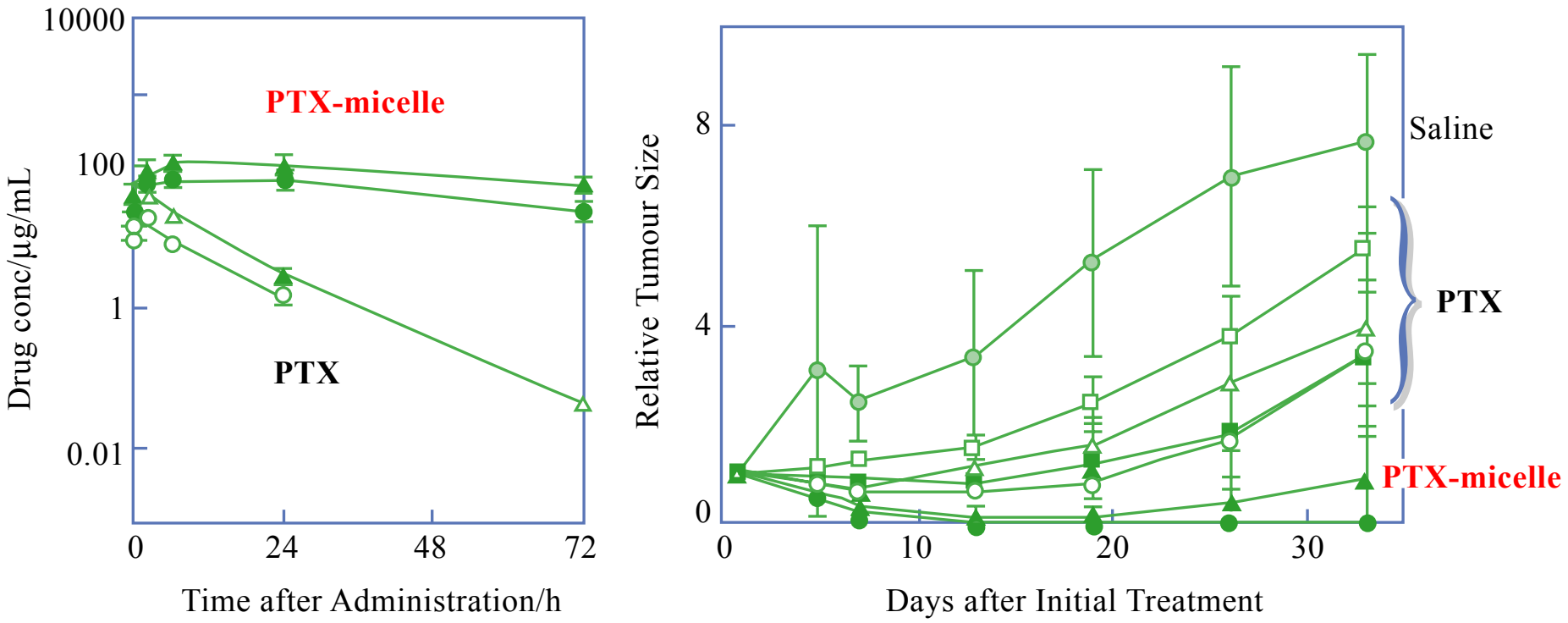


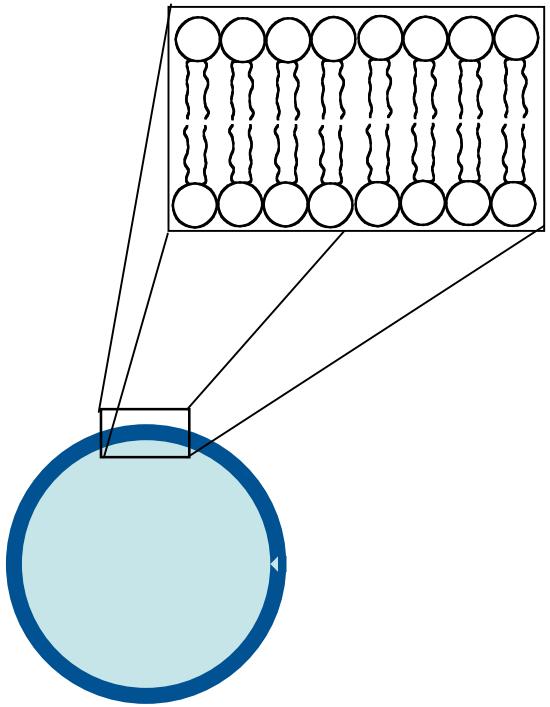
Figure by MIT OCW.

Hamaguchi et al. *British J Cancer*, **2005**, *92*, 1240.

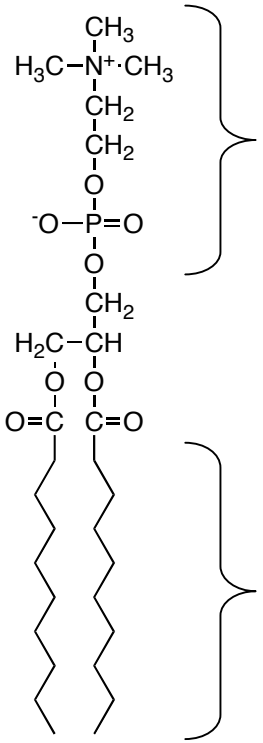
Micro (nano) capsules and spheres 3

Liposomes

Lipid bilayer



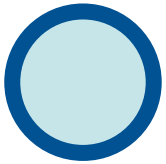
Liposome



Hydrophilic head

Hydrophobic tails

C_{12}-C_{20}



Small unilamellar vesicle (SUV): ~ 50 nm
Large unilamellar vesicle (LUV): > 1 μm

Multilamellar vesicle

Preparation of liposomes

1. Lipid thin film preparation

   Lipids are cast on a glass surface

2. Swelling thin film

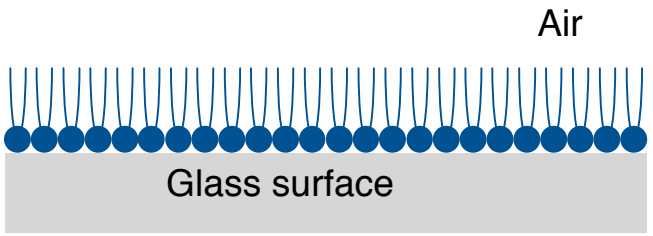
   Addition of aqueous media
   Tearing off from glass

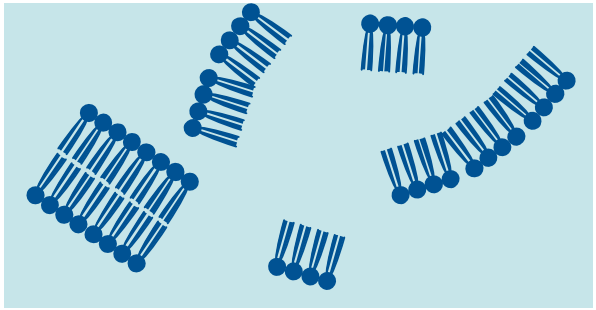
3. Ultrasound treatment

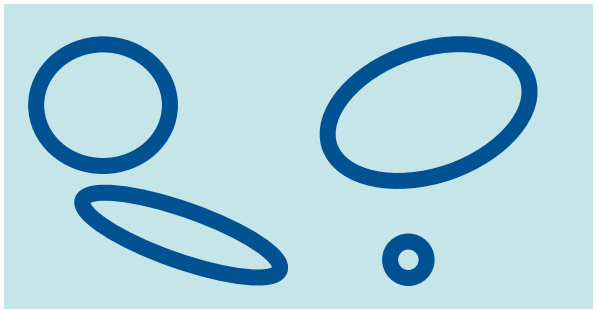
   Formation of liposomes
   with various shapes and sizes

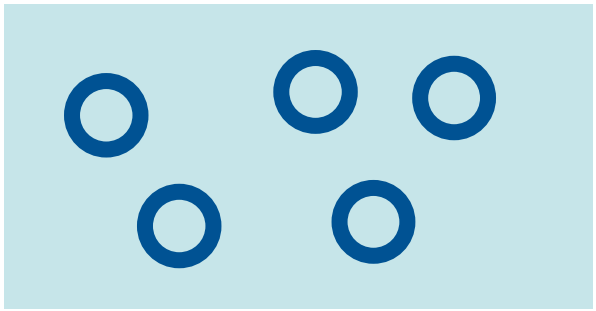
4. Extrusion

   Reconstruction of lipid membrane
   Size: ~ 100 nm









Cryo-TEM image of cationic liposomes

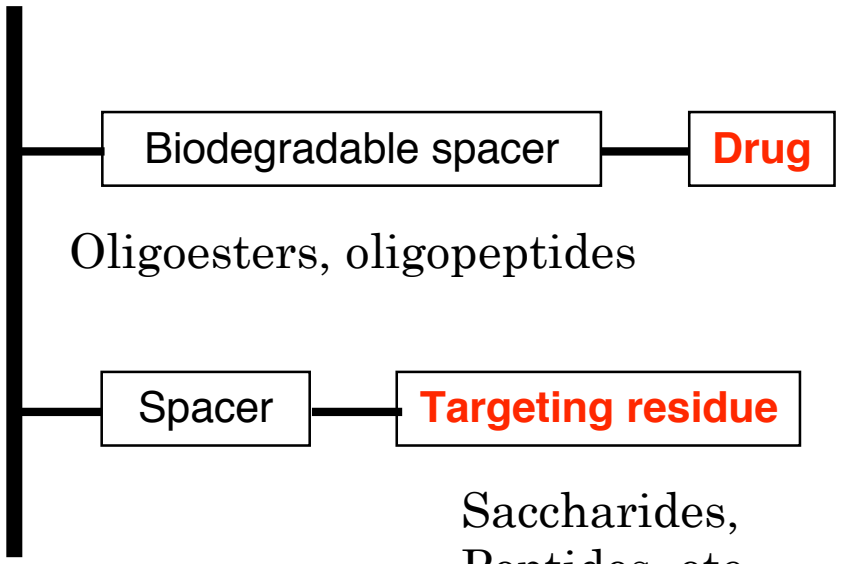
Photo removed for copyright reasons.

Alfredsson, *Current Opinion in Colloid & Interface Science,* **2005***, 10,* 269.

Active targeting

Polymer drug conjugate

Ringsdorf's model

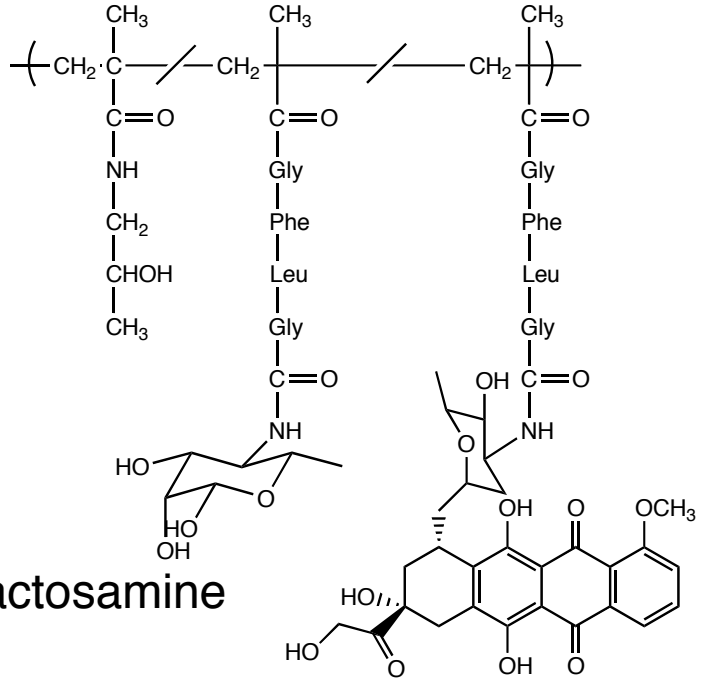


Water soluble
polymer backbone

Ringsdorf, *J Polym Sci Polymer Symp*, **1975**, *51*, 135

PK2 (Phase I/II)

Poly(*N*-(2-hydroxypropyl)methacrylamide)



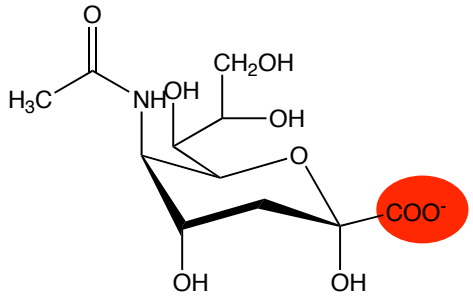
Galactosamine

Doxorubicin

Duncan R and Kopecek J et al.,
Biochimica et Biophysuca Acta, **1983**, *755*, 518

Targeting residue

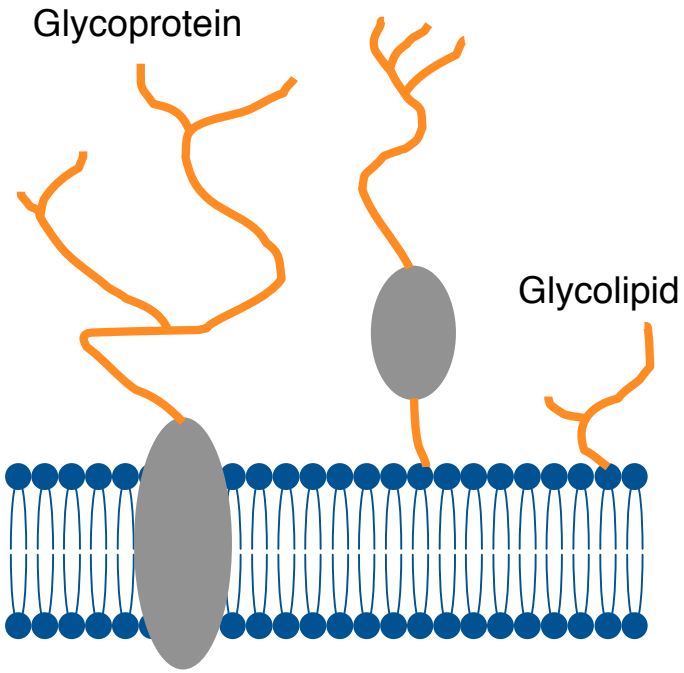
Saccharide determinants

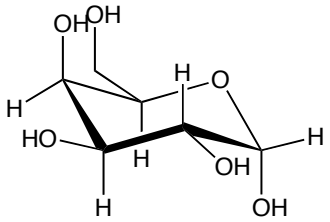


Sialic acid or

Neuramic acid

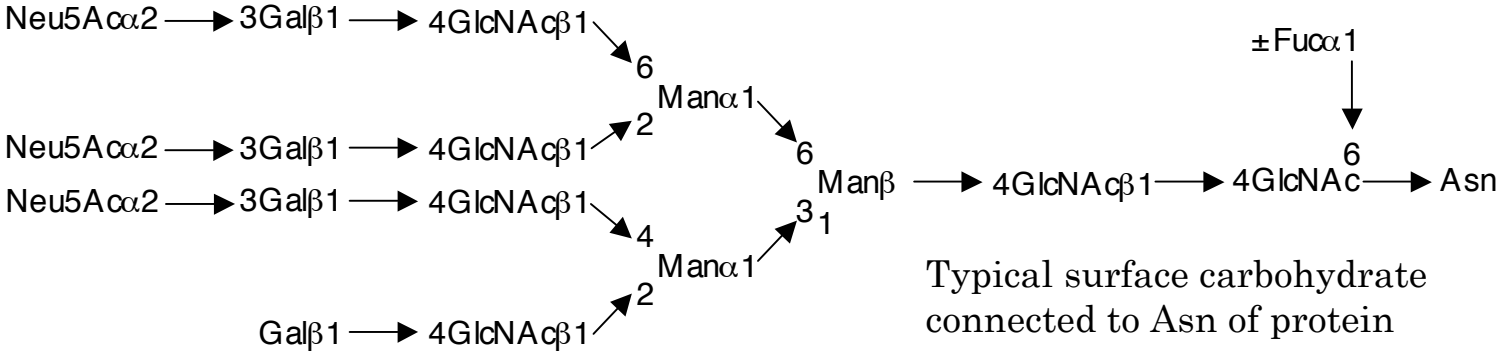
Terminal residue of carbohydrate chain





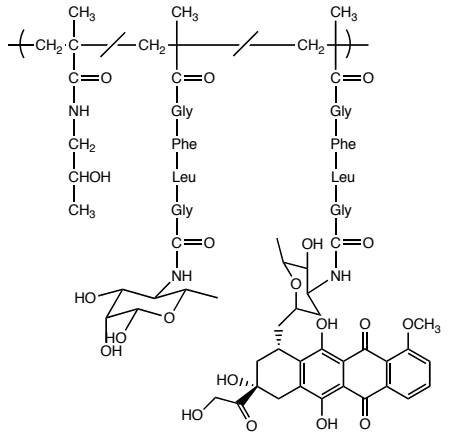
Galactose

Saccaride residue next to neuramic acid



Typical surface carbohydrate connected to Asn of protein

Tissue distribution of ^{123}I labeled PK2

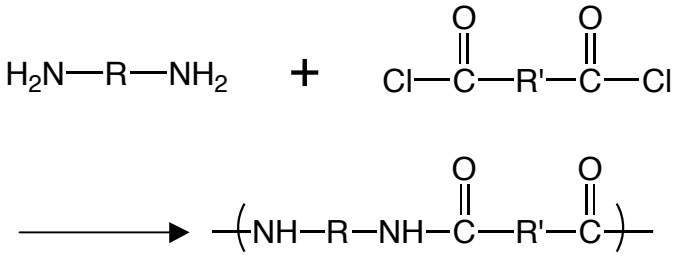


Photos removed for copyright reasons.

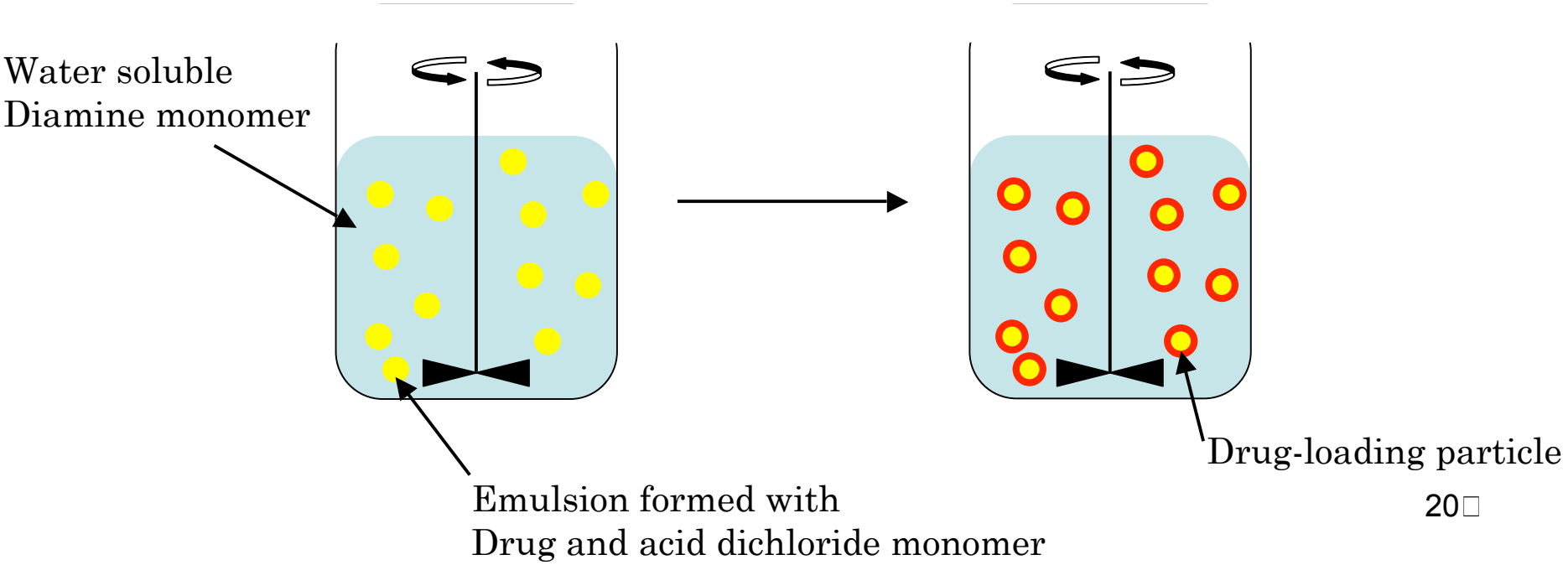
Julyan et al., *J Contr Release*, **1999**, *57*, 281

Third key point in DDS

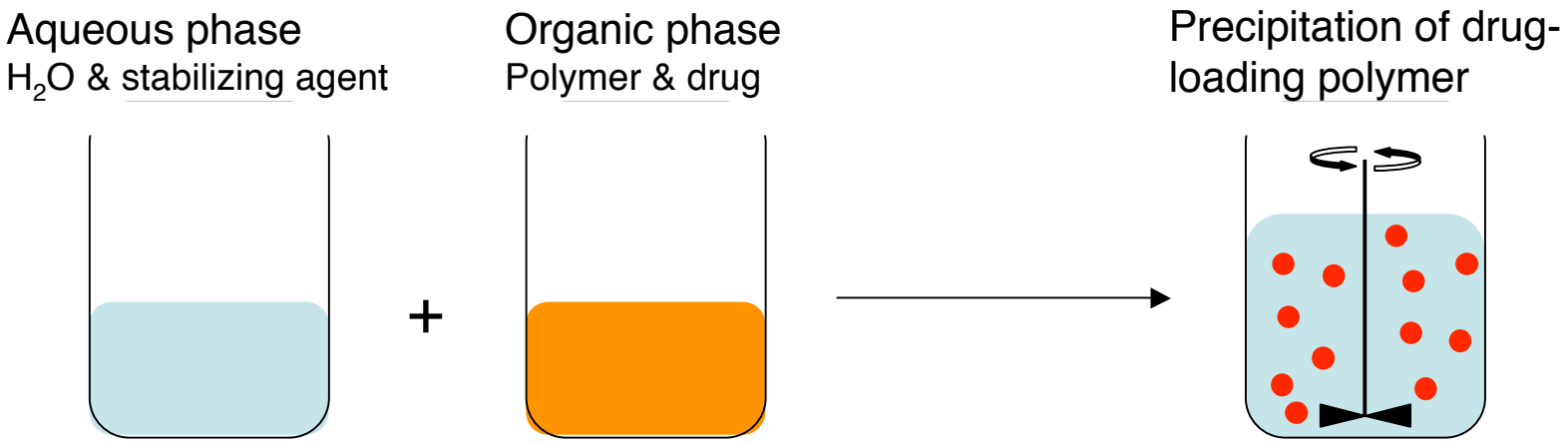
1. Controlling release rate
2. Site-specific delivery
3. **Drug formulation**



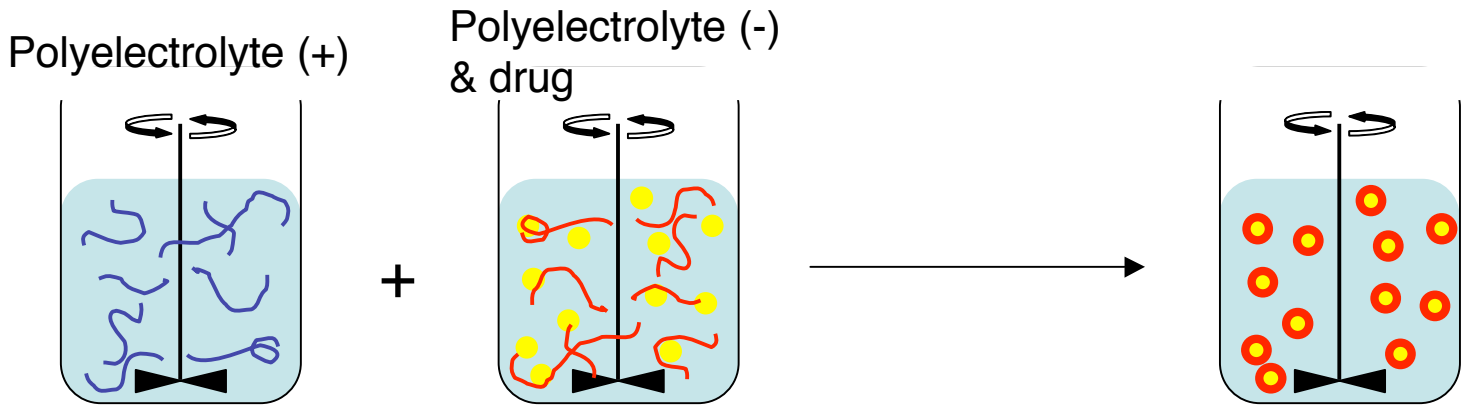
Interfacial polymerization of polyamides



Emulsification of polymer and drug

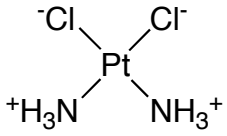


Coacervation of polymer and drug

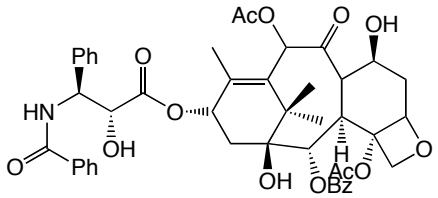


What are the drugs?

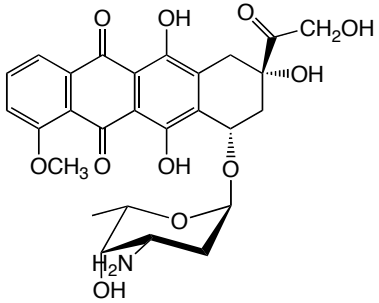
Typical anticancer drugs



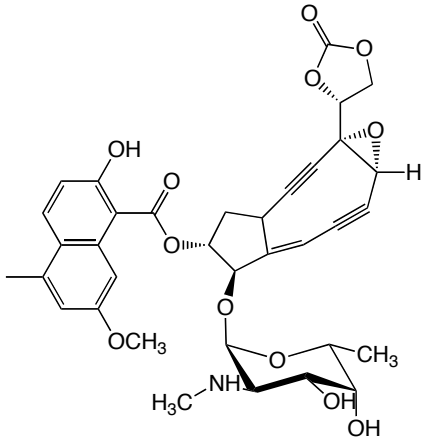
Cisplatin



Paclitaxel(Taxol®)



Doxorubicin



Neocarzinostatin chromophore

High molecular weight drugs

Proteins, peptides, hormones, cytokines

DNAs and RNAs etc.

Bioactive compounds are not stable!

Summary

1. Controlling release rate

Degradable matrix

Environmentally responsive matrix, Proton sponge

2. Site-specific delivery

Passive targeting	EPR effect, RES
Active targeting	Targeting residue

3. Drug formulation

Denature or deactivation