

Molecules and Particles as Nano- and Micro-scale Drug Carriers

Last time: molecular switches
Molecular railways
Proteins as motors in nanodevices

Today: nano- and micro-particle drug carriers

Reading:
D.A. Hammer and D.E. Discher, 'Synthetic cells- Self-assembling polymer membranes and bioadhesive colloids,' *Annu. Rev. Mater. Res.*, **31**, 387-404 (2001)
T.M. Allen and P.R. Cullis, 'Drug Delivery Systems: Entering the Mainstream,' *Science* **303**, 1818-1822 (2004)

ANNOUNCEMENTS:

TAKE-HOME EXAM 2 WILL BE GIVEN OUT NEXT TUESDAY, 5/2
AT END OF CLASS
→ USE ANY RESOURCES, DUE LAST DAY OF CLASS

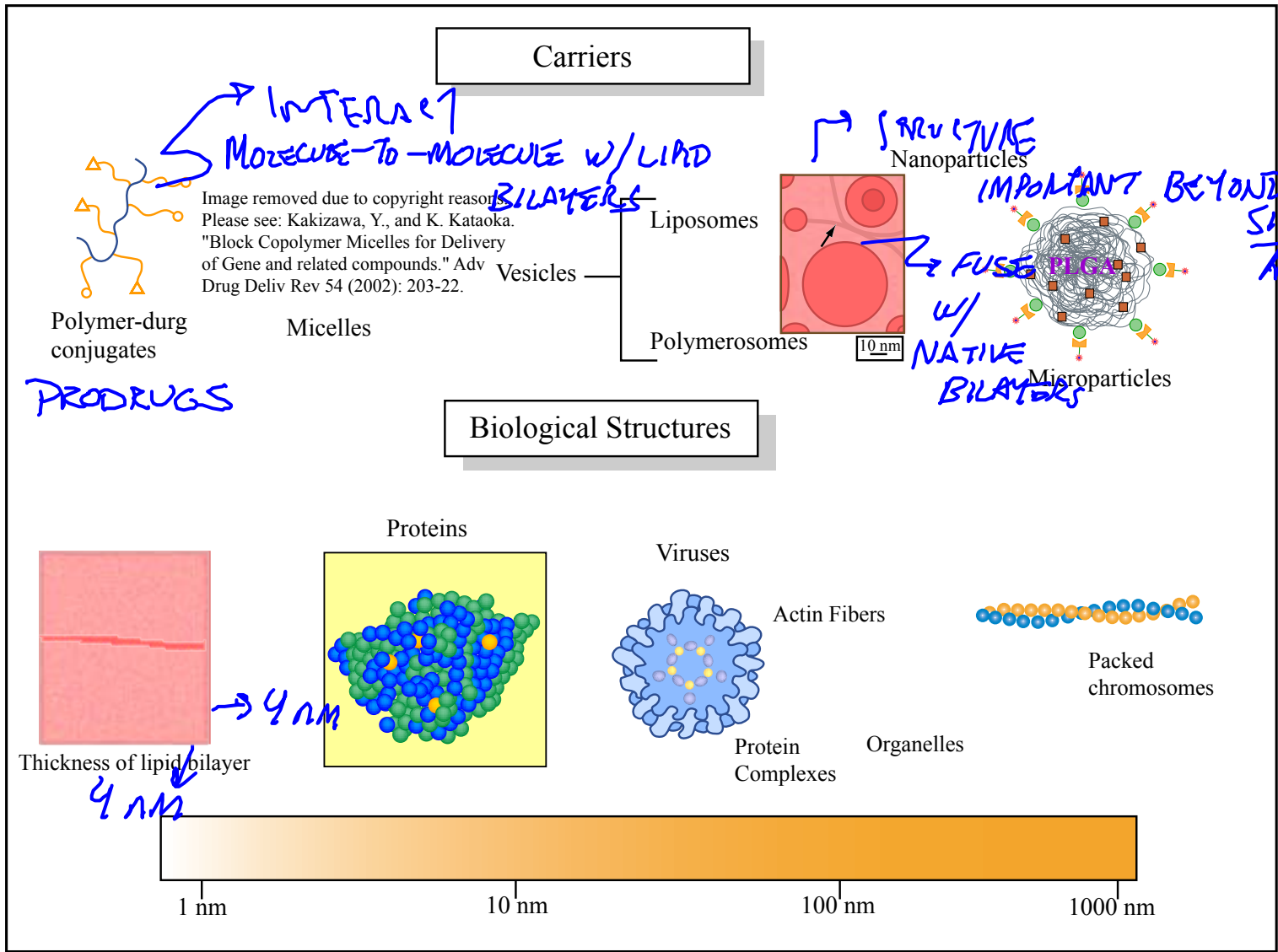


Figure by MIT OCW.

Objectives of molecular and particulate drug carriers:

- (I) Alter pharmacokinetics
 - How long is the drug active, and at what concentration is it present?
- (II) Alter biodistribution
 - Which tissues receive drug?
 - Enhance uptake at target tissue, reduce uptake where it is not desirable
- (III) Provide drug reservoirs
 - Fewer injections, sustained level of therapeutic

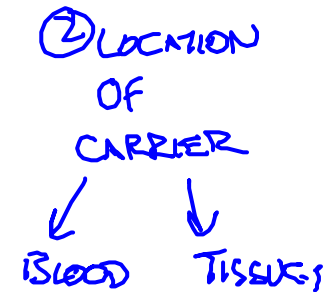
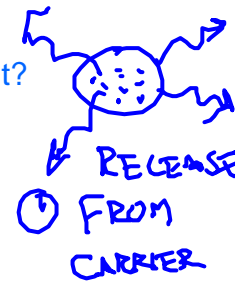


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Please see: Table 1 in Allen, and Cullis. *Science* 303 (2004): 1818.

Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

(1) EXTRACELLULAR BARRIERS:

Delivery of molecules to tissues from circulation, skin, or mucosal surfaces

ORAL

INTRAVENOUS

I.V. INJECTION

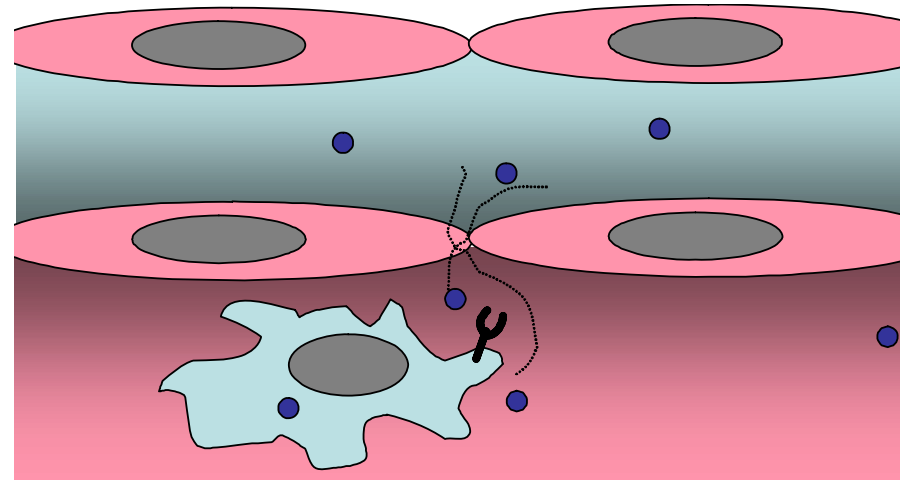


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Please see Neutra, M. R, and P. A. Kozlowski. "Mucosal Vaccines: The Promise and The Challenge." *Nat Rev Immunol* 6 (2006): 148.

Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

SKIN

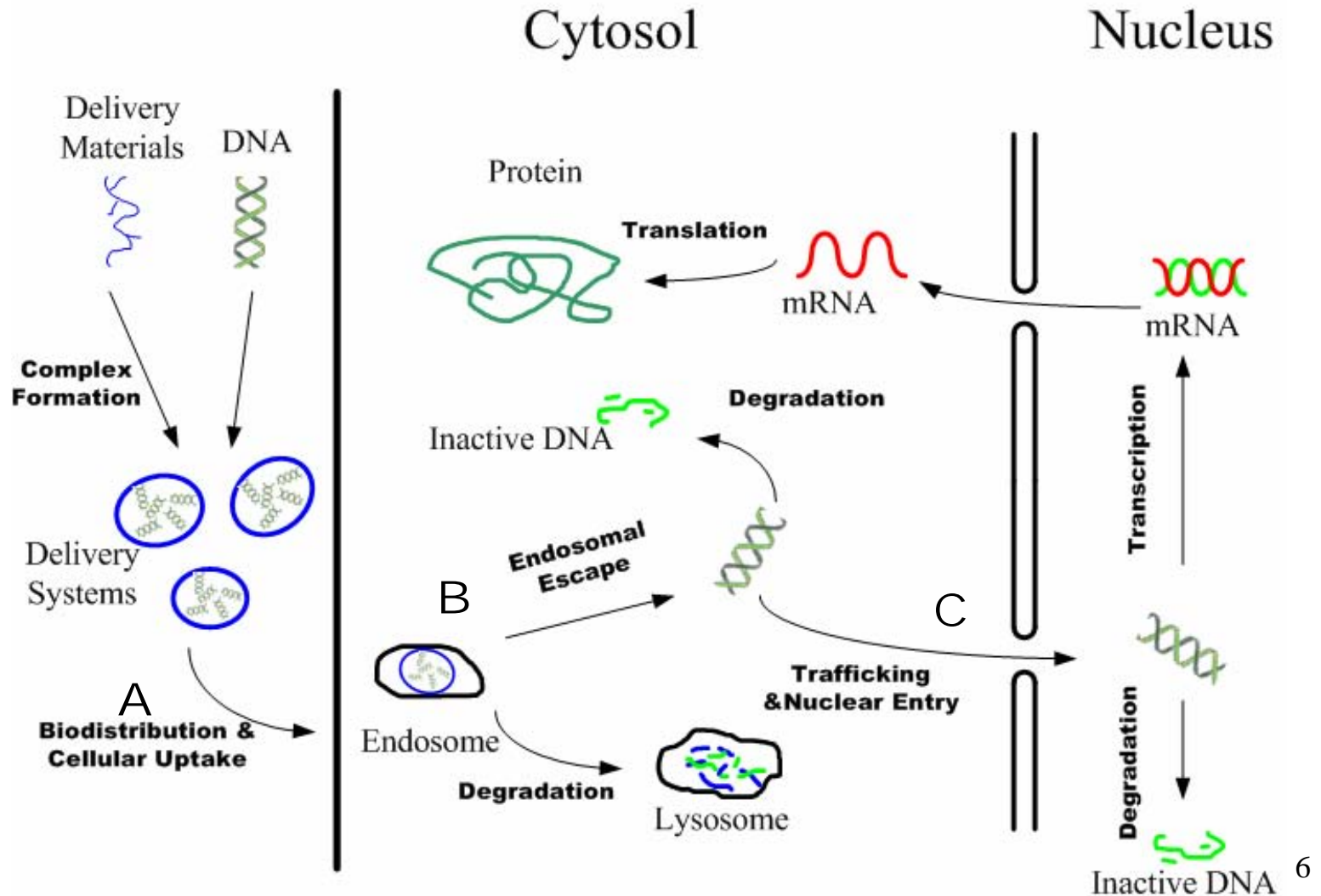
NASAL/LUNG MUCOSA

Images removed due to copyright restrictions.

Please see Neutra, M. R., and P. A. Kozlowski. "Mucosal Vaccines: The Promise and The Challenge." *Nat Rev Immunol* 6 (2006): 148.

Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

(2) INTRACELLULAR BARRIERS: Intracellular drug delivery

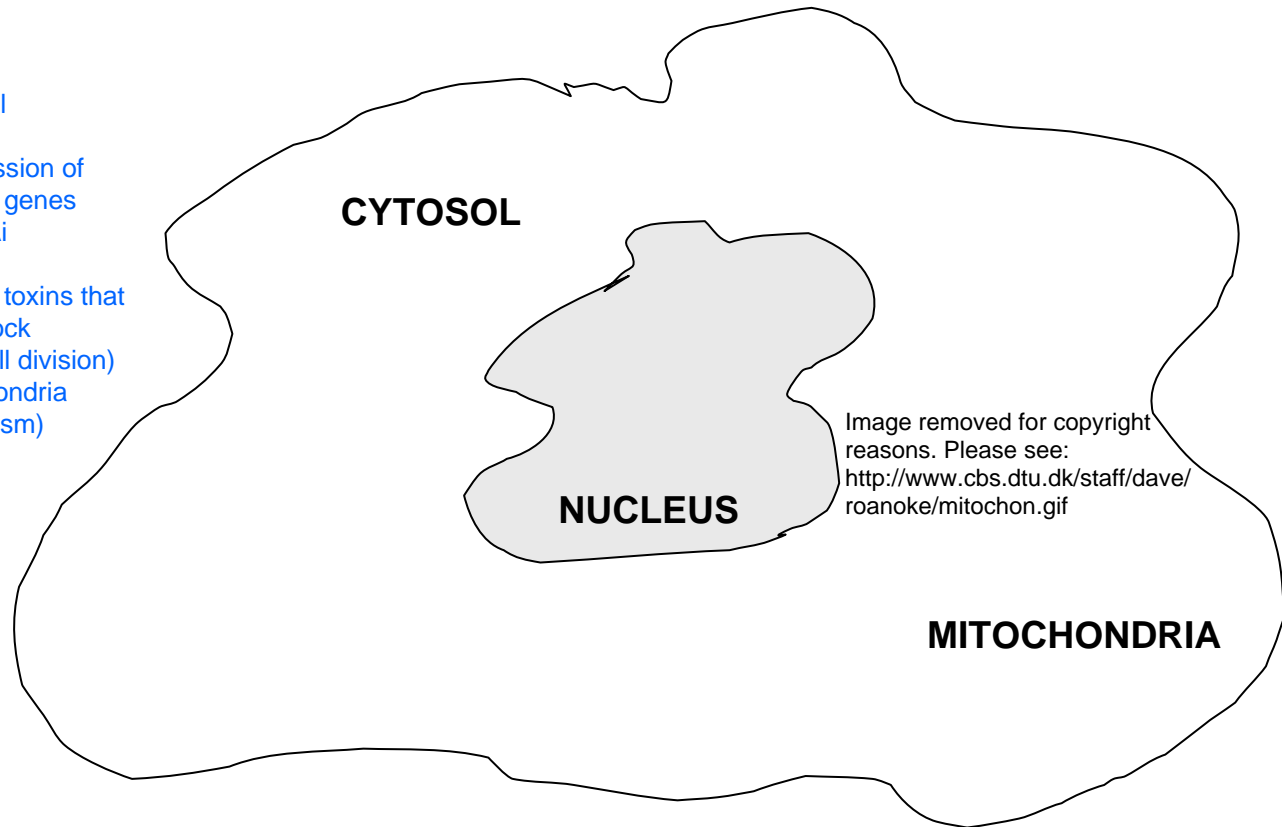


Applications of polymer-drug conjugates and particles as drug carriers and cellular markers: two general challenges

(2) INTRACELLULAR BARRIERS: Intracellular drug delivery

Applications requiring delivery of molecules to intracellular compartments:

- Vaccines
 - MHC restriction of T cell
- Gene delivery
 - Plasmid DNA for expression of missing/foreign genes
- Anti-sense therapy, siRNA/RNAi
- Therapeutic molecules
 - Intracellular toxins (e.g. toxins that bind DNA to block transcription/cell division)
- Drug delivery to mitochondria (affect metabolism)



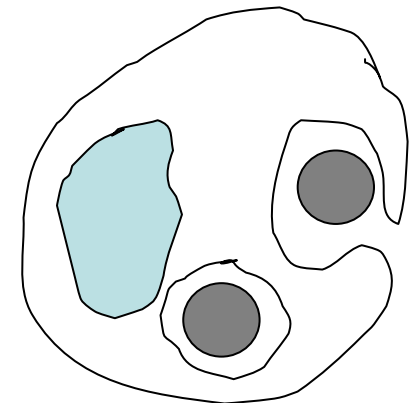
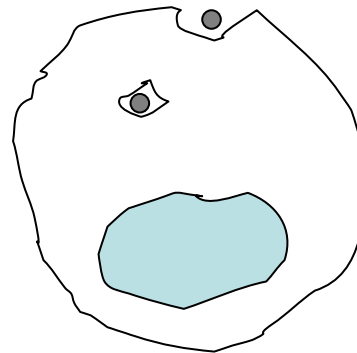
Objectives of nano- and micro-carriers:

(1) protection of cargos from premature degradation

COMPOUND	APPLICATION	EXAMPLE HALF-LIVES IN CIRCULATION	REFERENCES
Short peptides (5-20 amino acids)	Vaccine epitopes, ligands for drug targeting, peptide drugs	2 min., 5 min, 2 hrs	<i>J. Biol. Chem.</i> 48 , 48503 (2002); <i>J. Pharm. Sci.</i> 81 , 731 (1992)
Cytokines (polypeptides typically 5-20 KDa)	Regulation of tissue physiology (e.g., growth factors), disease treatment (e.g., interferon- α)	IFN-α 3-8 hrs interleukin-6 2.1 min tumor necrosis factor 3 min	<i>Nat Rev Drug Discov</i> 2 , 214-21 (2003)

EXTRACELLULAR CLEARANCE:

INTRACELLULAR CLEARANCE:



Protection of DNA from DNAses

Abbott laboratories anti-TNF antibody for treatment of Rheumatoid arthritis: 40 mg every 2 weeks... (active at nM conc.)

Objectives of nano- and micro-carriers:

(2) Avoiding the immune system

(I) Opsonization:

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Please see: <http://medtech.cls.msu.edu/ISL/immunology/opsonize.htm>

Internalization is also triggered by complement

Protein adsorption can trigger opsonization (via exposure of un-natural epitopes)

(II) anti-drug/carrier antibody production:

- B cells binding to a foreign protein, drug, or particle can be triggered to produce antibodies against the drug or carrier

- Even human proteins provided in non-physiological contexts may elicit antibodies (e.g., DNA)

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Please see: Abbas, A. K., and A. H. Lichtman. *Cellular and Molecular Immunology*. San Diego, CA: Elsevier, 2005. ISBN: 1416023895.

Objectives of nano- and micro-carriers:
(3) targeted delivery to select tissues or cells

Sketch ligand-mediated binding and uptake on cells

OVERVIEW OF MOLECULAR/PARTICULATE DRUG CARRIERS: STRUCTURE, SYNTHESIS, PROPERTIES

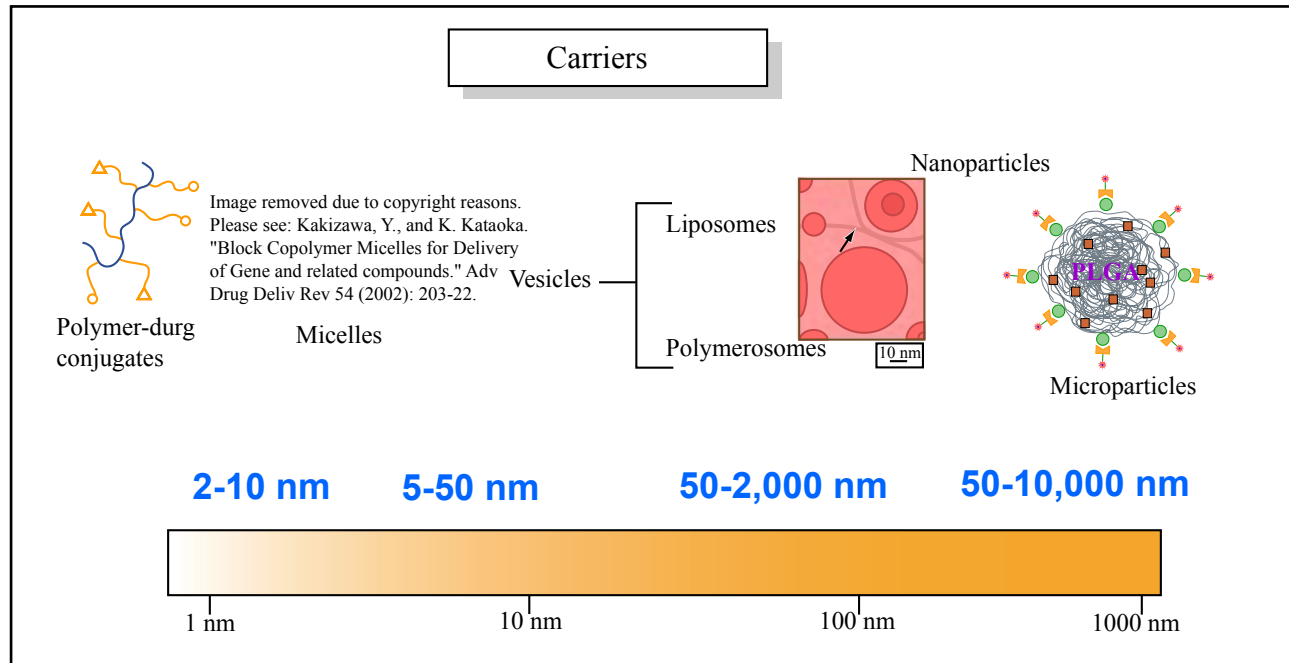


Figure by MIT OCW.

Polymer pro-drugs and markers

Role of polymeric carriers:

1. Control solubility of drug
2. Multivalency
 - High avidity binding to low-affinity receptors for detection/delivery
Cooperative binding – 2nd/3rd, ... binding event is facilitated by initial ligation
 - Potent delivery on a per-molecule basis
3. Aid penetration of tissues
4. 'stealth' functions

Polymer pro-drugs and markers

Architecture of polymeric carriers:

SKETCH FROM ADV MATER 1995
REVIEW

1. Requires water-soluble backbone
e.g., PEG, dextran, PHEMA

2. Drug may need to be selectively released
nonspecific- hydrolysis of side chains
triggered release- localized to specific microenvironment
pH
enzyme recognition

Polymer pro-drugs and markers

Endosomal enzyme-sensitive marker:

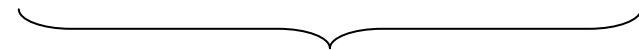
Fluorochromes quenched until enzyme clips backbone

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Please see: Weissleder, et al. *Nat Biotech* 17, 375 (1999).

Pro-Ile-Cys(Et)-Phe-Phe-Arg-Leu



cathepsin D substrate

Polymer pro-drugs and markers

Cell-activated polymer-fluorochrome conjugates for *in vivo* tumor imaging:

Sketch leaky tumor vasculature, conjugate uptake concept

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Please see: Weissleder, et al. *Nat Biotech* 17, 375 (1999).

Micelle carriers

Cargo-loaded micelles via polyion association:

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Please see: Figure 5 in Kakizawa, Y., and K. Kataoka.

"Block Copolymer Micelles for Delivery of Gene and Related Compounds." *Adv Drug Deliv Rev* 54 (2002): 203-22.

Images removed due to copyright reasons.

Please see: Kakizawa, Y., and K. Kataoka. "Block Copolymer Micelles

for Delivery of Gene and Related Compounds." *Adv Drug Deliv Rev* 54 (2002): 203-22.

Micelle drug carriers

Attachment of cargo molecules to core block of micelle:

Figure removed due to copyright restrictions.

Figure removed due to copyright restrictions.

Limitations:

Unstable at high dilution

Low cargo capacity

Further Reading

1. Torchilin, V. P. PEG-based micelles as carriers of contrast agents for different imaging modalities. *Advanced Drug Delivery Reviews* **54**, 235-252 (2002).
2. Weissig, V. & Torchilin, V. P. Drug and DNA delivery to mitochondria. *Adv Drug Deliv Rev* **49**, 1-2 (2001).
3. Kakizawa, Y. & Kataoka, K. Block copolymer micelles for delivery of gene and related compounds. *Adv Drug Deliv Rev* **54**, 203-22 (2002).
4. Torchilin, V. P. PEG-based micelles as carriers of contrast agents for different imaging modalities. *Adv Drug Deliv Rev* **54**, 235-52 (2002).
5. Harris, J. M. & Chess, R. B. Effect of pegylation on pharmaceuticals. *Nat Rev Drug Discov* **2**, 214-21 (2003).
6. Park, S. & Healy, K. E. Nanoparticulate DNA packaging using terpolymers of poly(lysine-g-(lactide-b-ethylene glycol)). *Bioconj Chem* **14**, 311-9 (2003).
7. Moghimi, S. M., Hunter, A. C. & Murray, J. C. Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacol Rev* **53**, 283-318 (2001).
8. Li, Y. et al. PEGylated PLGA nanoparticles as protein carriers: synthesis, preparation and biodistribution in rats. *J Control Release* **71**, 203-11 (2001).
9. Stolnik, S., Illum, L. & Davis, S. S. Long Circulating Microparticulate Drug Carriers. *Advanced Drug Delivery Reviews* **16**, 195-214 (1995).
10. Kozlowski, A. & Harris, J. M. Improvements in protein PEGylation: pegylated interferons for treatment of hepatitis C. *J Control Release* **72**, 217-24 (2001).
11. Efremova, N. V., Bondurant, B., O'Brien, D. F. & Leckband, D. E. Measurements of interbilayer forces and protein adsorption on uncharged lipid bilayers displaying poly(ethylene glycol) chains. *Biochemistry* **39**, 3441-51 (2000).
12. Halperin, A. Polymer brushes that resist adsorption of model proteins: Design parameters. *Langmuir* **15**, 2525-2533 (1999).