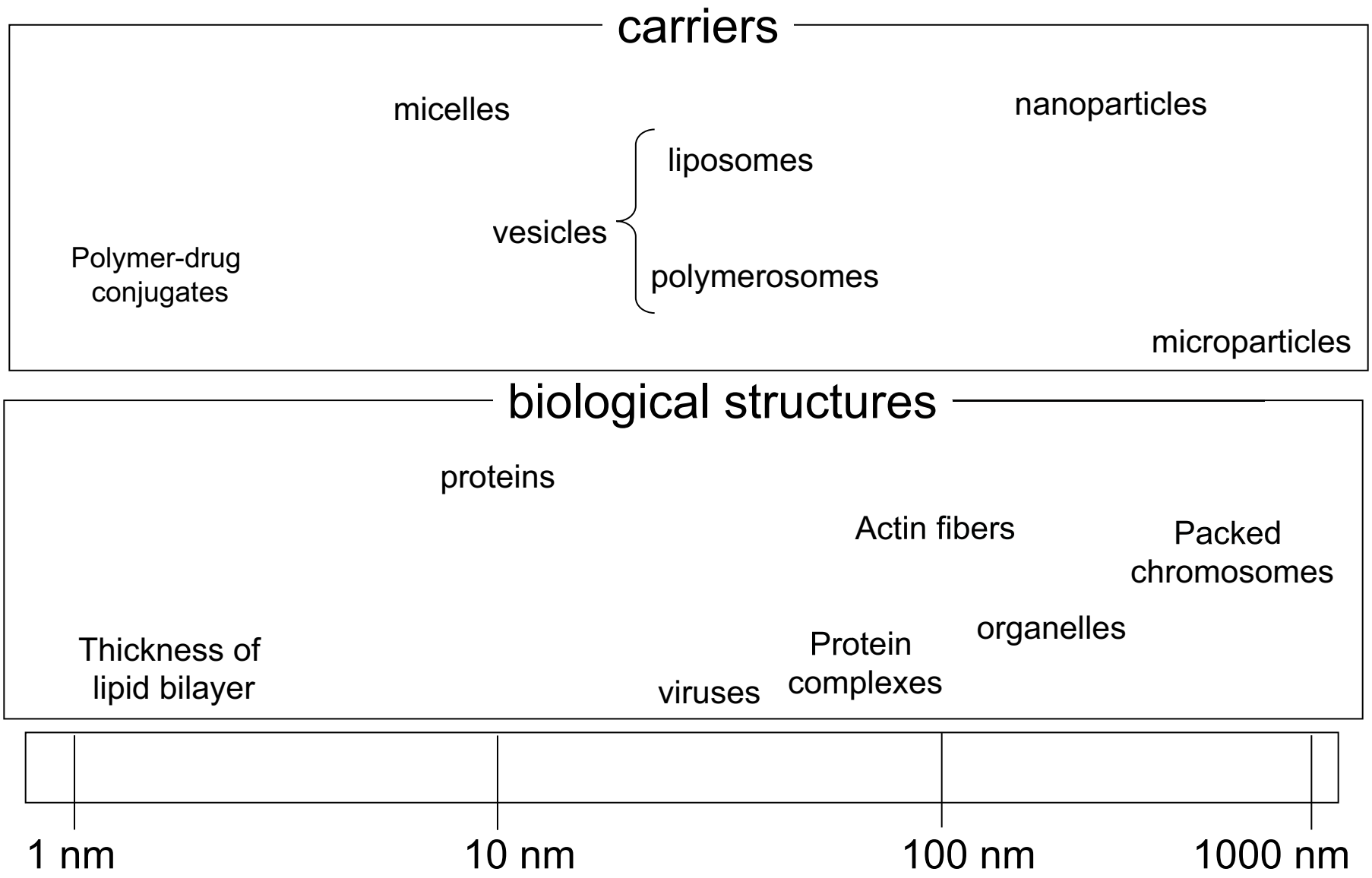
20.380 workshop:
Drug Carriers: Polymers, Vesicles, Nanoparticles and systemic delivery



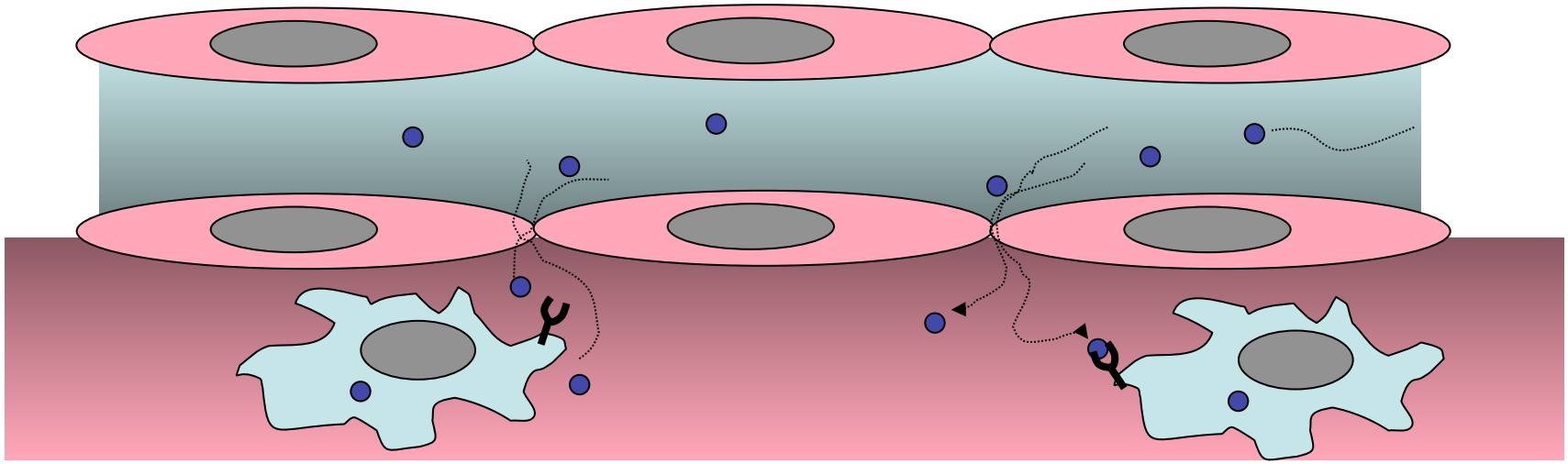
Images of various biological molecules removed due to copyright restrictions.

Objectives of molecular and particulate drug carriers:

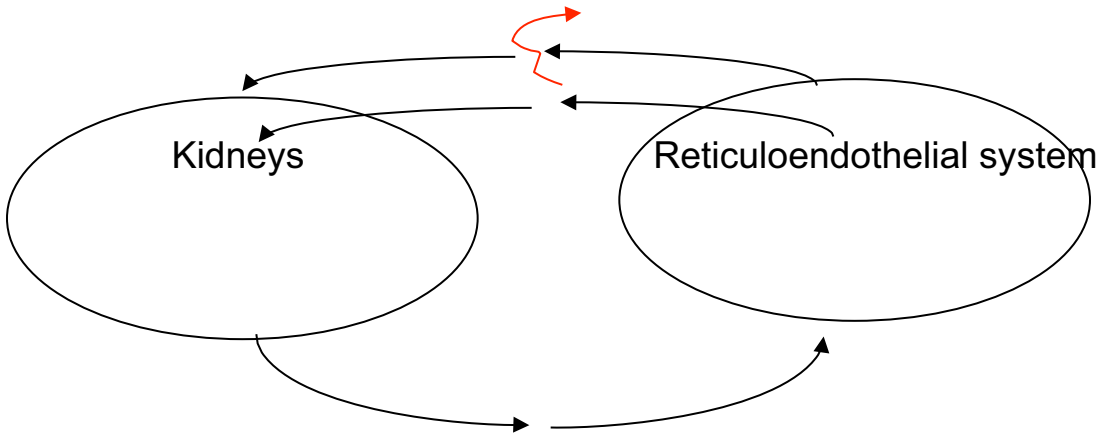
- (I) Alter pharmacokinetics
- (II) Alter biodistribution
- (III) Provide drug reservoirs

Table from *Science* removed due to copyright restrictions. See Table 1 from Allen, Theresa M. and Pieter R. Cullis. "Drug Delivery Systems: Entering the Mainstream." *Science* 303, no. 5665 (2004).

Delivery via systemic and oral routes

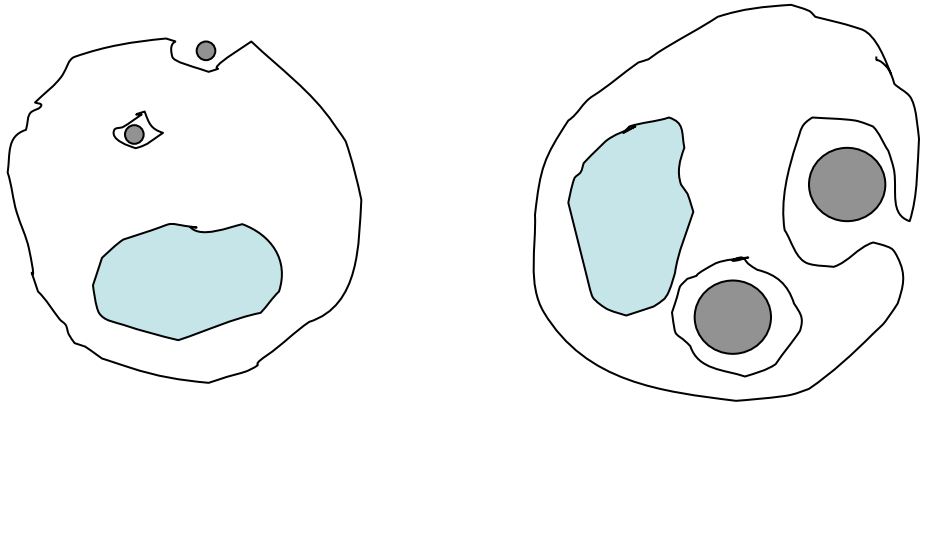


Size limits for penetration of tissue from circulation:



Objectives of nano- and micro-carriers: protection of cargos from premature degradation

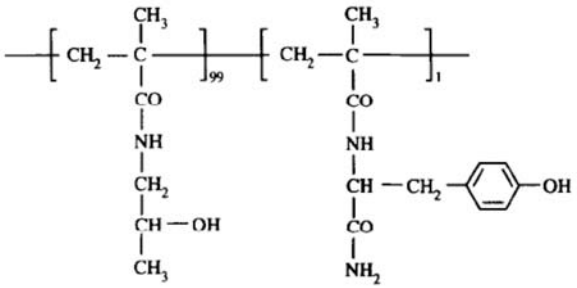
COMPOUND	APPLICATION	EXAMPLE HALF-LIVES IN CIRCULATION	REFERENCES
Short peptides (5-20 amino acids)	Vaccine epitopes, ligands for drug targeting, peptide drugs	2 min., 5 min, 2 hrs	*J. Biol. Chem.* **48**, 48503 (2002); *J. Pharm. Sci.* **81**, 731 (1992)
Cytokines (polypeptides typically 5-20 KDa)	Regulation 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	*Nat Rev Drug Discov* **2**, 214-21 (2003)

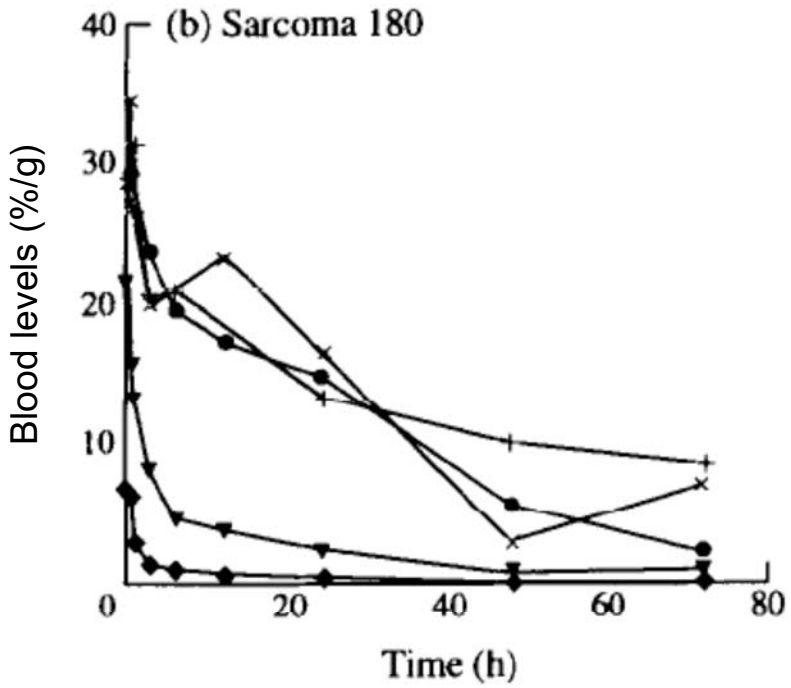


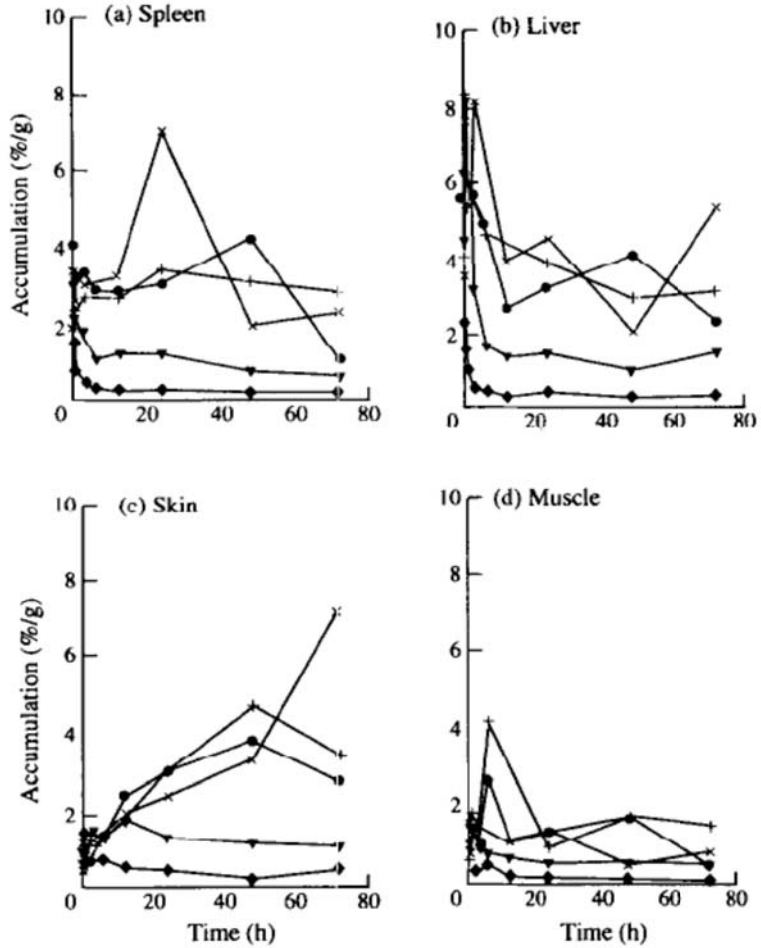
Objectives of nano- and micro-carriers:
(1) protection of cargos from premature degradation

i.v. proteins and polymers are rapidly cleared from the blood:

Poly(N-2-hydroxypropylmethacrylamide)







(Seymour Duncan *Eur. J. Cancer* **5** 766-770 (1995))

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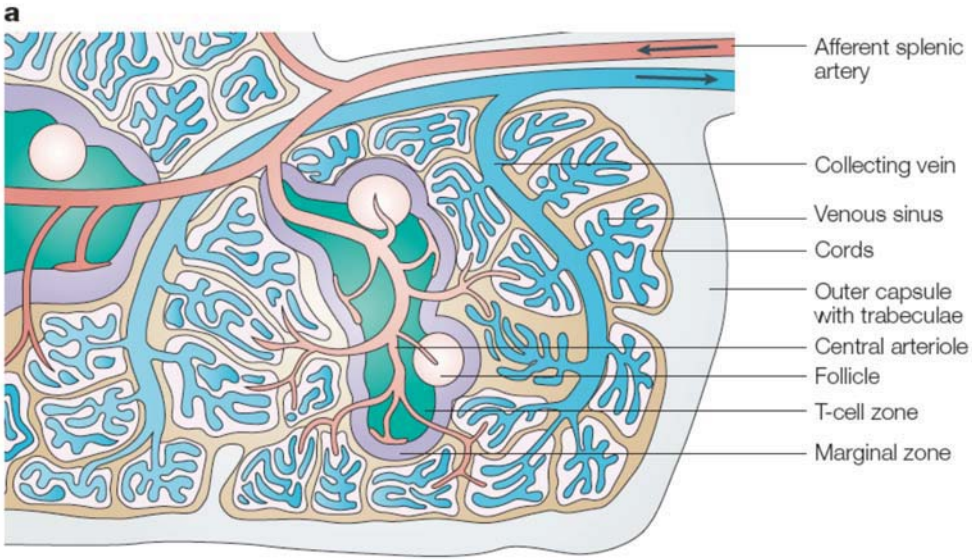
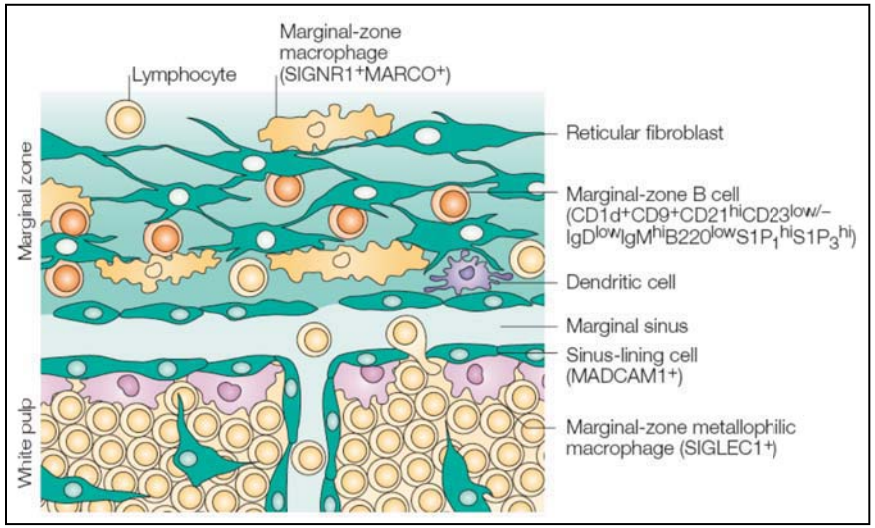
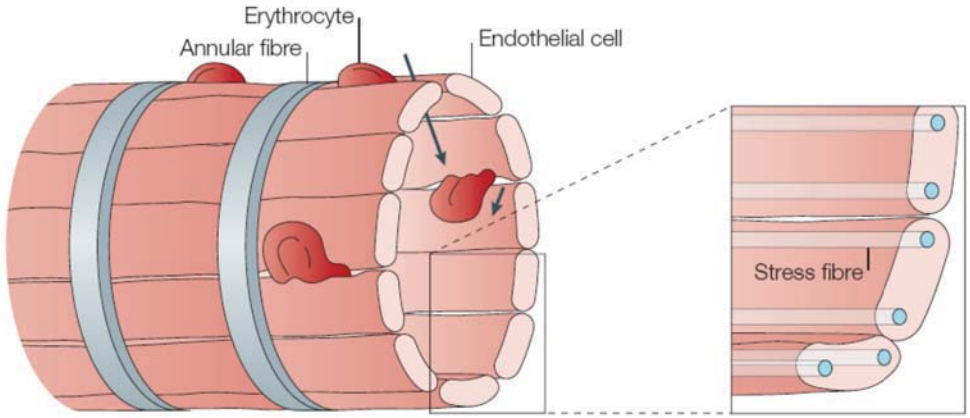
Fate of injected particles in vivo







(Mebius and Kraal Nature Reviews Immunology 5, 606-616 (August 2005))

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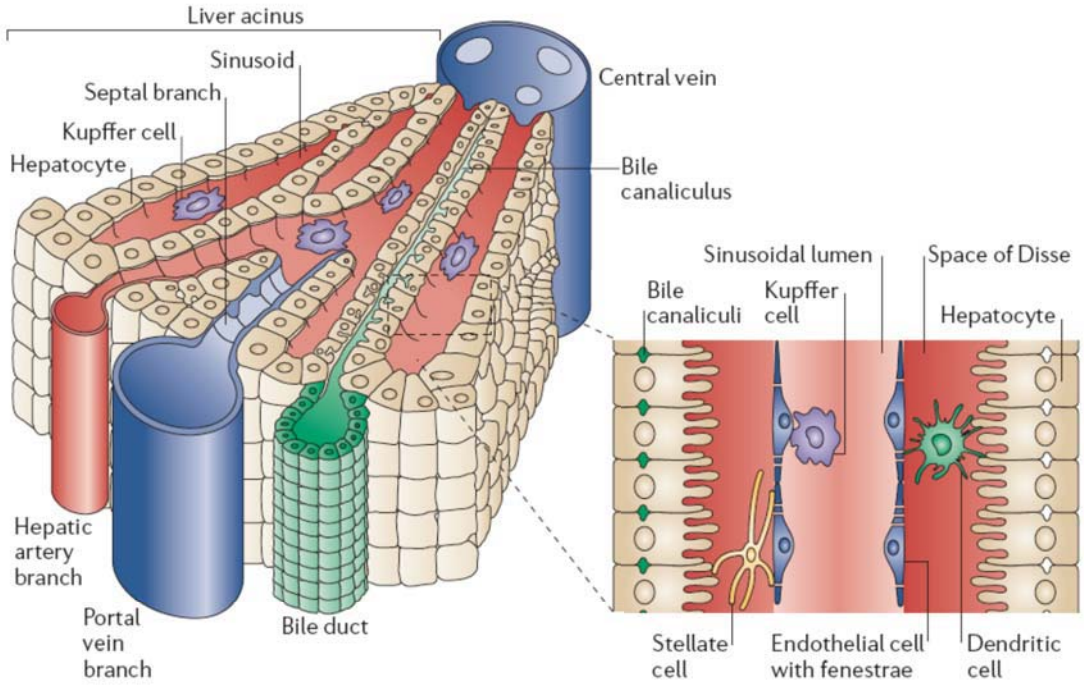
Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Source: Mebius, Reina E., and Georg Kraal. "Structure and Function of the Spleen." *Nature Reviews Immunology* 5 (2005). © 2005.

Fate of injected particles in vivo



(Adams and Ecksteen, Nat. rev. Immunol 6 244-251 (2006))

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Source:Adams, David H. and Bertus Eksteen. "Aberrant Homing of Mucosal T Cells and Extra-Intestinal Manifestations of Inflammatory Bowel Disease." *Nature Reviews Immunology* 6 (2006). © 2006.

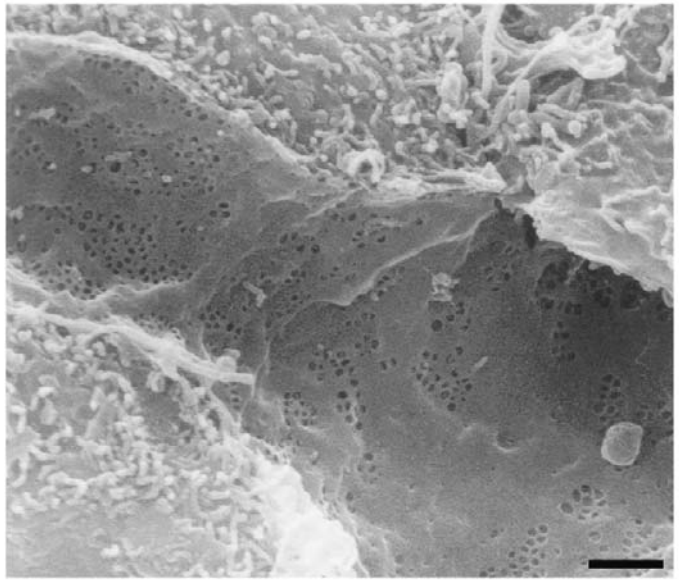
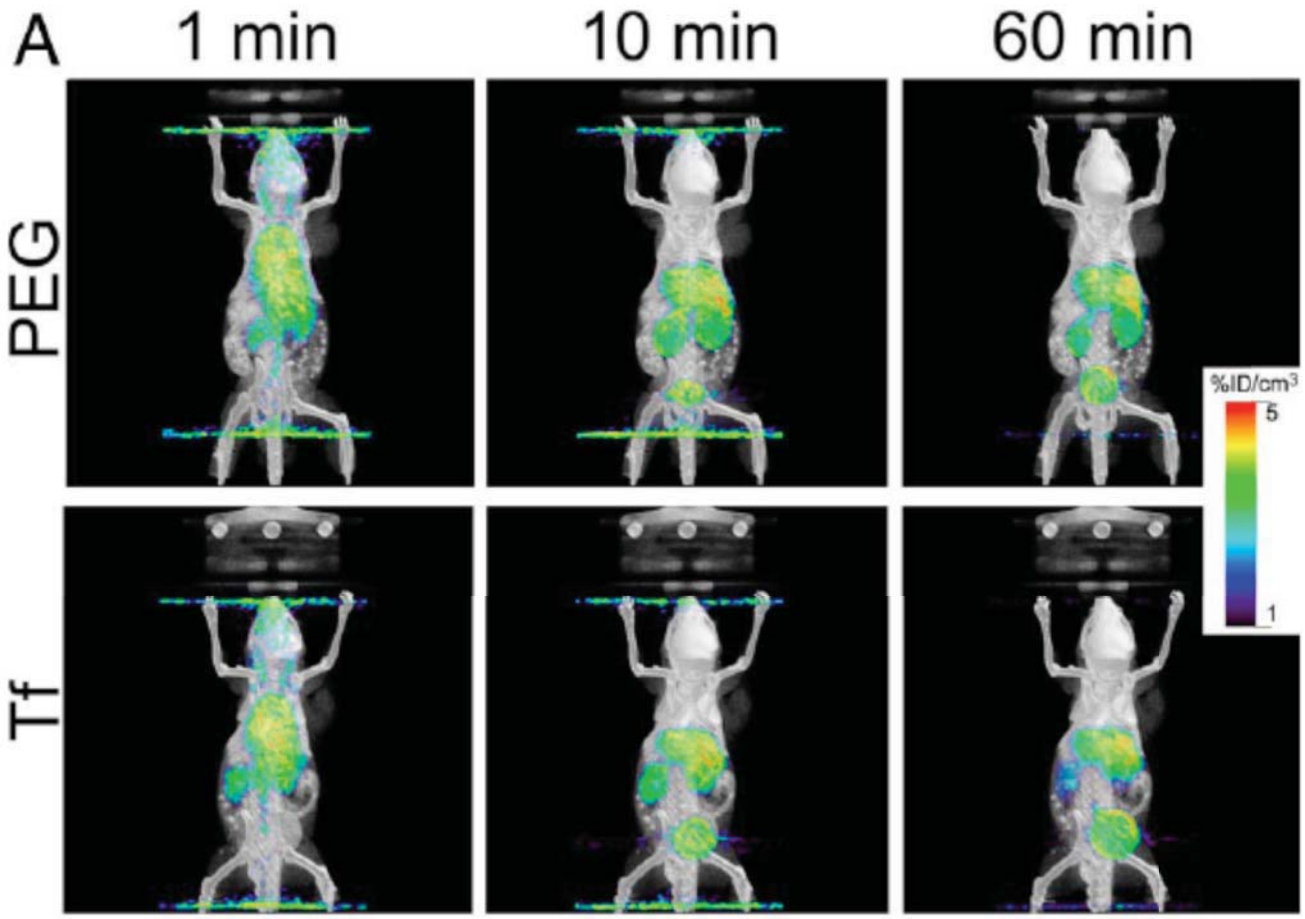


Figure 1
Low magnification scanning electron micrograph of the sinusoidal endothelium from rat liver showing the fenestrated wall. Notice the clustering of fenestrae in sieve plates. Scale bar, 1 μm.

(Braet and Wisse, *Comp. Hepatology* **1**, 1 (2002))

Source: Braet, Filip and Eddie Wisse. "Structural and Functional Aspects of Liver Sinusoidal Endothelial Cell Fenestrae: A Review." *Comparative Hematology* 1 (2002).

Fate of injected particles in vivo



(Bartlett, Davis et al. PNAS 2007)

Source: Bartlett, Derek W., et al. "Impact of Tumor-Specific Targeting on the Biodistribution and Efficacy of SiRNA Nanoparticles Measured by Multimodality in V*ivo I*maging." *Proceedings of the National Academy of Science* 104, no. 39 (2007). © 2007 National Academy of Sciences, USA.

Carriers must avoid immune-mediated clearance to stay in circulation/traffic to target tissues

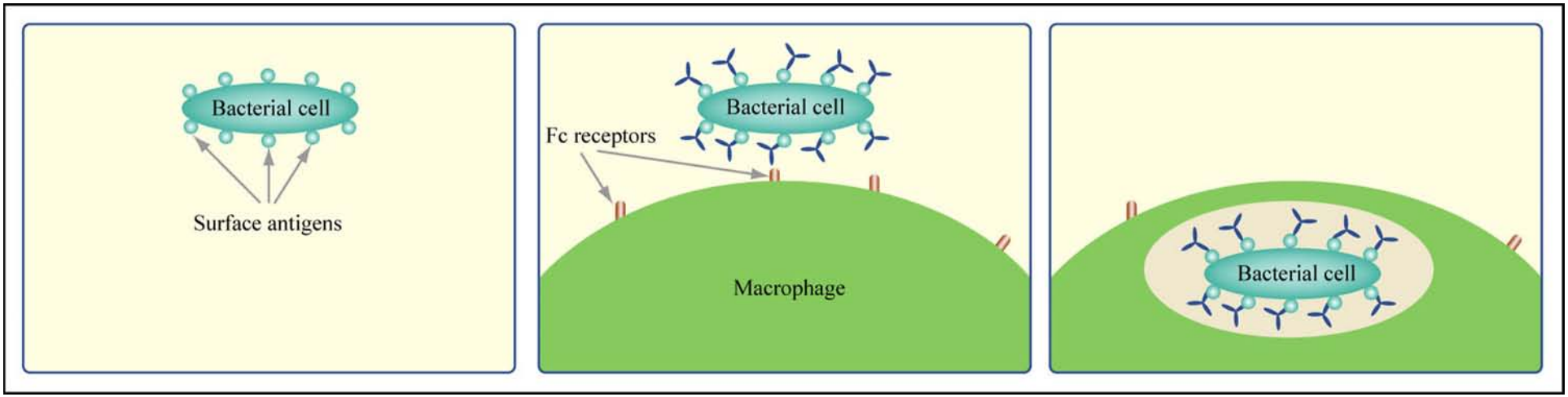
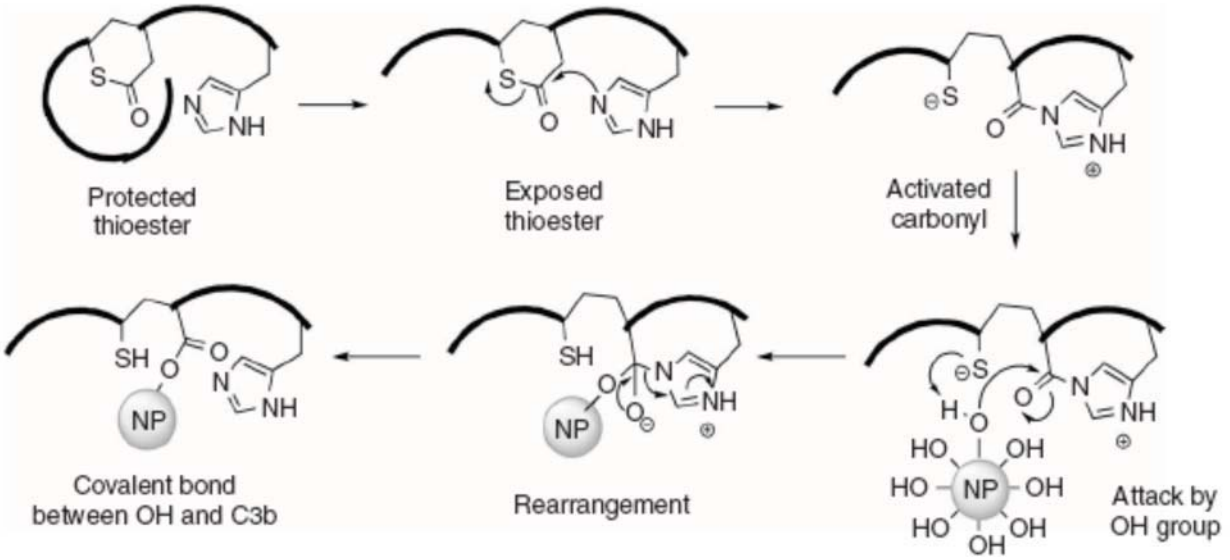


Image by MIT OpenCourseWare. Adapted from Michigan State University College of Natural Science, Biomedical Laboratory Diagnostics.



(Reddy, Swartz, Hubbell, et al. *Nat. Biotech*. (2007))

Reprinted by permission from Macmillan Publishers Ltd: Nature Biotechnology. Source: Reddy, Sai T., et al. "Exploiting lymphatic Transport and Complement Activation in Nanoparticle Vaccines." *Nature Biotechnology* 25 (2007). © 2007.

F.F. Davis (1977): showed showed that poly (ethylene glycol) conjugated to a protein is non-immunogenic and greatly increased protein half-lives *in vivo*

Micrograph of bacterial cell showing peptidoglycan cell wall removed due to copyright restrictions.

Diagram of ethylene glycol conjugated to a protein removed due to copyright restrictions.

T. Paustian, http://www.microbiologytext.com/index.php?module=Book&func=displayarticle&art_id=60

(*Annu Rev. Microbiol* **32**, 19 (1978))

(*J. Biol. Chem.* **252**, 3578 (1977))

PEGylated molecules:

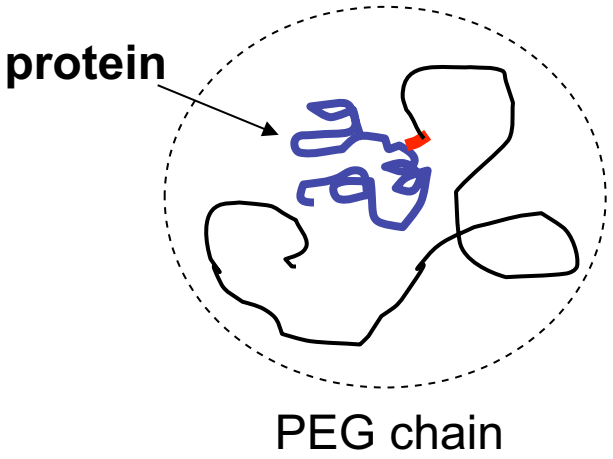


Table 1 | **Influence of pegylation on pharmacokinetics and pharmacodynamics***

Pharmacokinetic effect	Pharmacodynamic effect
Interferon-α2a	
Sustained absorption	*In vivo* antiviral activity increased 12- to 135-times
Increased half-life (from 3–8 h to 65 h)	Antitumour activity increased 18-fold
Decreased volume of distribution (from 31–73 l to 8–12 l)	Improved sustained response to chronic hepatitis C
Decreased systemic clearance (from 6.6–29.2 to 0.06–0.10 l/h)	
Interleukin-6	
Increased half-life (from 2.1–206 min)	Thrombopoietic potency increased 500-times
Tumour necrosis factor	
Increased half-life (from 3 to 45–136 min)	Antitumour potency increased 4-to 100-times

*Influence of pegylation on pharmacokinetics and pharmacodynamics of some therapeutic proteins, compared with corresponding native proteins (adapted from REF. 18).

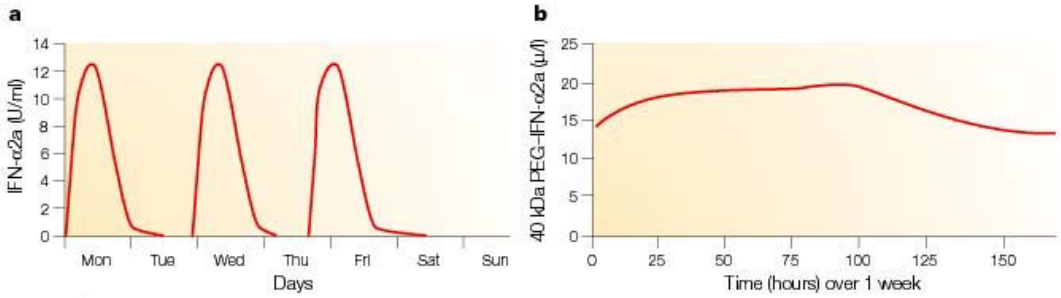
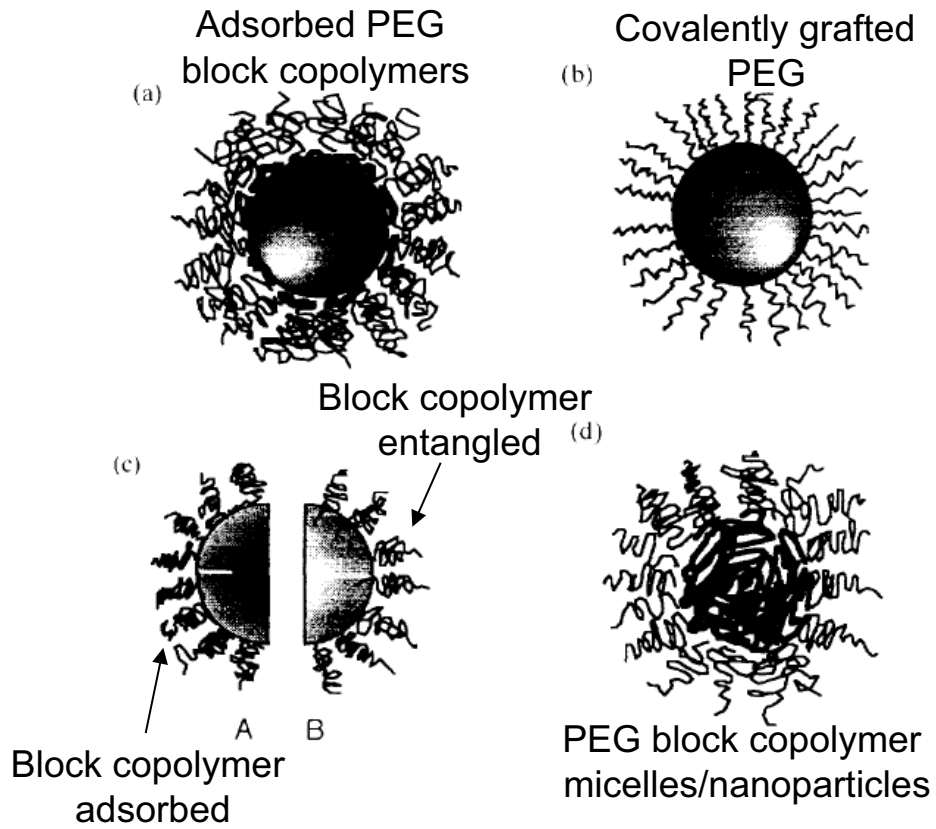


Figure 4 | **Pharmacokinetic profiles for interferon (IFN)-α2a and 40 kDa polyethylene glycol (PEG)–IFN-α2a.** These graphs represent blood levels in humans resulting from subcutaneous injection of **a** | IFN-α2a and **b** | branched PEG 40 (kDa) IFN-α2a. IFN-α2a is injected every other day and its short lifetime in circulation leads to pulsed blood concentrations levels which cycle below efficacious levels. The branched PEG 40 (kDa) IFN-α2a has a long circulating lifetime due to the presence of the PEG, and the once-weekly injection leads to near constant blood concentrations above the therapeutic level over the one-week period.

Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery.
Source: Harris, J. Milton and Robert B. Chess. "Effect of Pegylation on Pharmaceuticals."
Nature Reviews Drug Discovery 2 (2003). © 2003.

Synthesis of ‘stealth’ particles



(Stolnik et al. 1995)

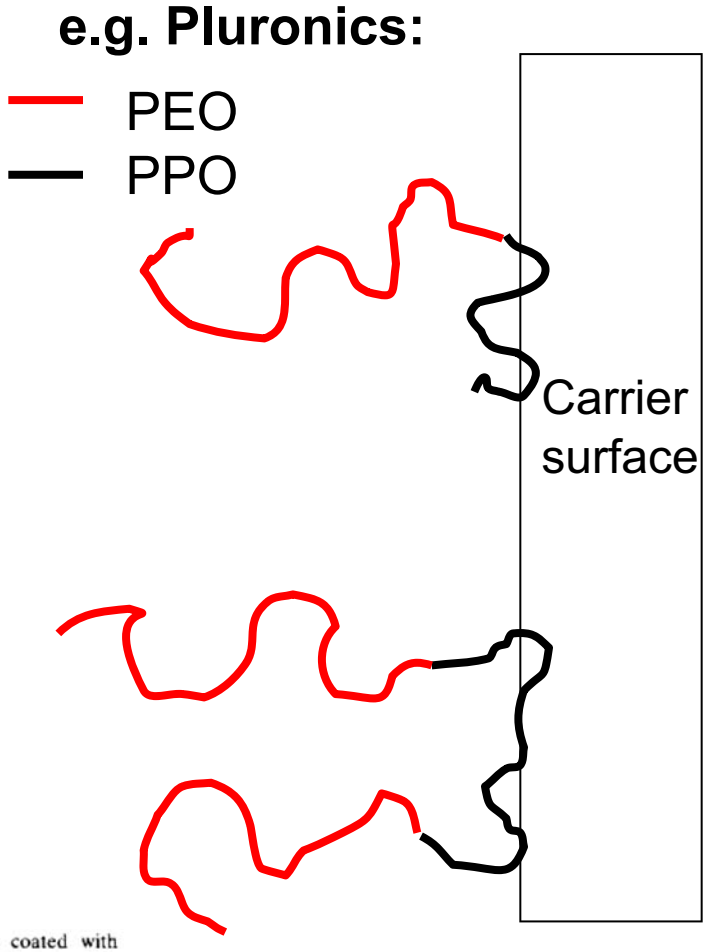
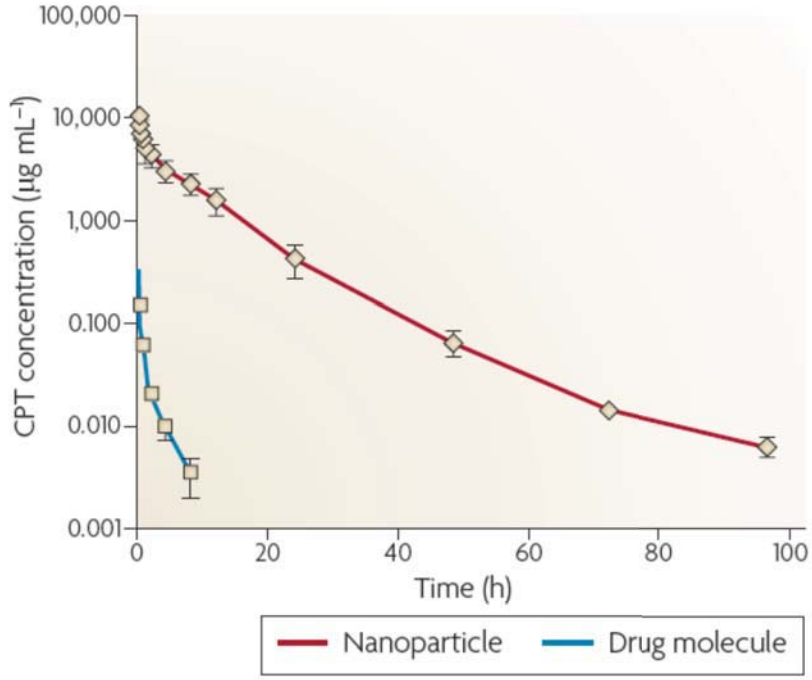


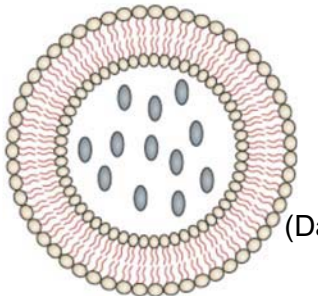
Fig. 1. Schematic diagram illustrating long-circulating nanoparticulate systems. (a) Polystyrene nanoparticles coated with Poloxamers and Poloxamines [5–7,21,22,57,62]. (b) Polystyrene nanoparticles with grafted PEO [41,95]. (c) Polylactide/glycolide nanoparticles with polylacide/glycolide-PEO copolymers, coated (A) or prepared from common solvent (B) [9,10,86,88]. (d) 'Self-forming' polylactide/glycolide-PEO block copolymers systems [11,98].

Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission. Source: Stolnik, S., L. Illum, and S. S. Davis. "Long Circulating Microparticulate Drug Carriers." *Advanced Drug Discovery* 16 (1995).

Clearance of particles from the blood

Figure showing change in dose over time from Science magazine removed due to copyright restrictions. For article, see Gref, R., et al. "Biodegradable Long-Circulating Polymeric Nanospheres." *Science* 263, no. 5153 (1994).





(Davis et al. Nat. Rev. Drug Disc. 7 771-782 2008)

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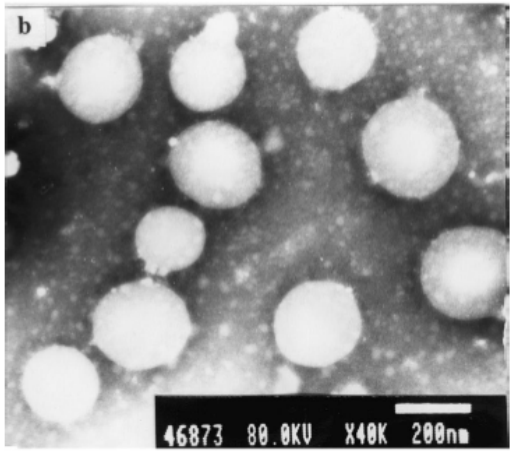
Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery. Source: Davis, Mark E., Zhuo (Georgia) Chen, and Dong M. Shin. "Nanoparticle Therapeutics: An Emerging Treatment Modality for Cancer." *Nature Reviews Drug Discovery* 7 (2008). © 2008.

TEM of nanoparticles



Release properties of diblock particles

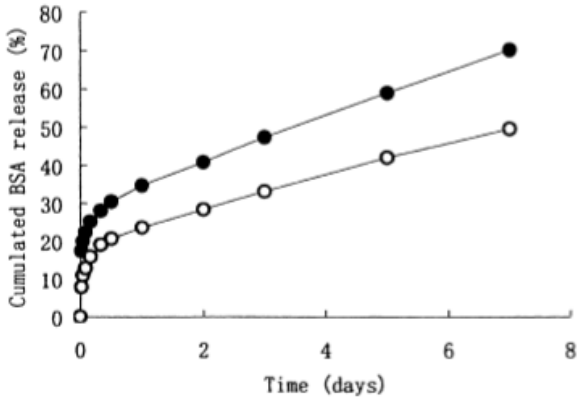


Fig. 6. Release profiles of BSA from PLGA (○) and PEG–PLGA (●) nanoparticles.

Increased $t_{1/2}$ in blood:

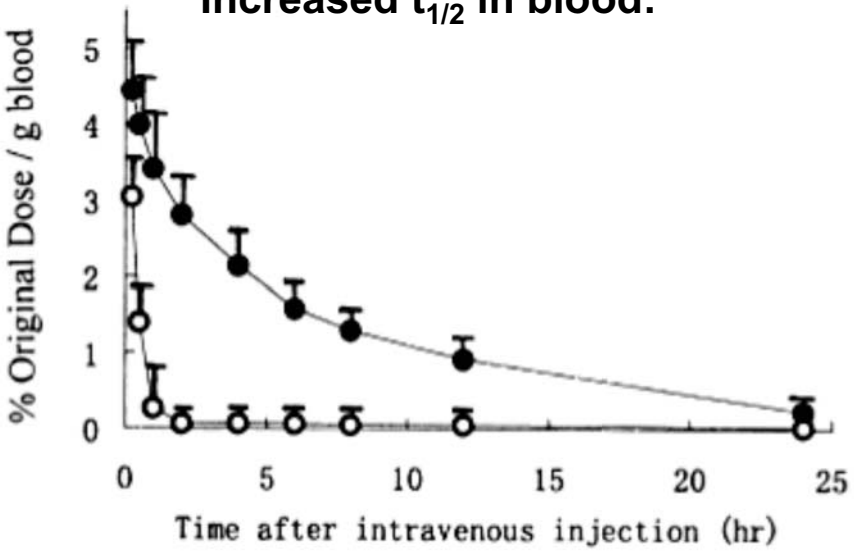
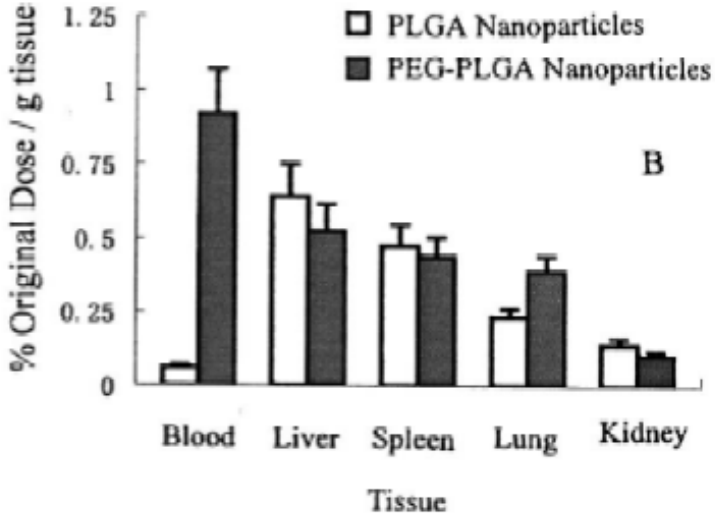


Fig. 7. Blood clearance curves of [^{125}I]BSA in PLGA (○) and PEG–PLGA (●) nanoparticles.

Altered biodistribution:



(Li et al., 2001)

Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission. Source: Li, Ya-Ping, et al. "PEGylated PLGA Nanoparticles as Protein Carriers: Synthesis, Preparation and Biodistribution in rats." *Journal of Controlled Release* 71, no. 2 (2001).

PASSIVE TARGETING OF TUMORS:
Enhanced permeation and retention (EPR) effect in tumors:

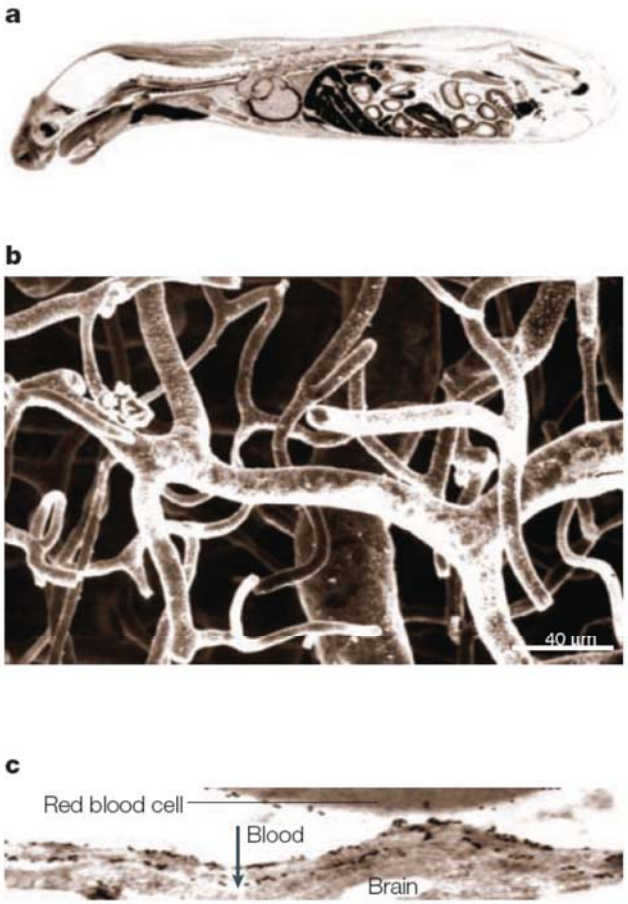
Enhanced permeation and retention (EPR) effect in tumors:

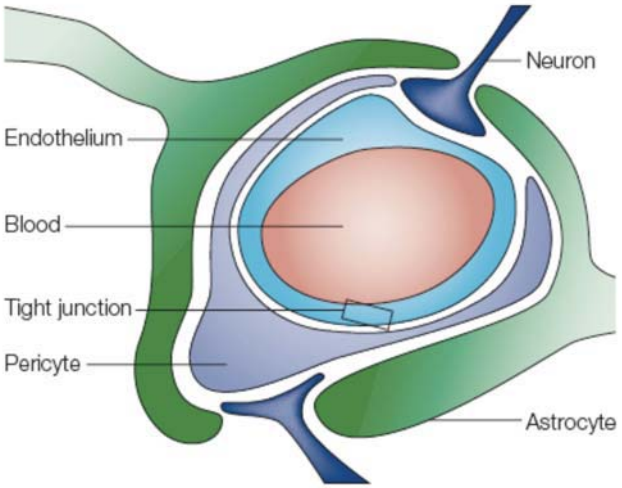
Figure removed due to copyright restrictions. See Figure 2a,b from Lammers, Twan, et al. "Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer–Based Drug Delivery Systems." *Neoplasia* 8, no. 10 (2006).

(Lammers et al. *Neoplasia* **8** 788-795 (2006))

Applications of polymer-drug conjugates and particles as drug carriers and cellular markers

Blood-brain barrier





(Pardridge *Nat. Rev. Drug Disc*. **1** 131 (2002))

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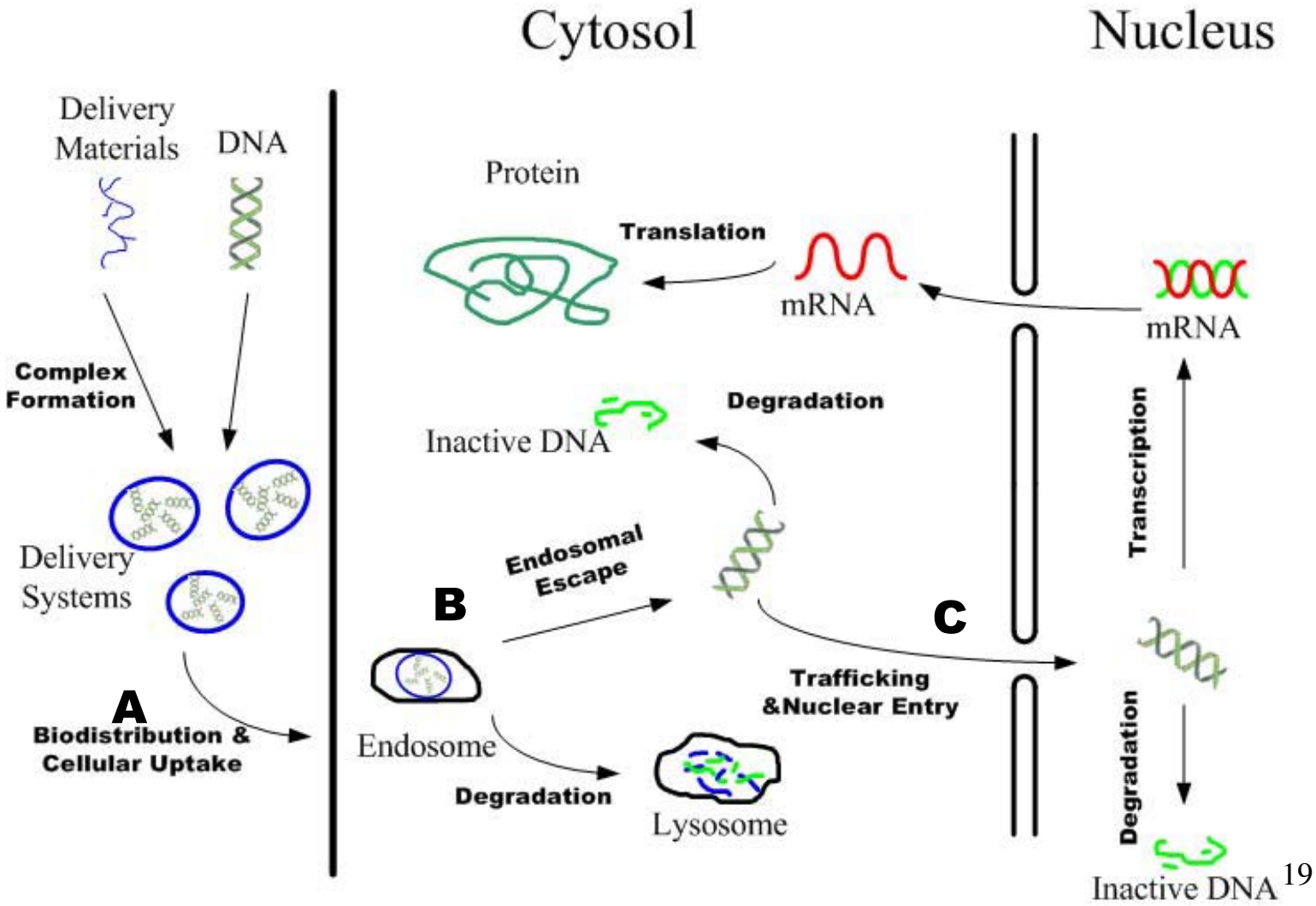
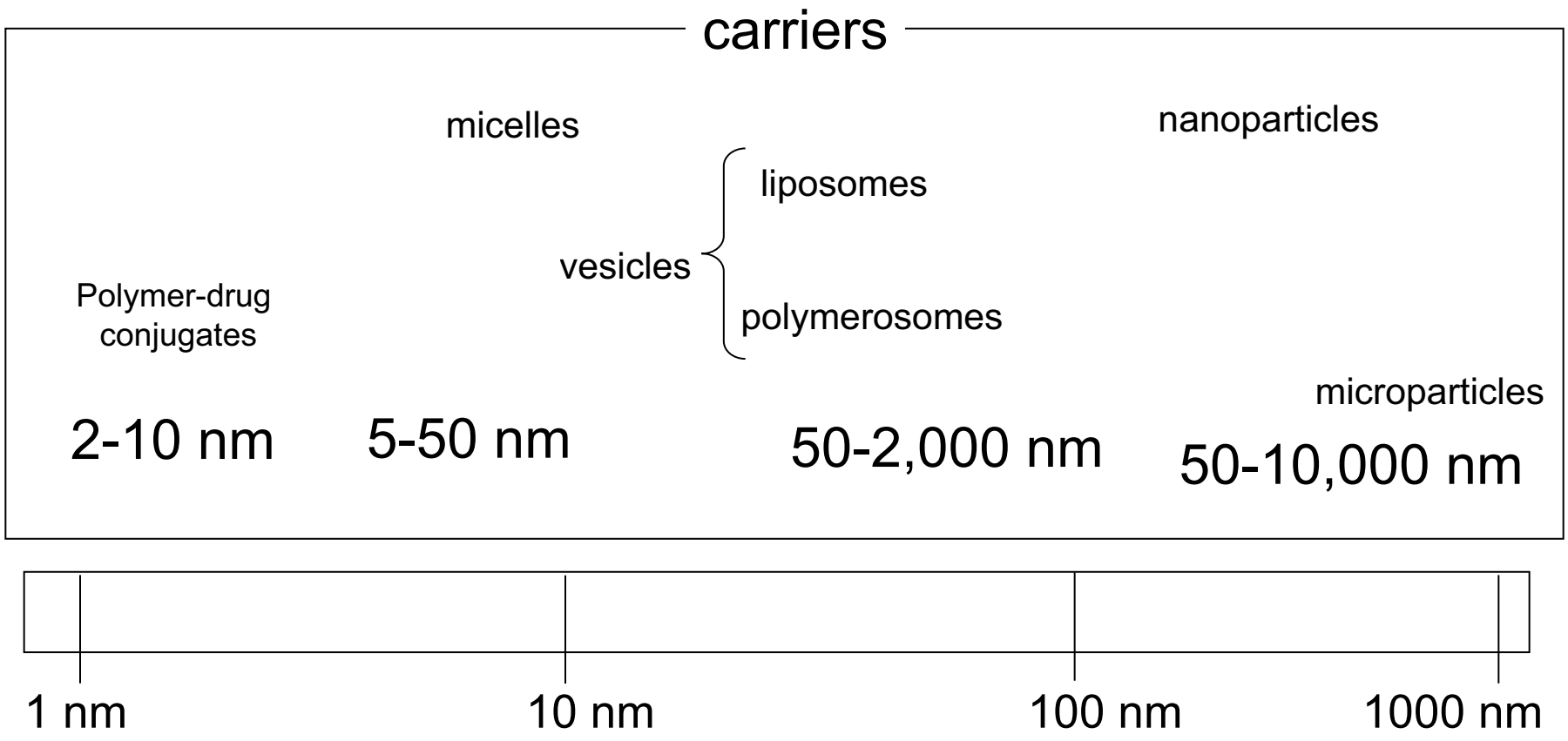
Applications of polymer-drug conjugates and particles as drug carriers and cellular markers

(2) INTRACELLULAR BARRIERS: Intracellular drug delivery



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

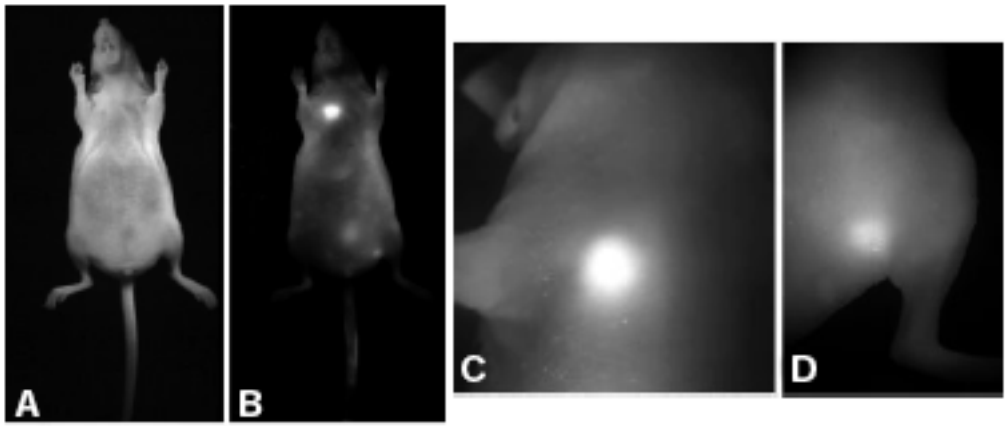


Images of various biological molecules removed due to copyright restrictions.

Polymer pro-drugs and markers

Polymer pro-drugs and markers

Figure removed due to copyright restrictions.
See Figure 1 from Tung, Ching-Hsuan, et al. "Preparation of a Cathepsin D Sensitive Near-Infrared Fluorescence Probe for Imaging." *Bioconjugate Chemistry* 10, no. 5 (1999).



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

cathepsin D substrate

Micelle carriers

Cargo-loaded micelles via polyion association:

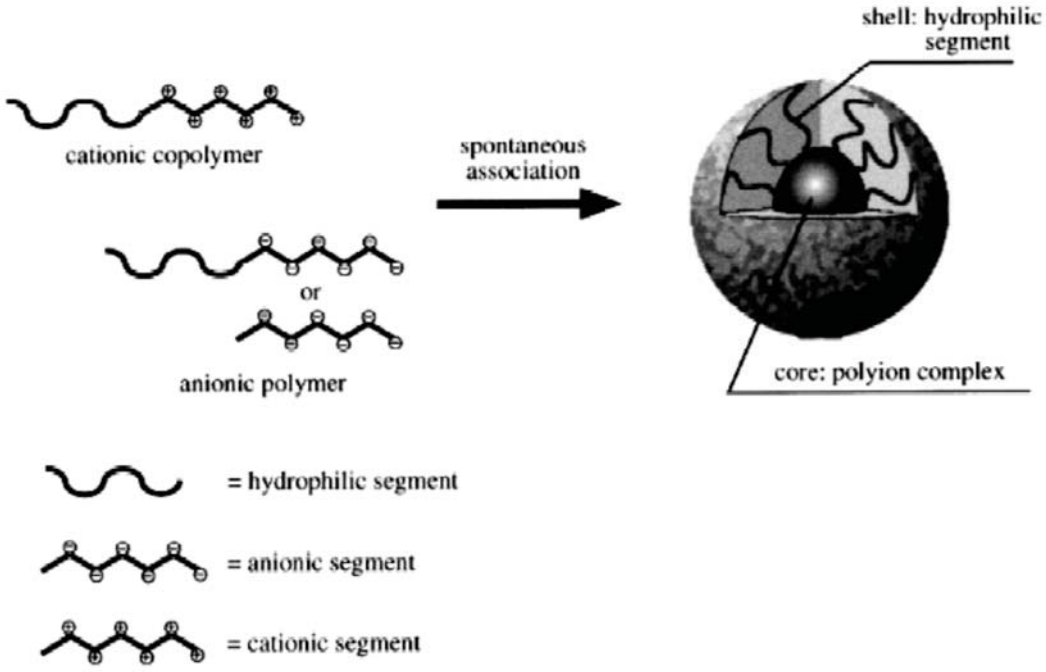

Fig. 1. Formation of polyion complex micelles.

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Source: Kakizawa, Yoshinori and Kazunori Kataoka. "Block Copolymer Micelles for Delivery of Gene and Related Compounds." *Advanced Drug Delivery Reviews* 54, no. 2 (2002).

Figure removed due to copyright restrictions. See Figure 3 from Kataoka, Kazunori, et al. "Spontaneous Formation of Polyion Complex Micelles with Narrow Distribution from Antisense Oligonucleotide and Cationic Block Copolymer in Physiological Saline." *Macromolecules* 29, no. 26 (1996).

Vesicle carriers

Liposomes – lipid bilayer vesicles formed typically using phospholipids mimicking the plasma membrane of cells

Virosomes – hybrids formed by fusion of liposomes with viral particles

Polymerosomes – synthetic vesicles formed using block copolymers as analogs of small-molecule amphiphiles

Liposome carriers

Diagram of liposome with drug entrapped in liposome interior removed due to copyright restrictions.

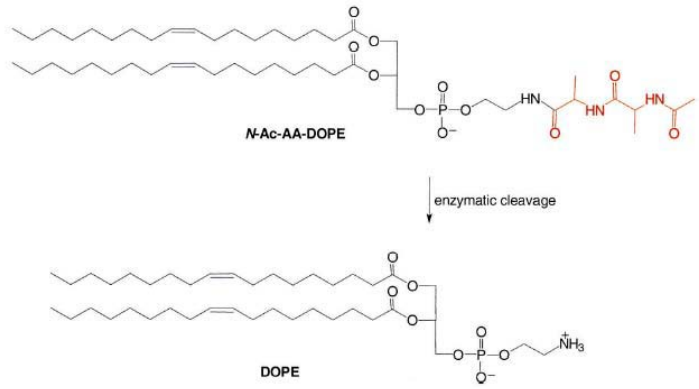


Fig. 2. Enzymatic conversion of *N*-AA–DOPE to DOPE. Elastase can cleave to the C-terminal side of dialanyl sequences. Cleavage generates a zwitterionic lipid from a negatively charged lipid.

Courtesy of Elsevier, Inc., http://www.sciencedirect.com.
Used with permission. Source: Meers, Paul. "Enzyme-Activated Targeting of Liposomes." *Advanced Drug Delivery Reviews* 53 (2001).

Figure removed due to copyright restrictions.
See Figure 6b from Bergstrand, Nill and Katarina Edwards.
"Aggregate Structure in Dilute Aqueous Dispersions of Phospholipids, Fatty Acids, and Lysophospholipids."
Langmuir 17 (2001).

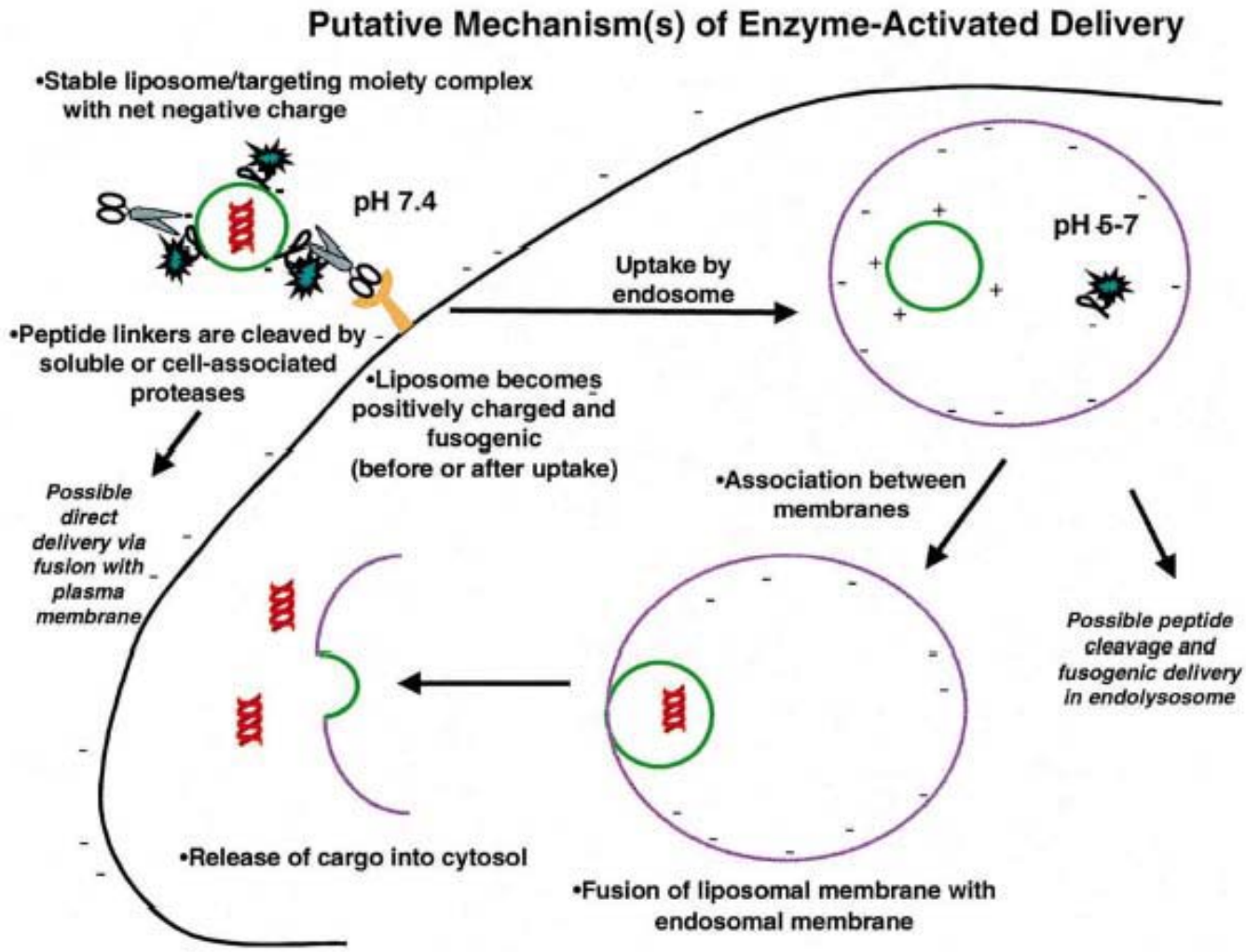


Fig. 1. Putative mechanisms of enzyme activated delivery. Liposomes may be activated to become fusogenic by enzymes near the surface of the cell, enzymes displayed on the surface of the cell or enzymes in the endolysosomal compartment. Charge reversal and fusogenic delivery can occur at the plasma membrane, within an endosome or via later cleavage in the endolysosome.

Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission. Source: Meers, Paul. "Enzyme-Activated Targeting of Liposomes." *Advanced Drug Delivery Reviews* 53 (2001).

Pros and cons of vesicular delivery

Advantages:

Disadvantages:

Particle surface engineering with lipids

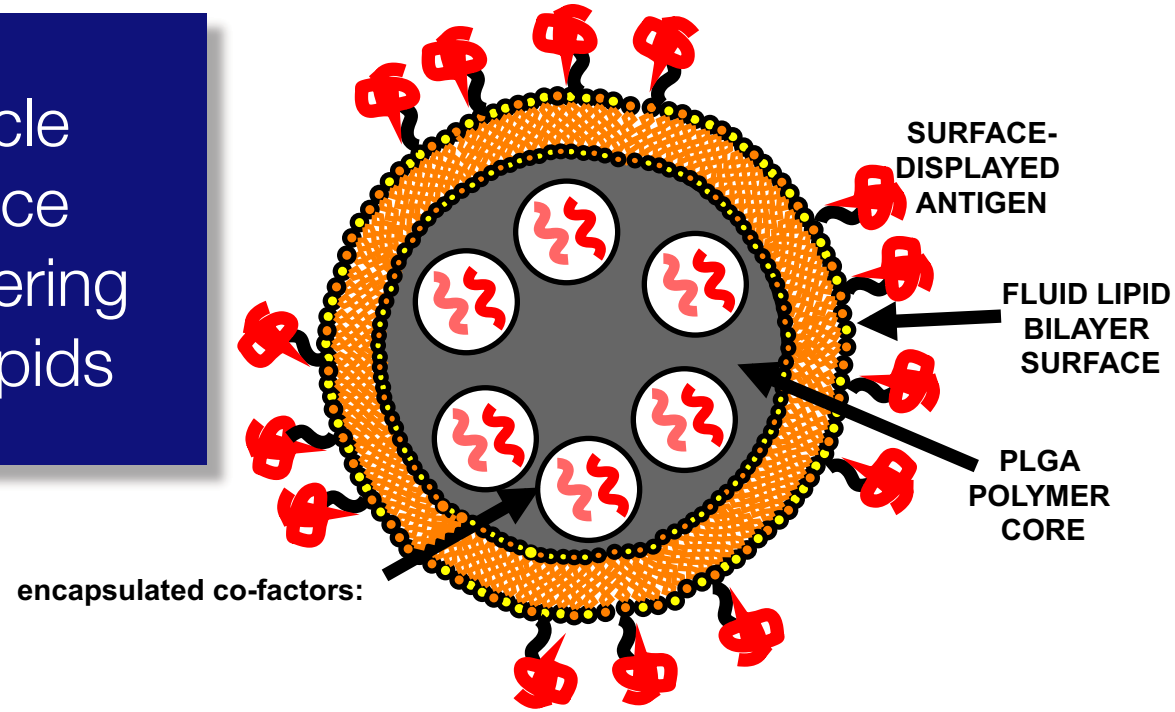


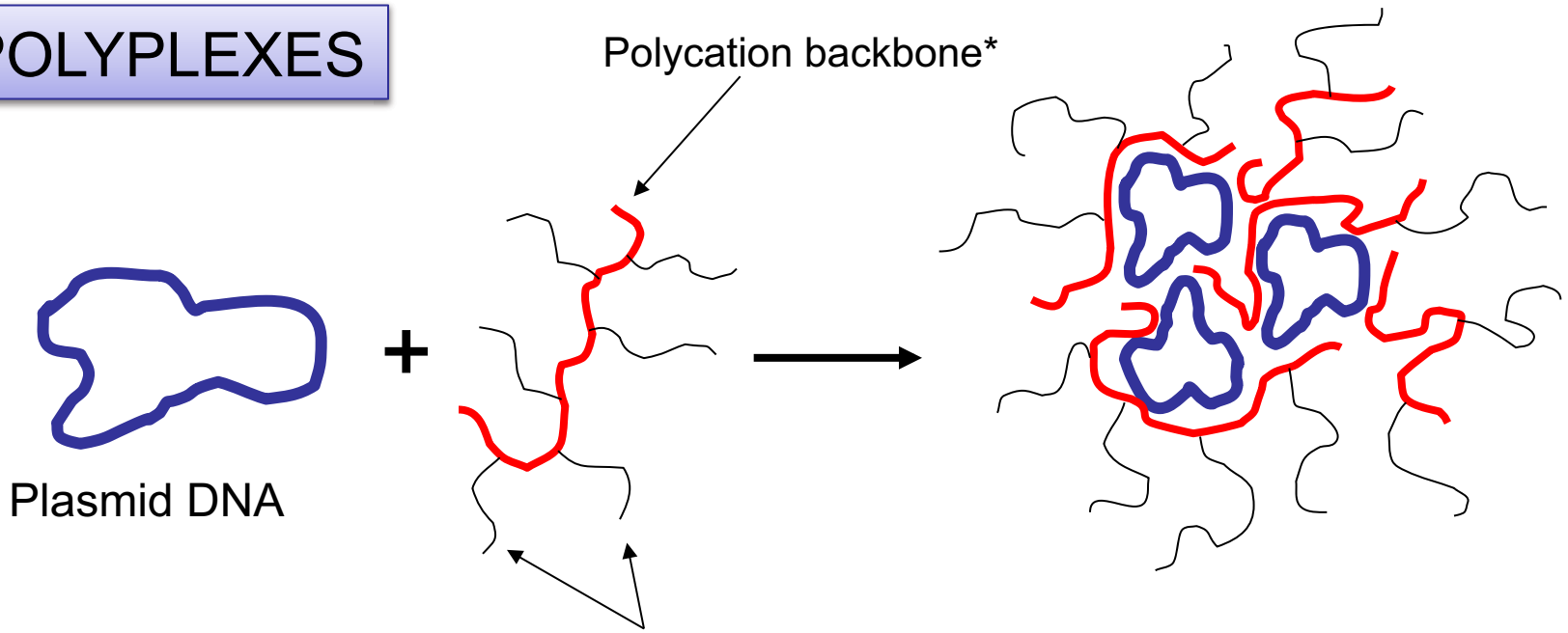
Figure removed due to copyright restrictions.
See Figures 1 and 3 from Bershteyn, Anna, et al.
"Polymer-Supported Lipid Shells, Onions, and Flowers."
Soft Matter 4, no. 9 (2008).

lipid segregation/self-assembly at the surface of nanoparticles

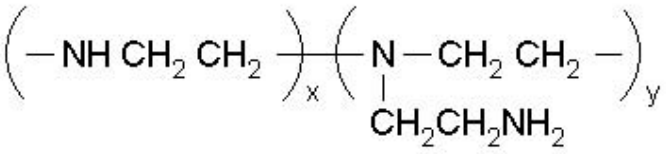
25:1 wt:wt polymer:lipid

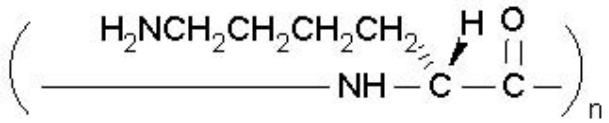
Figure removed due to copyright restrictions.
See Figures 1 and 3 from Bershteyn, Anna, et al.
"Polymer-Supported Lipid Shells, Onions, and Flowers."
Soft Matter 4, no. 9 (2008).

POLYPLEXES



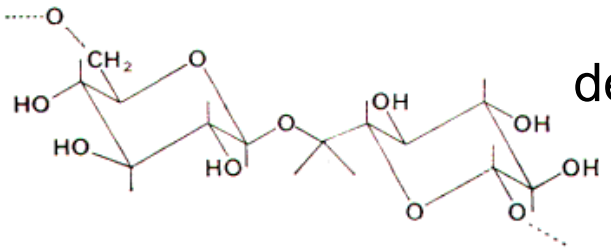
* Backbone components


PEI


• HBr PLL

** side chain components

$-(CH_2-CH_2-O)_n-$ PEO


dextran

Nanoparticle DNA packaging

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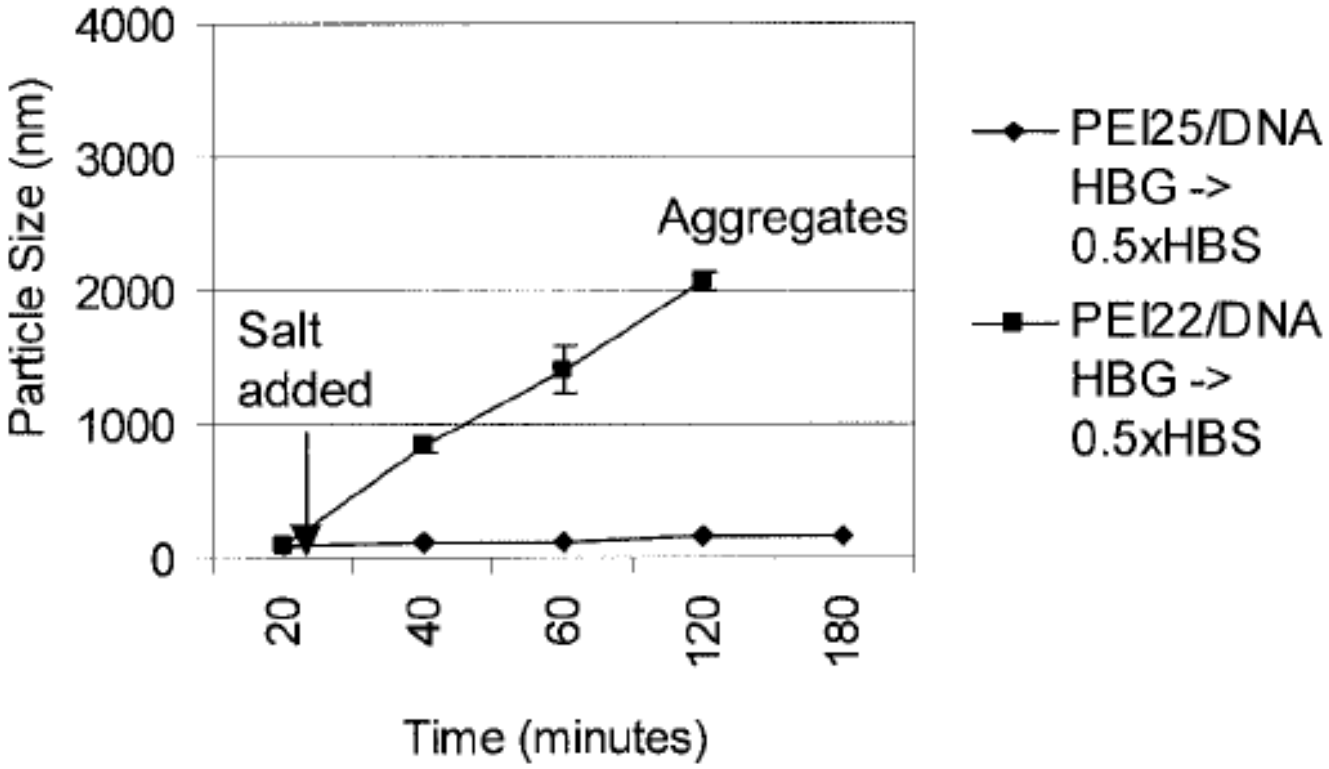
See Figures 2, 5, and 6 from Park, Susan and
Kevin E. Healy. "Nanoparticulate DNA Packaging
Using Terpolymers of Poly(lysine-g-(lactide-b-ethylene glycol))."
Bioconjugate Chemistry 14, no. 2 (2003).

Nanoparticle DNA packaging



0.5X HBS (Hank's buffered saline) = 75 mM NaCl, 20 mM HEPES,2.5% glucose
0.5X HBG (HEPES-buffered glucose) = 20 mM HEPES, 5% glucose

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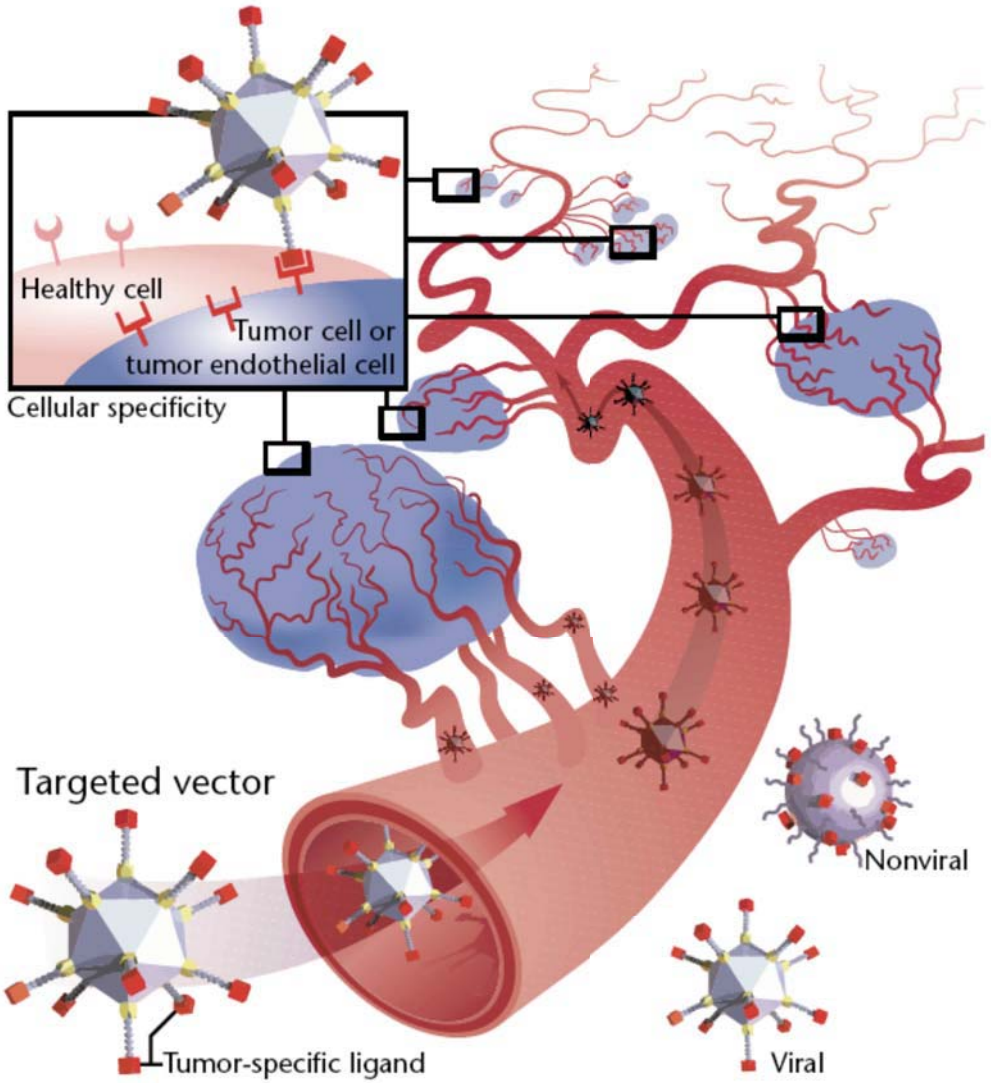
Source: Wightman, Lionel et al. "Different Behavior of Branched and Linear Polyethylenimine for Gene Delivery I*n Vitro* and *In Vivo*." *The Journal of Gene Medicine* 3, no. 4 (2001).

(Wightman et al., *J. Gene Med.* **3**, 362-372 (2001))

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



(Wickham *Nat. Med*. **9** 135 (2003))

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