DRUG TARGETING
Getting Vaccines to Dendritic Cells

Last Time: DNA vaccination

Today: Targeting particles/molecules to cells
Delivering activation signals to dendritic cells in vaccines

Reading: P. Carter, 'Improving the efficacy of antibody-based cancer therapies,' *Nat. Rev. Cancer* **1** 118 (2001)

Supplementary Reading:

ANNOUNCEMENTS:

What is drug targeting?

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Please see: Wickham. *Nature Medicine* 9, no. 1 (2003): 135.

Motivation for drug targeting: General

Motivation for drug targeting: Vaccines

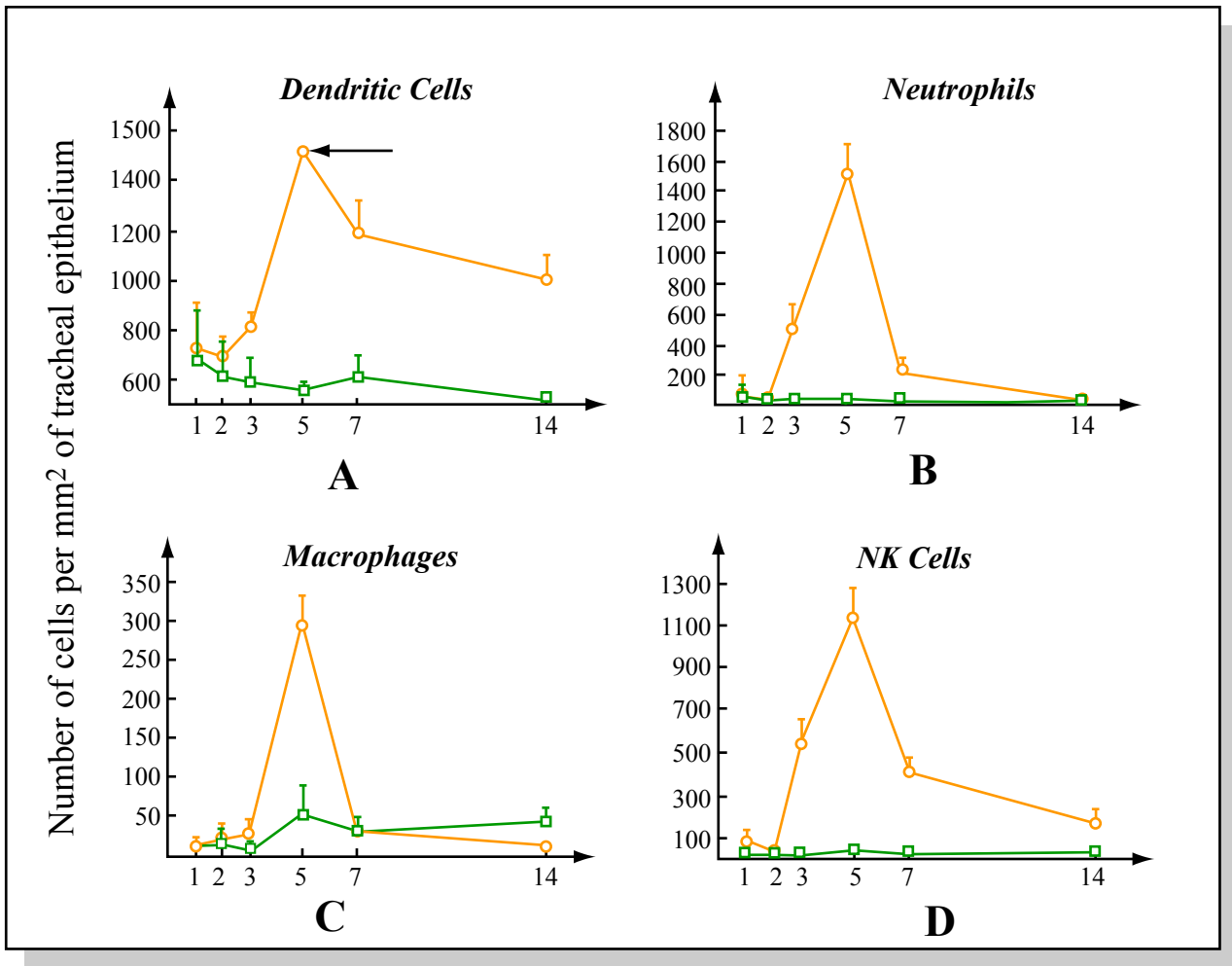

Figure by MIT OCW.

Approaches to targeted drug activity

1) Targeted delivery of active agent

2) Targeted activation of agent

3) ‘Reverse’ targeting

Major approaches for targeted delivery

1) receptor-ligand targeting

2) Pre-targeting

3) Antibody-based targeting

Example approaches: receptor-ligand-mediated targeting to vasculature

Mimicking lymphocyte responses to inflammation:

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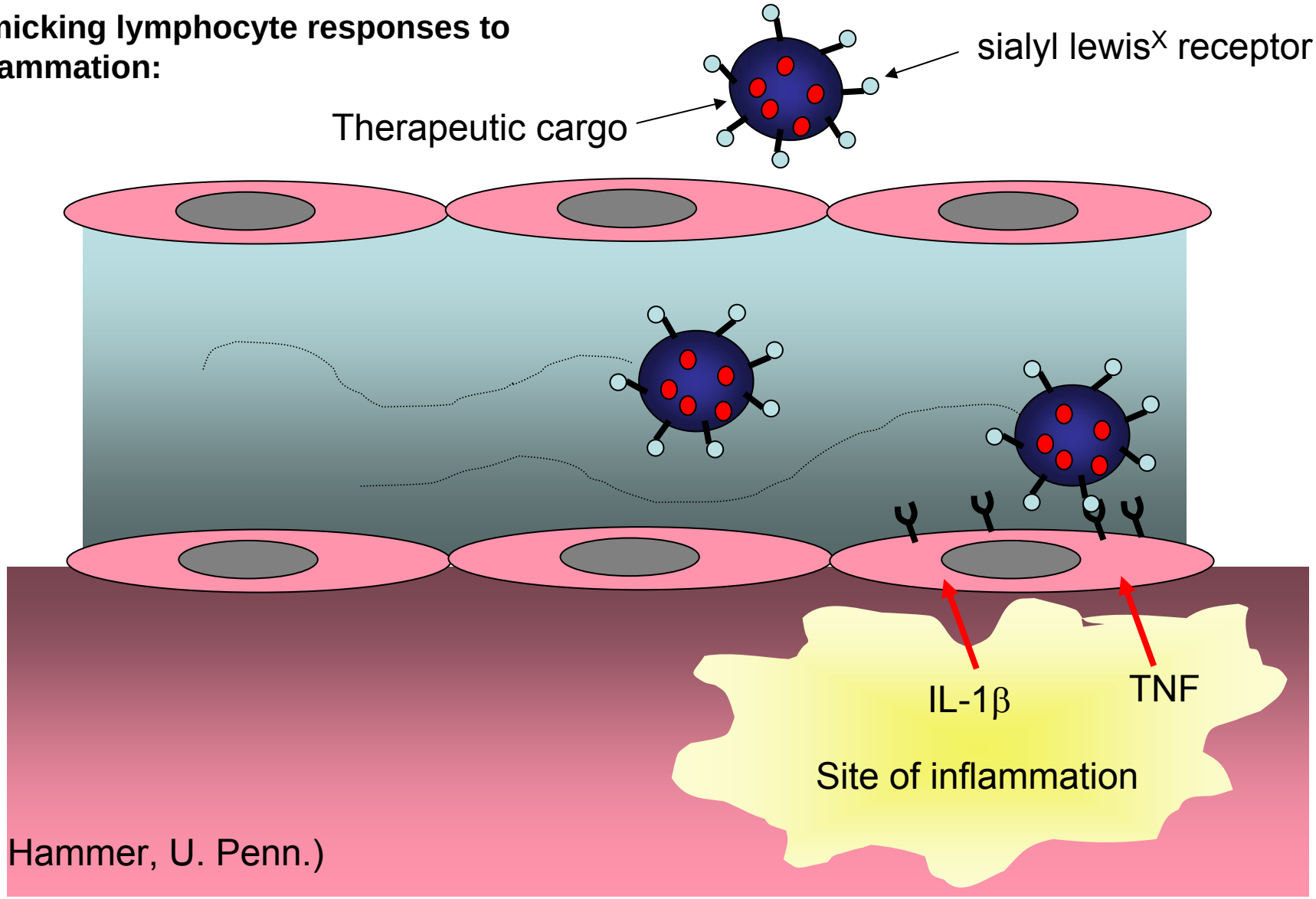
Please see: Figure 1 in Hogg, et al. *J Cell Sc* 116 (2003): 4695-4705.

Example approaches: receptor-ligand-mediated targeting to vasculature

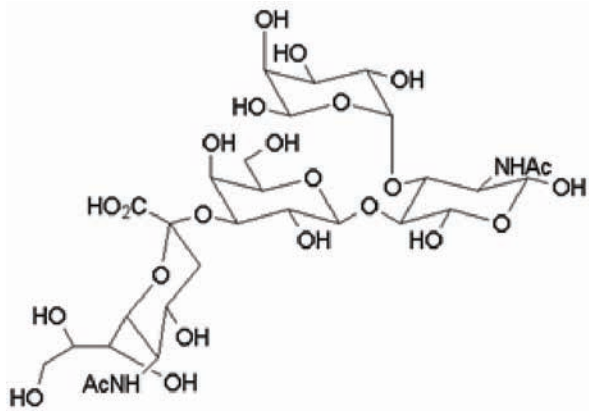
Mimicking lymphocyte responses to inflammation:



(D. Hammer, U. Penn.)

Example approaches: receptor-ligand-mediated targeting to vasculature

Mimicking lymphocyte responses to inflammation:



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Please see: Figure 2 in Cao, Y., and L. Lam. “Bispecific Anitbody Conjugates in Therapeutics.” *Adv Drug Delib Rev* 55 (2003): 171-97.

Pre-targeting drug delivery with bispecific antibodies

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Please see: Figure 2 in Eniola, A. O., and D. A. Hammer. *Biomaterials* 26 (2005): 661.

Antibody-based targeting

General structure of IgA, IgE, IgD, IgG:

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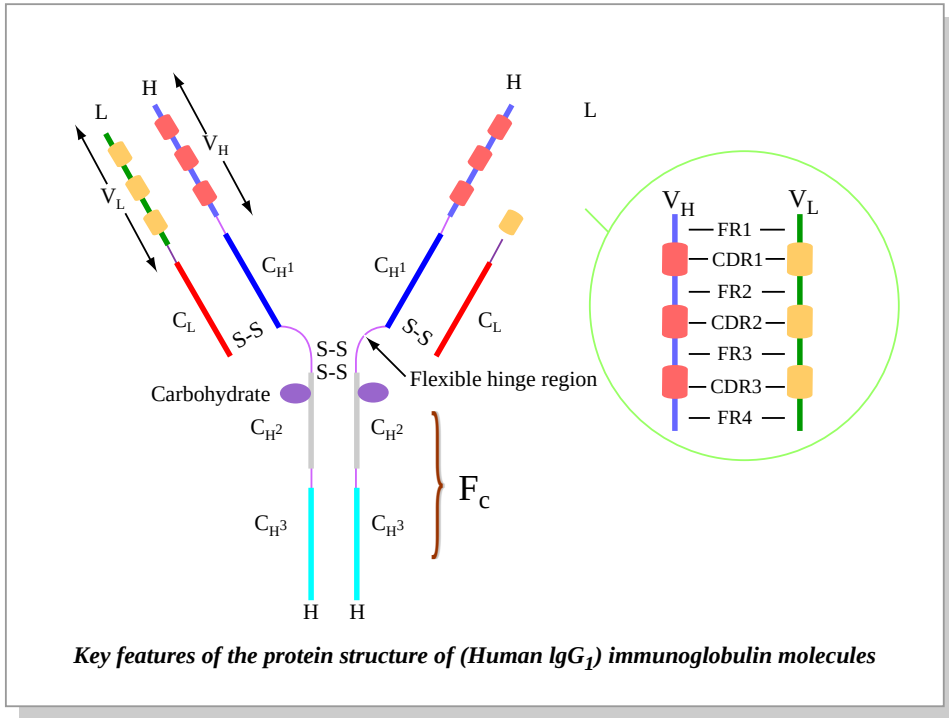

Figure by MIT OCW.

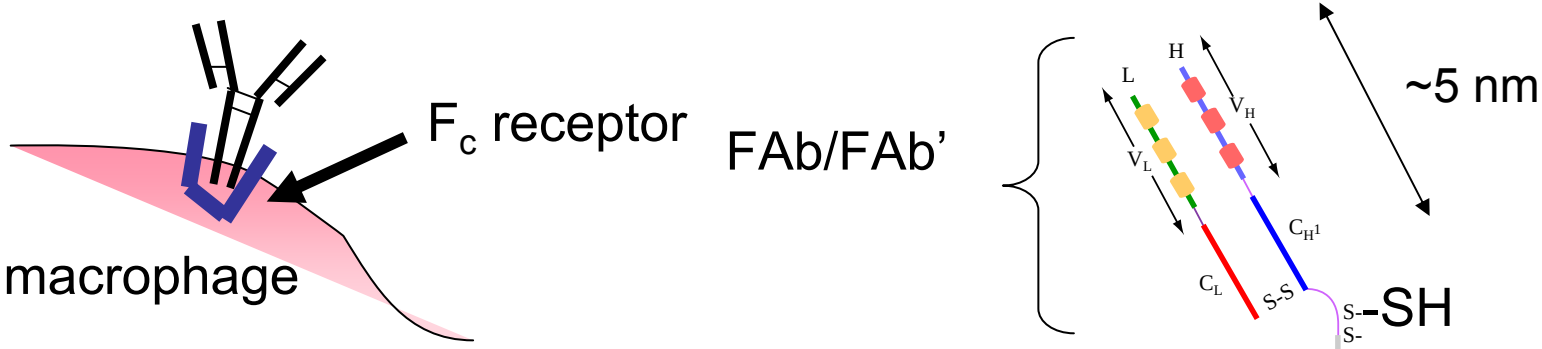

Figure by MIT OCW.

Generation of monoclonal antibodies against selected molecular targets

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Please see: Figures 4-12 in Elgert, K. D. *Immunology: Understanding the Immune System*. New York, NY: Wiley-Liss, 1996.

Synthesizing antibodies which avoid recognition by the immune system

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Please see: Figures 2 in Allen, T.M. "Ligand-targeted therapeutics in anticancer therapy." *Nat Rev Cancer* 2 (2002): 750-63.

Strategies for conjugation of antibodies to biomaterials

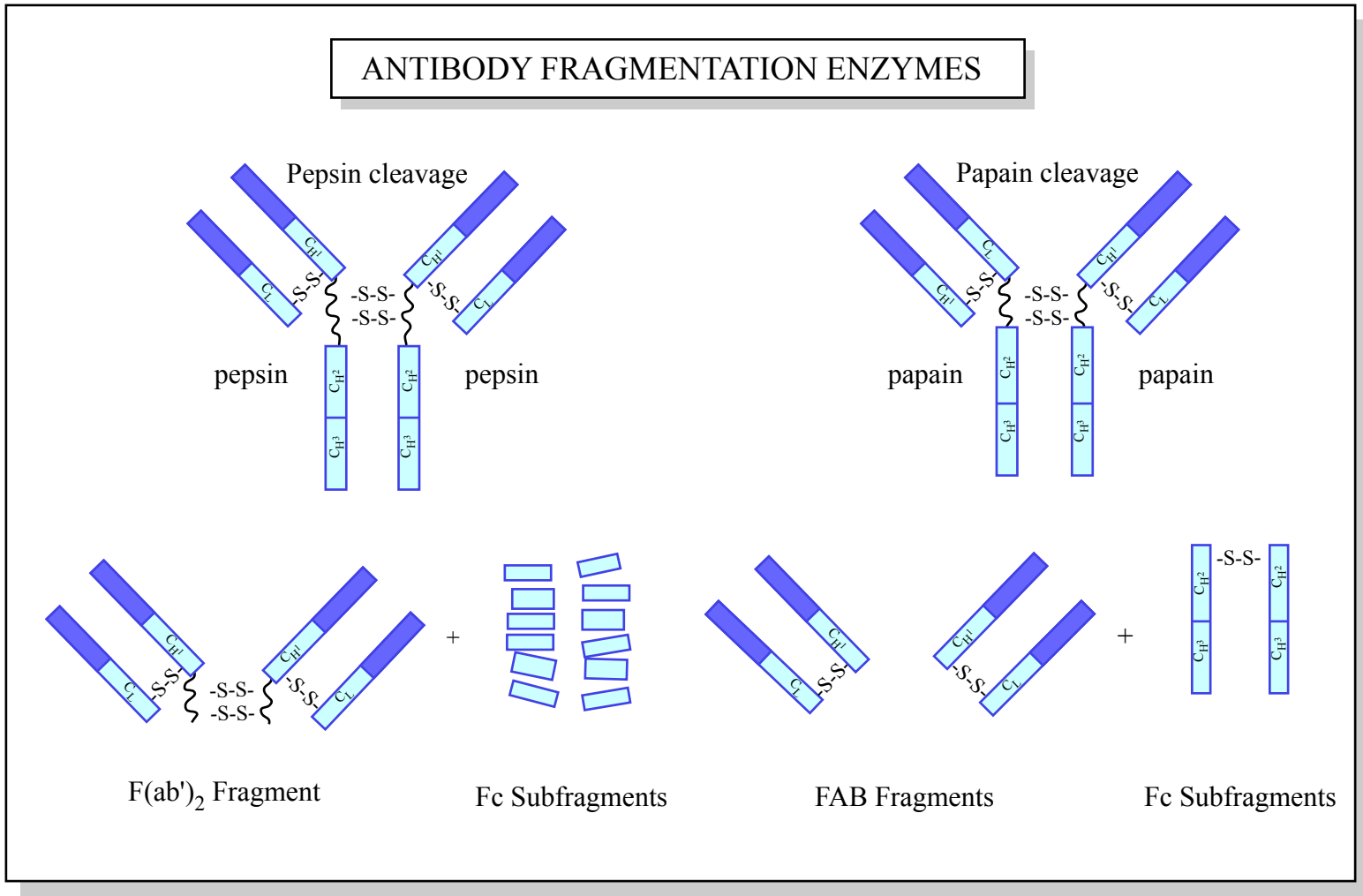
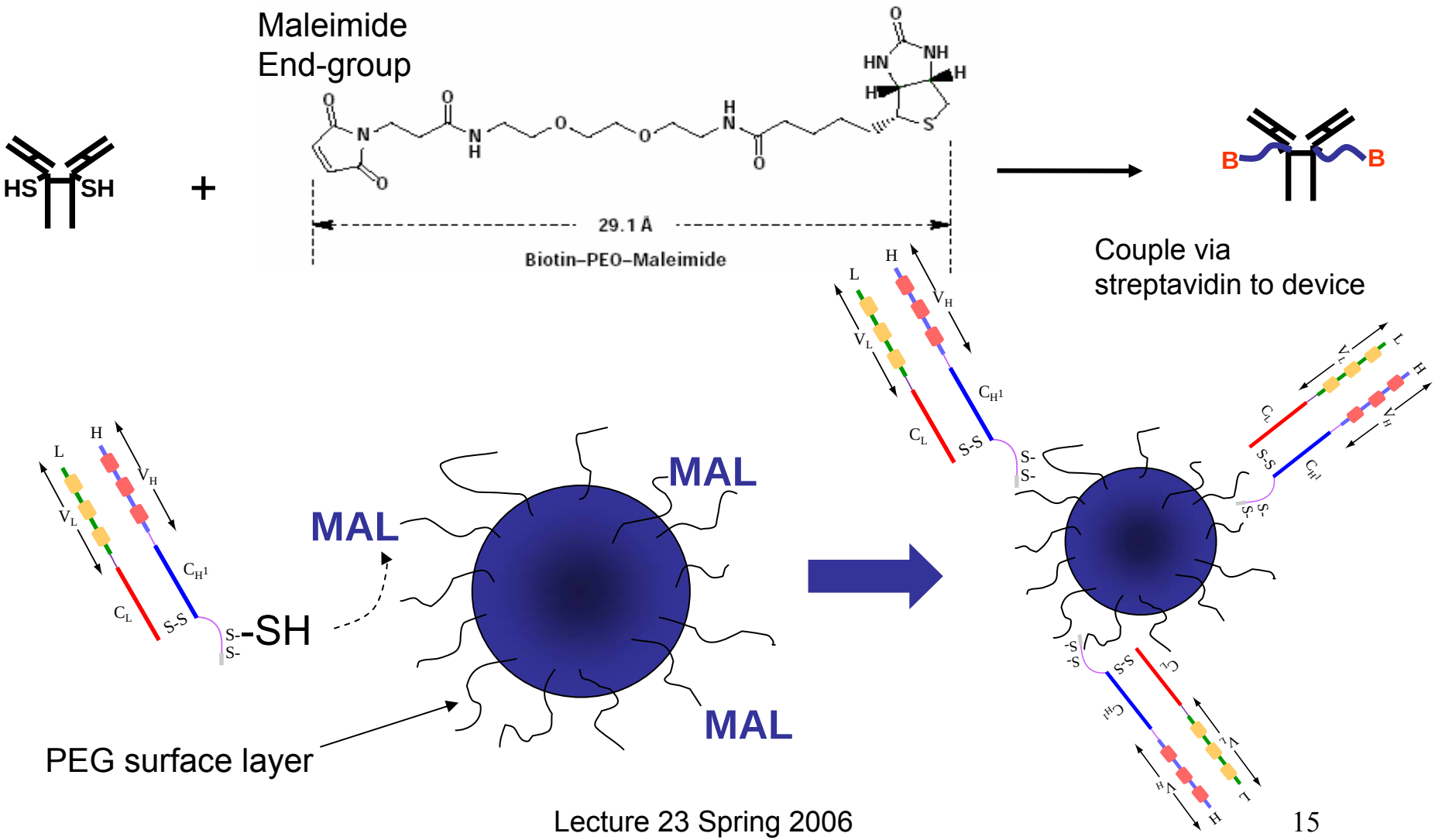


Figure by MIT OCW.

Strategies for conjugation of antibodies to biomaterials



Figures by MIT OCW.

Results from mAb-targeting

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Please see: Figure 4 in Daan, J. A. et al. “N Anotechnological Approaches for the Delivery of Macromolecules.” *J Controlled Release* 87, 81 (2003).

Graph removed due to copyright restrictions.
Please see: Park, J. W., et al. “Anti-HER2 Immunoliposomes: Enhanced Efficacy Attributable to Targeted Delivery.” *Clin Cancer Res* 8 (2002): 1172-81.

Application	Cellular target	Molecular target	Targeting ligand	Ligand type
Anti-cancer therapy	Various tumor cells Neovascular tissue	Folate receptor EGF receptor B-FN (fibronectin isoform)	Folate EGF anti-B-FN antibody	Protein ligand for target receptor preferentially expressed on target cells antibody against fibronectin isoform only expressed during embryonic development and in aggressive tumors
Anti-cancer therapy, pulmonary, cardiovascular, and inflammatory diseases	Endothelial cells	E-selectin P-selectin	sialyl Lewis^X receptor	receptor expressed at sites of inflammation
Anti-cancer therapy (leukemias and B cell lymphomas)	Transformed B lymphocytes	CD20	Anti-CD20 antibody	Antibody against target cell-surface protein unique to target class of cells (e.g. B cells)
Anti-cancer therapy (T cell lymphomas)	Transformed T lymphocytes	IL-2Rα (interleukin-2 receptor a chain	Anti-IL-2Rα antibody	Antibody against target cell-surface protein not expressed on normal resting cells

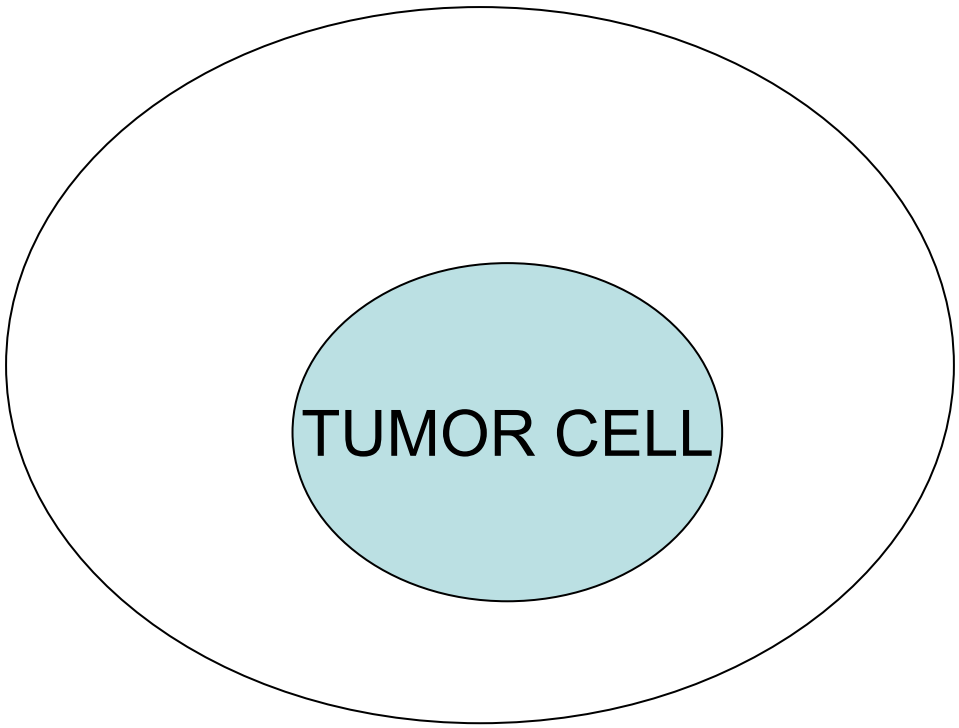
Cytotoxic drugs
- AraC
- Doxorubicin

Anti-tumor cytokines
- Interleukin-2
- Interleukin-12

Table removed due to copyright restrictions.
Please see: Table 1 in Allen, T. M. “Ligand Targeted Therapeutics in Anticancer Therapy.” *Nat Rev Cancer* 2 (2002): 750-63.

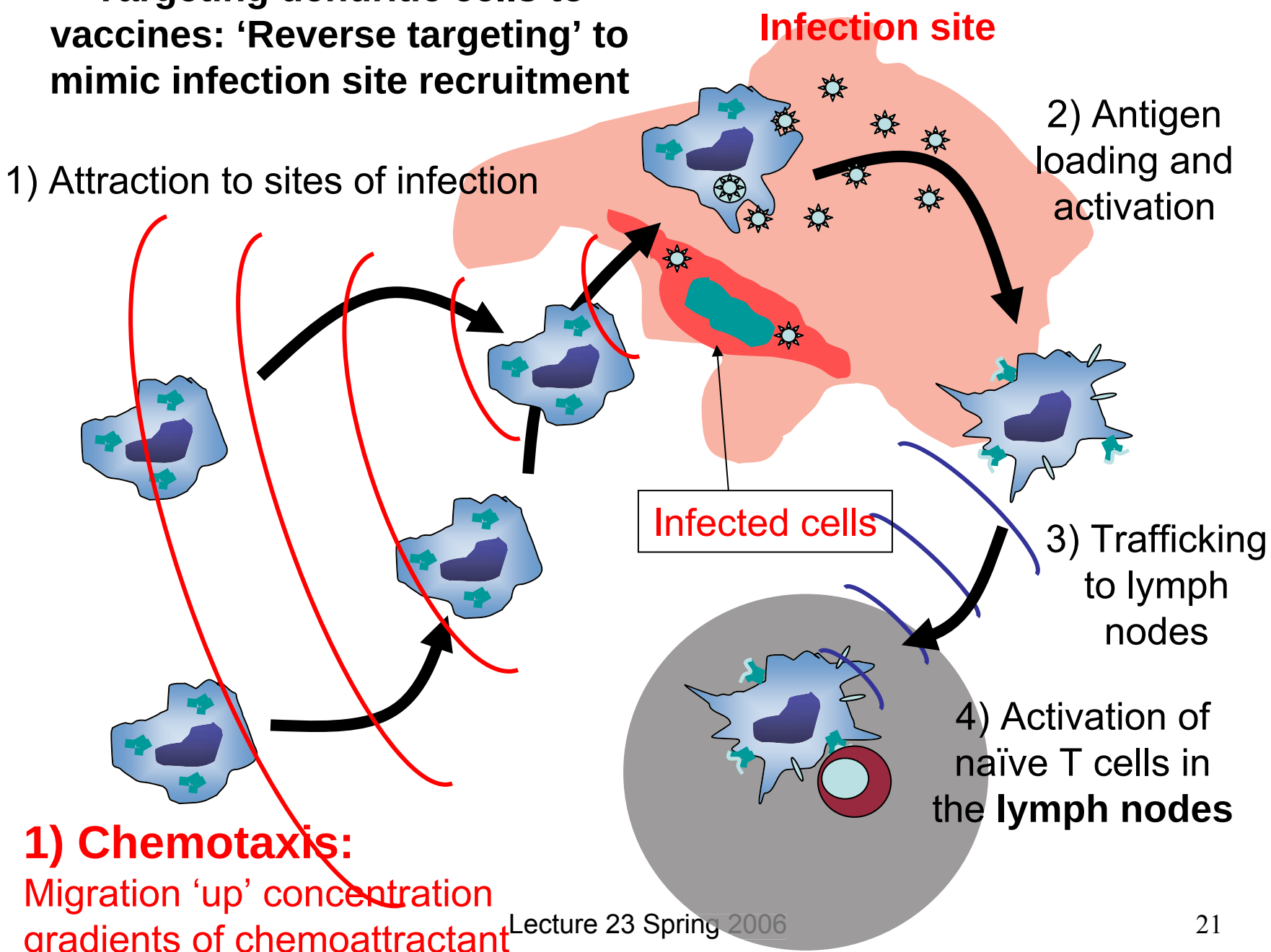
Example approaches: targeted activation of active agent

Antibody-directed enzyme prodrug therapy (ADEPT):



‘Reverse targeting’
Bringing cells to the drug

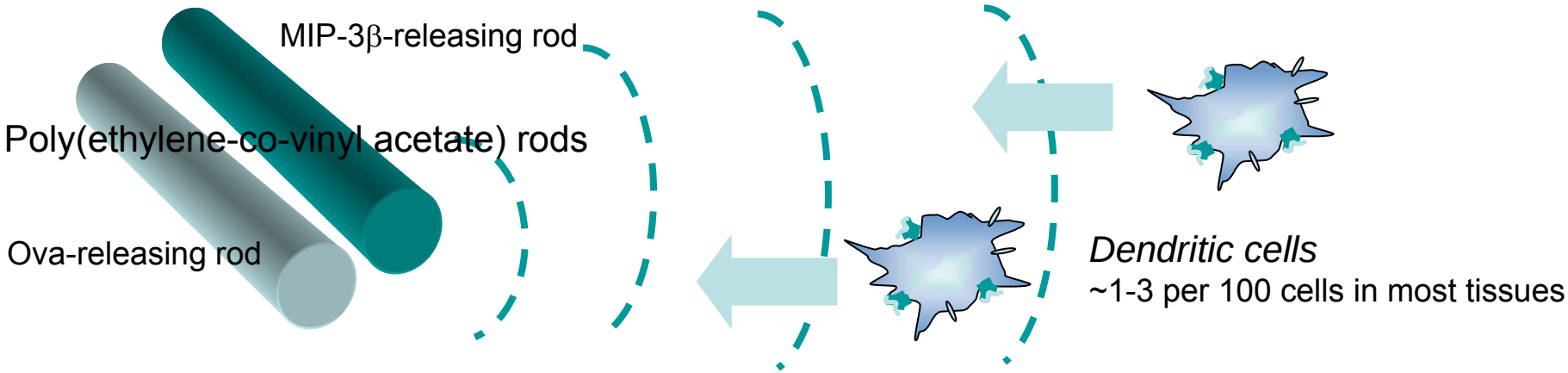
Targeting dendritic cells to vaccines: 'Reverse targeting' to mimic infection site recruitment



1) Chemotaxis:
Migration 'up' concentration gradients of chemoattractant

Targeting dendritic cells to vaccines

Attraction of target cells to device via chemotaxis:



Advantages relative to bolus chemoattractant injection:

 (Kumamoto et al. 2002)

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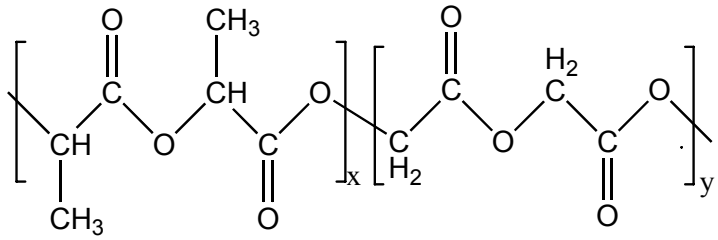
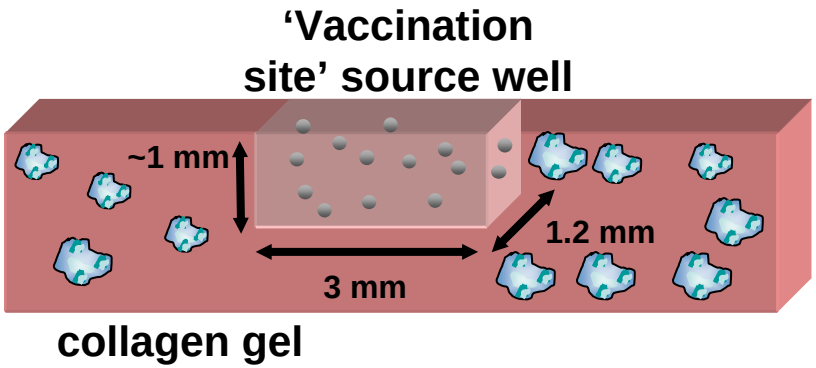
Please see: Kumamotos, T., et al. ”Induction of Tumor-specific Protective Immunity by in Situ Langerhans Cell Vaccine." *Nat Biotechnol* 20 (2002): 64-9.

PLGA





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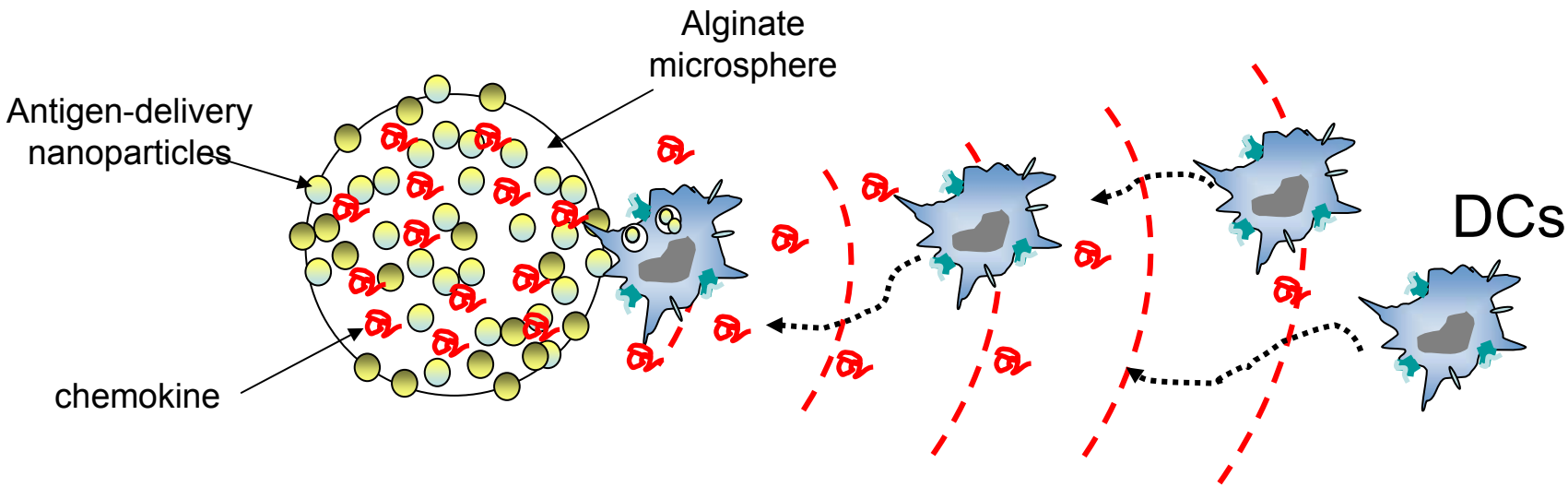
Please see: Zhao, X., et al. *Biomaterials* 26 (2005): 5048.

Dendritic cell attraction, antigen loading, and activation



How to encapsulate multiple factors under mild conditions for ‘reverse targeting’?

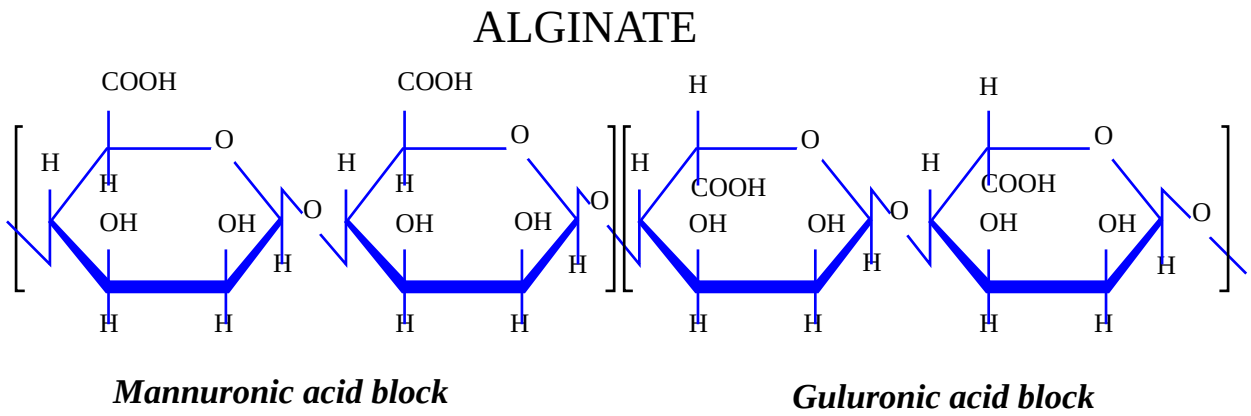
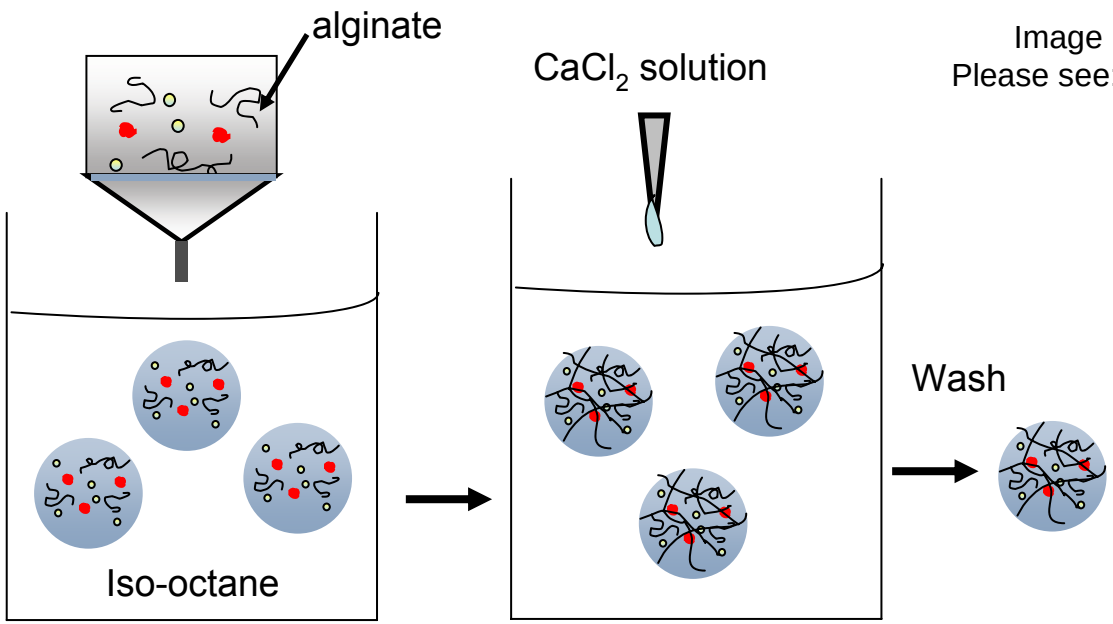


Figure by MIT OCW.



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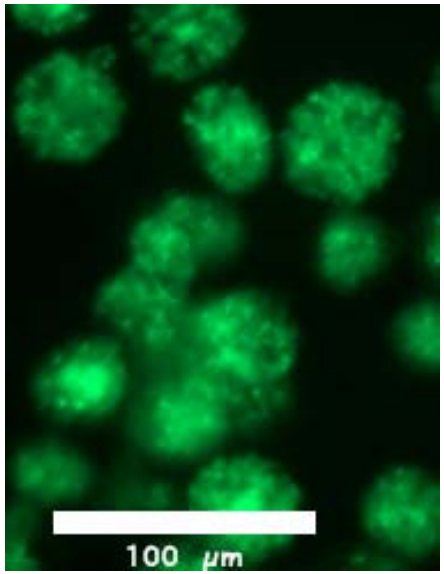
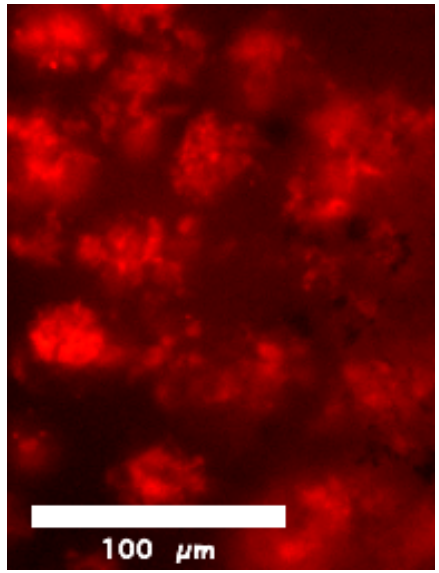
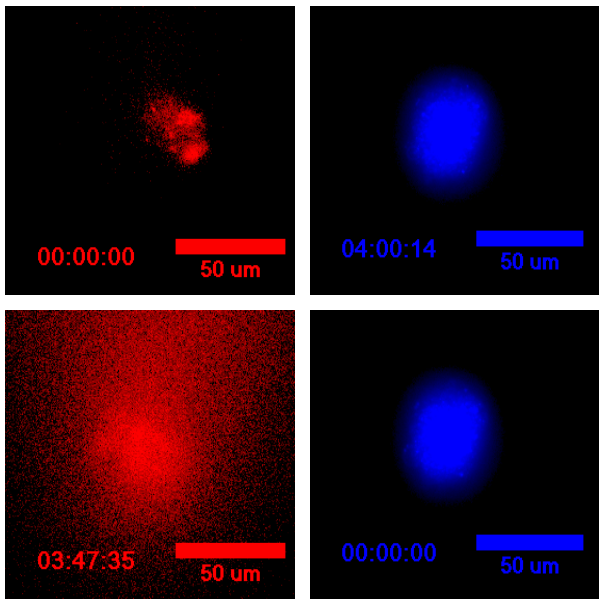
Please see: http://www.lsbu.ac.uk/water/hyalg.html

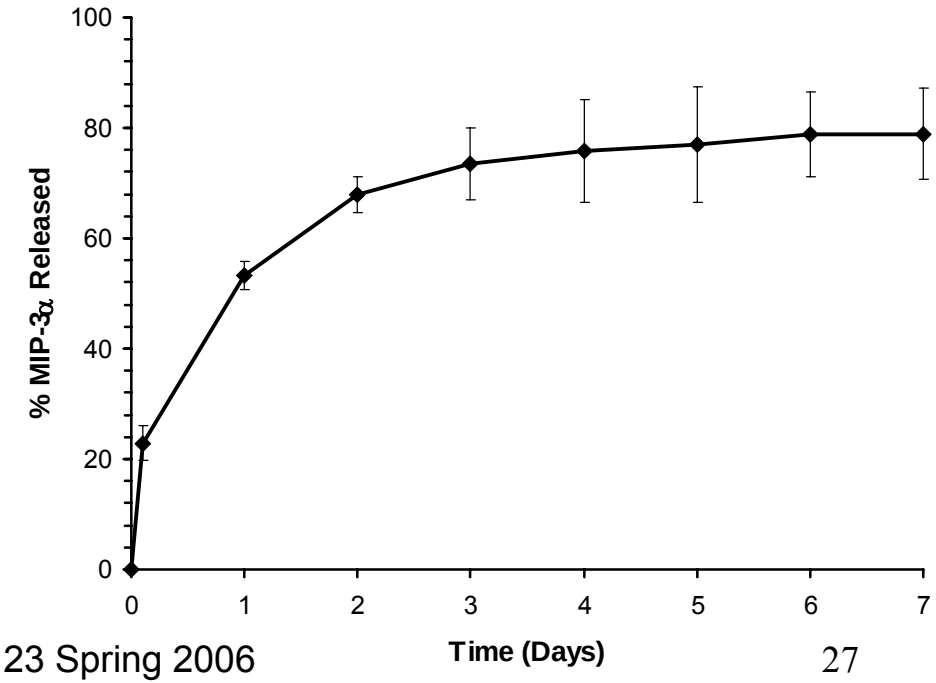
Fluorescent nanoparticles

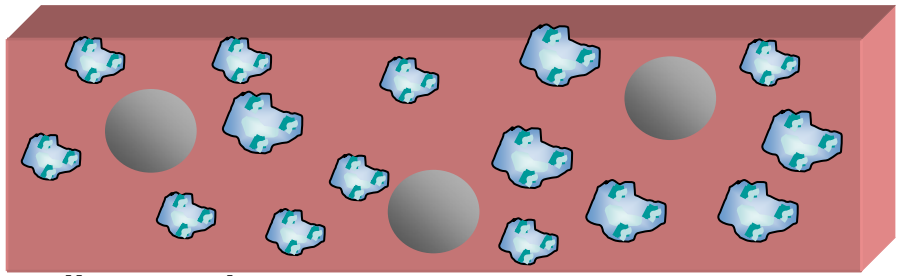


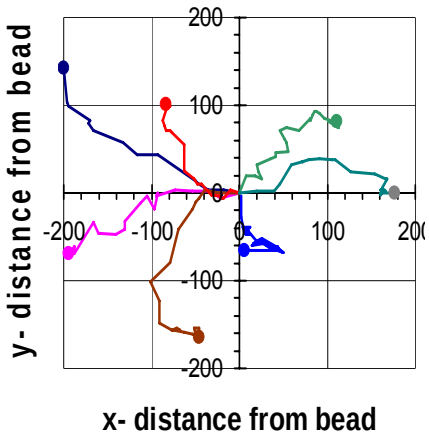
Fluorescent chemokine








collagen gel


y- distance from bead
x- distance from bead
200
100
0
-100
-200
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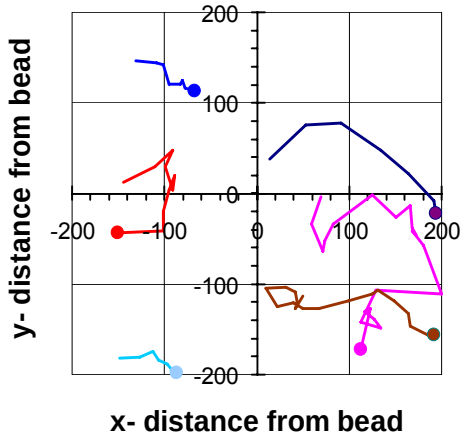
-100
0
100
200


y- distance from bead
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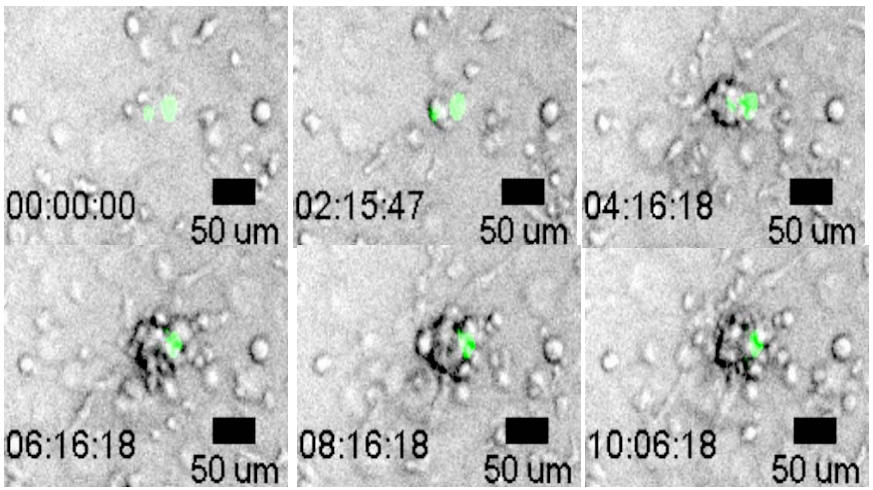
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02:15:47
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04:16:18
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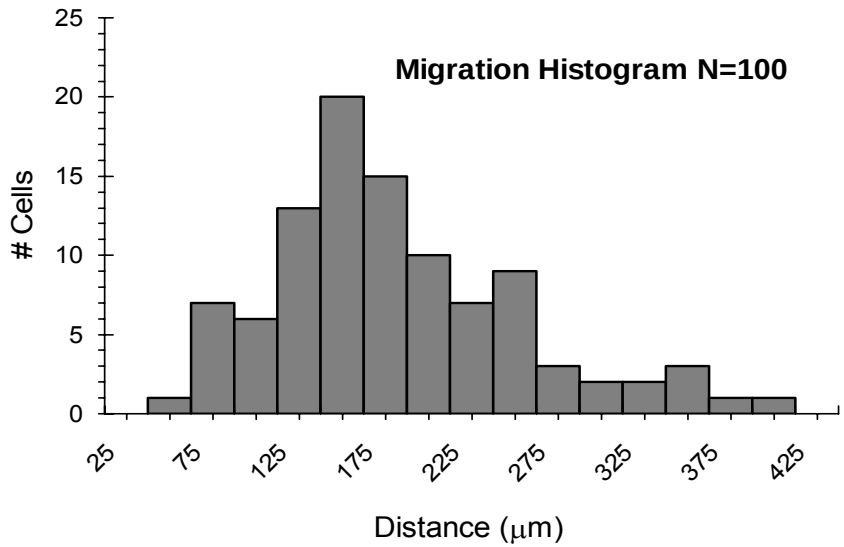
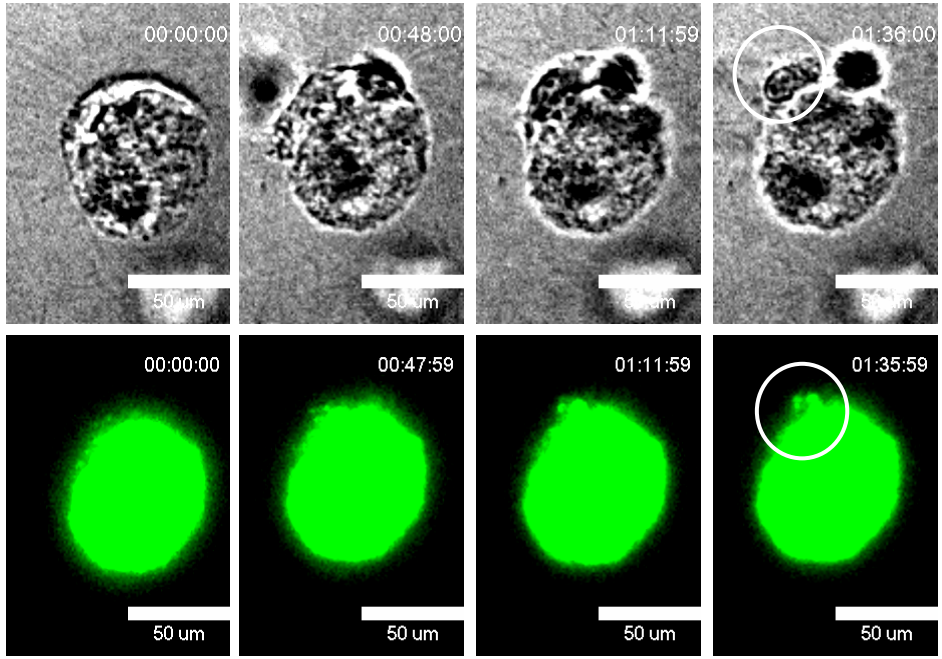

Migration Histogram N=100
Cells
Distance (μm)
25
20
15
10
5
0
25
75
125
175
225
275
325
375
425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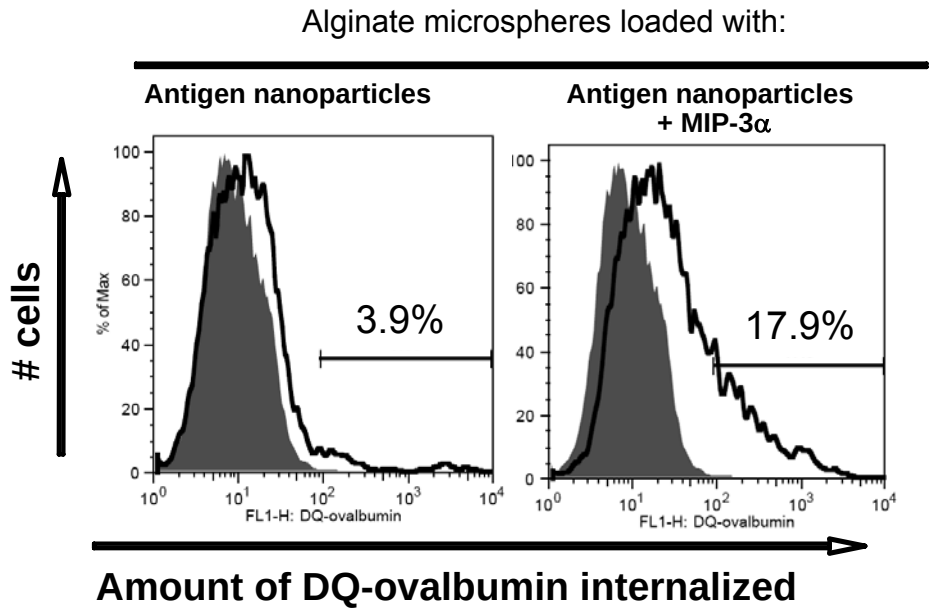
Alginate microspheres loaded with:
Antigen nanoparticles
Antigen nanoparticles
+ MIP-3α
# cells
% of Max
3.9%
17.9%
FL1-H: DQ-ovalbumin
FL1-H: DQ-ovalbumin
Amount of DQ-ovalbumin internalized

Issues in targeted delivery

Further Reading

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2. Eniola, A. O. & Hammer, D. A. Artificial polymeric cells for targeted drug delivery. *J Control Release* **87**, 15-22 (2003).
3. Halin, C. et al. Enhancement of the antitumor activity of interleukin-12 by targeted delivery to neovasculature. *Nat Biotechnol* **20**, 264-9 (2002).
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14. Cao, Y. & Lam, L. Bispecific antibody conjugates in therapeutics. *Adv Drug Deliv Rev* **55**, 171-97 (2003).
15. Park, J. W. et al. Anti-HER2 immunoliposomes: enhanced efficacy attributable to targeted delivery. *Clin Cancer Res* **8**, 1172-81 (2002).
16. Hong, K. et al. Anti-HER2 immunoliposomes for targeted drug delivery. *Ann N Y Acad Sci* **886**, 293-6 (1999).
17. Kumamoto, T. et al. Induction of tumor-specific protective immunity by in situ Langerhans cell vaccine. *Nat Biotechnol* **20**, 64-9 (2002).

Further Reading

1. Varga, C. M., Hong, K. & Lauffenburger, D. A. Quantitative analysis of synthetic gene delivery vector design properties. *Mol Ther* **4**, 438-46 (2001).
2. Varga, C. M., Wickham, T. J. & Lauffenburger, D. A. Receptor-mediated targeting of gene delivery vectors: insights from molecular mechanisms for improved vehicle design. *Biotechnol Bioeng* **70**, 593-605 (2000).
3. Segura, T. & Shea, L. D. Materials for non-viral gene delivery. *Annual Review of Materials Research* **31**, 25-46 (2001).
4. Segura, T. & Shea, L. D. Surface-tethered DNA complexes for enhanced gene delivery. *Bioconjugate Chemistry* **13**, 621-629 (2002).
5. Vijayanathan, V., Thomas, T. & Thomas, T. J. DNA nanoparticles and development of DNA delivery vehicles for gene therapy. *Biochemistry* **41**, 14085-94 (2002).
6. Demeneix, B. et al. Gene transfer with lipospermines and polyethylenimines. *Adv Drug Deliv Rev* **30**, 85-95 (1998).
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10. Rungsardthong, U. et al. Copolymers of amine methacrylate with poly(ethylene glycol) as vectors for gene therapy. *J Control Release* **73**, 359-80 (2001).
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13. Martin-Herranz, A. et al. Surface functionalized cationic lipid-DNA complexes for gene delivery: PEGylated lamellar complexes exhibit distinct DNA-DNA interaction regimes. *Biophys J* **86**, 1160-8 (2004).
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15. Kircheis, R., Wightman, L. & Wagner, E. Design and gene delivery activity of modified polyethylenimines. *Advanced Drug Delivery Reviews* **53**, 341-358 (2001).