

DNA delivery and DNA Vaccines

Last Time: intracellular drug delivery: enhancing cross priming for vaccines

Today: DNA vaccination

Reading: D.W. Pack, A.S. Hoffman, S. Pun, and P.S. Stayton, 'Design and development of polymers for gene delivery,' *Nat. Rev. Drug Discov.* **4** 581-593 (2005)

Supplementary Reading:

ANNOUNCEMENTS:

DIRECT ENTRY TO CYTOSOL: MEMBRANE-PENETRATING PEPTIDES

Models of membrane-penetrating peptide function

Penetratin:

Short peptide sequence from drosophila
transcription factor protein Antennapedia

RQIKIWFQNRRMKWKK

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Please see: Derossi, et al. *J Biol Chem* 271, no. 30 (1996): 18188.

ACTIVATION ON ENTRY TO THE CYTOSOL

Selective bond dissociation using reversible disulfide linkages

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Please see: Falnes. *Curr Opin Cell Biol* 12 (2000): 407.

**DIRECT ENTRY TO CYTOSOL:
PORE-FORMING PEPTIDES**

Pore-forming proteins/peptides as a tool
for membrane-penetrating drug carriers

Figures 1A, 1B, and 1C removed due to copyright restrictions.
Please see: Bhakdi. *Arch Microbiol* 165 (1996): 73.

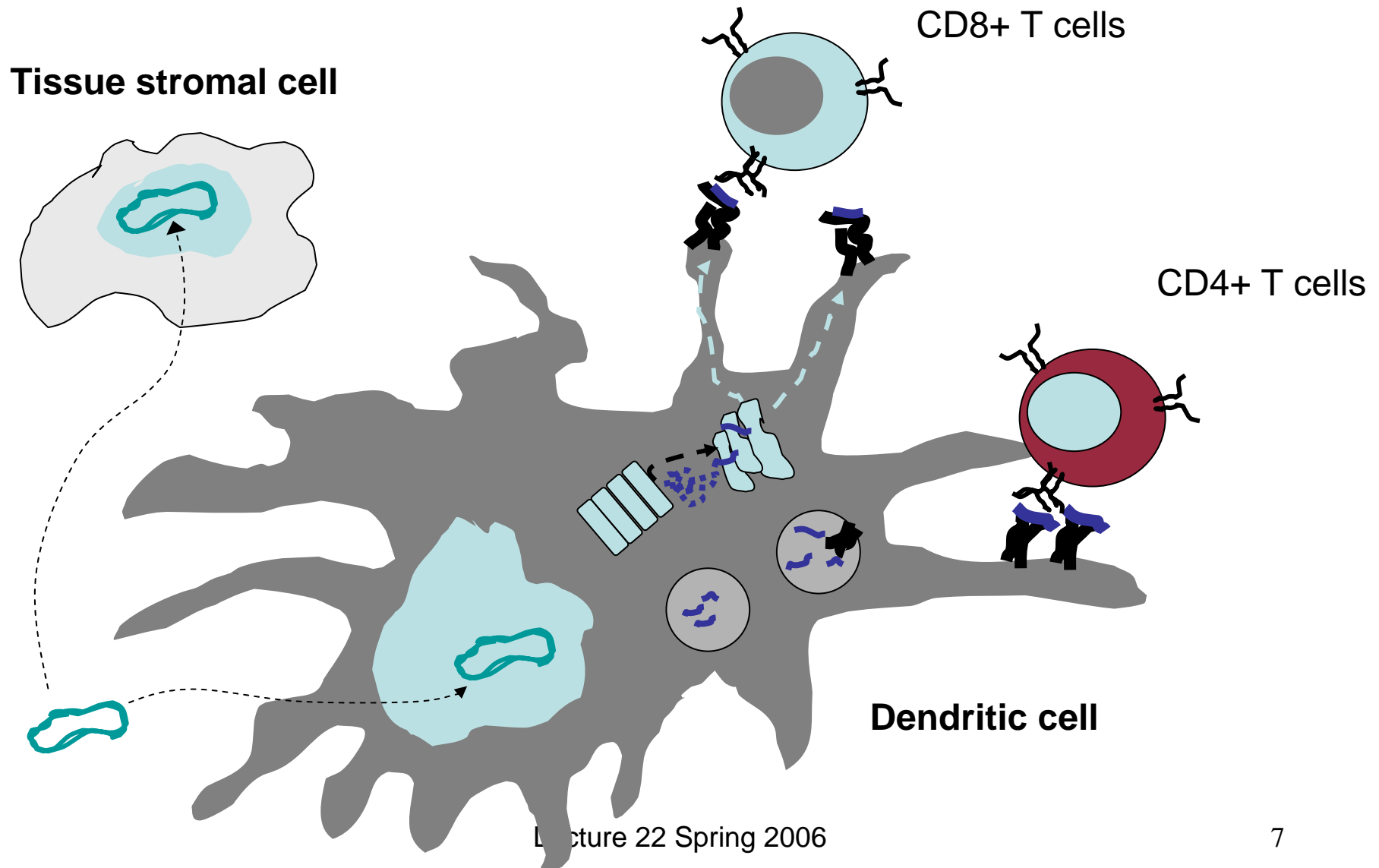
**DIRECT ENTRY TO CYTOSOL:
FUSOGENIC PEPTIDES**

fusogenic peptides: using viral entry
strategies for drug delivery

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Please see: Hawiger. *Curr Opin Chem Biol* 3 (1999): 89.

DNA DELIVERY AND DNA VACCINES

GENE THERAPY FOR VACCINATION: GENES THAT ENCODE ANTIGEN



Motivation for DNA vaccines

Why are synthetic vectors of interest?

idealized objectives of DNA delivery

2 classes of synthetic vectors we'll discuss:

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Please see: Vijayanathan, et al. *Biochemistry* 41, no. 48 (2002): 10485.

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Please see: Segura, T., and L. D. Shea. “Materials for non-viral gene delivery.”
Annual Review of Materials Research 31 (2001): 25-46.

Polyplex formation between polycations and plasmid DNA

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Please see: Pack, et al. *Nat Rev Drug Discov* (2005).

Packaging DNA for delivery and cytosolic release

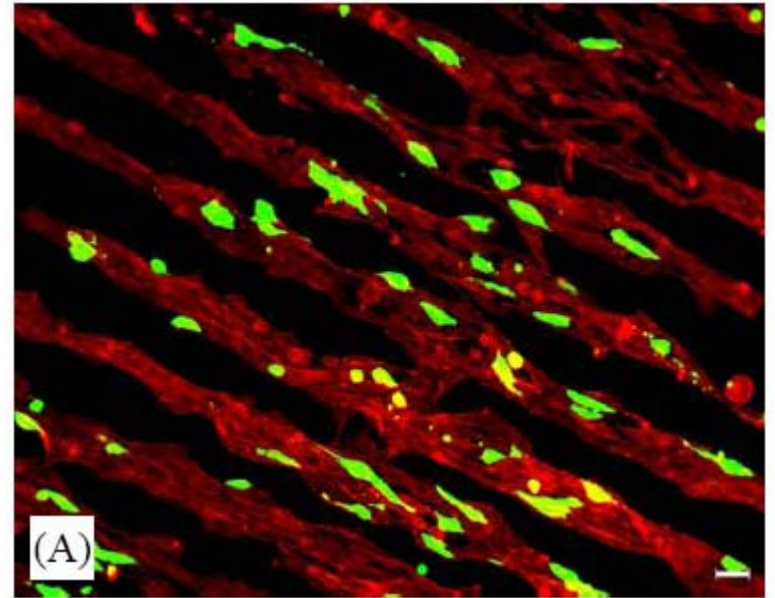
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Please see: Oupicky, D., A. L. Parker, and L.W. Seymour. “Laterally stabilized Complexes of DNA with Linear Reducible Polycations: Strategy for Triggered Intracellular Activation of DNA Delivery Vectors.” *J Am Chem Soc* 124 (2002): 8-9.

Polycation/DNA charge ratios in DNA packaging and release

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Please see: Segura et al. *Biomaterials* 26 (2005): 1575-1584.

Substrate-mediated DNA delivery



Segura et al. *Biomaterials* **26** 1575-1584 (2005)

NIH 3T3 fibroblasts

Lipid-DNA microstructures

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Please see: <http://avantipolarlipids.com/>

Lipid-DNA microstructures

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Please see: Figure 1 in Koltover, et al. *Science* 281 (1998): 78-81.

Lipid-DNA microstructures

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Please see: 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 (2004): 1160-8.

LIPID AND PARTICLE-BASED DNA CARRIERS

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TRANSPORT FROM THE CYTOSOL TO THE NUCLEUS

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Please see: Figure 1 in Escriou et al. *Adv Drug Delib Rev* 55 (2003): 295.

Figure removed due to copyright restrictions.
Please see: Figure 3 in Kircheis et al. *Adv Drug Delib Rev* 53 (2001): 2341.

Limitations of current materials

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Please see: Moghimi , et al. *Mol Therapy* 11 (2005): 990-995.

Built-in adjuvants: DNA vaccines encoding antigen and other factors

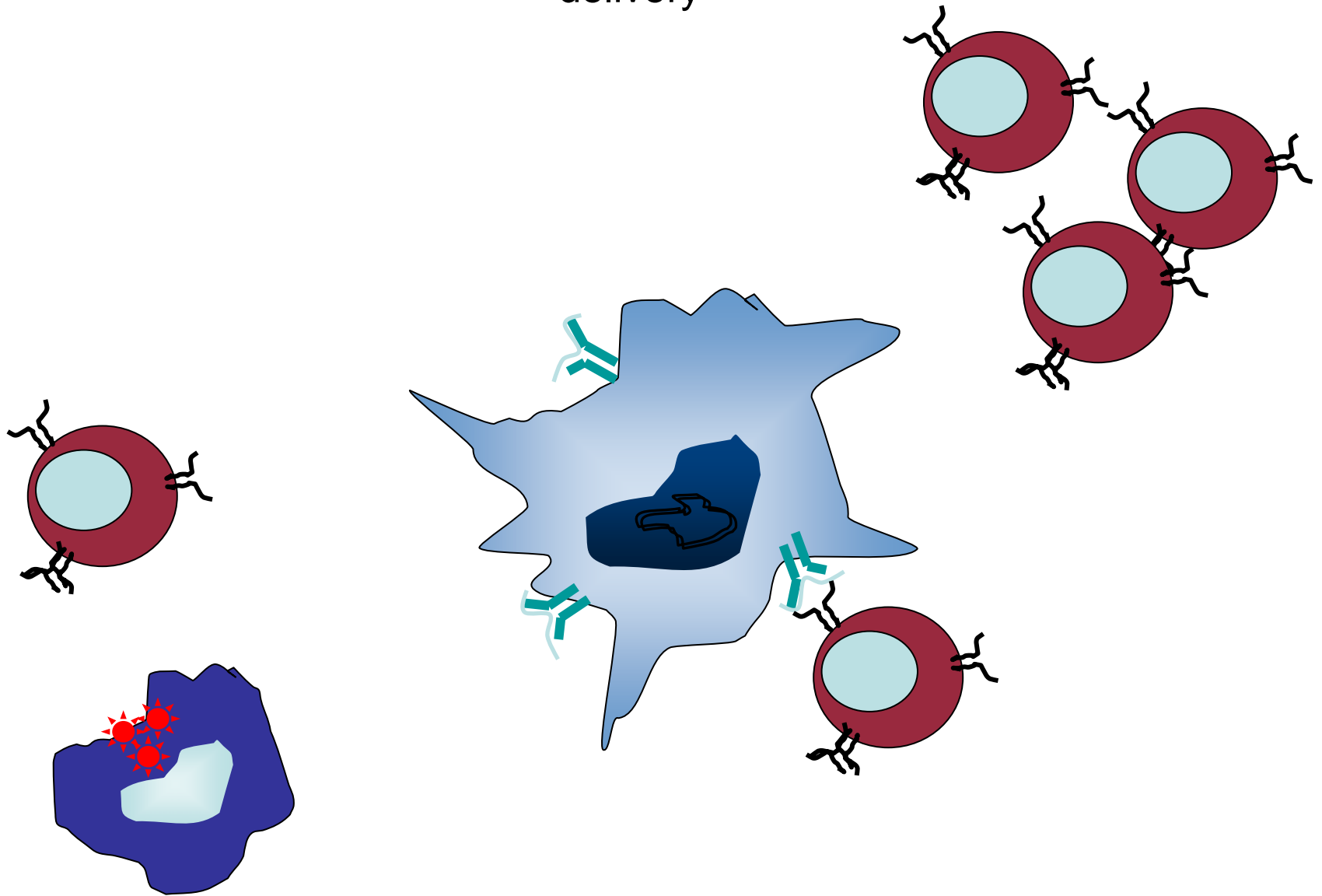
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Please see: Figure 1 in Sumida, et al. *J Clinical Invest* 114 (2004): 1334-1342.

Built-in adjuvants: DNA vaccines encoding antigen and other factors

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Please see: Sumida et al. *J. Clinical Invest* 114 (2004): 1334-1342.

Engineering the function of antigen presenting cells by DNA delivery



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).
7. Boussif, O. et al. A versatile vector for gene and oligonucleotide transfer into cells in culture and in vivo: polyethylenimine. *Proc Natl Acad Sci U S A* **92**, 7297-301 (1995).
8. Zanta, M. A., Boussif, O., Adib, A. & Behr, J. P. In vitro gene delivery to hepatocytes with galactosylated polyethylenimine. *Bioconjug Chem* **8**, 839-44 (1997).
9. Rungsardthong, U. et al. Effect of polymer ionization on the interaction with DNA in nonviral gene delivery systems. *Biomacromolecules* **4**, 683-90 (2003).
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).
11. Oupicky, D., Parker, A. L. & Seymour, L. W. Laterally stabilized complexes of DNA with linear reducible polycations: strategy for triggered intracellular activation of DNA delivery vectors. *J Am Chem Soc* **124**, 8-9 (2002).
12. Ewert, K. et al. Cationic lipid-DNA complexes for gene therapy: understanding the relationship between complex structure and gene delivery pathways at the molecular level. *Curr Med Chem* **11**, 133-49 (2004).
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).
14. Bonifaz, L. C. et al. In Vivo Targeting of Antigens to Maturing Dendritic Cells via the DEC-205 Receptor Improves T Cell Vaccination. *J Exp Med* **199**, 815-24 (2004).
15. Kircheis, R., Wightman, L. & Wagner, E. Design and gene delivery activity of modified polyethylenimines. *Advanced Drug Delivery Reviews* **53**, 341-358 (2001).