# 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

**Penetratin:**
Short peptide sequence from drosophila transcription factor protein Antennapedia

**RQIKIWFQNRRMKWKK**

(Derossi et al. 1996)

## Models of membrane-penetrating peptide function

# 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.


(Falnes 2000)

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



 (Bhakdi 1996) 

# fusogenic peptides: using viral entry strategies for drug delivery

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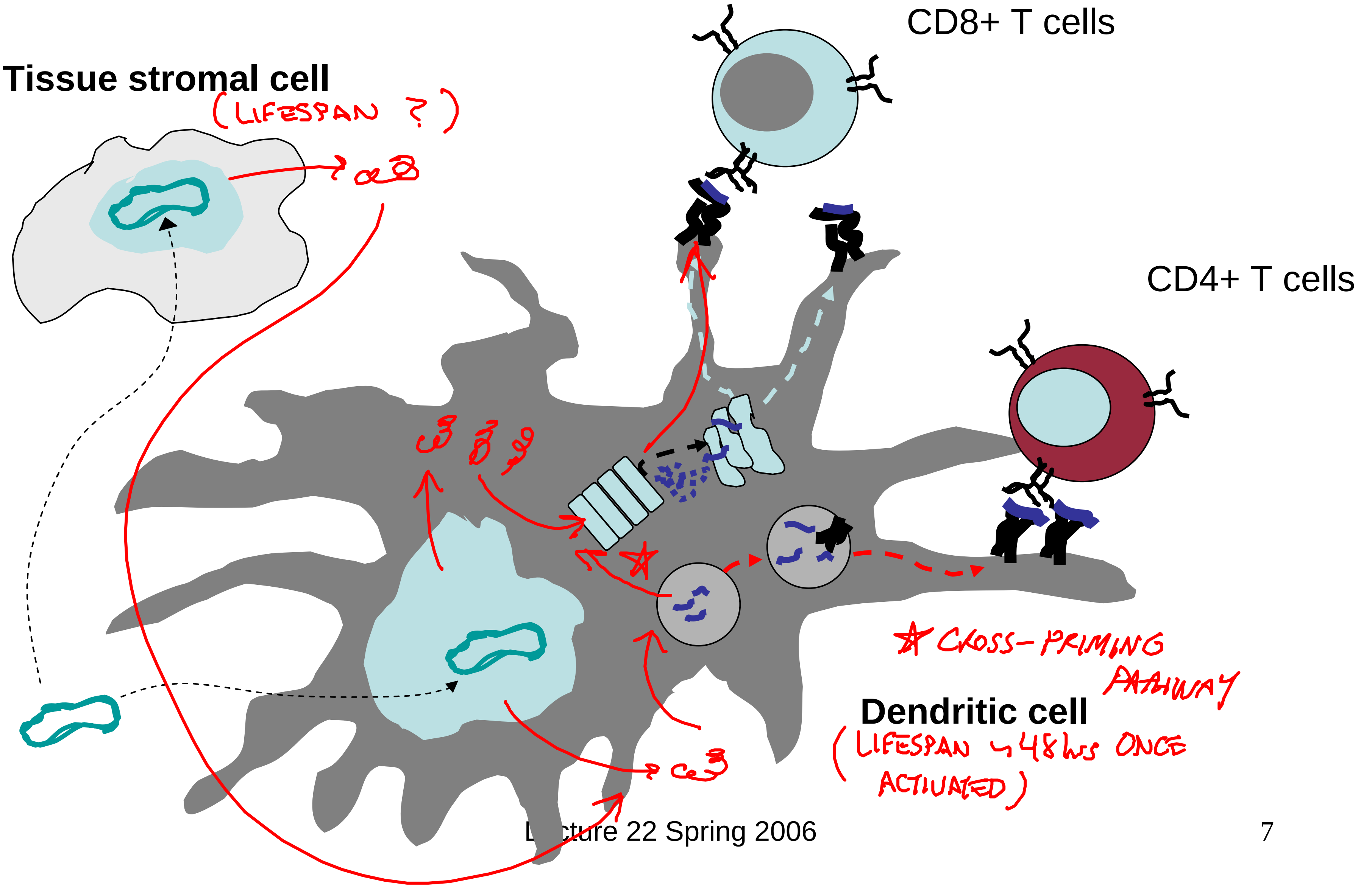
Please see: Hawiger. *Curr. Opin. Chem. Biol.* 3 (1999): 89.

 (Hawiger, 1999) 

# DNA DELIVERY AND DNA VACCINES

# GENE THERAPY FOR VACCINATION: GENES THAT ENCODE ANTIGEN



# Motivation for DNA vaccines

## Why are synthetic vectors of interest?

1. SELF-REPLICATING ANTIGEN!

   COMPARE TO ADENOVIRUS: MUCH MORE EFFICIENT IN Ag EXPRESSION → ≥ 95% TRANSFECTION EFFICIENCY (MOST DNA SYNTHETIC VECTORS EFFICIENCY ≤ 1%)

   ↑

   PRE-EXISTING ANTI-VECTOR IMMUNITY IN HUMANS TO ADENOVIRUS → (AS HIGH AS 80%)

2. SAFETY: WILL DNA INTEGRATE INTO GENOME?

3. DNA SYNTHETIC VECTORS USUALLY CHEAPER, EASIER TO PRODUCE, MORE ROBUST THAN LIVE VIRUS

4. POSSIBILITY TO ENCODE MULTIPLE FACTORS ("ADJUVANTS") IN ADDITION TO ANTIGEN

# 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.

(Vijayanathan et al. 2002)

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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).

(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.

(Oupicky et al. 2002)

# Polycation/DNA charge ratios in DNA packaging and release

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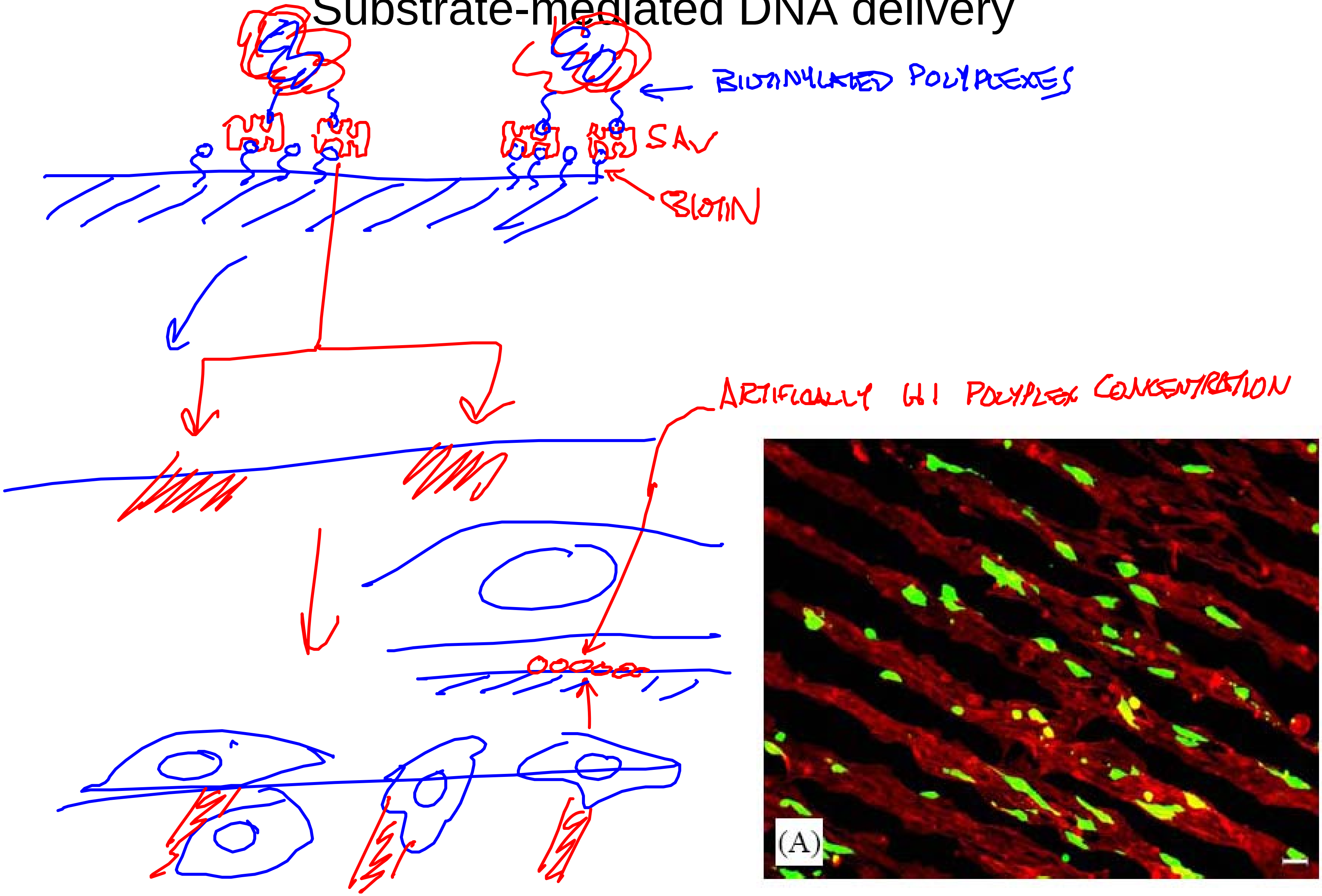
Please see: Segura et al. *Biomaterials* 26 (2005): 1575-1584.

# Substrate-mediated DNA delivery




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

NIH 3T3 fibroblasts

# Lipid-DNA microstructures

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

Koltover et al. *Science* **281** 78-81 (1998)

# 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.

Koltover et al. *Science* **281** 78-81 (1998)

# LIPID AND PARTICLE-BASED DNA CARRIERS

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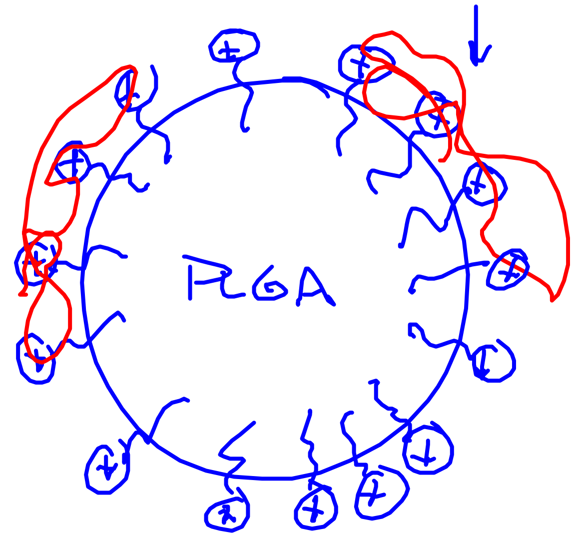
CHIRON:

FOR VACCINES

PLASMIDS PROTECTED FROM DNASE




(Martin-Herranz et al. 2004)

# 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.

(Escriou et al. 2003)

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

(Kircheis et al. 2001)

# Limitations of current materials

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



Moghimi et al. *Mol. Therapy* **11** 990-995 (2005)

# 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.

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

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

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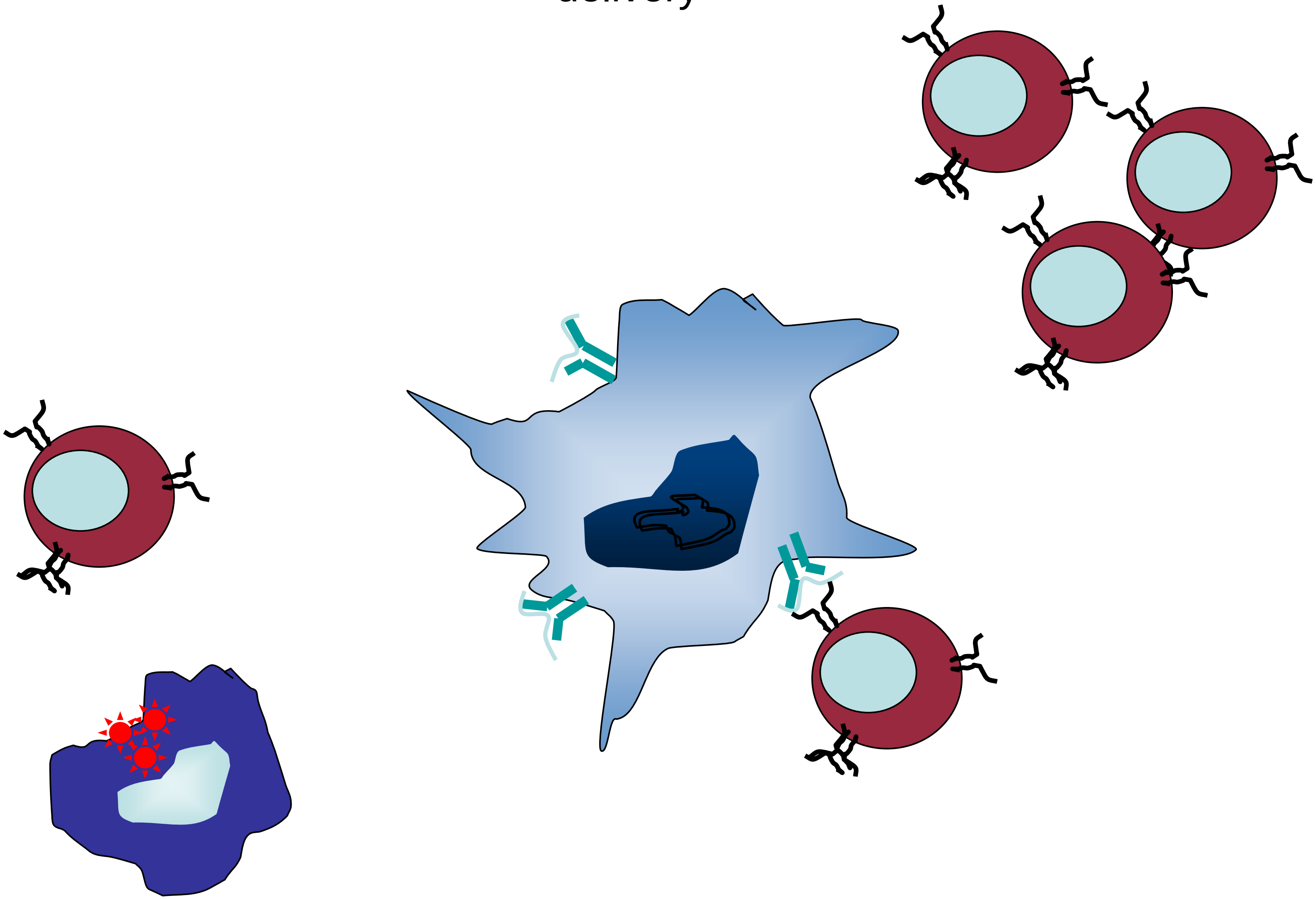
Please see: Sumida et al. J. *Clinical Invest.* 114 (2004): 1334-1342.

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

# Engineering the function of antigen presenting cells by DNA delivery



# Further Reading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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).