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

Models of membrane-penetrating peptide function

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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

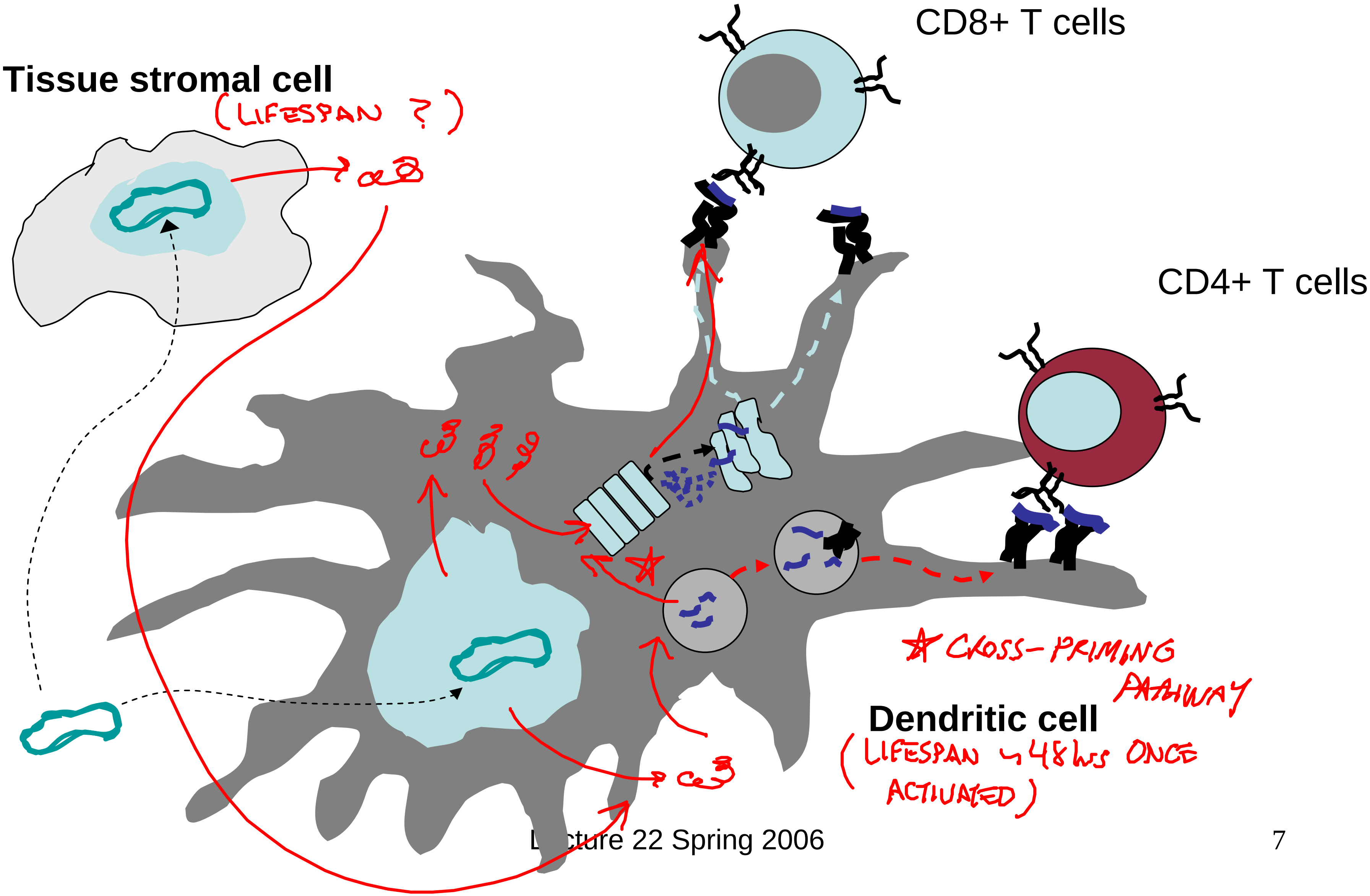
Figures 1A, 1B, and 1C removed due to copyright restrictions.
Please see: Bhakdi. *Arch Microbiol* 165 (1996): 73.

fusogenic peptides: using viral entry strategies for drug delivery

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?

1. SELF-REPLICATING ANTIGEN!

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

   ANTI-VECTOR PRE-EXISTING 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.

Image removed due to copyright restrictions.
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

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.

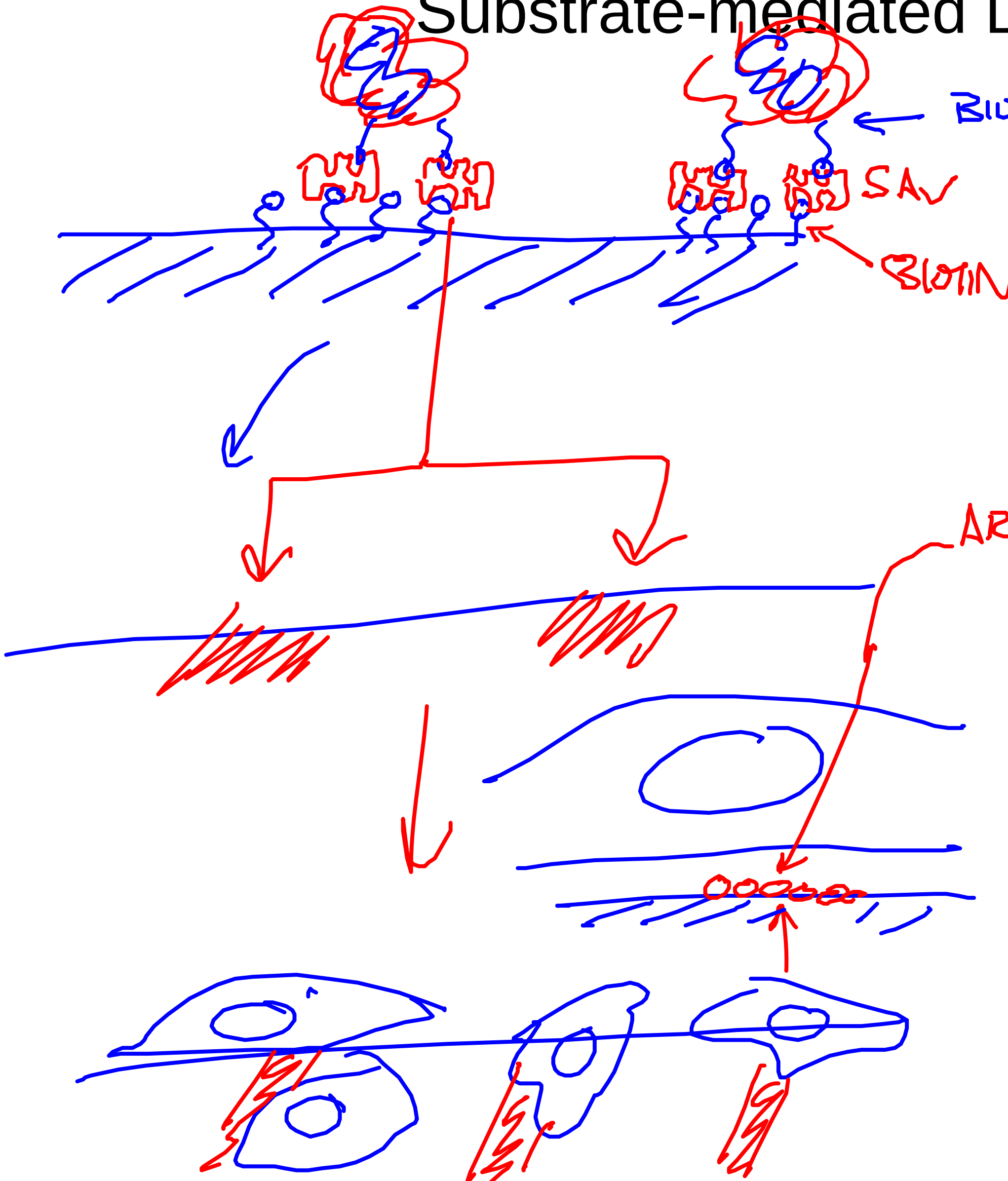
Substrate-mediated DNA delivery

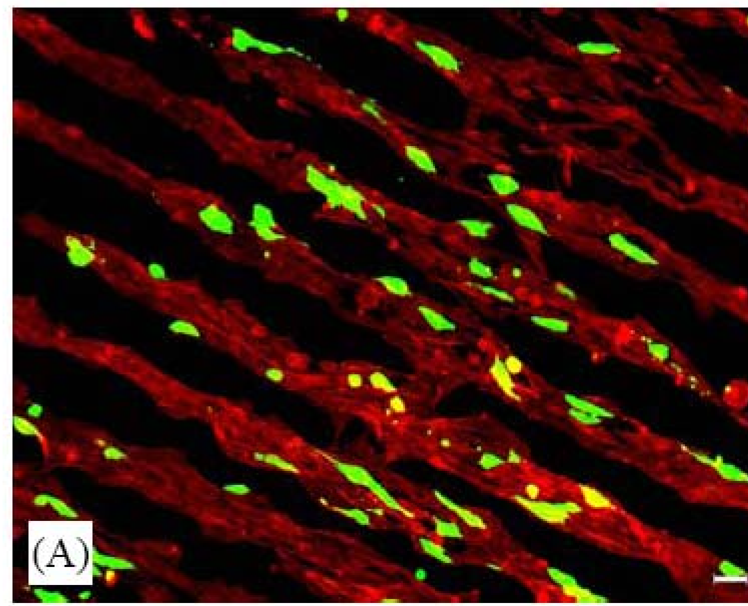
BIOTINYLATED POLYPLEXES

SAV

BIOTIN

ARTIFICIALLY HI POLYPLEX CONCENTRATION





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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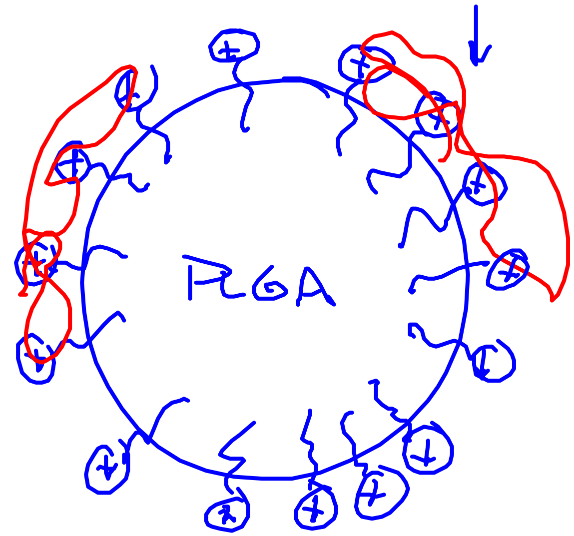
CHIRON:

FOR VACCINES

PLASMIDS PROTECTED FROM DNASE



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

Graph removed due to copyright restrictions.
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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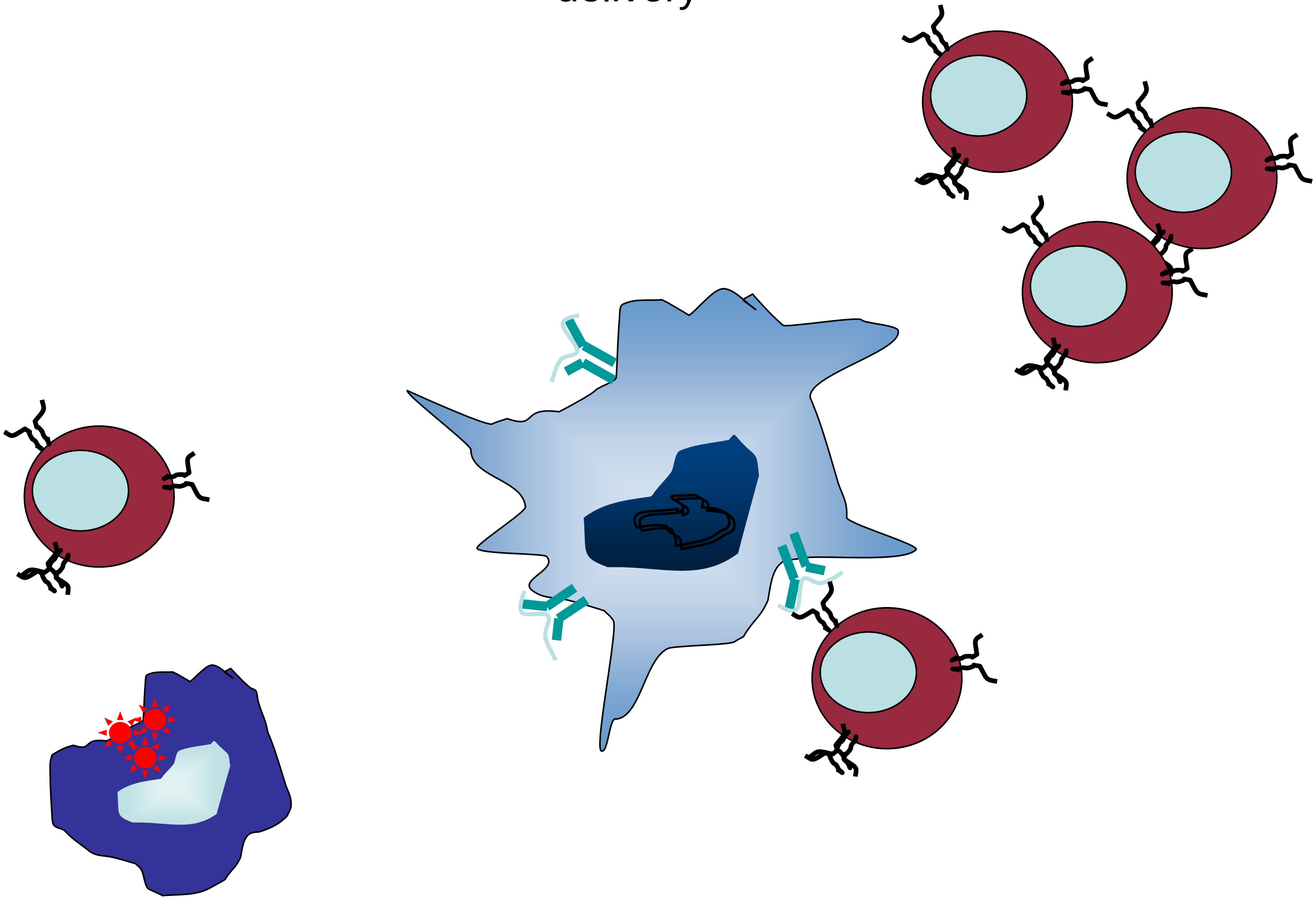
Please see: Sumida et al. J. *Clinical Invest* 114 (2004): 1334-1342.

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).