

Biomaterials as Adjuvants

Last Time: drug targeting

Today: Delivering activation signals to dendritic cells in vaccines

Reading:

Supplementary Reading:

ANNOUNCEMENTS:

Targeting vaccines to dendritic cells

Targets on DCs:

DEC-205

CD11c

TLR3

...particles, in general

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Please see: Kwon et al. *PNAS* 102 (2005): 18264-18268.

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Please see: Figure 4 in Kwon et al. *PNAS* 102 (2005): 18264-18268.

'REVERSE TARGETING', CONTINUED

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

1) Attraction to sites of infection

Infection site

2) Antigen loading and activation

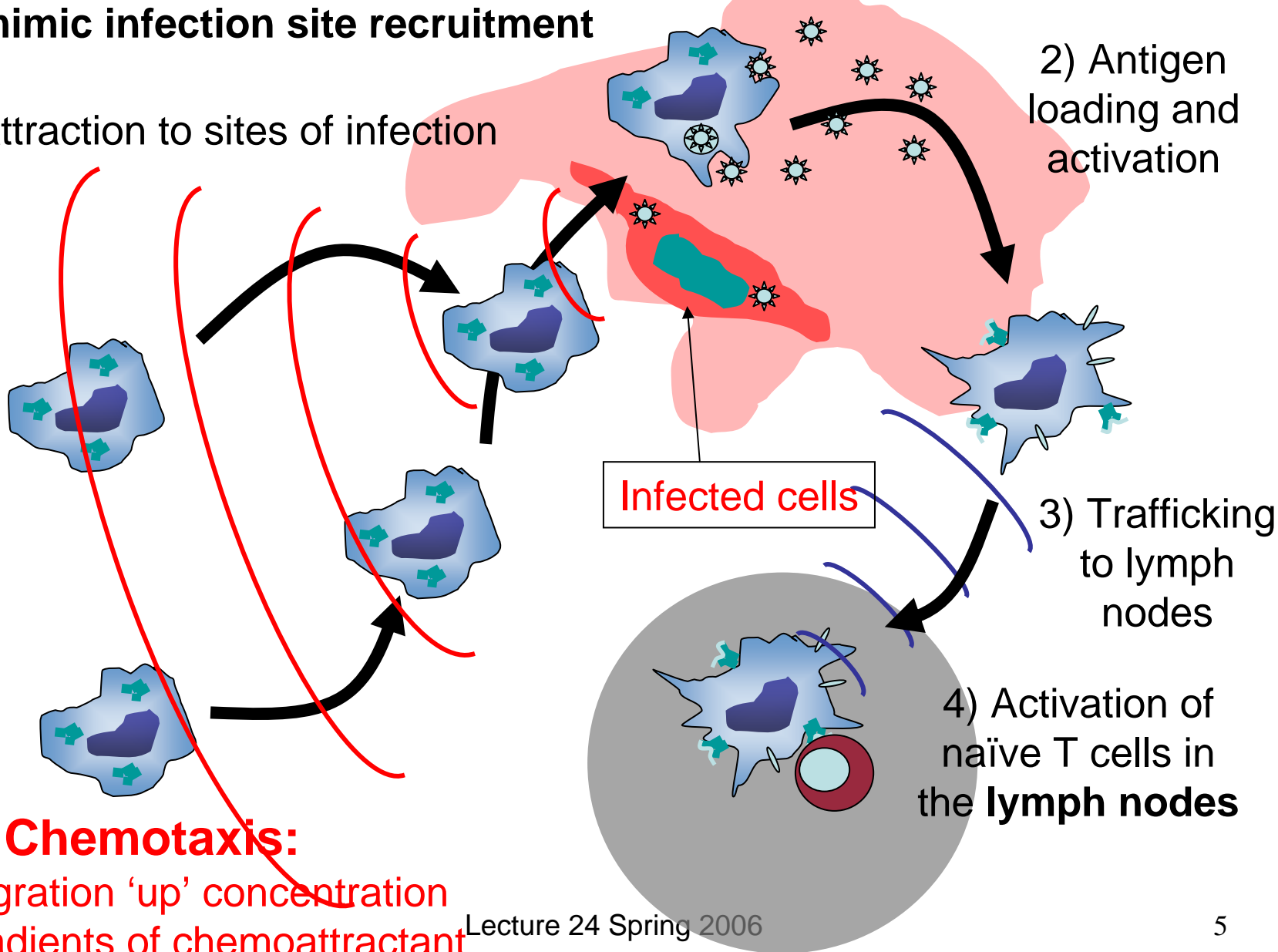
Infected cells

3) Trafficking to lymph nodes

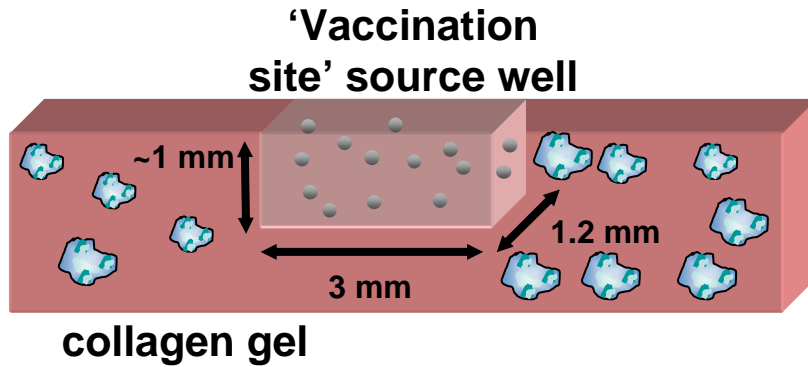
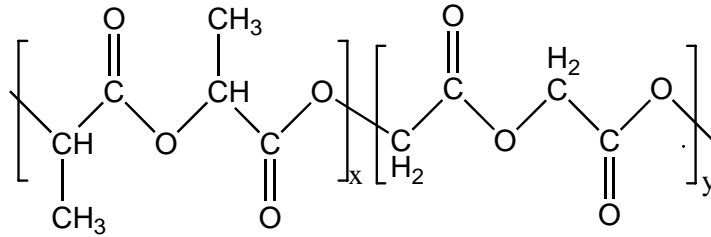
4) Activation of naïve T cells in the lymph nodes

1) Chemotaxis:

Migration 'up' concentration gradients of chemoattractant

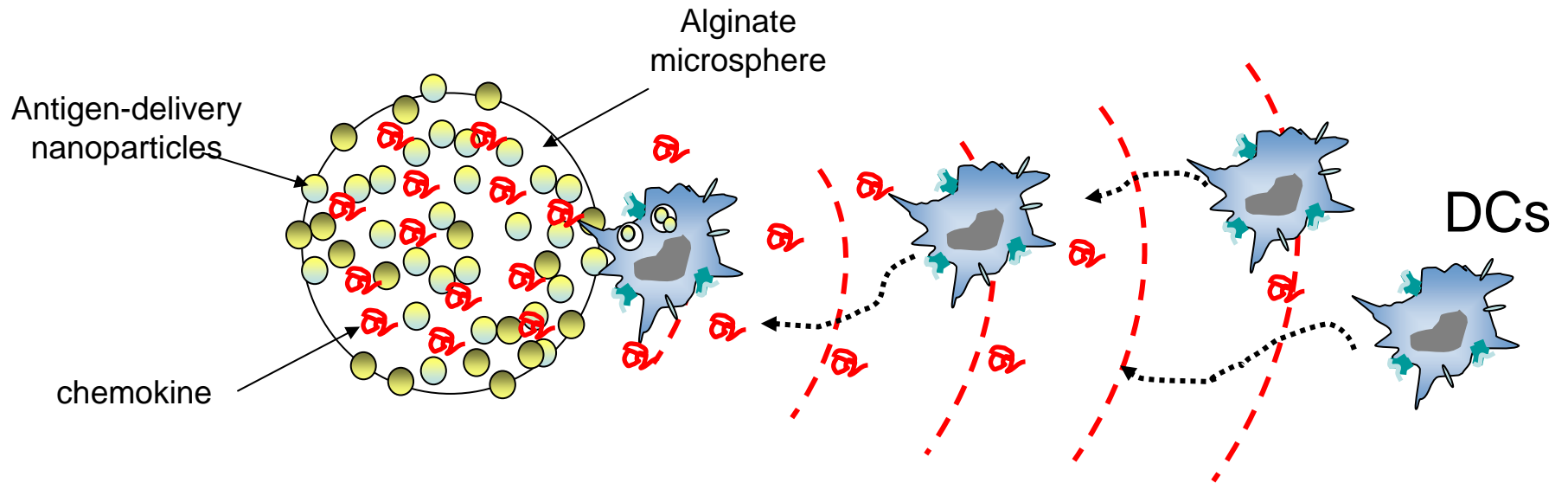


PLGA



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

Dendritic cell attraction, antigen loading, and activation



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

alginate

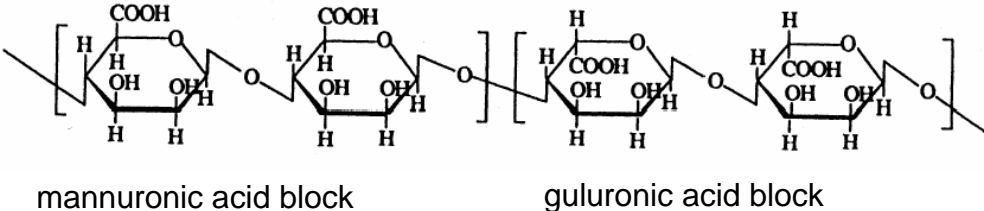
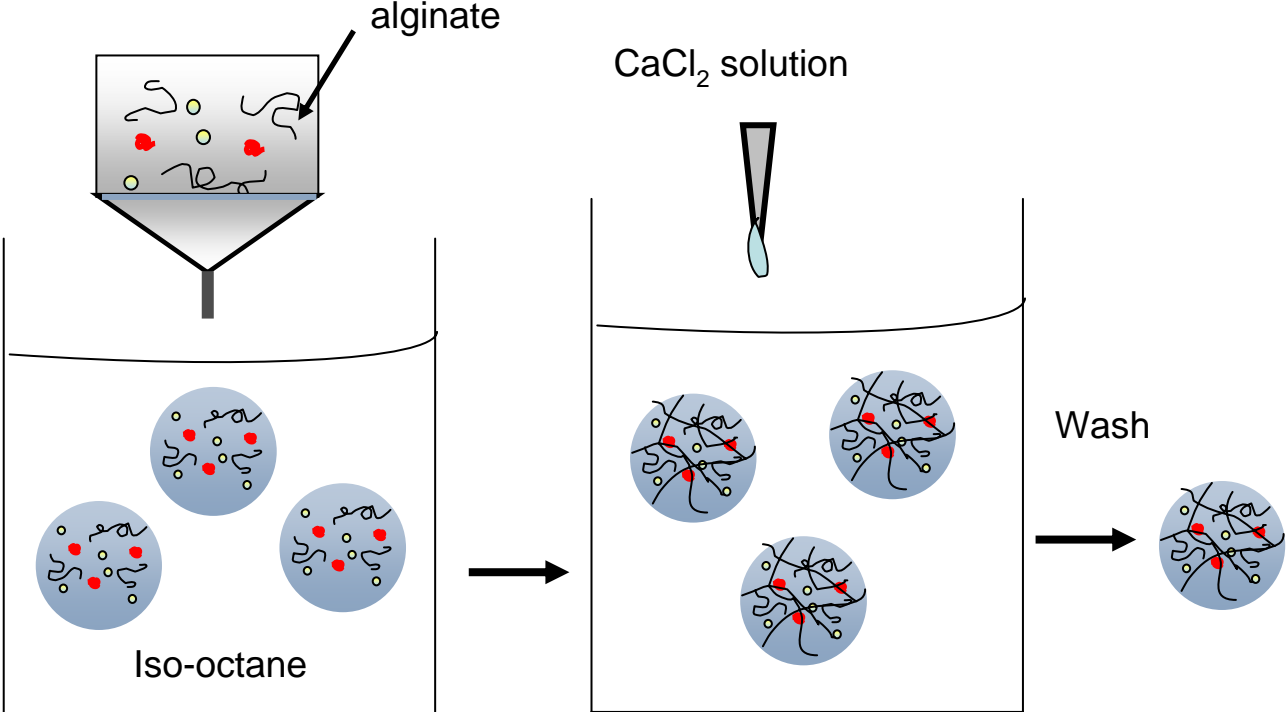
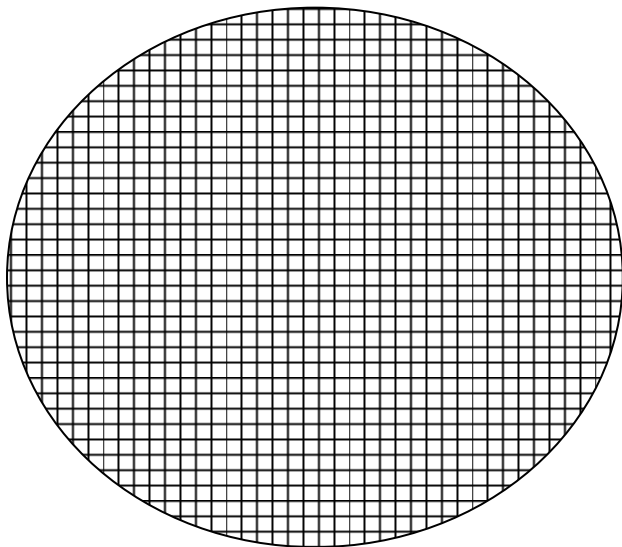
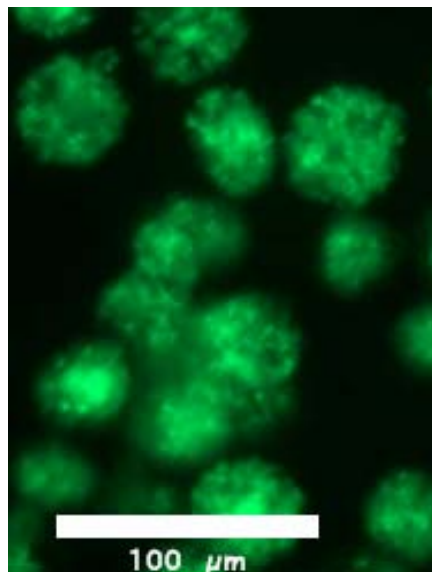


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Please see: <http://www.lsbu.ac.uk/water/hyalg.html>

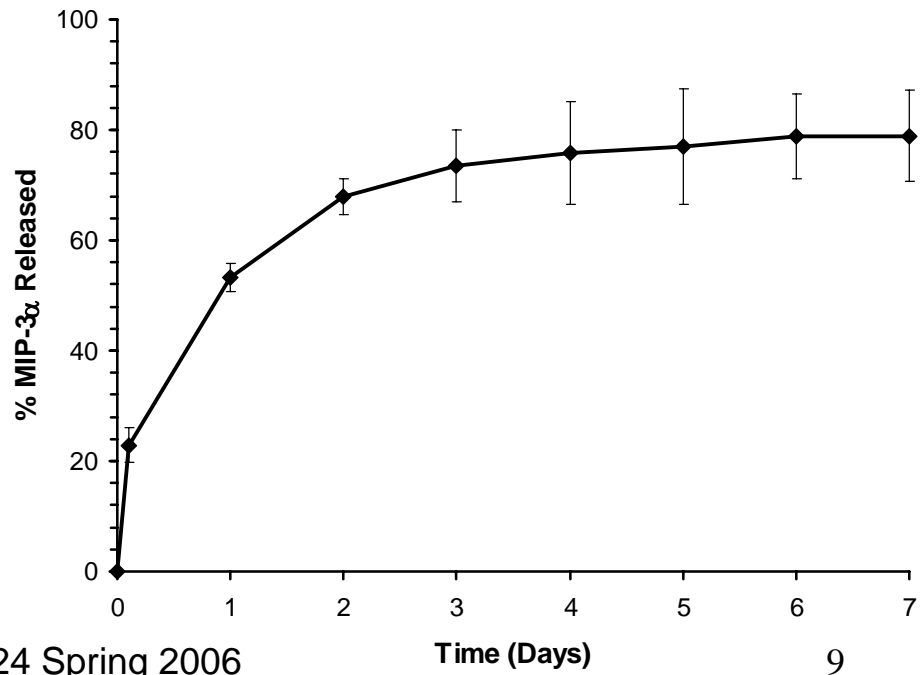
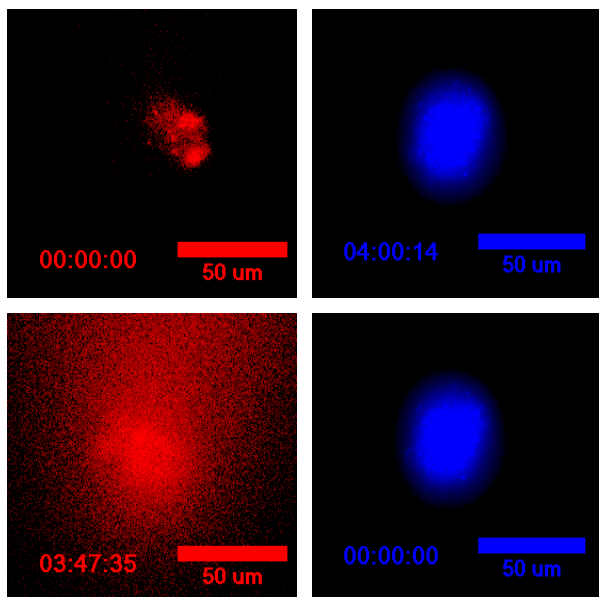
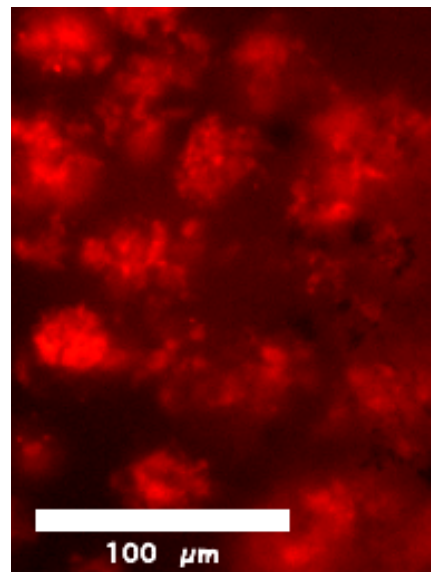


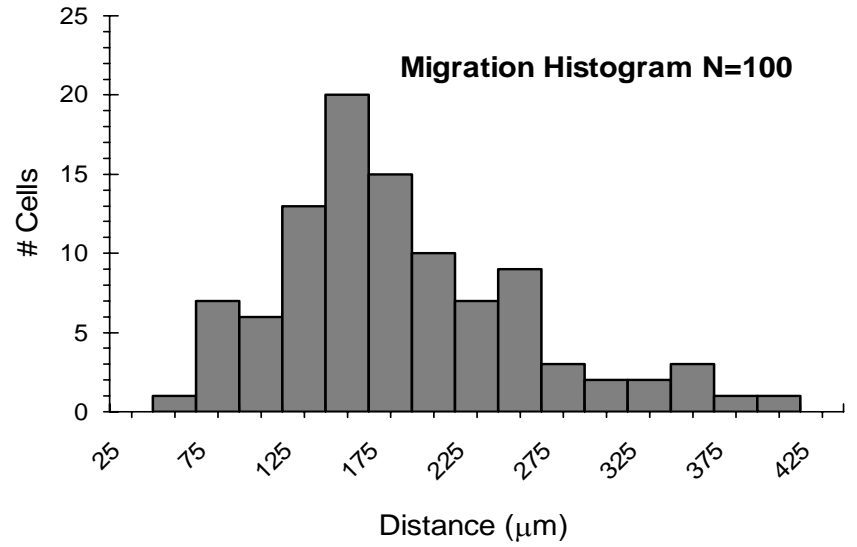
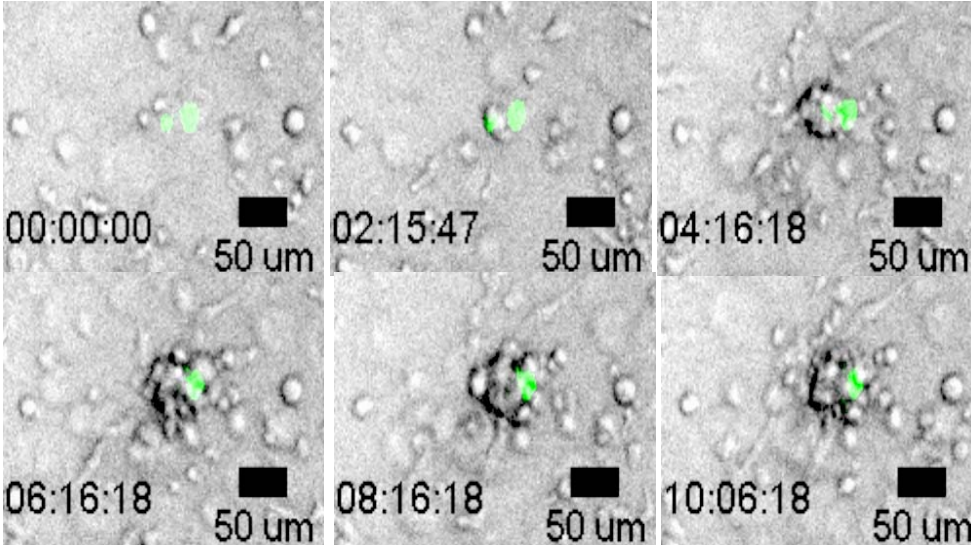
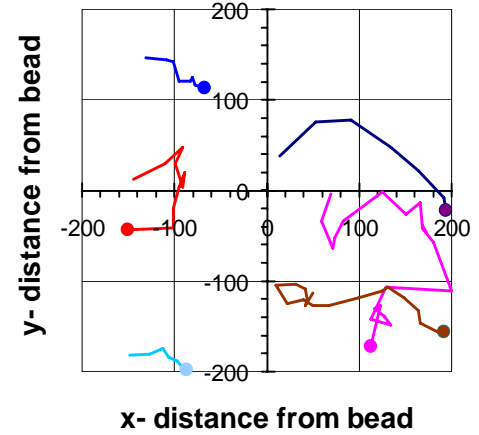
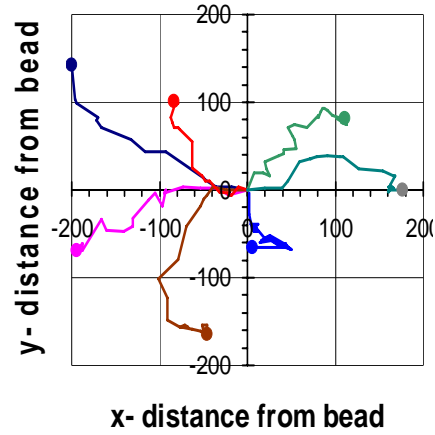
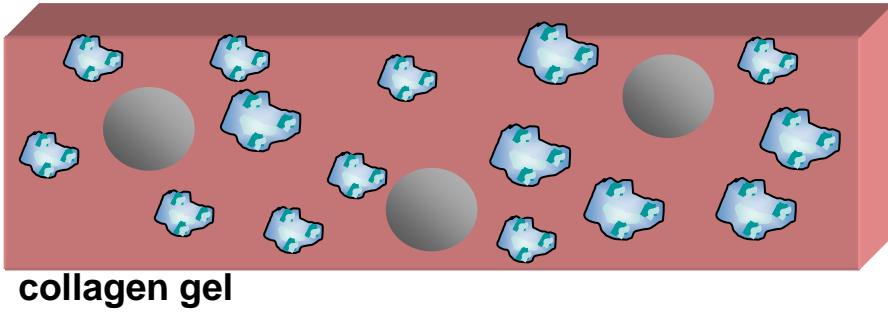


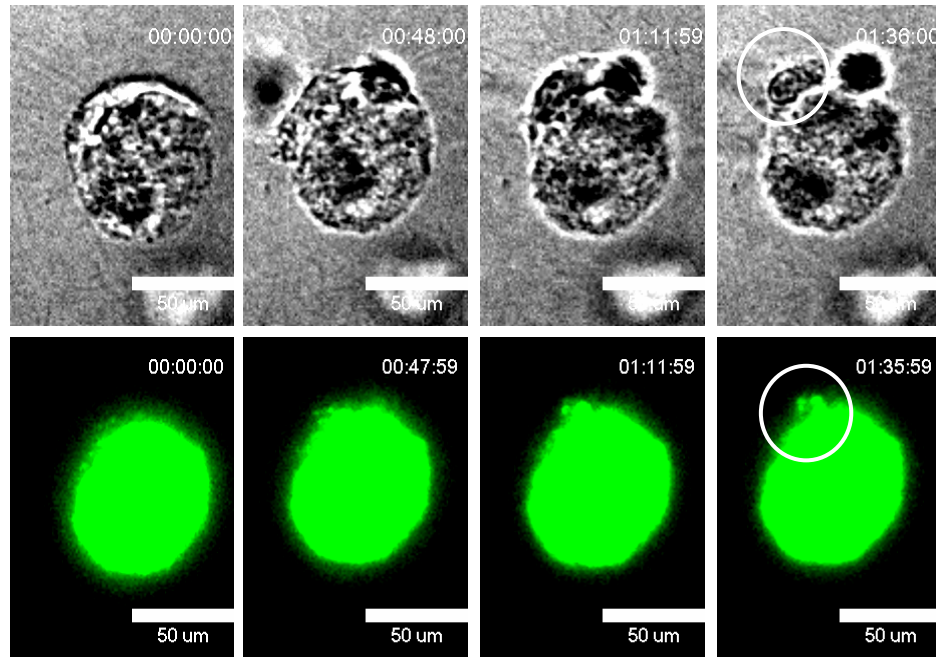
Fluorescent nanoparticles



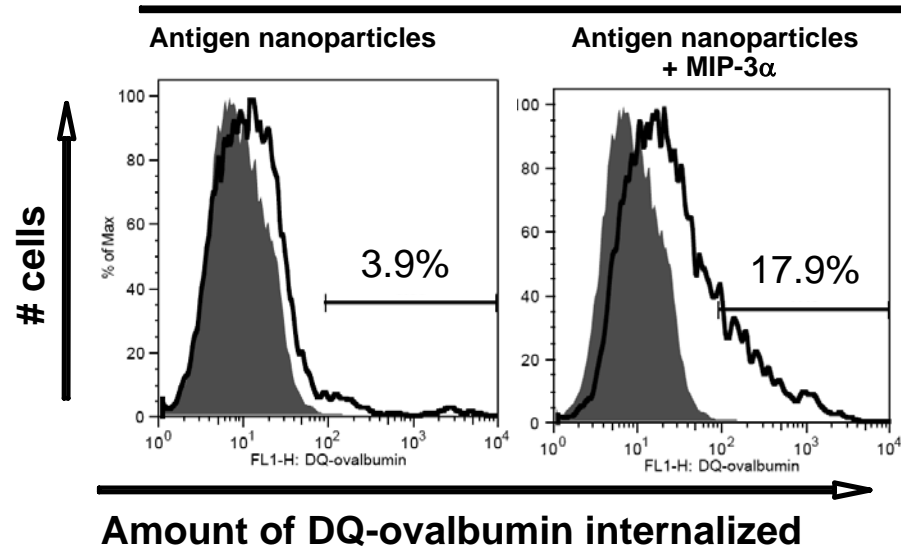
Fluorescent chemokine







Alginate microspheres loaded with:



Issues in targeted delivery

- Where is the target molecule expressed?
 - Is it expressed by normal tissues?
 - Is it stably expressed?
 - Can select out evasive tumor cells/viruses
- What is the affinity of binding?
- immune response to targeting agent

ADJUVANTING VACCINES WITH SYNTHETIC MATERIALS

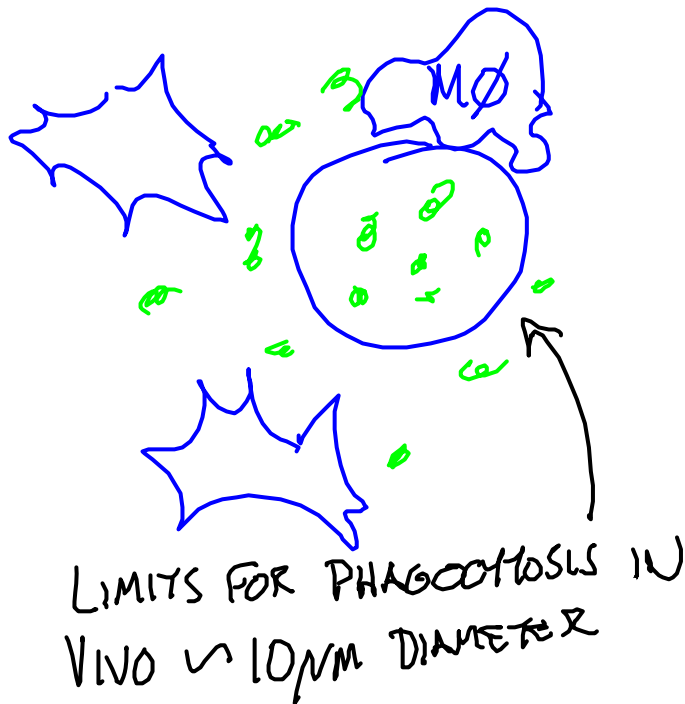
MIMICKING PATHOGEN-HOST INTERACTIONS TO STIMULATE
IMMUNITY

ADJUVANTING FUNCTIONS OF BIOMATERIALS

- Sustain delivery of antigen
 - Extracellular or intracellular
- Mimic pathogen delivery of activation signals to dendritic cells and B cells
 - Mimic multivalent surface structure of pathogens
 - Limit dose, but enhance response

SUSTAINING ANTIGEN DELIVERY TO DENDRITIC CELLS

EXTRACELLULAR DEPOTS



INTRACELLULAR DEPOTS



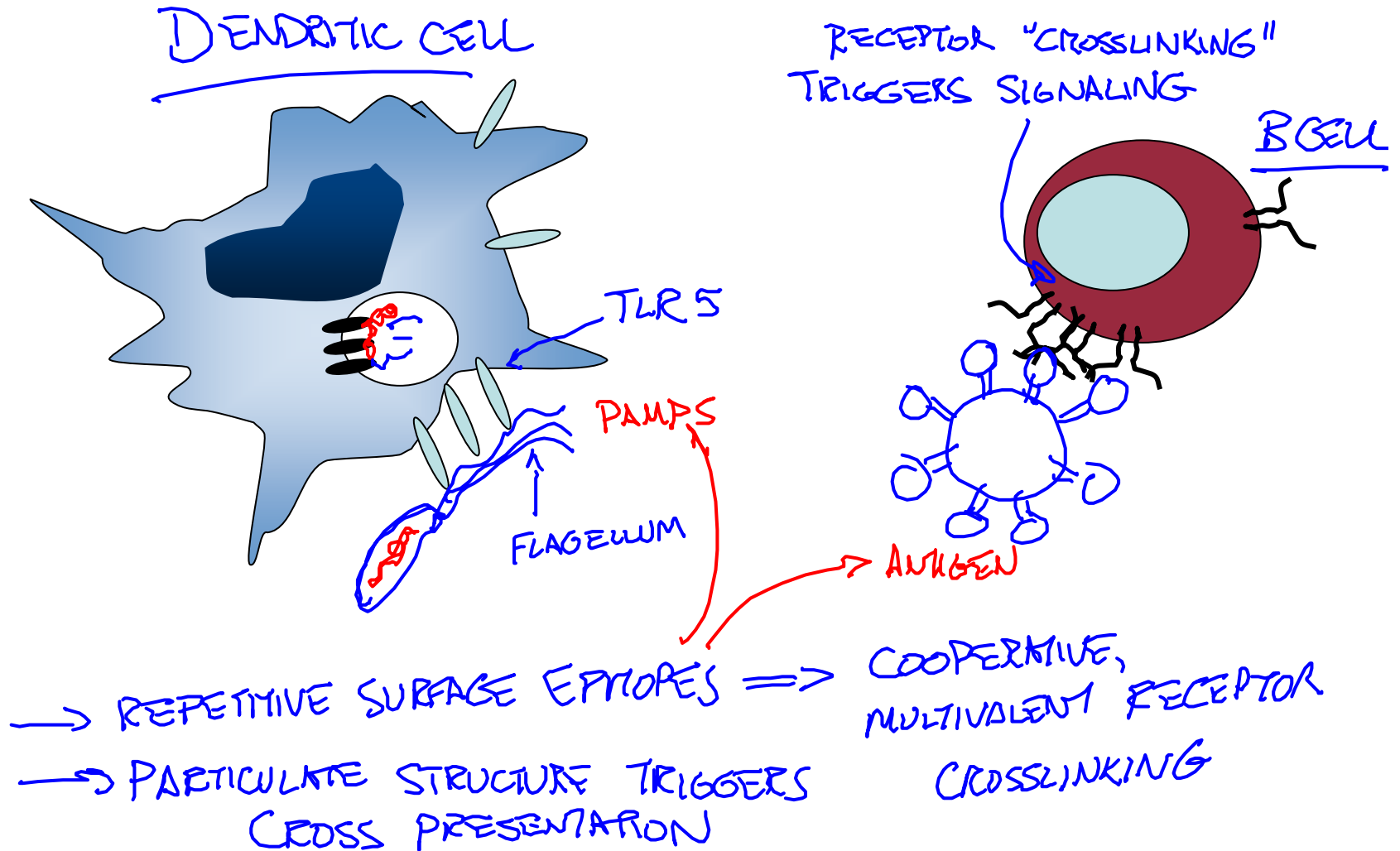
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Please see: Shen et al. *Immunology* 117 (2005): 78-88.

pathogens as biomaterials: how the structure of pathogens relates to immune responses

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Please see: <http://www.kripafoundation.org/Rehabilitation%20Programs/faqhiv.html>

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Please see: <http://textbookofbacteriology.net/BSRP.html>

pathogens as biomaterials: how the structure of pathogens relates to immune responses



Dose sparing of adjuvants by co-delivery in particles

Many immunostimulatory factors that activate DCs are also potent inflammatory stimuli:

T cell proliferation measured *ex vivo* 10d after 2 injections:

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Please see: Heikenwalder et al. *Nat. Med* 10 (2004): 187-192.

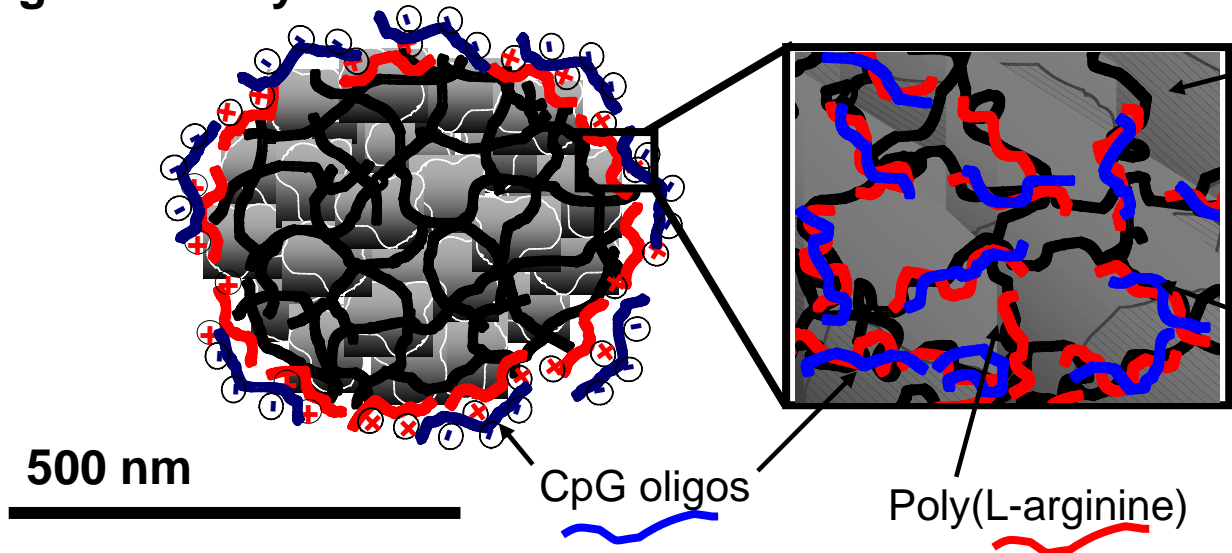
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Please see: Diwan et al. *Current Drug Deliv.* 1, no. 4 (2004): 405-412.

(Heikenwalder et al. *Nat. Med.* **10** 187-192 (2004)) (Diwan et al. *Curr. Drug Deliv.* **1**(4) 405-412 (2004))

Nanoparticles that mimic pathogen structural features

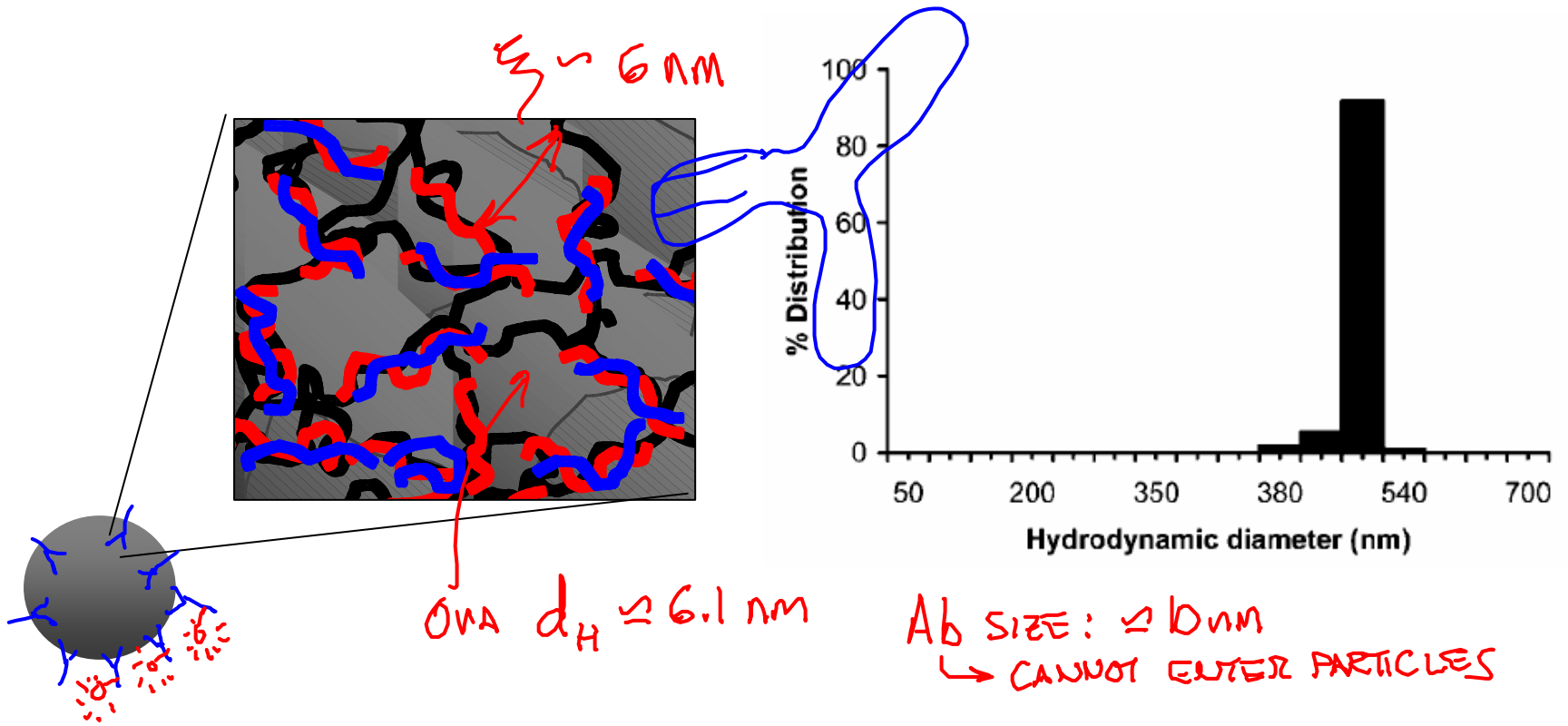
(1) Particulate antigen delivery



(2) surface display of repeated native Ag epitopes

(3) surface display of 'pathogen associated molecular patterns'

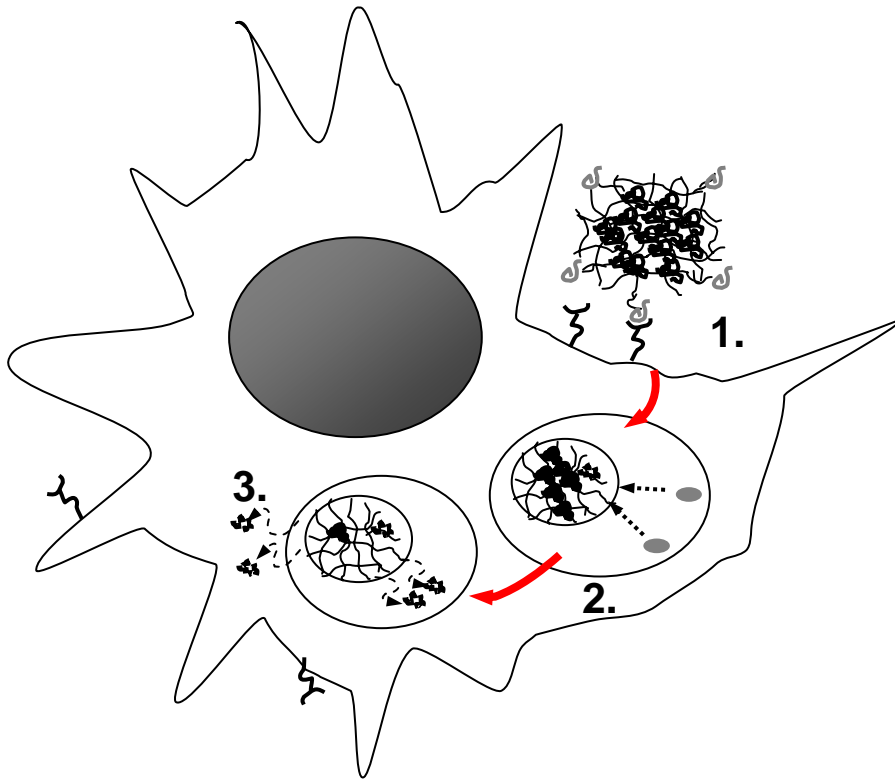
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Please see: S. Jain et al. *Biomacromolecules*. 6 (2005): 2590.



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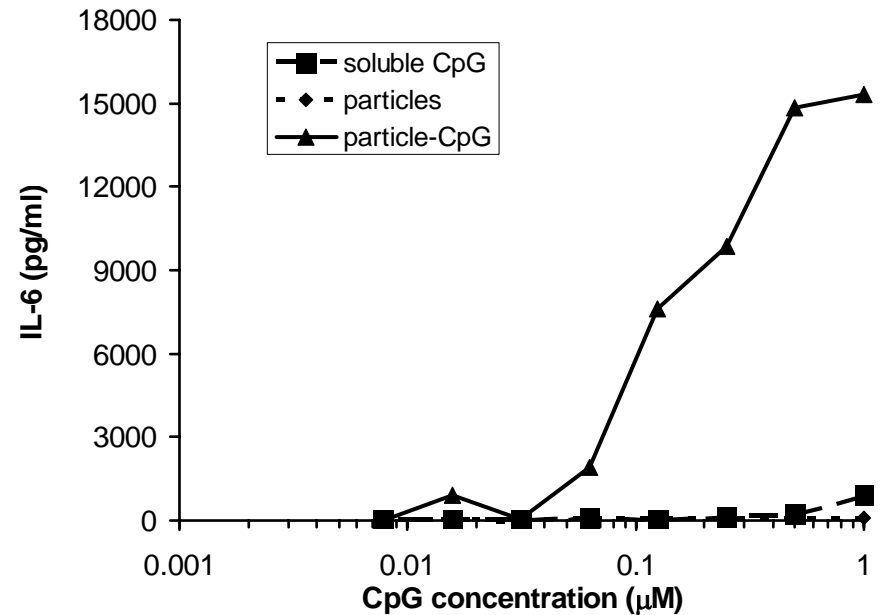
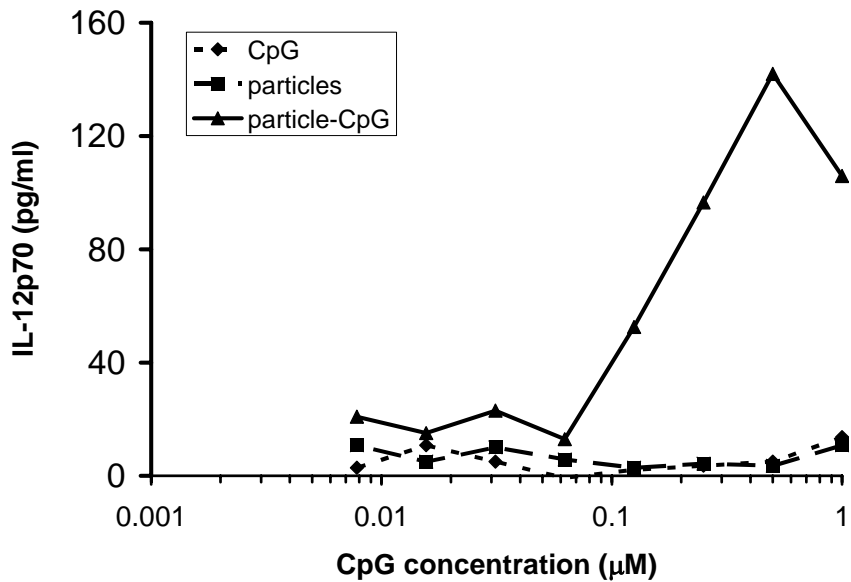
Proposed mechanism for antigen delivery to dendritic cells

Soluble Ova + CatD

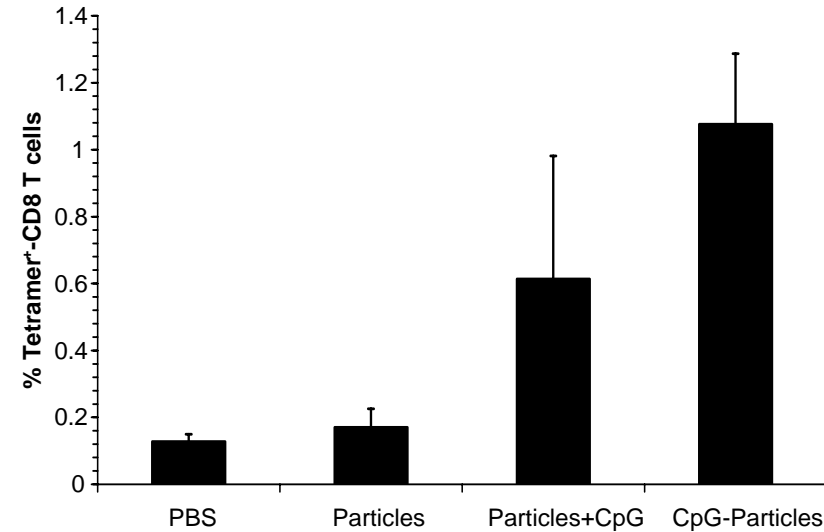
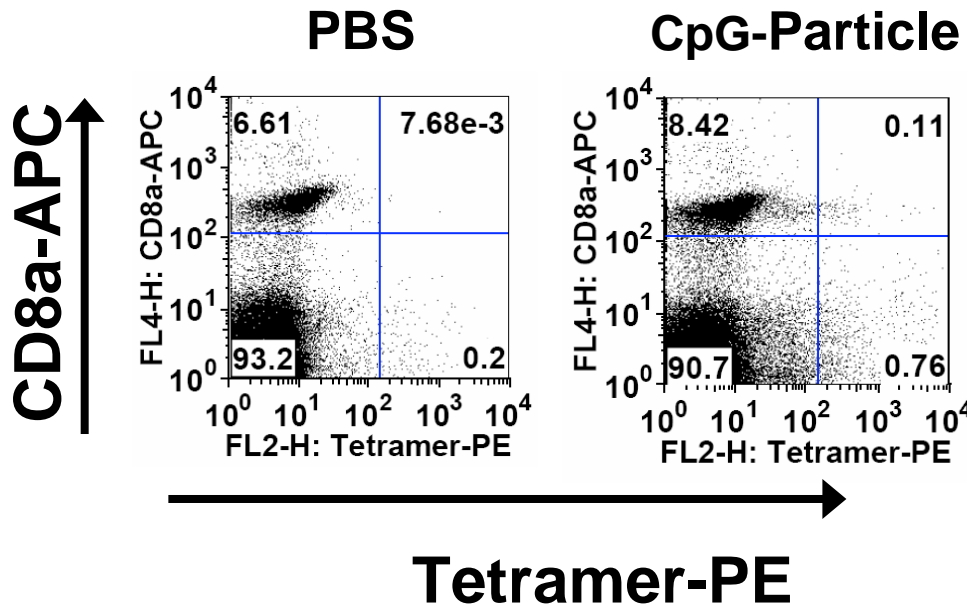
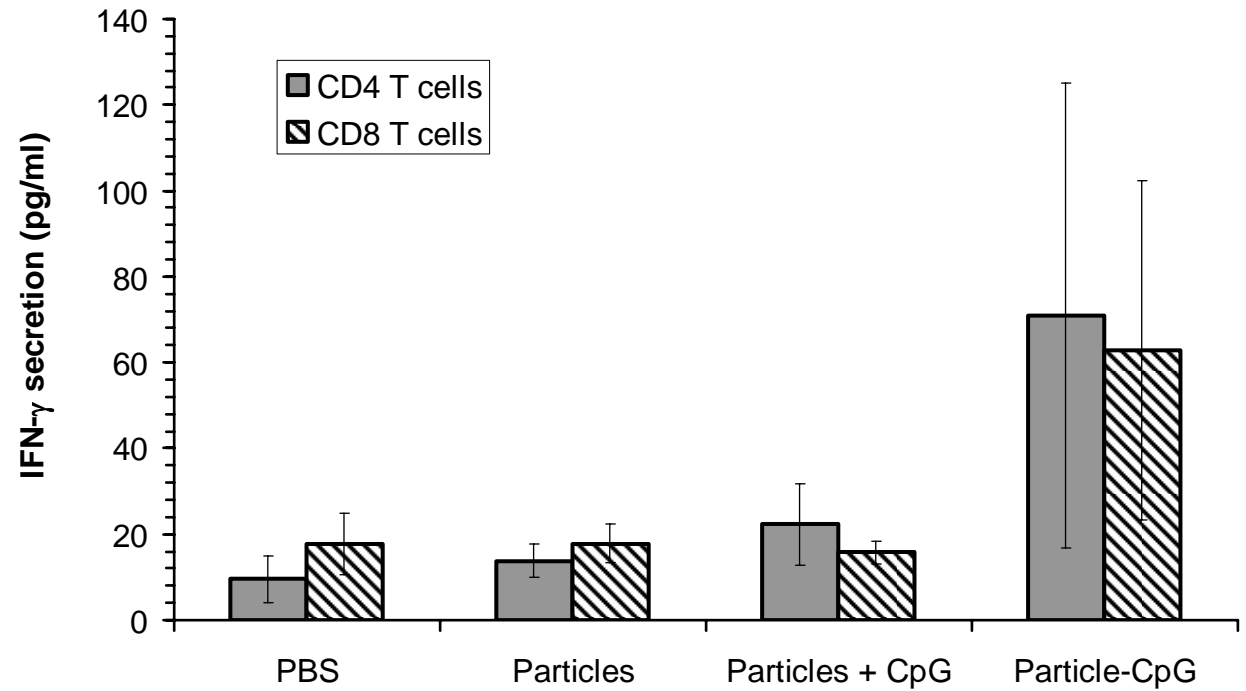


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Please see: S. Jain et al. *Biomacromolecules*. 6 (2005): 2590.

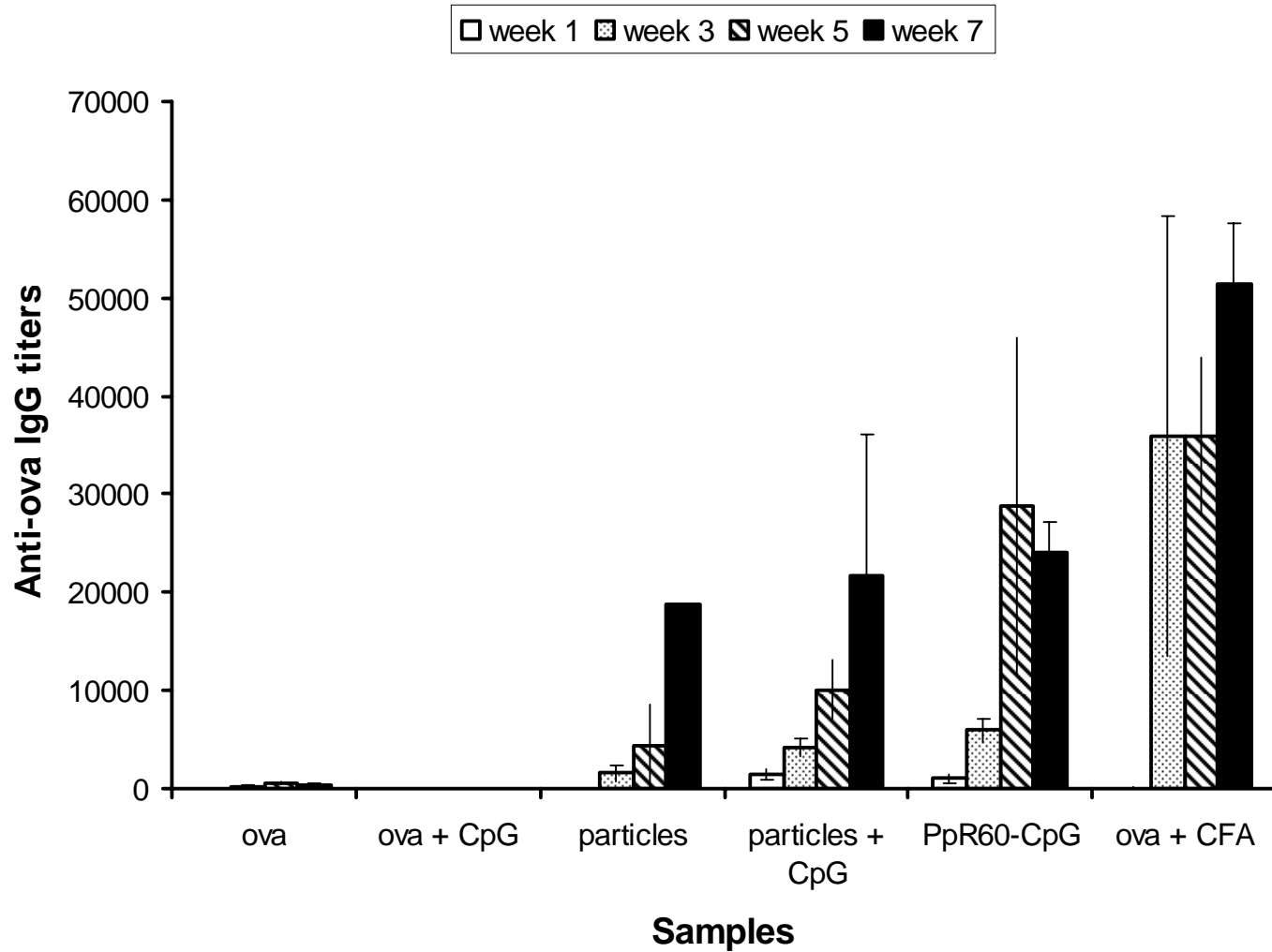
Cytokine Secretion by Activated DCs



**Mice (groups of 4)
given single
immunization s.c.;
Analysis of T cell
responses at 7 d:**

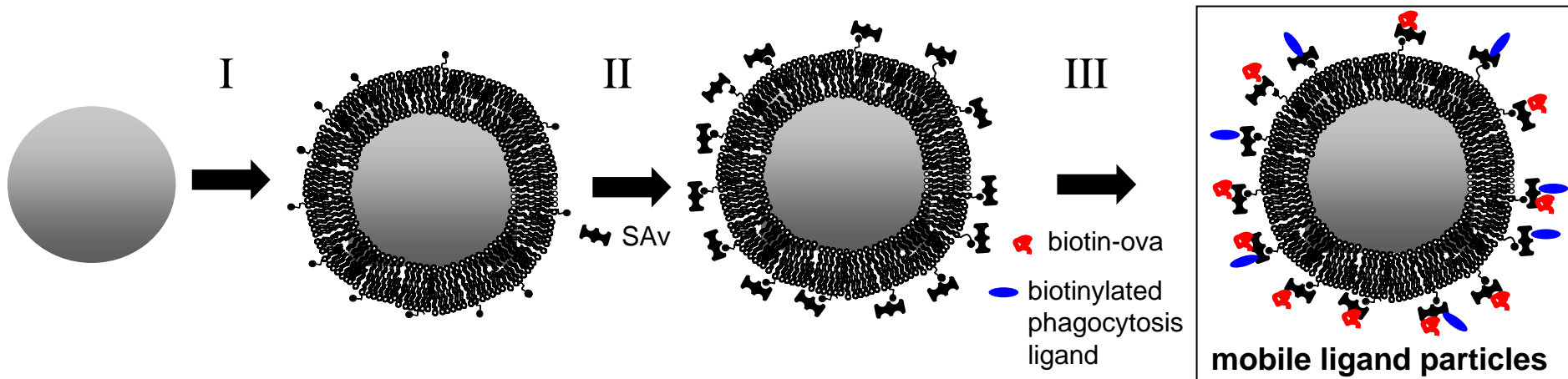


B Cell Activation *In Vivo*



Synthetic pathogens?

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Please see: Troutier et al. *Langmuir* 21 (2005): 1305-1313.



Synthetic pathogens?

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Please see: Figures 3 and 5 in Yu et al. *Adv. Mater.* 17 (2005): 1477-1480.