

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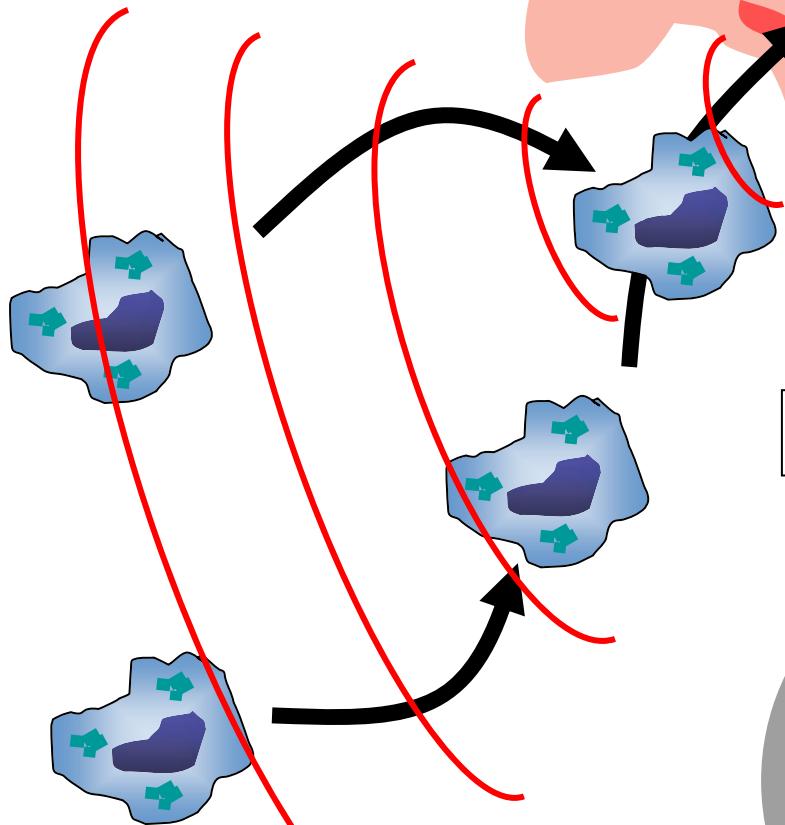
Please see: Kwon, et al. *PNAS* 102 (2005): 18264-18268.

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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



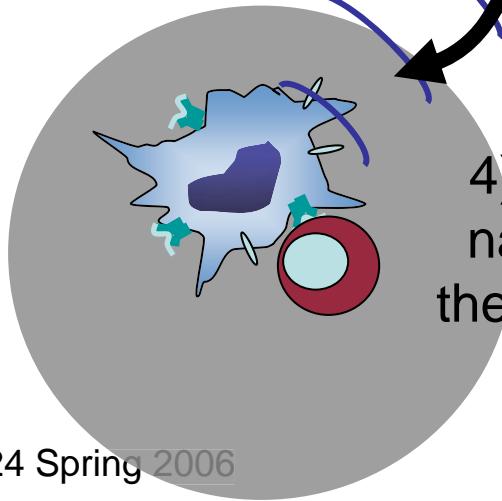
1) Chemotaxis:

Migration ‘up’ concentration gradients of chemoattractant

Infection site

Infected cells

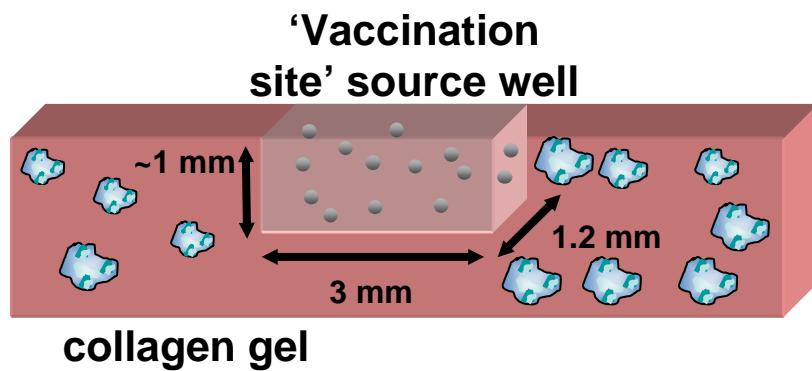
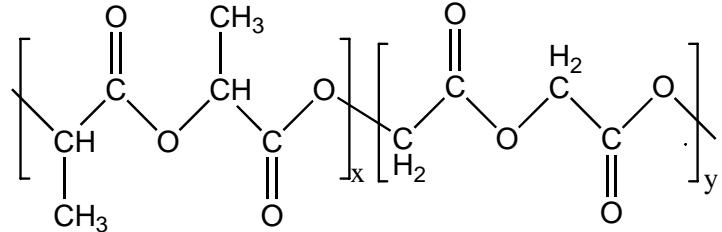
2) Antigen loading and activation



3) Trafficking to lymph nodes

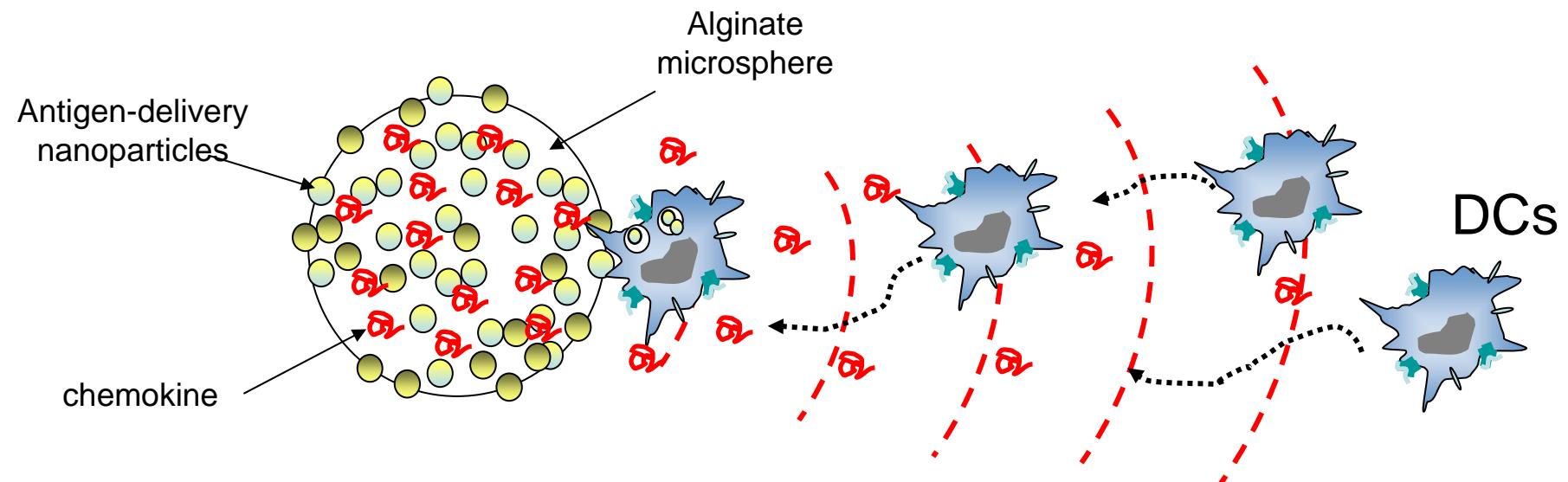
4) Activation of naïve T cells in the lymph nodes

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’?

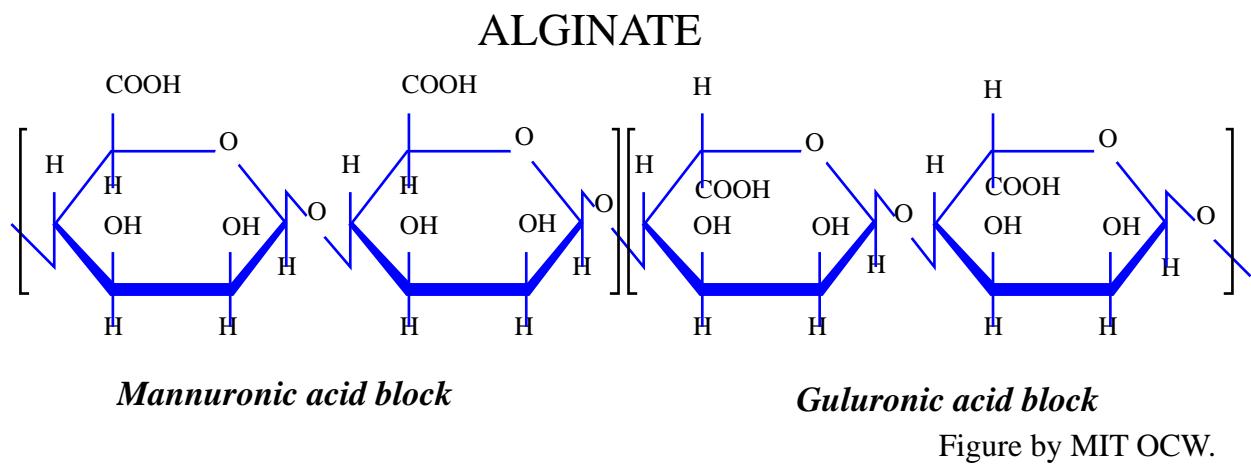
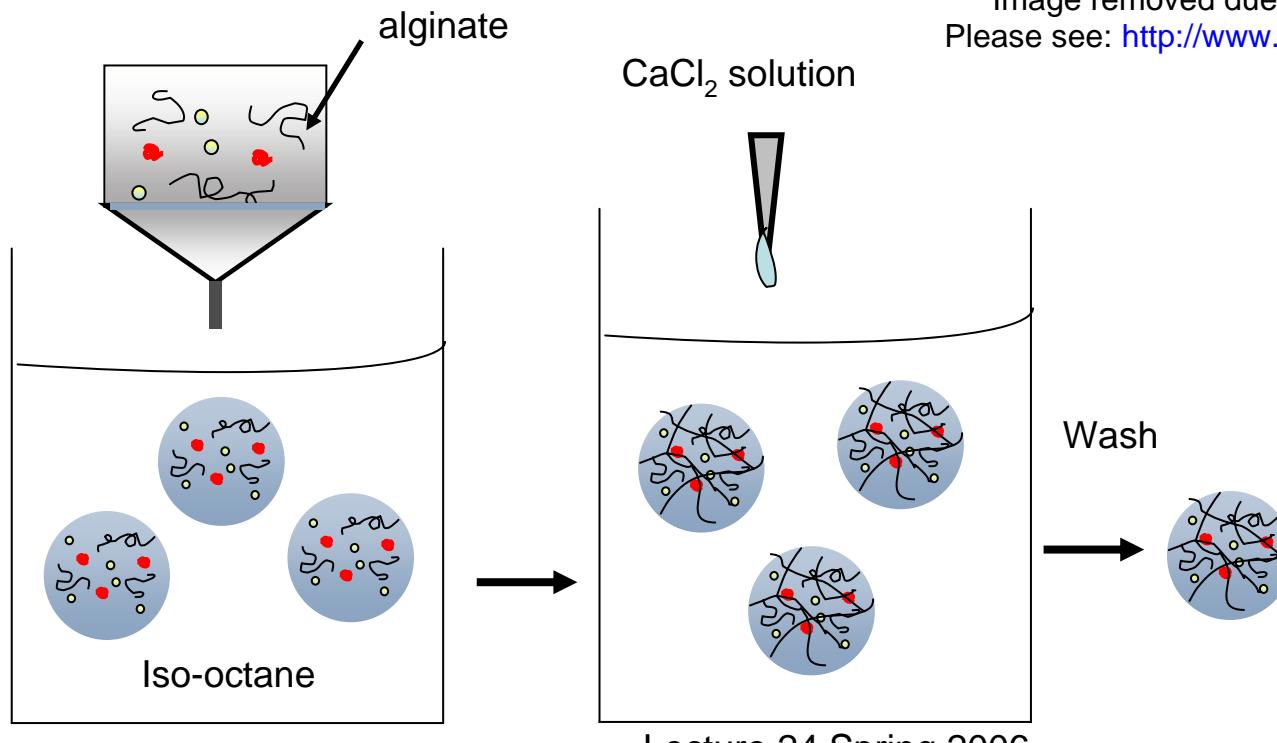
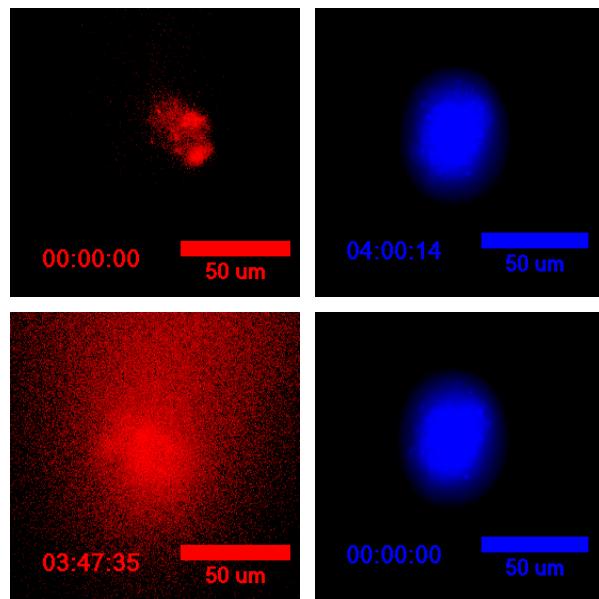
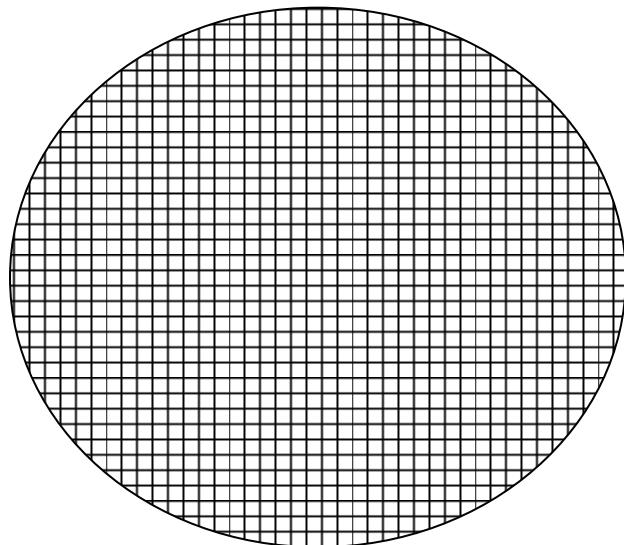


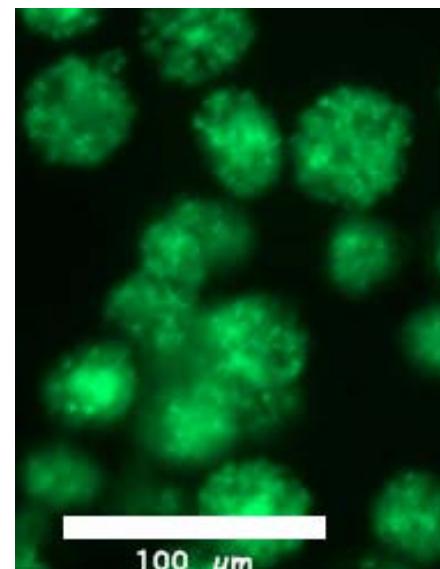
Figure by MIT OCW.

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

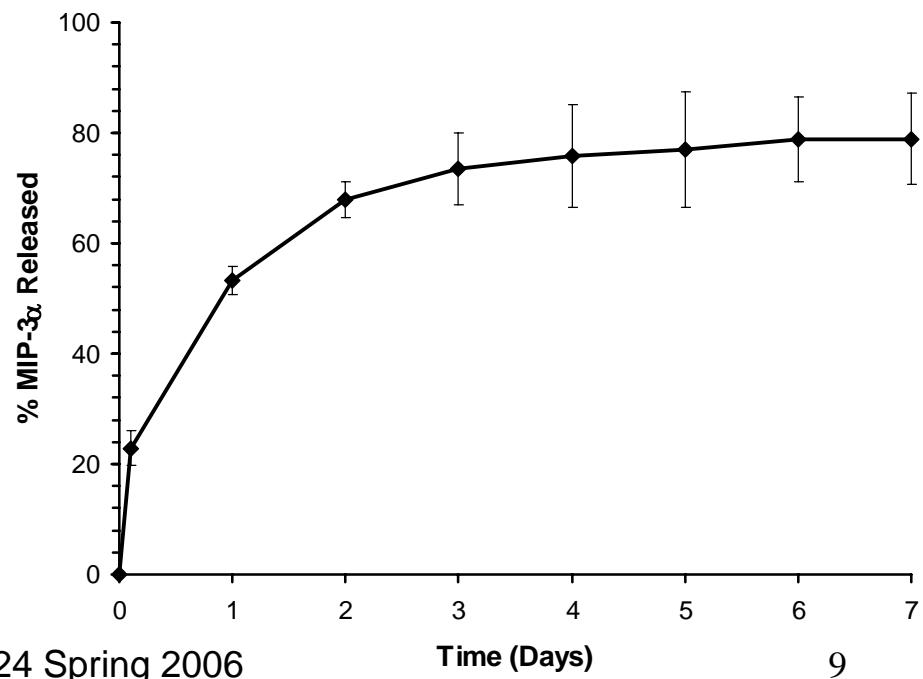
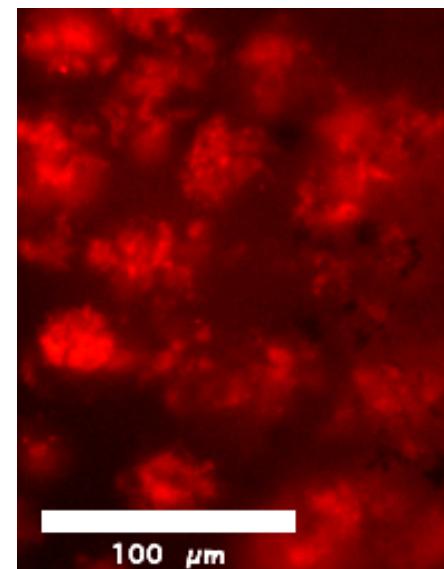


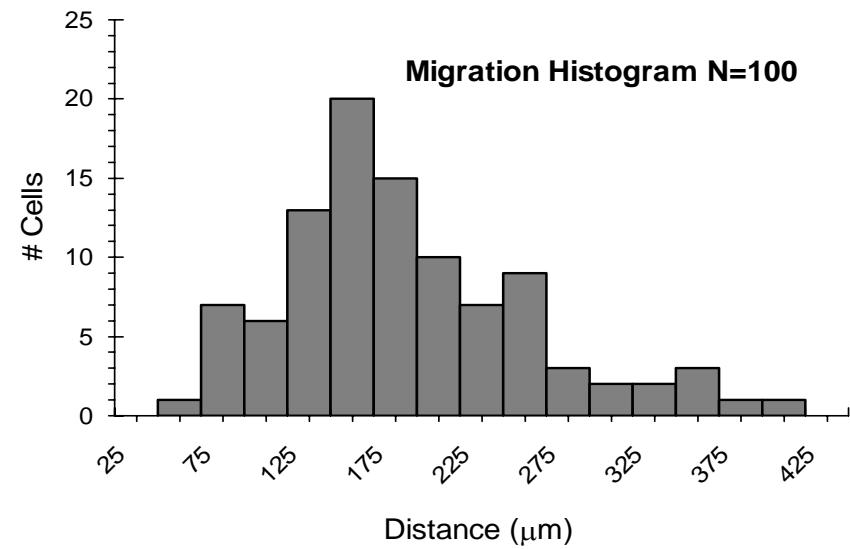
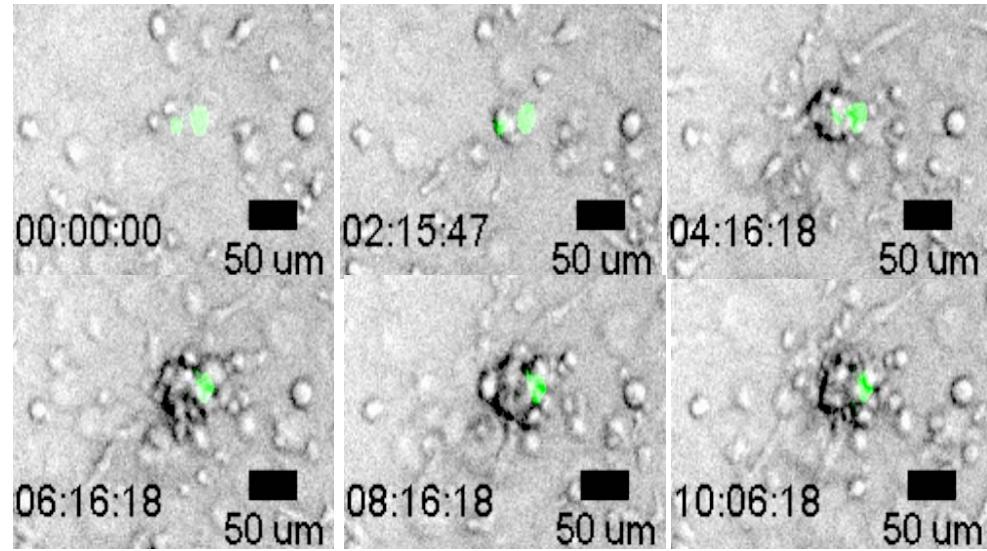
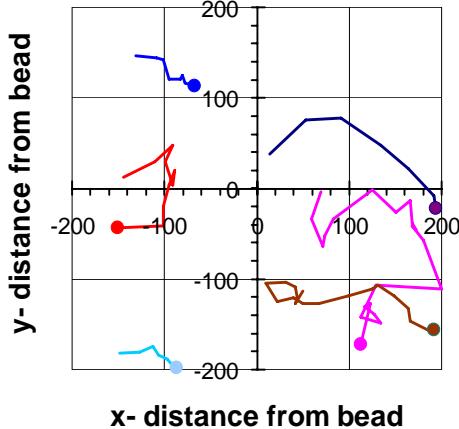
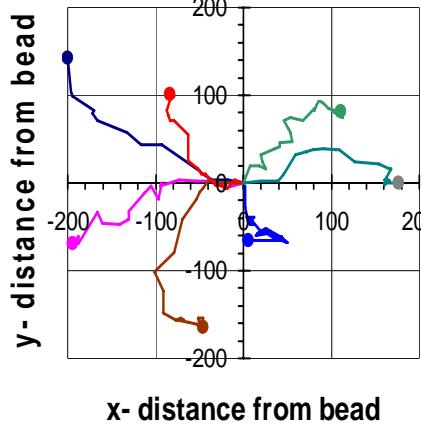
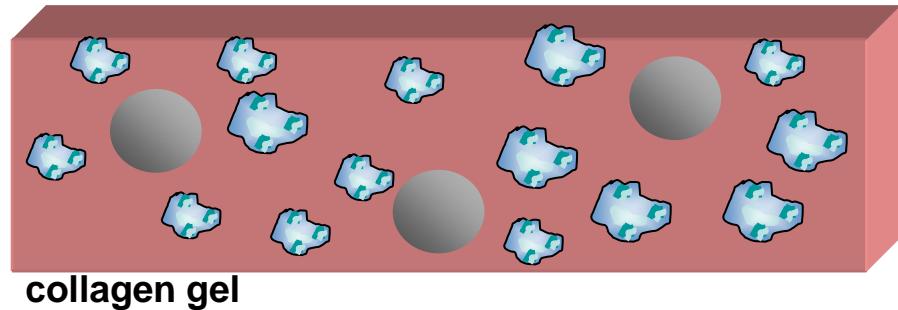


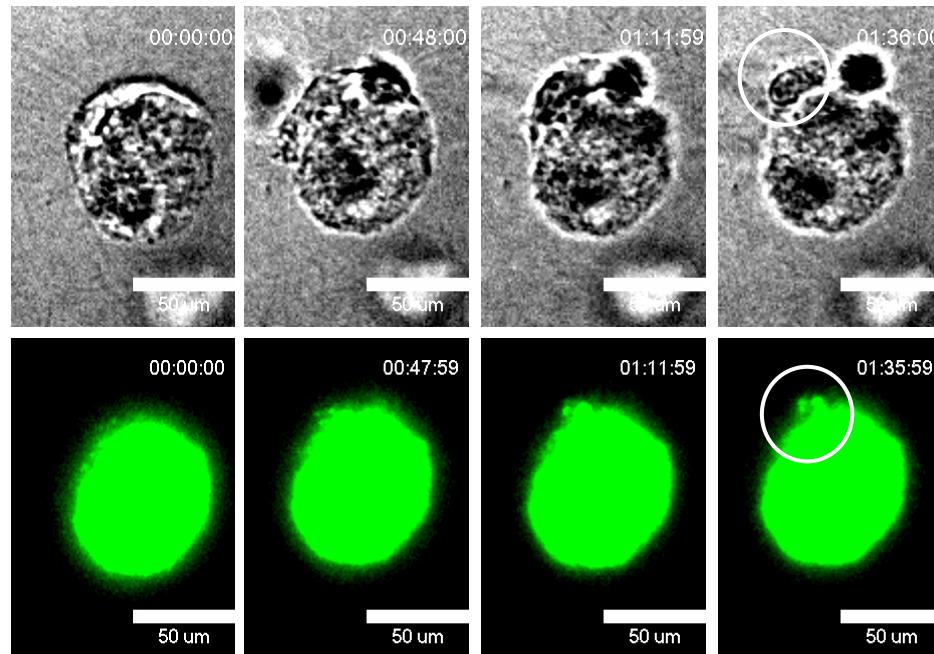
Fluorescent nanoparticles



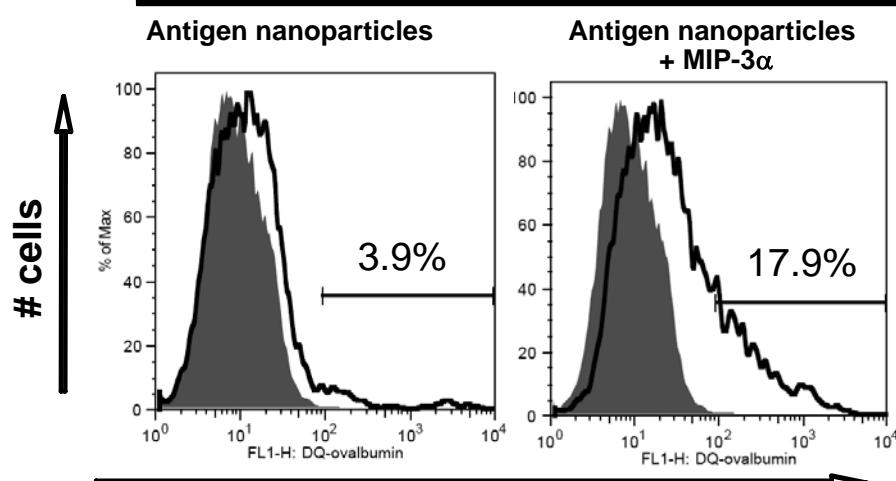
Fluorescent chemokine







Alginate microspheres loaded with:



Amount of DQ-ovalbumin internalized

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

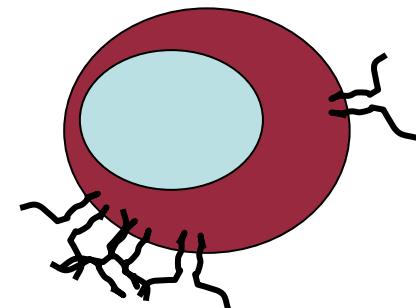
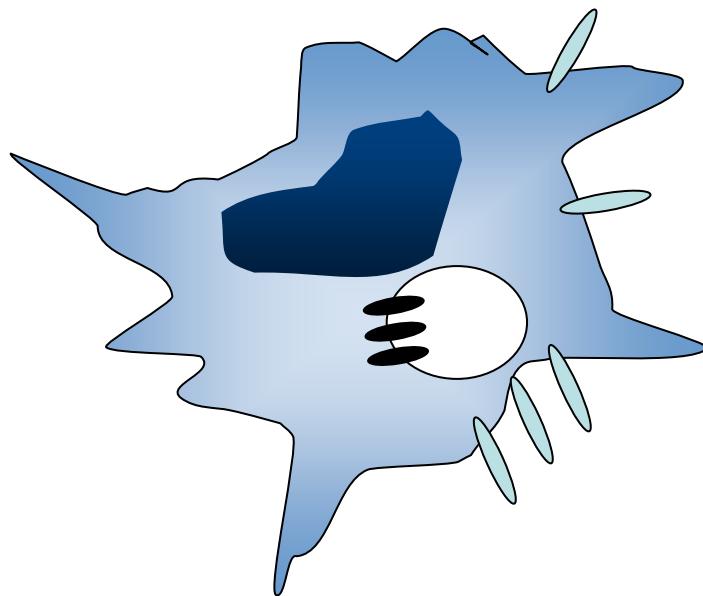
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pathogens as biomaterials: how the structure of pathogens relates to immune responses



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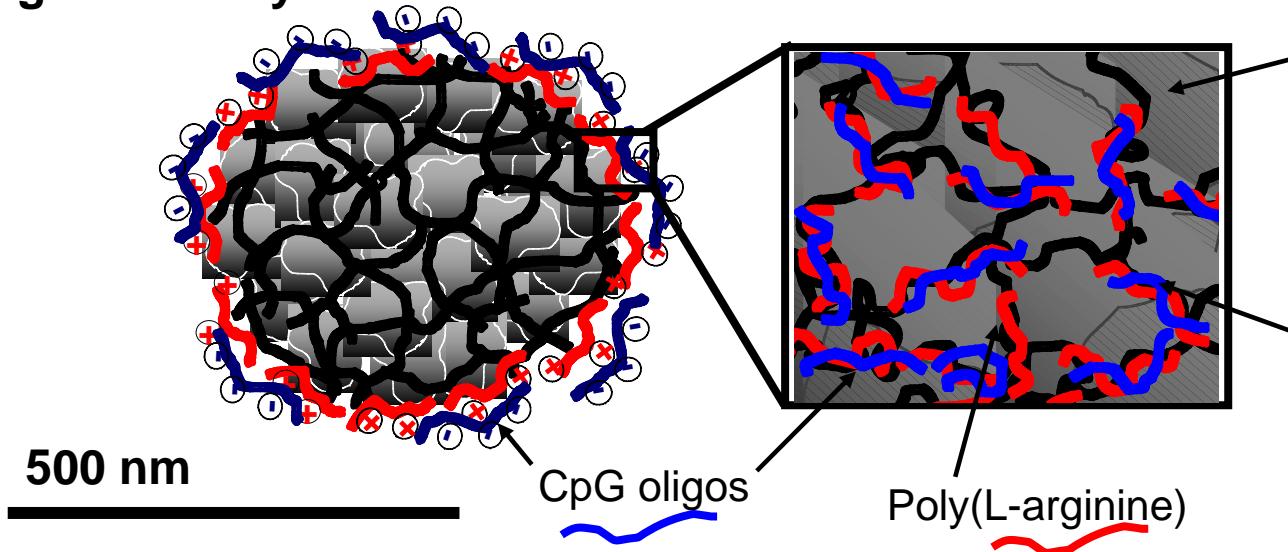
Please see: Heikenwalder, et al. *Nat Med* 10 (2004): 187-192.

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

Nanoparticles that mimic pathogen structural features

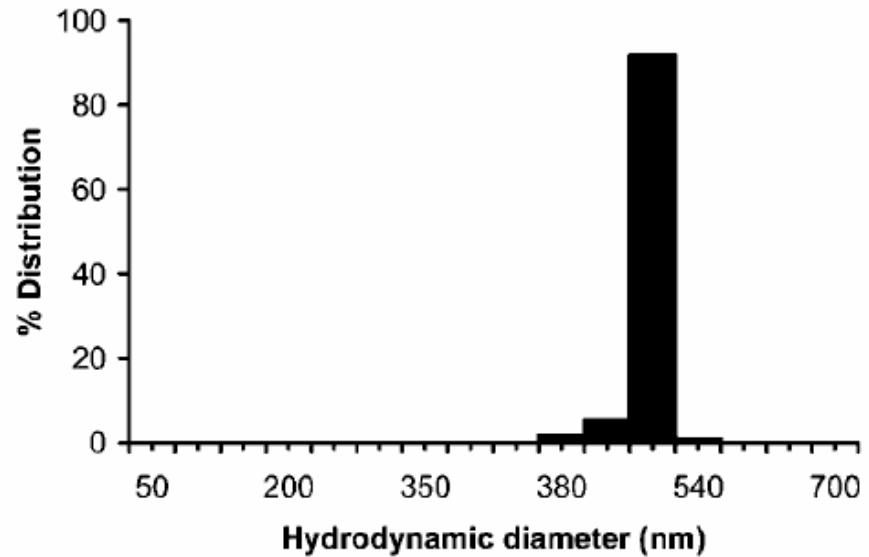
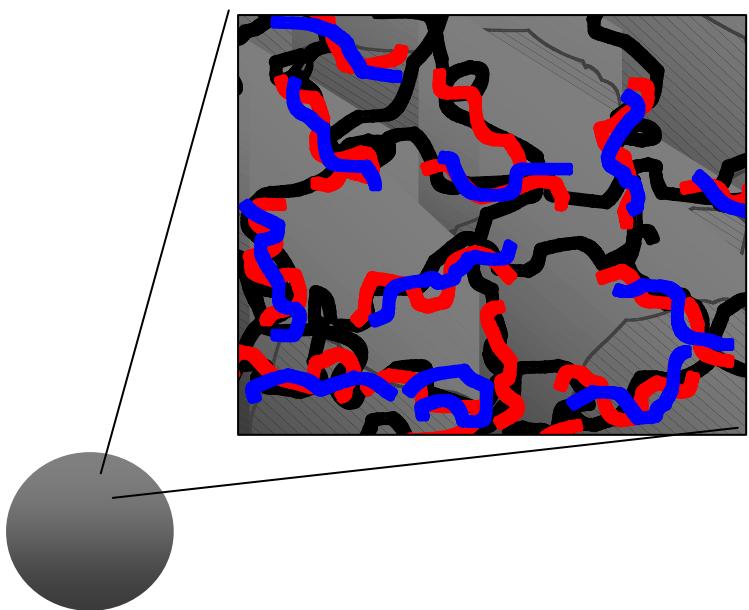
(1) Particulate antigen delivery



(2) surface display of repeated native Ag epitopes

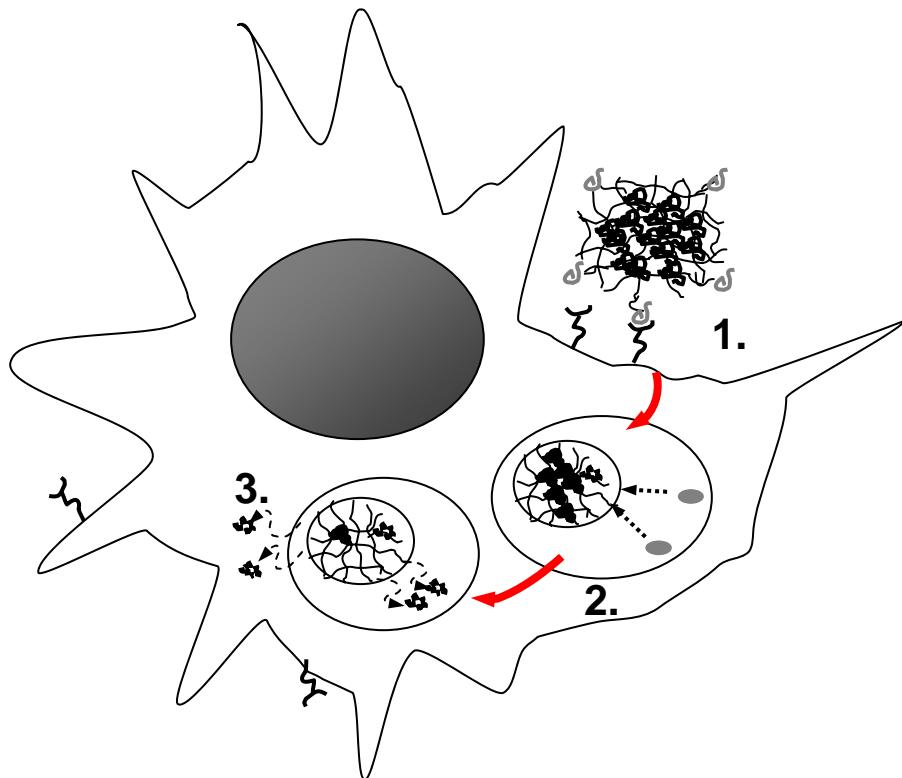
(3) surface display of 'pathogen associated molecular patterns'

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



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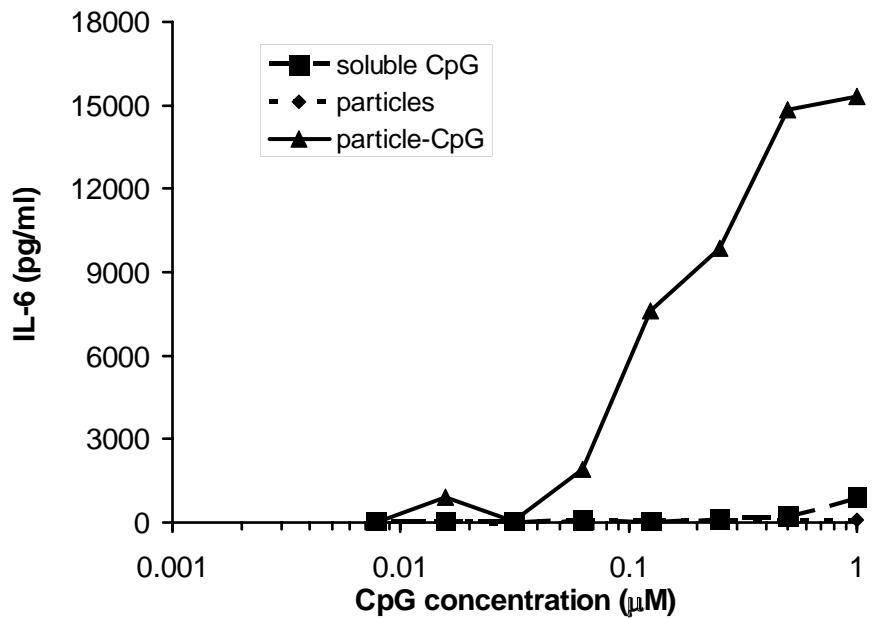
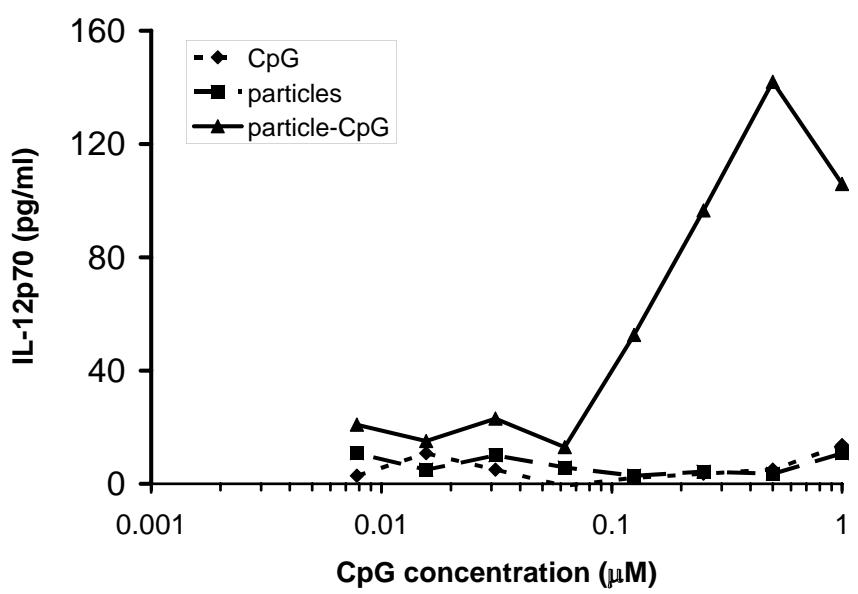
Proposed mechanism for antigen delivery to dendritic cells



Soluble Ova + CatD

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

Cytokine Secretion by Activated DCs



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

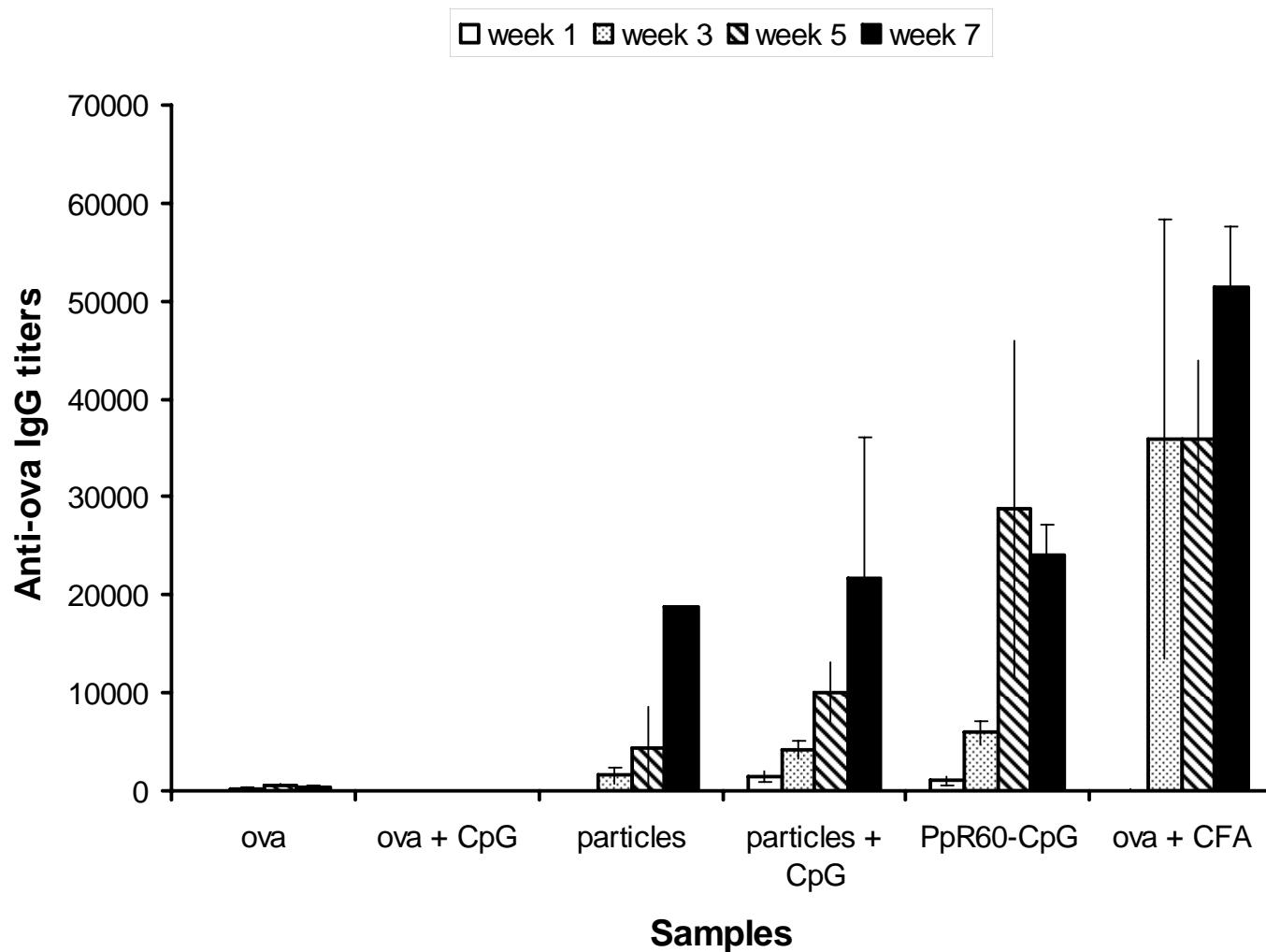
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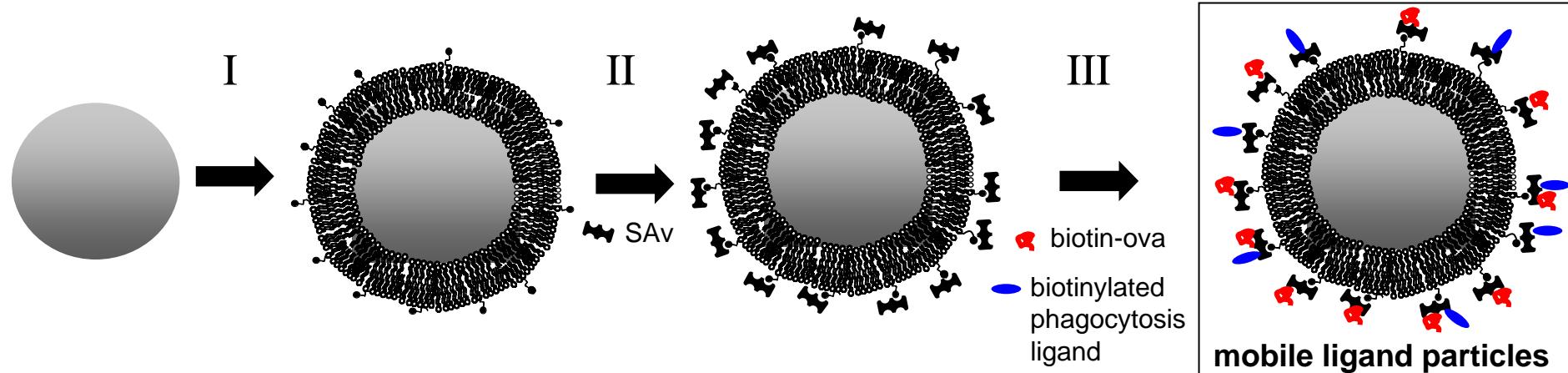
B Cell Activation *In Vivo*



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.