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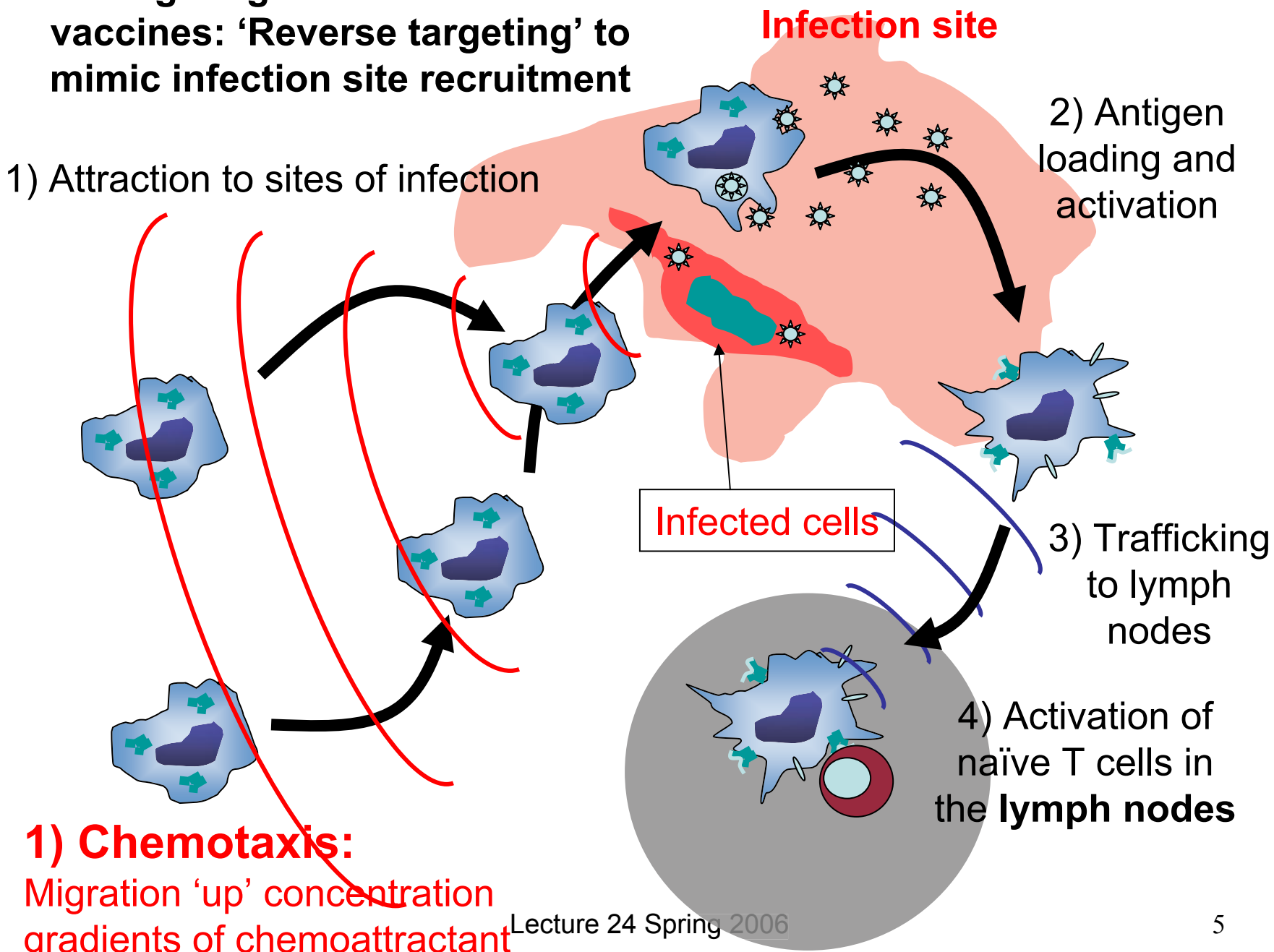
Please see: Kwon, et al. *PNAS* 102 (2005): 18264-18268.

Figure removed due to copyright restrictions.
Please see: Figure 4 in Kwon, et al. *PNAS* 102 (2005): 18264-18268.

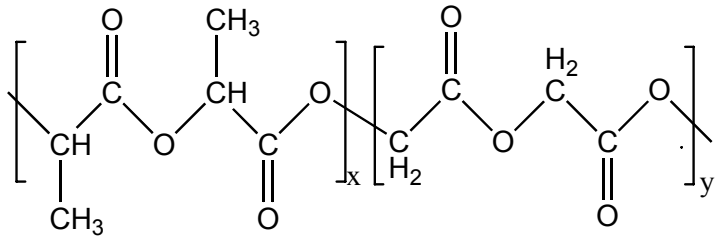
‘REVERSE TARGETING’, CONTINUED

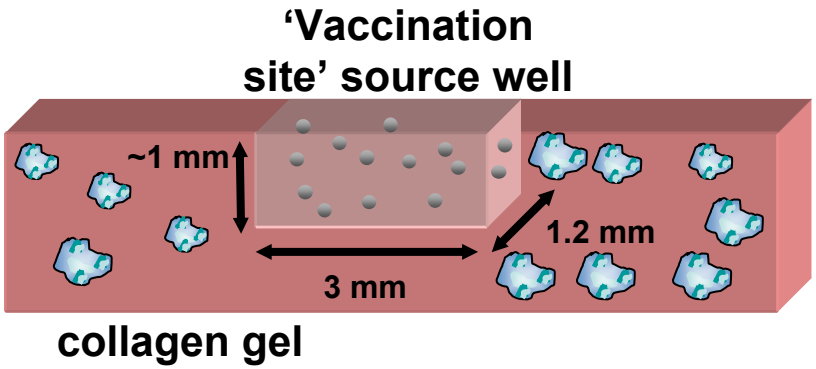
Targeting dendritic cells to vaccines: 'Reverse targeting' to mimic infection site recruitment



1) Chemotaxis:
Migration 'up' concentration gradients of chemoattractant

PLGA





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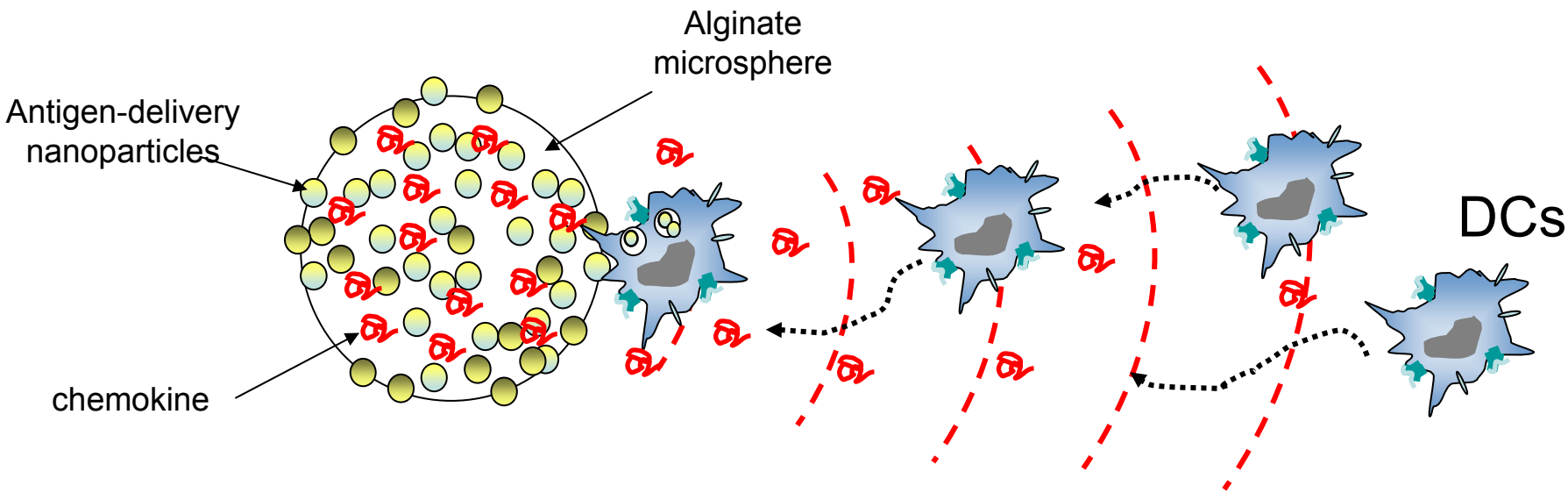
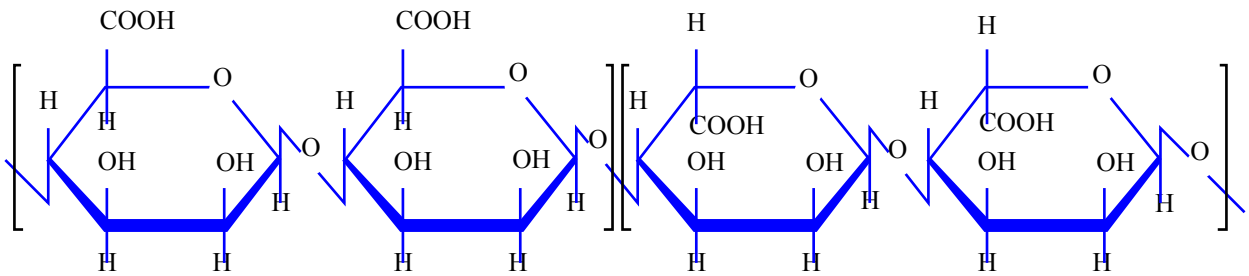
Please see: Zhao, X., et al. *Biomaterials* 26 (2005): 5048.

Dendritic cell attraction, antigen loading, and activation



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

ALGINATE



Mannuronic acid block

Guluronic acid block

Figure by MIT OCW.

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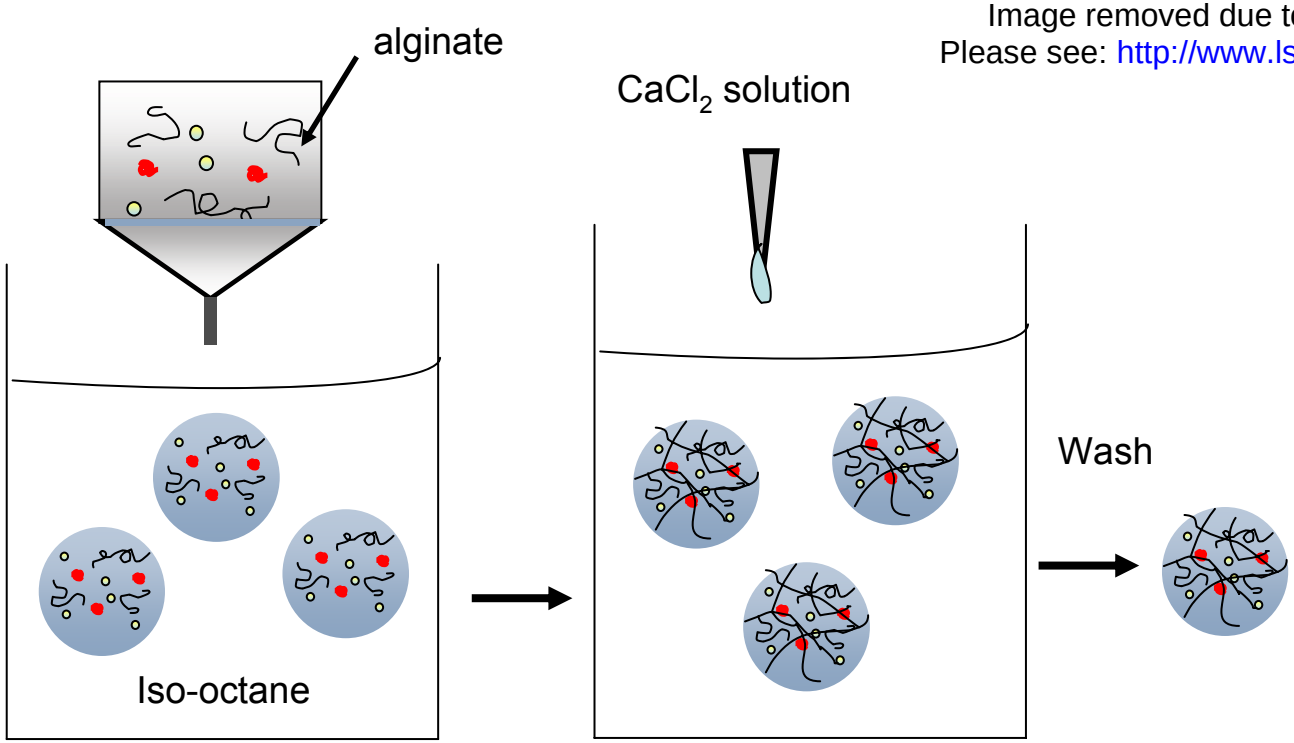
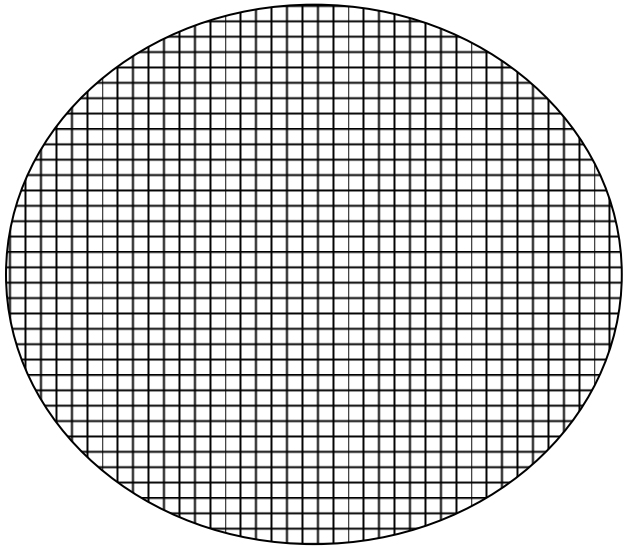
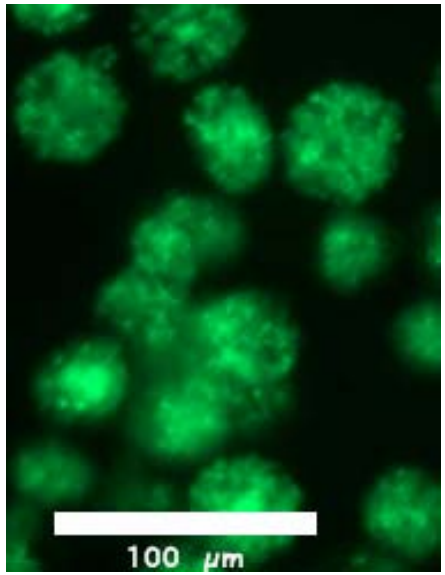
Please see: http://www.lsbu.ac.uk/water/hyalg.html

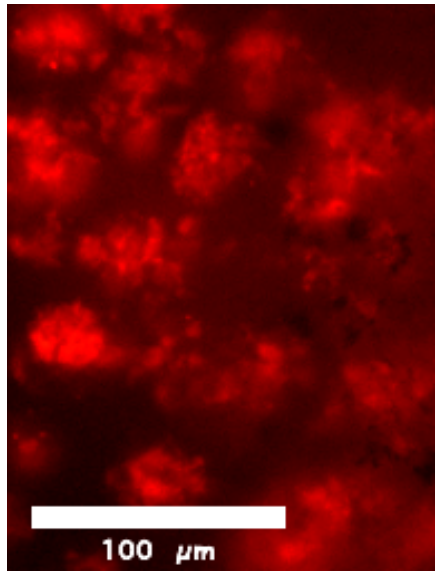


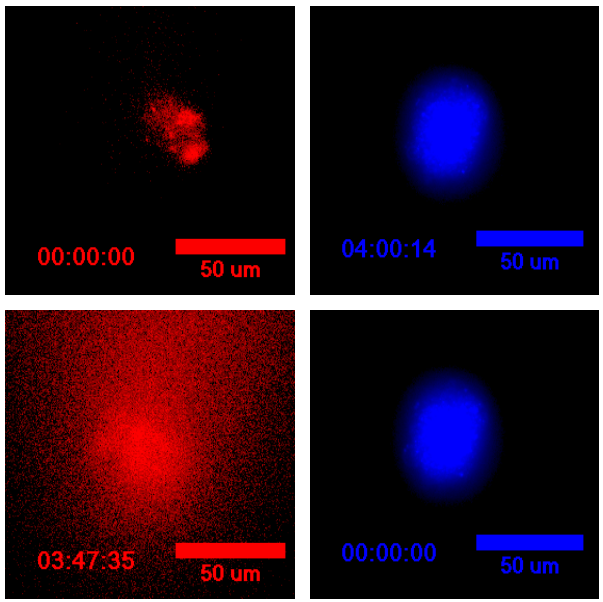


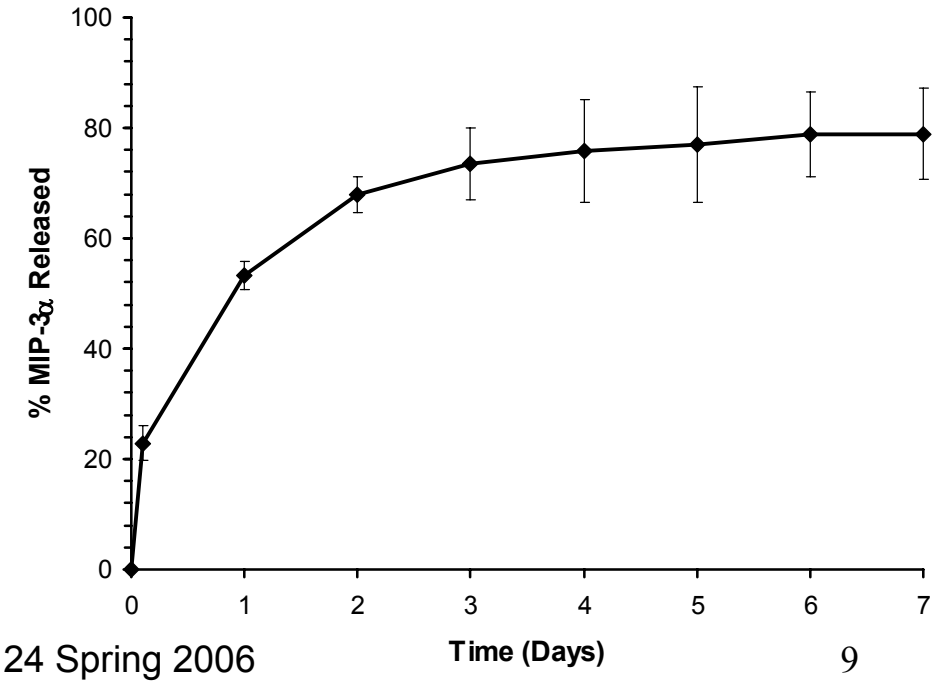
Fluorescent nanoparticles

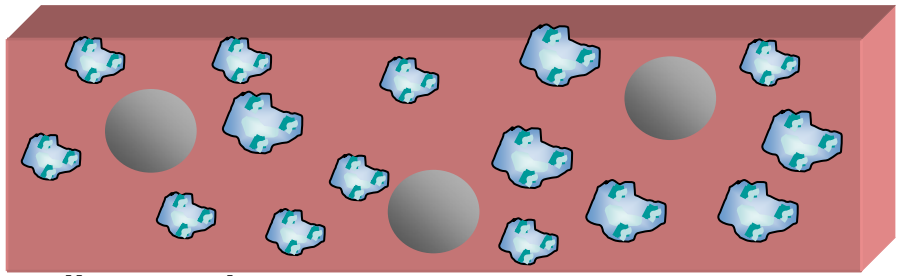


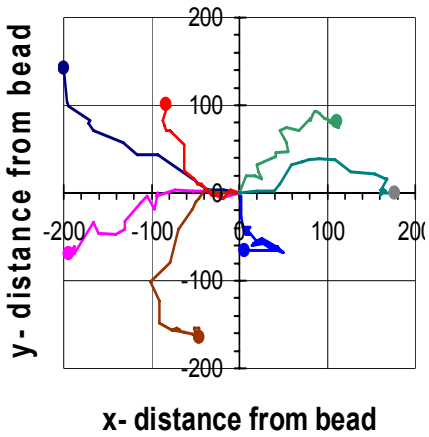
Fluorescent chemokine

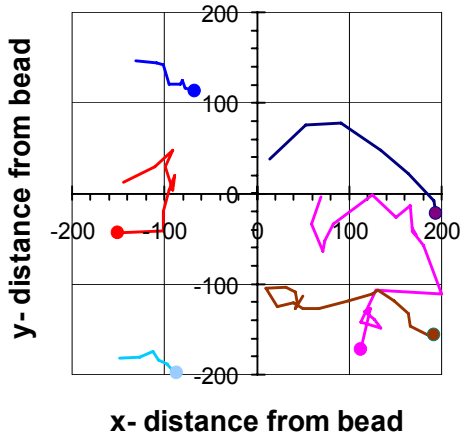


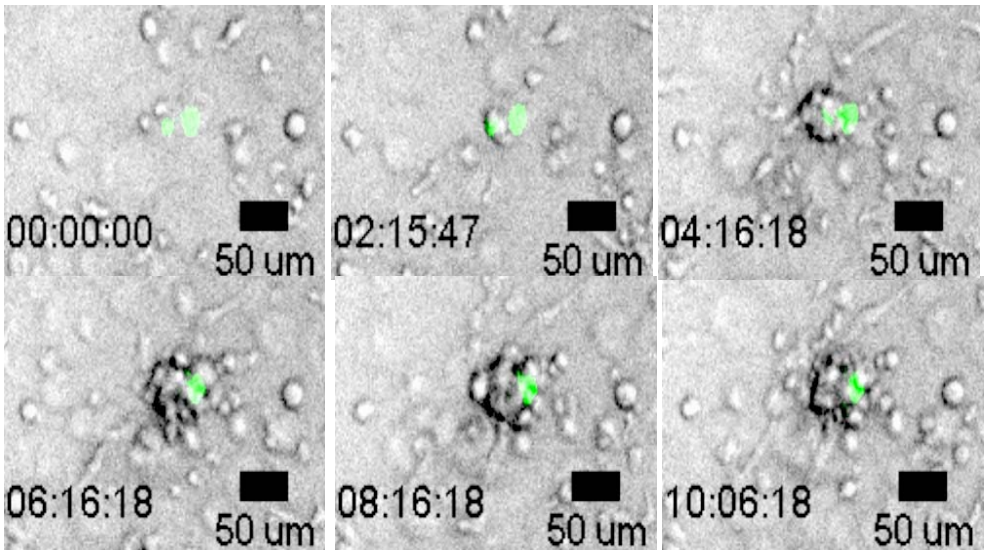


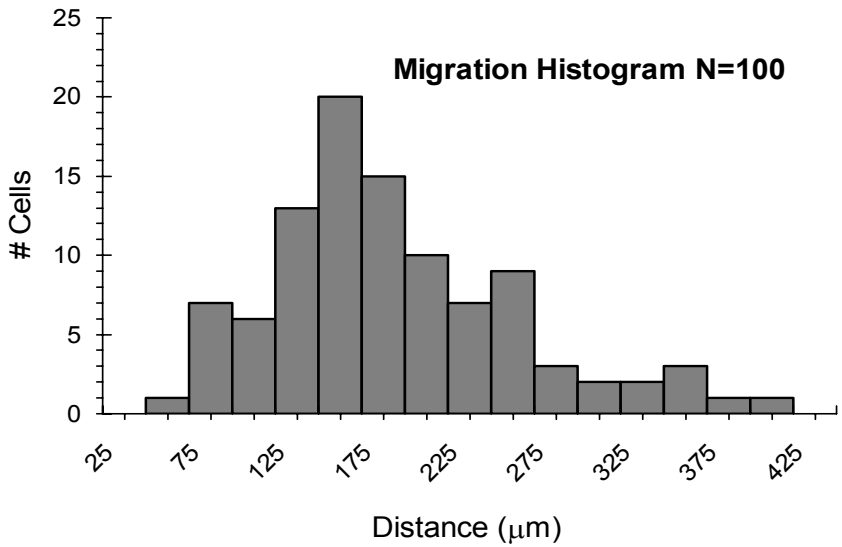


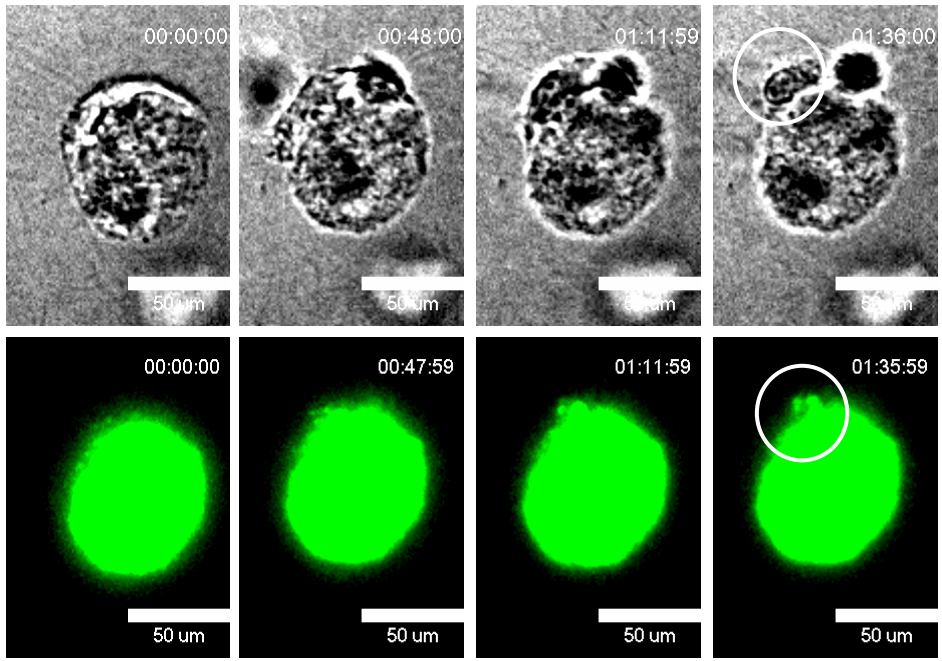

collagen gel

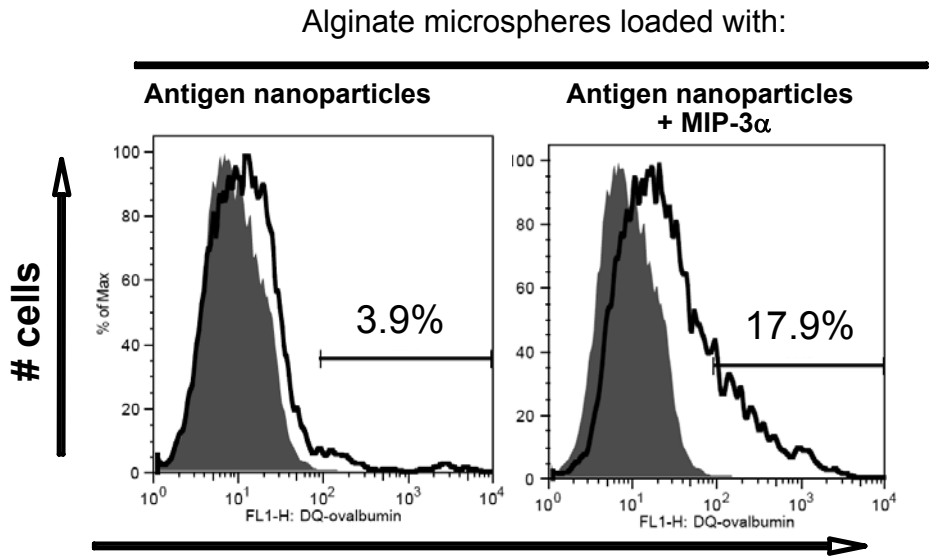

y- distance from bead
x- distance from bead
200
100
0
-100
-200
-200
-100
0
100
200


y- distance from bead
x- distance from bead
200
100
0
-100
-200
-200
-100
0
100
200


00:00:00
50 um
02:15:47
50 um
04:16:18
50 um
06:16:18
50 um
08:16:18
50 um
10:06:18
50 um


Migration Histogram N=100
Cells
Distance (μm)
25
20
15
10
5
0
25
75
125
175
225
275
325
375
425


00:00:00
00:48:00
01:11:59
01:36:00
50 um
00:00:00
00:47:59
01:11:59
01:35:59
50 um


Alginate microspheres loaded with:
Antigen nanoparticles
Antigen nanoparticles
+ MIP-3α
# cells
% of Max
3.9%
17.9%
FL1-H: DQ-ovalbumin
FL1-H: DQ-ovalbumin
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

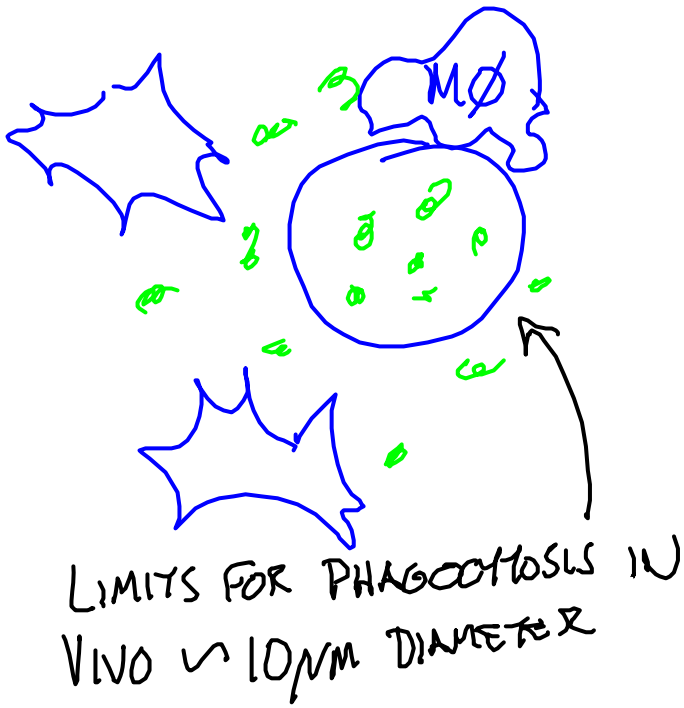
MIMICKING PATHOGEN-HOST INTERACTIONS TO STIMULATE IMMUNITY

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

PLGA NANOPARTICLES

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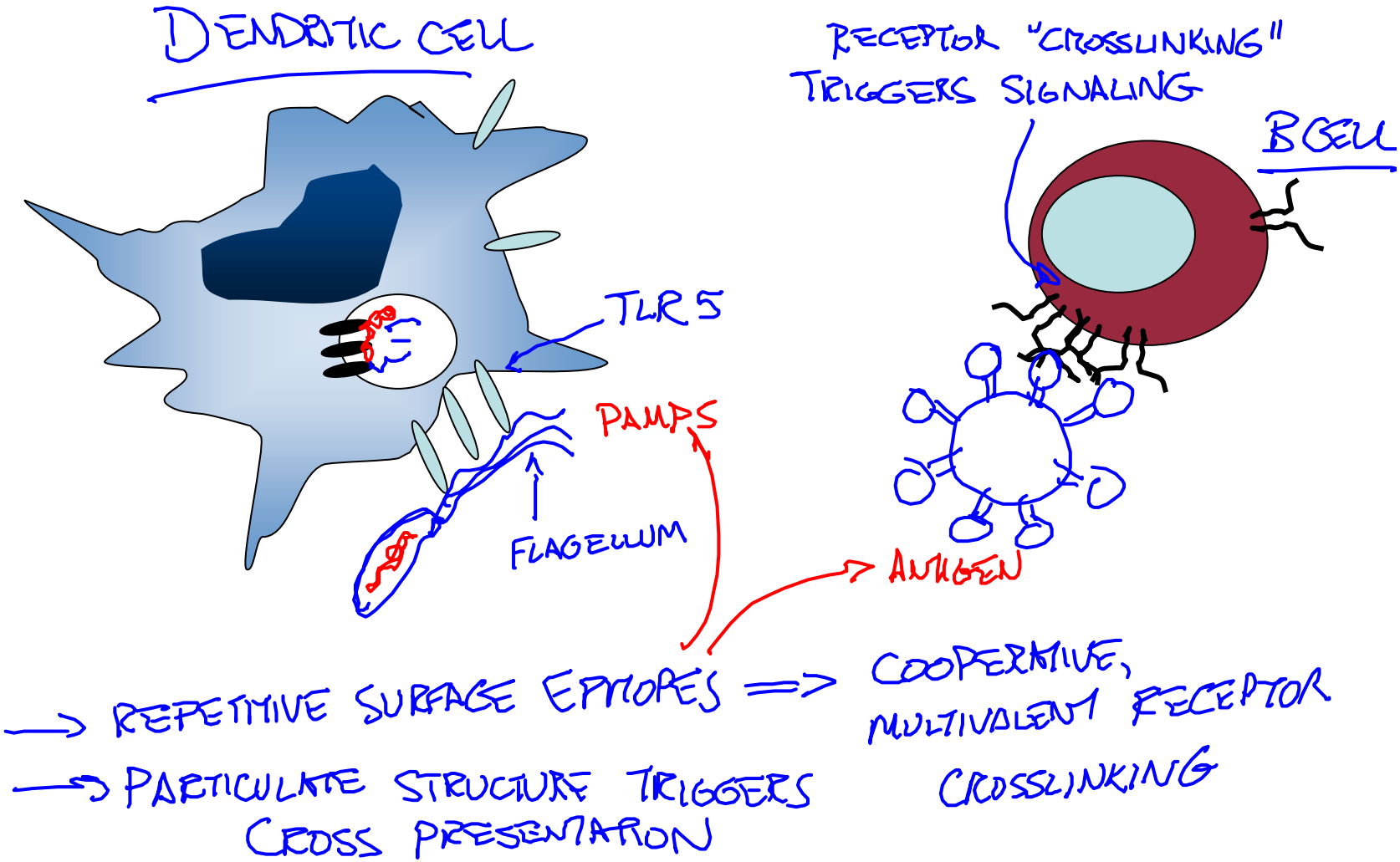
pathogens as biomaterials: how the structure of pathogens relates to immune responses



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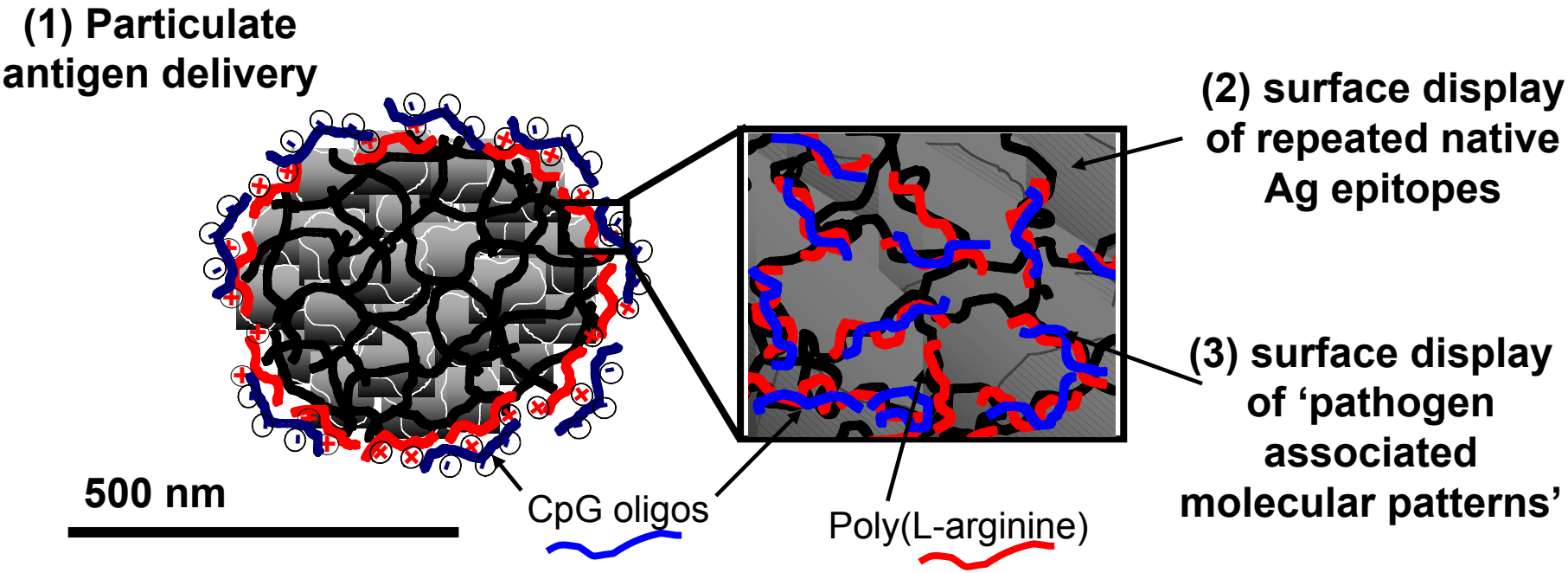
Please see: Heikenwalder, et al. *Nat Med* 10 (2004): 187-192.

Image removed due to copyright restrictions.
Please see: Diwan, et al. *Current Drug Deliv* 1, no. 4 (2004): 405-412.

Nanoparticles that mimic pathogen structural features



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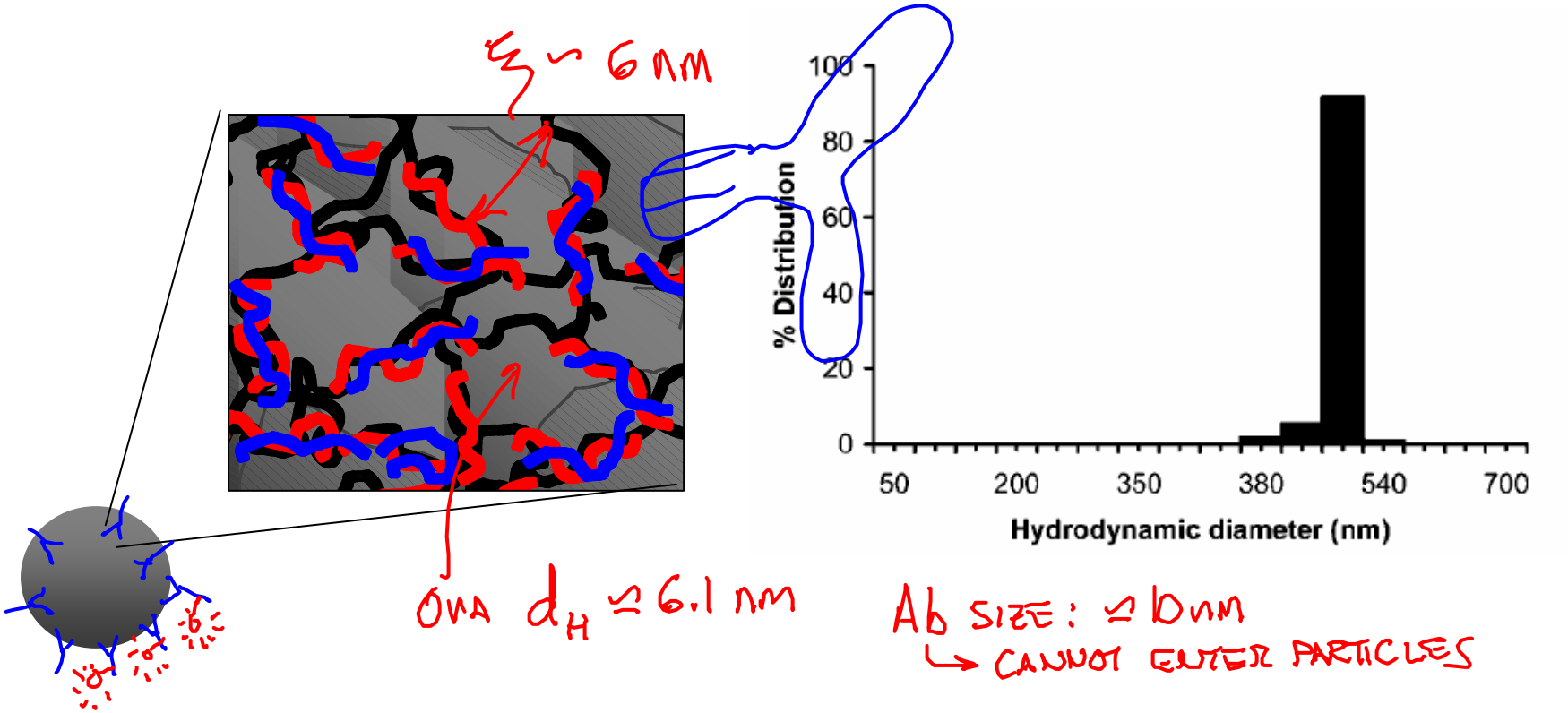
Please see: Jain, S., et al. *Biomacromolecules* 6 (2005): 2590.



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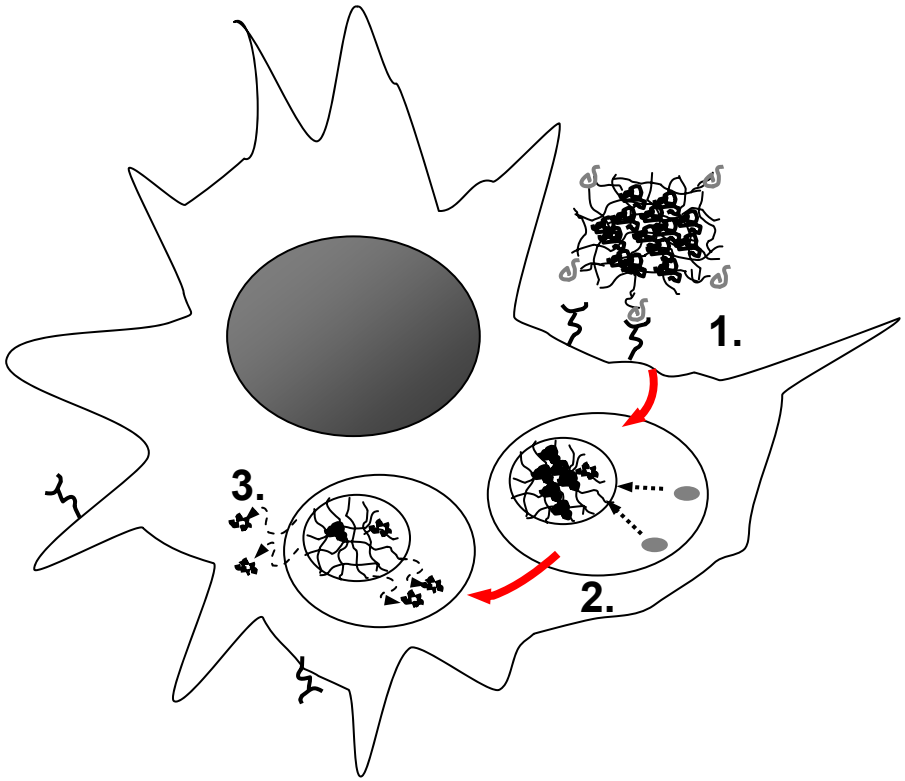
Please see: Jain, S., et al. *Biomacromolecules* 6 (2005): 2590.

Proposed mechanism for antigen delivery to dendritic cells



Soluble Ova + CatD

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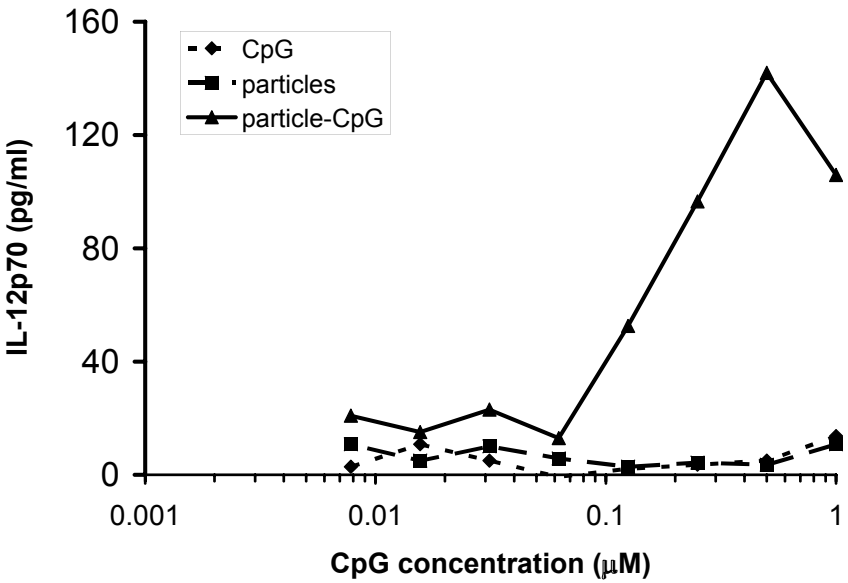
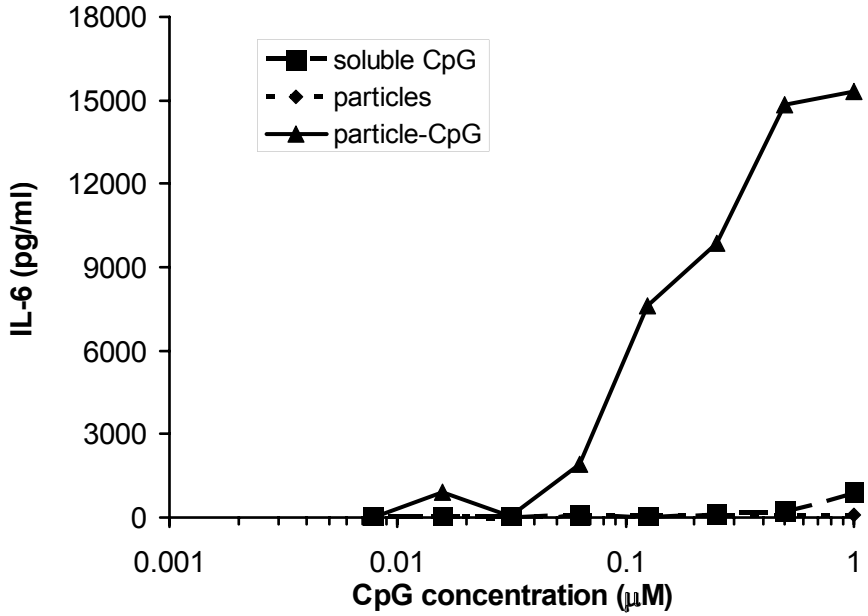
Please see: Jain, S. et al. *Biomacromolecules* 6 (2005): 2590.

Cytokine Secretion by Activated DCs





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

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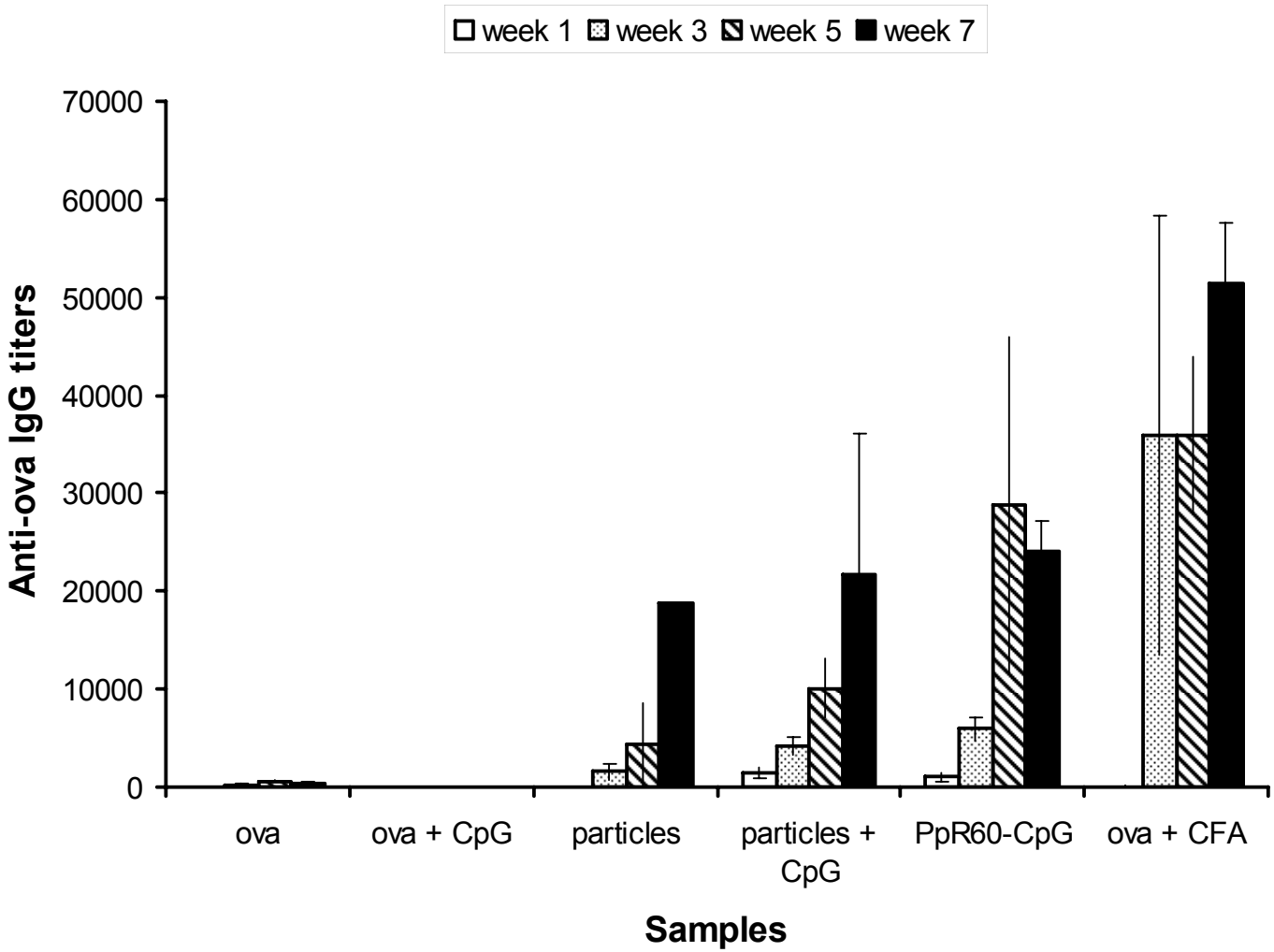
B Cell Activation *In Vivo*



Synthetic pathogens?

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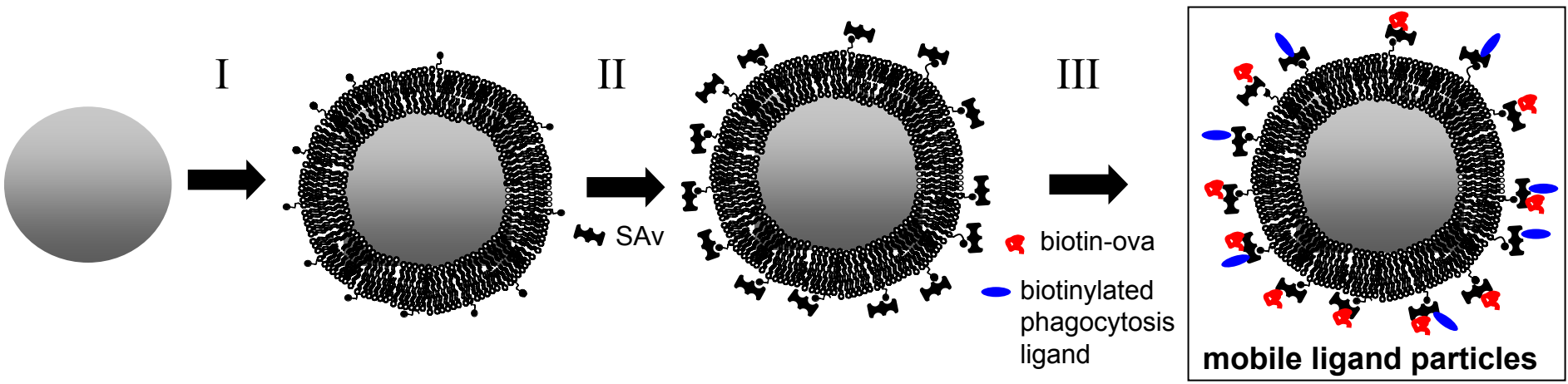
Please see: Troutier, et al. *Langmuir* 21 (2005): 1305-1313.



Synthetic pathogens?

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